Semipinacol rearrangement of *cis*-fused β-lactam diols into bicyclic lactams

by

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Abstract

The 6-azabicyclo[3.2.1]octane ring system is found in a wide variety of biologically active natural and non-natural products. The aim of this project is to prepare the 7,8-diketo-6-azabicyclo[3.2.1]octane structure *via* a semipinacol rearrangement of ring-fused β-lactams.

Chapter 1 introduces the pinacol and semipinacol rearrangement, including the use of cyclic sulfites and phosphoranes, and ring expansion of β-lactams. Previous work in the Grainger group for the synthesis of lactams *via* tandem radical cyclisation-dithiocarbamate group transfer is also discussed.

Chapter 2 describes the methodology developed for the semipinacol rearrangement of β-lactams. Access to suitable precursors for the semipinacol rearrangement is achieved through a sequence of 4-*exo trig* radical cyclisation, base-mediated dithiocarbamate group elimination and dihydroxylation. Formation of the 7,8-diketo-6-azabicyclo[3.2.1]octane ring system occurs through semipinacol rearrangement of the corresponding cyclic sulfites and phosphoranes.

In Chapter 3, the scope and limitations of the methodology are explored. Different substituents on the nitrogen of the β-lactam, groups on the cyclohexane moiety (methyl and oxygenation) and ring sizes are investigated.

An original approach to the total synthesis of peduncularine is described in Chapter 4. Synthesis of a suitably functionalised β-lactam and attempts to further transform it into the desired 7,8-diketo-6-azabicyclo[3.2.1]oct-3-ene structure are reported.

Work towards the total synthesis of calyciphylline D, calyciphylline F and caldaphnidine M is described in Chapter 5. Reductive amination and stereoselective reduction of piperitone are investigated. Use of a model system for the addition of nucleophiles into thiolactams is also described.

Abbreviations

↓↑	reflux
9-BBN-H	9-borabicyclo[3.3.1]nonane
Å	Angström
Ac	acetyl
AIBN	azobis-iso-butyronitrile
Alloc	allyloxycarbonyl ($-C(O)OCH_2CH=CH_2$)
aq.	aqueous
Bn	benzyl
BOC	*t*butyloxycarbonyl ($C(O)OC(CH_3)_3$)
br	broad
Bus	*tert*-butylsulfonyl
Bz	benzoyl ($C_6H_5C(O)-$)
C	Celsius
CAN	ceric ammonium nitrate ($(NH_4)_2Ce(NO_3)_6$)
cat	catalytic
CDI	1,1’-carbonyldiimidazole
conc.	concentrated
CPME	cyclopentyl methyl ether
CSA	camphor sulfonic acid
d	doublet
DCE	1,2-dichloroethane
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride

DIPEA	*N*,*N*-diisopropylethylamine
DLP	dilauroyl peroxide ($(C_{11}H_{24}COO)_2$)
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethyl sulfoxide
DPPA	diphenylphosphoryl azide
E	entgegen (opposite, *trans*)
ee	enantiomeric excess
EI	electron impact
eq	equivalent
ES	electrospray ionisation
FT-IR	Fourier transform infrared
g	gram(s)
h	hour(s)
HMDS	hexamethyldisilazane
HRMS	high resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons reaction
Hz	hertz
$h\nu$	light irradiation
Imid.	imidazole
*i*Pr	isopropyl
IR	infrared
J	coupling constant
KHMDS	potassium hexamethyldisilazide

L	litre(s)
LDA	lithium diisopropylamide
LG	leaving group
LHMDS	lithium hexamethyldisilazide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
M	molar
m	multiplet
m/z	mass/charge
*m*CBA	*meta*-chlorobenzoic acid
*m*CPBA	*meta*-chloroperbenzoic acid
min	minute(s)
mol	moles
mp	melting point
Ms	methanesulfonyl, mesyl
MS	molecular sieves
NaHMDS	sodium hexamethyldisilazide
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
p	para
PCC	pyridinium chlorochromate
Pet ether	60-80 °C petroleum ether

PhthN	phthalimido
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
ppm	part(s) per million
PPTS	pyridinium *para*-toluenesulfonate
PTSA	*para*-toluenesulfonic acid
q	quartet
rt	room temperature
s	singlet
SET	single electron transfer
t (NMR)	triplet
t	tertiary
T.S.	transition state
T	temperature
TBAB	tetra-*N*-butylammonium bromide
TBAF	tetra-*N*-butylammonium fluoride
TBAI	tetra-*N*-butylammonium iodide
TBS	*tert*-butyldimethylsilyl
TEAC	tetraethylammonium chloride ($Et_4N^+Cl^-$)
Tf	trifluoromethanesulfonyl (CF_3SO_2)
THF	tetrahydrofuran
tlc	thin layer chromatography
TMEDA	*N,N,N′,N′*-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate

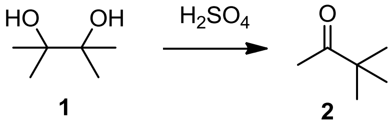
Ts	*para*-toluenesulfonyl, tosyl
UV	ultraviolet
vs.	versus
W	watt(s)
w/u	work-up
Z	zusammen (together, *cis*)

Contents

Chapter one: Introduction

1.1 *The pinacol rearrangement*

An acid-catalysed reaction of a vicinal diol, which results in dehydration and migration of an alkyl or aryl group or a hydrogen atom to form an aldehyde or a ketone is known as the pinacol rearrangement.[1] The name is derived from the earliest example recorded by Fittig in 1860 which described the transformation of pinacol **1** into pinacolone **2** (Scheme 1).[2]

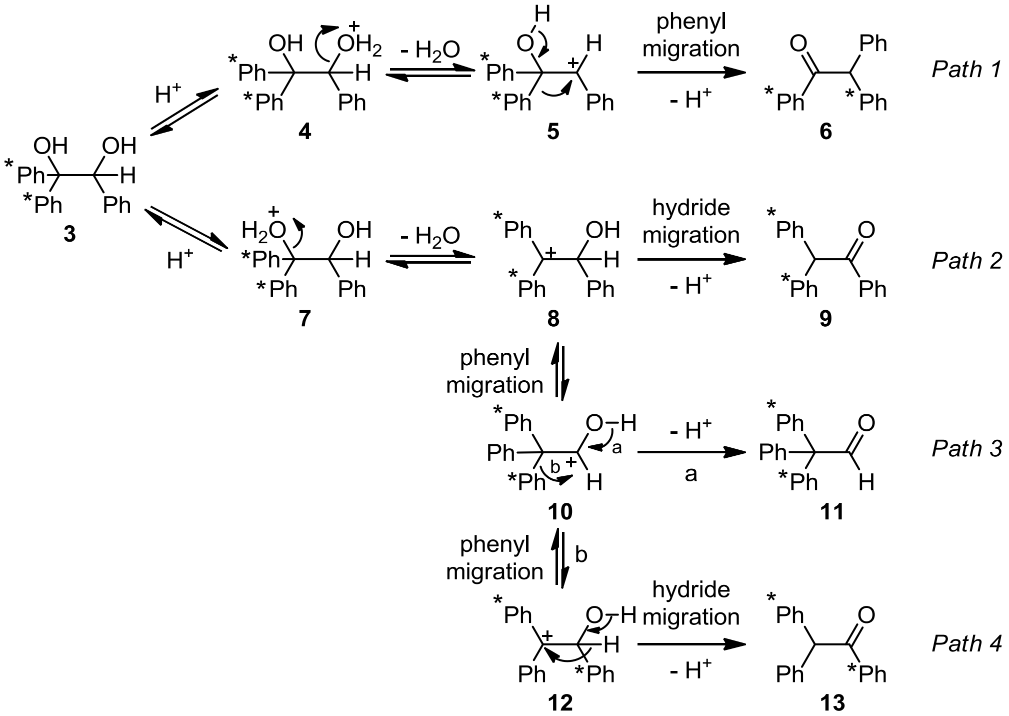


Scheme 1

All classes of 1,2-diols (primary, secondary, tertiary, alkyl- or aryl-substituted), a wide variety of acid catalysts and various solvents have been used in the pinacol rearrangement. Carbon-13 labelling studies on the rearrangement of triphenylethylene glycol **3** demonstrated that four different reaction pathways are possible (Table 1 and Scheme 2).[3]

Entry	**Catalyst**	**% Contribution of path**			
		1	**2**	**3**	**4**
1	conc. H_2SO_4	2.5	11.7	0	85.8
2	HCOOH	4.7	39.0	0	56.3
3	$(COOH)_2$	2.7	45.3	12.6	39.4
4	dilute H_2SO_4	3.2	67.4	16.5	12.9
5	HCl in dioxane-H_2O	0	96.1	3.9	0

Table 1: Influence of the nature of the acid towards the product outcome



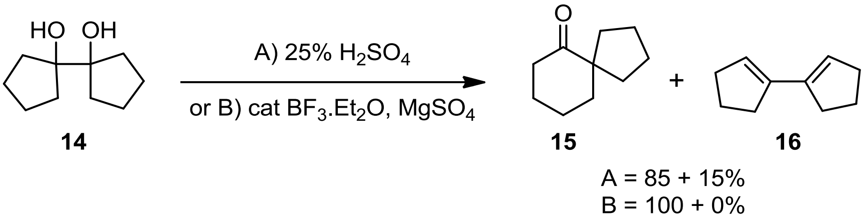
Scheme 2

Either of the hydroxyl groups may be protonated by the acid to give **4** and **7** which, after dehydration, form **5** and **8** (Scheme 2). The secondary carbocation **5** was found to be less stable than the tertiary one and so path 1 made a lower contribution in the semipinacol rearrangement of triphenylethylene glycol **3**.

When concentrated sulfuric acid or formic acid was used as the catalyst, pathway 4 was favoured. In this case, formation of the stable carbocation **8** was followed by two 1,2-migrations of phenyl groups and then one hydride shift to give ketone **13**. On the other hand, the use of dilute H_2SO_4 and HCl in dioxane-H_2O as a catalyst provided mainly ketone **9** which resulted from hydride migration to stable cation **8**. Aldehyde **11** resulted from the minor pathway 3 *via* a single 1,2-migration of a phenyl group. This study showed that the nature of the acid and therefore the carbenium ion formed affects the product outcome.

In the pinacol rearrangement, the relative migratory tendency of aryl > alkenyl > hydride > alkyl is generally observed. However, a general migratory aptitude is difficult to define because the energy of the transition state depends on the aptitude of the migrating group and on the electronic and/or steric effects of the non-migrating substituents.

The formation of side products such as epoxides and alkenes is an additional inconvenience in the pinacol rearrangement. However, a careful choice of acid catalyst can reduce, or even eliminate their appearance, as reported by Sands.[4-5] Cyclopentylcyclopentane-1,1'-diol **14** rearranged to give 85% of ketone **15** and 15% of undesired diene **16** when treated with 25% H_2SO_4. In order to suppress the formation of side product **16**, $BF_3{\cdot}Et_2O$ was used in a sub-stoichiometric amount with $MgSO_4$ as a dehydrating agent; full conversion to ketone **15** was observed under these conditions (Scheme 3).



Scheme 3

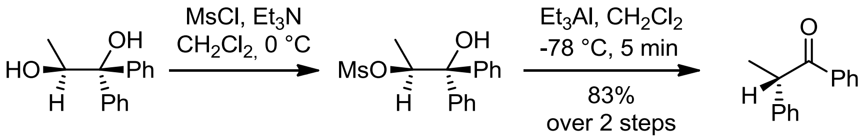
Few conclusions regarding the pinacol rearrangement can be made that are general for all diols under all reaction conditions. However, the following facts were reported in 1960 by Collins:[3]

- It is exclusively an intramolecular rearrangement.
- The course of the reaction depends on which hydroxyl group is most easily removed, which is linked to the stability of the carbenium ion intermediate.
- The group which migrates is the one which more effectively stabilizes a positive charge.
- Either racemisation or inversion may be observed. Racemisation may be explained by the formation of a carbocation intermediate or by further reaction of the product due to all the steps of the reaction mechanism being reversible.

1.2 The semipinacol rearrangement

The semipinacol rearrangement was originally defined by Tiffeneau in 1923 as a special case of the pinacol rearrangement, in which migration occurred towards the carbon of a tertiary or secondary diol. However, the term semipinacol is now used generally to describe all such rearrangements which are related to, or reminiscent of, the pinacol rearrangement.[6]

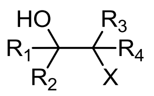
The main issue regarding the synthetic utility of the pinacol rearrangement is the lack of stereoselectivity. The formation of an achiral carbenium ion intermediate from an enantiopure starting material will allow the formation of a racemic mixture of products. In the semipinacol rearrangement, a concerted mechanism is postulated which does not involve the formation of a carbocation. Therefore, elimination of the leaving group is concomitant with 1,2-migration and leads to stereospecific inversion of configuration *via* an S_N2-type mechanism. In 1983, Suzuki used this feature to synthesize chiral ketones. Enantiopure diol **17** was first regioselectively mesylated at the less substituted secondary alcohol. Subsequent treatment with triethylaluminium afforded enantiopure ketone **19** in 83% yield over 2 steps (Scheme 4).[7]



17 **18** **19**

Scheme 4

The largest classes of semipinacol rearrangement are those derived from 2-heterosubstituted alcohols such as halohydrins, 2-amino alcohols, 2-hydroxy sulfides and 2-hydroxy selenides (Figure 1).

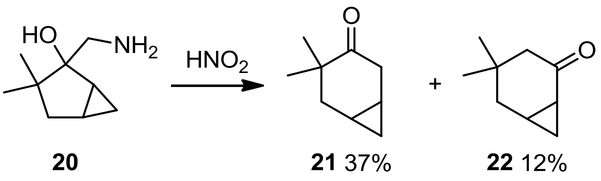


halohydrin: X = Br, Cl
2-amino alcohol: X = NH_2
2-hydroxy sulfide: X = SR
2-hydroxy selenide: X = SeR

Figure 1

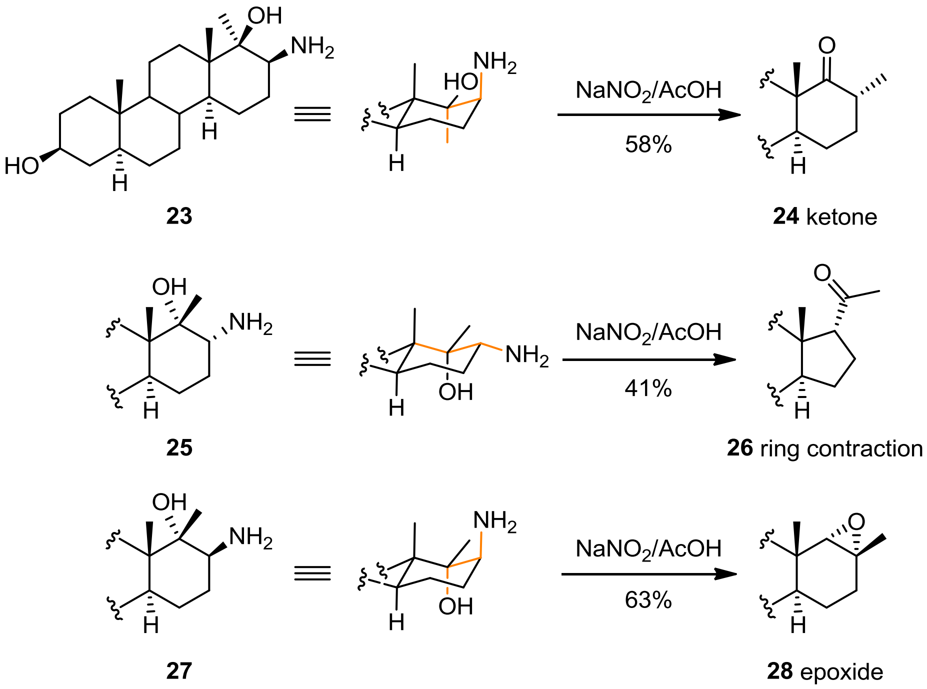
A specific example of the semipinacol rearrangement is the Tiffeneau-Demjanov rearrangement.[8] This reaction involves treatment of a primary 2-amino alcohol with nitrous acid and acetic acid. In general, the rearrangement is most effective when the hydroxyl group is tertiary. It is often associated with the formation of five- to eight-membered rings and generally a decrease in yield is observed as the ring size is increased.[9]

Studies also showed that the least substituted group has a greater tendency to migrate in ring expansion reactions. In 1980, Ford synthesized **21** *via* a Tiffeneau-Demjanov transposition to investigate its radical behaviour upon irradiation (Scheme 5).[10] Treatment of 1,2-amino alcohol **20** with nitrous acid gave a mixture of ketones **21** and **22**. Migration of the less substituted bond bearing the cyclopropane gave the major regioisomer **21** in 37% yield.



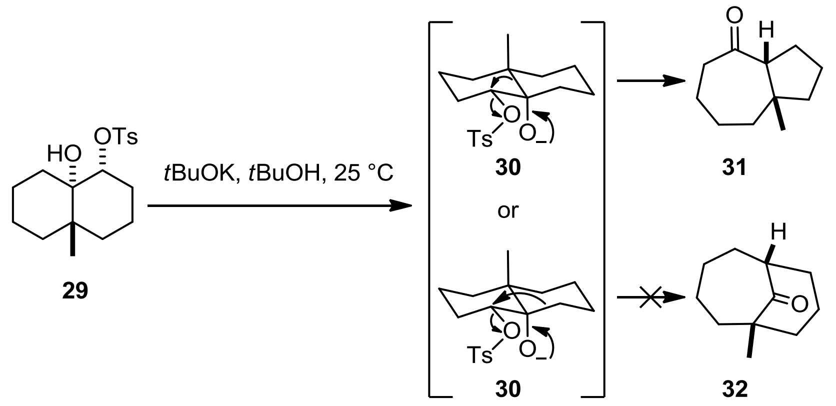
Scheme 5

Conformational effects are as important as migratory aptitude in a semipinacol rearrangement. Indeed, the work by Shoppee on the rigid steroidal framework demonstrated that different isomers of a 1,2-amino alcohol gave a range of products originating from diverse bond transposition when submitted to the same reaction conditions (Scheme 6).[11-12] Migration of the methyl group was observed when homosteroid **23** was submitted to nitrous acid to give **24** in 58% yield. Under the same reaction conditions, amino alcohol **25**, the diastereomer of **23**, underwent Tiffeneau-Demjanov rearrangement with ring contraction to give ketone **26**. Finally, when epimer **27** was subjected to the same conditions, epoxide **28** was formed because for this isomer the hydroxyl group is now antiperiplanar to the primary amine. This work demonstrated the importance of having both the leaving and migrating group antiperiplanar to each other for a semipinacol rearrangement to proceed.



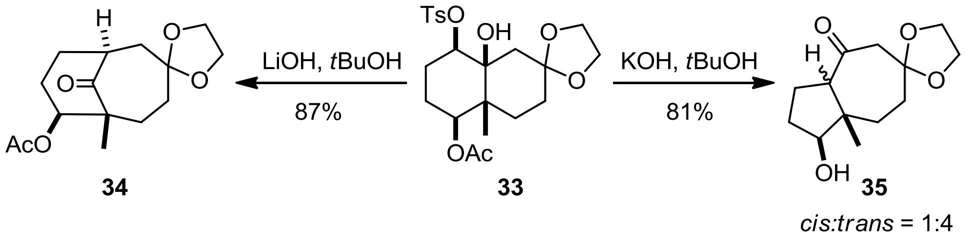
Scheme 6

Another feature of the semipinacol rearrangement is that it may be carried out under basic conditions. The anionic semipinacol rearrangement was first reported in 1961 by Mazur and Nussi.[13] 10-Methyl-decal-1,9-diol 1-tosylate **29** was transformed into *cis*-10-methylbicyclo-[5.3.0]decan-1-one **31** using *t*BuOK in *t*BuOH (Scheme 7). The bond migrating must be antiperiplanar to the tosylate leaving group and so *cis*-ketone **31** was formed as the sole isomer.



Scheme 7

Basic reaction conditions were subsequently used in 1982 by Heathcock in the synthesis of sesquiterpene antitumour lactones.[14] Tosylate **33** was reacted with an excess of LiOH or *t*BuOK, in dry *t*BuOH. Keto acetate **34** or a 1:4 mixture of *cis*:*trans* keto alcohol **35** were obtained depending on the base used (Scheme 8).

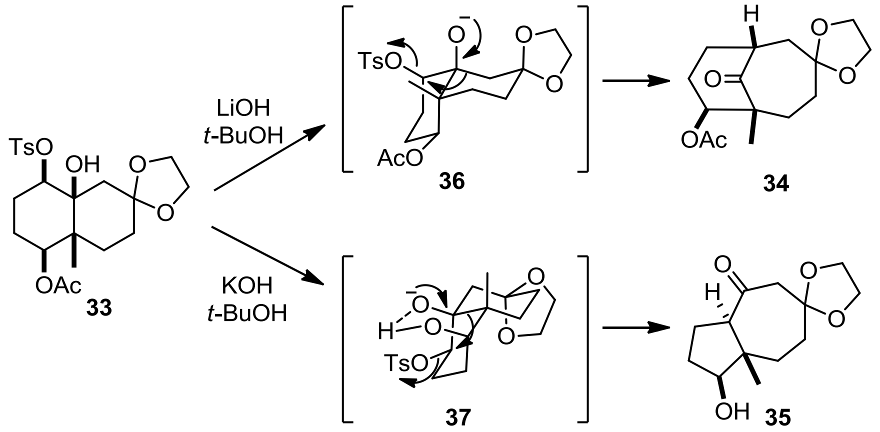


Scheme 8

The results obtained for this rearrangement were explained through conformational arguments (Scheme 9). The vicinal C-C bond which migrated during the rearrangement needed to be antiperiplanar to the tosylate.

When lithium hydroxide was used as the base, the rearrangement occurred without any saponification of the acetate functional group. The conformation adopted by the fused bicycle favoured the formation of bridged ketone **34** *via* migration of the C-CH_2 bond (Scheme 9). When potassium hydroxide was used as the base, saponification took place before rearrangement. A hydrogen bond between the two hydroxyl groups changed the conformation of intermediate **37** which placed the C-CCH_3 bond antiperiplanar to the tosylate group. *Trans-*

fused bicyclic ketone **35** was initially formed as a single diastereomer. The *cis:trans* mixture arose *via* subsequent base-catalysed enolate formation of *trans*-**35**.



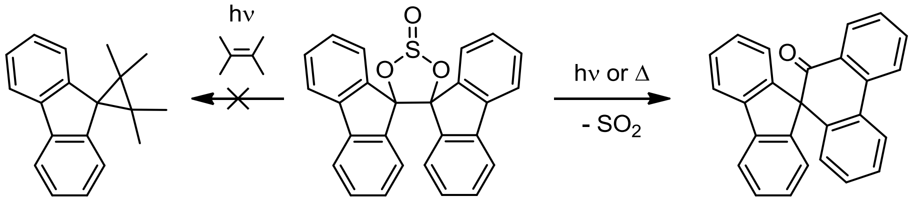
Scheme 9

A few conclusions have been drawn for the semipinacol rearrangement:

- They are more selective than pinacol rearrangements in terms of regiochemistry.
- The reaction conditions used are usually milder than for a pinacol rearrangement.
- The carbon atom bearing the migrating group is usually tertiary, while the migration terminus can be primary, secondary or tertiary.
- Migratory aptitude is not such an important factor in the semipinacol rearrangement. Electronic factors, relief of ring strain and substrate stereochemistry all influence the course of the migration.
- Inversion of configuration is observed in most cases, and this feature has been utilized in stereoselective synthesis.

1.3 Semipinacol rearrangement of cyclic sulfites

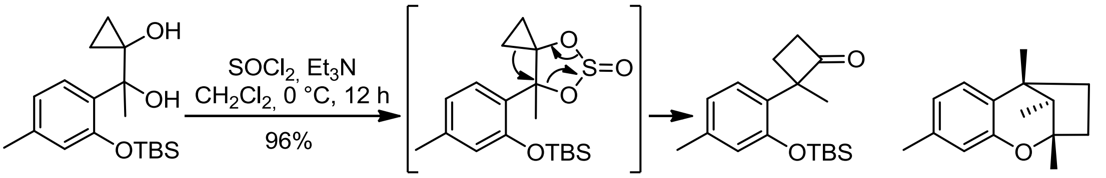
The first formal semipinacol rearrangement of cyclic sulfites was described in 1972 by Griffin and Manmade.[15] Their study on the formation of arylcarbenes using either light irradiation or thermolysis of cyclic sulfites demonstrated that 1,2-aryl migration was a competing pathway during carbene synthesis. Fluorenopinacol sulfite **38** gave only ketone **39** and none of the desired cyclopropane fluorene **40** (Scheme 10).



40 **38** **39**

Scheme 10

In 1995, Fukumoto and co-workers published their work on the synthesis of (–)-filiformin (Scheme 11).[16] This sesquiterpene was isolated in 1976 from *Laurencia filiformis*, an Australian red algae.[17] Their synthetic approach to this natural product utilized a semipinacol rearrangement of a cyclic sulfite intermediate **42** which was formed *in situ* by reacting diol **41** with thionyl chloride and triethylamine. The cyclic sulfite could not be isolated and 1,2-migration occurred over 12 h at 0 °C in CH_2Cl_2. Presumably, relief of ring strain is an additional driving force for this rearrangement to take place and to give cyclobutanone **43** in an excellent 96% yield.

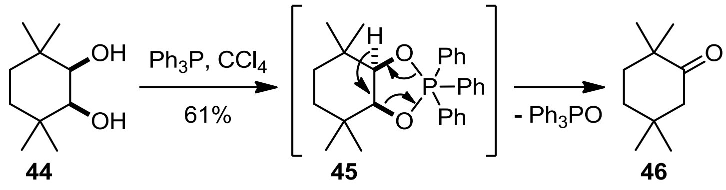


41 **42** **43** (-)-filiformin

Scheme 11

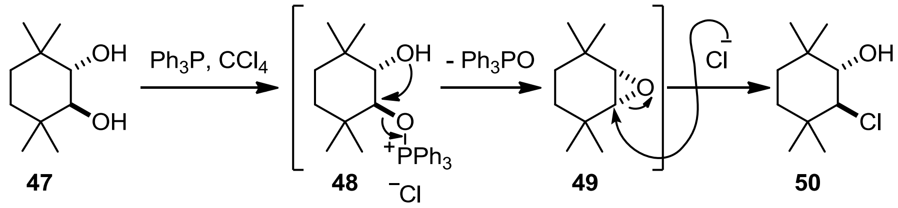
1.4 Semipinacol rearrangement of cyclic phosphoranes

In 1972, Applequist described the semipinacol rearrangement of *cis*-diol **44** by reacting it with PPh_3 in CCl_4 (Scheme 12).[18] Cyclic phosphorane **45,** although not isolated, was a likely intermediate and would give ketone **46** *via* a 1,2-hydride shift.



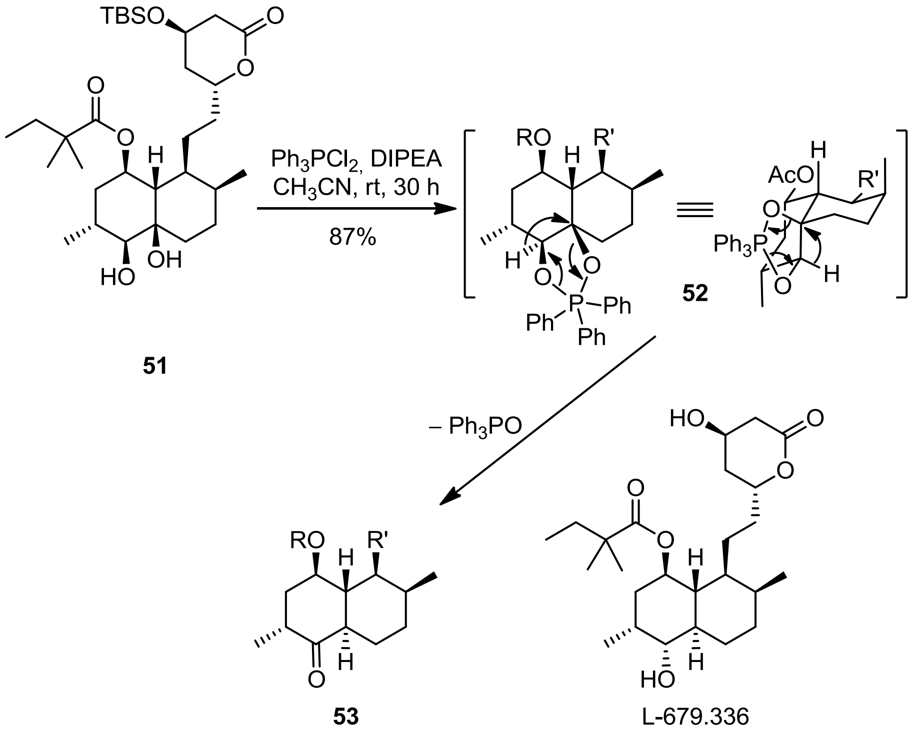
Scheme 12

Submitting *trans*-diol **47** to the same reaction conditions gave only *trans*-chlorohydrin **50** (Scheme 13). The abnormal retention of stereochemistry in **50** suggested the formation of epoxide **49** as an intermediate in this reaction. Cyclisation to form oxirane **49** was favoured over the formation of the *trans*-cyclic phosphorane due to the high ring strain in the latter.



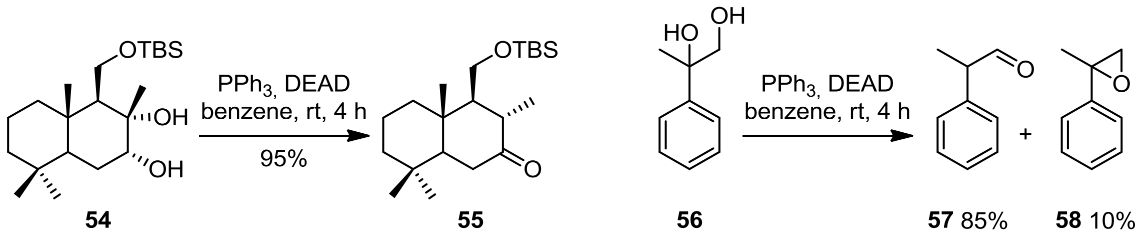
Scheme 13

In 1991, DeCamp and Mills used similar conditions to achieve the synthesis of L-679.336, a cholesterol-reducing drug.[19] After screening a variety of conditions for the transformation of diol **51** into ketone **53**, they discovered that the use of triphenylphosphine dichloride, formed *in situ* by reacting PPh_3 and hexachloroethane, in combination with Hünig's base, gave the desired ketone product **53** in 87% yield (Scheme 14).



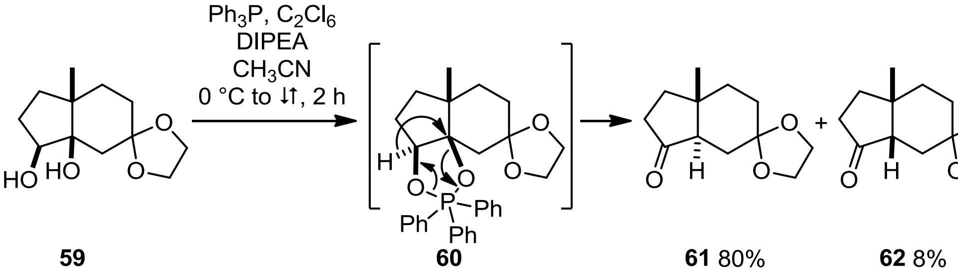
Scheme 14

In 2000, Barrero and co-workers used Mitsunobu conditions to conduct semipinacol rearrangements using a variety of 1,2-diols.[20] Acyclic and *trans*-1,2-diols reacted with PPh_3 and DEAD to form epoxides. In contrast, either cyclic phosphoranes or a product arising from semipinacol rearrangement were obtained from the corresponding *cis*-1,2-diols. For example, diol **54** gave ketone **55** as a single isomer in 95% yield whereas 2-phenylpropane-1,2-diol **56** gave a mixture of 2-phenylpropanal **57** and 2-methyl-2-phenyloxirane **58** (Scheme 15).



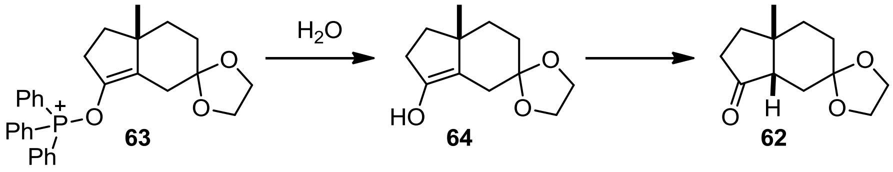
Scheme 15

In 2012, Grainger and co-workers published the synthesis of the core structure of dictyoxetane *via* the semipinacol rearrangement of cyclic phosphorane **60** (Scheme 16).[21] The major product obtained *via* 1,2-hydride shift was *trans*-hydrindanone **61**. A small amount of *cis*-hydrindanone **62** was also isolated.



Scheme 16

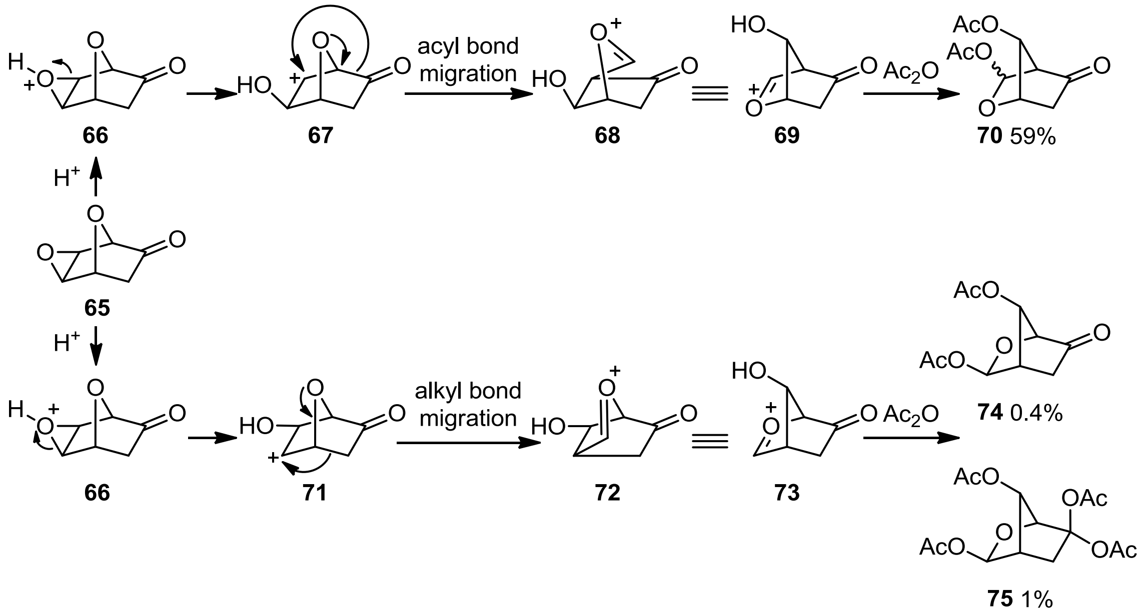
Investigations were conducted to establish how the unexpected product **62** might have arisen. The reaction was monitored using ^{31}P-NMR spectroscopy. This study demonstrated the *in situ* formation of triphenylphosphine dichloride from PPh$_3$ and hexachloroethane and the rapid reaction with diol **59** to form cyclic phosphorane **60** at rt. Heating to 60 °C was required to drive the reaction to completion and this was visualized by the formation of triphenylphosphine oxide. A small amount of enol phosphonium **63** was observed in the reaction mixture; hydrolysis of **63** and subsequent tautomerisation would lead to the more stable *cis*-structure **62** (Scheme 17).



Scheme 17

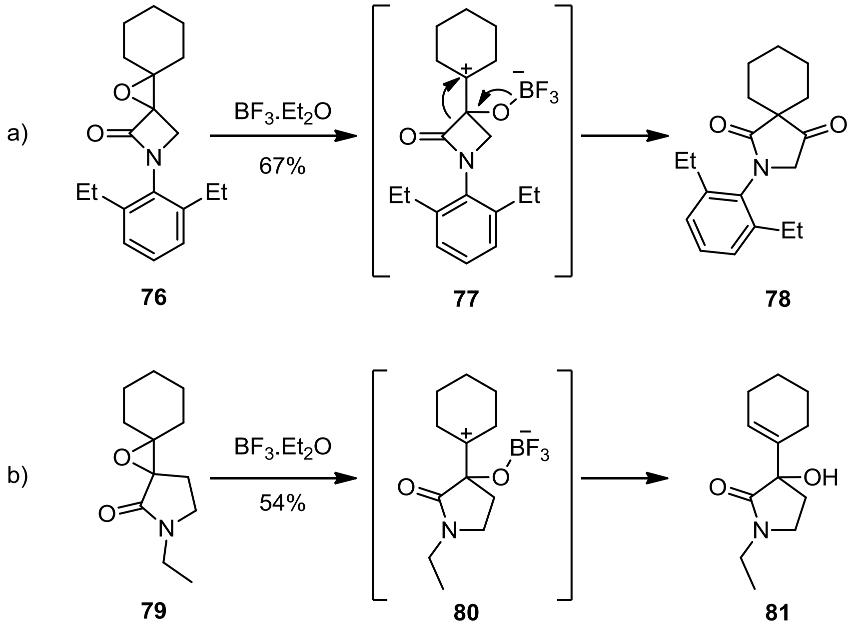
1.5 Semipinacol rearrangement of *β*-lactams

In 1987, Vogel reported studies into the relative migratory aptitude of acyl groups compared to alkyl groups in the Wagner-Meerwein transposition.[22] Treatment of epoxyketone **65** with acid followed by Ac$_2$O gave rise to three acetate derivatives, with **70** being the major product in 59% yield (Scheme 18). This indicated that stabilisation of the opened epoxide **67** or **71** was occurring mainly through acyl bond, and not alkyl bond, transposition. Alternatively, if the Wagner-Meerwein rearrangement was considered as a concerted process, an "energetically unbiased" situation would be obtained and therefore, the intrinsic higher migratory aptitude of the acyl group would give **70** as the major product.



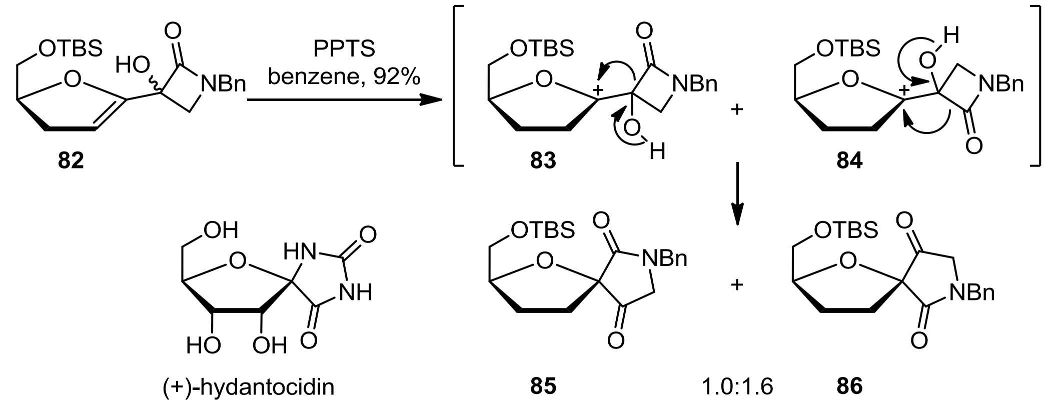
Scheme 18

The first reported semipinacol rearrangement of β-lactams came from Williams in 1992 (Scheme 19).[23] Starting from the dispiro-epoxy-β-lactam **76**, he described the formation of an intermediate carbocation using $BF_3.Et_2O$ as a Lewis acid, followed by a 1,2-migration of the acyl group to give spiro ketolactam **78** in 67% yield. On the other hand, when γ-lactam **79** was subjected to the same reaction conditions, only alkene **81** was formed, suggesting that a driving force for the rearrangement is the release of ring strain in the β-lactam.



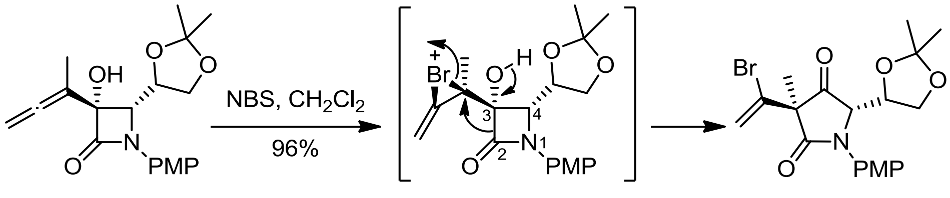
Scheme 19

In 1999, Paquette *et al.* reported progress towards the synthesis of analogues of (+)-hydantocidin, a potent herbicide extracted from *Streptomyces hygroscopicus*.[24] A semipinacol rearrangement was used to access the unusual spiro-furanose nucleoside structure (Scheme 20). Treatment of allylic alcohol **82** with PPTS in refluxing benzene gave a cyclic oxonium intermediate which adopted two different conformations **83** and **84** required for the rearrangement to occur. Exclusive migration of the acyl group gave a 1.0:1.6 mixture of spirolactams **85:86**.



Scheme 20

More recently, Alcaide and Almendros described the synthesis of a variety of fully substituted pyrrolidine-2,4-diones *via* controlled β-lactam ring expansions.[25] The regio- and stereoselective halogenation of allene **87** followed by a semipinacol rearrangement *via* migration of the acyl group gave **89** in 96% yield as a single diastereomer. Again, it was the C2-C3 bond of the β-lactam which migrated giving a single product.

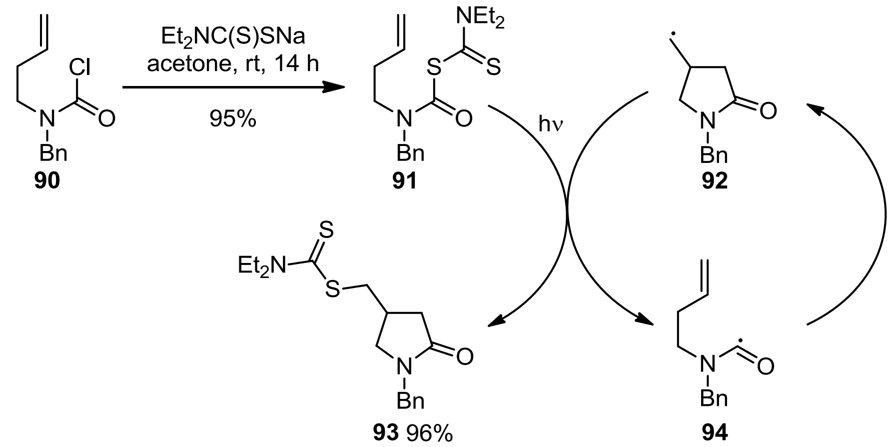


87 **88** **89**

Scheme 21

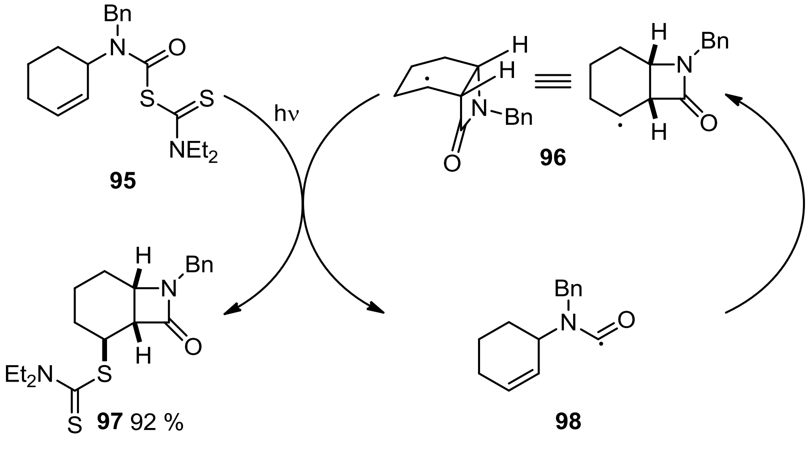
1.6 A radical cyclisation approach to lactams: previous work in the Grainger group

In 2004, Grainger and Innocenti described a dithiocarbamate group transfer cyclisation reaction of carbamoyl radicals (Scheme 22).[26] Dithiocarbamate **91** was readily prepared in high yield by reacting sodium diethyldithiocarbamate trihydrate with carbamoyl chloride **90**.[27] The radical process was initiated with a 500 W halogen lamp. 5-*Exo trig* cyclisation of carbamoyl radical **94** led to primary alkyl radical **92** which was then able to react with a molecule of starting material **91** to afford the desired lactam **93** in 96% yield and to propagate the chain process by reforming **94**.



Scheme 22

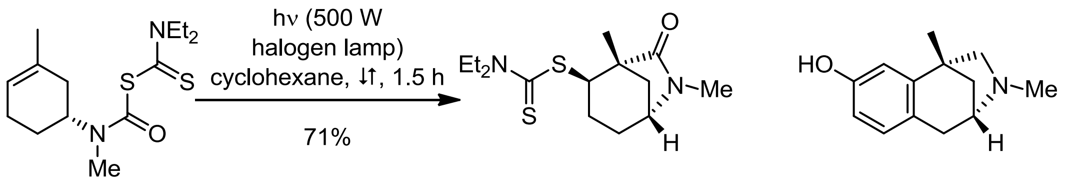
This radical cyclisation was used to form different ring sizes and fused-systems such as β-lactam **97** which was obtained as a single isomer in 92% yield (Scheme 23). The stereochemistry of the molecule was confirmed by X-ray crystallography (Figure 4). 4-*Exo trig* cyclisation of carbamoyl radical **98** formed secondary cyclohexyl radical **96**. Dithiocarbamate group transfer then occurred from the less hindered convex face to afford **97**.



Scheme 23

This efficient carbamoyl radical cyclisation – dithiocarbamate group transfer reaction was then used as a synthetic tool for natural product synthesis. In 2007, Welsh and Grainger published a formal synthesis of (-)-aphanorphine using this methodology (Scheme 24).[28] This alkaloid, extracted from the cyanobacteria *Aphanizomenon flos-aquae*, possesses a 6-

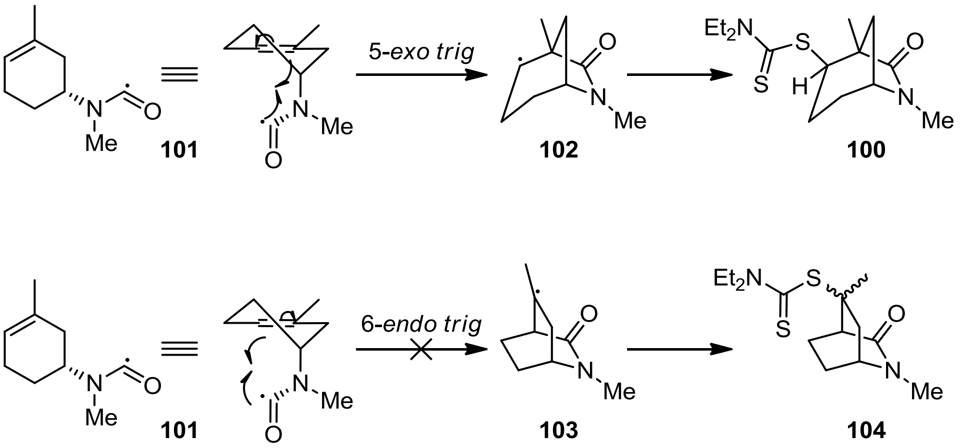
azabicyclo[3.2.1]octane structure. Irradiation of dithiocarbamate **99** gave a single isomer of γ-lactam **100** in 71% yield, the structure of which was confirmed by X-ray crystallography.



99 **100** (-)-aphanorphine

Scheme 24

This reaction could occur *via* either a *5-exo trig* or *6-endo trig* cyclisation of carbamoyl radical **101** (Scheme 25). The δ-lactam **104** which could be formed *via* 6-*endo trig* addition onto the alkene was not observed. Dithiocarbamate group transfer to the intermediate carbon-centred radical **102** gave **100** as a single stereoisomer.

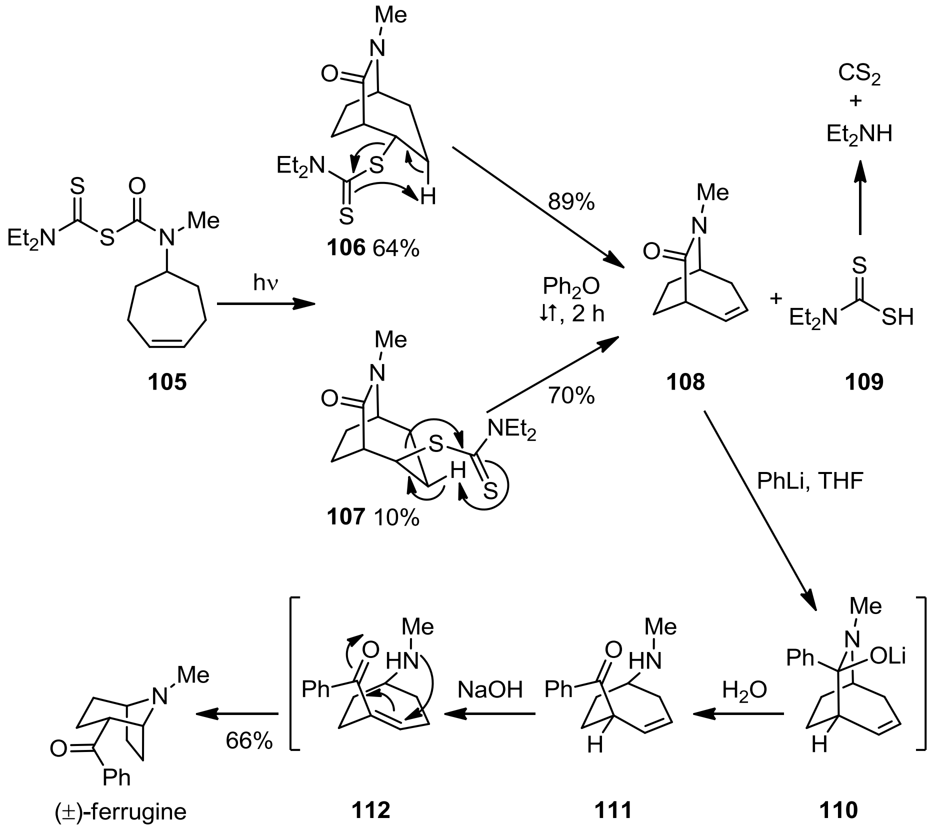


101 **102** **100**

101 **103** **104**

Scheme 25

In 2008, the total synthesis of (±)-ferrugine, an alkaloid found in the brown silky oak *Darlingia ferruginea*, was achieved in 9 steps.[29] Irradiation of dithiocarbamate **105** with a 500 W halogen lamp gave a 6.4:1.0 mixture of the bicyclic structures **106:107** *via* a 6-*exo trig* cyclisation (Scheme 26). The transfer of the dithiocarbamate group was therefore only moderately selective in this case. Thermal elimination of the dithiocarbamate moiety *via* a Chugaëv-like mechanism formed alkene **108** in 89% yield from **106** and 70% yield from **107**. The by-product for this reaction is diethylaminodithiocarbamic acid **109** which breaks down to diethylamine and carbon disulfide. Addition of PhLi onto lactam **108** formed lithiated intermediate **110** which, upon quenching with a dilute solution of NaOH, formed keto amine **111**. Isomerisation to form the conjugated alkene **112** followed by Michael addition gave ferrugine in 66% yield.



Scheme 26

1.7 Aims and objectives

The 6-azabicyclo[3.2.1]octane ring system is present in a wide range of biologically active synthetic and naturally occurring molecules (Figure 2). Representative examples include azaprophen,[30] aphanorphine,[31] a cocaine analogue **113**,[32] lyconadin A,[33] caldaphnidine M,[34] peduncularine,[35] sarain A,[36] nominine[37] and actinobolamine.[38]

The core structure present in these molecules has diverse origins. For example, actinobolamine[38] is the main degradation product from actinobolin, a potent broad spectrum antibiotic whereas caldaphnidine M was extracted from the twigs of *Daphnyphyllum calyciphyllum*, a tree found in mainland China.[34]

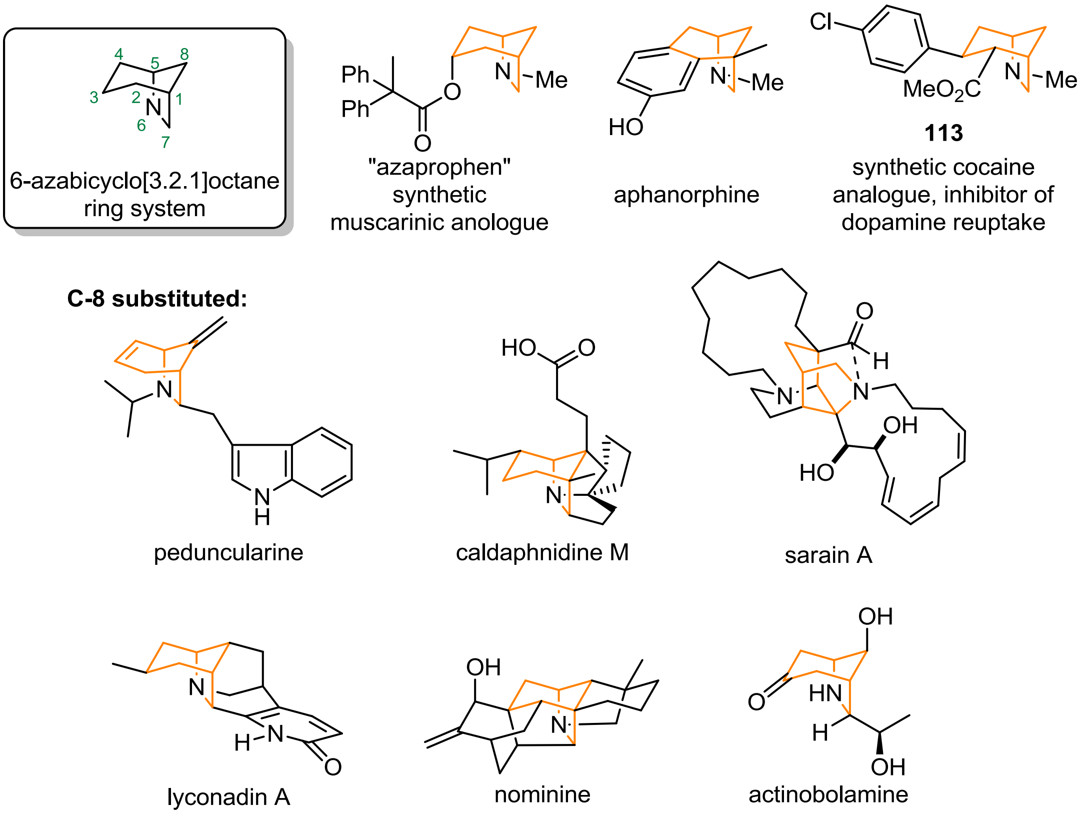
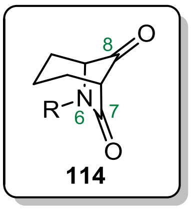


Figure 2

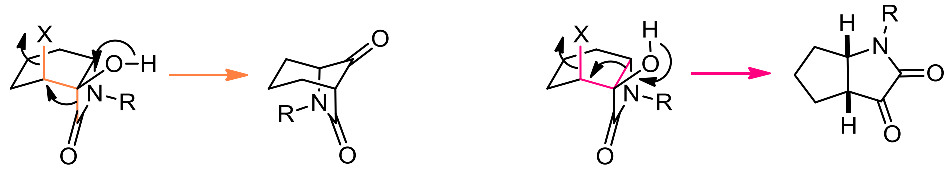
The 8-position of the 6-azabicyclo[3.2.1]ring system can bear a wide variety of functional groups. Lyconadin A, nominine and sarain A have a tertiary sp^3 carbon centre and a quaternary carbon is found in caldaphnidine M. Moreover, peduncularine bears a terminal alkene at this position whereas actinobolamine carries a carbon-oxygen single bond. It is therefore desirable to access structures which allow for further incorporation of various functional groups at the C-8 position. One way to incorporate a large variety of functional groups would be to install a ketone at the 8-position, making the 7,8-diketo-6-azabicyclo[3.2.1]octane ring system **114** a suitable target core structure for methodology development (Figure 3).



7,8-diketo-6-azabicyclo[3.2.1]octane
ring system

Figure 3

This bicyclic ketone could potentially be accessed using a pinacol or semipinacol rearrangement of a suitably functionalised *cis*-fused β-lactam **115** (Scheme 27). Migration may occur either from the “orange” or the “pink” bond and could therefore give respectively the desired 6-azabicyclo[3.2.1]octane-7,8-dione ring system **114** or the hexahydrocyclopenta[*b*]pyrrole-2,3-dione ring system **116**.

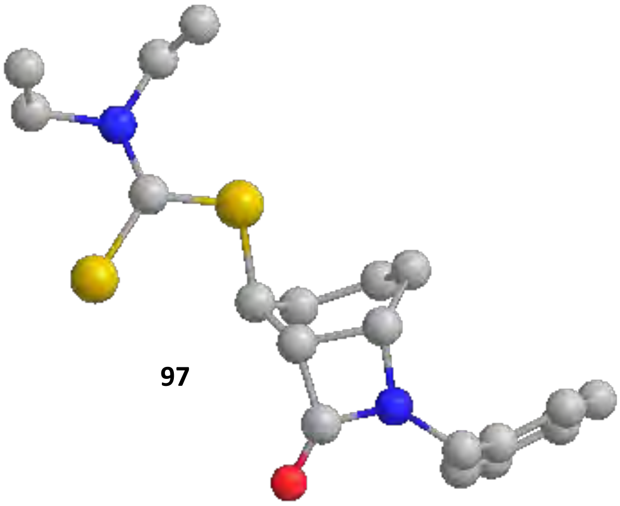


115 **114** **115** **116**

X = leaving group X = leaving group

Scheme 27

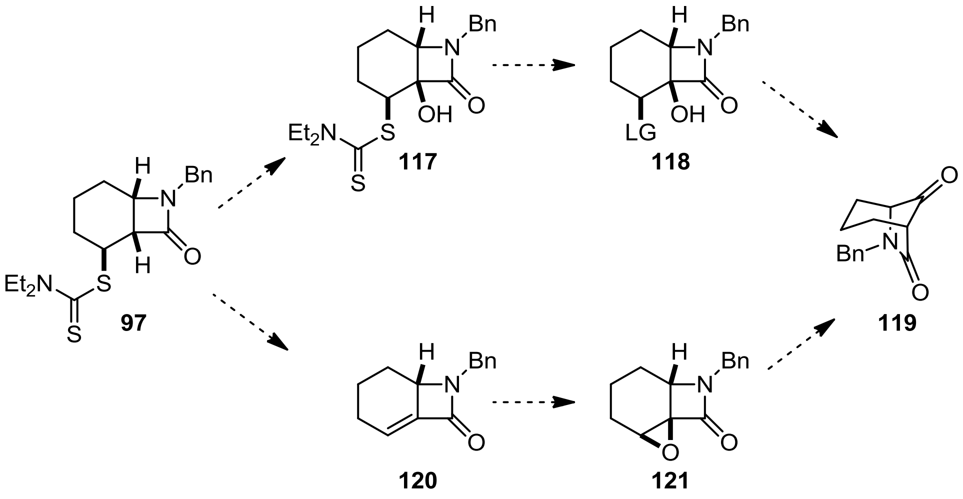
Previous work in the Grainger group described facile access to *cis*-fused β-lactam **97** *via* a 4-*exo trig* radical cyclisation of a dithiocarbamate derivative.[26] The X-ray crystal structure of **97** shows that the *cis*-ring junction forces the cyclohexane ring to adopt a boat conformation, placing the axial dithiocarbamate group antiperiplanar to the acyl group (Figure 4).[27] The acyl group in a β-lactam is known to have an intrinsically higher migratory aptitude than the alkyl group (section 1.5).[22] Moreover, if a hydroxyl group can be incorporated at the bridging carbon of β-lactam such as **97**, the dithiocarbamate moiety is a potential leaving group X for the semipinacol rearrangement of **115** (Scheme 27).[39]



97

Figure 4

Starting from the known β-lactam **97**, it is possible to access **119** using 2 different pathways (Scheme 28). α-Hydroxylation of **97** to form **117** will first be considered. The dithiocarbamate group will then be used as a leaving group or be transformed into one. An alternative would be to form conjugated alkene **120** *via* elimination of the dithiocarbamate moiety. Subsequent oxidation of the double bond will give epoxide **121** which will also be a suitable substrate for the semipinacol rearrangement.



Scheme 28

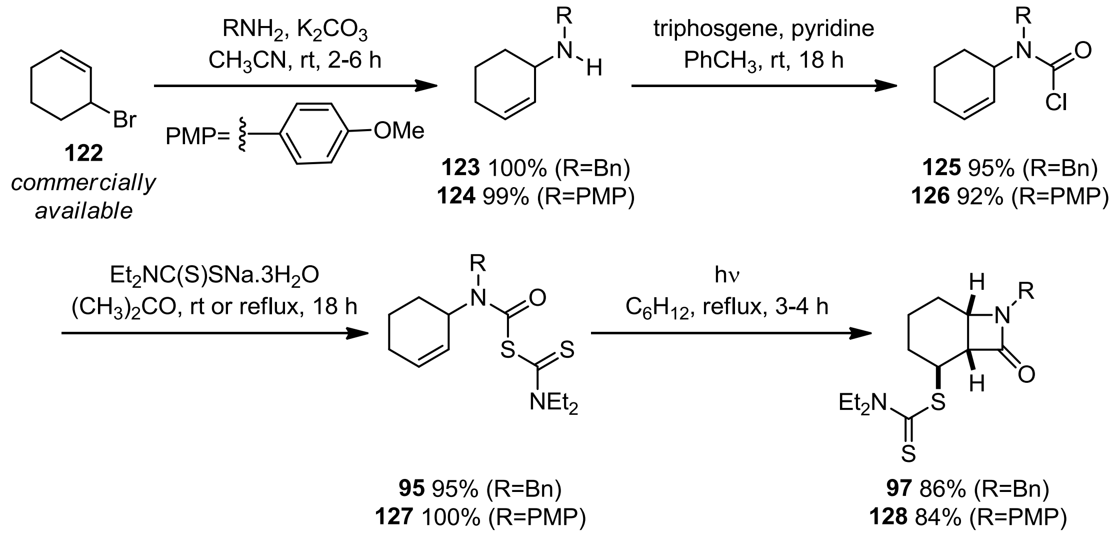
Chapter two:

Methodology development towards the semipinacol rearrangement of β-lactams

2.1 Synthesis of cis-fused *β*-lactams

Cis-fused β-lactams are intermediates in the proposed synthesis of the 6-azabicyclo[3.2.1]octane-7,8-dione ring system (Chapter 1, Scheme 28). The Grainger group has previously reported the synthesis of benzyl derivatives using radical chemistry.[26-27]

The literature synthetic sequence was reproduced starting with alkylation of commercially available 3-bromocyclohexene **122** using benzylamine and K_2CO_3 in CH_3CN at rt to give *N*-benzylcyclohex-2-enamine **123** in quantitative yield (Scheme 29). Amine **123** was reacted with triphosgene and pyridine in toluene to give carbamoyl chloride **125** in 95% yield. Dithiocarbamate derivative **95** was obtained in 95% yield by treatment of carbamoyl chloride **125** with commercially available sodium diethyldithiocarbamate trihydrate in acetone at rt. Irradiation of **95** with a 500 W halogen lamp for 4 h gave β-lactam **97** in 86% yield.



Scheme 29

This reaction sequence was also applied to the synthesis of the PMP derivatives (Scheme 29). The alkylation of **122** with *para*-anisidine and the subsequent carbamoyl chloride formation steps gave **124** and **126** in 99 and 92% yield respectively. Conversion of carbamoyl chloride **126** to dithiocarbamate **127** required additional heating compared to the conversion of **125** to **95**. The lower reactivity of *N*-aryl compared to *N*-alkyl or *N*-benzyl carbamoyl chlorides towards dithiocarbamate nucleophiles has previously been observed in the group.[27] Irradiation of dithiocarbamate **127** for 3 h afforded β-lactam **128** as a single isomer in 84% yield. Similar chemical shifts were observed for key proton and carbon environments in **128** compared with previously synthesized **97** (Figure 5). The relative stereochemistry of **128** was therefore assigned as shown, by analogy with **97**.

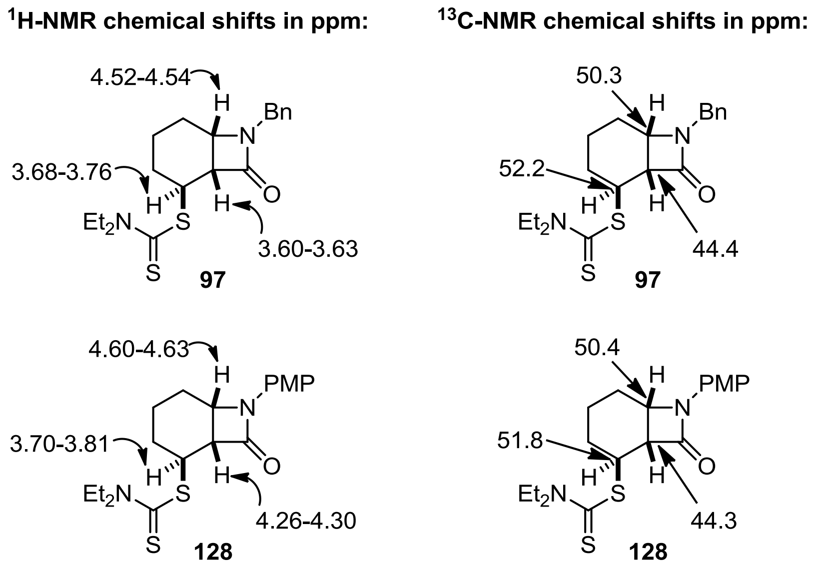
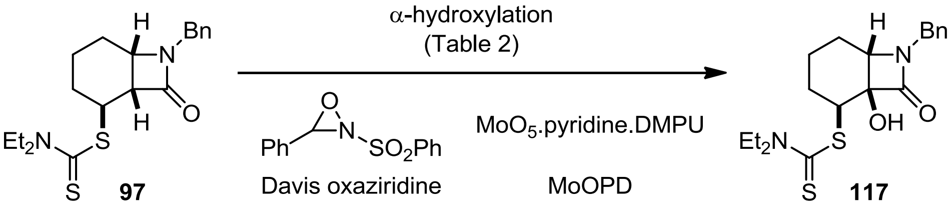


Figure 5

2.2 *α-Hydroxylation of the β-lactam*

An α-hydroxylation method developed in 1975 which uses a lithium base, molecular oxygen and triethylphosphite was applied to β-lactam **97** (Scheme 30 and Table 2, entry 1).[40-42] Only degradation of the reaction mixture was obtained. A new product was observed by tlc analysis when LHMDS was used in combination with the Davis oxaziridine.[43-44] However, only degradation was observed, both upon aqueous work-up or alternatively upon attempted direct purification of the concentrated reaction mixture by column chromatography (entries 2 and 3). An alternative oxidant, MoOPD, was then used in combination with LHMDS. Again, only degradation was observed.[45-46]



Scheme 30

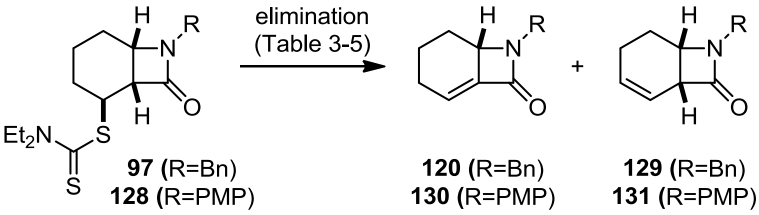
Entry	Reagents	work-up	T / time	Result
1	LHMDS (1.5 eq), THF then O_2 (1 atm) then $P(OEt)_3$	brine, Et_2O	-78 °C to 0 °C / 1 h then -78 °C / 2.5 h then rt / 2 h	degradation
2	LHMDS (1.5 eq), THF then Davis oxaziridine (1.5 eq)	brine, Et_2O	-78 °C to 0 °C / 1 h then -78 °C / 2.5 h	degradation
3	LHMDS (1.5 eq), THF then Davis oxaziridine (1.5 eq)	concentration	-78 °C to 0 °C / 1 h then -78 °C to rt / 2 h	degradation
4	LHMDS (1.5 eq), THF then MoOPD (1.5 eq)	concentration	-78 °C to 0 °C / 1 h then -78 °C to rt / 2 h	degradation

Table 2: α-Hydroxylation of β-lactam 97

In parallel to the α-hydroxylation of β-lactam **97**, the elimination of the dithiocarbamate group to give conjugated alkene **120** was investigated.

2.3 *Elimination of the dithiocarbamate group*

Elimination of the dithiocarbamate group of β-lactams **97** and **128** to give conjugated alkenes **120** and **129** was attempted under a range of conditions (Scheme 31). Most of the attempts were carried out on the PMP derivative. This *N*-substituent was preferred over benzyl because it visualized well under UV irradiation and with KMO_4 and vanillin tlc solutions, making tlc analysis of the reaction mixture easier.



Scheme 31

Entry	Reagents	work-up	T / time	Result
1	LDA (1.1 eq), THF	H_2O, EtOAc	-78 °C to rt / 18 h	**128**
2	quinoline (excess)	concentration	120 °C / 18 h	**128**
3	NaH (1.1 eq), THF	H_2O, EtOAc	rt / 26 h	**128**
4	*t*BuOK (1.1 eq), THF	1 M HCl, EtOAc	rt / 6 h	**128**
5	*t*BuOK (1.1 eq), THF	neutral	rt / 6 h	**128** 22% **130** 37%
6	*t*BuOK (1.1 eq), THF	dry loading	reflux / 4 h	degradation

Table 3: Base screening for the elimination of the dithiocarbamate on 128

Treatment of dithiocarbamate **128** with LDA in THF at low temperature did not afford any of the desired conjugated alkene **130** (Table 3, entry 1). The use of quinoline at high temperature, or NaH at rt, gave the same results (entries 2 and 3). Partial conversion was observed by tlc analysis when the reaction was ran with *t*BuOK as a base. However, only starting material **128** was recovered after an acidic work-up (entry 4). A neutral quench was then attempted, followed by purification by column chromatography. Only 37% of alkene **130** was isolated along with 22% of recovered starting material **128** (entry 5). Some of the organic components remained in the aqueous layer even after multiple extractions using a range of different solvent.

Refluxing THF was used in an attempt to drive the reaction to completion (Table 3, entry 6). After 4 h, the elimination appeared complete by tlc analysis and the reaction mixture was loaded onto silica to avoid the loss of material during the work-up. Unfortunately, alkene **130** was not isolated after purification.

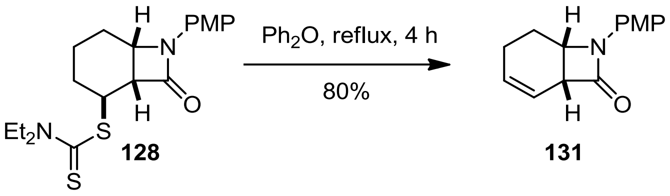
The elimination procedures described hereafter were not subjected to an aqueous work-up. The solvent was first removed under reduced pressure and the crude mixture obtained was dissolved in CH_2Cl_2 and purified by column chromatography.

Entry	Reagents	T / time	Result
1	NaHMDS (1 eq), THF	-78 °C / 4.5 h	**128** 22% **130** 46%
2	NaHMDS (1.5 eq), THF	-78 °C / 4.5 h	**130** 47%
3	NaHMDS (2 eq), THF	-78 °C / 4.5 h	**130** 50%
4	NaHMDS (3 eq), THF	-78 °C / 4 h	1:1 **130:131** 46%
5	NaHMDS (3 eq), CH_2Cl_2	-78 °C (4 h) rt (1 h)	degradation
6	NaHMDS (3 eq), THF	-78 °C / 1 h	1:1 **130:131** 42%
7	NaHMDS (1.5 eq), THF	-78 °C (7. 5 h) rt (18 h)	1:1 **130:131** 46%

Table 4: Elimination of the dithiocarbamate group using NaHMDS to form 130

NaHMDS, a soluble and stronger base than *t*BuOK, was then investigated. Treatment of **128** with 1 eq of NaHMDS in THF at low temperature gave the desired alkene **130** in 46% yield along with 22% of starting material **128** (Table 4, entry 1). The yield stayed moderate when 1.5 and 2 eq of NaHMDS were used (entry 2 and 3). An inseparable mixture of products was obtained after 4 h at -78 °C with 3 eq of base. After analysis of the ^{1}H-NMR spectrum, it appeared that the second product formed was alkene **131**.

Thermal elimination of dithiocarbamates is possible when a β-hydrogen is present on the molecule. It can be compared to the Chugaëv reaction which corresponds to the thermolysis of *O*-alkyl dithiocarbonates or thiocarbonates. It was developed in the Grainger group using refluxing Ph_2O.[29] To confirm the structure of the second product formed, the thermal elimination of **128** was carried out in refluxing Ph_2O (Scheme 32). Alkene **131** was produced as a single isomer in 80% yield and the ^{1}H-NMR spectrum obtained matched with the extra peaks present in the mixture formed when using NaHMDS for the elimination of the dithiocarbamate group.

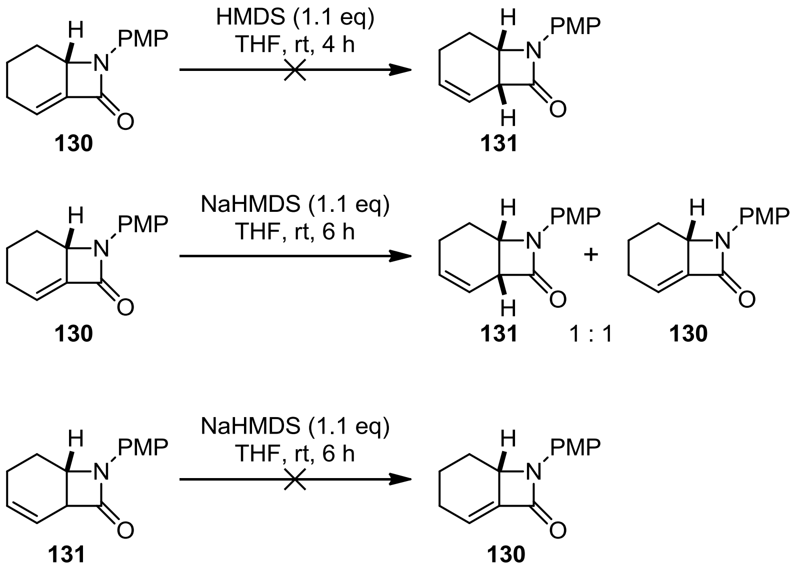


Scheme 32

The influence of the solvent on the isomerisation of the double bond was examined (Table 4, entry 5). When CH_2Cl_2 was used instead of THF, only SM was observed after 4 h at -78 °C, possibly because the base was not soluble in this solvent at low temperature. The reaction mixture was warmed up to rt but only degradation was detected after 1 h.

The effect of the reaction time on the isomerisation was also investigated. Using 3 eq of base at low temperature, similar results were obtained with a reaction time of 1 h or 4 h (Table 4, entry 4 and 6). Using 1.5 eq of NaHMDS for 7.5 h at -78 °C and 18 h at rt, a mixture of the two isomers was obtained whereas only **130** was isolated after 4.5 h at -78 °C (entry 2 and 7).

Various reactions were carried out to fully understand the isomerisation (Scheme 33). The effect of HMDS, a side product of the reaction, was investigated. Alkene **130** was reacted with HMDS for 4 h at rt. Only starting material was recovered indicating that HMDS is not detrimental to the stability of **130**. Both alkene isomers were then separately treated with NaHMDS for 6 h at rt. β-Lactam **130** gave a 1:1 mixture of isomers indicating that the isomerisation of the double bond probably happened after the elimination. On the other hand, only starting material was recovered for alkene **131**, confirming it was the more stable isomer. In conclusion, in order to avoid the synthesis of **131**, the reaction needed to be carried out with no more than 2 eq of base, at low temperature and for a short period of time to minimise isomerisation.



Scheme 33

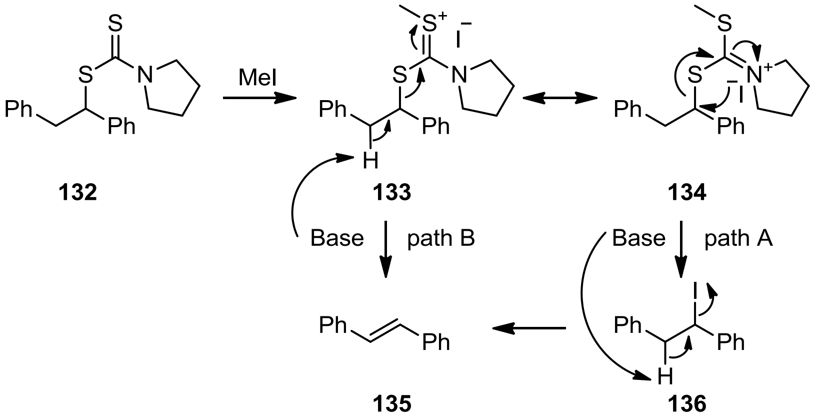
Some other reaction parameters were then examined to improve the yield of the elimination reaction. The influence of the counter ion of the base was investigated. Lithium, the smallest cation tested, proved to be the most favourable affording **130** in 61% yield, whereas it was obtained in 46% and 60% yield with the sodium and potassium counter ion, respectively (Table 4, entry 1 and Table 5, entries 1 and 2).

Entry	Reagents	T / time	Result
1	KHMDS (1.1 eq), THF	-78 °C / 5.75 h	**130** 60%
2	LHMDS (1.1 eq), THF	-78 °C / 4 h	**130** 61%
3	LHMDS (1.1 eq), THF	rt / 2.75 h	degradation
4	LHMDS (1.1 eq), THF	0 °C / 2.75 h	**130** 16%
5	LHMDS (1.1 eq), THF	-40 °C / 2.5 h	**130** 39%

Table 5: Influence of the base counterion and the temperature on the synthesis of 130

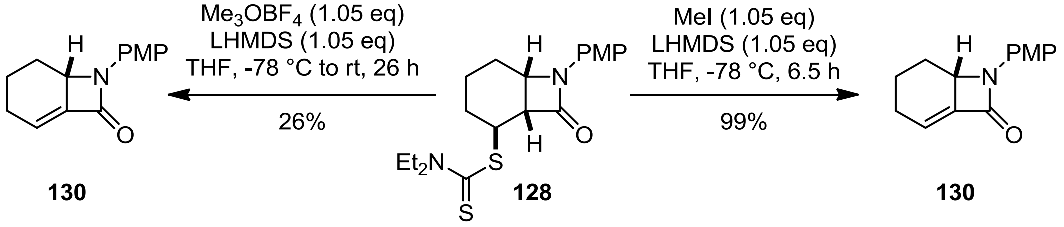
Using LHMDS, the effect of temperature was studied (Table 5). Addition of the base at rt gave only degradation (entry 3). At 0 °C, 16% of product was isolated, along with a significant amount of degradation products (entry 4). At -40 °C, the yield was 39% and no starting material was recovered (entry 5). The best yield was therefore obtained at -78 °C with 61% of alkene **130** formed (entry 2).

Further attempts to improve the yield of the elimination involved activation of the dithiocarbamate group as previously described by Hayashi and Oishi in 1977.[39] The elimination of the pyrrolidinecarbodithioate group was performed using Li_2CO_3, LiF and an excess of MeI with HMPA as the solvent. After 24 h at rt, alkene **135** was formed in an excellent 95% yield (Scheme 34). The elimination was believed to proceed *via* alkylated intermediate **133/134**. This activated group can be directly eliminated under the basic conditions (path B) or displaced by iodine which is subsequently expelled by the base (path A).



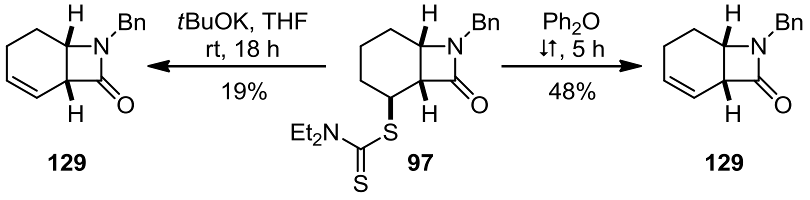
Scheme 34

Similar conditions were used on β-lactam **128**. Two different reagents were examined for the alkylation: MeI and Meerwein's salt, Me_3OBF_4 (Scheme 35).[47] Running the reaction at low temperature and using LHMDS as the base, alkene **130** was obtained as a single isomer and in 99% yield with MeI whereas only 26% of **130** was formed with Me_3OBF_4. The low yield could be explained by the instability of this alkylating agent. Indeed, it is sold as a white solid and it was found as a brown slightly fuming solid even when stored under argon and in the fridge. It was therefore decided to use MeI to drive the elimination reaction to completion.



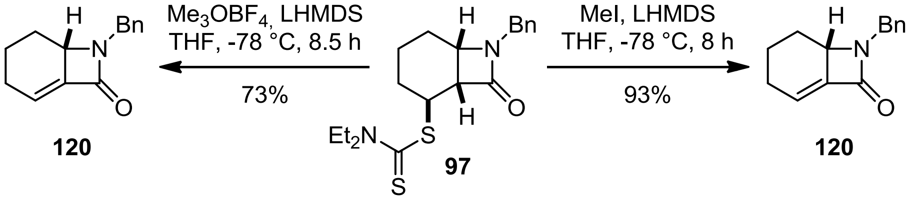
Scheme 35

Similar conditions were applied in parallel to the benzyl derivatives. Isomer **129** was formed when the dithiocarbamate derivative **97** was treated with *t*BuOK in THF at rt for 18 h (Scheme 36). In order to confirm the structure formed, thermal elimination in refluxing Ph_2O was also conducted and alkene **129** was obtained as a single isomer in 48% yield.



Scheme 36

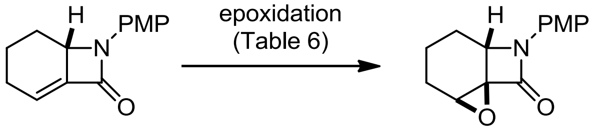
Activation of the dithiocarbamate group with MeI gave alkene **120** in 93% yield and when using a fresh batch of Meerwein's salt, alkene **120** was formed in 73% yield (Scheme 37).



Scheme 37

2.4 Synthesis and semipinacol rearrangement of epoxide

As previously described in Chapter 1 (Section 1.5), in 1992, Williams reported a semipinacol rearrangement of epoxy β-lactams with $BF_3.Et_2O$.[23] In order to apply the chemistry described, epoxidation of the double bond in lactam **130** was investigated under a range of conditions (Scheme 38 and Table 6).



130 **137**

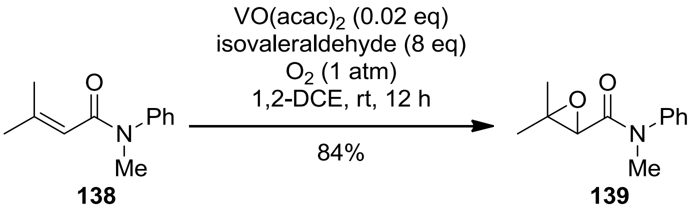
Scheme 38

Entry	Reagents	work-up	T / time	Result
1	*t*BuOOH in toluene (1.5 eq) *n*BuLi (1.1 eq), THF	Na_2SO_3	-78 °C to rt 18 h	**130**
2	*t*BuOOH in toluene (1.5 eq) LHMDS (1.1 eq), THF	Na_2SO_3	-78 °C to rt 18 h	**130**
3	VO(acac)$_2$ (0.02 eq) isovaleraldehyde (8 eq) O_2 (1 atm), 1,2-DCE	/	rt / 18 h	**130**
4	*m*CPBA (1.1 eq), CH_2Cl_2	H_2O EtOAc	0 °C to rt 3 h	no isolation
5	*m*CPBA (1.1 eq), CH_2Cl_2	KF	0 °C 6 h	**130** 42% **137** 23%
6	*m*CPBA (2.2 eq), CH_2Cl_2	KF	0 °C 6.5 h	**130** 23% **137** 52%
7	*m*CPBA (3 eq), CH_2Cl_2	KF	0 °C 6.5 h	**137** 55%
8	*m*CPBA (3 eq), CH_2Cl_2	KF	0 °C to rt 5 h	**137** 70%

Table 6: Epoxidation of alkene 130

Due to the electron-deficient nature of the double bond, the first attempts were carried out using nucleophilic conditions as described in the procedure developed by Kumari and Vankar (Table 6, entries 1 and 2).[48] Although that procedure used *t*BuOOH in benzene, it was decided to use *t*BuOOH in toluene as this reagent had been reported to be more stable.[49] Following the literature procedure, *n*BuLi was used but without any success. Treatment of alkene **130** with LHMDS, an alternative base chosen for its efficiency in the elimination reaction, also resulted in no reaction and recovered starting material.

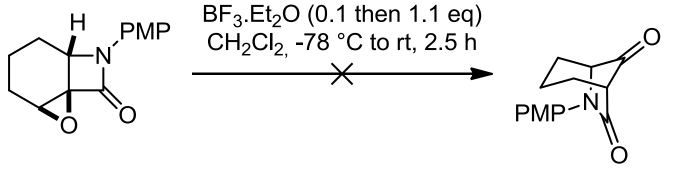
An epoxidation method specific for α,β-unsaturated carboxamides, developed in 1991 by Mukaiyama, was then investigated.[50] The communication described an oxygenation of α,β-unsaturated carboxamides such as **138** into 2,3-epoxycarboxamide **139**. After optimisation of the reaction conditions, **139** was obtained in 84% yield using 1 atm of molecular oxygen as the oxidant, isovaleraldehyde as the reductant and oxovanadium(IV) complex as a catalyst (Scheme 39). The study showed that epoxidation of the double bond is promoted by the interaction of VO(acac)$_2$ with the amide group. The optimal conditions described by Mukaiyama were applied to alkene **130.** However only starting material was recovered after 18 h at rt (Table 6, entry 3).



Scheme 39

Further attempts for the epoxidation of alkene **130** were made using *m*CPBA as the oxidant in CH$_2$Cl$_2$. The reaction was incomplete with 1.1 eq of *m*CPBA but isolation was attempted nevertheless to confirm that the desired product **137** was formed. As for the elimination reaction, an aqueous work-up resulted in loss of the material (Table 6, entry 4). The use of KF to remove the residual *m*CBA formed during the reaction enabled isolation of epoxide **137** in 23% yield (entry 5).[51-52] An increase in yield was observed when a slight excess of *m*CPBA was used (entries 6 and 7). The best yield was obtained with 3 eq of *m*CPBA and when the reaction mixture was allowed to warm to rt over 1 h after addition of the oxidant (entry 8).

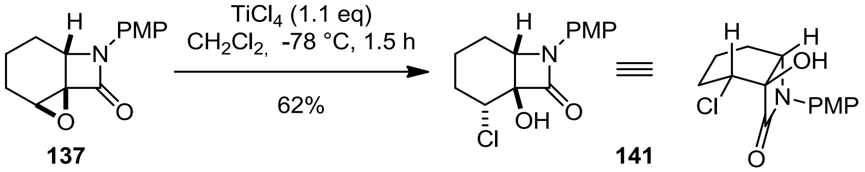
With access to epoxide **137** in good yield, Williams' reaction conditions were attempted for its rearrangement (Scheme 40). No consumption of starting material was observed on tlc analysis with 0.1 eq of BF$_3$.Et$_2$O at low temperature. One equivalent of Lewis acid was then added and the reaction mixture was progressively warmed to rt. Disappearance of starting material occurred in 1 h at rt. However, only degradation products were obtained after attempted purification.



137 **140**

Scheme 40

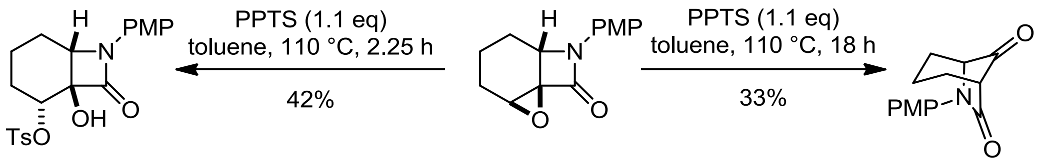
Titanium(IV) chloride was then tested for the rearrangement of epoxide **137** (Scheme 41). This Lewis acid had been previously used by Cha and co-workers for the semipinacol rearrangement of an epoxysilyl ether in the total synthesis of (+)-asteltoxin.[53] The reaction was complete after 1.5 h at -78 °C. However, the product isolated in 62% yield was α-hydroxy chloride **141**. It resulted from the opening of the epoxide by chloride anion, presumably on the less hindered tertiary carbon. Coupling constants for the proton next to Cl were 5.2 and 9.6 Hz which suggested an axial-axial and an axial-equatorial coupling thus indicating a *trans* configuration, assuming the cyclohexyl ring sits in a boat conformation to accommodate the *cis* ring fusion of the β-lactam as observed for dithiocarbamate **97** (Scheme 23 and Figure 4).



137 **141**

Scheme 41

PPTS was subsequently used to catalise the reaction (Scheme 42). Disappearance of the starting material did not occur at rt or 50 °C when using 1.1 eq of this weak acid. The reaction appeared complete on tlc after 2.25 h in refluxing toluene. However, the product isolated was not the desired bicyclic ketone **140** but the *trans* α-hydroxy tosylate **142**, presumably obtained *via* opening of the epoxide with the *para*-toluenesulfonate anion. The *trans* configuration was assigned using ^{1}H-NMR spectroscopic analysis. Coupling constants for the proton adjacent to the tosylate were 5.8 and 11.8 Hz which implied an axial-axial and an axial-equatorial coupling thus indicating a *trans* configuration. Increasing the reaction time to 18 h resulted in the formation of **140** in a moderate 33% yield.

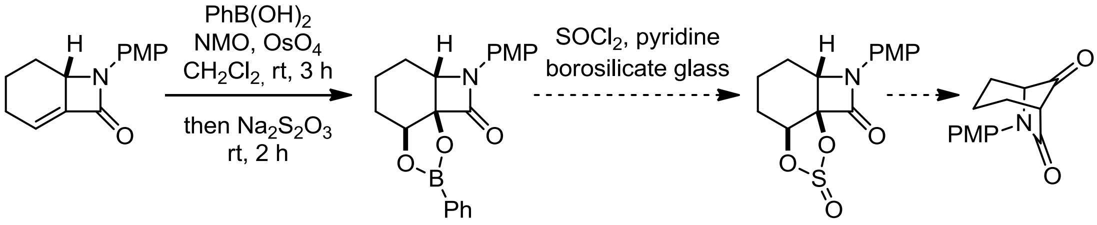


142 **137** **140**

Scheme 42

2.5 Synthesis and pinacol rearrangement of diol

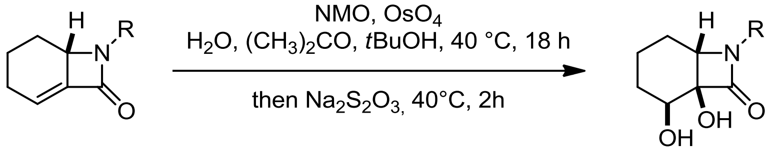
The problems encountered during the isolation of alkene **130** and epoxide **137** using aqueous work-up indicated significant water solubility or hydrolytic instability for these compounds. It was therefore decided to use anhydrous conditions for the dihydroxylation of alkene **130**. In 1988, Narasaka *et al.* described a convenient anhydrous methodology using a combination of OsO_4 and dihydroxyphenylborane.[54] In this procedure, phenylboronic acid replaces water as the agent which "strips" the diolate from the osmium in the NMO/OsO_4 dihydroxylation complex. Treatment of alkene **130** with phenylboronic acid, NMO and cat. OsO_4 afforded phenylboronic ester **143** in a moderate 65% yield (Scheme 43). Further transformation of **143** would involve transformation to cyclic sulfite **144** using Matteson's reaction conditions[55] and subsequent semipinacol rearrangement as described in Chapter 1 (Section 1.3).



130 **143** 65% **144** **140**

Scheme 43

In parallel to the synthesis of phenyl boronic ester **143**, Upjohn dihydroxylation was also carried out using catalytic OsO_4 with NMO as a co-oxidant in a mixture of H_2O, acetone and *t*BuOH (Scheme 44).[56] Surprisingly, diol **146** was obtained in 81% yield. It is worth mentioning that the quality of OsO_4 influences the yield of the dihydroxylation. Indeed the best yields were obtained with new batches of reagent, when the aqueous solution was still a pale yellow colour instead of brown. The same conditions were applied to alkene **120** and diol **145** was obtained in 74% yield.

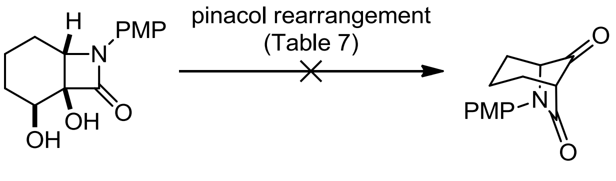


120 (R=Bn)
130 (R=PMP)

145 74% (R=Bn)
146 81% (R=PMP)

Scheme 44

With access to the β-lactam diols, their subsequent pinacol rearrangement was investigated. Previous studies showed that epoxy lactam **137** required high temperature, long reaction times and the use of a Brønsted acid to rearrange to **140** (Section 2.3). The first attempt was therefore conducted in toluene at 80 °C for 18 h using PPTS to induce the reaction (Scheme 45 and Table 7, entry 1). Only starting material was recovered. It was then decided to use a stronger acid, PTSA, to catalise the reaction. Only degradation was obtained when refluxing diol **146** with PTSA in toluene for 18 h (entry 2). To avoid degradation, PTSA was used at rt but **146** was not soluble in toluene at this temperature (entry 3). The solvent was changed to THF. After 7 h at rt, no conversion was observed and the same result was obtained after refluxing the reaction mixture for 18 h (entry 4).



146

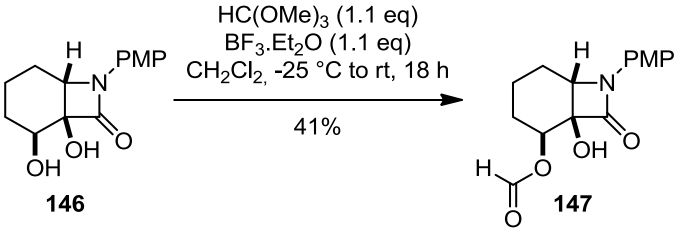
140

Scheme 45

Entry	Reagents	T / time	Result
1	PPTS (1.2 eq), toluene	80 °C / 18 h	**146**
2	PTSA (1.1 eq), toluene	reflux / 18 h	degradation
3	PTSA (1.1 eq), toluene	rt / 5 h	**146**
4	PTSA (1.1 eq), THF	rt then reflux / 6.5 h	**146**

Table 7: Attempts to form 140 from a pinacol rearrangement of 146

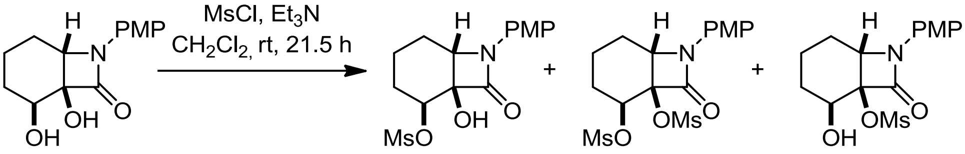
The final attempt at the pinacol rearrangement of diol **146** was made under anhydrous conditions as described by Kita *et al.* in 1997.[57] Treatment of diol **146** with trimethyl orthoformate and $BF_3.Et_2O$ formed formate ester **147** in 41% yield instead of the desired bicyclic ketone **140** (Scheme 46).



Scheme 46

2.6 Activation of the secondary alcohol and semipinacol rearrangement

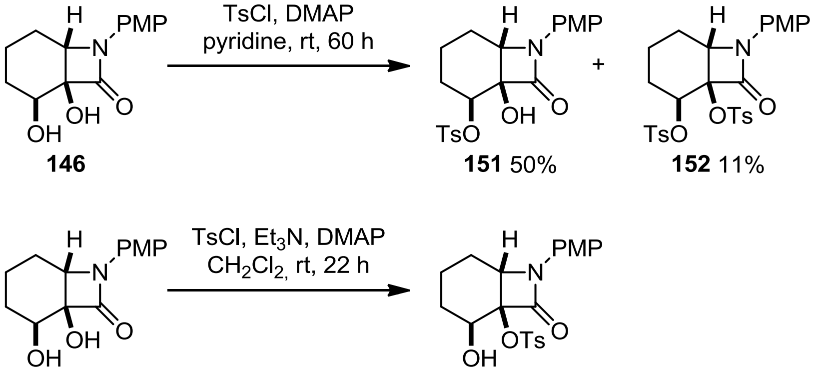
The lack of success for the pinacol rearrangement of diol **146** suggested that activation of the secondary alcohol was needed for the rearrangement to occur. The first activating group envisioned was methanesulfonate (Scheme 47). Treatment of diol **146** with 1.05 eq of MsCl and 2 eq of Et_3N in dry CH_2Cl_2 for 18 h only gave partial conversion. Therefore an additional equivalent of reagents was added and after a further 3 h, the starting material was completely consumed. Dimesylate **149** and monomesylate **150** were obtained in 58% and 9% yield respectively after purification. Formation of the dimesylated compound appeared to be favoured over the monomesylated because it was the main compound evident by tlc analysis even when some starting material remained.



146 **148** 0% **149** 58% **150** 9%

Scheme 47

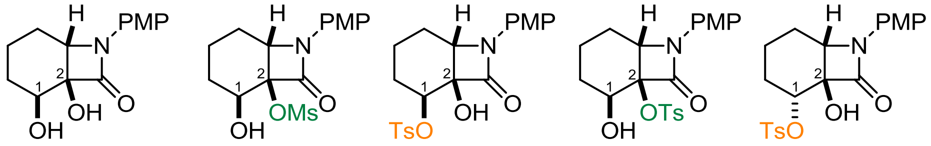
The larger *para*-toluenesulfonate group was then investigated. Two different procedures were tested in parallel (Scheme 48). The reaction performed in pyridine using 3 eq of TsCl and cat. DMAP gave monotosylate **151** and ditosylate **152** in 50% and 11% yield respectively after 60 h at rt. On the other hand, when the reaction was carried out with cat. DMAP, 1.1 eq of TsCl and Et_3N in dry CH_2Cl_2, some starting material remained after 18 h. Therefore 1.1 eq of reagents were added and the reaction was complete after a further 4 h. Purification by column chromatography gave monotosylated **153** as the sole product in 71% yield.



146 **153** 71%

Scheme 48

The two different sets of procedures gave different ^{1}H- and ^{13}C-NMR spectra of the monotosylated compound. Furthermore, the data did not match with the previously synthesized *trans* monotosylated compound **142** obtained from PPTS promoted opening of epoxide **137** (Scheme 42). This suggested that depending on the conditions used, the tosylation reaction was selective for one hydroxyl group and therefore two regioisomers were formed. Careful analysis of the ^{13}C-NMR data showed a 10 ppm downfield shift on the carbon bearing the tosylate group in comparison with diol **146** (Figure 6). It was concluded that when the tosylation was performed with Et_3N only the tertiary hydroxyl group was activated giving **153** whereas with pyridine it was the secondary alcohol and **151** was formed. The same comparison was made with the monomesylated compound obtained using Et_3N and similar selectivity for the tertiary hydroxyl group was discovered.



146
C-1 67.6
C-2 82.2

150
C-1 67.1
C-2 91.3

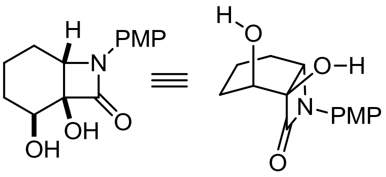
151
C-1 79.1
C-2 82.3

153
C-1 66.9
C-2 91.6

142
C-1 80.9
C-2 83.5

Figure 6

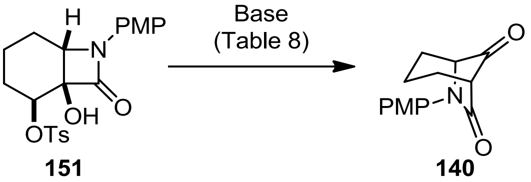
The selective formation of **150** and **153** was surprising because the activation of tertiary alcohols is usually difficult due to steric hindrance. This presumably is not true for diol **146** because the *cis*-ring junction is expected to force the cyclohexane ring to adopt a boat conformation (Figure 7). The secondary alcohol is more hindered than expected as it resides in the flagstaff position. In contrast, the tertiary alcohol may be more accessible as it is on the convex face and pseudo-equatorial on the 6-membered ring. It may also be that using the stronger base Et_3N promotes tosyl group migration from the secondary to the tertiary alcohol, although this was not tested.



146

Figure 7

The semipinacol rearrangement of **151** was attempted under basic conditions. Pyridine, DIPEA and LHMDS gave **140** in 65%, 53% and 13% yield respectively (Scheme 49 and Table 8). These results demonstrated that a strong base like LHMDS was detrimental to the reaction.

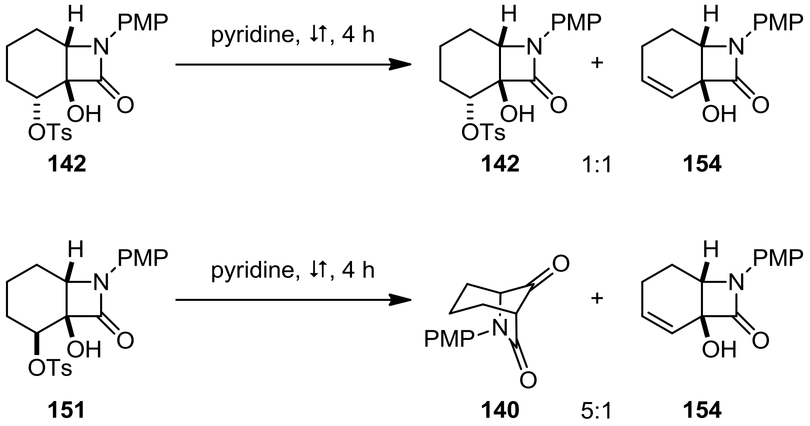


Scheme 49

Entry	Reagents	T / time	Result
1	pyridine (5 eq), toluene	reflux / 8 h	**140** 65%
2	DIPEA (5 eq), toluene	reflux / 8 h	**140** 53%
3	LHMDS (1.1 eq), THF	0 °C to rt / 4.5 h	**140** 13%

Table 8: Influence of the base for the semipinacol rearrangement of 151

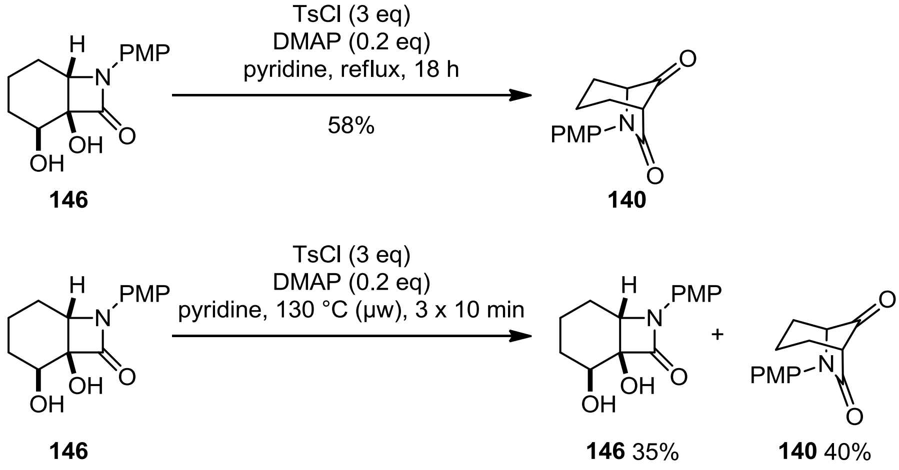
The difference in reactivity of the *cis* and *trans* monotosylated compound was explored further (Scheme 50). Both isomers were refluxed in parallel in pyridine for 4 h. Hydrogen-NMR analysis of the crude product for *trans* isomer **142** showed a 1:1 mixture of starting material and another unknown product. *Cis* isomer **151** gave a 5:1 mixture of **140** and of the same mystery compound. This structure possesses two protons in the ethylenic region suggesting it could be alkene **154**, the product formed by elimination of the tosylate group.



Scheme 50

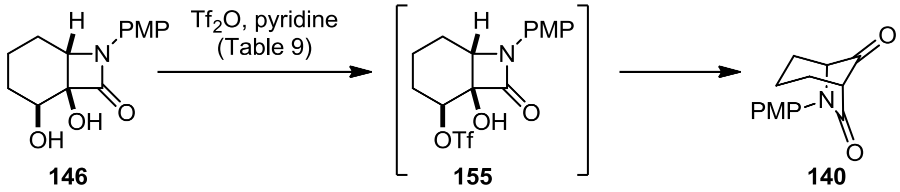
One-pot activation and semipinacol rearrangement of diol **146** was attempted because the reaction procedures to form the tosylate and react it further were similar. Treatment of diol

146 with 3 eq of TsCl and a sub-stoichiometric amount of DMAP in refluxing pyridine for 18 h gave **140** in 58% yield (Scheme 51). The same conditions were applied with microwave irradiation instead of normal heating. The reaction appeared complete on tlc after three 10-minute periods at 130 °C. However **140** was obtained in 40% yield along with 35% of starting material **146**.



Scheme 51

This one-pot reaction proceeded in a moderate 58% yield even if all the starting material seemed consumed and no side products were isolated after purification. To improve the yield, a better activating group such as triflate, known to be 2.10^4 to 2.10^5 times more reactive than the comparable tosylate,[58] could be employed. The transformation of the secondary alcohol into a triflate leaving group was carried out using Tf_2O and pyridine. Because this leaving group is known to be highly reactive, isolation of triflate **155** was not attempted (Scheme 52 and Table 9).



Scheme 52

Entry	Reagents	T / time	Result
1	Tf_2O (1.05 eq), pyridine	0 °C to rt 3 h	**146** 16% **140** 33%
2	Tf_2O (1.05 eq), pyridine	-40 °C to 0 °C 8 h	**146** 33% **140** 41%
3	Tf_2O (1.05 eq), pyridine	-40 °C 4.25 h	**140** 49%
4	Tf_2O (1.05 eq), 2,6-lutidine	-40 °C 4.25 h	**146** 61% **140** 12%
5	Tf_2O (1.05 eq), pyridine (2.1 eq) CH_2Cl_2	0 °C 4.25 h	**140** 35%
6	Tf_2O (1.05 eq), pyridine (2.1 eq) CH_2Cl_2	-78 °C to 0 °C 5.25 h	**140** 42%
7	Tf_2O (2 x 1.05 eq), pyridine (5 eq) CH_2Cl_2	-40 °C 7 h	**140** 59%
8	Tf_2O (2.1 eq), pyridine (5 eq) CH_2Cl_2	-40 °C to -5 °C 6.5 h	**140** 22%

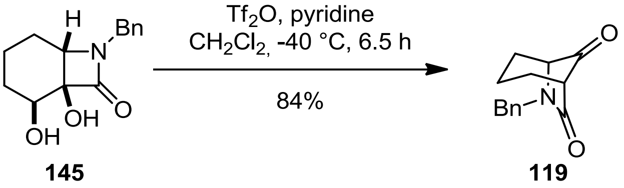
Table 9: Semipinacol rearrangement of diol 146 using in situ triflate activation

The first attempts were carried out using 1 eq of Tf_2O in pyridine. The base was used as a solvent as in the one-pot rearrangement with the tosylated compound. When Tf_2O was added at 0 °C, the reaction mixture turned black indicating that some degradation may be occurring and **140** was obtained in 33% yield along with 16% of the starting material after 3 h (Table 9, entry 1). The addition was then carried out at -40 °C (entries 2 and 3). When the reaction mixture was progressively warmed to 0 °C, **140** was isolated in 41% yield, whereas a slightly better 49% yield was achieved when maintaining the temperature at -40 °C. The semipinacol rearrangement *via* triflate **155** was investigated using 2,6-lutidine, a less nucleophilic base than pyridine.[59] The reaction occurred more slowly with 2,6-lutidine giving **140** in only 12% yield along with 61% of recovered starting material **146** after 4.25 h, compared to the 49% yield obtained when pyridine was used (entries 3 and 4).

Further reactions were carried out in dry CH_2Cl_2 with a slight excess of pyridine. When the reaction was conducted at 0 °C, a low yield of 35% was obtained which was similar to the yield obtained using pyridine as the solvent (Table 9, entries 1 and 5). No reaction was observed at -78 °C, it was therefore necessary to warm the reaction to -40 °C and then to 0 °C for the reaction to proceed to completion and give 42% of **140** (entry 6).

After 4 h at -40 °C, some starting material was still present with 1.05 eq of Tf_2O and 5 eq of pyridine. A further equivalent of Tf_2O was added and after 3 h, the reaction appeared complete by tlc analysis and gave **140** in 59% yield after purification (Table 9, entry 7). The yield being improved by the use of 2 eq of Tf_2O, it was decided to use 2 eq of Tf_2O from the start of the reaction in the hope that this might decrease the reaction time (entry 8). Unfortunately, a precipitate appeared during the addition which did not dissolve even when warming the reaction mixture to -5 °C. No rearranged product was obtained and only 22% of starting material **146** was recovered.

The optimum reaction conditions were also applied to the benzyl derivative **145** using 1.5 eq of Tf_2O, providing **119** in 84% yield (Scheme 51). However when trying to reproduce the procedure, **119** was obtained in only 35% yield along with 59% of the starting material.



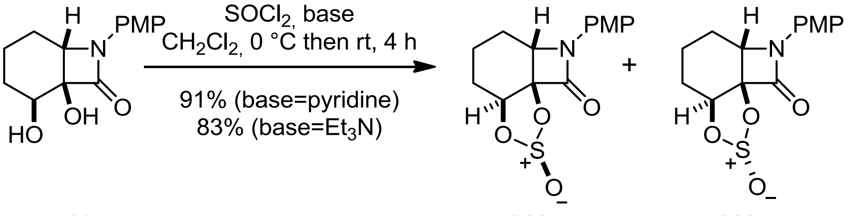
Scheme 53

The use of Tf_2O gave the best yield so far for the semipinacol rearrangement of β-lactam diols. However, the reaction procedure was hard to reproduce. The temperature of the reaction mixture was definitely an important parameter. The addition needed to be done at -40 °C otherwise the reaction mixture turned black immediately. The low temperature was also required throughout the reaction to avoid degradation but resulted in a sluggish conversion.

2.7 Cyclic activation and semipinacol rearrangement

To avoid regioselective issues in activating the secondary over the tertiary alcohol, cyclic activation of β-lactam diols was investigated. Cyclic sulfites were first considered because they have been used in a semipinacol rearrangement (Section 1.3) and because the only by-product formed is sulfur dioxide which is a gas. Therefore there is no need for a work-up and no loss of material.

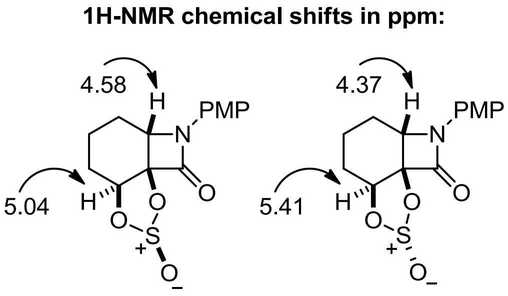
Two bases, pyridine and Et_3N, were tested in combination with thionyl chloride in the synthesis of cyclic sulfite **144**.[60-61] In each case both isomers of **144** were formed as a 1:1 mixture. When pyridine was used, a 91% combined yield was obtained whereas with Et_3N, a slightly lower 83% combined yield was found (Scheme 54).



146 **144a** **144b**

Scheme 54

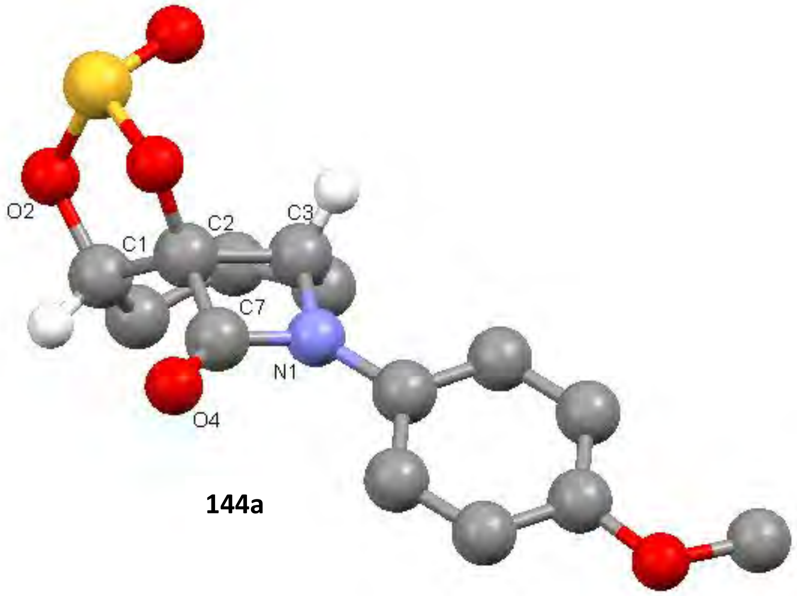
It was possible to separate the isomers by a careful column chromatography. Proton-NMR analysis enabled to identify the sulfinyl stereocentre in sulfites **144a** and **144b** (Figure 8). The anisotropy of the sulfinyl group results in a downfield shift of the proton adjacent to oxygen for **144b** (5.41 ppm) compared with **144a** (5.04 ppm).[62-65]



144a **144b**

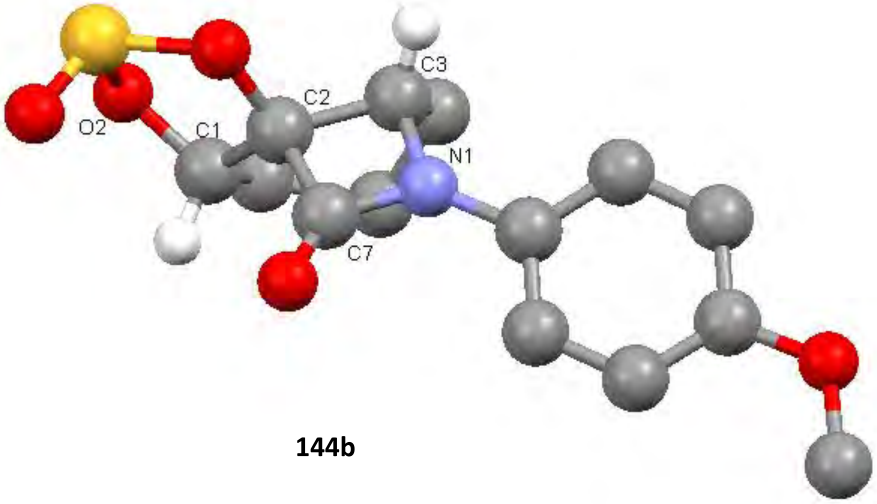
Figure 8

The relative stereochemistry was also confirmed by X-ray crystallography analysis (Figure 9 and Figure 10). In both cases the C2-C7 bond is shorter than the C2-C3 bond (Table 10). In addition, as seen in the O2-C1-C2-C7 and the O2-C1-C2-C3 torsion angles, the migrating C2-C7 bond is better aligned with the breaking C1-O2 bond than the C2-C3 bond.



144a

Figure 9



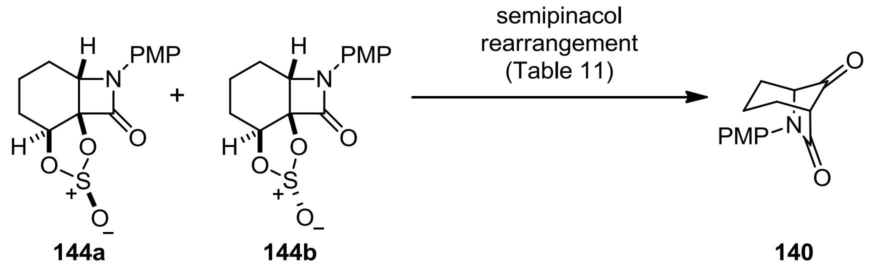
144b

Figure 10

		144a	**144b**
Bond length	C2-C7	1.5394(17)	1.542(2)
	C2-C3	1.5617(17)	1.558(2)
Torsion angle	O2-C1-C2-C7	147.23(11)	140.95(13)
	O2-C2-C2-C3	-108.61(12)	-117.46(14)

Table 10: Selected bond lengths and torsion angles for 144a and 144b

The isolation of **144a** and **144b** showed that spontaneous semipinacol rearrangement does not occur under the reaction conditions used for the synthesis of cyclic sulfite **144** (Section 1.3, Scheme 11).[16] Different conditions were tested to promote the rearrangement of **144** (Scheme 55 and Table 11). Five relatively high-boiling solvents with different chemical properties were first investigated. CH_3CN is a polar solvent whereas toluene, triethylbenzene and Ph_2O are non-polar. Pyridine was also used because this base was enabling the rearrangement of tosylate **151**. Refluxing the mixture of cyclic sulfite **144** in CH_3CN and toluene led to recovery of the starting material (Table 11, entries 1 and 2). When pyridine was used as a solvent, the reaction was complete by tlc analysis but only 23% of diol **146** was isolated (entry 3). Some conversion was observed when the temperature was raised to 150 °C. However, the reaction rate increased at 190 °C and bicyclic ketone **140** was obtained in 77% yield after 3.5 h when using triethylbenzene (entry 4). A 91% yield of **140** was observed after only 2 h with Ph_2O (entry 5).

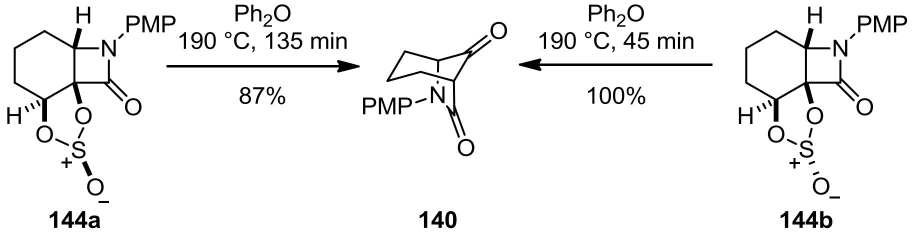


Scheme 55

Entry	Reagents	work-up	T / time	Result
1	CH_3CN	concentration	reflux / 5 h	**144**
2	toluene	concentration	reflux / 5 h	**144**
3	pyridine	concentration	reflux / 23 h	**146** 23%
4	triethylbenzene	/	190 °C / 3.5 h	**140** 77%
5	Ph_2O	/	190 °C / 2 h	**140** 91%
6	DMF	H_2O, EtOAc	reflux / 4 h	**144** 31%
7	DMSO	H_2O, EtOAc	150 °C / 18 h	degradation
8	DMF	concentration	reflux / 6 h	**144** 4% **156** 58%
9	$BF_3.Et_2O$ (2.1 eq) toluene	MeOH then concentration	reflux / 4 h	**157** 50%
10	$BF_3.Et_2O$ (2.1 eq) toluene	concentration	reflux/ 18 h	degradation
11	$BF_3.Et_2O$ (2.1 eq) toluene	H_2O, EtOAc	reflux / 6 h	**140** 49%

Table 11: Semipinacol rearrangement of cyclic sulfite 144

The difference in reactivity for both isomers of the cyclic sulfite was investigated (Scheme 56). Quantitatively, it was observed that **144a** required a longer reaction (135 min) time than **144b** (45 min) for the reaction to go to completion and the yield for the semipinacol rearrangement was also lower. Analysing the X-ray data, this difference in rate is counterintuitive. Indeed, the migrating C2-C7 bond in **144a** is shorter than in **144b** (1.5394(17) vs. 1.542(2)). Moreover, the O2-C1-C2-C7 torsion angle shows a better antiperiplanar alignment between the leaving group and the migrating group in **144a** than in **144b** (147.23(11) vs. 140.95(13)). On the other hand, the S=O and C=O dipoles in **144b** are more closely aligned than in **144a**. Reduction in the overall dipole moment may rationalize the faster and higher yielding rearrangement of **144b** compared to **144a**.



Scheme 56

The semipinacol rearrangement of cyclic sulfite **144** occurred in an excellent yield at 190 °C in Ph_2O, a non-polar solvent. Further attempts were made using high-boiling polar solvents to stabilize a possible cation intermediate in order to lower the reaction temperature. Refluxing **144** in DMF for 4 h followed by an aqueous work-up afforded only 31% of recovered starting material (Table 11, entry 6). A similar result was observed when heating the reaction mixture to 150 °C in DMSO. None of the rearranged product was obtained and the reaction mixture was degraded (entry 7). Surprisingly, a second attempt at refluxing cyclic sulfite **144** in DMF followed by purification of the concentrated reaction mixture afforded amine **156** in 58% yield (Figure 11 and Table 11, entry 8).[66-67]

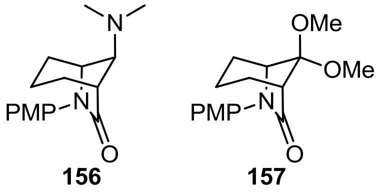
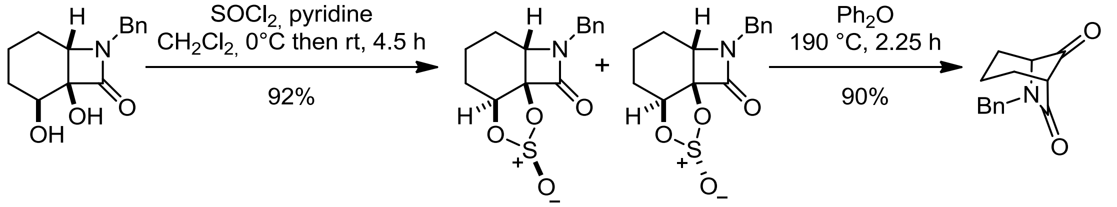


Figure 11

The semipinacol rearrangement of cyclic sulfite **144** in polar solvents did not prove successful. Another possibility to reduce the temperature for this reaction would be to use a non-polar solvent like toluene and a Lewis acid to catalise the reaction. Refluxing a mixture of **144** and $BF_3.Et_2O$ in toluene for 4 h, followed by a work-up with MeOH to avoid losing the product in the aqueous layer, afforded acetal **157** in 50% yield suggesting that **140** was formed *in situ* using these conditions (Table 11, entry 9 and Figure 11). When the reaction mixture was concentrated without quenching the acid, only degradation was observed (entry 10).

Surprisingly, the rearranged product **140** was obtained in 49% yield when carrying out the reaction with $BF_3.Et_2O$ for 3 h in refluxing toluene followed by an aqueous work-up (entry 11).

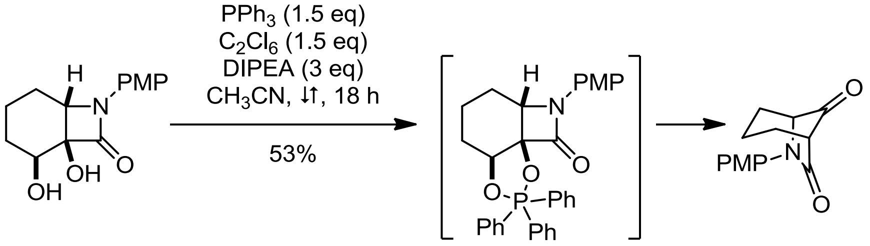
The best conditions developed for the semipinacol rearrangement of *N*-PMP cyclic sulfite β-lactam **144** were then applied on the *N*-Bn derivative (Scheme 57). Treatment of diol **145** with thionyl chloride and pyridine in CH_2Cl_2 afforded a 1:1 mixture of sulfite **158** in 92% yield. Heating **158** for 2.25 h at 190 °C in Ph_2O gave bicyclic ketone **119** in an excellent 90% yield.



145 **158a** **158b** **119**

Scheme 57

The use of a cyclic phosphorane as first outlined in 1972 by Applequist was also considered (Section 1.4).[18] Treatment of diol **146** with a mixture of DIPEA and Ph_3PCl_2, formed *in situ* from PPh_3 and C_2Cl_6, in refluxing CH_3CN for 18 h as described in the literature procedure by DeCamp, afforded bicyclic ketone **140** in a moderate 53% yield (Scheme 58).[19]

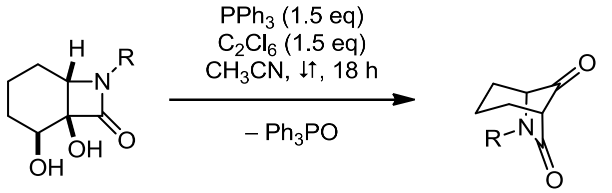


146 **159** **140**

Scheme 58

The work previously carried out on this reaction indicated that bicyclic ketone **140** was quite robust to acids and sensitive to polar reagents. It was therefore decided to run the reaction without DIPEA previously used to neutralize the HCl liberated *in situ* by the reaction of PPh_3 with C_2Cl_6. This time the semipinacol rearrangement occurred in an excellent 94% yield for *N*-

PMP derivative **140** and 97% yield for *N*-Bn derivative **119** (Scheme 59). The formation of Ph_3PO as a side product did not prove to be a problem for the purification.

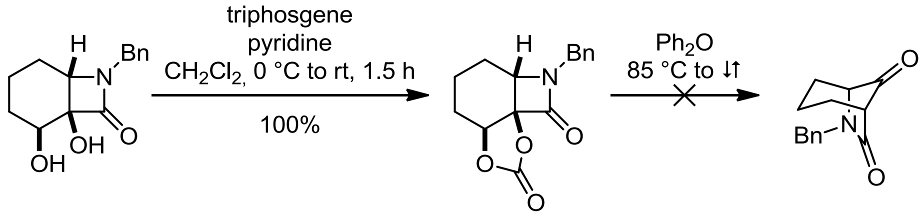


145 (R=Bn)
146 (R=PMP)

119 97% (R=Bn)
140 94% (R=PMP)

Scheme 59

Finally, cyclic carbonates were also investigated as a potential activating group.[68] As for the cyclic sulfites, the rearrangement would be particularly interesting because the only by-product formed would be gaseous carbon dioxide. Treatment of diol **145** with triphosgene and pyridine in CH_2Cl_2 afforded **160** in quantitative yield (Scheme 60). Unfortunately, progressively heating (85 °C to 260 °C) **160** in Ph_2O did not afford the desired bicyclic ketone **119**, whereas it was formed in 90% yield at 190 °C from cyclic sulfite **158** (Scheme 57).



145

160

119

Scheme 60

2.8 Structural assignment of the rearranged product and further functionalisation

Two different isomers could be obtained *via* the semipinacol rearrangement of the *cis*-fused β-lactams (Figure 12). Migration may occur either from the “orange” or the “pink” bond and could therefore give respectively the desired 6-azabicyclo[3.2.1]octane-7,8-dione ring system **140** or the hexahydrocyclopenta[*b*]pyrrole-2,3-dione ring system **161**. As mentioned in the introduction, it is the bond antiperiplanar to the leaving group which generally migrates, *i.e.*

the “orange” bond in the β-lactams synthesized due to the boat conformation adopted. Moreover, the literature also states that *N*-acyl groups migrate more readily than alkyl groups in β-lactams which would favour migration of the “orange” bond.

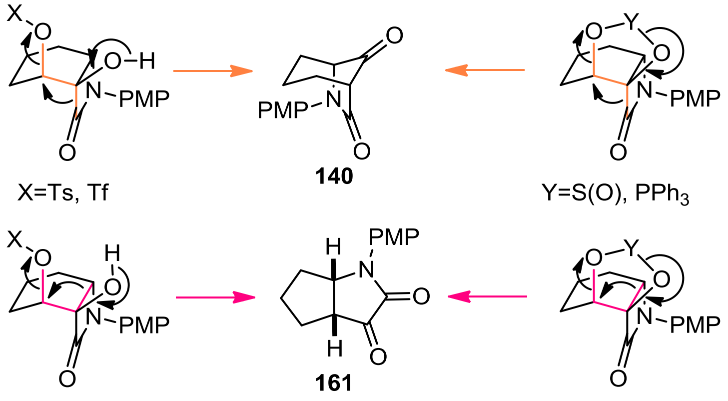
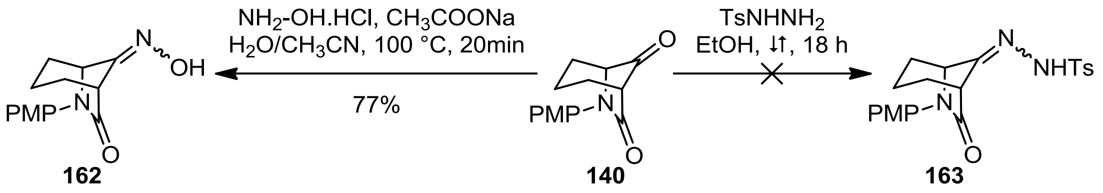


Figure 12

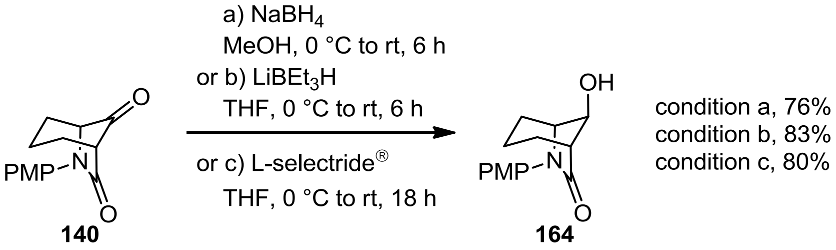
It was not possible to determine which isomer was formed in the rearrangement reaction using NMR or IR spectroscopy. Comparison with similar molecules from the literature was attempted but it did not permit the unambiguous assignment of the structure.[69-71]

Crystallographic analysis of the compound formed from the semipinacol rearrangement would unambiguously assign its structure. Attempts to crystallize **140** proved originally unsuccessful as the product was an amorphous solid, even after purification by column chromatography. Tosylhydrazones and oximes generally possess crystalline structures. Treatment of **140** with tosylhydrazine in refluxing EtOH led only to degradation (Scheme 61).[72] The synthesis of oxime **162** was carried out using 7 eq of hydroxylamine hydrochloride and NaOAc in a mixture of H_2O and CH_3CN.[73] These conditions gave an inseparable 1:1 mixture of the *E:Z* isomers of oxime **162** in 77% yield. Unfortunately, NMR spectroscopic analysis of **162** did not aid in the identification of the rearranged product, and since **162** was an oil it could not therefore be crystallized.



Scheme 61

The final transformation carried out on the rearrangement product **140** was the selective reduction of the ketone to the secondary alcohol. Treatment of **140** with $NaBH_4$, $LiBEt_3H$ or L-selectride® gave alcohol **164** as a single isomer in 76%, 83% and 80% yield respectively (Scheme 62).



Scheme 62

An nOe NMR experiment was conducted on **164** to determine which isomer was formed (Figure 13). When the proton next to the hydroxyl group was excited, it did not show any nOe enhancement to the axial proton of the 6-membered ring whereas a very small nOe was observed to the aromatic protons. This suggested that the hydroxyl group was axial. The ^{13}C-NMR spectrum of the secondary alcohol indicated that it was probably the 8-hydroxy-6-(4-methoxyphenyl)-6-azabicyclo[3.2.1]octan-7-one **164** which was formed rather than 3-hydroxy-1-(4-methoxyphenyl)hexahydrocyclopenta[*b*]pyrrol-2(1*H*)-one **165**. Indeed, the downfield peak at 46.4 ppm on the ^{13}C-NMR spectrum corresponded to a carbon next to a carbonyl group. It was possible to find this arrangement of atoms in **164** but not in **165** (Figure 13).

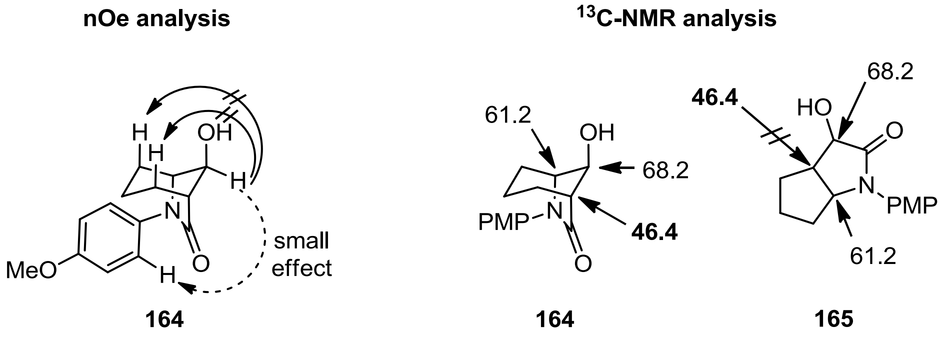


Figure 13

X-ray crystallography analysis confirmed that the 6-azabicyclo[3.2.1]octane ring system **140** was formed during the semipinacol rearrangement (Figure 14). Surprisingly, the hydrate crystallized instead of the ketone, suggesting that the formation of a sp^3 instead of a sp^2 hybridized bridging carbon releases ring strain. Moreover, the hydroxyl groups were involved in intermolecular hydrogen bonds which stabilized the structure (Figure 15 and Table 12). This crystal was grown in acetone which often contains traces of water which could attack the ketone.

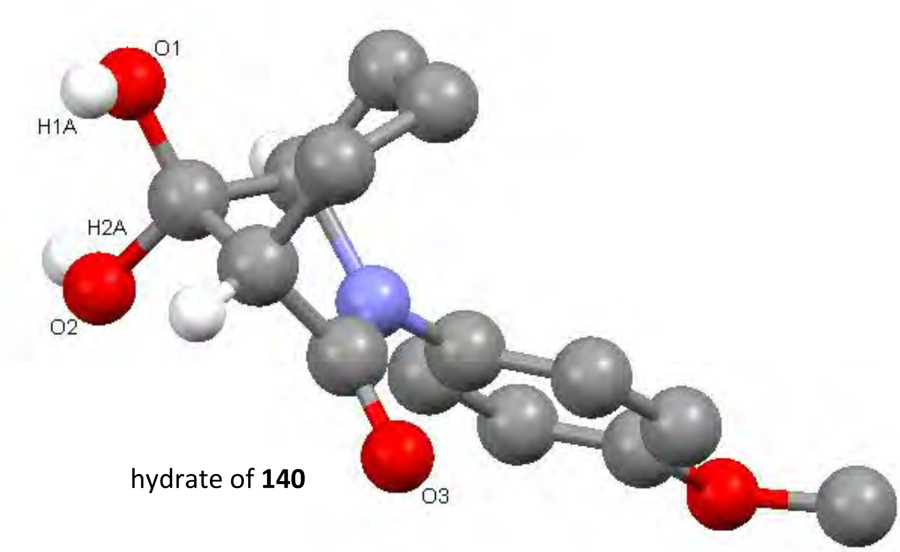


Figure 14

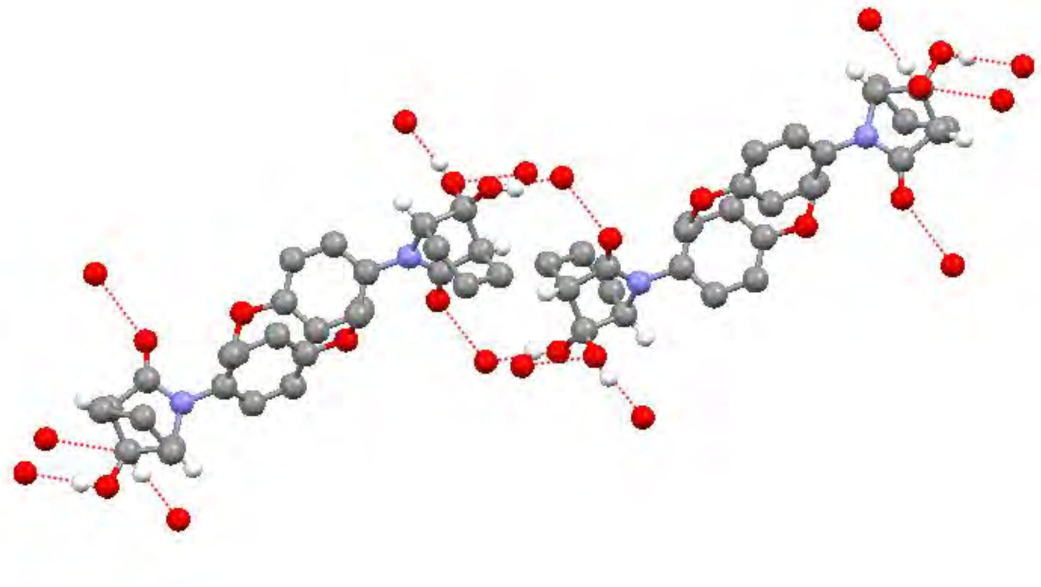


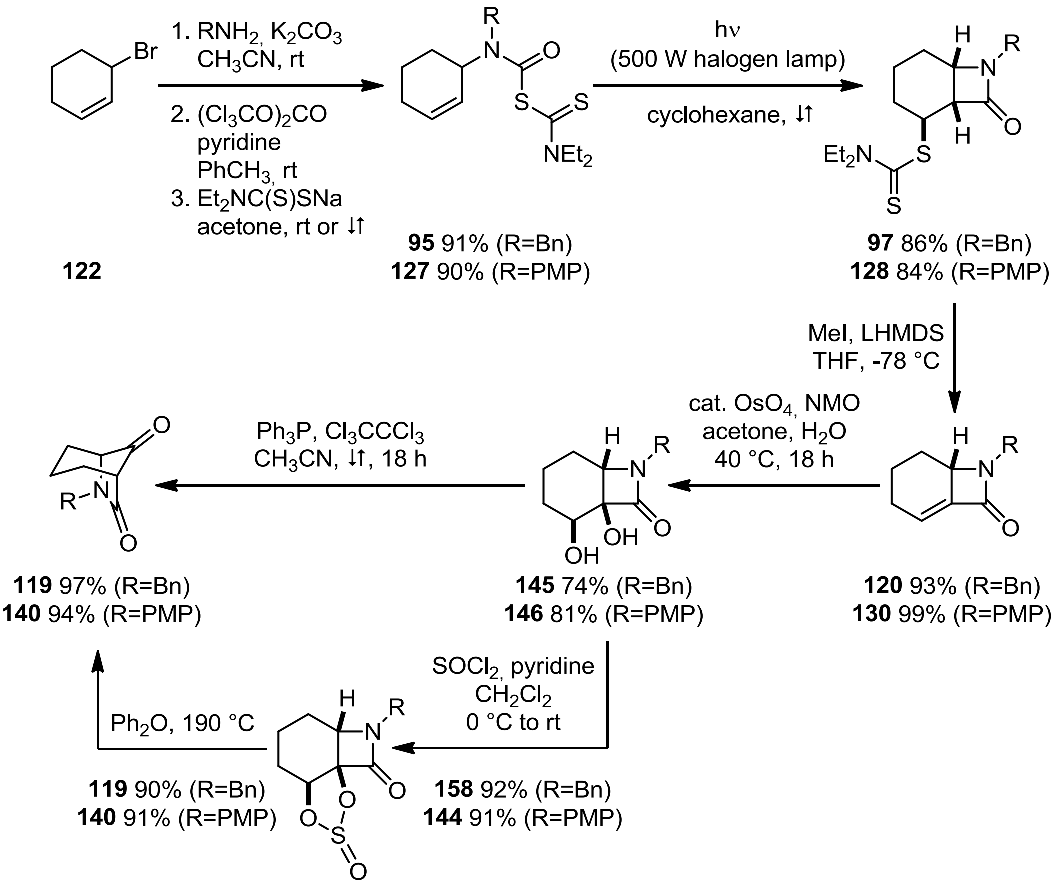
Figure 15

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1A)...O(2)#1	0.84	1.97	2.768(7)	157.3
O(2)-H(2A)...O(3)#2	0.84	1.88	2.706(7)	168.6

Table 12: Hydrogen bonds for 140

2.9 Conclusions

The synthesis of the 6-azabicyclo[3.2.1]octane ring system was successfully achieved in seven steps *via* a semipinacol rearrangement of cyclic phosphorane or in eight steps when using cyclic sulfites (Scheme 63). Elimination of the dithiocarbamate group was achieved through the combination of LHMDS, a strong base, and methyl iodide. The resulting alkene was dihydroxylated to give a diol as a single diastereomer which was then rearranged.

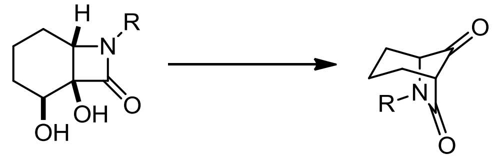

Br
1. RNH2, K2CO3
CH3CN, rt
2. (Cl3CO)2CO
pyridine
PhCH3, rt
3. Et2NC(S)SNa
acetone, rt or ⇅
122
R
N
O
S
S
NEt2
95 91% (R=Bn)
127 90% (R=PMP)
hν
(500 W halogen lamp)
cyclohexane, ⇅
H
R
N
O
H
Et2N
S
S
97 86% (R=Bn)
128 84% (R=PMP)
MeI, LHMDS
THF, -78 °C
H
R
N
O
120 93% (R=Bn)
130 99% (R=PMP)
cat. OsO4, NMO
acetone, H2O
40 °C, 18 h
H
R
N
OH
O
OH
145 74% (R=Bn)
146 81% (R=PMP)
Ph3P, Cl3CCCl3
CH3CN, ⇅, 18 h
O
R
N
O
119 97% (R=Bn)
140 94% (R=PMP)
SOCl2, pyridine
CH2Cl2
0 °C to rt
H
R
N
O
O
O
S
O
158 92% (R=Bn)
144 91% (R=PMP)
Ph2O, 190 °C
119 90% (R=Bn)
140 91% (R=PMP)

Scheme 63

Chapter three:

Methodology scope and limitations

The 7,8-diketo-6-azabicyclo[3.2.1]octane ring systems **119** and **140** were successfully synthesized *via* a semipinacol rearrangement of *cis*-fused β-lactam diols **145** and **146** (Scheme 64).



145 (R=Bn)
146 (R=PMP)

119 (R=Bn)
140 (R=PMP)

Scheme 64

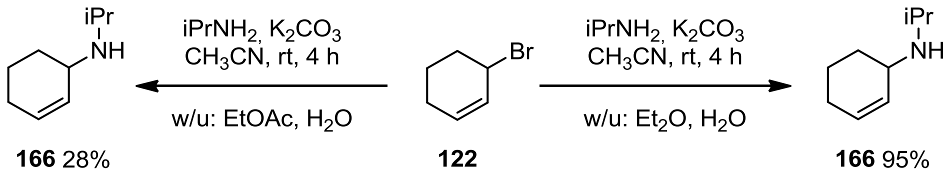
In this Chapter, additional R groups (*i*Pr, C_8H_{17}, PMB, Ts, H) on the nitrogen will be investigated in order to determine if electron-withdrawing or electron-donating groups will influence the rearrangement. The complexity on the cyclohexane ring will be increased with incorporation of methyl groups and oxygenation. Finally, the synthesis and rearrangement of different cycloalkane-fused β-lactams will be attempted.

3.1 Use of different N-substituents

3.1.1 *N*-Isopropylamine derivative

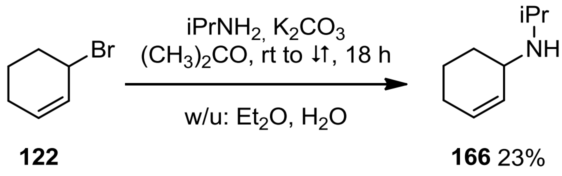
Peduncularine, an alkaloid formed of a 6-azabicyclo[3.2.1]oct-3-ene ring system, possesses an isopropyl substituent on the nitrogen (Figure 2, Section 1.7). The effect of this alkyl group on the methodology was investigated. Alkylation of 3-bromocyclohexene **122** using isopropylamine and K_2CO_3 in CH_3CN initially proved problematic (Scheme 65). Full conversion was observed after 4 h at rt but only 28% of **166** was isolated after a work-up using EtOAc to extract the aqueous layer. This was attributed to the low molecular weight of amine **166** (MW 139 g.mol^{-1}) which conferred a high volatility for this molecule. Using Et_2O instead of EtOAc for the extraction solved the problem and **166** was isolated in 95% yield on a 1.5 g scale. Purification was not attempted because column chromatography would have required using

EtOAc or Et_3N to elute the desired product **166**. However, repetition of this reaction proved difficult even when carefully concentrating Et_2O under reduced pressure.



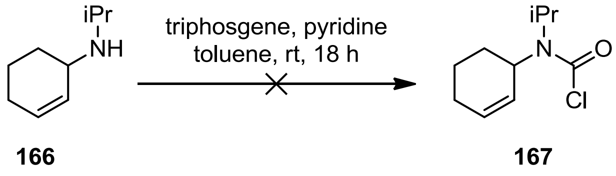
Scheme 65

As it was difficult to isolate **166**, the reaction was carried out using acetone instead of CH_3CN because of its lower boiling point which should facilitate the work-up (Scheme 66). Even after 6.5 h at rt, the reaction was not complete and heating to reflux for 18 h was required. Some degradation was observed and purification of the crude mixture gave amine **166** in a low 23% yield.



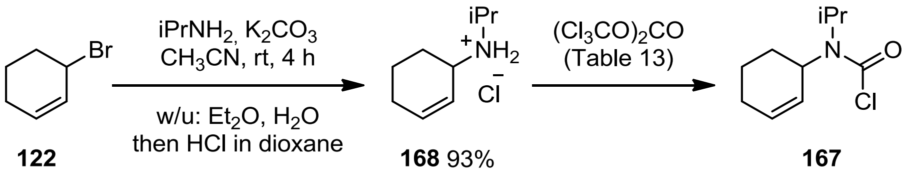
Scheme 66

Synthesis of carbamoyl chloride **167** was attempted using triphosgene and pyridine in toluene (Scheme 67). After 18 h at rt, complete consumption of the starting material was observed but tlc analysis did not show any new components. Poor mass recovery was obtained after work-up.



Scheme 67

Another strategy was developed to access carbamoyl chloride **167**. It was decided to isolate isopropylamine **166** as its hydrochloride salt to avoid any volatility issues (Scheme 68). Amine hydrochloride **168** was obtained as a viscous oil in 93% yield after work-up and further purification was not required.



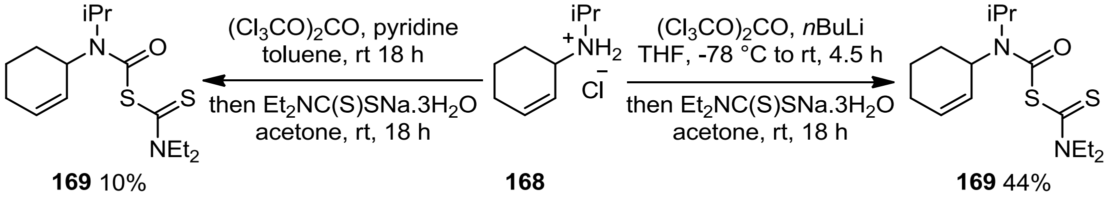
Scheme 68

When **168** was treated with 2.5 eq of pyridine and 0.37 eq of triphosgene, consumption of the starting material was observed but only degradation was obtained after 18 h at 60 °C or 115 °C (Table 13, entries 1 and 2). A new product was observed on tlc when a mixture of triphosgene and *n*BuLi in THF was used (entry 3). However, a different product was detected after the work-up indicating possible hydrolytic instability of carbamoyl chloride **167.**

Entry	Reagents	T / time	Result
1	$(Cl_3CO)_2CO$ (0.37 eq), pyridine (2.5 eq) toluene	60 °C / 18 h	degradation
2	$(Cl_3CO)_2CO$ (0.37 eq), pyridine (2.5 eq) toluene	reflux / 18 h	degradation
3	$(Cl_3CO)_2CO$ (0.37 eq), *n*BuLi (2.2 eq) THF	-78 °C to rt / 5 h	degradation

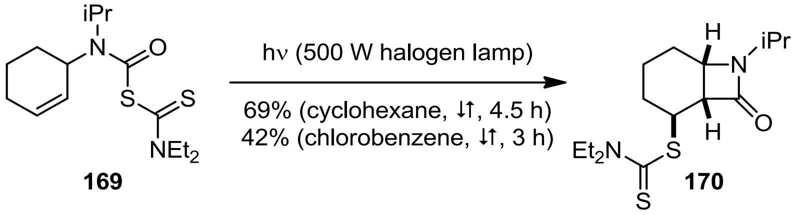
Table 13: Attempts to synthesize carbamoyl chloride 167 from 168

Formation of dithiocarbamate **169** in one pot from **168** was then investigated (Scheme 69). Amine hydrochloride **168** was treated with triphosgene and pyridine in toluene at rt for 18 h. The reaction mixture was concentrated, the residue obtained was re-suspended in acetone and sodium diethyldithiocarbamate trihydrate was added. After 18 h at rt, 10% of dithiocarbamate **169** was formed. The yield was improved to 44% when the reaction was carried out using *n*BuLi in THF and when the dithiocarbamate salt was added directly to the ethereal mixture along with a small amount of acetone to improve solubility.



Scheme 69

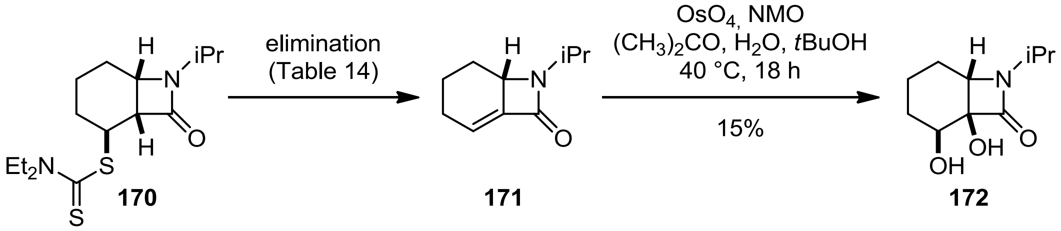
Irradiation of **169** with a 500 W halogen lamp gave β-lactam **170** in 69% yield after 4.5 h in cyclohexane and in 42% yield after 3 h in chlorobenzene (Scheme 70).



Scheme 70

Elimination of the dithiocarbamate group in **170** proved problematic (Scheme 71 and Table 14). Alkene **171** was formed in 33% yield when 1.1 eq of LHMDS and MeI were used (entry 1). The yield increased to 56% with 1.6 eq but the reaction did not go to completion with 28% of starting material being recovered (entry 2). Interestingly, isomerisation to the non-conjugated alkene did not occur even when warming the reaction to rt. Increasing the amount of base and alkylating agent did not drive the reaction to completion (entry 3).

Diol **172** was synthesized in 15% yield when alkene **171** was treated with cat. OsO_4 and NMO for 18 h at 40 °C (Scheme 71). This reaction was carried out only once. With only a small amount of diol **172** formed, the semipinacol rearrangement could not be attempted.



Scheme 71

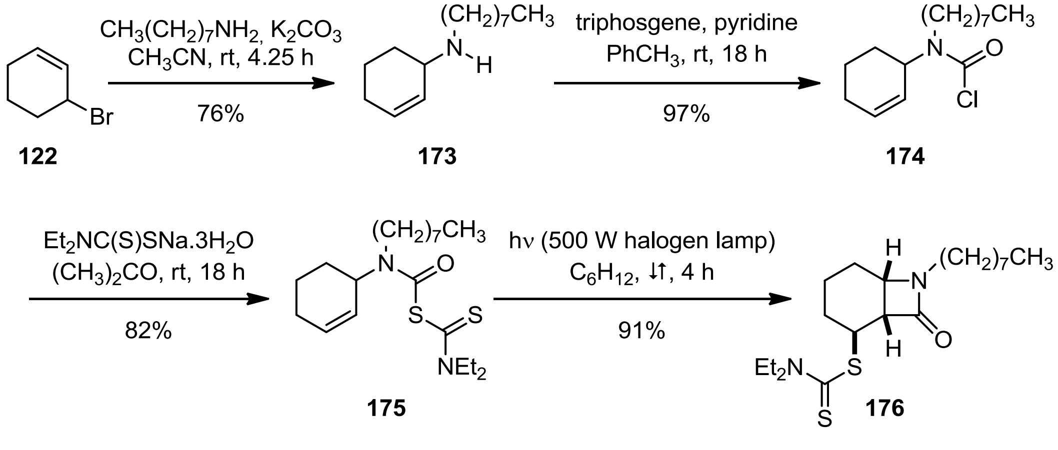
Entry	Reagents in THF	T / time	Result
1	MeI, LHMDS (1.1 eq)	-78 °C / 7.5 h	**170** 43% **171** 33%
2	MeI, LHMDS (1.6 eq)	-78 °C to rt / 18 h	**170** 28% **171** 56%
3	MeI, LHMDS (3 eq)	-78 °C to rt / 18 h	1:1 mixture **170:171**

Table 14: Synthesis of alkene 171 via elimination of the dithiocarbamate group

In summary, with an isopropyl substituent on the nitrogen, the synthetic sequence to obtain diol **172** was poor yielding throughout. Due to its low molecular weight, amine **166** was difficult to handle and it was poorly reactive towards the formation of carbamoyl chloride **167**. Radical cyclisation to form β-lactam **170** was efficient and stereoselective, but elimination of the dithiocarbamate group and subsequent oxidation of alkene **171** were problematic.

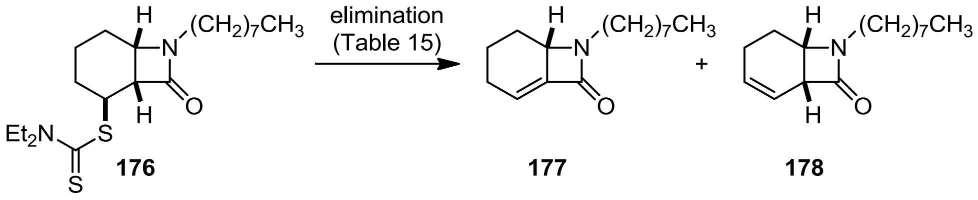
3.1.2 *N*-Octylamine derivative

The semipinacol rearrangement could not be attempted for the *N*-isopropyl substituent due to the difficulty in accessing diol **172**. It was therefore decided to explore the influence of a linear alkyl chain which will still be electron-donating but less sterically demanding. Reaction of 3-bromocyclohexene **122** with 1-octylamine afforded **173** in 76% yield (Scheme 72). Treatment of secondary amine **173** with triphosgene and pyridine in toluene at rt for 18 h gave carbamoyl chloride **174** in 97% yield after work-up. Formation of the radical cyclisation precursor **175** occurred in 82% yield using sodium diethyldithiocarbamate trihydrate in acetone at rt for 18 h. Irradiation of **175** in cyclohexane for 4 h with a 500 W halogen lamp gave β-lactam **176** as a single isomer in an excellent 91% yield.



Scheme 72

As for the *N*-isopropyl β-lactam **170**, the elimination of the dithiocarbamate group in **176** proved to be problematic (Scheme 73 and Table 15). Conversion from dithiocarbamate **176** to alkene **177** was very slow when using 1.1 eq of MeI and LHMDS (entry 1). To drive the reaction to completion, 0.5 eq of reagents were added and the mixture was warmed from -78 °C to rt over 18 h. Unsurprisingly, a 1.0:0.58 mixture of alkenes **177:178** was obtained in 89% yield. Separation of the isomers by column chromatography was difficult but nevertheless possible. The portionwise addition of 1.6 eq of LHMDS and MeI to a solution of dithiocarbamate **176** in THF at -78 °C followed by warming to rt over 5 h gave alkene **177** in 72% yield contaminated with 22% of starting material **176** (entry 2).



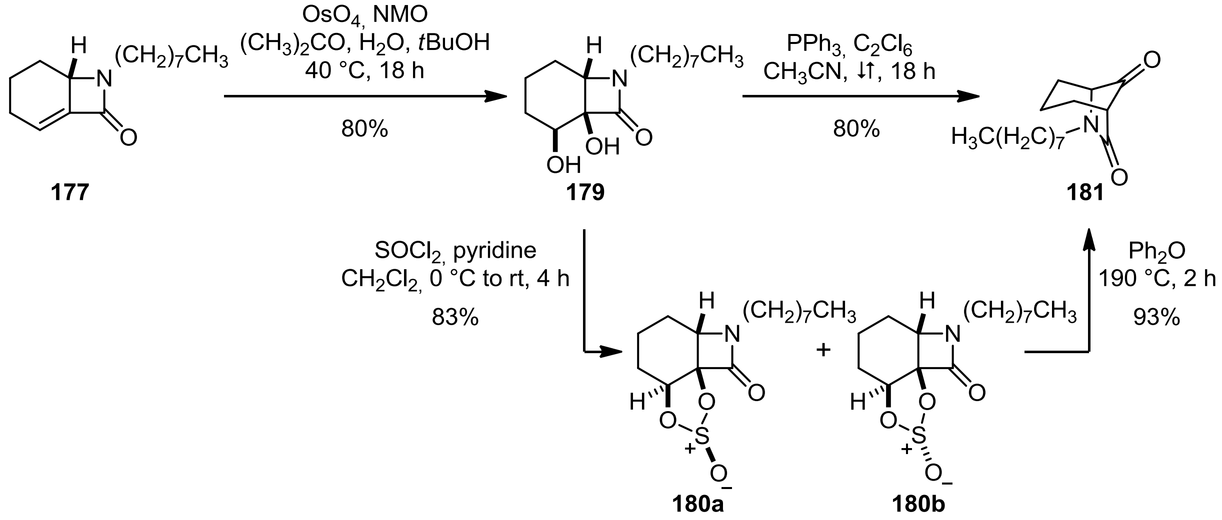
Scheme 73

Entry	Reagents in THF	T / time	Result
1	MeI, LHMDS (1.1+0.5 eq)	-78 °C to rt / 18 h	**177:178** 1.0:0.58 89%
2	MeI, LHMDS (1.6 eq)	-78 °C to rt / 36 h	**177** 72% mixed with **176** 22%
3	MeI, LHMDS (10 eq)	-78 °C / 2.5 h	**176** 13% **177** 51%
4	MeI, LHMDS (10 eq)	-78 °C / 5 h	**177:178** 1.0:0.29 74%
5	MeI, LHMDS (10 eq)	-78 °C to rt / 4 h	**177** 73% mixed with 13% **176:178**
6	MeI, LHMDS (2 x 1.5 eq)	-78 °C / 10 h	**177** 67%
7	MeI, LHMDS (4 x 1 eq)	-78 °C / 9 h	**177** 68%

Table 15: Synthesis of alkene 177 via elimination of the dithiocarbamate group

An excess of reagents was required to drive the elimination to completion. The use of 10 eq of base and MeI at -78 °C gave partial conversion after 2.5 h and full conversion after 5 h (Table 15, entries 3 and 4). When the reaction was allowed to warm to rt over 4 h, the conversion was good affording 73% of alkene **177** mixed with a small amount of **176** and **178** (entry 5). Finally, it was decided to keep the reaction mixture at -78 °C and to add the reagents portionwise. Alkene **177** was isolated cleanly in 67% yield and 68% yield when using 3 or 4 eq respectively (entries 6 and 7).

Dihydroxylation of alkene **177** using NMO and a sub-stoichiometric amount of OsO_4 afforded diol **179** in 80% yield (Scheme 74). Formation of cyclic sulfites **180** proceeded in 83% yield using thionyl chloride and pyridine in CH_2Cl_2 for 4 h. The 1:1 mixture of isomers was separated to allow characterisation.[62] The semipinacol rearrangement of a 1:1 mixture of **180** gave bicyclic ketone **181** in 93% yield after 2 h at 190 °C, 77% yield over 2 steps from **179**. Treatment of diol **179** with PPh_3 and C_2Cl_6 for 18 h in refluxing CH_3CN afforded bicyclic ketone **181** in 80% yield.



Scheme 74

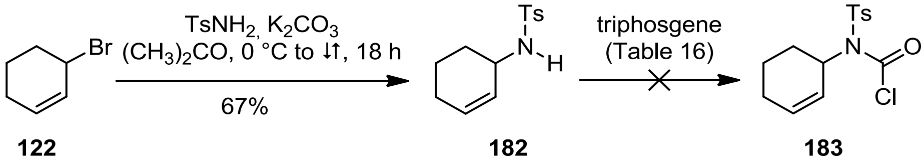
In summary, 7,8-diketo-6-azabicyclo[3.2.1]octane ring structure **181** was obtained in an overall 24% yield from 3-bromocyclohexene **122** *via* a semipinacol rearrangement with cyclic phosphorane activation. A similar overall 23% yield was obtained using cyclic sulfite activation. Apart from the elimination of the dithiocarbamate group, all of the steps afforded the desired compounds in high yield. The basic elimination required optimisation and the yield was improved even if it was lower than that obtained with the *N*-Bn and *N*-PMP derivatives.

3.1.3 *N*-Tosylamine derivative

An electron-withdrawing group on the nitrogen might influence the semipinacol rearrangement of *cis*-fused β-lactam diols. Moreover, it could play a role in the radical cyclisation-dithiocarbamate group transfer. Indeed, Rigby and co-workers described in 1998 the formation of *N*-Ts carbamoyl radicals from Se-phenyl selenocarbamates and subsequent 5-*exo trig* cyclisation.[74] Their results contrasted with the work from Barrett *et al.* which showed that non-fully substituted carbamoyl radicals obtained from Se-phenyl selenocarbamates afforded only formamides.[75]

Reaction of tosylamine with 3-bromocyclohexene **122** and K_2CO_3 in refluxing acetone afforded sulfonamide **182** in 67% yield (Scheme 75).[76] Formation of the carbamoyl chloride derivative **183** proved difficult (Table 16). Reacting tosylamine **182** with triphosgene and pyridine in toluene afforded only starting material after 18 h at rt (entry 1). Refluxing the reaction mixture for 4.5 h after 18 h at rt did not improve the conversion (entry 2). Spagnolo and co-workers published the synthesis of tosyl-substituted carbamoyl chlorides using a mixture of triphosgene and pyridine in benzene.[77] Unfortunately, changing the solvent to benzene did not afford the desired carbamoyl chloride **183** (entry 3). Increasing the temperature to 40 °C or 115 °C only resulted in recovered starting material after 18 h (entry 4 and 5).[78]

Use of a stronger base than pyridine was considered**.** NaH, LHMDS, DBU and *n*BuLi in toluene at different temperatures gave no reaction (Table 16, entry 6-10).[79-80] When using 2.5 eq of *n*BuLi or LHMDS in THF, no conversion was observed (entry 11 and 12).[81] Finally, using NaH in DMF at 115 °C did not afford the desired product (entry 13).

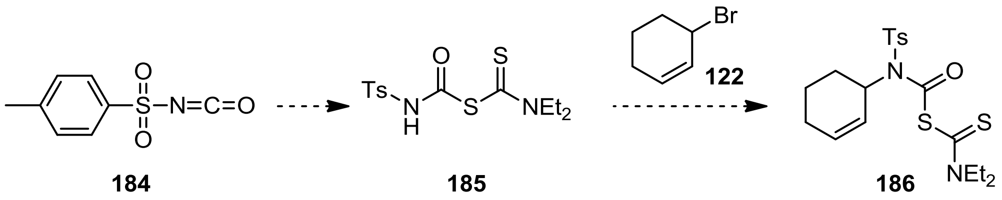


Scheme 75

Entry	Reagents	T / time	Result
1	$(Cl_3CO)_2CO$ (0.37 eq), pyridine (1.2 eq) toluene	rt / 18 h	**182**
2	$(Cl_3CO)_2CO$ (0.37 eq), pyridine (1.2 eq) toluene	rt (18 h) then reflux (4.5 h)	**182**
3	$(Cl_3CO)_2CO$ (0.37 eq), pyridine (1.2 eq) benzene	0 °C to rt / 5 h	**182**
4	$(Cl_3CO)_2CO$ (0.37 eq), pyridine (1.2 eq) toluene	40 °C / 18 h	**182**
5	$(Cl_3CO)_2CO$ (0.37 eq), pyridine (1.2 eq) toluene	reflux / 18 h	**182**
6	$(Cl_3CO)_2O$ (0.37 eq), NaH (1.2 eq) toluene	rt to reflux / 18 h	**182**
7	$(Cl_3CO)_2O$ (0.37 eq), LHMDS (1.2 eq) toluene	0 °C to rt / 4.5 h	**182**
8	$(Cl_3CO)_2O$ (0.37 eq), LHMDS (2.5 eq) toluene	rt to reflux / 5 h	**182**
9	$(Cl_3CO)_2O$ (0.37 eq), DBU (5 eq) toluene	reflux / 18 h	**182**
10	$(Cl_3CO)_2O$ (0.37 eq), *n*BuLi (2.5 eq) toluene	-78 °C to rt / 18 h	**182**
11	$(Cl_3CO)_2O$ (0.37 eq), *n*BuLi (2.5 eq) THF	-78 °C to rt / 18 h	**182**
12	$(Cl_3CO)_2O$ (0.37 eq), LHMDS (2.5 eq) THF	-78 °C to rt / 18 h	**182**
13	$(Cl_3CO)_2O$ (0.37 eq), NaH (5 eq) DMF	115 °C / 18 h	**182**

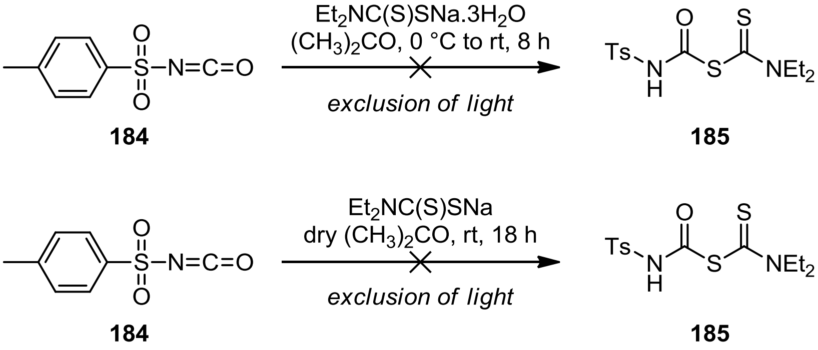
Table 16: Attempts to synthesize carbamoyl chloride 183

The difficulty in forming carbamoyl chloride **183** might be due to the product being highly unstable. Formation of dithiocarbamate **185** followed by reaction with 3-bromocyclohexene **122** to form dithiocarbamate **186** was considered as an alternative strategy to avoid the use of a carbamoyl chloride intermediate (Scheme 76).



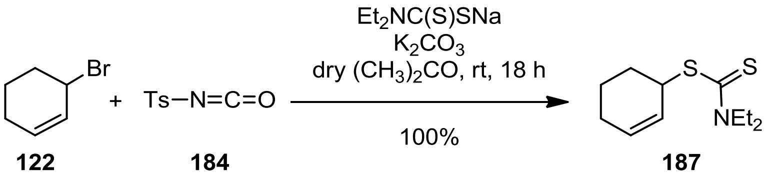
Scheme 76

The first attempt to synthesize **185** involved treatment of a solution of commercially available isocyanate **184** with sodium diethyldithiocarbamate trihydrate with the exclusion of light (Scheme 77). Consumption of the isocyanate was observed at rt but **185** was not isolated. When the same reaction was attempted with dry acetone as solvent and P_2O_5-dried dithiocarbamate salt, a yellow solid was obtained. Unfortunately, the ^{1}H-NMR spectrum did not show any aromatic protons, ruling out the formation of **185**.



Scheme 77

The lack of success for the formation of dithiocarbamate **185** might also be due to its instability. A one-pot procedure for the formation of **186** was attempted using tosyl isocyanate **184**, dry sodium diethyldithiocarbamate and K_2CO_3 in dry acetone (Scheme 78). The reaction mixture turned bright yellow upon addition of the dithiocarbamate sodium salt. However after five seconds, a white suspension reformed. After 18 h at rt, full consumption of the starting material was observed and dithiocarbamate **187** was obtained in quantitative yield.

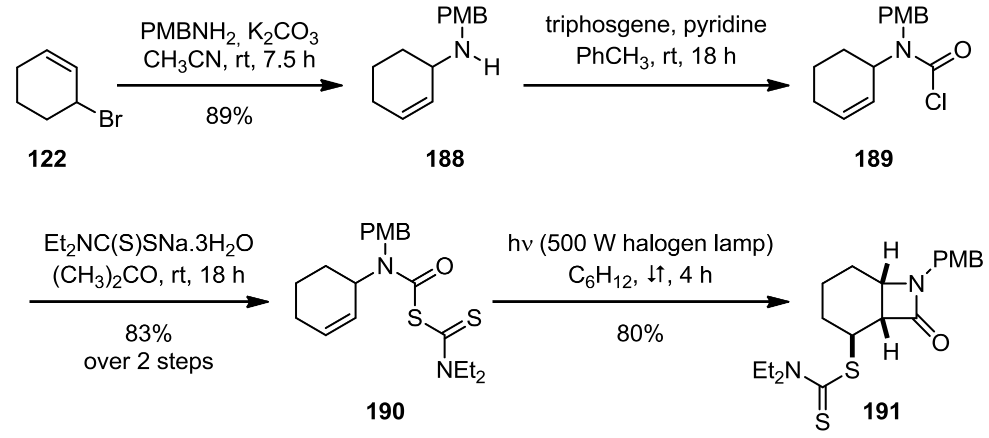


Scheme 78

In summary, the influence of a tosyl substituent on the nitrogen of the lactam functional group for the radical cyclisation and the semipinacol rearrangement could not be assessed. Indeed, it was not possible to form carbamoyl chloride **183** or dithiocarbamate **186** under a wide range of conditions, suggesting the electron-withdrawing nature of the tosyl group reduces the nucleophilicity of the nitrogen and/or decreases the stability of **183**.

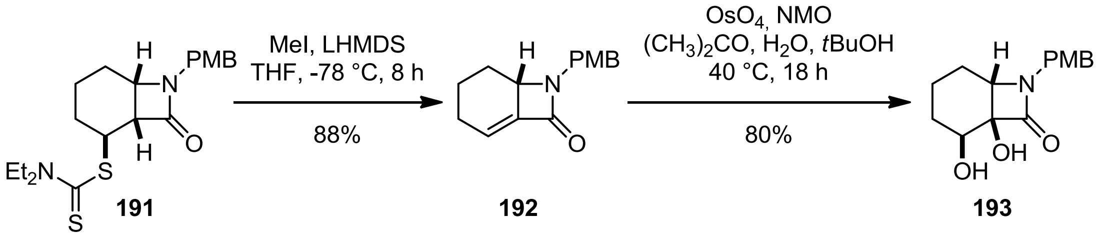
3.1.4 *N-para*-Methoxybenzylamine derivative

The scope of the methodology was extended to a PMB protecting group on the nitrogen. This group is of particular interest because it can be deprotected under generally mild oxidative conditions, orthogonal to the reducing conditions required for the removal of a benzyl group from nitrogen.[82] Further functional group transformation of the lactam after the rearrangement would then be facilitated. Treatment of 3-bromocyclohexene **122** with $PMBNH_2$ and K_2CO_3 afforded secondary amine **188** in 89% yield (Scheme 79). Complete conversion to form carbamoyl chloride **189** was observed when **188** was reacted with a mixture of triphosgene and pyridine in toluene. However, after purification by column chromatography, **189** was formed in only 39% yield. To avoid degradation, it was decided to treat crude carbamoyl chloride **189** with sodium diethyldithiocarbamate trihydrate and dithiocarbamate **190** was now obtained in an excellent 83% yield over 2 steps. Irradiation of **190** in cyclohexane for 4 h with a 500 W halogen lamp gave β-lactam **191** in 80% yield as a single isomer.



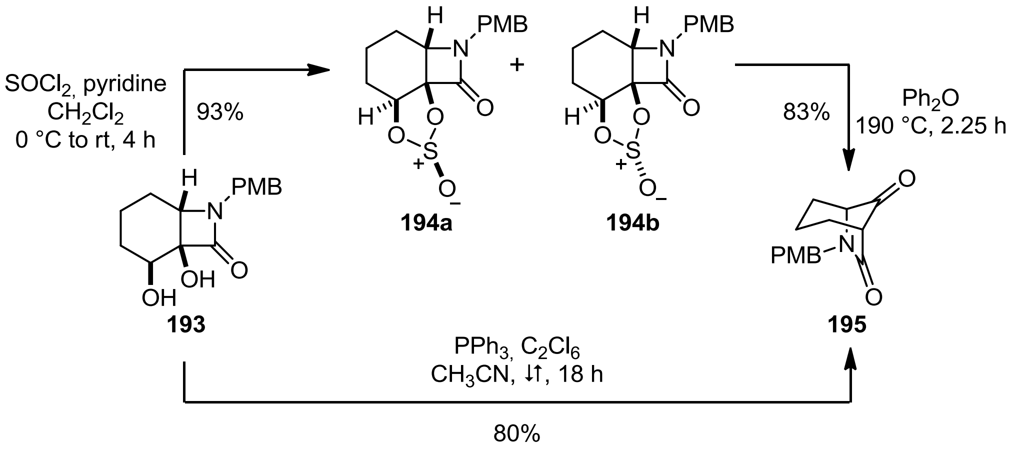
Scheme 79

Low-temperature elimination of the dithiocarbamate group with LHMDS and MeI gave conjugated alkene **192** in 88% yield (Scheme 80). Dihydroxylation using cat. OsO_4 and NMO afforded diol **193** in 80% yield as a single isomer.



Scheme 80

Cyclic sulfites **194a** and **194b** were obtained as a 1:1 mixture in 93% yield and subsequent heating at 190 °C for 2.25 h in Ph_2O afforded **195** in 83% yield or 77% yield over 2 steps from **193** (Scheme 81). Finally, the semipinacol rearrangement of diol **193** using cyclic phosphorane activation to form the 7,8-diketo-6-azabicyclo[3.2.1]octane structure **195** proceeded in 80% yield upon treatment of **193** with PPh_3 and hexachloroethane in refluxing CH_3CN.

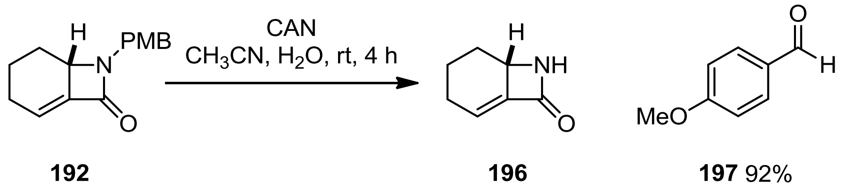


Scheme 81

In summary, bicyclic ketone **195** can be synthesized in 32% or 33% overall yield from 3-bromocyclohexene **122** *via* a semipinacol rearrangement of cyclic sulfites **194** or cyclic phosphorane activation of diol **193**, respectively. All of the steps were high yielding (>80%) and apart from carbamoyl chloride **189**, all of the intermediates were stable.

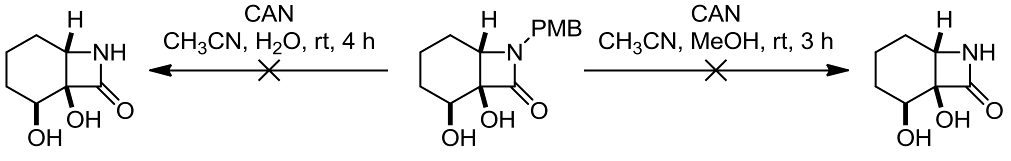
3.1.5 *N*-H derivative by deprotection of the PMB group

Finally, the semipinacol rearrangement of a non-protected β-lactam was investigated. Deprotection of the PMB group was first considered because on an amide it can be removed under neutral oxidative conditions with CAN.[83-84] In the reaction sequence developed, it was in theory possible to deprotect the amide functional group either on alkene **192** or diol **193**. Treatment of alkene **192** with 4.5 eq of CAN in a 2:1 mixture of CH_3CN:H_2O for 4 h at rt did not afford secondary lactam **196** (Scheme 82).[85] The starting material was completely consumed and *para*-methoxybenzaldehyde **197** was isolated in 92% yield, thus indicating that **196** was probably unstable under the reaction conditions.



Scheme 82

The same behaviour was observed when diol **193** was treated with CAN in a 2:1 mixture of $CH_3CN:H_2O$ for 1 h at rt (Scheme 83). Using a 2:1 mixture of CH_3CN:MeOH as described by Isobe did not enable the isolation of diol **198**.[86]



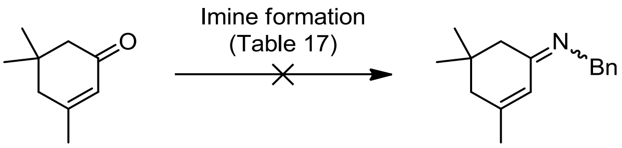
198 **193** **198**

Scheme 83

In summary, it was not possible to investigate the semipinacol rearrangement in the absence of a substituent on nitrogen. Formation of **197** indicates that deprotection was probably taking place. However, isolation of strained alkene **196** or polar diol **198** proved impossible.

3.2 *Presence of methyl groups on the cyclohexane moiety*

Isophorone **199** is a readily available ketone possessing a gem-dimethyl and a methyl-substituted cyclic alkene which made it an ideal starting point to incorporate methyl groups on the cyclohexane ring fused to the β-lactam. The synthesis of imine **200** was attempted using $TiCl_4$ and an excess of benzylamine (Scheme 84 and Table 17, entry 1).[87] Degradation was obtained after 1 h in refluxing hexane. Only starting material was observed when the reaction was carried out with $TiCl_4$ in solution in toluene for 18 h at 75 °C (entry 2). The same result was observed using 4 Å molecular sieves as a desiccant in CH_2Cl_2 (entry 3).[88]



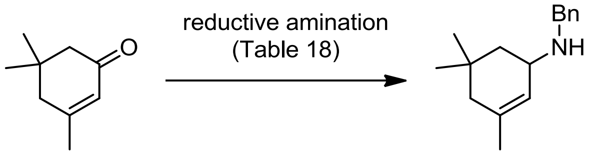
199 **200**

Scheme 84

Entry	**Reagents**	**T / time**	**Result**
1	$BnNH_2$ (6 eq), $TiCl_4$ (1.3 eq) hexane	0 °C to reflux / 1 h	degradation
2	$BnNH_2$ (1.05 eq), $TiCl_4$ in $PhCH_3$ (1.3 eq) $PhCH_3$	0 °C to 75 °C / 18 h	**199**
3	$BnNH_2$ (1.05 eq), MS 4Å CH_2Cl_2	rt (3 h) then reflux (3 h)	**199**

Table 17: Benzylimine formation on isophorone

Imine **200** may be quite unstable which made its isolation difficult. Reductive amination to form benzylamine **201** was therefore attempted (Scheme 85 and Table 18). Using 1.05 eq of $BnNH_2$ and $Ti(O\textit{i}Pr)_4$, no conversion was observed at rt and heating was required to observe some conversion. An additional equivalent of benzylamine was needed to drive the imine formation to completion. Subsequent reduction with $NaBH_4$ gave amine **201** in a modest 38% yield (entry 1). Using 3 eq of benzylamine from the start did not afford complete formation of imine **200** and an additional 3 eq were necessary. Amine **201** was obtained in 68% yield after *in situ* reduction of the imine which required 3 eq of $NaBH_4$ in refluxing MeOH (entry 2). With 9 eq of benzylamine from the beginning, the imine synthesis was complete after 7.5 h and subsequent reduction afforded amine **201** in 57% yield (entry 3). This particular reaction was carried out on a larger scale (10 times) than for entry 2, which might explain the lower yield.



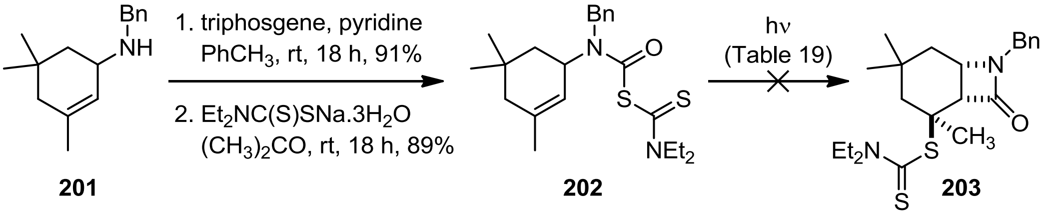
199 **201**

Scheme 85

Entry	Reagents in MeOH	T / time	Result
1	$BnNH_2$ (2 x 1.05 eq), Ti(O*i*Pr)$_4$ (1.05 eq) then $NaBH_4$ (1.05 eq)	rt to reflux / 18 h then 0 °C to rt / 2 h	**201** 38%
2	$BnNH_2$ (2 x 3 eq), Ti(O*i*Pr)$_4$ (1.05 eq) then $NaBH_4$ (1 + 2 eq)	reflux / 18 h then reflux / 18 h	**201** 68%
3	$BnNH_2$ (9 eq), Ti(O*i*Pr)$_4$ (1.05 eq) then $NaBH_4$ (4 eq)	reflux / 7.5 h then reflux / 18 h	**201** 57%

Table 18: Reductive amination of isophorone199

Treatment of amine **201** with triphosgene and pyridine in toluene for 18 h at rt afforded a carbamoyl chloride which proved unstable to purification on silica gel. Repeating the reaction and submitting the crude material obtained to sodium diethyldithiocarbamate in acetone at rt for 18 h afforded **202** in 81% yield over 2 steps (Scheme 86). When dithiocarbamate **202** was irradiated with a 500 W halogen lamp in cyclohexane or in isopropanol, the starting material was recovered (Table 19, entries 1 and 2). Degradation of the reaction mixture was observed when chlorobenzene was used as the solvent (entry 3).

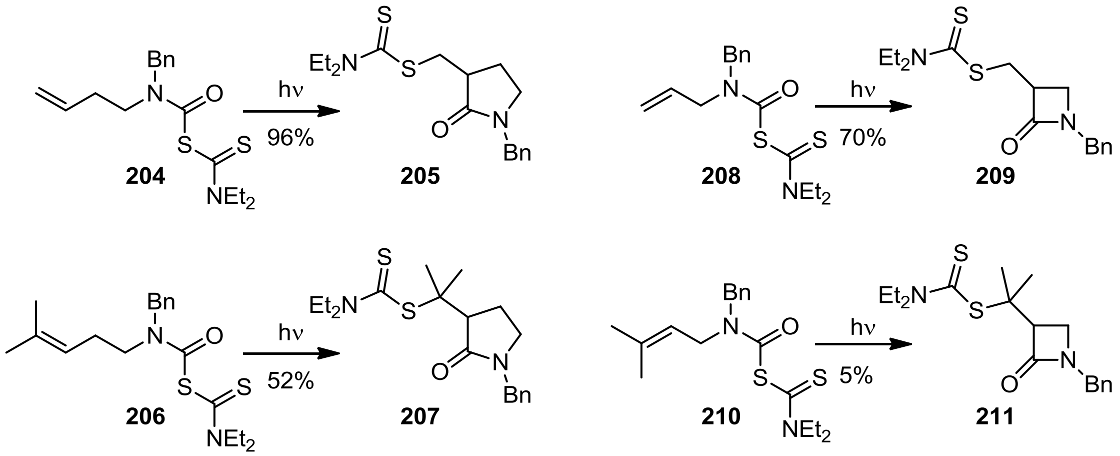


Scheme 86

Entry	Solvent	T / time	Result
1	hν, cyclohexane	reflux / 4.25 h	**202**
2	hν, *i*PrOH	reflux / 4.25 h	**202**
3	hν, C_6H_5Cl	reflux / 7 h	degradation

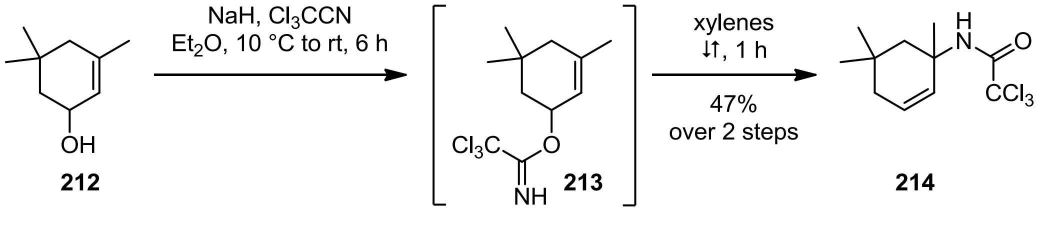
Table 19: Attempts to synthesize β-lactam 203 via radical cyclisation

Previous work in the Grainger group had shown that a dithiocarbamate group transfer on a tertiary radical is possible even if it decreases the overall efficiency of the process. Indeed, irradiation of **204** in cyclohexane afforded γ-lactam **205** *via* a 5-*exo trig* cyclisation in 96% yield whereas **207** which bears two geminal methyl groups was obtained in only 52% yield from dithiocarbamate **206** (Scheme 87).[26-27] Moreover, when the 4-*exo trig* radical cyclisation was studied, only trace amounts of β-lactam **211** were formed compared to **209** being obtained in 70% yield. This shows that the combination of a slower and potentially reversible 4-*exo trig* cyclisation with a less efficient group transfer on a tertiary radical did not allow the formation of β-lactam **203**.



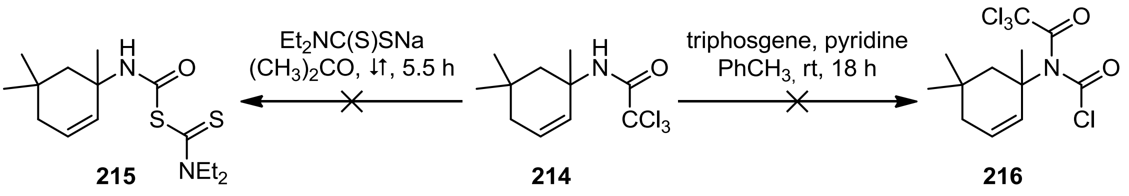
Scheme 87

An alternative for the incorporation of methyl groups on the cyclohexane ring fused to the β-lactam was to start from isophorol **212** which is also commercially available. Reacting **212** with NaH and trichloroacetonitrile formed imidate **213** which was used directly in the next step without any purification (Scheme 88). Refluxing **213** in xylenes afforded trichloroacetamide **214** in 47% yield over 2 steps *via* an Overman rearrangement.[89]



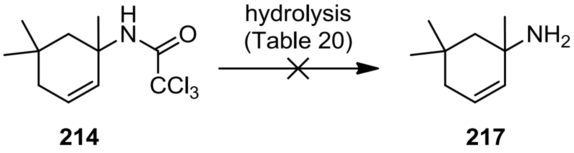
Scheme 88

In 2003, Wynne demonstrated that thioesters could be formed from trichloroacetyl chlorides *via* nucleophilic substitution with thiols.[90] Displacement of the trichloromethyl group of **214** with sodium diethyldithiocarbamate was therefore investigated. When acetamide **214** was treated with sodium diethyldithiocarbamate for 5.5 h in refluxing acetone, starting material was recovered (Scheme 89). Thinking that the trichloroacetyl group could act as a protecting group, it was decided to form carbamoyl chloride **216** by reacting **214** with triphosgene and pyridine in toluene. After 18 h at rt, only starting material was observed.



Scheme 89

Hydrolysis of the trichloroacetamide functional group is possible under strongly basic or acidic conditions.[91-94] No reaction was observed when **214** was refluxed for 18 h in a 1 M aqueous solution of NaOH (Scheme 90 and Table 20, entry 1).



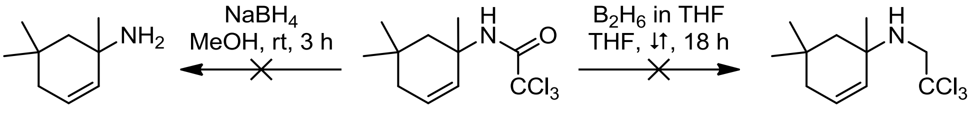
Scheme 90

Entry	Reagents	T / time	Result
1	NaOH (1 M aq), EtOH	reflux / 18 h	**214**
2	NaOH (6 M aq), EtOH	85 °C / 8 h	**214**
3	NaOH (6 M aq), EtOH	reflux / 18 h	degradation
4	NaOH (6 M aq), EtOH	150 °C (µw) / 1.5 h	degradation
5	NaOH (2.5 eq), EtOH	reflux / 3 h	**214**
6	HCl (6 M aq), MeOH	reflux / 4 h	**214**

Table 20: Hydrolysis of the trichloroacetyl group in 214

The same result was obtained when **214** in a 1:1 mixture of EtOH and 6 M aq. solution of NaOH was heated at 85 °C for 8 h (Table 20, entry 2). After 18 h at reflux or 1.5 h at 150 °C, degradation was observed (entries 3 and 4). Under anhydrous conditions, no reaction was observed after 3 h in refluxing ethanol (entry 5). Finally, strongly acidic conditions did not afford any of the desired allylic amine **216** (entry 6).

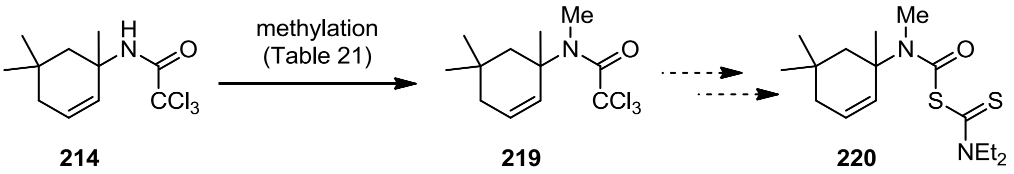
In 2010, Tomkinson and co-workers described a selective reduction of the trichloroacetimidate group over a carbamate functional group using $NaBH_4$.[95] Treatment of acetamide **214** with 4 eq of $NaBH_4$ added portionwise did not afford any of the reduced product **217** (Scheme 91). An alternative reduction procedure was treatment of **214** with BH_3.[96] Starting material was recovered after 18 h in refluxing THF instead of the expected protected amine **218**.



217 **214** **218**

Scheme 91

The degradation observed during the attempted hydrolysis of acetamide **214** suggested that amine **217** might be unstable. It was therefore decided to alkylate acetamide **214** prior to transformation of the amide functional group (Scheme 92).[91] A 1.0:0.5 ratio of **214:219** was obtained when 1.2 eq of NaH and 1.4 eq of MeI in combination with a sub-stoichiometric amount of 18-crown-6 were used (Table 21, entry 1). NaH was introduced at -15 °C and the reaction mixture was progressively allowed to warm to rt. Increasing the temperature to reflux of THF improved the conversion and a greater amount of **219** was formed when an excess of reagents was used (entry 2). Complete methylation was observed with 5 eq of base and 10 eq of MeI (entry 3). Unfortunately, degradation of the reaction mixture also increased and acetamide **219** was isolated in only 19% yield.

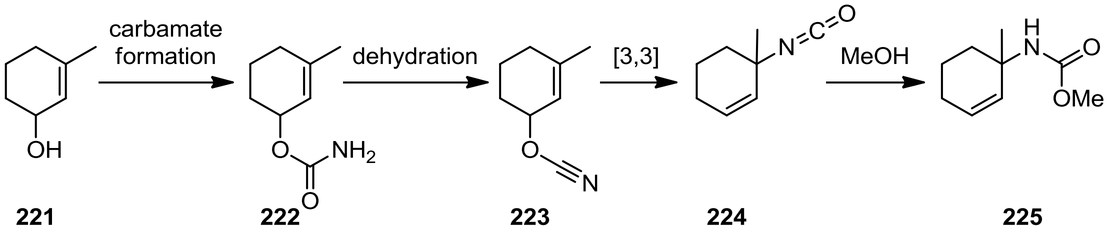


Scheme 92

Entry	Reagents in THF	T / time	Result
1	NaH (1.2 eq), MeI (1.4 eq)	-15 °C then rt (2 h) then reflux (21 h)	1.0:0.5 **214:219**
2	NaH (2.5 eq), MeI (5 eq)	-15 °C then rt (3.5 h) then reflux (18 h)	1.0:3.8 **214:219**
3	NaH (5 eq), MeI (10 eq)	-15 °C then rt / 5.5 h	**219** 19%

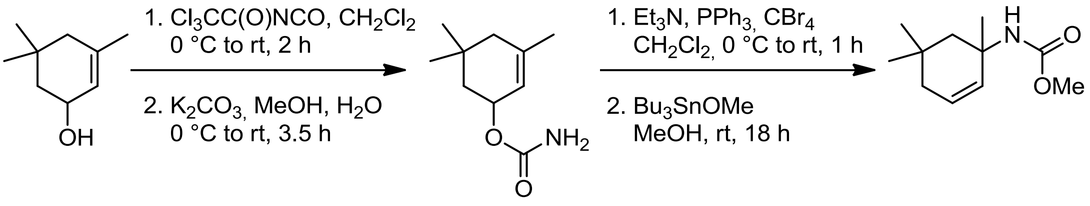
Table 21: N-methylation of acetamide 214

Another strategy for the synthesis of the trimethylcyclohexane substrate was considered. In 1997, Ichikawa described the preparation of amino sugars through an allyl cyanate to isocyanate rearrangement (Scheme 93).[97] Carbamate **222** was dehydrated to give allyl cyanate **223** which then underwent a [3,3]-sigmatropic rearrangement to form isocyanate **224**. Addition of a nucleophile such as MeOH gave carbamate **225**.



Scheme 93

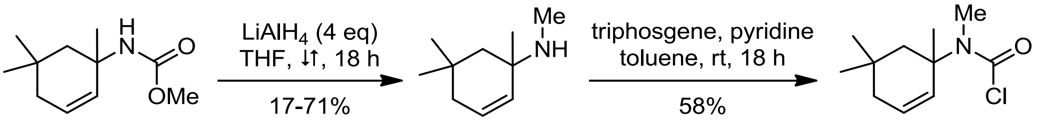
Following the literature procedure, isophorol **212** was reacted with commercially available trichloroacetyl isocyanate and subsequent methanolysis gave carbamate **226** (Scheme 94). Dehydration under Appel reaction conditions followed by nucleophilic addition of methanol gave carbamate **227** in 62% yield.[98]



212 **226** **227** 62%

Scheme 94

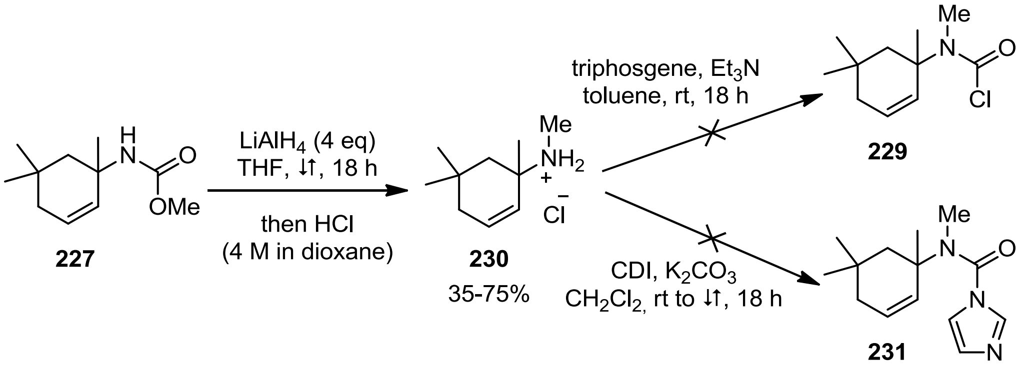
The reduction of the carbamate group proceeded in 71% yield with 4 eq of $LiAlH_4$ in refluxing THF (Scheme 95).[99] However, a much lower 17% yield was obtained when the reaction was carried out on a large scale which was ascribed to the potential volatility of amine **228**. Carbamoyl chloride **229** was formed in 58% yield of the crude material. Purification by column chromatography was attempted and afforded only degradation.



227 **228** **229**

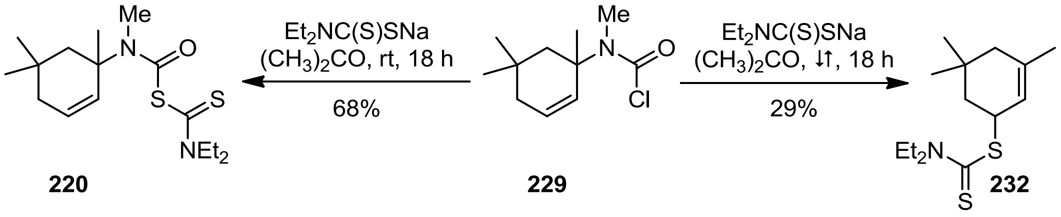
Scheme 95

As it was difficult to repeatedly synthesize amine **228** in high yield, an alternative strategy was necessary to access a sufficient quantity of carbamoyl chloride **229**. It was decided to isolate methylamine **228** as its hydrochloride salt **230** (Scheme 96). On a small scale, hydrochloride amine **230** was formed in 75% yield. Unfortunately, the yield decreased again when the reduction was carried out on a larger scale. Treatment of **230** with 4.4 eq of Et_3N and 0.7 eq of triphosgene did not afford the desired carbamoyl chloride **229**. After 18 h at rt, degradation of the reaction mixture was observed. The same result was obtained when **230** was reacted with carbonyldiimidazole and K_2CO_3 in refluxing CH_2Cl_2.[28]



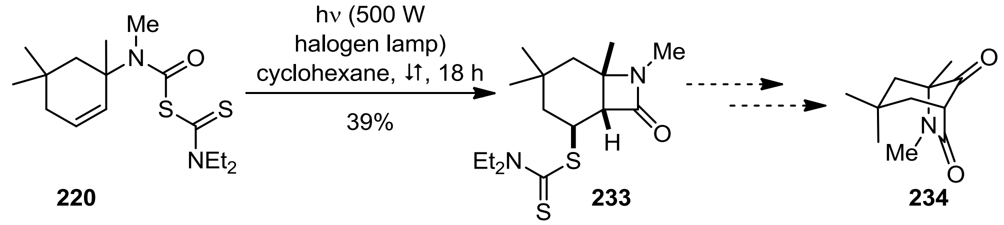
Scheme 96

Treatment of carbamoyl chloride **229** with sodium diethyldithiocarbamate in acetone for 18 h at rt gave **220** in 68% yield (Scheme 97). To improve the yield, the reaction mixture was heated at reflux for 18 h. Surprisingly, **232** was formed in 29% yield along with some degradation instead of the desired dithiocarbamate **220**. This product may arise from the decomposition of dithiocarbamate **220**.[100]



Scheme 97

Formation of β-lactam **233** *via* a 4-*exo trig* radical cyclisation proceeded in a modest 38% yield after 18 h of irradiation (Scheme 98). No further conditions were tried to improve the yield of the cyclisation and carry on the synthesis to form bicyclic ketone **234** because there was insufficient material available. Moreover, all the difficulties encountered for these derivatives did not provide an efficient route for the synthesis of **233**.



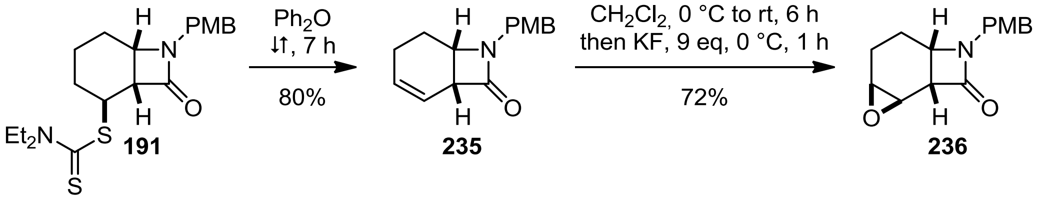
Scheme 98

In summary, the semipinacol rearrangement of the trimethyl derivatives was not attempted because it was not possible to access an appropriate *cis*-fused β-lactam diol. Starting from isophorone **199**, reductive amination afforded *N*-Bn amine **201** in moderate yield. High-yielding synthesis of dithiocarbamate **202** was achieved but the radical cyclisation-dithiocarbamate group transfer only gave degradation of the reaction mixture or recovered starting material. Starting from isophorol **212**, β-lactam **233** was formed in 7% yield *via* carbamate **227**. The subsequent synthetic pathway was not investigated because of the poor overall yield obtained.

3.3 Oxygenation on the cyclohexane ring

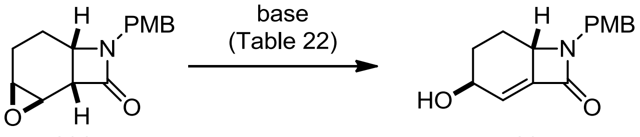
Further functionalisation of the 6-azabicyclo[3.2.1]octane ring structure is desirable for target synthesis. For example, actinobolamine bears a ketone functional group at the 3-position of the 6-azabicyclo[3.2.1]octane ring system (Figure 2, Section 1.7).

Incorporation of a functional group on the cyclohexane moiety was first investigated on the *N*-PMB derivatives. Thermal elimination of the dithiocarbamate group gave alkene **235** in 80% yield after 7 h in refluxing Ph_2O (Scheme 99). Treatment of **235** with 3 eq of *m*CPBA and subsequent work-up using potassium fluoride afforded epoxide **236** in 72% yield as a single isomer. The relative stereochemistry could not be assigned based on the ^{1}H-NMR spectrum of epoxide **236**, however the stereoselective formation of *cis* epoxide **236** was proposed based on attack of *m*CPBA on the less hindered convex face of alkene **235**.



Scheme 99

The base-catalysed ring opening of epoxide **236** did not occur using 0.1 eq of K_2CO_3 in MeOH as described by Stevenson (Scheme 100 and Table 22, entry 1).[101] Starting material was also recovered when 1.6 eq of NaH was used, even in refluxing THF (entry 2). Full conversion to alcohol **237** was observed when using 1.6 eq of LHMDS. However, only moderate yields were obtained after a mildly acidic work-up or when the reaction mixture was directly purified by column chromatography (entries 3 and 4).



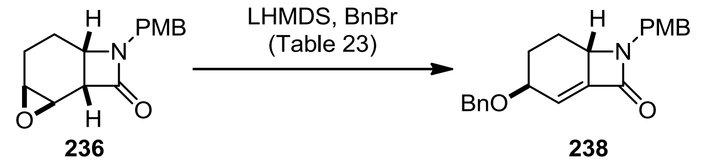
236 **237**

Scheme 100

Entry	Reagents	work-up	T / time	Result
1	K_2CO_3 (0.1 eq), MeOH	H_2O/Et_2O	rt / 4 h	**236**
2	NaH (1.6 eq), THF	H_2O/Et_2O	0 °C to reflux / 4 h	**236**
3	LHMDS (1.6 eq), THF	NH_4Cl / Et_2O	-78 °C to 0 °C / 3 h	**237** 52%
4	LHMDS (1.6 eq), THF	preabsorb onto silica	-78 °C to 0 °C / 1.5 h	**237** 52%

Table 22: Base-catalysed ring-opening of epoxide 236

The moderate yield for the synthesis of alcohol **237** suggested that the product was either partially water soluble and/or unstable on silica gel. One-pot epoxide ring-opening and alcohol protection was therefore investigated and protecting groups like benzyl and methyl were first considered. Treatment of epoxide **236** with LHMDS and BnBr at rt afforded degradation of the reaction mixture (Scheme 101 and Table 23, entry 1). When the reaction mixture was cooled to 0 °C, alcohol **237** was the only product formed in 26% yield (entry 2). Finally, traces (<10%) of the desired benzyl-protected alcohol **238** were obtained when using LHMDS and BnBr in combination with TBAI (entry 3).[102]

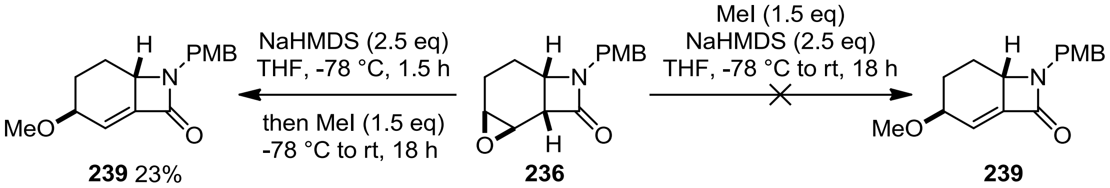


Scheme 101

Entry	Reagents in THF	T / time	Result
1	LHMDS (1.6 eq), BnBr (1.2 eq)	rt / 6.25 h	degradation
2	LHMDS (1.6 eq), BnBr (1.2 eq)	0 °C to rt / 7 h	**237** 26%
3	LHMDS (2.5 eq) BnBr (1.2 eq), cat. TBAI	0 °C to rt / 18 h	**238** <10%

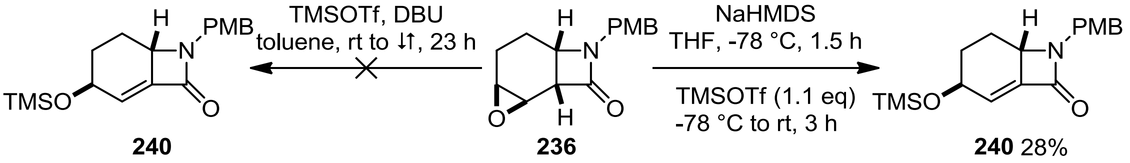
Table 23: Synthesis of benzyl-protected alcohol 238

Treatment of epoxide **236** with NaHMDS for 1.5 h at -78 °C and subsequent addition of MeI gave methyl ether **239** in 23% yield (Scheme 102). Reversing the addition of the reagents to allow the activation of the epoxide prior to its ring-opening resulted in degradation of the reaction mixture.



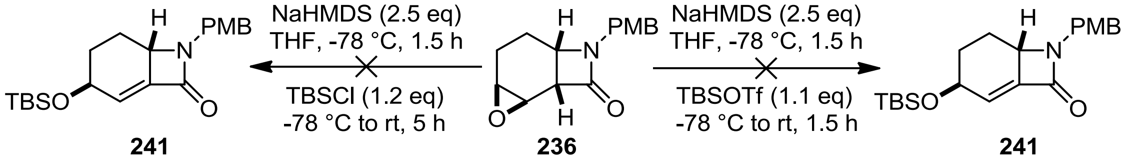
Scheme 102

Silyl protecting groups were also investigated. Treatment of epoxide **236** with DBU and TMSOTf as described by Noyori afforded mainly starting material at rt and degradation of the reaction mixture in refluxing toluene (Scheme 103).[103] Using NaHMDS and TMSOTf proved more successful and TMS ether **240** was obtained in 28% yield. However, this compound proved to be quite unstable even when stored at 4 °C under an argon atmosphere.



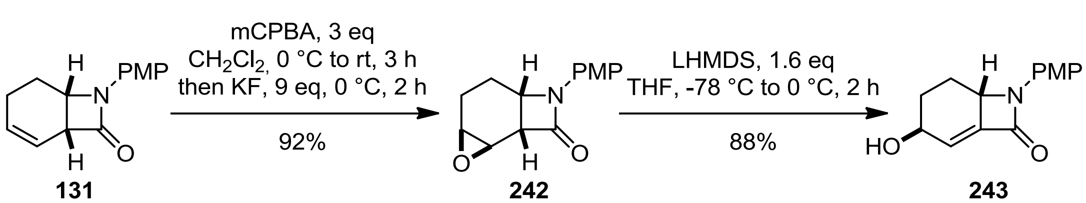
Scheme 103

The TBS protecting group, known to be more stable under acidic and basic conditions, was then considered.[104] Unfortunately, only degradation of the reaction mixture was obtained when epoxide **236** was reacted with NaHMDS in combination with TBSCl or TBSOTf (Scheme 104).



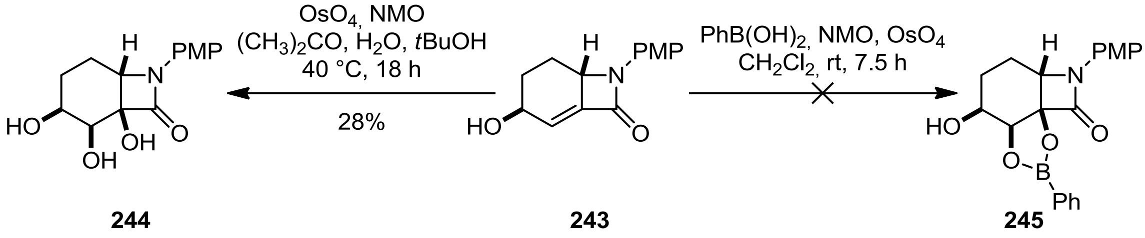
Scheme 104

In parallel to the experiments carried out on the *N*-PMB derivatives, the *N*-PMP reactivity was studied. Epoxidation of alkene **131** using *m*CPBA gave epoxide **242** in 92% yield as a single isomer. The relative stereochemistry could again not be assigned based on the basis of the ^{1}H-NMR spectrum of epoxide **242** and the relative stereochemistry was confirmed on a later compound. Low-temperature ring-opening of the epoxide using 1.6 eq of LHMDS afforded **243** in 88% yield without the need for additional purification.



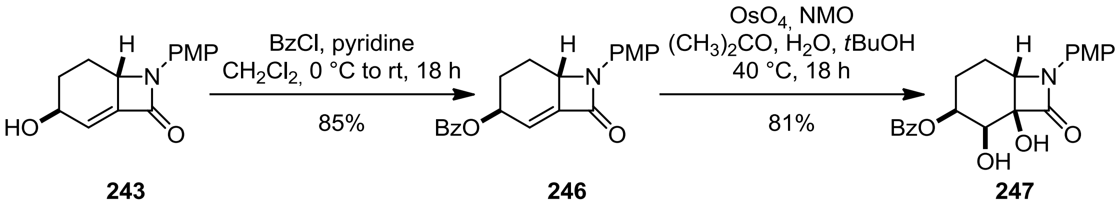
Scheme 105

Dihydroxylation of alkene **243** using a sub-stoichiometric amount of OsO_4 and NMO as a co-oxidant gave triol **244** in 28% yield (Scheme 106). This compound was difficult to solubilise in organic solvents and the NMR analysis had to be performed in DMSO-d_6. This solubility issue can explain the low yield for this reaction. In 1988, Narasaka described a dihydroxylation procedure under anhydrous conditions which involved formation of a boronic ester, which would avoid solubility problems as they are generally soluble in organic solvents.[54] Unfortunately, treatment of alkene **243** with phenylboronic acid, NMO and cat. OsO_4 afforded degradation of the reaction mixture.



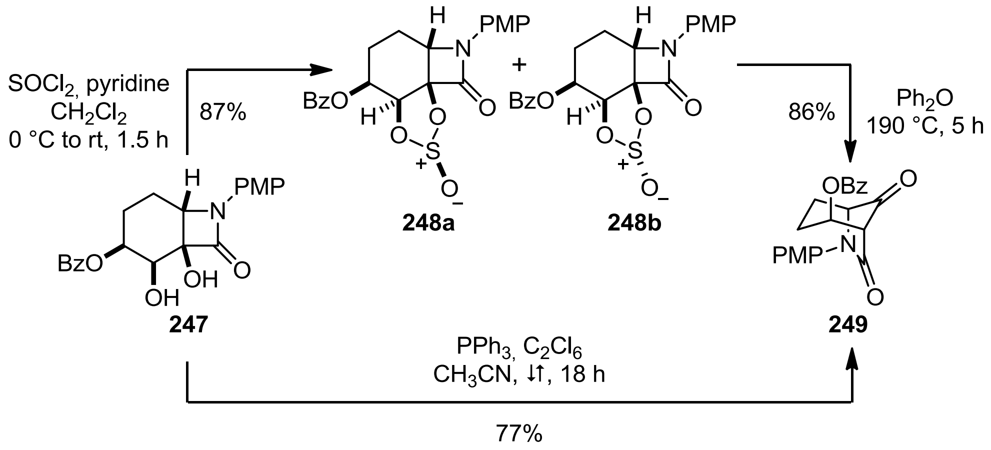
Scheme 106

It was therefore decided to protect the secondary alcohol before dihydroxylation of the alkene (Scheme 107). The benzoyl protecting group was chosen because it can be easily cleaved under mildly basic conditions.[105] Reacting **243** with an excess of benzoyl chloride and pyridine in CH_2Cl_2 afforded benzoate **246** in 85% yield.[106] The Upjohn dihydroxylation reaction then gave diol **247** in 81% yield as a single diastereomer.



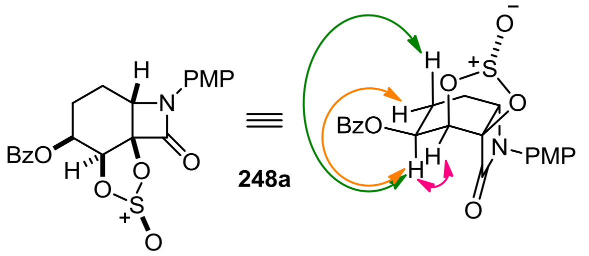
Scheme 107

Cyclic sulfites **248a** and **248b** were obtained as a 1:1 mixture in 87% yield and subsequent heating to 190 °C for 5 h in Ph_2O afforded **249** in 83% yield or 75% yield over 2 steps from **247** (Scheme 108). Finally, the semipinacol rearrangement of diol **247** *via* cyclic phosphorane activation to form the 6-azabicyclo[3.2.1]octane structure **249** proceeded in 77% yield upon treatment with PPh_3 and hexachloroethane in refluxing CH_3CN.



Scheme 108

The relative stereochemistry of the *O*-benzoyl substituent was confirmed by analysis of the 1H-NMR spectrum of cyclic sulfite **248a** (Figure 16). The proton adjacent to the OBz is seen as a ddd with coupling constants of 2.4 Hz, 3.9 Hz and 9.4 Hz suggesting two axial-equatorial interactions and one axial-axial interaction. If the other isomer was formed, there would be only small *J* values corresponding to two equatorial-equatorial and one axial-equatorial interactions.



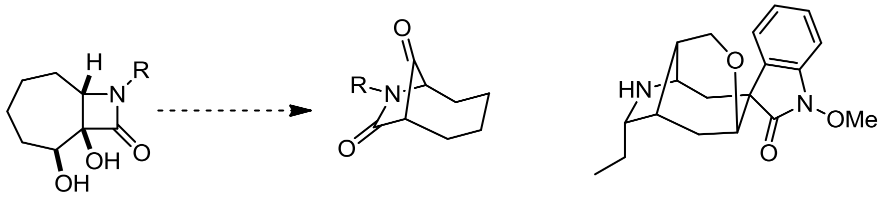
Coupling constants:
2.4 Hz, 3.9 Hz and 9.4 Hz

Figure 16

In summary, the synthesis of oxygenated bicyclic ketone **249** was achieved in six or seven steps and 34% or 33% overall yield from dithiocarbamate **128**. Protection of the secondary alcohol was necessary to pursue the synthetic plan. The *N*-PMP derivatives gave better results for the epoxide ring-opening under basic conditions than did the *N*-PMB compounds.

3.4 Construction of the core structure of gelsedine

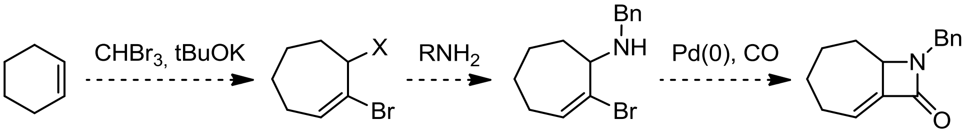
Gelsedine is an indole alkaloid found within the plant genus *Gelseminium* (Scheme 109). The sole asymmetric total synthesis was achieved in 1999 by Hiemstra and co-workers.[107] Construction of the 7-azabicyclo[4.2.1]nonane ring system **251** using the new methodology was investigated.



250 **251** (+)-gelsedine

Scheme 109

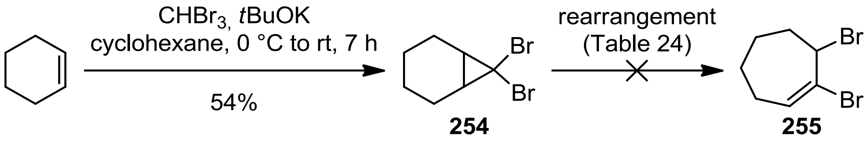
The initial strategy to synthesize β-lactam **253** was *via* a palladium-catalysed intramolecular carbonylative coupling of bromobenzylamine **252** as previously described by Mori and co-workers in 1985 (Scheme 110).[108]



X=Br, OH, OAc **252** **253**

Scheme 110

Treatment of cyclohexene with 3 eq of bromoform and *t*BuOK gave 6,6-dibromobicyclo[4.1.0]hexane **254** in 54% yield (Scheme 111).[109] The rearrangement of **254** into dibromo cycloheptene **255** did not occur in refluxing CH_3CN (Table 24, entry 1). Increasing the temperature by using a 1:1 mixture of toluene:CH_3CN or using microwave irradiation gave the same result (entries 2 and 3). Degradation was obtained when **254** in DMF or NMP was heated to reflux (entries 4 and 5).

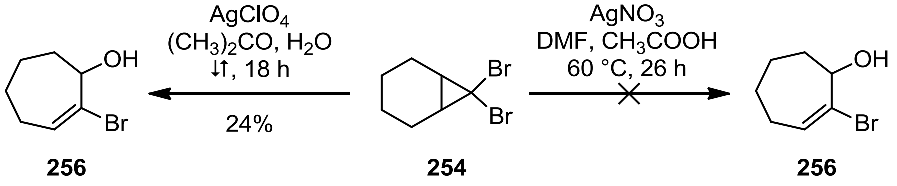


Scheme 111

Entry	Solvent	T / time	Result
1	CH_3CN	reflux / 3 d	**254**
2	1:1 CH_3CN:toluene	reflux / 2 d	**254**
3	CH_3CN	150 °C (µw) / 1.5 h	**254**
4	DMF	reflux / 3 d	degradation
5	NMP	200 °C (µw) / 2 h	degradation

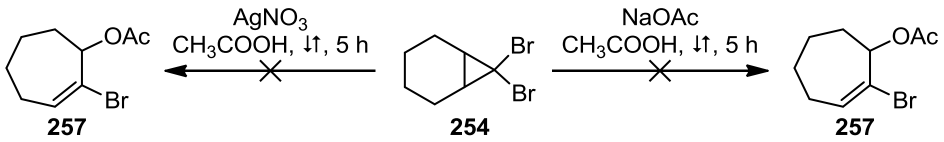
Table 24: Synthesis of 255 via thermal rearrangement

Dibromobicyclohexane **254** was then treated with silver(I) perchlorate in a refluxing 9:1 mixture of acetone:H_2O as described by Jones in 1980 (Scheme 112).[110] The desired 2-bromo-2-cyclohepten-1-ol **256** was formed in 24% yield. Unfortunately, when the reaction was carried out on a larger scale, only degradation was observed. An alternative literature procedure was to react **254** with silver(I) nitrate in a 5:1 mixture of DMF:CH_3COOH at 60 °C for 26 h.[111] Degradation of the reaction mixture was obtained using this procedure.



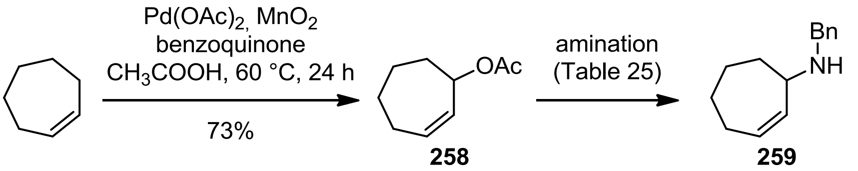
Scheme 112

Following Sandler's procedure, cyclopropane **254** was reacted with silver(I) nitrate in CH_3COOH in order to form acetate **257** (Scheme 113).[109] After refluxing the reaction mixture for 5 h, degradation was observed. Starting material was recovered when using sodium acetate in CH_3COOH.



Scheme 113

The synthetic strategy had to be rethought because of the problems encountered for the rearrangement of 6,6-dibromobicyclo[4.1.0]hexane **254**. Allylic acetate **258** was formed in 73% yield *via* a palladium-catalysed acetoxylation as described by Heumann and Åkermark in 1990 (Scheme 114).[112] Palladium-catalysed amination using benzylamine afforded allylic amine **259** in 12% yield after 72 h at rt (Table 25, entry 1).[113-114] Full conversion was not observed after 18 h at rt when the catalyst loading was increased to 20 mol%. However, when the reaction mixture was heated at 50 °C for 28 h, benzylamine **259** was obtained in 44% yield (entry 2). A similar yield was obtained after only 18 h in refluxing THF (entry 3).

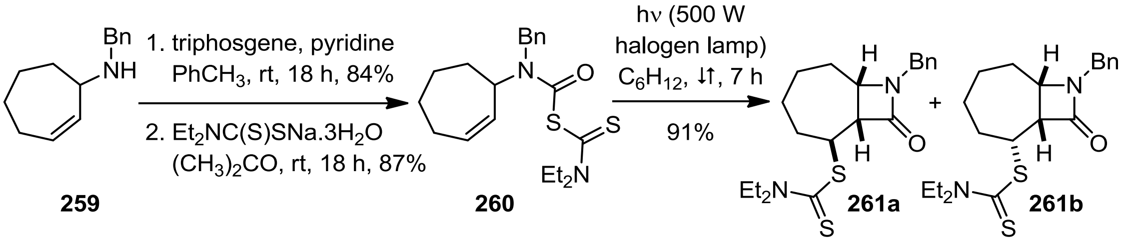


Scheme 114

Entry	Reagents in THF	T / time	Result
1	$Pd(OAc)_2$ (5 mol%), PPh_3 (25 mol%) $BnNH_2$ (1.2 eq)	rt / 72 h	**259** 12%
2	$Pd(OAc)_2$ (20 mol%), PPh_3 (1.0 eq) $BnNH_2$ (1.5 eq)	rt (18 h) then 50 °C (28 h)	**259** 44%
3	$Pd(OAc)_2$ (20 mol%), PPh_3 (1.0 eq) $BnNH_2$ (1.5 eq)	reflux / 18 h	**259** 46%

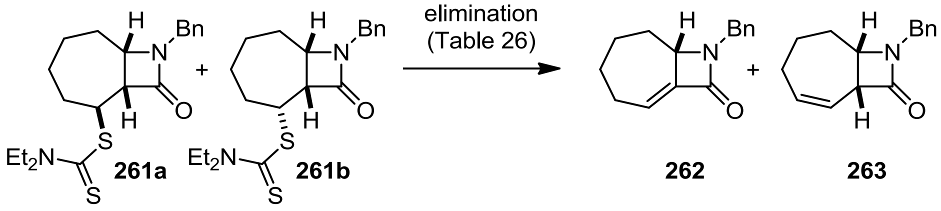
Table 25: Palladium-catalysed amination of 258

Dithiocarbamate **260** was isolated in 73% yield over 2 steps from benzylamine **259** (Scheme 115). Irradiation of **260** for 7 h with a 500 W halogen lamp gave an inseparable mixture of β-lactams **261a** and **261b**.



Scheme 115

Treatment of the mixture of isomers **261** with 1.1 eq of LHMDS and MeI gave a 1.6:1.0 inseparable mixture of starting material **261** and conjugated alkene **262** (Scheme 116 and Table 26, entry 1). Conversion was improved when 2.1 eq of reagents were used and the reaction mixture was warmed progressively to rt (entry 2). Suprisingly, non-conjugated alkene **263**, generally obtained with an excess of base and/or higher temperature, was not observed. Only degradation of the reaction mixture was recovered when 4.2 eq of LHMDS and MeI were utilised or when *n*BuLi was used as a base (entries 3 and 4).



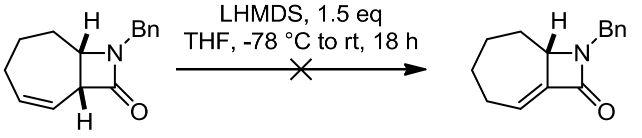
Scheme 116

Entry	Reagents	T / time	Result
1	MeI, LHMDS (1.1 eq), THF	-78 °C / 8 h	1.6:1.0 **261:262**
2	MeI, LHMDS (2.1 eq), THF	-78 °C to rt / 18 h	0.8:1.0 **261:262**
3	MeI, LHMDS (2 x 2.1 eq), THF	-78 °C to rt / 18 h	degradation
4	MeI, *n*BuLi (2 eq), THF	-78 °C / 3.5 h	degradation
5	Ph_2O	reflux / 1 h	1.9:7.9:1.0 **261:262:263**
6	Ph_2O	reflux / 3 h	1.0:0.65 **262:263** 84%

Table 26: Synthesis of alkene 262 via elimination of the dithiocarbamate group

Refluxing the mixture of isomers **261** in Ph_2O for 1 h afforded a complex mixture of starting material and alkenes (Table 26, entry 5). After 3 h, the elimination proceeded in 84% yield and gave a 1.0:0.65 mixture of isomers **262:263** which could be partially separated by column chromatography (entry 6).

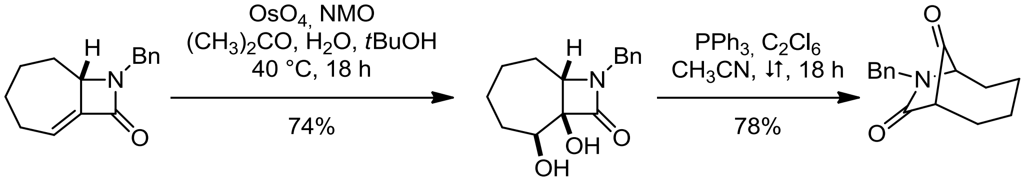
Isomerisation of the double bond into conjugation was attempted with 1.5 eq of LHMDS (Scheme 117). Only starting material was recovered after 18 h.



263 **262**

Scheme 117

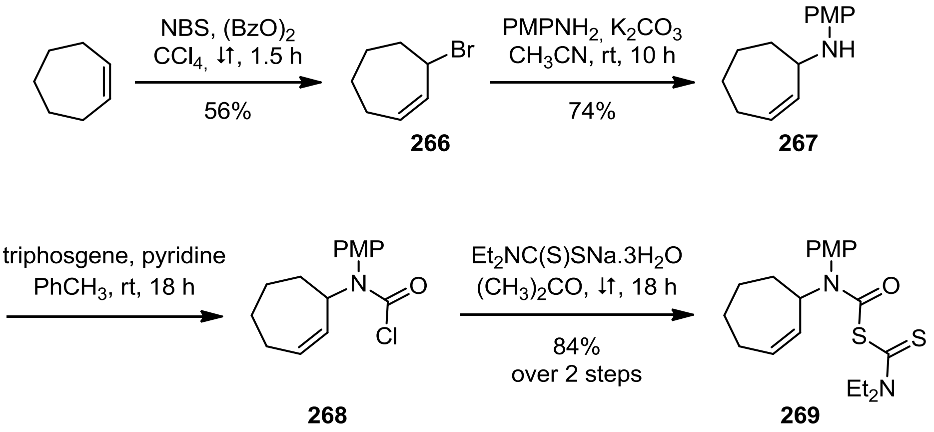
Dihydroxylation of conjugated alkene **262** afforded diol **264** in 74% yield as a single isomer (Scheme 118). Treatment of **264** with PPh_3 and C_2Cl_6 in refluxing CH_3CN gave **265**, the core structure of gelsedine, in 78% yield.



262 **264** **265**

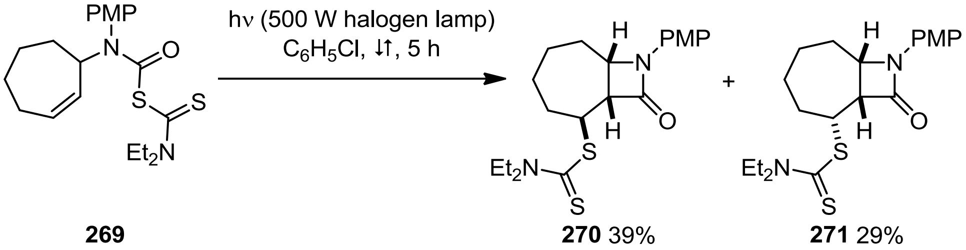
Scheme 118

In parallel to the work on the *N*-Bn, the reactivity of the *N*-PMP derivatives was investigated. Knowing there were some difficulties in the formation of benzylamine **259** (Scheme 114 and Table 25), it was decided to adopt a different approach (Scheme 119). Bromocycloheptene **266** was obtained in 56% yield when cycloheptene was reacted with NBS and benzoyl peroxide in refluxing CCl_4 for 1.5 h.[115] Alkylation with *para*-anisidine gave secondary amine **267** in 74% yield. Synthesis of carbamoyl chloride **268** and subsequent reaction with the commercially available dithiocarbamate salt in refluxing acetone formed **269** in 84% yield over 2 steps.

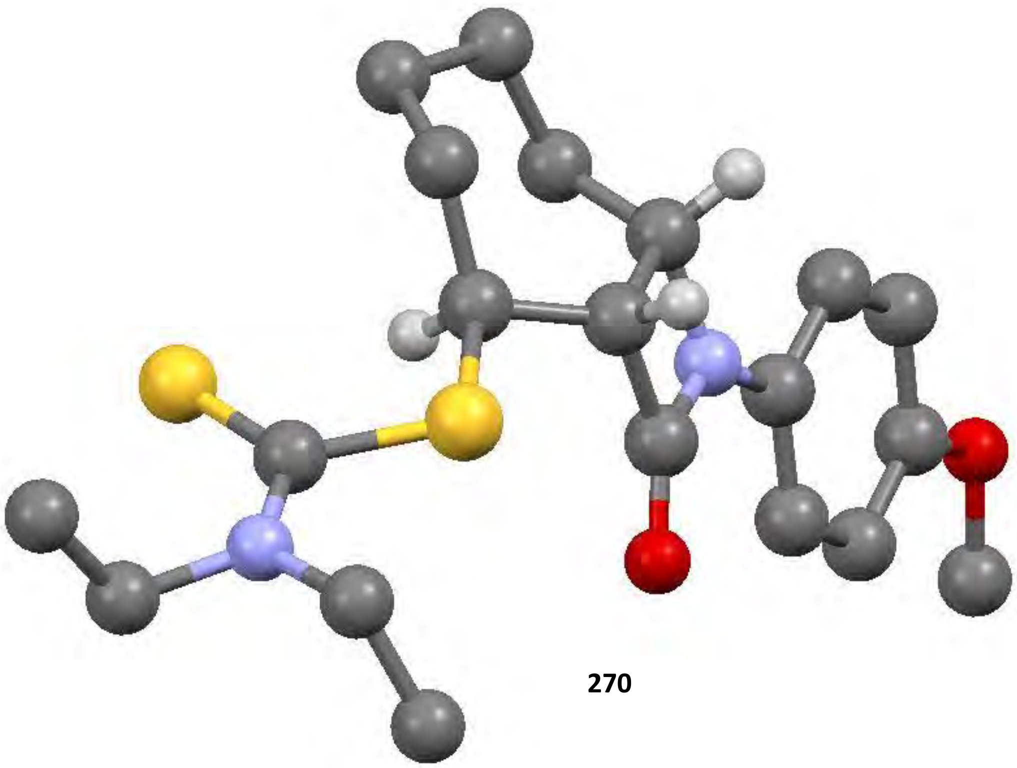


Scheme 119

Irradiation of dithiocarbamate **269** in chlorobenzene for 5 h with a 500 W halogen lamp gave *cis* β-lactam **270** in 39% yield and *trans* β-lactam **271** in 29% yield (Scheme 120). It was possible to separate both epimers by column chromatography and the relative stereochemistry was confirmed by X-ray crystallography of the *cis* isomer **270** (Figure 17).



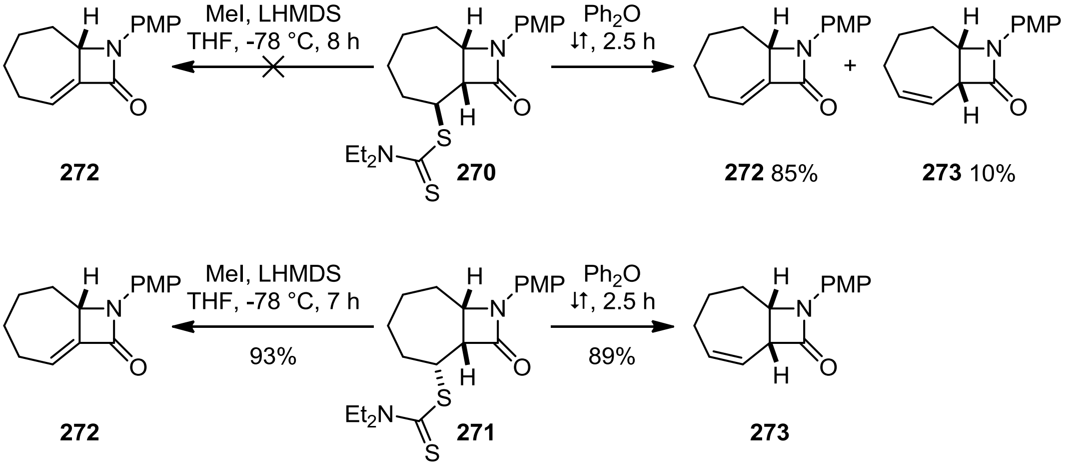
Scheme 120



270

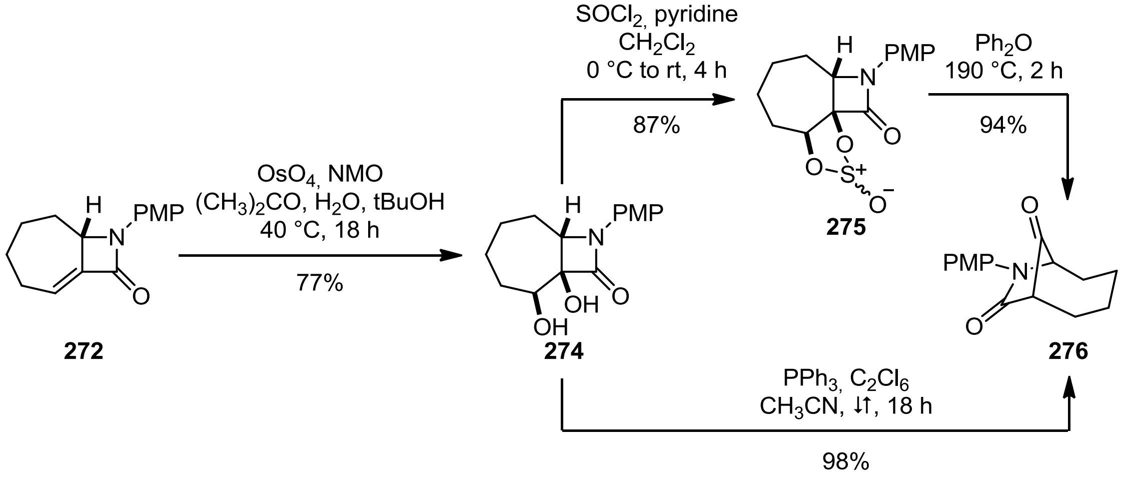
Figure 17

Interestingly, both epimers had different reactivities towards elimination of the dithiocarbamate group (Scheme 121). *Cis* β-lactam **270** did not react under basic conditions and conjugated alkene **272** was obtained in 85% isolated yield along with 10% of the non-conjugated isomer **273** after 2.5 h in refluxing Ph_2O. The formation of the conjugated isomer **272** from the thermal elimination of cycloheptane-fused β-lactam **270** stands in contrast to the thermal elimination of cyclohexane-fused systems which are always observed to give the non-conjugated alkene (Chapter 2). Presumably, the greater flexibility of the seven-membered ring means the conjugated alkene is no longer strained and represents the thermodynamic product. On the other hand, *trans* β-lactam **271** gave conjugated alkene **272** in 93% yield when MeI and LHMDS were used whereas thermal elimination afforded **273** in 89% yield after 2.5 h in refluxing Ph_2O. It was therefore possible to obtain conjugated alkene **272** from both *cis* isomer **270** and *trans* **271** using thermal or basic elimination respectively. Rationalisation of the elimination of the dithiocarbamate group will be discussed in Chapter four (Section 4.13).



Scheme 121

Diol **274** was obtained in 77% yield when conjugated alkene **272** was reacted with a sub-stoichiometric amount of OsO_4 and NMO as a co-oxidant (Scheme 122). The semipinacol rearrangement of **274** *via* cyclic phosphorane activation gave **276** in 98% yield. Treatment of diol **274** with pyridine and thionyl chloride in CH_2Cl_2 for 4 h formed cyclic sulfite **275** as a 1:1 mixture of diastereomers in 87% yield. Heating the mixture to 190 °C for 2 h in Ph_2O afforded **276**, the core structure of gelsedine, in 94% yield.

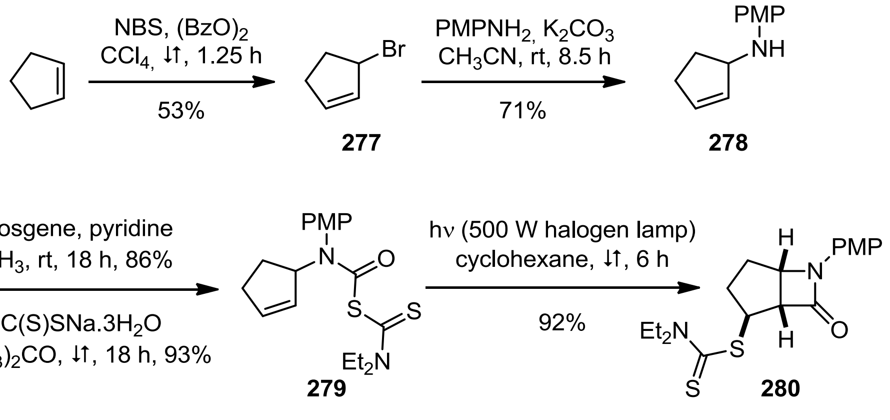


Scheme 122

In summary, it was possible to synthesize the core structure of gelsedine in seven steps starting from cycloheptene. Radical cyclisation-dithiocarbamate group transfer of cycloheptane-fused β-lactams **260** and **269** was not as stereoselective as for the cyclohexane-fused systems. Indeed, both *cis* and *trans* isomers were formed with *trans* β-lactams being the minor component. Fortunately, both *cis* and *trans* isomers could be converged to alkene **272** *via* elimination of the dithiocarbamate group under appropriate conditions.

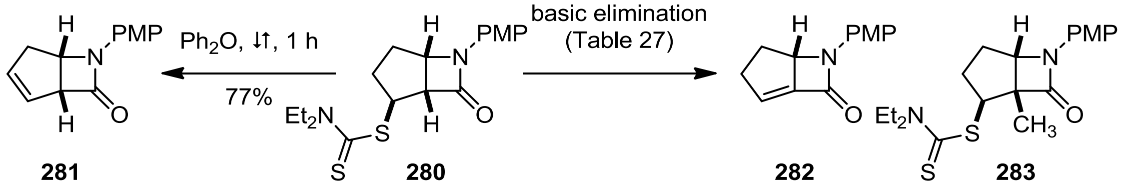
3.5 *Application to cyclopentane-fused β-lactam*

For the synthesis of the core structure of gelsedine, the semipinacol rearrangement of the fused 7-membered system was achieved in excellent yield. It was therefore decided to study the semipinacol rearrangement of a fused 5-membered β-lactam. Treatment of cyclopentene with NBS and a sub-stoichiometric amount of benzoyl peroxide in refluxing CCl_4 for 1.25 h afforded 3-bromocyclopentene **277** in 53% yield (Scheme 123).[115] The alkylation reaction using *para*-anisidine and K_2CO_3 proceeded in 71% yield. The substrate for the radical reaction **279** was formed in 80% yield over 2 steps and subsequent irradiation in cyclohexane for 6 h afforded β-lactam **280** in 92% yield as a single isomer.



Scheme 123

Thermal elimination of the dithiocarbamate group was attempted and alkene **281** was formed in 77% yield after 1 h in refluxing Ph_2O (Scheme 124). Elimination under basic conditions proved more problematic (Table 27). The starting material was recovered when **280** was treated with 1.1 eq of LHMDS and MeI, even when the reaction mixture was warmed to rt (entry 1). Some conversion was observed when 5 eq of reagents were used. Unfortunately, methylated β-lactam **283** was synthesized in 9% yield instead of conjugated alkene **282** (entry 2). The literature conditions reported in 1977 by Hayashi *et al.* were applied to **280** and the elimination did not occur (entry 3).[39]

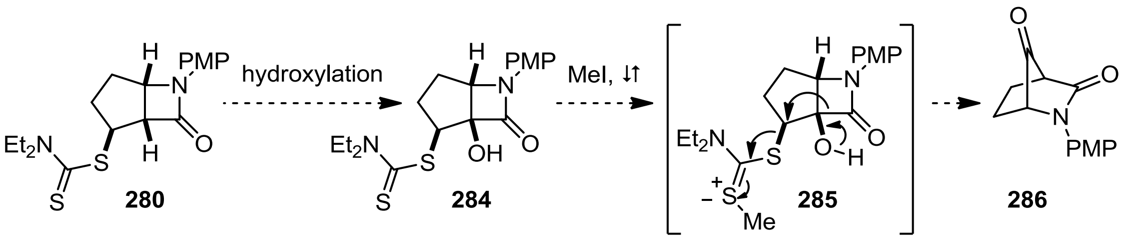


Scheme 124

Entry	Reagents	T / time	Result
1	MeI, LHMDS (1.1 eq), THF	-78 °C to rt / 7 h	**280**
2	MeI, LHMDS (5 eq), THF	-78 °C to rt / 7.5 h	**280** 49% **283** 9%
3	MeI, LiF, Li_2CO_3 (1.1 eq), DMF	rt to reflux / 18 h	**280**

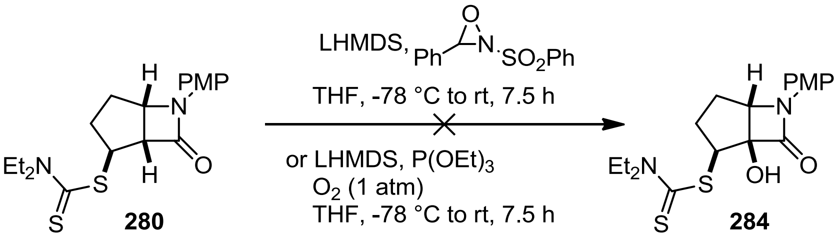
Table 27: Attempts to synthesize alkene 282 via elimination of the dithiocarbamate group

Direct elimination was impossible suggesting that alkene **282** was a very strained fused bicyclic system. An alternative would be to α-hydroxylate the β-lactam to form **284** and then to alkylate the dithiocarbamate moiety in order to make it a suitable leaving group which would allow formation of **286** *via* a semipinacol rearrangement (Scheme 125).



Scheme 125

Starting material was recovered when **280** was treated with 1.5 eq of LHMDS and the Davis oxaziridine (Scheme 126).[43] An alternative α-hydroxylation method developed in 1975 which uses a lithium base, molecular oxygen and triethylphosphite was also applied to β-lactam **280**.[40-41] Only starting material was observed during this reaction.

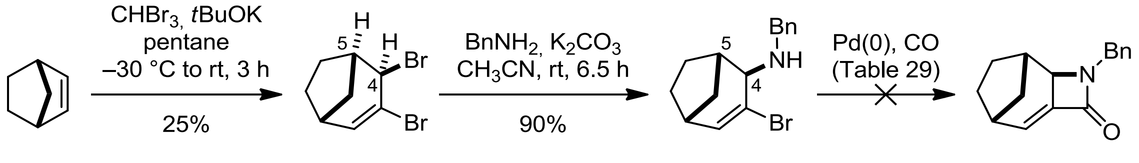


Scheme 126

In summary, the semipinacol rearrangement of the cyclopentane-fused β-lactam was not attempted because it was not possible to access a suitably functionalised β-lactam. Base-mediated elimination of the dithiocarbamate group on **280** proved impossible, suggesting that alkene **282** was a very strained bicyclic structure. Alternatively, the formation of α-hydroxylactam **284** was unsuccessful.

3.6 Semipinacol rearrangement of a norbornene derivative

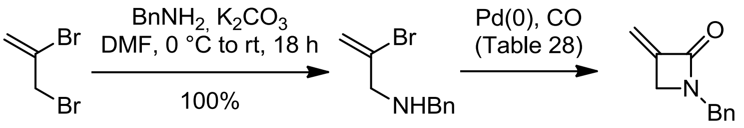
Norbornene is a bridged cyclic hydrocarbon which can be easily transformed thanks to its reactive double bond. In order to increase structural complexity, the semipinacol rearrangement of a norbornene derivative was investigated. Addition of dibromocarbene, formed *in situ* from bromoform and *t*BuOK, onto norbornene gave a dibromocyclopropane structure, which rearranged immediately to afford the known *exo*-3,4-dibromobicyclo[3.2.1]oct-2-ene **287** in 25% yield (Scheme 127).[116] According to Moser and co-workers, molecular models of the *endo* and *exo* isomers show that the dihedral angle between H-4 and H-5 should be around 44° and 78°, respectively.[117] Following the Karplus equation, these dihedral angles should give a coupling constant between 7-8 Hz with a 45° angle or 2-3 Hz with a 78° angle. Proton-NMR spectroscopic analysis showed H-4 as a doublet with a *J* value of 2.8 Hz, confirming that the *exo* isomer was formed. Attack from the more hindered *endo* face is also predicted to be less favourable. Subsequent treatment with benzylamine and K_2CO_3 in CH_3CN for 6.5 h at rt gave allylic amine **288** in 90% yield.[118] A similar coupling constant of 2.4 Hz was found between H-4 and H-5 indicating that the *exo* amine was formed. The initial strategy to synthesize β-lactam **289** was *via* a palladium-catalysed intramolecular carbonylative coupling as described by Mori and co-workers in 1985.[108]



287 **288** **289**

Scheme 127

Before applying the literature conditions to amine **288**, a representative example was repeated. Amine **291** was synthesized in quantitative yield by reacting commercially available 2,3-dibromopropene **290** with benzylamine and K_2CO_3 in DMF at rt.



290 **291** **292**

Scheme 128

Entry	Reagents under CO (1 atm)	T / time	Result
1	$Pd(OAc)_2$ (2 mol%), PPh_3 (8 mol%) *n*Bu_3N (1.2 eq), DMF	100 °C / 70 min	**292** 27%
2	$Pd(OAc)_2$ (2 mol%), PPh_3 (8 mol%) *n*Bu_3N (1.2 eq), DMF	100 °C / 2 h	**292** 30%
3	$Pd(OAc)_2$ (2 mol%), PPh_3 (8 mol%) *n*Bu_3N (1.2 eq), HMPA	100 °C / 5 h	**292** 34%
4	$Pd(OAc)_2$ (10 mol%), PPh_3 (40 mol%) *n*Bu_3N (2 eq), DMF	85 °C / 4.5 h	**292** 34%
5	$Pd(OAc)_2$ (10 mol%), PPh_3 (40 mol%) *n*Bu_3N (2 eq), HMPA	100 °C / 4.5 h	**292** 37%
6	$Pd(PPh_3)_4$ (10 mol%) *n*Bu_3N (2 eq), CH_3CN	65 °C / 2.5 h	**291**
7	$Pd(PPh_3)_4$ (10 mol%) Et_3N (2 eq), CH_3CN	65 °C / 2.5 h	**291**
8	$Pd(PPh_3)_4$ (10 mol%), PPh_3 (40 mol%) *n*Bu_3N	120 °C / 5 h	**292** 15%

Table 28: Synthesis of β-lactam 292 via palladium-catalysed carbonylation

The palladium-catalysed reaction was first run with 2 mol% of $Pd(PPh_3)_4$, formed *in situ* from $Pd(OAc)_2$ and PPh_3, and tributylamine in DMF for 70 min (Table 28, entry 1). β-Lactam **292** was formed in 27% yield. After 2 h at 100 °C, **292** was obtained in 30% yield and when the reaction was carried out in HMPA, 34% of **292** was isolated (entries 2 and 3). Increasing the catalyst loading to 10 mol% and the quantity of amine to 2 eq gave a slightly better yield of **292** in HMPA (37% vs. 34%) and in DMF (34% vs. 30%) (entries 4 and 5).

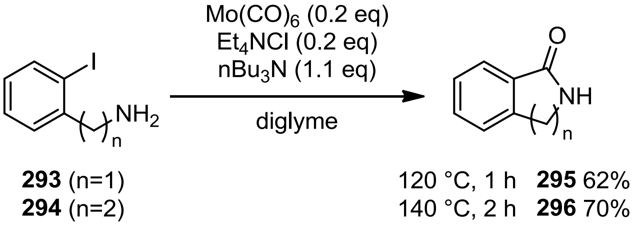
In 1990, Meyer and Crisp described the synthesis of α,β-unsaturated lactam **292** using freshly prepared $Pd(PPh_3)_4$, $n$$Bu_3N$ in CH_3CN at 65 °C and under CO (1 atm).[119-120] The literature procedure was applied to amine **291**, unfortunately the carbonylative coupling did not occur when using $n$$Bu_3N$ or Et_3N, as a non-toxic substitute (Table 28, entries 6 and 7). The final attempt to increase the yield for this reaction followed a procedure described by Guiry in the synthesis of lipoxin A_4 and B_4 analogues.[121] The reaction was carried out in $n$$Bu_3N$ at 120 °C for 5 h and β-lactam **292** was obtained in 15% yield (entry 8).

In parallel to the synthesis of β-lactam **292**, the same procedures were applied to amine **288** (Scheme 127 and Table 29). Treatment of amine **288** with freshly prepared $Pd(PPh_3)_4$ and Et_3N in DMF or DMPU at 100 °C did not give any of the desired product **289** (entries 1 and 2). The combination of palladium-tetrakis(triphenylphosphine) and $n$$Bu_3N$ as the solvent afforded only degradation of the reaction mixture (entry 3). The same behaviour was observed when the active catalyst was formed *in situ* and using DMF as the solvent (entry 4).

Entry	Reagents under CO (1 atm)	T / time	Result
1	$Pd(PPh_3)_4$ (5 mol%), PPh_3 (10 mol%) Et_3N (1.2 eq), DMF	100 °C / 6 h	**288**
2	$Pd(PPh_3)_4$ (5 mol%), PPh_3 (10 mol%) Et_3N (1.2 eq), DMPU	100 °C / 6 h	**288**
3	$Pd(PPh_3)_4$ (10 mol%), PPh_3 (40 mol%) *n*Bu_3N	120°C / 7.5 h	degradation
4	$Pd(OAc)_2$ (10 mol%), PPh_3 (40 mol%) *n*Bu_3N (2 eq), DMF	100°C / 2 h	degradation

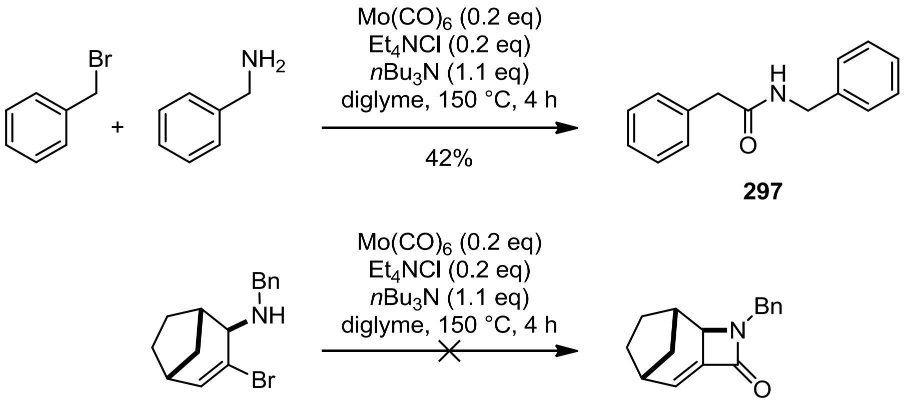
Table 29: Attempts to synthesize fused β-lactam 289 via palladium-catalysed carbonylation

An alternative to palladium catalysis was explored. In 2010, Yamane described the carbamoylation of aryl halides using molybdenum hexacarbonyl $Mo(CO)_6$, TEAC and *n*Bu_3N in diglyme at 150 °C.[122] The formation of γ- and δ-lactams **295** and **296** in moderate yield *via* an intramolecular aminocarbamoylation was also presented (Scheme 129).



Scheme 129

Before applying the literature conditions to amine **288**, the catalysis was repeated using readily available materials. Amide **297** was synthesized in 42% yield (lit. yield 52%) proving the ability to carry out the reaction (Scheme 130). Unfortunately, when the same conditions were applied to benzylamine **288**, the starting material was recovered after 4 h at 150 °C.

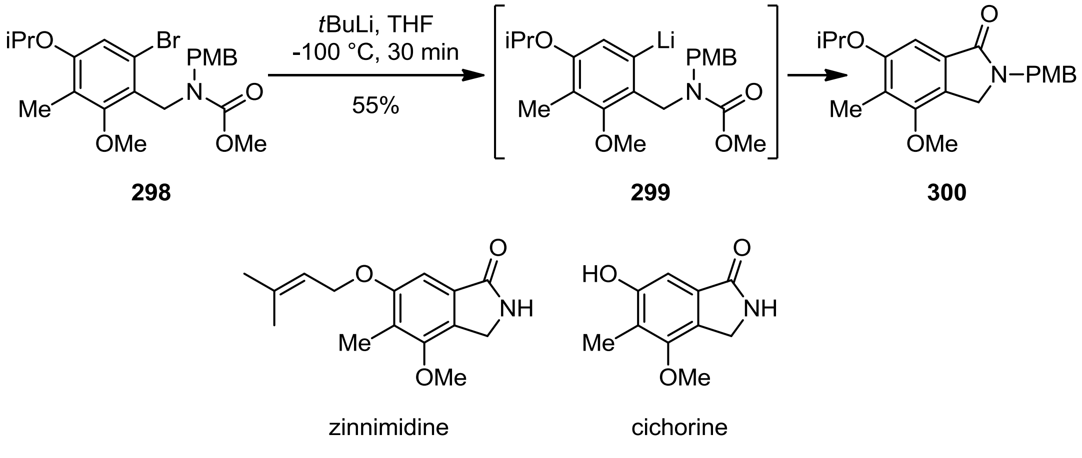


297

288 **289**

Scheme 130

An alternative route was considered for the synthesis of β-lactam **289**. In 2005, Couture and co-workers published the total syntheses of phytotoxins zinnimidine and cichorine (Scheme 131).[123] Formation of γ-lactam **300** was achieved in 55% yield by treatment of **298** in THF at -100 °C with *t*BuLi. The lithiated intermediate **299** formed could react with the carbamate functional group which acted as an internal electrophile. Further work on this cyclisation reaction showed that it was possible to use *n*BuLi on its own or in combination with TMEDA instead of *t*BuLi.[124-125]



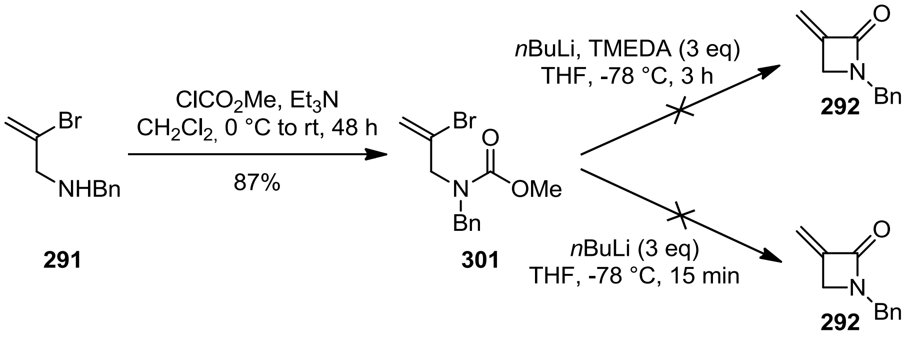
298 **299** **300**

zinnimidine cichorine

Scheme 131

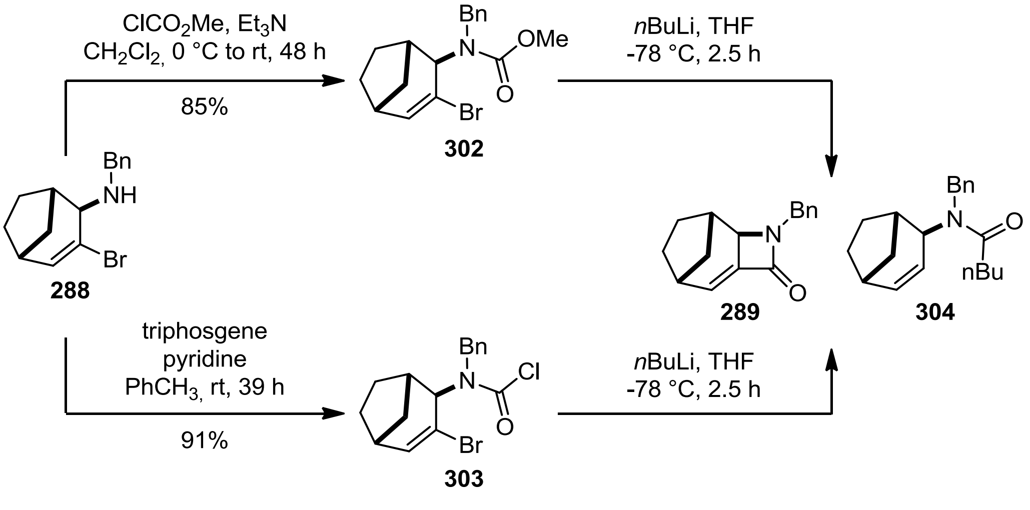
This chemistry was first applied to the synthesis of known β-lactam **292** (Scheme 132). Carbamate **301** was formed in 87% yield using an excess of methylchloroformate and Et_3N in CH_2Cl_2. Degradation was observed when **301** in THF at -78 °C was treated with *n*BuLi and

TMEDA and a complex mixture was obtained after 15 min at -78 °C when *n*BuLi was used on its own.



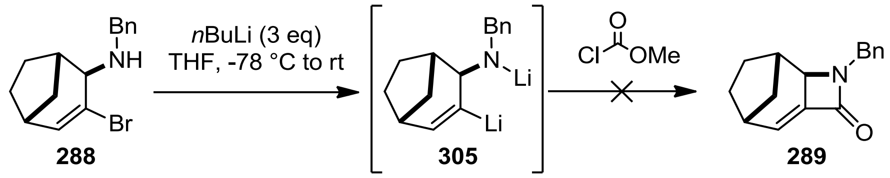
Scheme 132

Carbamate **302** was obtained in 85% yield using an excess of methyl chloroformate and Et$_3$N in CH$_2$Cl$_2$ (Scheme 133). Cyclisation to form β-lactam **289** did not occur when **302** was treated with 3 eq of *n*BuLi in THF at -78 °C. Amide **304** was obtained instead. Carbamoyl chloride could facilitate the reaction as chloride is a better leaving group. Treatment of amine **288** with triphosgene and pyridine in toluene gave **303** in 91% yield. Unfortunately, **304** was formed in 25% yield along with some degradation when **303** was treated with *n*BuLi in THF at -78 °C.



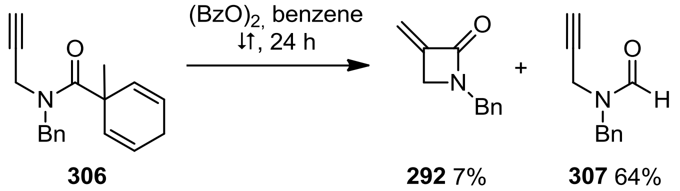
Scheme 133

Treatment of **288** in THF at -78 °C with an excess of *n*BuLi should in theory form doubly lithiated intermediate **305** (Scheme 134). Subsequent addition of methylchloroformate could afford **289**. However, degradation of the reaction mixture was observed.



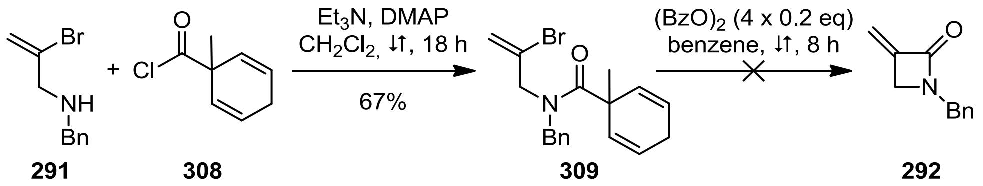
Scheme 134

An alternative to a cyclisation *via* lithiated intermediates would be to use radicals. Walton and co-workers described the synthesis of β-lactam **292** in 7% yield *via* a 4-*exo dig* cyclisation of amide **306** (Scheme 135).[126] Formamide **307** was the major product obtained.



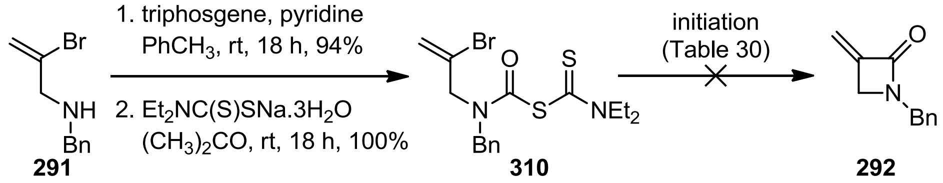
Scheme 135

Similarly, formation of β-lactam **292** from amide **309** *via* 4-*exo trig* radical cyclisation and subsequent β-elimination of bromine radical could be considered (Scheme 136).[127] Treatment of benzylamine **291** with acyl chloride **308**, Et_3N and a sub-stoichimetric amount of DMAP in CH_2Cl_2 gave amide **309** in 67% yield. Treatment of **309** with portionwise addition of $(BzO)_2$ in refluxing benzene only afforded degradation of the reaction mixture.



Scheme 136

An alternative substrate for the radical reaction could be dithiocarbamate **310**, which was synthesized in 94% overall yield from amine **291** (Scheme 137). Degradation was obtained *via* chemically- or light-induced radical initiation (Table 30).

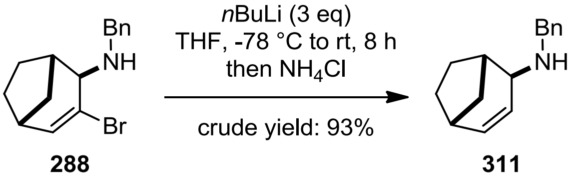


Scheme 137

Entry	Reagents	T / time	Result
1	DLP (7 x 0.2 eq), cyclohexane	reflux / 4.25 h	degradation
2	hν, cyclohexane	reflux / 7 h	degradation
3	hν, chlorobenzene	reflux / 7 h	degradation

Table 30: Attempts to synthesize β-lactam 292 via radical cyclisation

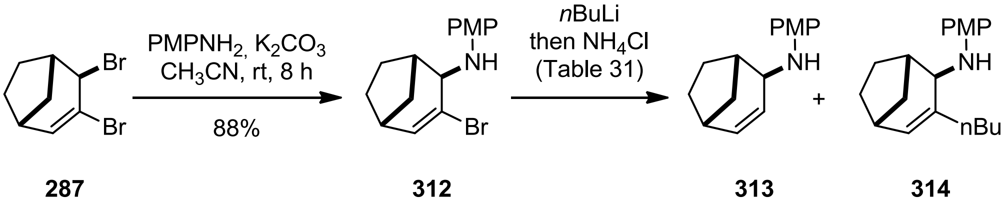
Another approach to the study of the semipinacol rearrangement of norbornene derivatives would be with the synthesis of β-lactam **289** *via* the radical cyclisation-dithiocarbamate group transfer methodology developed. Full conversion to amine **311** was observed when vinyl bromide **288** in THF was treated with *n*BuLi. Unfortunately, purification of this secondary amine proved difficult (Scheme 138).



Scheme 138

This alternative strategy was applied to the *N*-PMP derivatives which were generally easier to purify (Scheme 139). Treatment of 3,4-dibromobicyclo[3.2.1]oct-2-ene **287** with *para*-anisidine and K_2CO_3 in CH_3CN gave bromo amine **312** in 88% yield. As for allylic amine **288**, a small coupling constant of 2.0 Hz was found between H-4 and H-5 suggesting that the *exo* amine was formed.[117] No conversion was observed when amine **312** was treated with *n*BuLi in THF at -78 °C. Warming the reaction mixture to rt afforded allylamine **313** in 49% yield along with 18% of tertiary alkene **314** (Table 31, entry 1). When the reaction was carried out at 0 °C for 1 h, a

1.0:1.0:0.7 complex mixture of **312:313:314** was obtained (entry 2). The yield was improved to 88% of **313** when *n*BuLi was added at -78 °C and the reaction mixture was allowed to progressively warm to 10 °C over 4.5 h (entry 3).

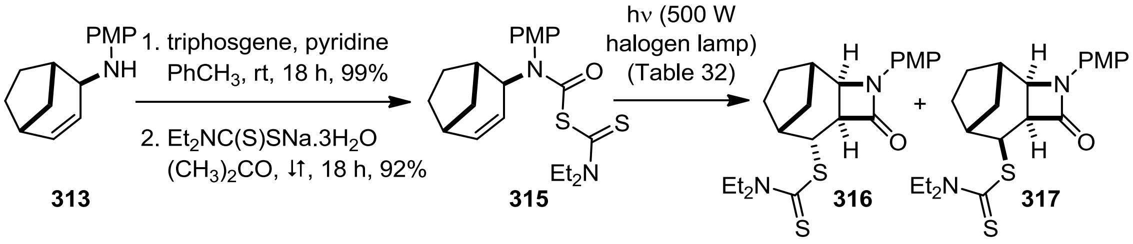


Scheme 139

Entry	Reagents	T / time	Result
1	*n*BuLi (3 eq), THF	-78 °C (1 h) then rt (3 h)	**313** 49% **314** 18%
2	*n*BuLi (3 eq), THF	0 °C / 1 h	1.0:1.0:0.7 **312:313:314**
3	*n*BuLi (3 eq), THF	-78 °C to 10 °C / 4.5 h	**313** 88%

Table 31: Formation of allylic amine 313 via debromination of 312

Dithiocarbamate **315** was obtained in an overall 91% yield from amine **313** in 2 steps (Scheme 140). Irradiation of **315** in cyclohexane with a 500 W halogen lamp for 3.5 h gave **316** in 65% yield and **317** in 16% yield (Table 32, entry 1). A similar overall yield, but with a greater amount of **317** formed, was observed when the radical cyclisation reaction was carried out in chlorobenzene (entry 2). It was possible to conduct the irradiation at rt using a flask which was enclosed in a water jacket. No conversion was observed when cyclohexane or isopropanol were used at rt because dithiocarbamate **315** was not soluble in these solvents at this temperature (entries 3 and 4). When 1,2-DCE was used, the substrate was soluble but only degradation was observed after irradiating the reaction mixture for 3.5 h at rt (entry 5). The relative stereochemistry of each isomer was originally unknown. Assignment was made after further functional group transformation and X-ray crystallography of a subsequent intermediate.

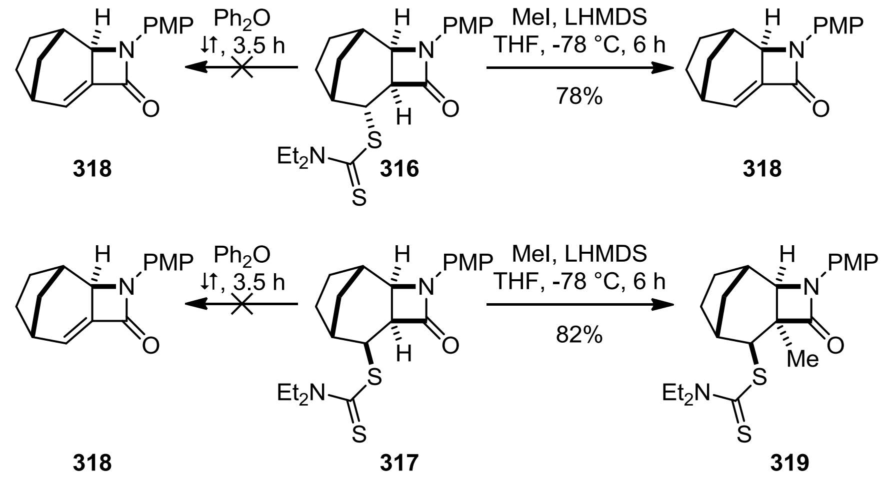


Scheme 140

Entry	Solvents	T / time	Result
1	hν, cyclohexane	reflux / 3.5 h	**316** 65% **317** 16%
2	hν, chlorobenzene	reflux / 4.5 h	**316** 62% **317** 20%
3	hν, cyclohexane	rt / 4 h	**315**
4	hν, *i*PrOH	rt / 3 h	**315**
5	hν, 1,2-DCE	rt / 3.5 h	degradation

Table 32: Radical cyclisation-dithiocarbamate group transfer of 315

Thermal elimination of the dithiocarbamate functional group *via* a Chugaëv-like reaction did not proceed for either isomer (Scheme 141). After 3.5 h in refluxing Ph_2O, degradation was obtained with **316** whereas the starting material was recovered with **317**. These results were unsurprising given the mechanism for the Chugaëv elimination *via* a *syn*-elimination with a 6-membered cyclic transition state. Elimination under basic conditions gave alkene **318** as a single isomer in 78% yield when β-lactam **316** was reacted with 1.5 eq of LHMDS and MeI in THF at -78 °C for 6 h. Applying the same reaction conditions to *trans* isomer **317** gave methylated β-lactam **319** in 82% yield whose structure was confirmed by X-ray crystallography (Figure 18). This structure also defines the relative stereochemistry for β-lactams **316** and **317**. Rationalisation of the elimination of the dithiocarbamate group will be discussed in Chapter four (Section 4.13).



Scheme 141

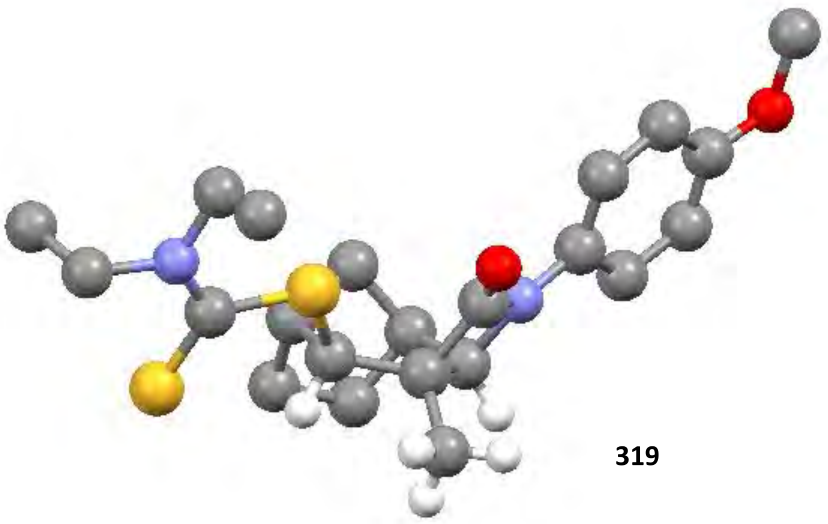
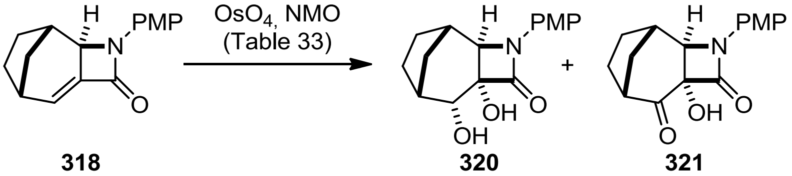


Figure 18

Alkene **318** was treated with a sub-stoichiometric amount of OsO_4 and 2.4 eq of NMO in a mixture of H_2O, acetone and *t*BuOH for 18 h at 40 °C (Scheme 142 and Table 33, entry 1). Diol **320** was formed in 93% yield as a single diastereomer but it was contaminated with 14% of α-hydroxyketone **321**. The stereochemistry of **320** and **321** was assigned on the basis that *syn*-dihydroxylation from the opposite face would give a highly strained β-lactam. The two products **320** and **321** were not separable by column chromatography. In 1989, the kinetics of the OsO_4-catalysed dihydroxylation of cyclohexene and α-pinene were studied by Matteson and Erdik.[128] The results showed that the over-oxidation pathway was disfavoured when pyridine was added or when a greater ratio of co-oxidant was used. Treatment of **318** with 5 eq of NMO rather than 2.4 eq gave an inseparable mixture of diol and ketone in a similar ratio as before (entry 2). Addition of pyridine gave diol **320** as the sole product but only in 12% yield (entry 3).



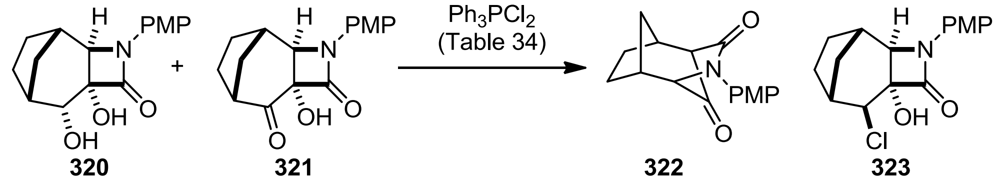
Scheme 142

Entry	Reagents	T / time	Result
1	OsO_4 (cat.), NMO (2.4 eq) $(CH_3)_2CO$, H_2O, *t*BuOH	40 °C / 18 h	**320:321** 93%
2	OsO_4 (cat.), NMO (5 eq) $(CH_3)_2CO$, H_2O, *t*BuOH	40 °C / 18 h	**320:321** 87%
3	OsO_4 (cat.), NMO (2.4 eq) pyridine (10 eq) $(CH_3)_2CO$, H_2O, *t*BuOH	40 °C / 18 h	**320** 12%

Table 33: Dihydroxylation of alkene 318

Full conversion was not observed when diol **320** contaminated by α-hydroxyketone **321** was treated with Ph_3PCl_2, formed *in situ* from a 1:1 mixture of PPh_3 and C_2Cl_6, in refluxing CH_3CN (Scheme 143 and Table 34, entry 1). After 18 h at 40 °C, the starting material was recovered in 38% yield along with 30% of halohydrin **323**. Benzonitrile, a higher-boiling solvent compared to CH_3CN, was then used (entry 2). Complete conversion and formation of **323** as the sole product were observed by tlc analysis. However, isolation from benzonitrile was not possible. Further attempts to effect the semipinacol rearrangement were carried out using microwave irradiation to heat the reaction mixture because they allow higher temperature than the set boiling point of the solvent. After 2 h at 120 °C, no more starting material was observed and **323** was isolated in 17% yield (entry 3). Formation of **323** increased after 5 h at 120 °C or 3 h at

150 °C (entries 4 and 5). However, tricyclic ketone **322** was never produced *via* the semipinacol rearrangement of diol **320** using cyclic phosphorane activation.

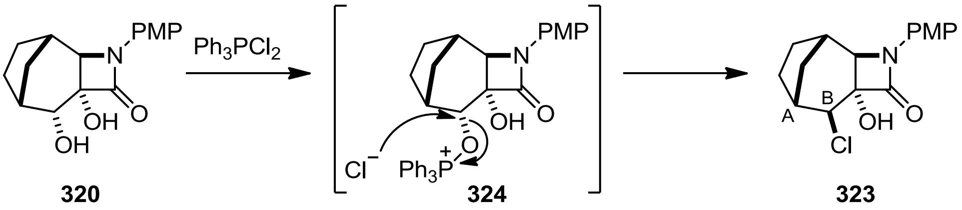


Scheme 143

Entry	Reagents	T / time	Result
1	PPh$_3$, C$_2$Cl$_6$ (1.5 eq) CH$_3$CN	reflux / 18 h	**320:321** 38% **323** 30%
2	PPh$_3$, C$_2$Cl$_6$ (1.5 eq) PhCN	reflux / 18 h	**323**
3	PPh$_3$, C$_2$Cl$_6$ (1.5 eq) CH$_3$CN	120 °C (µw) / 2 h	**323** 17%
4	PPh$_3$, C$_2$Cl$_6$ (1.5 eq) CH$_3$CN	120 °C (µw) / 5 h	**323** 24%
5	PPh$_3$, C$_2$Cl$_6$ (1.5 eq) CH$_3$CN	150 °C (µw) / 3 h	**323** 23%

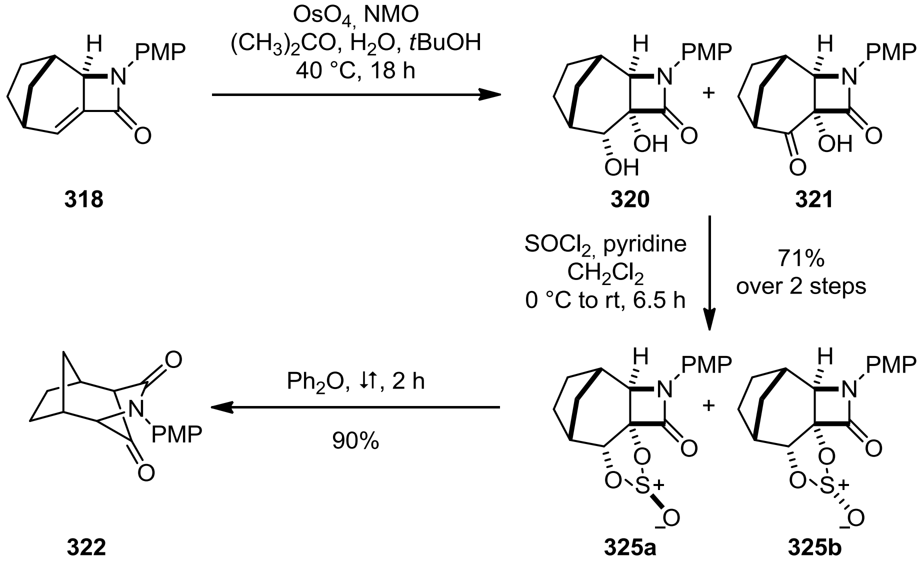
Table 34: Attempts to form 322 via a semipinacol rearrangement using cyclic phosphoranes

In 1972, Applequist described the formation of a halohydrin with retention of configuration from a *trans* diol (Scheme 13, Section 1.4).[18] Formation of an epoxide intermediate would afford retention of the stereochemistry. However, it is unlikely that *cis* diol **320** would form a highly strained *trans* epoxide on an already strained ring system. Inversion of the configuration *via* a S$_N$2 displacement is therefore more likely (Scheme 144). In addition, the 1H-NMR spectrum of halohydrin **323** shows that the proton adjacent to the chlorine appears as a singlet at 4.64 ppm suggesting that the dihedral angle between H-A and H-B is around 90°. This would be consistent with the molecular model of **323**.



Scheme 144

The synthesis of the cyclic sulfites **325a** and **325b** in a 1:1 ratio allowed the separation of α-hydroxyketone **321**. The overall yield for this transformation was 71% from alkene **318** (Scheme 145). No conversion was observed when **325** was heated in Ph_2O at 190 °C for 3 h or at 220 °C for 1 h. However after only 2 h in refluxing Ph_2O, the semipinacol rearrangement of **325** was complete and tricyclic ketone **322** was obtained in 90% yield.



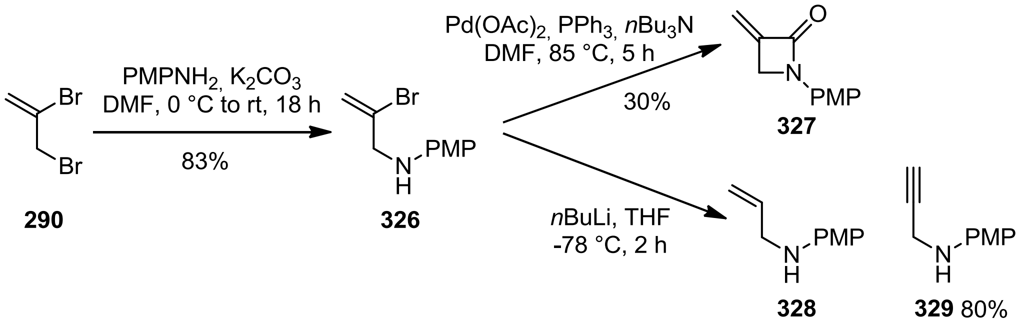
Scheme 145

In summary, tricyclic ketone **322** was synthesized in nine steps and 23% overall yield from known dibromooctene **287**. Attempts to form *N*-Bn alkene **289** *via* a palladium-catalysed intramolecular carbonylative coupling or various lithiation and radical cyclisations were unsuccessful. Alternatively, *N*-PMP alkene **318** was formed by basic elimination of the dithiocarbamate functional group of β-lactam **316**. Further transformation afforded a 1:1 mixture of cyclic sulfites **325** which rearranged in refluxing Ph_2O. However semipinacol rearrangement *via* cyclic phosphorane activation of diol **320** did not occur.

3.7 *Application of the methodology to a non-fused β-lactam*

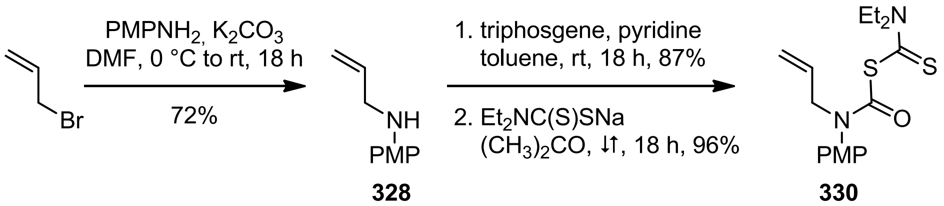
The semipinacol rearrangement of fused 6- or 7-membered ring β-lactams has been described. The investigation of a non-fused system was then considered. Indeed, this should indicate if the ring-fusion favours the alignment between the leaving and migrating group and/or if the release of the ring strain in the fused system plays a role.

The first approach chosen was to synthesize alkene **327** *via* the palladium-catalysed intramolecular carbonylative coupling as previously described by Mori (Scheme 146).[108] Allylic amine **326** was synthesized in 83% yield by reacting commercially available 2,3-dibromopropene with *para*-anisidine and K_2CO_3 in DMF. Unfortunately, the synthesis of β-lactam **327** proceeded in only 30% yield using 10 mol% $Pd(PPh_3)_4$ formed *in situ* in combination with *n*Bu_3N in DMF at 85 °C. In order to use **326** which was synthesized in gramme quantities, the debromination was attempted *via* lithium-halogen exchange. However, alkyne **329** was obtained in 80% yield instead of alkene **328**. A similar transformation has been observed by Barluenga *et al.*, and is proposed to occur through decomposition of the deprotonated amine by elimination of hydrogen bromide.[129]



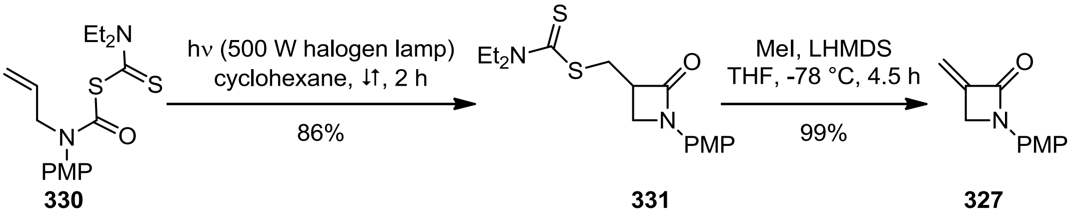
Scheme 146

Alkene **328** was alternatively formed in 72% yield by alkylation of allylbromide with *para*-anisidine and K_2CO_3 in DMF at 80 °C for 8 h (Scheme 147). Dithiocarbamate **330** was obtained in 84% over two steps.



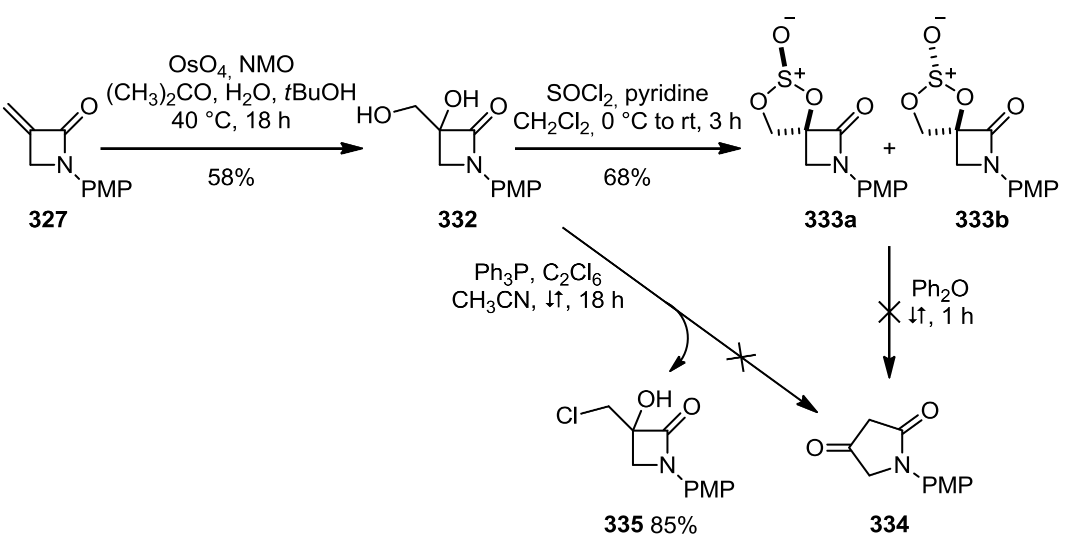
Scheme 147

Irradiation of dithiocarbamate **330** in cyclohexane with a 500 W halogen lamp for 2 h gave β-lactam **331** in 86% yield (Scheme 148). Low-temperature elimination of the dithiocarbamate group proceeded in 99% yield using 1.5 eq of MeI and LHMDS in THF for 4.5 h. Overall, alkene **326** was formed in 58% yield over 5 steps from commercially available allyl bromide.



Scheme 148

Diol **332** was obtained in 58% yield using a sub-stoichiometric amount of OsO_4 and NMO as a co-oxidant (Scheme 149). Cyclic sulfites **333a** and **333b** were formed in 30% yield and 38% yield respectively using thionyl chloride and pyridine in CH_2Cl_2. Only starting material was observed when **333** was heated at 190 °C for 2.5 h in Ph_2O. Refluxing the reaction mixture for 1 h afforded degradation suggesting that the semipinacol rearrangement of cyclic sulfites **333** might be occurring but that the product formed **334** was probably unstable at this high temperature. Treatment of diol **332** with Ph_3PCl_2 in refluxing CH_3CN gave 85% of halohydrin **335**. Inspection of a molecular model suggested that the alignment of the leaving group and the migrating group was not optimal. In addition, S_N2 attack on the primary carbon of the cyclic phosphorane is expected to be more favourable than attack on the secondary carbon of the fused systems. Hence, this alternative reaction pathway dominates.

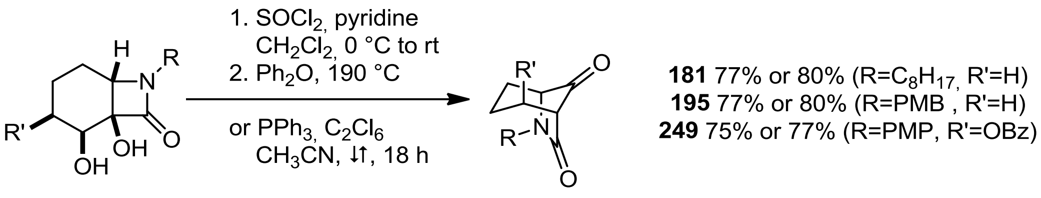


Scheme 149

In summary, the precursor for the semipinacol rearrangement, diol **332**, was obtained in 30% yield from allyl bromide **290** *via* six straightforward transformations. However, activation *via* a cyclic phosphorane or cyclic sulfite did not afford the desired β-ketolactam **334**.

3.8 Conclusions

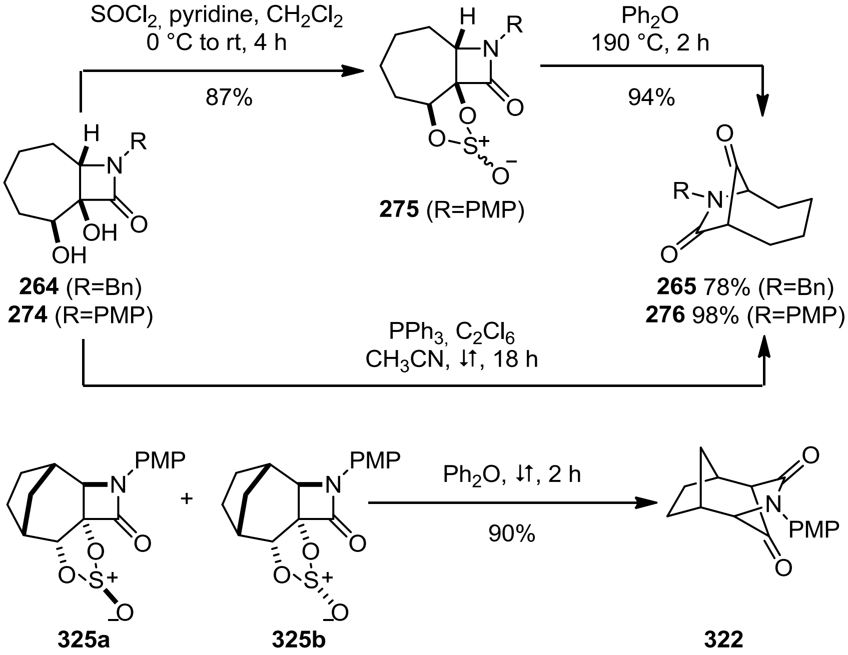
The scope of the semipinacol rearrangement of *cis*-fused β-lactams developed in Chapter one has been extended. Indeed, bicyclic diols **181** and **195** were efficiently formed *via* formation of cyclic sulfites or *in situ* rearrangement of cyclic phosphoranes (Scheme 150). It was also possible to incorporate a protected alcohol on the cyclohexane moiety and therefore to synthesize benzoate-protected bicyclic ketone **249**.



Scheme 150

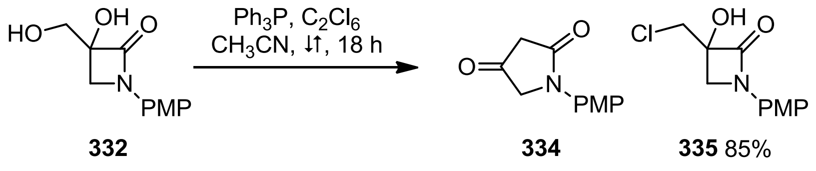
However, access to the precursor for the semipinacol rearrangement in good yield proved impossible for *N*-Ts and *N*-*i*Pr derivatives. The same issue was faced when starting from isophorone **199** and isophorol **212**.

The methodology was also applied to different ring sizes (Scheme 151). The core structure of gelsedine **265/276** was formed in excellent yield *via* activation with either cyclic phosphorane or cyclic sulfite intermediates. The complex tricyclic structure **322** was also synthesized *via* the semipinacol rearrangement of cyclic sulfites **325a** and **325b**. However, the semipinacol rearrangement of fused-cyclopentane β-lactam could not be attempted because the synthesis of alkene **282** and α-hydroxylactam **284** were unsuccessful.



Scheme 151

Non-fused β-lactam **332** did not afford β-ketolactam **334** (Scheme 152). Halohydrin **335** was instead synthesized in 85% yield suggesting that a better antiperiplanar alignment was obtained in the fused structures or that the competing S_N2 pathway was not occurring because of increased steric hindrance.



Scheme 152

Chapter four:

Studies towards the synthesis of peduncularine

4.1 Peduncularine: background and significance

Peduncularine was first isolated from the small Tasmanian tree *Aristotelia peduncularis* in 1971 by Bick and co-workers (Figure 19).[35] They reported the first structure elucidation of this natural product in the same year and corrected their structural analysis in 1992 after the first total synthesis by Speckamp *et al*. was reported.[70,130]

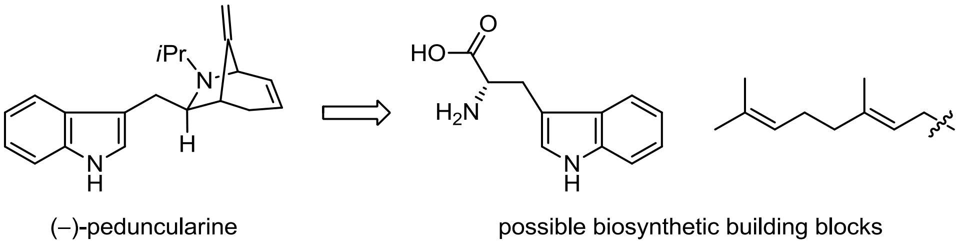


Figure 19

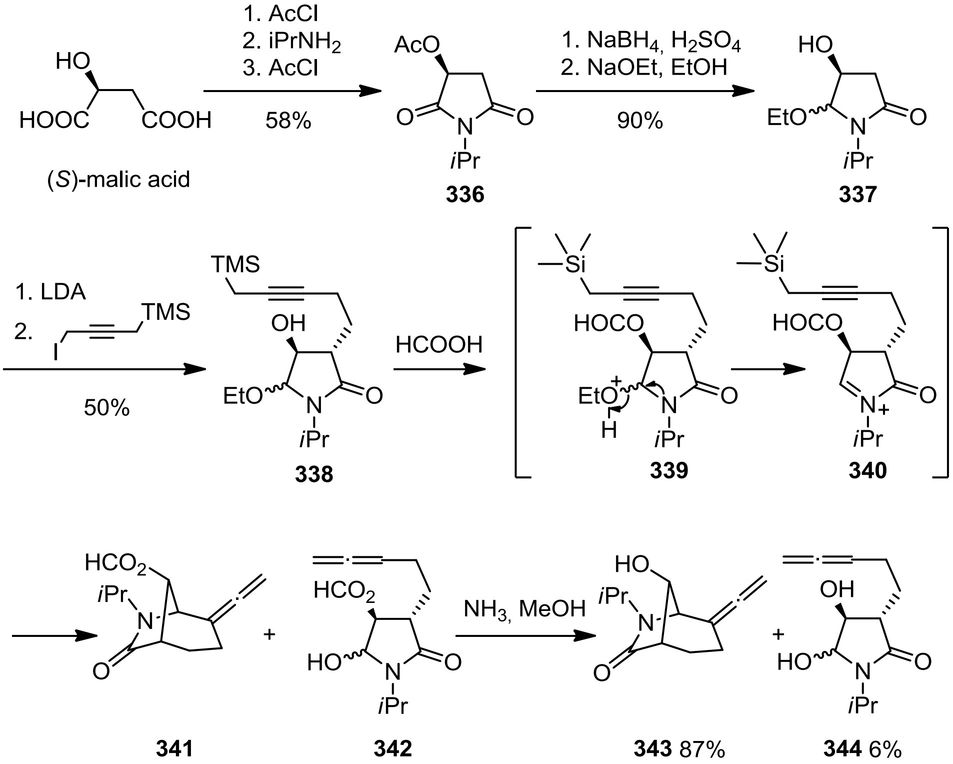
This natural product is the main alkaloid found in different species from the genus *Aristotelia*. It has been isolated as the free amine or as the hydrochloride salt in the form of a crystalline solid. It is made up of a synthetically challenging 6-azabicyclo[3.2.1]oct-3-ene ring system with a 3-indolyl methyl substituent. The biosynthesis of this molecule is thought to be derived from tryptophan and a non-rearranged geranyl subunit as building blocks.

Tribes from the southern hemisphere have been using plants of the genus *Aristotelia* for their medicinal properties. It has also been reported in 1985 that peduncularine displays some biological activity against breast cancer cell lines.[131]

4.2 Speckamp's total synthesis of (–)-peduncularine

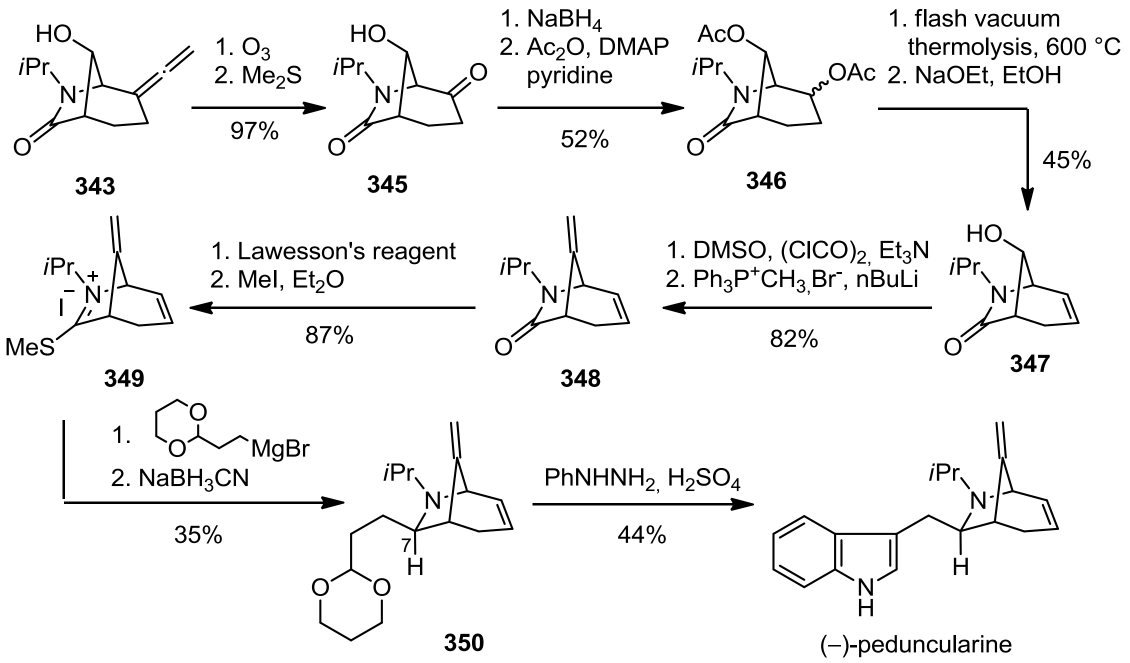
The first total synthesis of (–)-peduncularine was reported in 1989 by Speckamp *et al.*[70] Reaction of inexpensive (*S*)-malic acid with acetyl chloride followed by isopropylamine and acetyl chloride gave enantiomerically pure imide **336** in 68% yield over three steps (Scheme 153). Lactam **337** was obtained *via* regioselective reduction using $NaBH_4$ followed by ethanolysis of the acetate functional group. Low-temperature alkylation of lactam **337** with 5-iodo-1-(trimethylsilyl)-2-pentyne was achieved with good stereoselectivity in 50% yield.

Treatment of lactam **338** with formic acid protonated the ethoxy group which was eliminated with concomitant formation of *N*-acyliminium ion **340** which can undergo an intramolecular reaction with the propargyl silane. Treatment of a mixture of **341** and **342** with methanolic ammonia formed the core structure **343** of peduncularine in an excellent 87% yield along with a small amount of allene **344**.



Scheme 153

Ozonolysis gave ketone **345** which was then reduced and the resulting alcohol was protected to give diacetate **346** (Scheme 154). This lactam was subjected to flash vacuum thermolysis at 600 °C followed by ethanolysis to give alcohol **347** in 45% yield. Swern oxidation of the alcohol followed by Wittig olefination gave alkene **348**, a key intermediate in the synthesis of peduncularine. The final steps in the synthesis involved formation of the corresponding thiolactam and alkylation with methyl iodide to give the iminium salt **349**. Grignard addition followed by reduction with $NaBH_3CN$ gave **350** in a modest 35% yield (42% of the C-7 isomer was also formed). Finally, Fischer-indole synthesis using phenylhydrazine gave (–)-peduncularine in 19 steps and 0.7% overall yield.

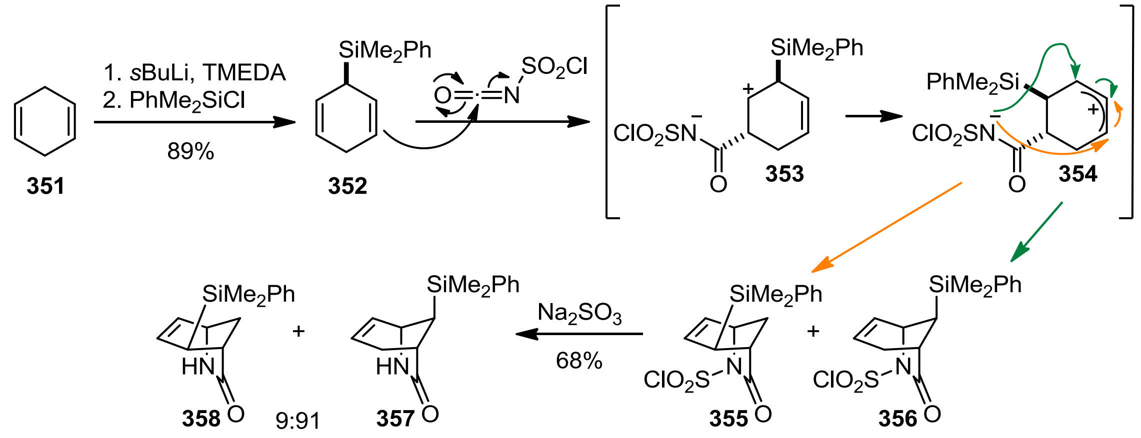


Scheme 154

4.3 *Woerpel's total synthesis of peduncularine*

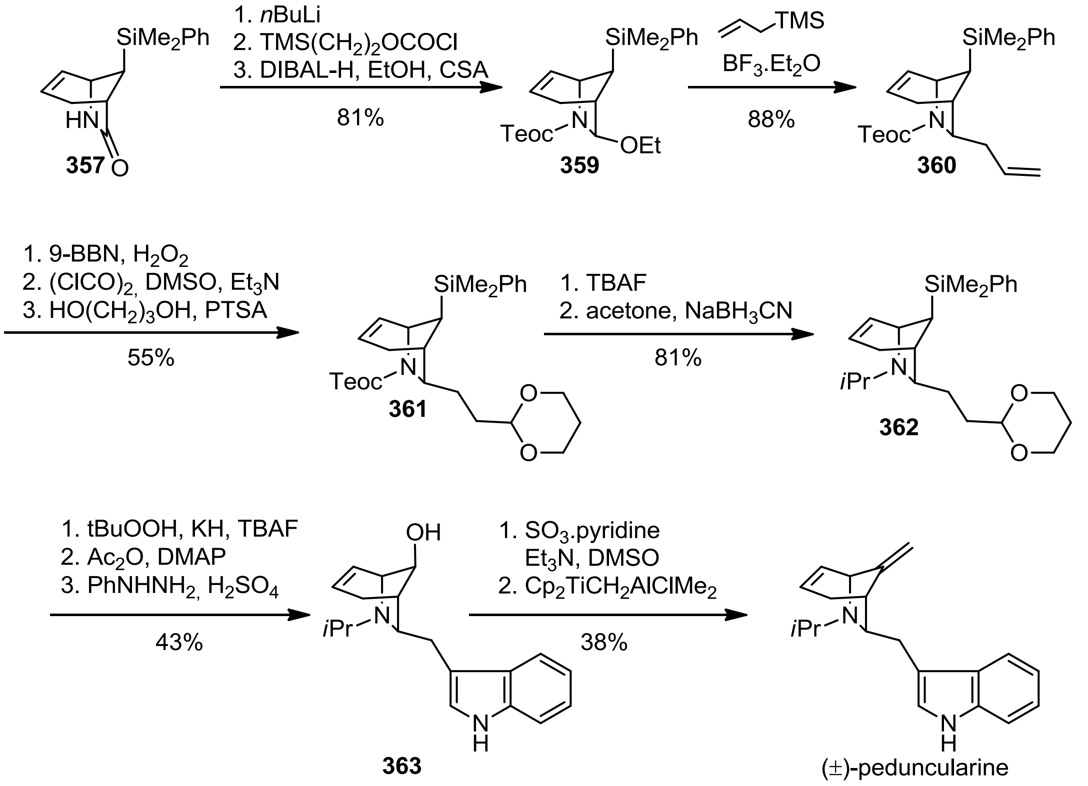
Having reported a formal synthesis of (±)-peduncularine in 2000,[132] Roberson and Woerpel published the second total synthesis in 2002.[133] Cyclohexadienylsilane **352** was prepared by deprotonation of 1,4-cyclohexadiene **351** using *s*BuLi and TMEDA followed by trapping of the lithiated intermediate with chlorodimethylphenylsilane (Scheme 155).

The construction of the core structure **357** was achieved *via* a [3+2]-cycloaddition using cyclohexadienylsilane **352** and chlorosulfonyl isocyanate. Due to steric hindrance, the attack occurred on the opposite face of the silyl group to give **353**. Following a 1,2-migration of the silyl moiety, allylic cation **354** cyclised to afford a 91:9 mixture of regioisomers **355:356**. The core structure of peduncularine **357** was obtained in 68% yield after *in situ* reduction using sodium sulfite.



Scheme 155

Protection of the lactam with a Teoc group and selective reduction with DIBAL-H in EtOH provided hemiacetal **359** (Scheme 156). This intermediate was selectively alkylated under Hosomi-Sakurai reaction conditions to give terminal alkene **360** as a single diastereomer. Cyclic acetal **361** was obtained in three straightforward steps: regioselective hydroboration using 9-BBN, Swern oxidation and acid-catalysed acetal formation.

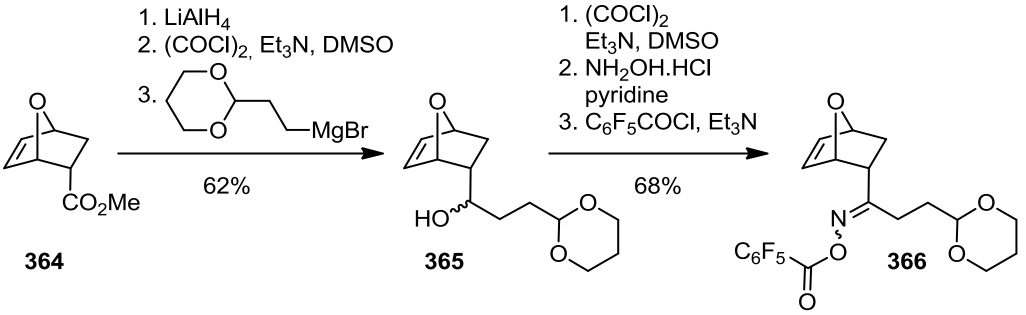


Scheme 156

Deprotection of the Teoc group using TBAF followed by reductive amination with acetone and $NaBH_3CN$ formed isopropylamine **362**. The dimethylphenylsilyl group was oxidized to give a secondary alcohol which was transformed *in situ* to the acetate to facilitate purification. The Fischer-indole synthesis gave alcohol **363** which was oxidized to the ketone and subsequent use of the Tebbe reagent gave (±)-peduncularine in 16 linear steps and 5.5% overall yield.

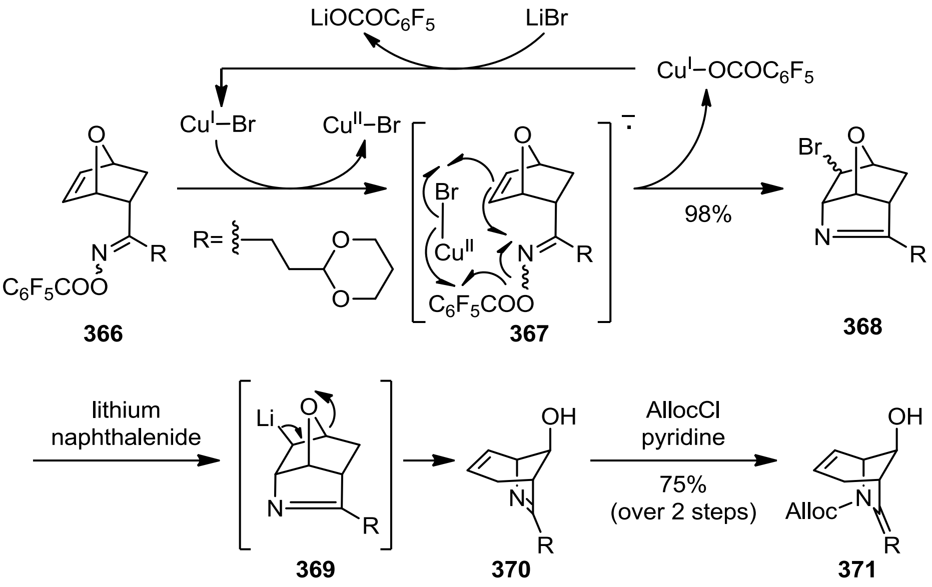
4.4 Kitamura's total synthesis of peduncularine

In 2006, Kitamura and co-workers described the third total synthesis of (±)-peduncularine.[134] The synthesis started with ester **364** which was previously synthesized by Kotsuki in 55% yield.[135] Reduction of ester **364** with $LiAlH_4$ followed by Swern oxidation and Grignard addition onto the aldehyde gave alcohol **365** in 68% yield over 3 steps (Scheme 157). Ketone formation from the secondary alcohol and further treatment with $NH_2OH.HCl$ gave an oxime functional group which was reacted with perfluorobenzoyl chloride and triethylamine to afford *O*-pentafluorobenzoyloxime **366**.



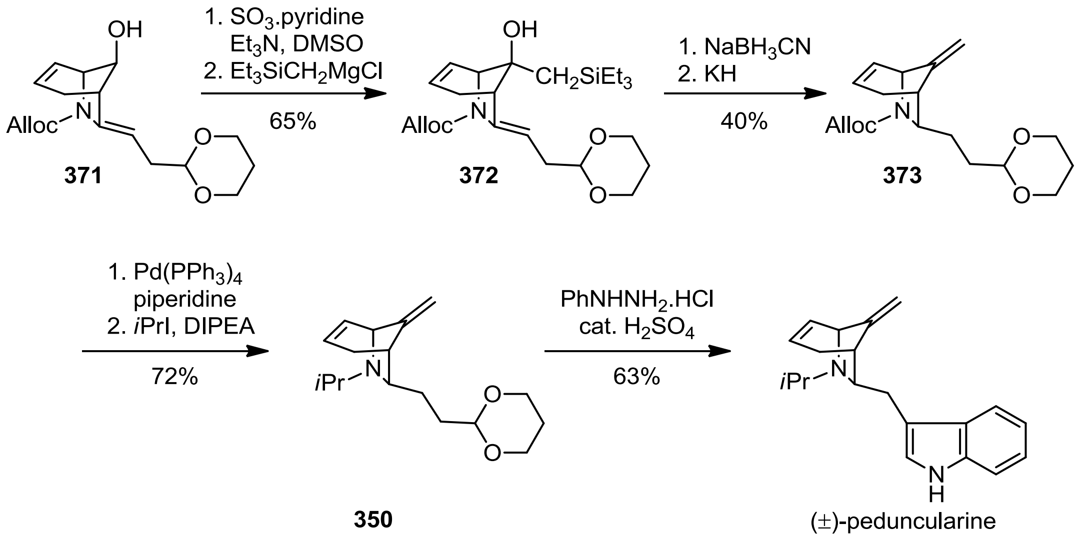
Scheme 157

The synthesis of the 6-azabicyclo[3.2.1]oct-3-ene ring structure was achieved *via* a radical cyclisation of oxime **366** followed by a reductive ring opening (Scheme 158). Reaction of oxime **366** with a Cu(I) salt gave, *via* electron transfer, radical anion **367** which can cyclise to form a 1:2.2 mixture of epimers of cyclic imine **368** in 98% yield. Treatment of bromide **368** with lithium naphthalenide gave alcohol **370** as a single isomer *via* β-elimination. The readily hydrolysed imine **370** was reacted with AllocCl and pyridine to afford stable protected enamine **371** in 75% yield over 2 steps.



Scheme 158

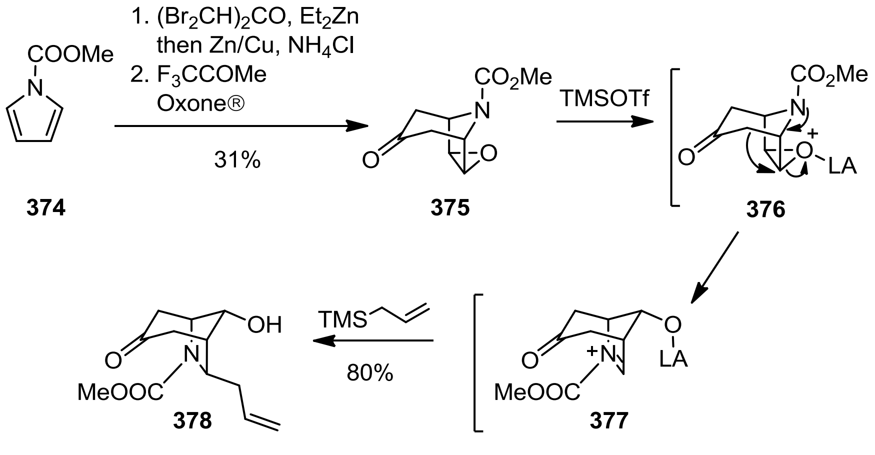
Parikh-Doering oxidation of alcohol **371** followed by stereoselective Grignard addition gave tertiary alcohol **372** (Scheme 159). Reduction of enamine **372** with $NaBH_3CN$ and Peterson olefination using KH afforded amine **373** in 40% yield (20% of the C-7 isomer was also formed). Tertiary amine **350** was obtained *via* deprotection of the allyloxycarbonyl group and isopropylation using isopropyliodide and DIPEA. Finally, Fischer-indole synthesis using phenylhydrazine produced (±)-peduncularine in a 3.6% overall yield and 15 steps from known ester **364**.



Scheme 159

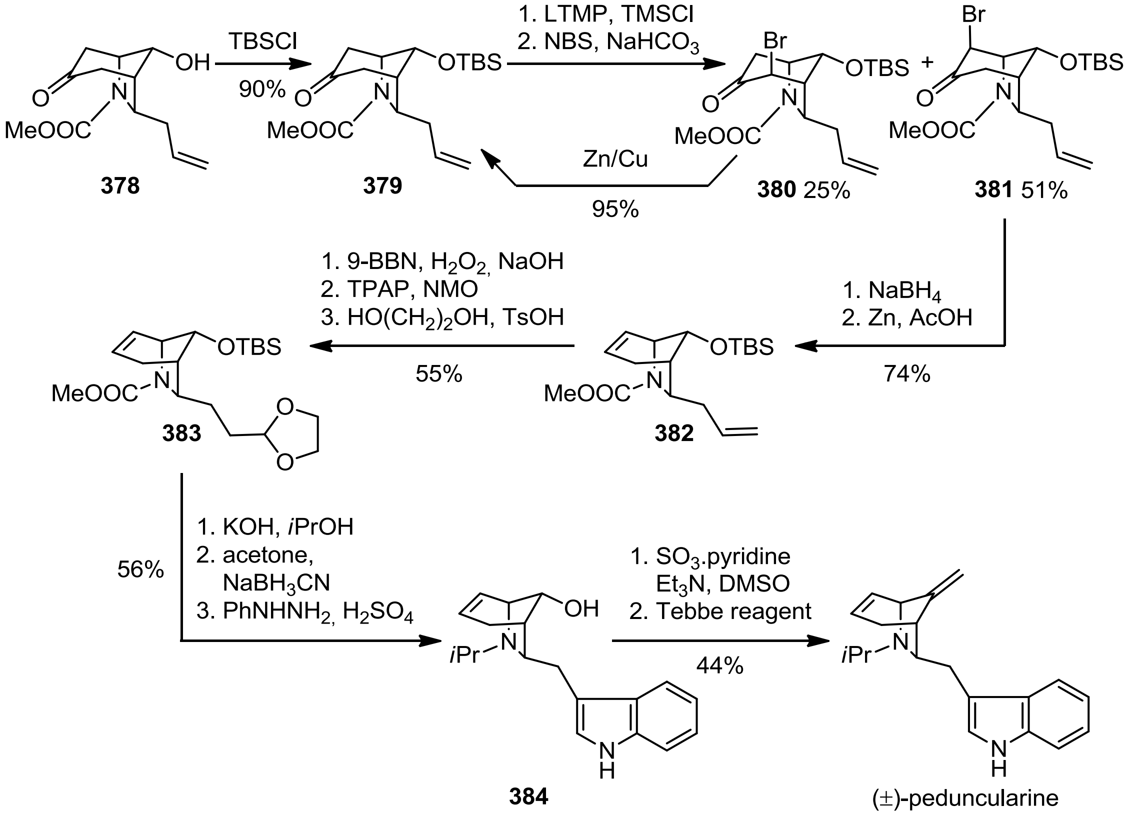
4.5 Hodgson's total synthesis of peduncularine

The most recent total synthesis of (±)-peduncularine was published in 2010 by Hodgson and co-workers.[136] Synthesis of epoxytropone **375** was performed in two steps *via* a [4+3]-cycloaddition of pyrrole **374** with tetrabromoacetone followed by a debromination and a stereoselective epoxidation (Scheme 160). Epoxide **375** was rearranged *via* a Lewis acid-catalysed 1,2-shift to give iminium **377** which was trapped with allyltrimethylsilane as in Robertson and Woerpel's synthesis to give **378**, the core structure of peduncularine, as the required single stereoisomer in an excellent 80% yield.



Scheme 160

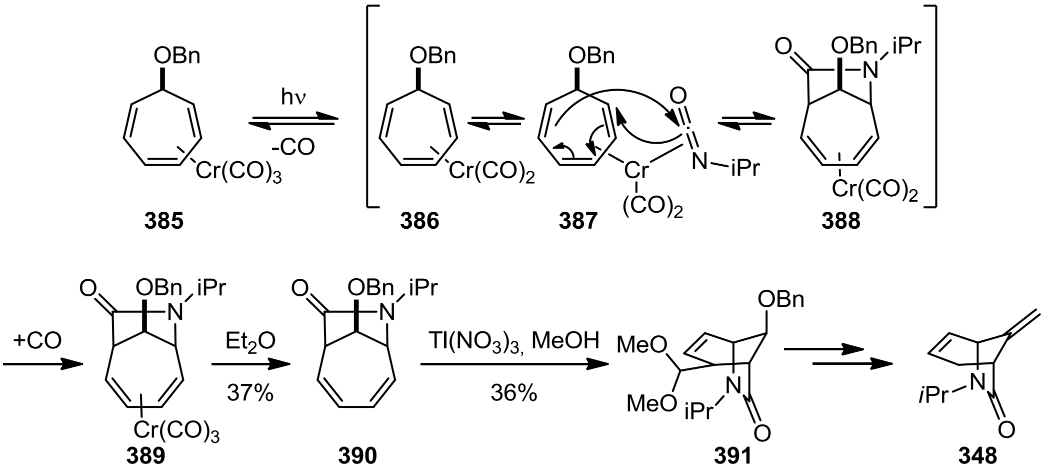
Protection of the secondary alcohol with a TBS group gave **379** in 95% yield (Scheme 161). Regioselective bromination *via* the corresponding silyl enol ether afforded the desired bromo regioisomer **381** in 51% yield. The other isomer **380** formed in 25% yield was recycled to ketone **379** in 90% yield. Completion of the total synthesis was achieved in a similar manner to the work previously described by Woerpel (Section 4.3). Overall, Hodgson synthesized (±)-peduncularine in 15 steps and 1.16% yield. Although the overall yield is lower than Woerpel's synthesis, the lowest yielding reaction is the [4+3]-cycloaddition which is the first step in the synthesis and scaling it up was presumably not a problem.



Scheme 161

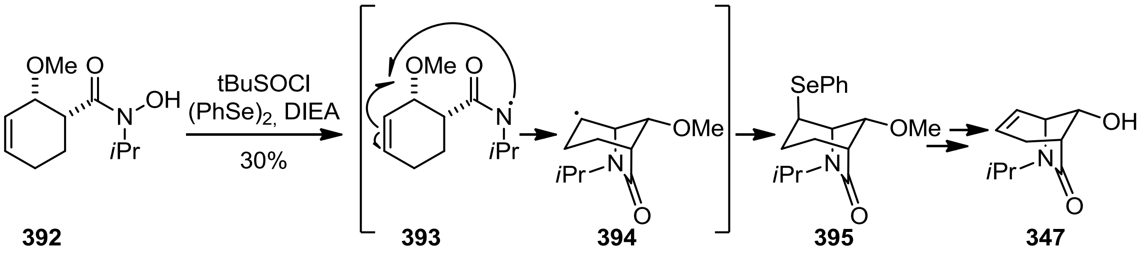
4.6 Formal syntheses of peduncularine

In 1999, Rigby and Meyer designed a synthesis of the core structure of peduncularine using a [6+2]-cycloaddition followed by a Tl(III) oxidative rearrangement to form the 6-azabicyclo[3.2.1]ring system (Scheme 162).[137-139] A loss of a carbon monoxide ligand from Cr-complexed cycloheptatriene **385** occurred *via* light irradiation and allowed coordination with isopropyl isocyanate to give intermediate **387**. Cycloaddition followed by capture of a molecule of carbon monoxide and decomplexation gave **390** in a modest 37% yield. The azabicyclo[4.3.1]nonane ring system then underwent an oxidative ring contraction to give the core structure **391** in 36% yield. A succession of functional group transformations afforded alkene **348**, an intermediate synthesized originally in Speckamp's synthesis. It was formed in only eight steps from commercially available tropylium fluoroborate complex compared to the 14 steps required by Speckamp.



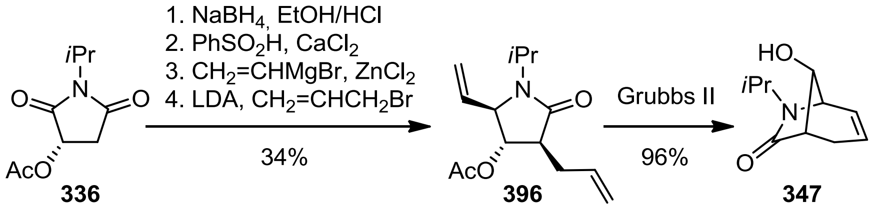
Scheme 162

In 2000, Weinreb reported the shortest at the time, albeit low-yielding, formal synthesis of peduncularine.[140] Intermediate **347** from Speckamp's synthesis was accessed in only five steps compared to the original twelve steps outlined above (Section 4.2). The key step was to subject hydroxamic acid **392** to amidyl radical cyclisation conditions to give **395** as a single diastereomer in 30% yield (Scheme 163).



Scheme 163

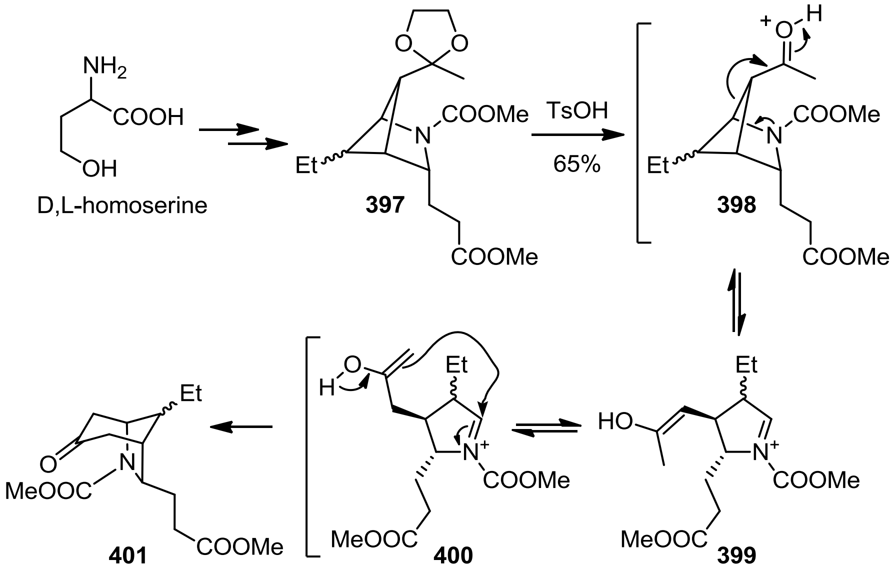
In 2003, Martin *et al.* proposed a concise route for the formal synthesis of (–)-peduncularine using ring-closing metathesis (Scheme 164).[141] The known secondary alcohol **347** was obtained from **336**, an intermediate in Speckamp's synthesis, in five steps and 32% yield compared to the original nine steps and 8.9% yield (section 4.2).



Scheme 164

4.7 Winkler's approach to the bicyclic core of peduncularine

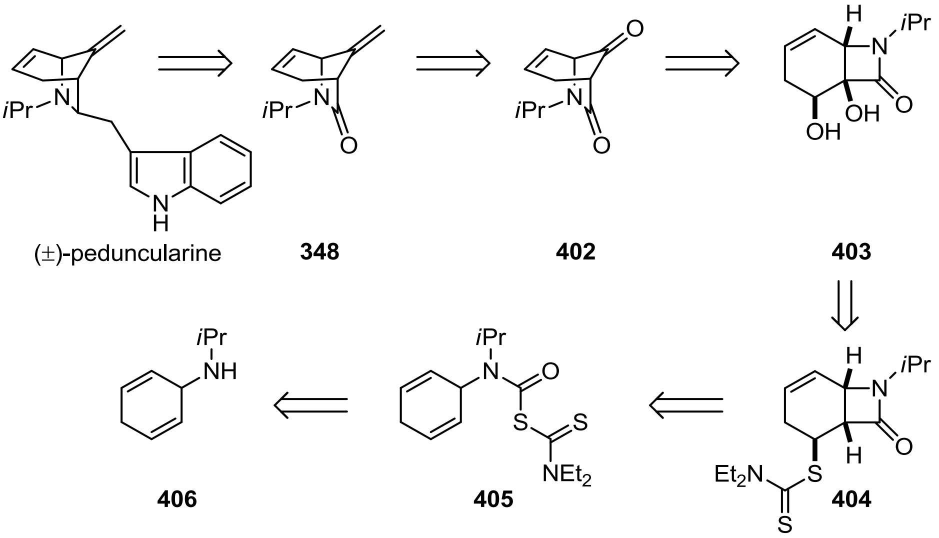
In 2006, Ragains and Winkler synthesized (±)-peduncularine's core structure.[142] The synthesis started with D,L-homoserine which, after a succession of transformations, afforded **397**. The formation of the 6-azabicyclo[3.2.1]octane ring structure **401** was achieved in 65% yield *via* an acid-catalysed retro-Mannich/Mannich reaction (Scheme 165).



Scheme 165

4.8 *Aims and objectives*

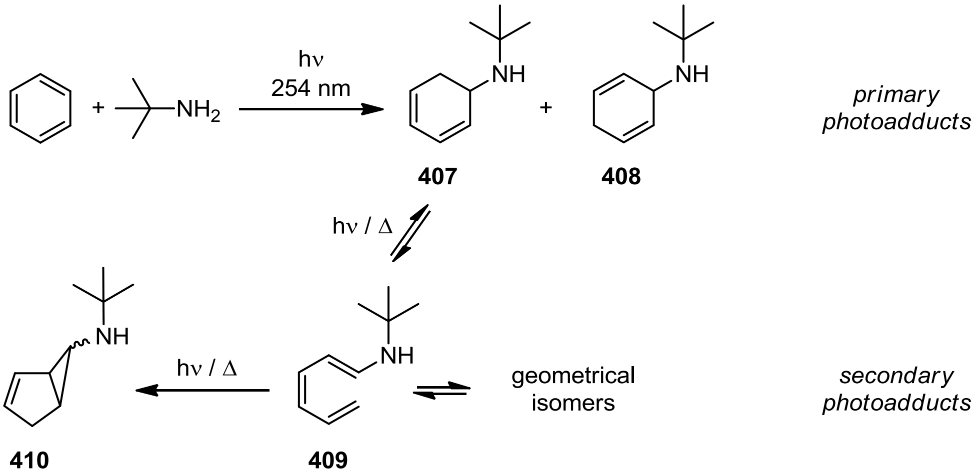
A novel formal synthesis of (±)-peduncularine was envisaged around creation of the known intermediate **402** from Speckamp's synthesis *via* a semipinacol rearrangement of diol **403** (Scheme 166). This diol could be obtained by dihydroxylation of a conjugated alkene formed *via* elimination of the dithiocarbamate group in **404**. β-Lactam **404** would be synthesized using a 4-*exo trig* radical cyclisation-dithiocarbamate group transfer of cyclohexadiene **405** and the precursor for this reaction could potentially be prepared in two straightforward steps from the novel isopropylamine **406**. Diene **406** was proposed to arise from the photocyclisation of benzene and isopropylamine.



Scheme 166

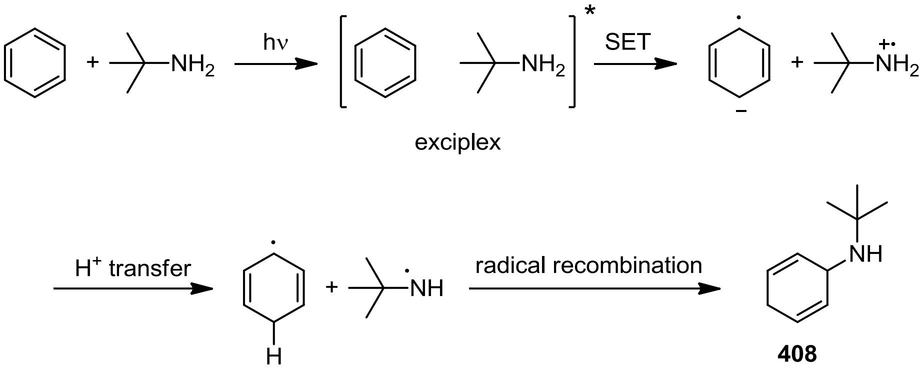
4.9 *Photoaddition of benzene to amines*

In 1967, Bryce-Smith and Gilbert published the first 1,4-photoaddition of piperidine or cyclohexylamine onto benzene.[143] Their work was extended in 1977 with the incorporation of $t\mathrm{BuNH_2}$ in order to simplify NMR spectra analysis.[144] Irradiation of a 1:1 mixture of benzene:$t\mathrm{BuNH_2}$ for 24 h with a low-pressure mercury lamp gave a 1:1:2:5 mixture of **409:410:407:408** and unreacted starting material (Scheme 167). The major components were amine **407** and **408** which were primary photoadducts. Conjugated diene **407** was not light-stable and further irradiation produced secondary photoadducts **409** and **410** as minor components.



Scheme 167

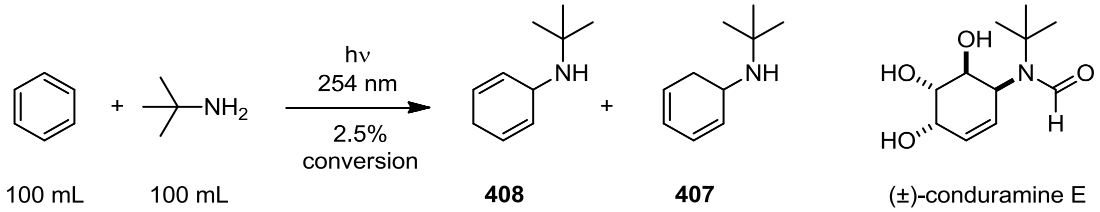
Irradiation of benzene and *t*BuNH$_2$ produces an excited state complex formed of excited state benzene (S$_1$) and ground state amine (S$_0$). Single electron transfer gives benzene radical anion and amine radical cation, which, after proton transfer, generates cyclohexadienyl and aminyl radicals which combine to give amine **408**, the main product from this reaction.



Scheme 168

In 2010, Russell *et al.* employed this photoamination in their total synthesis of (±)-conduramine E (Scheme 169).[145-146] They used a low-pressure mercury lamp with a falling film photochemical reactor. This set-up allowed the reaction to be run on a large scale (200 mL) and to get a high exposure to the light by having a consistent thin-film flow. Only 2.5%

conversion was observed for this photoamination after irradiating the mixture for 16 h. However, as the reaction was run on a large scale and the non reacted starting materials were easily removed by distillation, this was not an issue. The desired diene **408** was contaminated with conjugated diene **407** even after purification by Kugelrohr distillation.

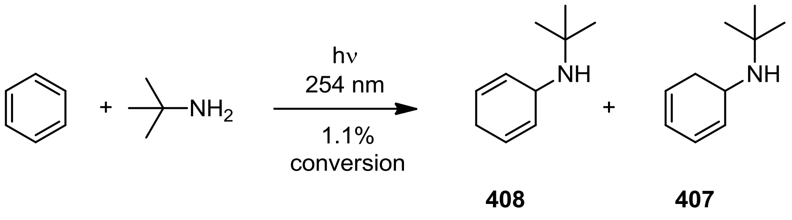


Scheme 169

Results and discussion

4.10 Synthesis of N-isopropylcyclohexa-2,5-dienamine

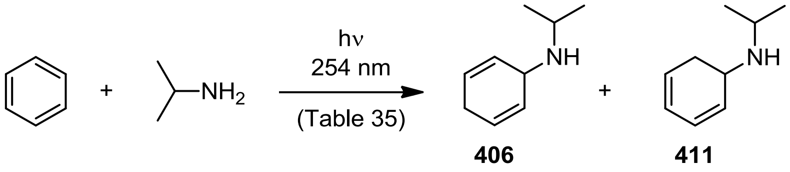
The photoamination of benzene and *t*BuNH$_2$ was repeated successfully with the equipment available in the Grainger laboratory: a quartz immersion well reactor and a low-pressure mercury lamp (Scheme 170). After 21 h of irradiation, 1.1% conversion was observed and a 3.3:1 mixture of **408:407** was obtained after purification.



Scheme 170

Having established conditions for the photoaddition of *t*BuNH$_2$ to benzene, the analogous addition of *i*PrNH$_2$ was investigated (Scheme 171, Table 35). The reaction was first carried out without any cooling of the lamp (entry 1). After 18 h, considerable evaporation was noticed and the side of the well closer to the lamp was coated with what was assumed to be polymeric compound which prevented the light from passing through into the reaction mixture. To avoid evaporation and coating, cooling with a water jacket was used for the next attempt and the reaction proceeded in a similar conversion giving an inseparable mixture of amines **406** and **411** (entry 2).

Knowing the photoamination occurred even at room temperature with a water jacket, the reaction time was increased to 87 h without any risk of evaporation. An increase in conversion was observed and 2.81 g of material was synthesized (Table 35, entry 3).



Scheme 171

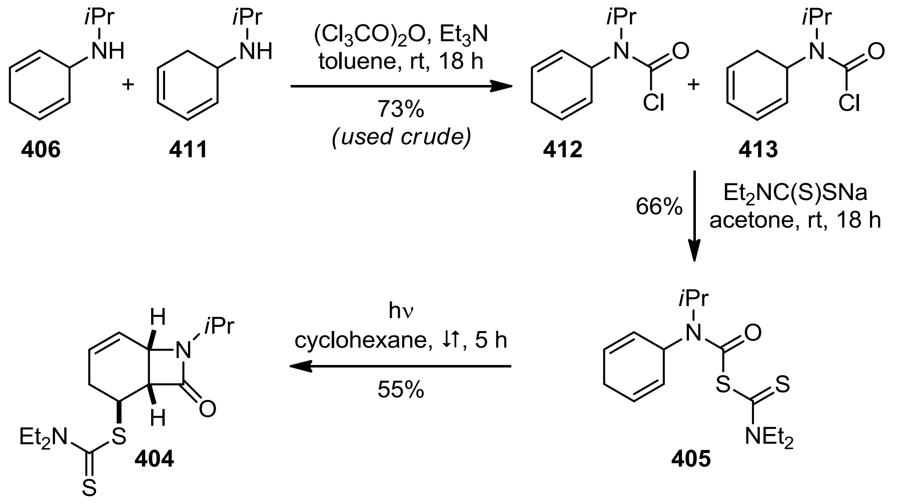
Entry	Reagents	Cooling	Time	Product
1	1:1 benzene:*i*PrNH$_2$ (300 mL)	✗	18 h	0.623 g (1.0:0.5 **406:411**)
2	1.85:1 benzene:*i*PrNH$_2$ (200 mL)	✓	18 h	0.412 g
3	1:1 benzene:*i*PrNH$_2$ (340 mL)	✓	87 h	2.81 g
4	1:1 benzene:*i*PrNH$_2$ (340 mL)	✓	62 h	1.51 g (1.00:0.17 **406:411**)

Table 35: Photoamination of benzene and iPrNH$_2$

The mixture of isopropylamines **406** and **411** was unstable, with the pale yellow oil obtained after purification by distillation turning black after 30 min at room temperature. Only partial characterisation was therefore possible and the amines had to be reacted further immediately after purification.

4.11 Synthesis of the isopropylamine β-lactam

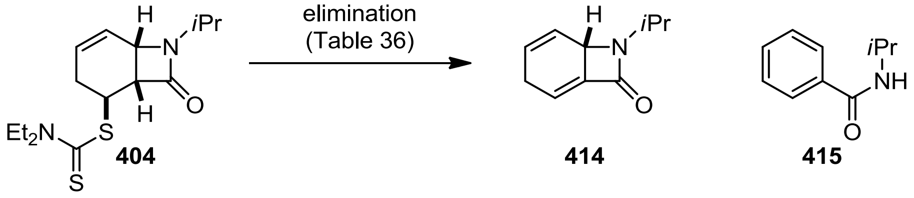
The inseparable mixture of isopropylamines **406** and **411** was treated with triphosgene and Et$_3$N to give a mixture of carbamoyl chlorides **412** and **413** in 73% yield (Scheme 172). Purification *via* column chromatography was attempted at this stage but degradation occurred and it was therefore decided to use the crude product in the next step. Formation of the radical cyclisation precursor using three equivalents of sodium diethyldithiocarbamate in acetone at rt gave **405** in 66% yield as a single isomer after careful separation of the other regioisomer by column chromatography. Irradiation with a 500 W halogen lamp provided **404** in 55% yield. The reaction was complete after 5 h and one major product was formed by tlc analysis. The stereochemistry of **404** was assigned by analogy to similar systems but has not been unambiguously determined (Section 2.1).



Scheme 172

4.12 *Elimination towards a cyclohexadiene β-lactam*

Elimination of the dithiocarbamate group in **404** to give **414** was first attempted using 1.1 eq of iodomethane and LHMDS at -78 °C (Scheme 173). The reaction mixture was warmed to rt when no product of elimination could be observed after 5.5 h at -78 °C. However, only starting material was obtained even after leaving the reaction for 18 h at rt (Table 36, entry 1). The same result was observed using a Meerwein salt to activate the dithiocarbamate (entry 2). When using ten equivalents of iodomethane and LHMDS or 1.1 equivalents of LDA, some conversion was observed after warming the reaction mixture to rt (entries 3 and 4). Unfortunately, the product isolated was *N*-isopropylbenzamide **415**. Increasing the amount of LDA in solution only resulted in a larger amount of this side product being formed (entries 5 and 6).

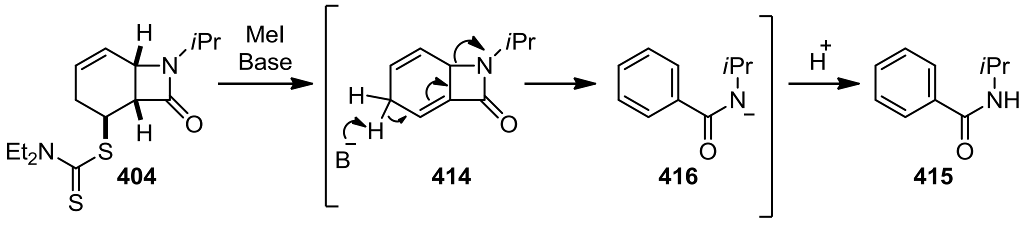


Scheme 173

Entry	Reagents	eq	T / time	Result
1	MeI, LHMDS, THF	1.1	-78 °C to rt 18 h	**404**
2	Me_3OBF_4, LHMDS, THF	1.1	-78 °C to rt 18 h	**404**
3	MeI, LHMDS, THF	10	-78 °C to rt 18 h	**404** 98% **415** 2%
4	MeI, LDA, THF	1.1	-78 °C to rt 18 h	**404** 65% **415** 22%
5	MeI, LDA, THF	2.0	-78 °C to rt 18 h	1.0:0.5 **404:415**
6	MeI, LDA, THF	5.0	-78 °C to rt 18 h	1:2 **404:415**
7	MeI, *t*BuLi, THF	1.1	-78 °C to rt 6.5 h	1.00:0.19 **404:415**
8	MeI, LiF, Li_2CO_3, DMF	1.1	rt to reflux 18 h	**404**
9	MeI, *t*BuOK, THF	1.1	rt to reflux 7 h	**404**

Table 36: Elimination of the dithiocarbamate group in 404

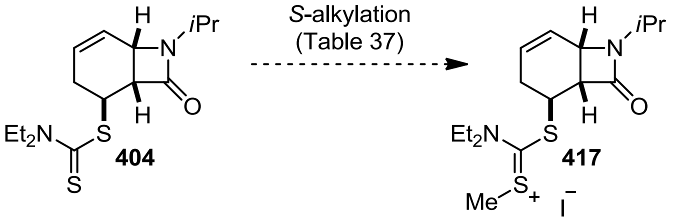
The formation of amide **415** could be explained by further deprotonation of the desired conjugated lactam **414** (Scheme 174). A strong driving force for the reaction to occur is opening of the β-lactam and formation of a benzene ring. The same result was observed when using *t*BuLi as a base (Table 36, entry 7).



Scheme 174

A different set of conditions was reported in 1977 by Hayashi *et al.* for the elimination of the pyrrolidine dithiocarbamate moiety.[39] It uses LiF, Li_2CO_3 and iodomethane. However, the elimination of the diethyl dithiocarbamate group was not successful for β-lactam **404**, even in refluxing DMF (Table 36, entry 8). When using *t*BuOK as a stronger heterogeneous base, only the starting material was recovered (entry 9).

Formation of the potential intermediate **417** using different solvents and temperature was attempted (Scheme 175, Table 37). Unfortunately, only starting material was recovered each time.

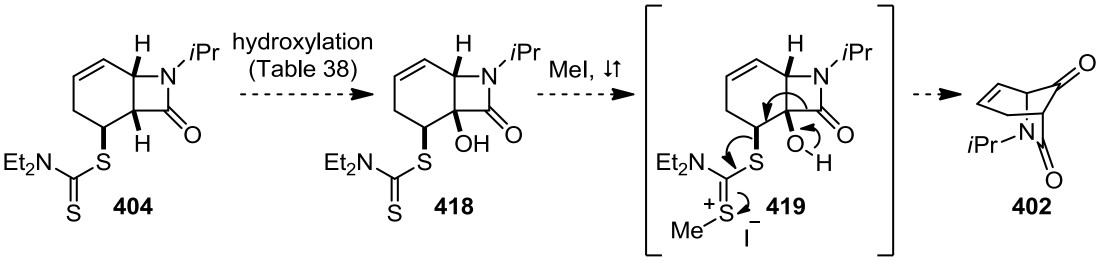


Scheme 175

Entry	Reagents	Solvent	T / time	Result
1	MeI (5 eq)	THF	rt / 2 h	**404**
2	MeI (excess)	MeI	rt / 18 h	**404**
3	MeI (5 eq)	CH_3CN	reflux / 18 h	**404**
4	MeI (5 eq)	toluene	reflux / 18 h	**404**

Table 37: Attempts to S-alkylate dithiocarbamate 404

An alternative to dithiocarbamate elimination was to α-hydroxylate the β-lactam to form **418** and then to alkylate the dithiocarbamate moiety in order to make it a suitable leaving group for the semipinacol rearrangement (Scheme 125, Table 38). Treatment of **404** with 1.5 eq of LHMDS and the Davis oxaziridine resulted in some consumption of starting material.[43] However *N*-isopropylbenzamide **415** and unreacted starting material **404** were the only products isolated after purification (entries 1 and 2). Interestingly, a higher yield of side product **415** is obtained using only 1.5 eq of LHMDS and Davis oxaziridine compared to using 10 eq of LHMDS and MeI (Table 36, entry 3). An alternative α-hydroxylation method developed in 1975 which uses a lithium base, molecular oxygen and triethylphosphite was also applied to β-lactam **404** (entry 3).[40-41] Only starting material was observed during this reaction.

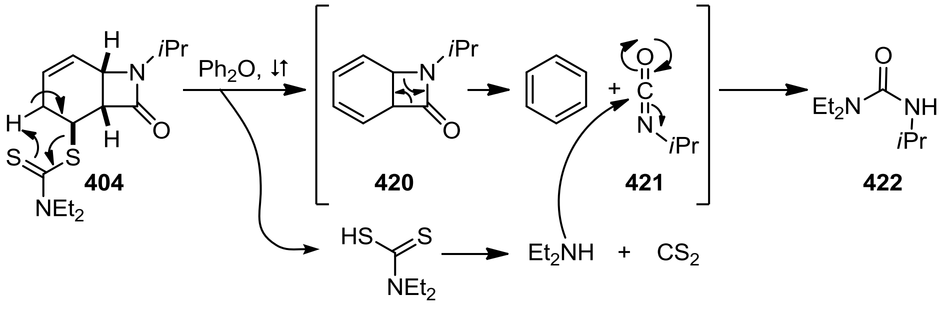


Scheme 176

Entry	Reagents in THF	T / time	Result
1	LHMDS (1.5 eq) Davis oxaziridine (1.5 eq)	-78 °C to rt to reflux 18 h	**404** 59% **415** 41%
2	LHMDS (1.5 eq) Davis oxaziridine (1.5 eq)	0 °C to rt 18 h	**404** 11% **415** 89%
3	LHMDS (1.5 eq), O_2 $P(OEt)_3$ (2 eq)	-78 °C to rt 5 h	**404**

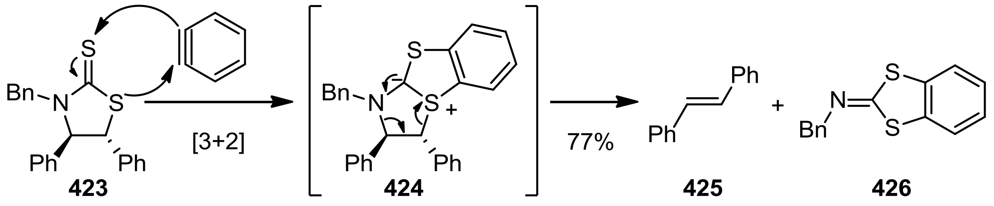
Table 38: Attempts to α-hydroxylate 404

Refluxing β-lactam **404** in Ph_2O to achieve a Chugaëv-like elimination of the dithiocarbamate moiety resulted in the formation of urea **422** in 34% yield (Scheme 177). Upon elimination, diene **420** was presumed to undergo a retro [2+2]-cycloaddition to form isocyanate **421** and benzene. The isocyanate can then react with diethylamine, a side product from the elimination reaction, and give urea **422**.



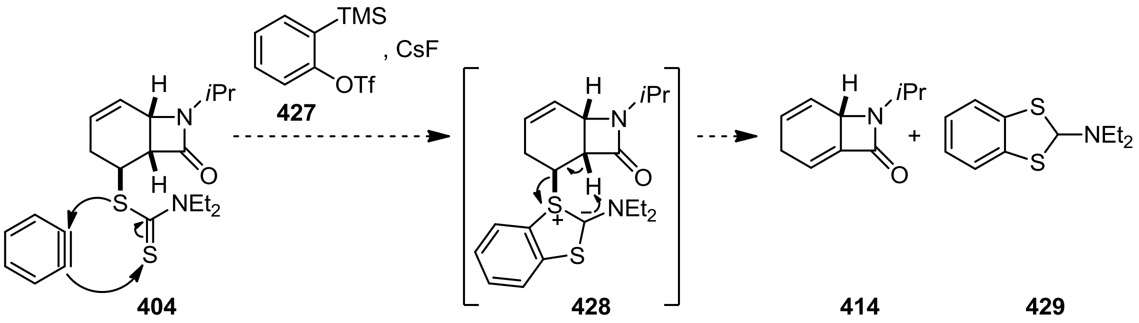
Scheme 177

A benzyne-induced alkene formation was proposed as an alternative to the use of iodomethane and a strong base for the elimination of the dithiocarbamate group. Recent work from Hwu and Hsu described that 1,3-thiazolidine-2-thiones **423** can react in a [3+2]-cycloaddition fashion to form a tricyclic structure **424** which can then undergo a retro [3+2]-cycloaddition to give alkene **425** in 77% yield (Scheme 178).[147]



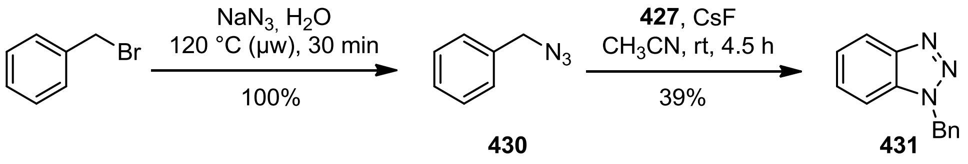
Scheme 178

If applied to lactam **404**, the [3+2]-cycloaddition of the dithiocarbamate group onto benzyne would give tetracyclic structure **428** which could abstract the acidic proton α to the carbonyl and give diene **414** and benzo-1,3-dithiol **429** as a side product (Scheme 179).



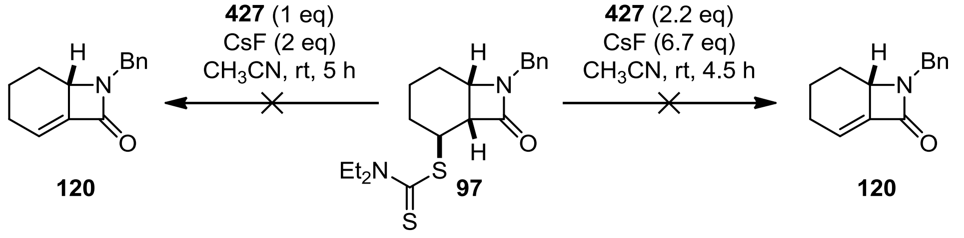
Scheme 179

Before attempting this unprecedented elimination, it was decided to confirm the formation of benzyne *in situ* through reaction with easily accessible starting materials using literature conditions. The recent work by Chandrasekhar *et al.* for the synthesis of benzotriazole **431** was selected.[148] Microwave irradiation of benzyl bromide and sodium azide in water at 120 °C for 30 min afforded benzyl azide **430** in quantitative yield (Scheme 180).[149] Formation of triazole **431** was achieved in a moderate 39% yield (lit. yield 82%) proving the formation of benzyne *in situ* from 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **427** and cesium fluoride.



Scheme 180

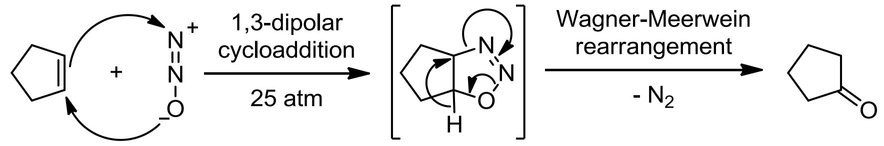
The same reaction conditions were applied to β-lactam **97** (Scheme 181). This substrate was chosen in preference to lactam **404** because previous work had shown that conjugated alkene **120** was a stable compound which could be formed in excellent yield. Unfortunately, only the starting material was recovered even when an excess of benzyne was present in solution. Due to the lack of success for this reaction, it was not attempted on unsaturated β-lactam **404**.



Scheme 181

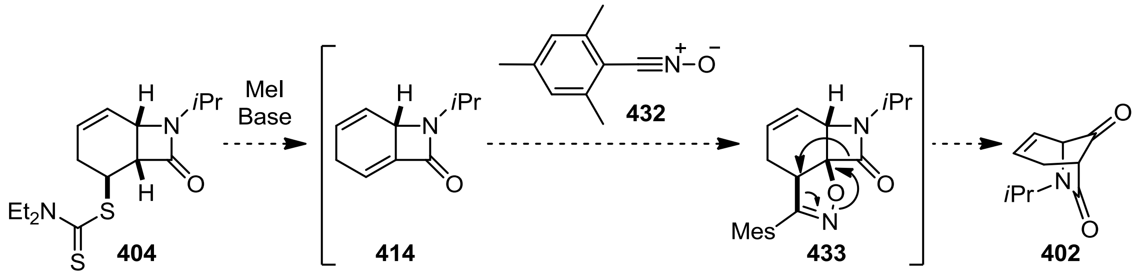
The isolation of benzamide **415** suggested that the desired diene **414** was formed in the reaction mixture but was unstable. It was envisaged that a precursor for the semipinacol rearrangement could be formed by *in situ* trapping of unstable **414**.

In 2002, Dubkov and co-workers reported the oxidation of cyclopentene to cyclopentanone using nitrous oxide (Scheme 182).[150] This reaction was postulated to proceed *via* a 1,3-dipolar cycloaddition followed by a Wagner-Meerwein rearrangement through loss of N_2 as a driving force.[151]



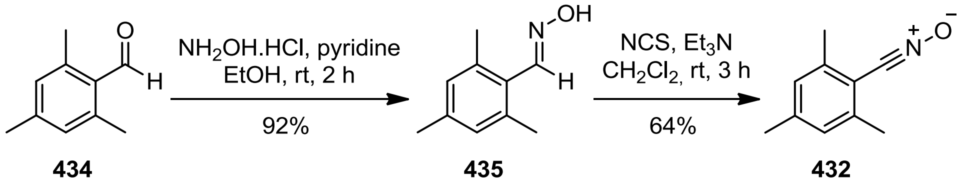
Scheme 182

Due to the difficulty in accessing gaseous nitrous oxide, it was decided to run the 1,3-dipolar cycloaddition using a stable nitrile oxide. It was proposed that diene **414** would react with benzonitrile *N*-oxide **432** to form tricyclic **433** which could then rearrange to give bicyclic ketone **402** along with an aromatic nitrile by-product (Scheme 183).



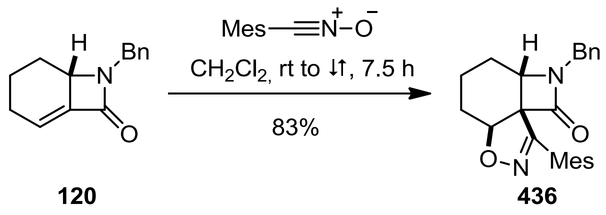
Scheme 183

The synthesis of nitrile oxide **432** was achieved in 2 steps following the literature procedure developed by Bode (Scheme 184).[152-153] Oxime **435** was formed in 92% yield by condensing hydroxylamine onto aldehyde **434**. Treatment of the oxime with NCS and triethylamine gave stable benzonitrile oxide **432** in 64% yield.



Scheme 184

It was decided to try the 1,3-dipolar cycloaddition on alkene **120** as a model system. The addition proceeded in 83% yield and gave **436** as a single isomer (Scheme 185).



Scheme 185

Analysis of the ^{1}H-NMR spectrum showed a downfield proton at 5.13 ppm which corresponds to a hydrogen adjacent to an electronegative atom and particularly an oxygen. The same analysis was made for the ^{13}C-NMR spectrum where a CH carbon found at 79.6 ppm is too downfield to correspond to a carbon adjacent to a C=N group (Figure 20). It was concluded that the tricyclic structure formed corresponded to the regioisomer **436** that cannot undergo the desired semipinacol rearrangement. The cycloaddition was not attempted on lactam **404** because **433** would not be obtained.

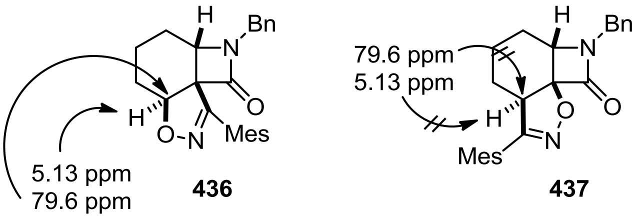
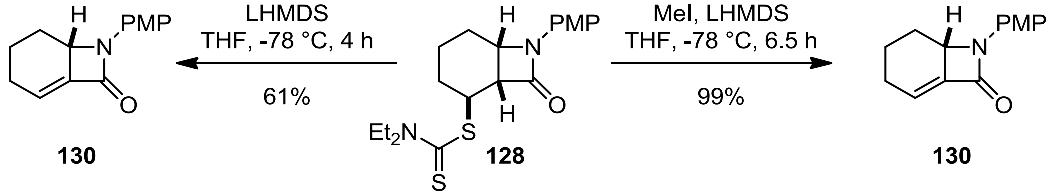


Figure 20

4.13 Elimination of the dithiocarbamate group: summary

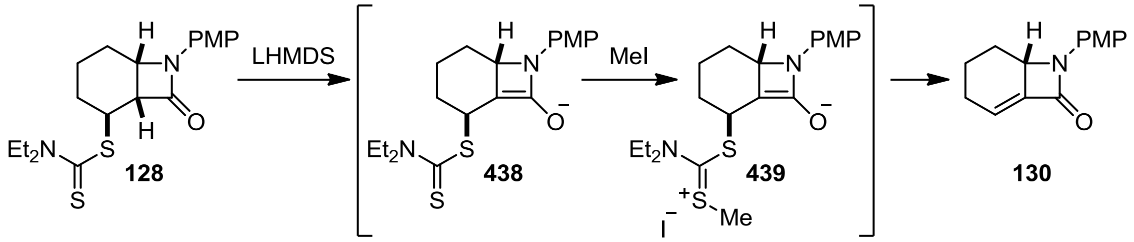
These final experiments on the elimination of the dithiocarbamate group in **404**, particularly the failure to observe *S*-alkylated **417**, taken together with results described in Chapters 2 and 3 allow some tentative conclusions to be drawn on the mechanism of the reaction.

The basic elimination of the dithiocarbamate group on the PMP derivative **128** occurred in a moderate 61% yield when LHMDS was used on its own. Addition of iodomethane allowed the reaction to go to completion and alkene **130** was formed in 99% yield (Scheme 186).



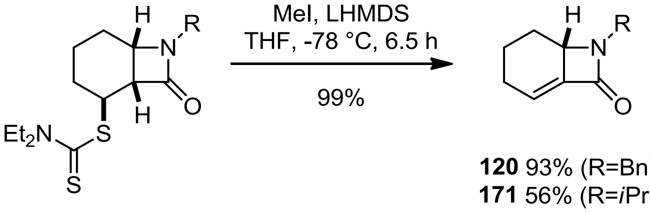
Scheme 186

The presence of the lactam functional group suggests that the elimination may occur *via* a E_1cB mechanism (Scheme 187). Another hypothesis would be that the alkylation occurs on the deprotonated β-lactam **438** instead of **128**.



Scheme 187

The yield of the elimination was excellent with PMP, Bn and PMB groups on the nitrogen whereas only moderate yields were obtained for the *N*-*i*Pr and *N*-$(CH_2)_7CH_3$ derivatives (Scheme 188). Alkyl chains add electron density to a system and therefore destabilize an anion intermediate. The branched isopropyl group is more electron-donating than the octyl group which could explain the lower yield obtained for this reaction.

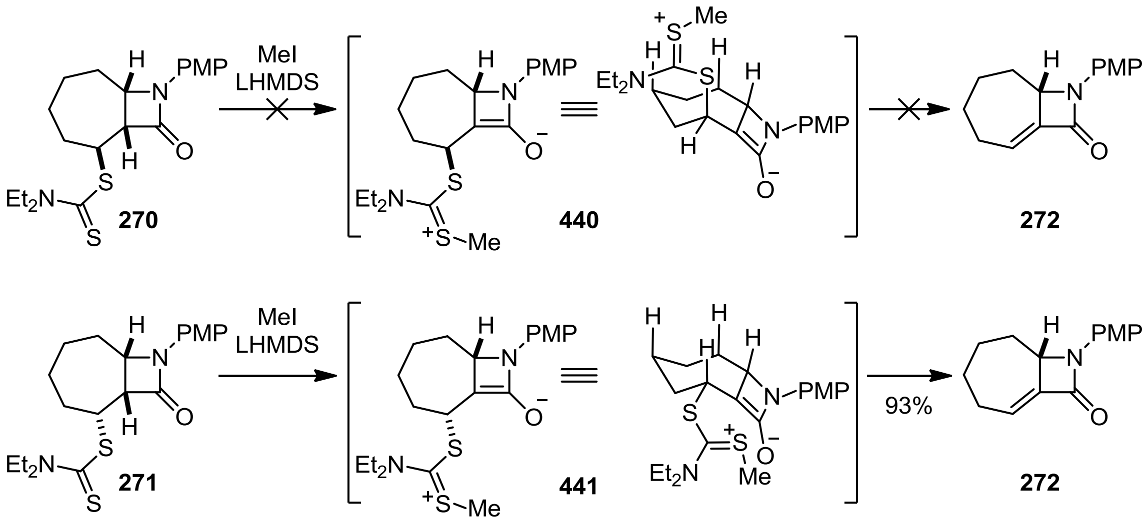


97 (R=Bn) / **170** (R=*i*Pr)
176 (R=$(CH_2)_7CH_3$) / **191** (R=PMB)

120 93% (R=Bn)
171 56% (R=*i*Pr)
177 67% (R=$(CH_2)_7CH_3$)
192 88% (R=PMB)

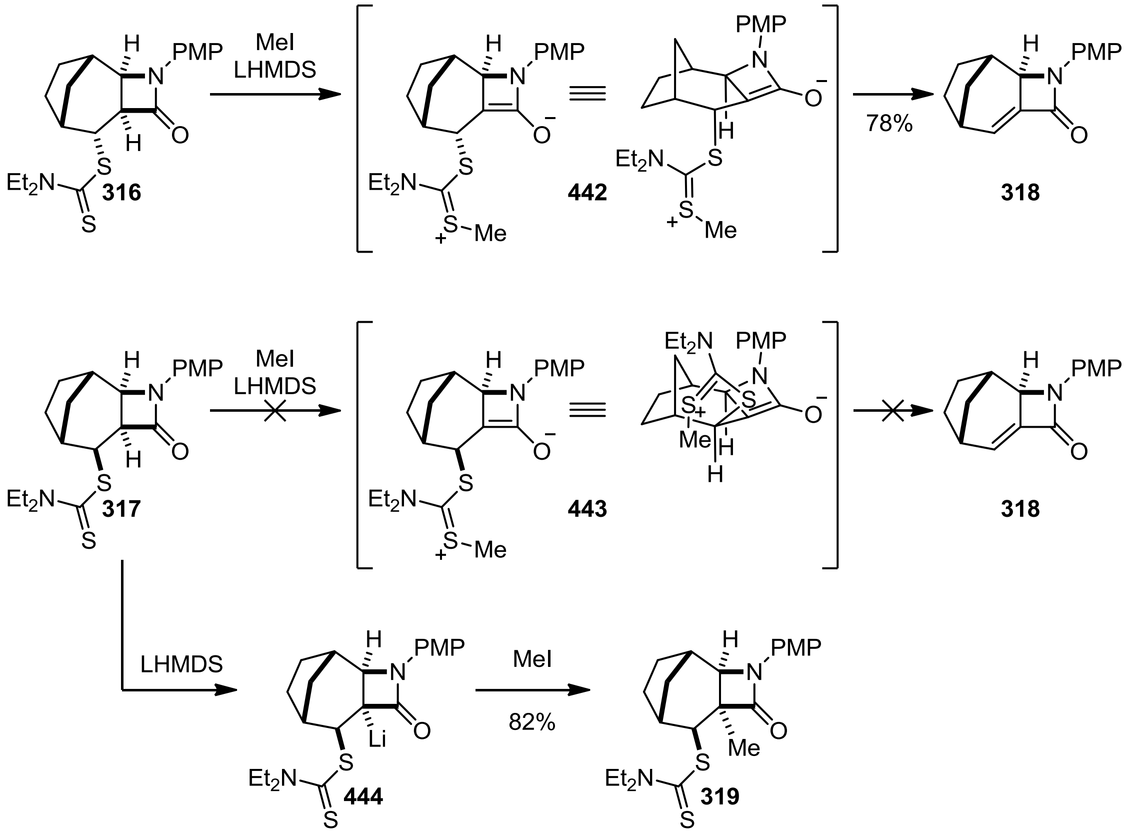
Scheme 188

Basic elimination of the dithiocarbamate on the cycloheptane-fused system occurred in 93% yield on *trans* **271** whereas only the starting material was recovered from *cis* **270** (Scheme 189). Inspection of molecular models of deprotonated epimers **440** and **441** shows that the dithiocarbamate group is in an axial position for **440**, generating 1,3-diaxal interactions. On the other hand, the dithiocarbamate group is in an equatorial position in **441** and therefore the elimination will be possible.



Scheme 189

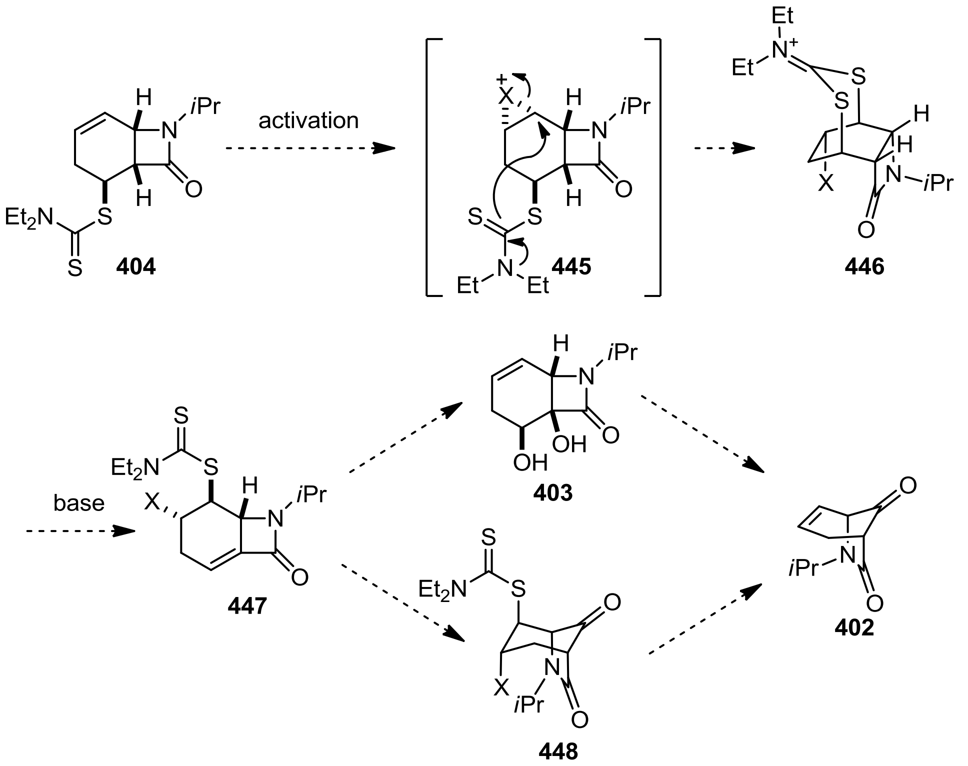
For the norbornene derivatives, the bridge forces the molecule to adopt a specific conformation (Scheme 190). This time, isomer **316** will have the dithiocarbamate group in a pseudo-axial position, away from the bridge. The steric interactions will be minimal for deprotonated **442** and elimination will be possible. This hypothesis was confirmed experimentally. Indeed alkene **318** was obtained in 78% yield from **316**. On the other hand, the steric clash between the pseudo-equatorial dithiocarbamate group and the bridge will not allow the formation of the flat intermediate **443** for isomer **317**. Elimination will therefore not be possible and the lithiated intermediate **444** will be trapped by iodomethane to form **319** in 82% yield.



Scheme 190

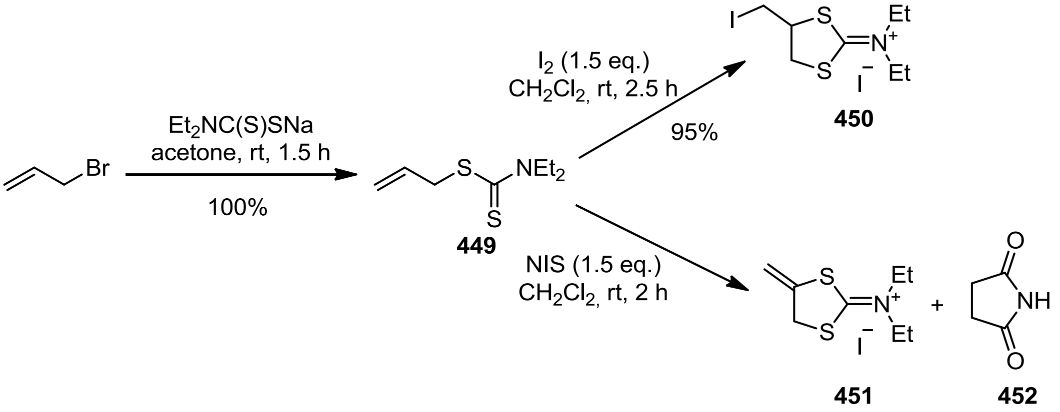
4.14 Dithiocarbamate cyclisation onto activated alkenes

An alternative strategy to synthesize the substrate for the semipinacol rearrangement would be to activate the double bond in β-lactam **404** in order to form tricyclic structure **446** which would be prone to elimination to give conjugated alkene **447** (Scheme 191). Dihydroxylation of the double bond followed by manipulation of the dithiocarbamate and X groups to install an alkene would give **402**. Alternatively the double bond could be installed after semipinacol rearrangement.



Scheme 191

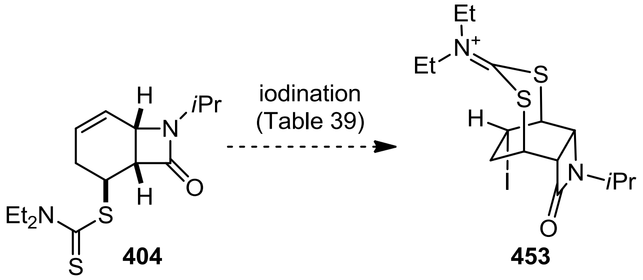
According to the work published by Saidi *et al.* it is possible to activate a double bond with iodine and form a 1,3-dithiolane derivative *via* intramolecular attack of a dithiocarbamate group onto the iodonium cycle.[154] Before applying the literature conditions to dithiocarbamate **404**, a representative example was repeated (Scheme 192).



Scheme 192

Allyl dithiocarbamate **449** was synthesized in quantitative yield from allyl bromide and sodium diethyldithiocarbamate in acetone. Following the literature procedure, treatment of **449** with iodine in CH_2Cl_2 at rt for 2.5 h and subsequent concentration of the reaction mixture gave 1,3-dithiolane **450** in 95% yield (lit. yield: 100%). Use of NIS instead of iodine gave an inseparable mixture of methylene 1,3-dithiolane **451** and succinimide **452**. This latter reaction was consistent with elimination of iodide from **450** presumably by the succinimidate anion acting as a base. This behaviour appeared ideal for the proposed transformation of **404** to form conjugated alkene **447** in one pot (Scheme 191).

No consumption of starting material was observed when treating β-lactam **404** with iodine in CH_2Cl_2 at -78 °C, at rt or at reflux (Scheme 193 and Table 39, entries 1 and 2). Increasing the reaction temperature by changing the solvent (1,2-DCE, chlorobenzene) only resulted in recovered starting material or degradation (entries 3 and 4).



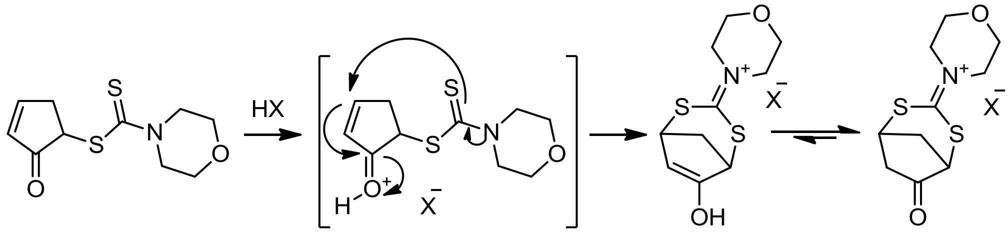
Scheme 193

Entry	Reagents	Solvent	T / time	Result
1	I_2 (1.5 eq)	CH_2Cl_2	-78 °C / 4.5 h	**404**
2	I_2 (1.5 eq)	CH_2Cl_2	rt to reflux / 18 h	**404**
3	I_2 (1.5 eq)	1,2-DCE	reflux / 4.5 h	**404**
4	I_2 (1.5 eq)	chlorobenzene	reflux / 1.5 h	degradation
5	I_2 (1.5 eq)	THF	rt	**404**
6	NIS (1.5 eq)	CH_2Cl_2	rt to reflux / 5 h	degradation

Table 39: Dithiocarbamate cyclisation onto activated alkene in 404

The use of THF, a more polar solvent, did not favour the salt formation (Table 39, entry 5). Finally, NIS gave similar results as iodine. Only starting material was seen at rt and the reaction mixture degraded when the temperature was raised to 40 °C (entry 6).

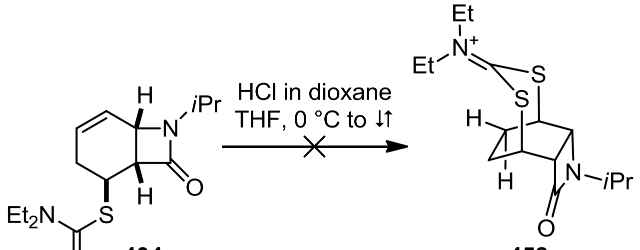
Instead of iodine, it is possible to use strong acids to activate a double bond towards nucleophilic attack. The work published in 1994 by Hartke and Timpe shows that a dithiocarbamic ester **454** can cyclize intramolecularly onto the alkene in a 1,4-addition fashion to give iminium salt **457** (Scheme 194).[155]



454 **455** **456** **457**

Scheme 194

Treatment of lactam **404** with anhydrous HCl at 0 °C and rt resulted in recovered starting material. Refluxing the reaction mixture in THF afforded degradation (Scheme 195).



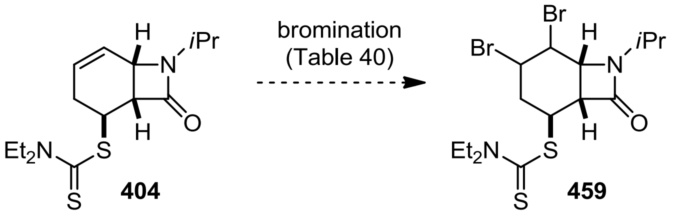
404 **458**

Scheme 195

4.15 Protection of the double bond

Elimination of the dithiocarbamate group produced amide **415** and urea **422** as side products instead of the expected alkenes **414** and **420** under basic and thermal conditions respectively (Scheme 174 and Scheme 177). In both cases, the main driving force was the formation of an aromatic ring and this undesired pathway occurred because of the double bond present in the carbocycle of **404** compared to previous systems (Sections 2.2 and 3.1). Protection of the double bond was therefore explored towards the proposed formal synthesis of peduncularine.

The first reaction investigated was bromination of the double bond (Scheme 196).[156] Addition of bromine to a solution of **404** in CH_2Cl_2 at 0 °C gave degradation of the reaction mixture after 30 min (Table 40, entry 1). When the addition was carried out at -78 °C, there was no consumption of the starting material, even when warming the solution to 0 °C. However, degradation occurred at rt (Table 40, entry 2). Finally, use of a 2:1 mixture of CCl_4:$CHCl_3$, a mixed solvent described by Hakimelahi,[156] afforded recovery of **404** even after stirring at rt for 3 h, because **404** was not soluble in this solvent combination (Table 40, entry 3).

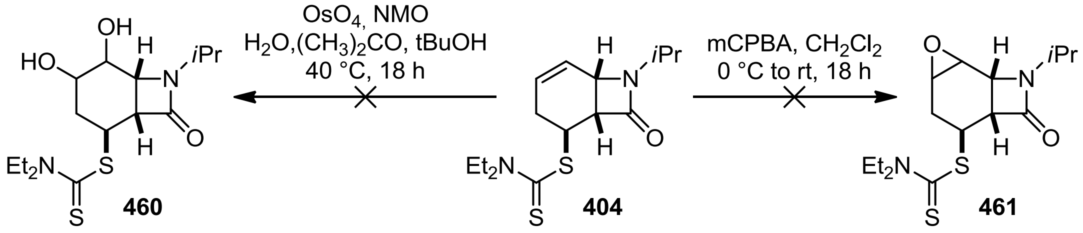


Scheme 196

Entry	Reagents	Solvent	T / time	Result
1	Br_2 (1.4 eq)	CH_2Cl_2	0 °C to rt / 30 min	degradation
2	Br_2 (1 eq)	CH_2Cl_2	-78 °C to rt / 4.5 h	degradation
3	Br_2 (1 eq)	2:1 CCl_4:$CHCl_3$	rt / 1.5 h	**404**

Table 40: Attempts to brominate the double bond in 404

The unsuccessful control of the bromination led to an investigation into oxygenation of the alkene, with the view that a diol or an epoxide could be subsequently reduced back to an alkene at a later stage of the synthesis. However, neither dihydroxylation nor epoxidation occurred, with only starting material **404** recovered. This suggested again that the double bond in **404** is relatively unreactive (Scheme 197). Notably the dithiocarbamate functionality was not oxidised under these conditions.[157-159]



Scheme 197

4.16 Conclusions

β-Lactam **404** was successfully synthesized as a possible intermediate in the synthesis of (±)-peduncularine. However, the double bond in **404**, required for the natural product, opened up alternative reaction pathways which meant **404** could not be converted to a semipinacol rearrangement precursor.

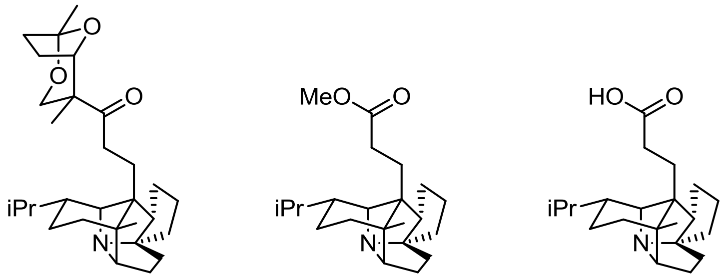
In order to complete the formal synthesis of this natural product *via* a semipinacol rearrangement, selective protection of the double bond prior to the radical cyclisation will be necessary. This could potentially be achieved *via* desymmetrisation of isopropylamine **406** and would possibly allow for an asymmetric synthesis, although the additional steps required make this approach less attractive.

Chapter five:

Studies towards the synthesis of calyciphylline D, calyciphylline F and caldaphnidine M

5.1 Calyciphylline D, calyciphylline F and caldaphnidine M: background and significance

In 2007, calyciphylline D and F were isolated by Kobayashi and co-workers from the leaves of *Daphniphyllum calycinum*, a tree found in mainland China (Figure 21).[160-161] A year later, they discovered caldaphnidine M in the roots of the same tree.[34] These natural products possess a fused-pentacyclic skeleton containing a 8-azatricyclo-[4.2.1.0.^{4,8}]nonane ring system. To date, a total synthesis of calyciphylline D, calyciphylline F or caldaphnidine M has not been achieved.



calyciphylline D calyciphylline F caldaphnidine M

Figure 21

Biosynthetically, these natural products are proposed to be generated from amide **462** *via* an oxidative degradation of C-7 followed by formation of nitrogen to C-6 bond (Figure 22).[162] Amide **462** could itself be derived from daphnimacropin, which was discovered in 1966 by Nakano *et al.*[163] Daphnimacropine possesses a daphnane skeleton. In 1990, Heathcock and co-workers proposed that the daphnane structure was biosynthetically generated from secodaphniphylline which itself originated from proto-daphniphylline.[164] Proto-daphniphylline is thought to be the first pentacyclic alkaloid to be formed in the biosynthesis of the *Daphnyphyllum* alkaloids and it has been suggested that it is biosynthesized from squalene.

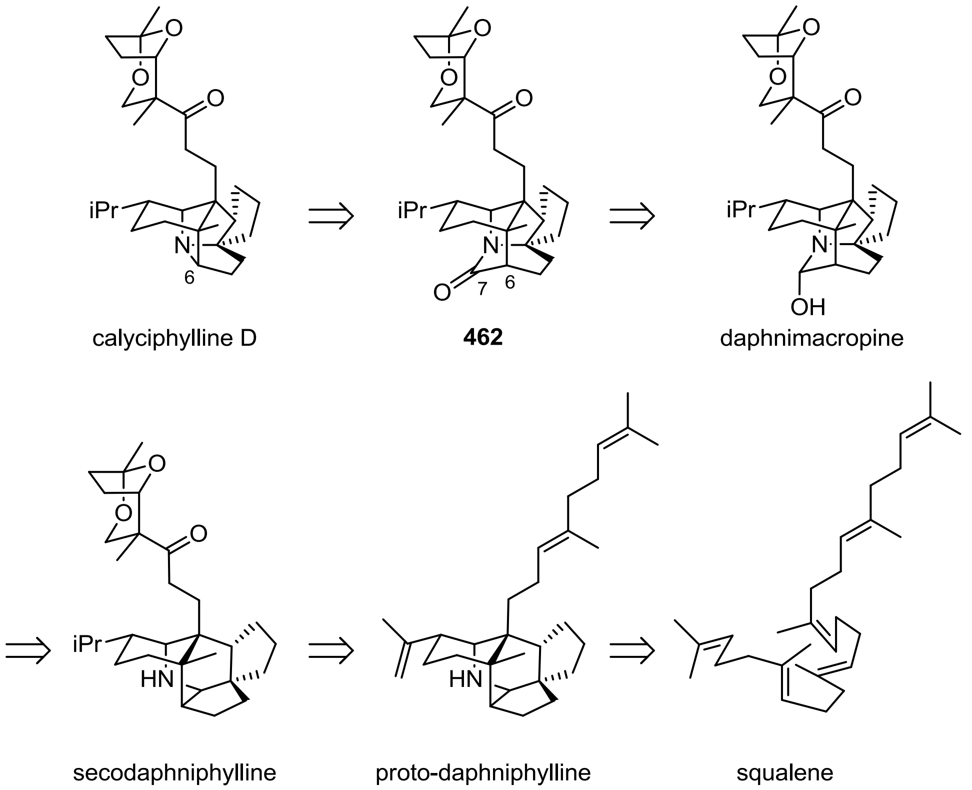
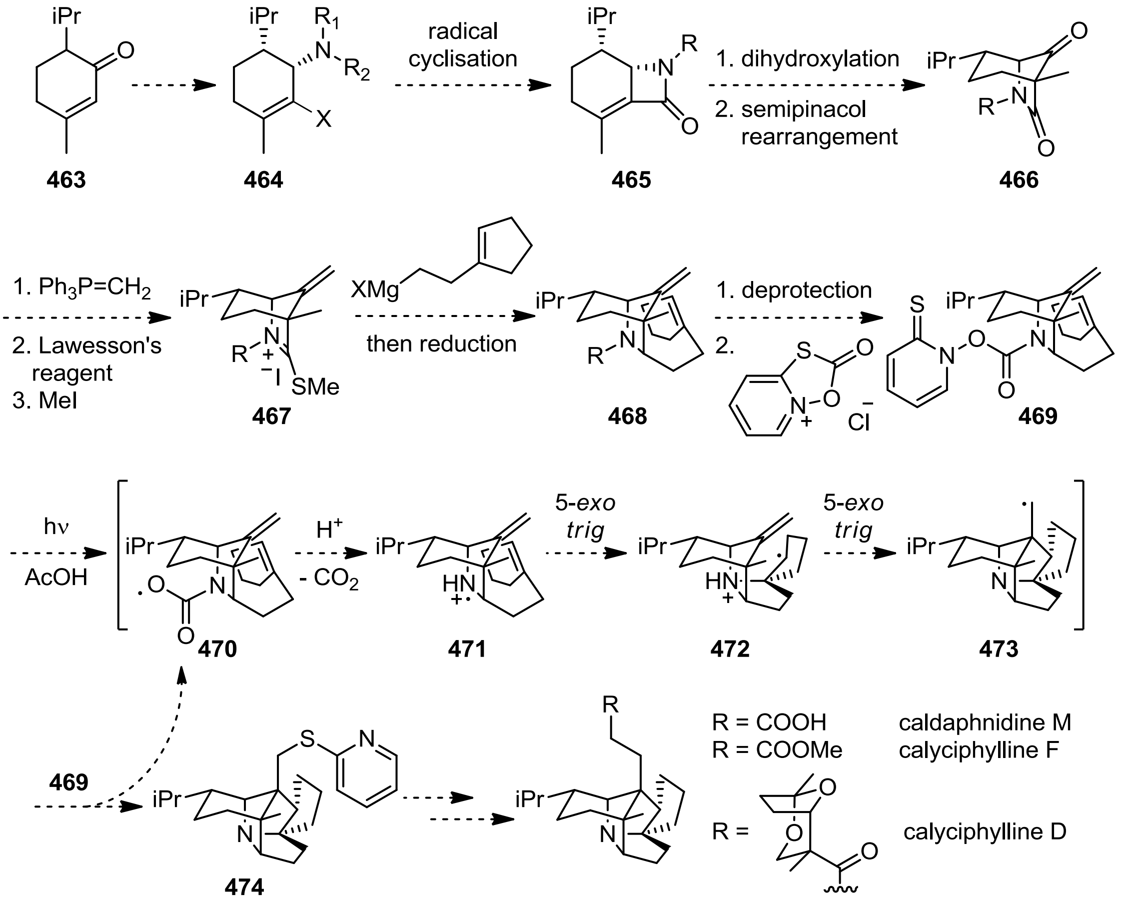


Figure 22

5.2 *Aims and objectives*

The intricate fused pentacyclic skeleton of the recently isolated *Daphniphyllum calycinum* alkaloids caldaphnidine M, calyciphylline F and calyciphylline D represents a considerable synthetic challenge. A proposed synthesis of these natural products would start from the commercially available monoterpene piperitone **463** (Scheme 198). The reductive amination onto piperitone will have to be stereoselective to allow the isopropyl group and the amine to be *cis* to each other. Alkene **465** will be obtained *via* radical cyclisation of cyanamide (**464**, R_2=CN, X=Br, I) or *via* radical cyclisation-dithiocarbamate group transfer and subsequent elimination of the dithiocarbamate group (**464**, R_2=C(O)SC(S)NEt$_2$, X=H). The synthesis of the 7,8-diketo-6-azabicyclo[3.2.1]octane core structure **466** will be achieved *via* dihydroxylation of the double bond and semipinacol rearrangement. Carbonyl functional group transformation will afford alkylated thioamide **467**. Grignard addition followed by a reduction will give amine **468** which after deprotection and subsequent reaction with 1-oxa-2-oxo-3-thiaindolizinium chloride will give Barton ester **469**, a suitable substrate for a tandem aminium radical cyclisation.[165-166] Initiation of the reaction followed by decarboxylation will give aminium radical **471** which will undergo two successive 5-*exo trig* radical cyclisations to form primary radical **473** which will react with **469** to give pyridylsulfide **474** and propagate the chain process. Subsequent functional group transformation will afford caldaphnidine M, calyciphylline F and calyciphylline D.

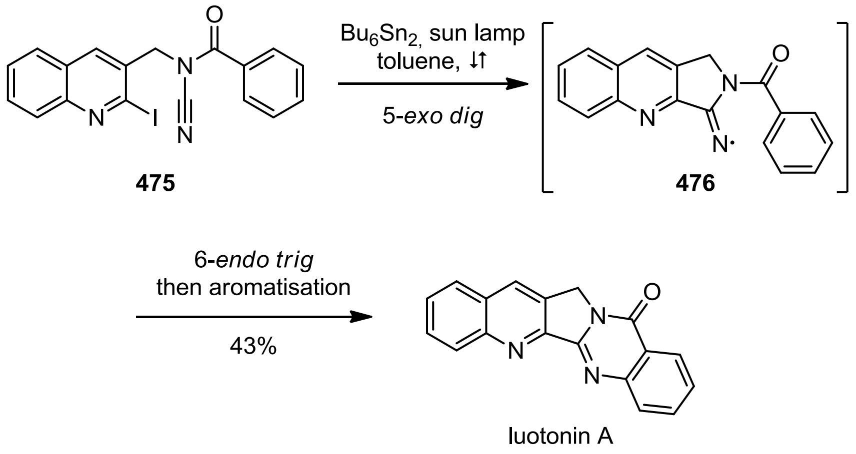


Scheme 198

Results and discussion

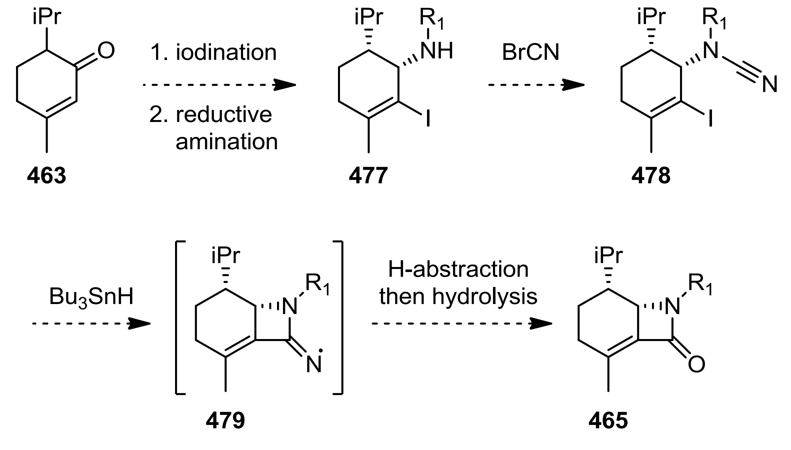
5.3 Towards the total synthesis via radical cyclisation of cyanamide

The first route investigated to access **465** was *via* radical cyclisation of a cyanamide. This reaction was first considered because of the prior difficulties encountered for the radical-cyclisation dithiocarbamate group transfer onto a trisubstituted alkene (Section 3.2). Malacria and co-workers described the use of *N*-acylcyanamide **475** in the total synthesis of luotonin A, a natural product extracted from a medicinal plant from China, *Peganum nigellastrum* (Scheme 199).[167] A tandem 5-*exo dig* and 6-*endo trig* radical cyclisation afforded luotonin A in 43% yield.



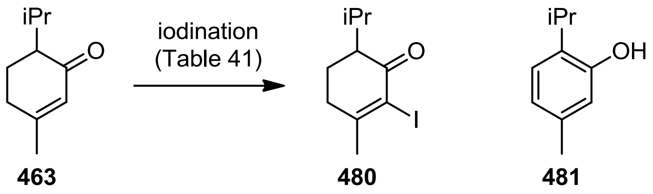
Scheme 199

Iodination of piperitone **463** and subsequent reductive amination will give **477**. Reaction with cyanogen bromide should afford radical cyclisation precursor **478**. The synthesis of alkene **465** would arise from a 4-*exo dig* cyclisation of cyanamide **478** to form iminyl radical **479**. After H-abstraction, the resulting imine could be hydrolysed to form β-lactam **465** (Scheme 200).



Scheme 200

The iodination did not occur when piperitone **463** was treated with 2 eq of iodine and 20 eq of pyridine or Et_3N in CH_2Cl_2 (Scheme 201 and Table 41, entries 1 and 2).[168] A 1:1 mixture of pyridine:CCl_4 was then used as a solvent.[169] Some conversion was observed after 21 h at rt and heating was required to drive the reaction to completion. Unfortunately, the desired halogenated ketone **480** was not formed. Instead, thymol **481** was obtained in 61% yield (entry 3).[170] Using a sub-stoichiometric amount of DMAP and making sure the reaction mixture was carried out in the exclusion of light allowed the formation of **480** in 21% yield (entry 4).[171] The yield was improved to 31% when the reaction concentration was increased (entry 5).[172]

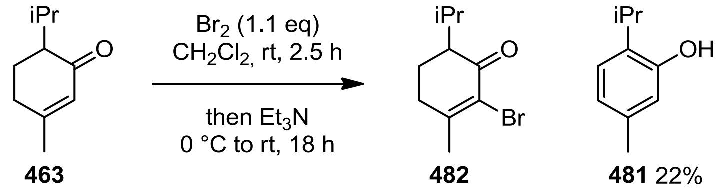


Scheme 201

Entry	**Reagents**	**Solvent**	**T / time**	**Result**
1	I_2 (2 eq) pyridine (20 eq)	CH_2Cl_2 (0.1 M)	0 °C to rt / 18 h	**463**
2	I_2 (2 eq) Et_3N (20 eq)	CH_2Cl_2 (0.1 M)	0 °C to rt / 18 h	**463**
3	I_2 (2 eq)	CCl_4, pyridine (0.1 M)	0 °C to rt / 21 h then reflux / 24 h	**481** 61%
4	I_2 (2 eq) DMAP (0.2 eq)	CCl_4, pyridine (0.4 M)	49 °C / 18 h *exclusion of light*	**480** 20%
5	I_2 (2 eq)	CH_2Cl_2, pyridine (0.66 M)	40 °C / 18 h *exclusion of light*	**480** 31%

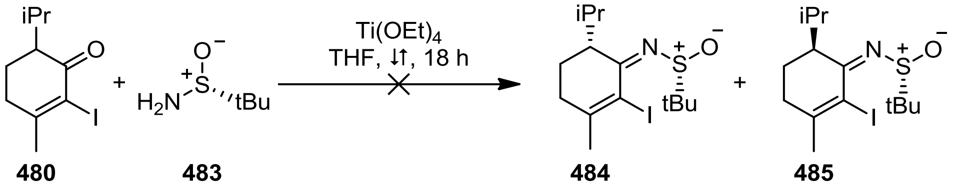
Table 41: Iodination of piperitone to synthesize 480

Bromination of piperitone **463** was also investigated (Scheme 202).[173] Addition of bromine to a solution of piperitone in CH_2Cl_2 cleanly formed a new product by tlc analysis after 2.5 h at rt. Subsequent addition of Et_3N at 0 °C and warming the reaction mixture to rt over 18 h did not afford halogenated ketone **482**. Thymol **481** was obtained in 22% yield after purification and some degradation was also observed.[170]



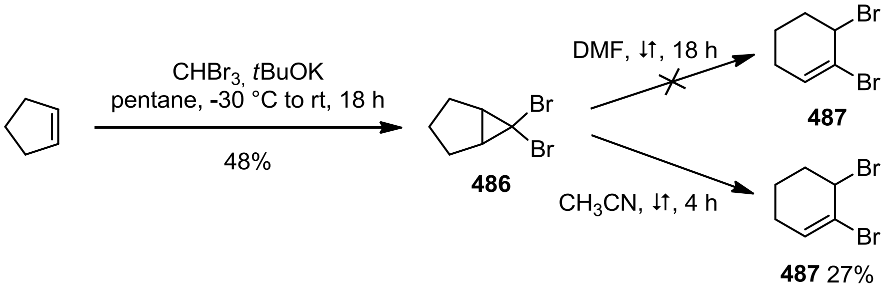
Scheme 202

Sulfinimine formation from halogenated ketone **480** to form **484:485** was attempted using enantiopure (*R*)-*t*BuSONH$_2$ **483** in combination with Ti(OEt)$_4$ (Scheme 203).[174-175] No conversion was observed by tlc analysis and the starting material was recovered after 18 h in refluxing THF.



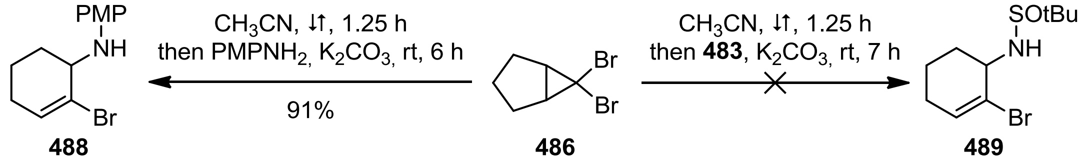
Scheme 203

Before trying to optimise the formation of **480** and **484:485**, it was decided to try the radical cyclisation on a model system. Treatment of cyclopentene with bromoform and *t*BuOK afforded dibromocyclopropane **486** in 48% yield after purification by distillation (Scheme 204).[176-177] Degradation was obtained when **486** was heated at reflux for 18 h in DMF whereas after 4 h in refluxing CH$_3$CN, 2,3-dibromocyclohexene **487** was isolated in 27% yield.



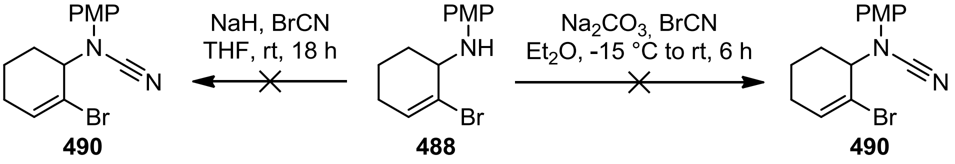
Scheme 204

One-pot rearrangement of dibromocyclopropane **486** and alkylation was also attempted (Scheme 205). Refluxing **486** in CH$_3$CN for 1.25 h and subsequent addition of PMPNH$_2$ and K$_2$CO$_3$ afforded bromo amine **488** in 91% yield after 6 h at rt. Unfortunately, **489** was not isolated using **121** under the same reaction conditions. Only the rearrangement occurred and **487** was obtained in 74% yield.



Scheme 205

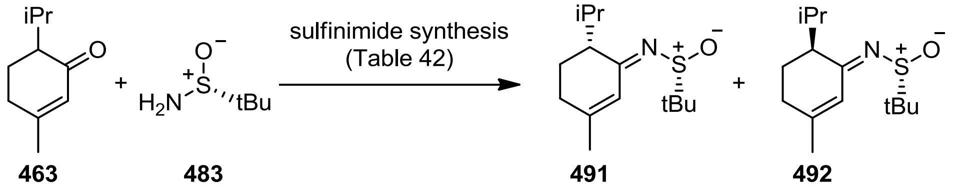
Reaction of bromoamine **488** with 1 eq of sodium hydride and 3 eq of cyanogen bromide in THF at rt for 18 h did not afford the desired cyanamide **490** (Scheme 206). Starting material was also recovered when 2 eq of Na_2CO_3 in combination with 1 eq of BrCN were used. Because of the difficulties encountered for the halogenation of piperitone and the lack of reactivity of bromoamine **488** towards cyanogen bromide, it was decided not to pursue the synthesis of β-lactam **465** *via* a radical cyclisation onto cyanamide **478**.



Scheme 206

5.4 Towards the total synthesis via reductive amination of piperitone

Synthesis *via* a reductive amination was first investigated using Ellman's sulfinamide chemistry.[174,178] The use of enantiomerically pure sulfinamide **483** should allow for the resolution of racemic piperitone **463** through formation of diastereomeric sulfinimines **491** and **492**. The resulting sulfinyl stereocentre in **491** and **492** should further direct reduction to set the *cis* configuration between the isopropyl group and the nitrogen on the cyclohexene ring although the extent of induction will also depend on the neighbouring isopropyl stereocentre. Reaction of piperitone **463** with (*R*)-2-methyl-2-propanesulfinamide **483** and $Ti(OEt)_4$ in refluxing THF for 40 h afforded a separable mixture of the sulfinimes **491** and **492** in 25% overall yield (Scheme 207 and Table 42, entry 1).[175] When the reaction was carried out for 78 h, the yield was improved to 44% (entry 2). Increasing the amount of reagents affected the yield and imines **491:492** were formed in 56% optimum yield using 2.1 eq of **483** and 4.2 eq of $Ti(OEt)_4$ after 72 h in refluxing THF (entries 3-6).



Scheme 207

Entry	Reagents	Solvent	T / time	Result
1	**483** (1.1 eq) $Ti(OEt)_4$ (2.2 eq)	THF	reflux / 40 h	2.6:1.0 **491:492** 25%
2	**483** (1.1 eq) $Ti(OEt)_4$ (2.0 eq)	THF	reflux / 78 h	3:1 **491:492** 44%
3	**483** (2 x 1.1 eq) $Ti(OEt)_4$ (2 x 2.2 eq)	THF	reflux / 24 h	5:1 **491:492** 30%
4	**483** (2.1 eq) $Ti(OEt)_4$ (4.2 eq)	THF	reflux / 36 h	**463** 56% 5.3:1.0 **491:492** 25%
5	**483** (2.1 eq) $Ti(OEt)_4$ (4.2 eq)	THF	reflux / 72 h	2.7:1.0 **491:492** 56%
6	**483** (2.1 eq) $Ti(OEt)_4$ (4.2 eq)	THF	reflux / 7 d	**463** 28% **491:492** 48%
7	**483** (1.1 eq) $Ti(OEt)_4$ (2.2 eq)	CPME	reflux / 6 h	**463** 26% **491:492** 39%
8	**483** (1.1 eq) $Ti(OEt)_4$ (2.2 eq)	CPME	reflux / 60 h	degradation
9	**483** (1 eq) $Ti(OEt)_4$ (2 eq)	/	70 °C (µw) / 6 h	**493** 55% 3.5:1.0 **491:492** 8%
10	**483** (1 eq) $Ti(OEt)_4$ (2 eq)	/	70 °C (µw) / 14 h	**463** 24% 6:1 **491:492** 14%
11	**483** (1 eq) $Ti(OEt)_4$ (2 eq)	/	105 °C (µw) / 5 h	3.7:1.0 **491:492** 28%
12	**483** (1 eq) $Ti(OEt)_4$ (2 eq)	/	140 °C (µw) / 5 h	degradation

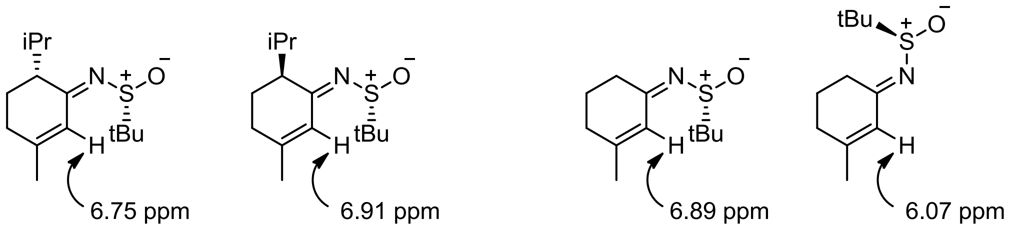
Table 42: Synthesis of sulfinimines 491 and 492

The solvent was changed from THF to CPME, a higher boiling ethereal solvent. Imines **491:492** were obtained in 39% yield along with 26% of recovered starting material after only 6 h in refluxing CPME (Table 43, entry 7). However, only degradation was observed after 60 h (entry

8). Finally, sulfinimine formation was carried out neat under microwave irradiation.[179] Poor conversion was observed at 70 °C, even after 14 h (Table 43, entries 9 and 10). Increasing the temperature to 105 °C gave **491:492** in 28% yield whereas only degradation was obtained after 5 h at 140 °C (entries 11 and 12).

As described by Guijarro and co-workers, steric hindrance probably affected the yield and complete conversion was never observed for this reaction, explaining the moderate yields obtained.[179] Notably, sulfinimine formation is moderately diastereoselective, suggesting either one enantiomer of piperitone **463** reacts faster with sulfinamide **483** or that **491** is the more thermodynamically stable diastereomer.

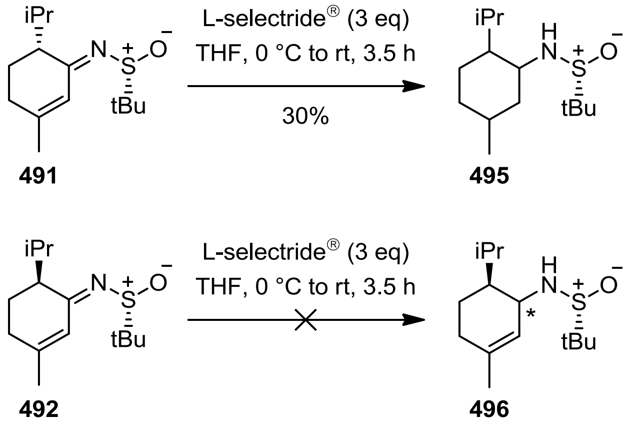
Only one imine geometry was obtained for **491** and **492**. The bulky isopropyl group should favour the formation of *Z*-imines because of the steric clash that would be obtained in *E*-ketimines. Analysis of ^{1}H-NMR spectrum shows an olefinic proton at 6.75 ppm for **491** and 6.91 ppm for **492** (Figure 23). Comparison with *Z*-ketimine **493** and *E*-ketimine **494** previously synthesized by Guijarro confirmed the *Z*-stereochemistry.[179] Indeed, the olefinic protons are seen at 6.89 ppm for the *Z*-isomer compared to an upfield proton at 6.07 ppm for the *E*-isomer. The relative stereochemistry between the *i*Pr and *t*Bu groups could not be assigned at this stage of the synthesis, but was subsequently determined by X-ray crystallography on a later intermediate.



491 **492** **493** **494**

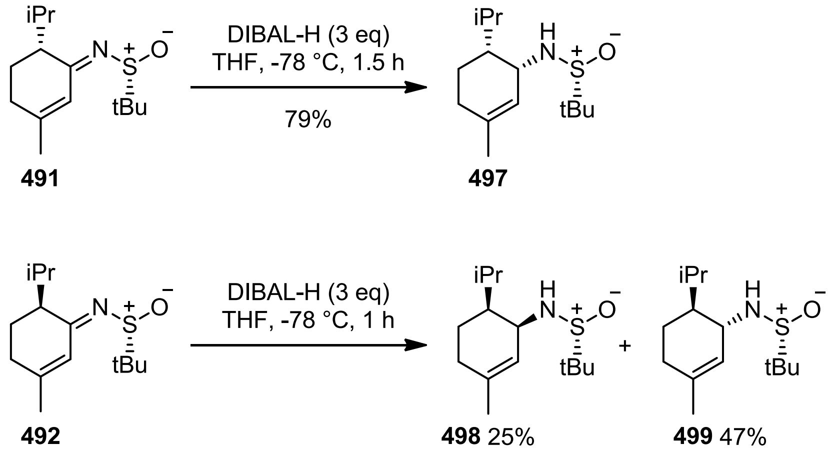
Figure 23

Reduction of the sulfinimine functional group was carried out on both isomers and was first attempted using 3 eq of L-selectride® in THF (Scheme 208).[180] After 3.5 h, over-reduction was observed and amine **495** was isolated in 30% yield as a single isomer with undefined stereochemistry from **491**, whereas degradation occurred with isomer **492**.



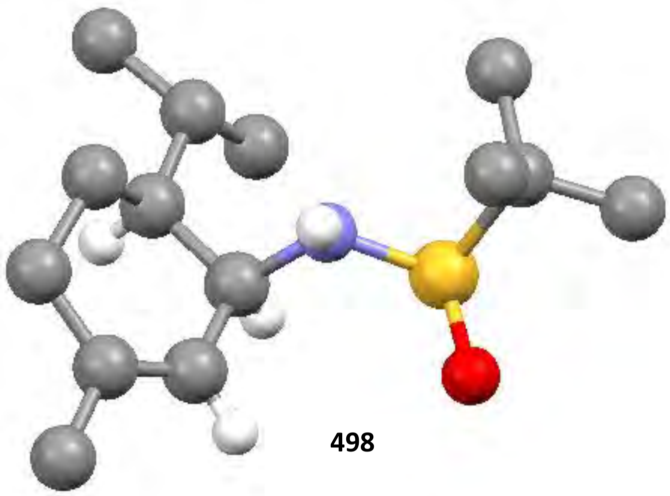
Scheme 208

The reduction was then attempted using 3 eq of DIBAL-H in THF. After 1.5 h at -78 °C, amine **497** was obtained in 79% yield as a single isomer from sulfinimine **491**. On the other hand, isomer **492** afforded 2 epimers, *cis* sulfinamide **498** in 25% yield and *trans* sulfinamide **499** in 47% yield.



Scheme 209

The stereochemistry of the minor product **498** was assigned by X-ray crystallography (Figure 24). This also corroborated the stereochemistry of its epimer **499** and by deduction the stereochemistry of sulfinimines **491** and **492** were also defined.



498

Figure 24

Comparison of the ^{1}H-NMR spectra for the different sulfinamides gave some information for the stereochemistry of **497** (Figure 25). Similar chemical shifts were found for **497** and **498**, especially for the isopropyl group and the proton next to the nitrogen. This suggested that the same *cis* stereochemistry was present.

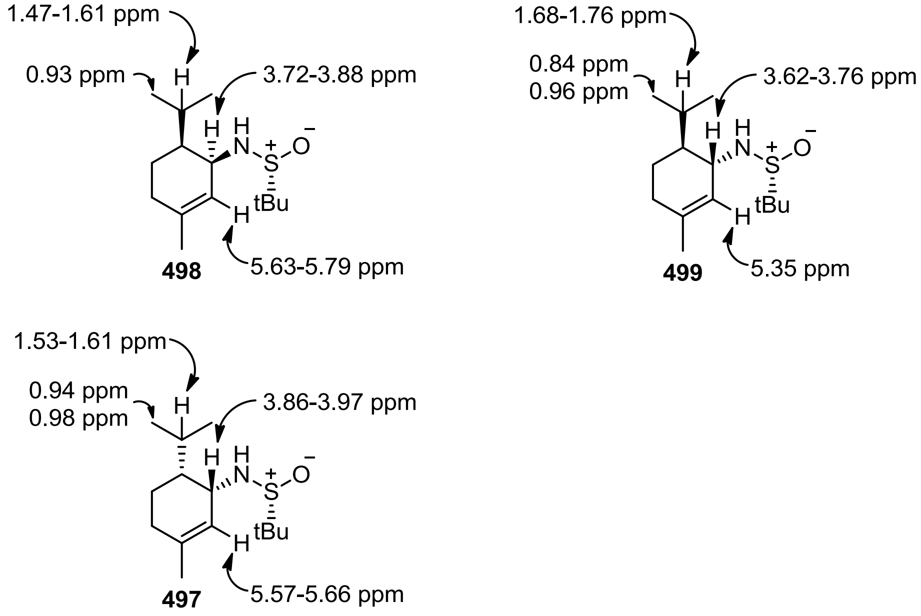


Figure 25

The reduction of the sulfinimine functional group with DIBAL-H has been described to proceed *via* a closed transition state such as **500** where the sulfinyl oxygen participates in the delivery of the hydride (Figure 26).[178,181] The larger group, the carbon bearing the isopropyl for imines **491** and **492**, needs to be in the pseudo equatorial position.

Sulfinimide **492** could be reduced *via* two closed transition states (Figure 26). Pathway B will be more favoured than pathway A because **501** has the *i*Pr and *t*Bu groups in equatorial positions. On the other hand, **500** has the *i*Pr group in an equatorial but the *t*Bu in an axial position which is less favoured. This could explain why *trans* sulfinamide **499** is the main product formed from the reduction of **492**.

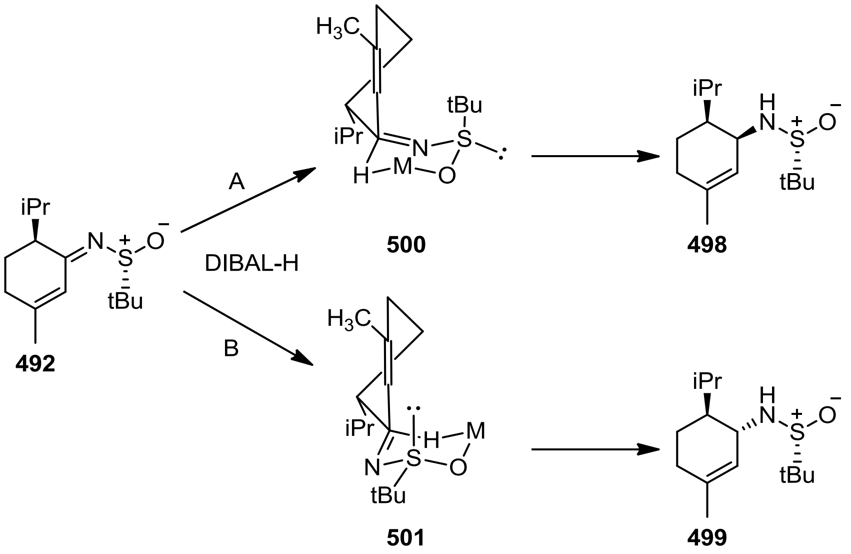


Figure 26

Two transition states are also possible for isomer **491**. Sulfinamide **503**, which was not obtained experimentally, would be formed by pathway A. However, intermediate **502** will be the least favoured because both bulky groups are in axial positions on their respective rings. On the other hand, pathway B forms **504** which bears the *i*Pr group in axial position but the bigger *t*Bu group will be equatorial. This could explain why only *cis* sulfinimide **497** was isolated after the reduction of sulfinimide **491**.

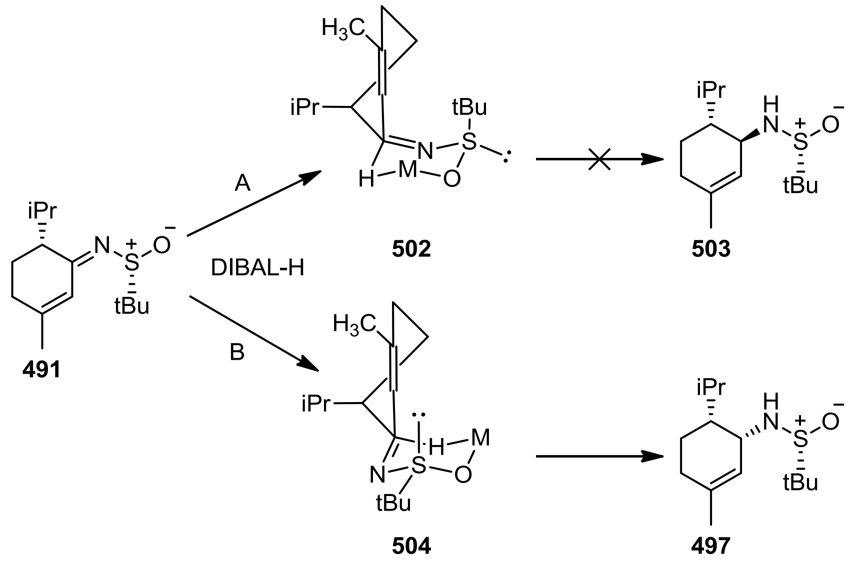
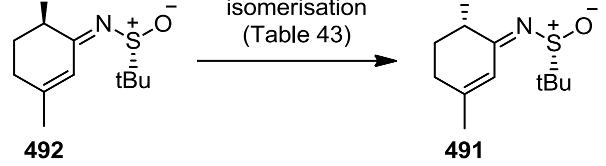


Figure 27

Sulfinimine **491** is the major product from the imine formation reaction and it gave the best stereoselectivity towards the formation of the *cis* sulfinamide by reduction of the sulfinimide functional group. As the separation of **491** and **492** was difficult by column chromatography, the isomerisation of the isopropyl group was considered (Scheme 210 and Table 43). Deprotonation of sulfinimines and reaction of the resulting metalloenamine is precedented.[178,182] However, no examples have been reported for α,β-unsaturated systems. Treatment of imine **492** with LHMDS in THF afforded only the recovered starting material (entry 1). The same result was observed when using KHMDS, even in excess (entries 2 and 3). Some isomerisation was seen on tlc analysis when LDA, a stronger base, was used (entry 4). However, **492** was recovered after the work-up. Better results were obtained using DBU in refluxing CH_3CN (entry 5). Indeed, a 1:1 mixture of isomers was formed but complete conversion to isomer **491** was not observed when the reaction time was increased.

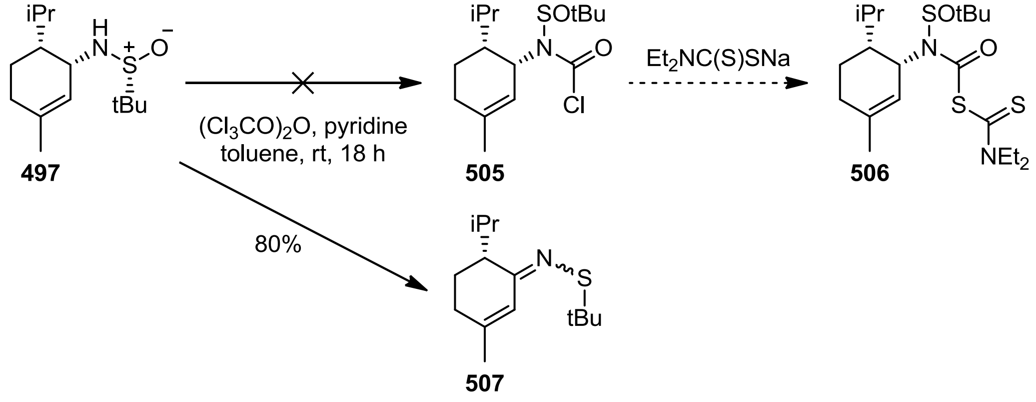


Scheme 210

Entry	Reagents	T / time	Result
1	LHMDS (3 eq), THF	0 °C to rt / 5 h	**492**
2	KHMDS (1.5 eq), THF	-78 °C to rt / 8 h	**492**
3	KHMDS (10 eq), THF	-78 °C to rt / 10 h	**492**
4	LDA (1.5 eq), THF	0 °C to rt / 3 h	**492**
5	DBU (1.5 eq), CH_3CN	reflux / 9 h	1:1 **491:492**

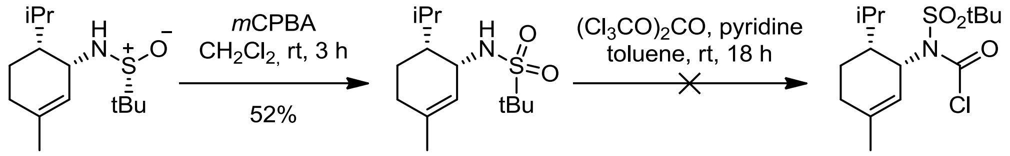
Table 43: Isomerisation of imine 492

With access to *cis* sulfinamide **497**, subsequent transformation to access dithiocarbamate **506** was considered (Scheme 211). Treatment of **497** with triphosgene and pyridine in toluene did not give the desired carbamoyl chloride **505** but afforded a 3:1 mixture of *cis*:*trans* thioimine **507** in 80% yield. This product might arise from a Pummerer-like reaction of **497**.[183]



Scheme 211

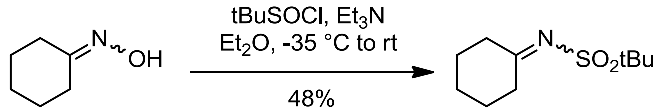
Oxidation of **497** to form Bus-protected amine **508** should improve the stability. Treatment of **497** with 1.3 eq of *m*CPBA in CH_2Cl_2 at rt afforded **508** in 52% yield (Scheme 212).[184] Unfortunately, as for the tosyl derivatives, treatment of **508** with pyridine and triphosgene in toluene gave only recovered starting material.



497 **508** **509**

Scheme 212

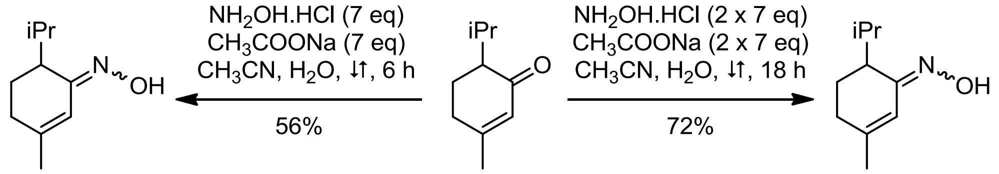
An alternative strategy to form sulfonamides would be *via* oxime formation as originally described by Hudson in 1978.[185] This radical rearrangement process was used more recently by Weinreb and co-workers to synthesize Bus-protected *N*-sulfonylimine **511** which was obtained in 48% yield from oxime **510** using *t*BuSOCl and Et_3N in Et_2O (Scheme 213).[186]



510 **511**

Scheme 213

Synthesis of oxime **512** was achieved in a moderate 56% yield by treatement of piperitone **463** with 7 eq of hydroxylamine hydrochloride in combination with sodium acetate (Scheme 214).[73] The yield was improved when 14 eq were added in two portions. A 3:1 mixture of *Z:E* oxime **512** was obtained in 72% yield after 18 h. This synthetic route was not pursued any further because of the prior difficulties which were found for the formation of carbamoyl chloride **509** from **508**. However, the synthesis of oxime **512** in good yield showed it was worth exploring the formation of other imines or oximes.



512 **463** **512**

Scheme 214

A 3:1 mixture of *Z:E* oxime **512** was obtained. The bulky isopropyl group should favour the formation of *Z*-oxime because a higher steric interaction would be obtained for *E*-oxime.

Analysis of the ^{1}H-NMR spectrum shows an olefinic proton at 6.83 ppm for **512a** and 5.83 ppm for **512b** (Figure 23). The oxygen is closer to the olefinic proton for the *Z*-isomer which explains the higher chemical shift.

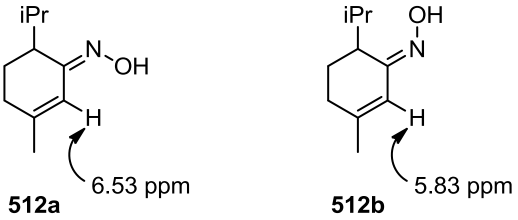
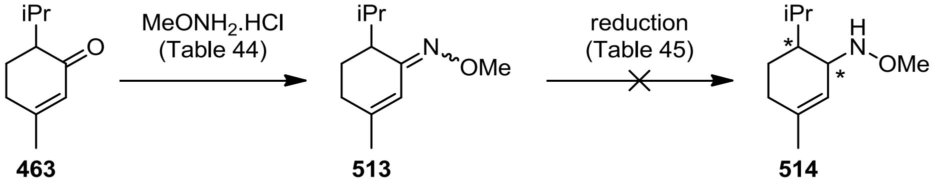


Figure 28

The synthesis of methyl oxime **513** and subsequent reduction was also investigated (Scheme 215). Treatment of piperitone **463** with methoxylamine hydrochloride and sodium acetate in a 5:1 mixture of MeOH:H_2O did not give any oxime **513** when the reaction was carried out at a concentration of 0.02 M (Table 44, entry 1).[187] Increasing the concentration to 0.1 M and 1.0 M gave a 3.5:1.0 mixture of *Z:E* oxime **513** in 24% and 59% yield respectively (entries 2 and 3).



Scheme 215

Entry	Reagents in 5:1 MeOH:H_2O	Concentration	T / time	Result
1	$MeONH_2$.HCl (10 eq) AcONa (11 eq)	0.02 M	rt / 18 h then reflux / 4 h	**463**
2	$MeONH_2$.HCl (5 eq) AcONa (5.1 eq)	0.1 M	reflux / 66 h	**513** 24%
3	$MeONH_2$.HCl (5 eq) AcONa (5.1 eq)	1.0 M	reflux / 18 h	**513** 59%

Table 44: Synthesis of methyl oxime 513

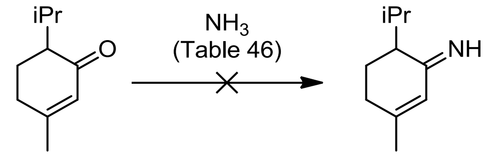
The reduction of methyl oxime **513** proved difficult. Treatment of **513** with $NaBH_3CN$ in AcOH afforded only starting material (Table 45, entry 1).[188] The same result was obtained when TFA, a stronger Brønsted acid, or $BF_3.Et_2O$, a strong Lewis acid, were used in combination with

$NaBH_3CN$ (entries 2 and 3).[189-190] No reaction was also observed with B_2H_6 in refluxing THF (entry 4).[191] No conversion was obtained when $LiAlH_4$, a stronger reducing agent, was used in refluxing THF or 1,4-dioxane (entries 5 and 6).[192] Disappearance of the starting material was observed in diglyme, a higher boiling ether. Unfortunately, alkoxyamine **514** was not isolated after the work-up and attempts to form the hydrochloride salt of alkoxyamine **514** afforded only degradation (entries 7 and 8).

Entry	Reagents	T / time	Result
1	$NaBH_3CN$ (2 eq) CH_3COOH	rt to reflux / 9 h	**513**
2	$NaBH_3CN$ (3 eq) CF_3COOH (2 eq), DMF	0 °C to reflux / 4.5 h	**513**
3	$NaBH_3CN$ (1.6 eq) $BF_3.Et_2O$ (2.5 eq), MeOH	0 °C to reflux / 18 h	**513**
4	B_2H_6 (3 eq), THF	rt to reflux / 18 h	**513**
5	$LiAlH_4$ (3 eq), THF	reflux / 8 h	**513**
6	$LiAlH_4$ (3 eq), 1,4-dioxane	reflux / 8 h	**513**
7	$LiAlH_4$ (3 eq), diglyme	reflux / 18 h	degradation
8	$LiAlH_4$ (3 eq), diglyme then HCl in dioxane	reflux / 2.5h	degradation

Table 45: Attempts for the reduction of methyl oxime 513

Because of the difficulties found in reducing methyl oxime **513**, imine formation was considered. Ammonia was first investigated as it is the smallest amine and hence a good nucleophile (Scheme 216).[193] However, no conversion was observed when piperitone **463** was treated with $Ti(OiPr)_4$ and NH_3 in solution in EtOH, even when refluxing the reaction mixture (Table 46, entry 1). Using $Ti(OEt)_4$, a Lewis acid which catalysed the synthesis of sulfinimines **491** and **492**, did not give any of the desired product (entry 2). Starting material was also recovered after refluxing a solution of ammonia in THF in combination with $Ti(OEt)_4$ for 22 h or when the reaction mixture was heated at 150 °C in a sealed tube for 24 h (entries 3 and 4).



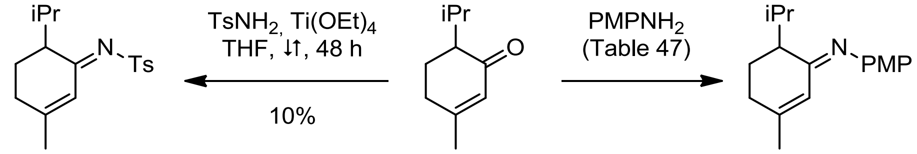
463 **515**

Scheme 216

Entry	Reagents	T / time	Result
1	NH_3 in EtOH (2 M, 5 eq) Ti(O*i*Pr)$_4$ (2 eq)	reflux / 18 h	**463**
2	NH_3 in EtOH (2 M, 5 eq) Ti(OEt)$_4$ (2 eq)	reflux / 18 h	**463**
3	NH_3 in THF (0.5 M, 5 eq) Ti(OEt)$_4$ (2 eq)	reflux / 22 h	**463**
4	NH_3 in THF (0.5 M, 5 eq) Ti(OEt)$_4$ (2 eq)	150 °C / 24 h	**463**

Table 46: Attempts to synthesize imine 515

The lack of success for the synthesis of **515** might be due to the primary imine being unstable to the reaction conditions as it was not seen on tlc analysis. Synthesis of *N*-Ts imine **516** as a single isomer was then achieved in 10% yield by treating piperitone **463** with 1.1 eq of $TsNH_2$ and 2.2 eq of Ti(OEt)$_4$ in refluxing THF for 48 h (Scheme 217). Under the same reaction conditions, PMP imine **517** was synthesized in 41% yield as a 1:7.6 mixture of *E:Z* isomers (Table 47, entry 1). Using an excess of amine improved the yield to 73% (entry 2). However, **517** was difficult to purify by column chromatography as some close running by-products by tlc analysis were also formed. Microwave irradiation was then used to avoid degradation of the reaction mixture. Imine **517** was formed in a moderate 39% yield after 18 h at 65 °C (entry 3). The conversion improved at 85 °C and **517** was obtained in 47% yield (entry 4). Unfortunately, the by-products were still formed and the purification was as difficult.



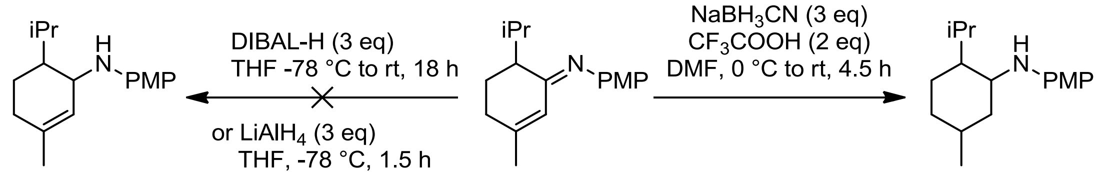
516 **463** **517**

Scheme 217

Entry	Reagents in THF	T / time	Result
1	$PMPNH_2$ (1.1 eq) $Ti(OEt)_4$ (2.2 eq)	reflux / 48 h	**517** 41%
2	$PMPNH_2$ (3 eq) $Ti(OEt)_4$ (2.2 eq)	reflux / 12 h	**517** 73%
3	$PMPNH_2$ (3 eq) $Ti(OEt)_4$ (2.2 eq)	65 °C (µw) / 18 h	**517** 39%
4	$PMPNH_2$ (3 eq) $Ti(OEt)_4$ (2.2 eq)	85 °C (µw) / 14 h	**517** 47%

Table 47: Synthesis of imine 517 from piperitone 463

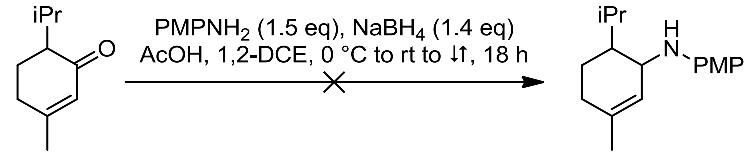
Low-temperature reduction of imine **517** with $LiAlH_4$ or DIBAL-H afforded only recovered starting material instead of amine **518** (Scheme 218). Treatment of **517** with $NaBH_3CN$ and TFA in DMF afforded a mixture of two products which did not bear any alkene proton, therefore suggesting over-reduction of imine **517** to give **519**.[189]



518 **517** **519**

Scheme 218

One-pot imine formation and subsequent reduction was also attempted using sodium triacetoxyborohydride formed *in situ* from $NaBH_4$ and AcOH.[194-195] No conversion was observed and the starting material was recovered after 18 h in refluxing 1,2-DCE.

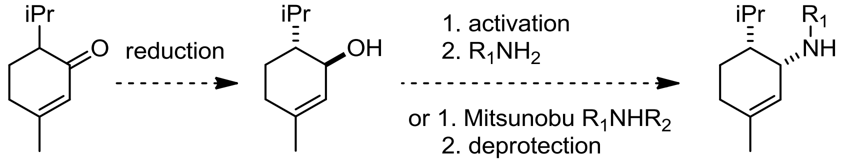


463 **518**

Scheme 219

5.5 Towards the total synthesis via cis and trans piperitol

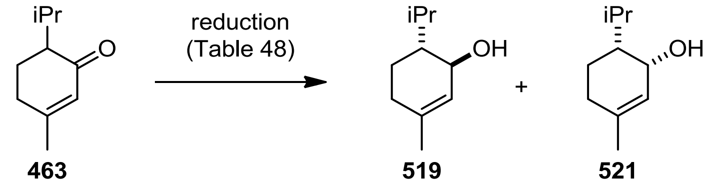
An alternative approach to the natural products was required because of unsuccessful or low-yielding access to imines and their subsequent reduction (Scheme 220). *Trans* piperitol **519** could be obtained by a stereoselective reduction of piperitol **463**. Activation of the alcohol and subsequent nucleophilic displacement *via* a S_N2 mechanism would then give *cis* amine **520**. Mitsunobu reaction could also be considered as it should also give *cis* amine **520** after deprotection.



463 **519** **520**

Scheme 220

Treatment of piperitone **463** with 1 eq of $LiAlH_4$ in Et_2O at 0 °C afforded *trans* piperitol **519** in 55% yield and *cis* piperitol **521** in 19% yield (Scheme 221 and Table 48, entry 1).[196-197] The relative stereochemistry was assigned by comparison with the literature as these molecules have been previously synthesized by Serra and co-workers.[198] The ratio was reversed under Luche reaction conditions and **519** was obtained in 22% yield along with 51% of **521** (entry 2).[199-200] As separation by column chromatography was quite difficult, Meerwein-Pondorf-Verley reduction was also attempted in the hope that only the more stable isomer would be formed.[201-202] However, a 6.5:1.4 ratio of **519:521** was obtained after 46 h in refluxing *i*PrOH (entry 3).

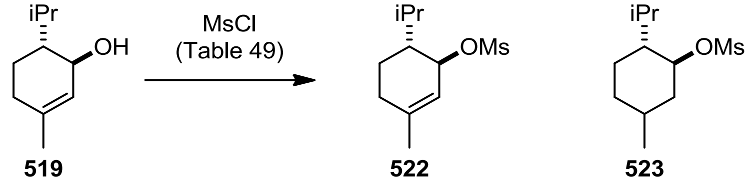


Scheme 221

Entry	Reagents	T / time	Result
1	$LiAlH_4$ (1 eq), Et_2O	0 °C / 3 h	**519** 55% **521** 19%
2	$NaBH_4$ (2 x 1 eq) $CeCl_3.7H_2O$ (1 eq), MeOH	0 °C / 3.5 h	**519** 22% **521** 51%
3	$(iPrO)_3Al$ (20 eq), *i*PrOH	reflux / 46 h	6.5:1.4 **519:521** 60%

Table 48: Reduction of piperitone 463

Mesylation of *trans* piperitol **519** was first considered (Scheme 222). Treatment of **519** with MsCl, Et_3N and a sub-stoichiometric amount of DMAP afforded degradation of the reaction mixture after 5.5 h at rt (Table 49, entry 1). The same result was observed under similar conditions with the temperature kept at 0 °C (entry 2).[203] The mesylation was also carried out with MsCl in pyridine and mesylate **523** was the sole product isolated in 6% yield. Reduction of the double bond was unexpected and a mechanism for this transformation under these reaction conditions has not been defined.

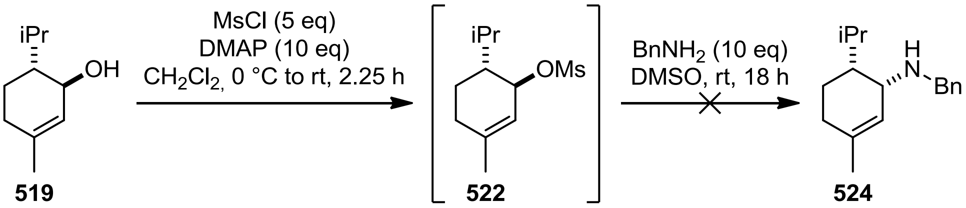


Scheme 222

Entry	Reagents	T / time	Result
1	MsCl (1.5 eq), Et_3N (2.3 eq) DMAP (0.1 eq), CH_2Cl_2	0 °C to rt / 5.5 h	degradation
2	MsCl (1.7 eq), Et_3N (1.3 eq) DMAP (0.2 eq), CH_2Cl_2	0 °C / 3 h	degradation
3	MsCl (1.5 eq), pyridine	rt / 3 h	**523** 6%

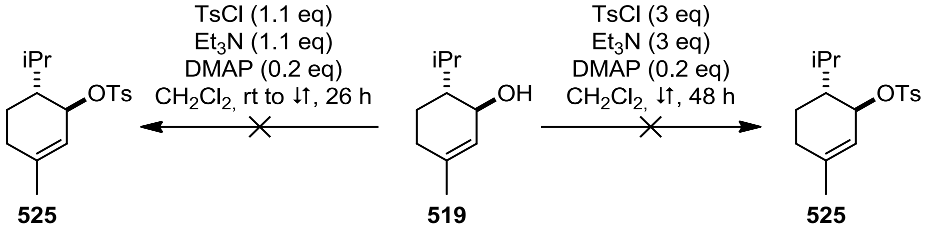
Table 49: Attempts to synthesize mesylate 522

Degradation of the reaction mixture indicated that if mesylate **522** was formed, it was quite unstable under the reaction conditions. A one-pot reaction was therefore attempted to form benzylamine **524** (Scheme 223).[204] *Trans* piperitol **519** was first reacted with MsCl and DMAP in CH_2Cl_2. After rapid filtration through celite, the crude product was dissolved in DMSO and $BnNH_2$ was added. Again, only traces of mesylate **523** were observed.



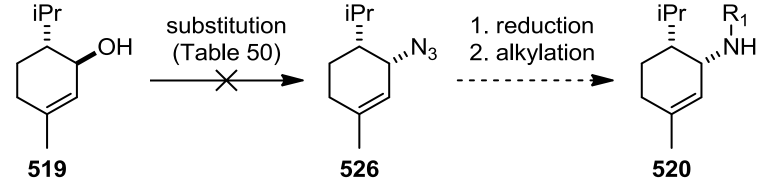
Scheme 223

The tosylation of *trans* piperitol **519** was subsequently investigated (Scheme 224). No conversion was observed when 1.1 eq of TsCl and Et_3N in combination with a sub-stoichiometric quantity of DMAP were added to **519** in CH_2Cl_2 at rt. Heating the reaction mixture to reflux for 18 h did not afford the desired tosylate **525**. Proton-NMR of the crude material showed mainly TsCl. Using an excess of reagents did not improve the conversion and again the only product observed by tlc analysis was TsCl.



Scheme 224

An alternative route to amine **520** is *via* formation of azide **526** (Scheme 225 and Table 50). Treatment of *trans* piperitol **519** with Ms_2O and DIPEA in THF followed by addition of tetrabutylammonium azide afforded degradation and 28% of the starting material **519** was recovered (entry 1).[205] When using Tf_2O as a substitute to Ms_2O to activate the alcohol, the reaction mixture degraded after 18 h at rt (entry 2). The same result was obtained with DPPA and DBU in toluene or using TFA and NaN_3 in chloroform (entries 3 and 4).[206-207]

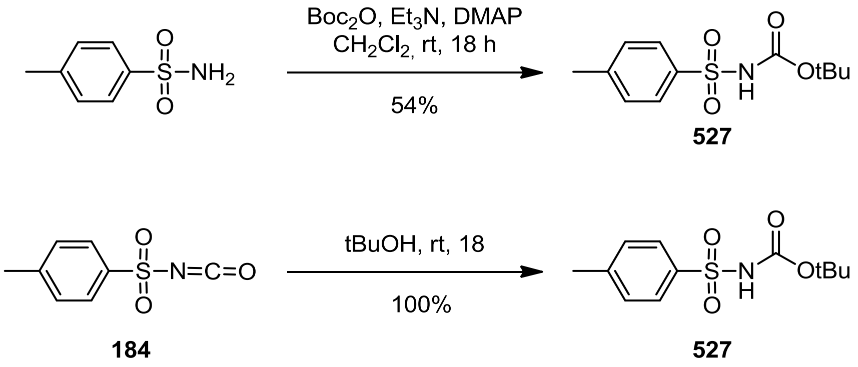


Scheme 225

Entry	Reagents	T / time	Result
1	Ms_2O, DIPEA, THF then Bu_4NN_3	-60 °C to rt / 21 h	**519** 28%
2	Tf_2O, pyridine, Bu_4NN_3, CH_2Cl_2	-78 °C to rt / 18 h	degradation
3	DPPA, DBU, toluene	0 °C to rt / 2 h	degradation
4	CF_3COOH, NaN_3, $CHCl_3$	rt / 20 min	degradation

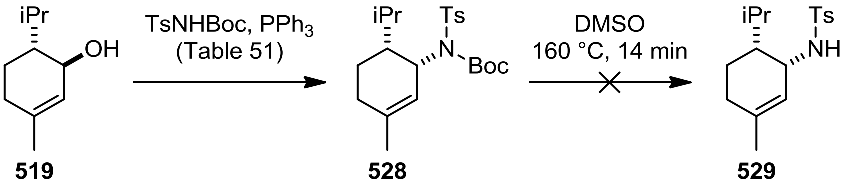
Table 50: Attempts to synthesize azide 526

The Mitsunobu reaction was then considered. Preparation of the nucleophile TsNHBoc **527** was achieved in 54% yield by treatment of $TsNH_2$ with Boc_2O, Et_3N and a sub-stoichiometric quantity of DMAP (Scheme 226).[208] An alternative procedure was to react commercially available tosylisocyanate **184** in *t*BuOH at rt for 18 h.[209] TsNHBoc **527** was obtained in quantitative yield without the need for purification.



Scheme 226

Reaction of *trans* piperitol **519** with TsNHBoc **527**, PPh$_3$ and DIAD in THF gave fully protected amine **528** in 20% yield after 43 h at rt (Scheme 227 and Table 51, entry 1).[208] The yield increased to 26% when the mixture was stirred for 52 h at rt (entry 2). The same yield was obtained when heating to reflux for 7 h after 18 h at rt (entry 3). The low yield obtained for the synthesis of **528** was surprising because complete consumption of the starting material was observed by tlc analysis. Subsequent Boc-deprotection was attempted using microwave irradiation in DMSO.[210] Unfortunately, degradation was observed.

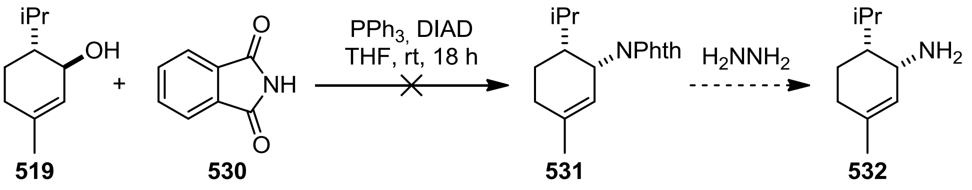


Scheme 227

Entry	Reagents	T / time	Result
1	PPh$_3$ (3 eq), **527** (1.5 eq) DIAD (2.5 eq), THF	rt / 43 h	**528** 20%
2	PPh$_3$ (3 eq), **527** (1.5 eq) DIAD (2 eq), THF	rt / 52 h	**528** 24%
3	PPh$_3$ (3 eq), **527** (1.5 eq) DIAD (2 eq), THF	rt / 43 h then reflux / 7 h	**528** 26%

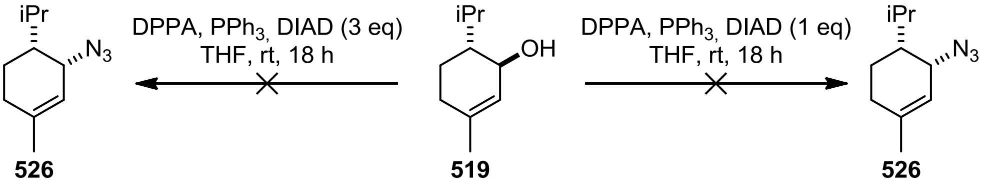
Table 51: Synthesis of 528 via a Mitsunobu reaction

Phthalimide **530** was also considered as a suitable nucleophile for the Mitsunobu reaction as it could be easily deprotected with hydrazine.[211] Treatment of **519** with 1.3 eq of PPh$_3$, phthalimide **530** and DIAD in THF did not afford **531** (Scheme 228). Conversion was observed without the formation of a new component by tlc analysis.



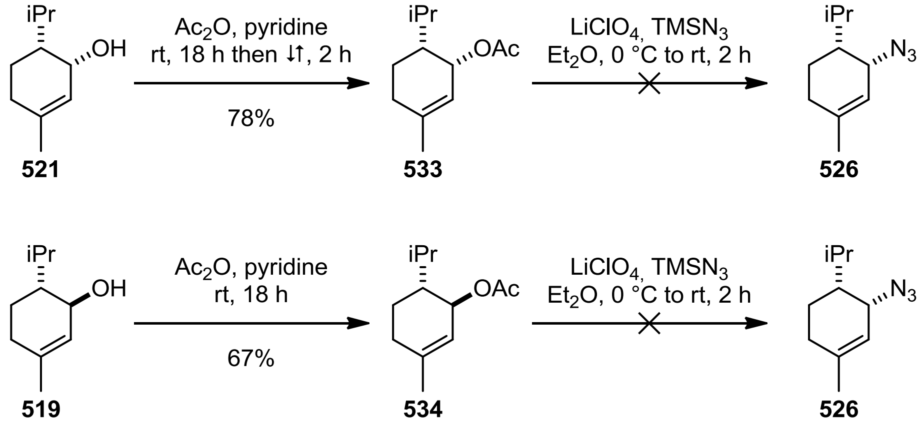
Scheme 228

Finally, the Mitsunobu reaction was attempted on **519** using diphenylphosphoryl azide as the nucleophile (Scheme 229).[212] With 1 eq of DPPA, PPh_3 and DIAD, no reaction was observed. Complete conversion was seen after 6 h at rt with 3 eq of reagents. However, the desired azide **526** was not isolated and only traces of a by-product bearing three protons in the ethylenic region of the ^{1}H-NMR spectrum were isolated.



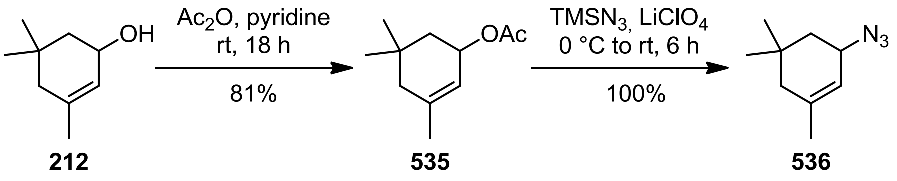
Scheme 229

The formation of azide **526** *via* acetates **533:534** was also investigated (Scheme 230). Treatment of *cis* piperitol **521** with Ac_2O in pyridine afforded *cis* acetate **533** in 78% yield.[213] *Trans* acetate **534** was obtained from **519** in 67% yield under the same reaction conditions. Treatment of each isomer with an excess of $LiClO_4$ and $TMSN_3$ afforded the same unknown product.[214] Unfortunately, both ^{1}H-NMR spectra showed a mixture of two products which possess two protons in the ethylenic region, ruling out the formation of **526**.



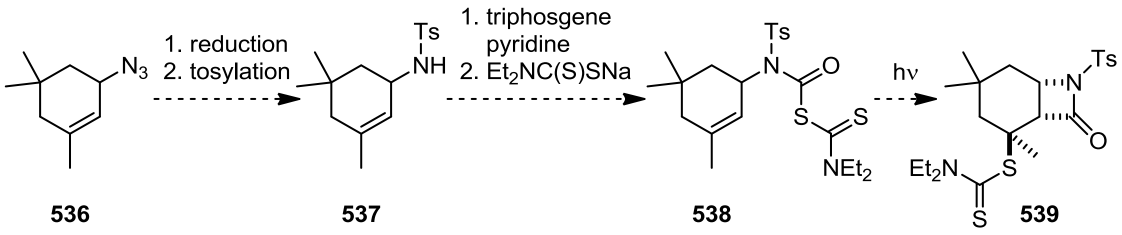
Scheme 230

The formation of this by-product was intriguing. It was therefore decided to apply the same procedure onto isophorol **212** (Scheme 231). Acetate **535** was formed in 81% yield and subsequent treatment with $LiClO_4$ and $TMSN_3$ afforded azide **536** in quantitative yield without the need for purification. This proved the reliability of Pearson's procedure and that it was not suitable for piperitone derivatives, possibly because of the steric hindrance of the isopropyl group.



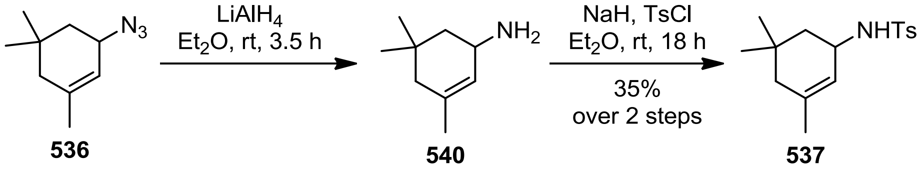
Scheme 231

As it was easy to access **536**, it was decided to further transform the azide functional group to form tosyl amine **537** (Scheme 232). Subsequent modification of **537** would afford dithiocarbamate **538** which could be a suitable model substrate to attempt the 4-*exo trig* radical cyclisation-dithiocarbamate group transfer on a trisubstituted alkene to form β-lactam **539**.



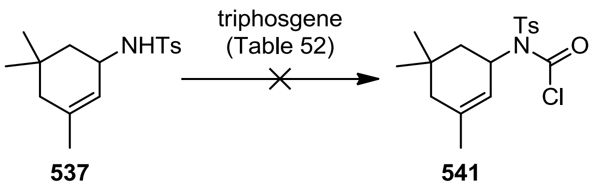
Scheme 232

Reduction of **536** with $LiAlH_4$ in Et_2O afforded primary amine **540** which was assumed to be volatile due to its low molecular weight (MW 139 $g.mol^{-1}$).[215] It was therefore reacted directly with NaH and TsCl to give tosylamine **537** in 35% yield over the two steps.



Scheme 233

Further transformation of tosylamine **537** into carbamoyl chloride **541** was investigated (Scheme 234 and Table 52). Starting material **537** was recovered when pyridine and triphosgene in toluene were used (entry 1). Addition of DMAP to catalyse the reaction or heating the mixture to reflux also afforded starting material (entries 2 and 3). When using a stronger base, KHMDS or LHMDS, in combination with pyridine and triphosgene, no conversion was observed (entries 4 and 5).

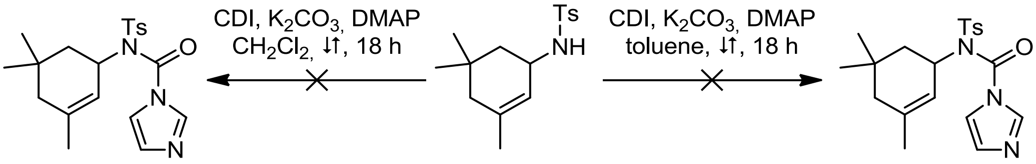


Scheme 234

Entry	Reagents in toluene	T / time	Result
1	$(Cl_3CO)_2CO$, pyridine	rt / 18 h	**537**
2	$(Cl_3CO)_2CO$, pyridine, DMAP	rt / 18 h	**537**
3	$(Cl_3CO)_2CO$, pyridine, DMAP	reflux / 18 h	**537**
4	KHMDS then $(Cl_3CO)_2CO$, pyridine	rt / 18 h	**537**
5	LHMDS then $(Cl_3CO)_2CO$, pyridine	rt / 18 h	**537**

Table 52: Attempts to synthesize carbamoyl chloride 541

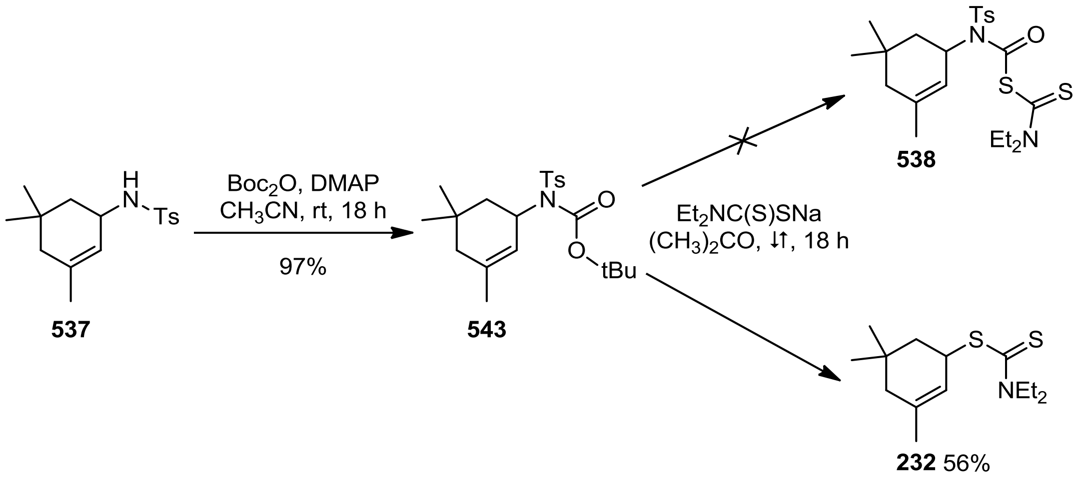
Treatment of tosylamine **537** with CDI and K_2CO_3 in combination with a sub-stoichiometric amount of DMAP in refluxing CH_2Cl_2 or toluene again afforded recovered starting material **537** instead of **542** (Scheme 235).[28,216]



542 **537** **542**

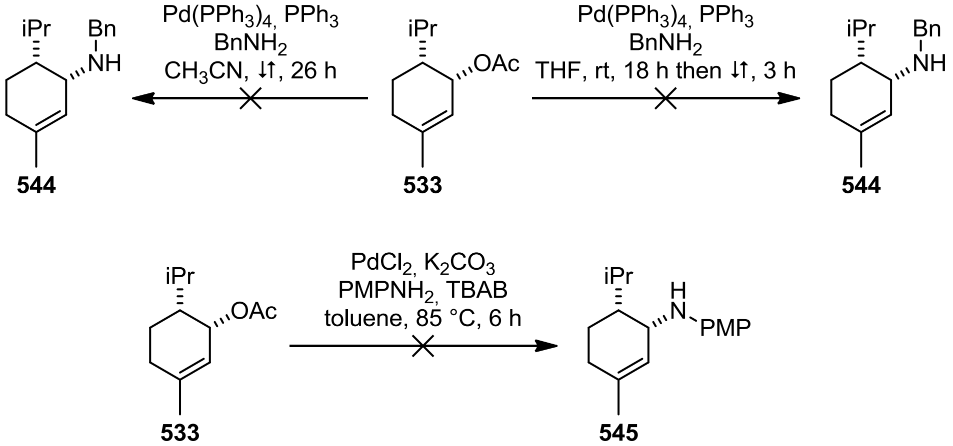
Scheme 235

Surprisingly, Boc-protected tosylamine **543** was synthesized in 97% yield using Boc_2O with DMAP in CH_3CN at rt (Scheme 236).[217] Reaction of **543** with sodium diethyldithiocarbamate did not afford the desired dithiocarbamate **538** but gave **232** in 56% yield. This product may arise from decomposition of dithiocarbamate **538**.[100] The route using azide **526** for the total synthesis of calyciphylline D, calyciphylline F and caldaphnidine M was not developed any further because of the difficulty in forming dithiocarbamate **538** on the model system.



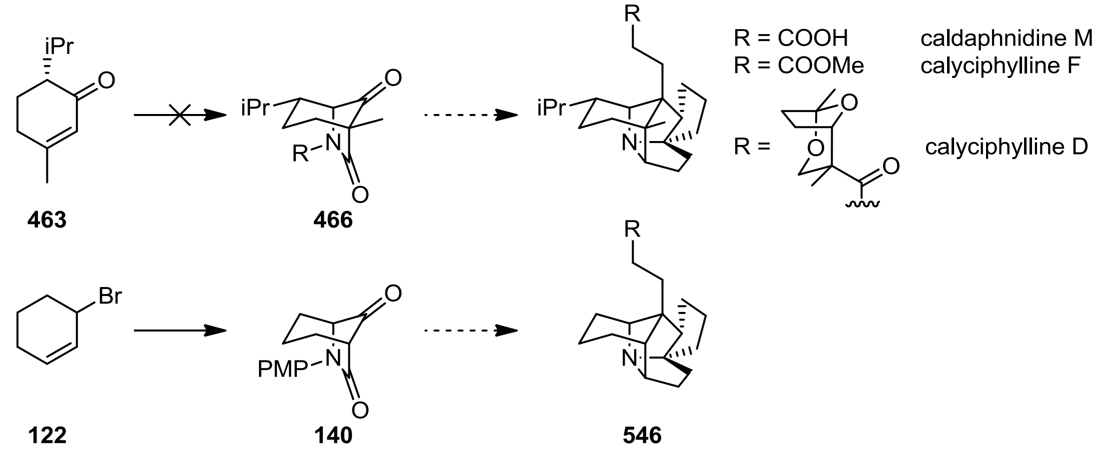
Scheme 236

An alternative route was therefore developed and it was decided to react *cis* acetate **533** with Pd(0) to form allylic Bn or PMP amines (Scheme 237). The palladium-catalysed allylic amination of **533** with 10 mol% of freshly prepared Pd(PPh$_3$)$_4$, 20 mol% of PPh$_3$ and 3 eq of BnNH$_2$ in refluxing CH$_3$CN afforded degradation of the reaction mixture.[218] Using the same reagents in THF, the starting material was recovered after 18 h at rt followed by 3 h at reflux. *Para*-anisidine was then considered for the allylic amination.[219] Reaction of **533**, PMPNH$_2$, K$_2$CO$_3$, TBAB and PdCl$_2$ in toluene at 85 °C for 6 h gave only starting material.



Scheme 237

All the efforts to functionalise piperitone **463** to create suitable intermediates for the formation of bicyclic ketone **466** were unsuccessful (Scheme 238). On the other hand, bicyclic ketone **140** had previously been synthesized successfully from commercially available 3-bromocyclohexene **122**. It was therefore decided to investigate the construction of the fused pentacyclic core structure **546** of calyciphylline D, calyciphylline F and caldaphnidine M starting from bicyclic ketone **140**.

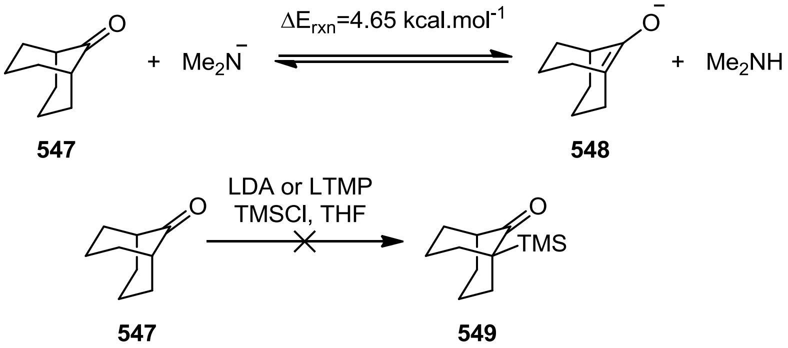


Scheme 238

5.6 Bridgehead functionalisation of the 7,8-diketo-6-azabicyclo[3.2.1]octane ring system

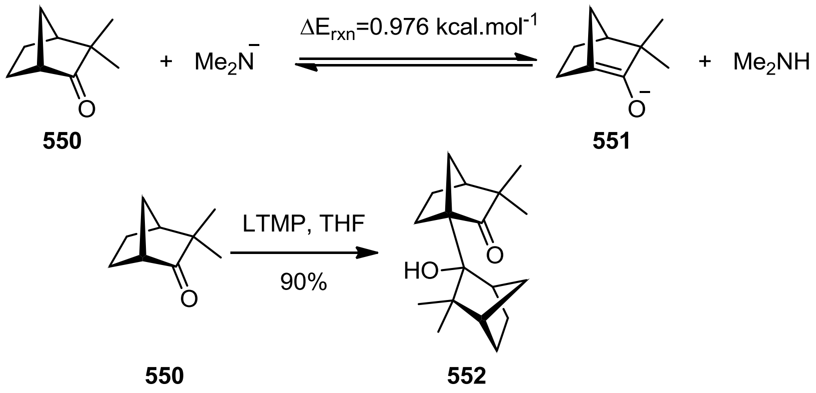
In order to get closer to the structure of the natural product, functionalisation of the 1-position through bridgehead deprotonation on the 7,8-diketo-6-azabicyclo[3.2.1]octane structure **140** was investigated. Computational analysis of the bridgehead deprotonation reaction was first conducted. The geometry optimisations were performed by Professor Chris Hayes from the University of Nottingham using the B3LYP/6-31G*//B3LYP/6-31G* computational method. This calculation method had been previously used in predicting the bridgehead deprotonation of a variety of ketones, lactams, lactones and imides.[220] The study showed that if a positive ΔE_{rxn} was obtained, the deprotonation was unfavourable whereas if it was a negative value, the deprotonation would be thermodynamically feasible. There are also borderline situations with small positive ΔE_{rxn} values which indicated that the deprotonation was possible but poor control was obtained with condensation with the starting material occurring instead of alkylation. These theoretical results were reproduced experimentally.

Ketone **547** showed a positive ΔE_{rxn} (ΔE_{rxn}=4.65 kcal.mol^{-1}) indicating that the deprotonation was unfavourable (Scheme 239). Bridgehead lithiation and subsequent alkylation using either LDA or LTMP as a base in combination with TMSCl proved impossible experimentally. Self-condensation was not observed in the absence of TMSCl.



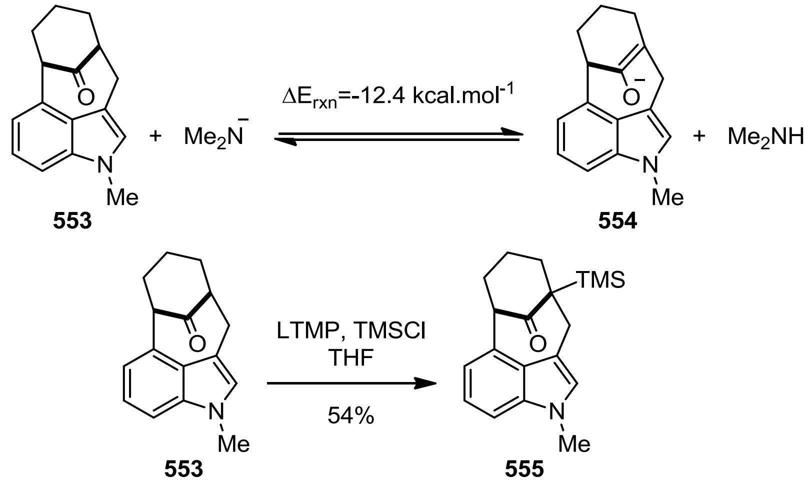
Scheme 239

Camphelinone **550** showed a small positive ΔE_{rxn} (ΔE_{rxn}=0.976 kcal.mol^{-1}) indicating that the deprotonation was unfavourable (Scheme 240). However, aldol adduct **552** was obtained in 90% yield experimentally, suggesting that deprotonation to form **551** was occurring and it was followed by condensation with **550**.



Scheme 240

A relevant structure for comparison with **140** is ketoindole **553**, synthesized by Simpkins and co-workers, as it possesses a ketone carbonyl carbon as the sole bridging atom.[221] Its deprotonation had been investigated towards the total synthesis of welwistatin[220] and a negative ΔE_{rxn} was obtained using the calculation (ΔE_{rxn}=-12.4 kcal.mol^{-1}), suggesting that the metallation was possible (Scheme 241). This was confirmed experimentally as TMS-substituted **555** was obtained in 54% yield using LTMP and TMSCl in THF.



Scheme 241

The calculations conducted by Professor Chris Hayes showed negative ΔE_{rxn} (ΔE_{rxn}=-20.0 kcal.mol-1 for **557** and -29.1 kcal.mol^{-1} for **559**) for the deprotonation of phenyl- and methyl-substituted bicyclic ketones **556** and **558**. Bridgehead deprotonation should therefore be thermodynamically favourable. However, it is not possible to say from this calculation if the deprotonation is kinetically feasible.

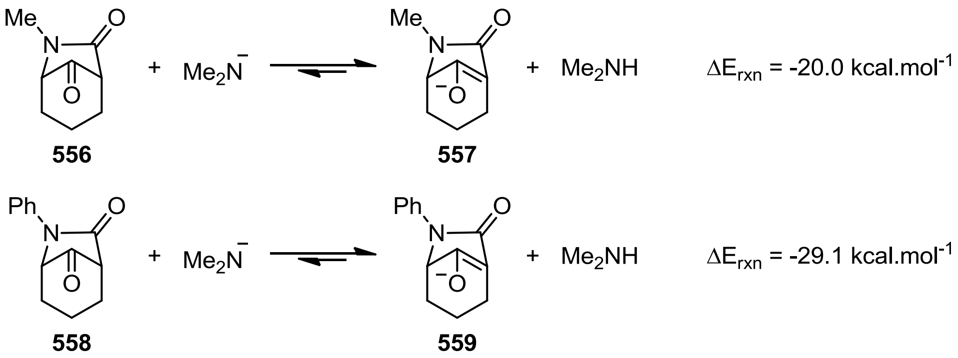
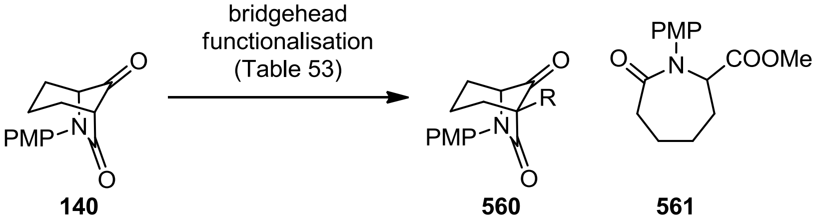


Figure 29

Following Simpkins' procedure, bicyclic ketone **140** was treated with 2 eq of LTMP formed *in situ* from TMP and *n*BuLi and 10 eq of TMSCl at -78 °C (Scheme 242).[220,222] The starting material was only sparingly soluble in THF at this temperature. No conversion was observed by tlc analysis even when the reaction mixture was warmed to rt (Table 53, entry 1). Quenching the reaction with D_2O did not show any deuterium incorporation and the starting material was recovered. The same result was observed using LHMDS, another non nucleophilic strong base, in CH_2Cl_2 (entry 2). Methylation of the bridgehead position in **140** was then investigated. Treatment of **140** with LHMDS followed by addition of MeI afforded only starting material in CH_2Cl_2 and 25% of lactam **561** in DMF (entries 3 and 4).

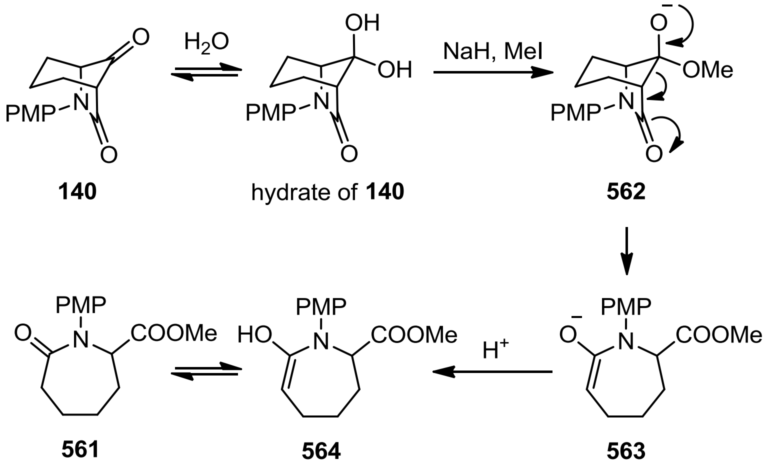


Scheme 242

Entry	R	Reagents	T / time	Result
1	TMS	TMP, *n*BuLi, LiCl (2 eq) TMSCl (10 eq), THF	-78 °C to rt 18 h	**140**
2		LHMDS (2 eq) TMSCl (10 eq), CH_2Cl_2	0 °C to rt 18 h	**140**
3	CH_3	LHMDS (2 eq), CH_2Cl_2 then MeI (10 eq)	0 °C to rt 7 h	**140**
4		LHMDS (2 eq), DMF then MeI (10 eq)	0 °C to rt 4 h	**561** 25%
5		NaH (2 eq), DMF then MeI (10 eq)	rt 3 h	**561** 90%
6		NaH (2 eq), DMF then Me_3OBF_4 (10 eq)	rt 3 h	**561** 81%
7		3 Å MS, NaH (2 eq), THF then MeI (10 eq)	rt to 40 °C 3.5 h	unidentified products
8		3 Å MS, NaH (2 eq), THF then MeI (10 eq)	rt to 40 °C 18 h + 15 min	unidentified products

Table 53: Bridgehead functionalisation of 140

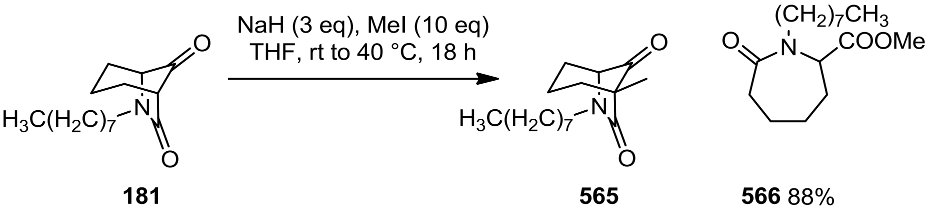
It was then decided to use thermodynamic conditions for the deprotonation. When **140** was reacted with NaH in DMF, lactam **561** was obtained in 90% yield with MeI and 81% yield with Me_3OBF_4 (Table 53, entries 5 and 6). This product is likely to arise from deprotonation of the hydrated form of bicyclic ketone **140** (Scheme 243). The ring-opening probably releases the strain present in the bicyclic structure and is a possible driving force for this reaction.



Scheme 243

The same yields for the formation of lactam **561** were observed when MeI was distilled or DMF was dried over molecular sieves prior to use, in order to remove any traces of H_2O. When the bicyclic ketone **140** was stirred for 30 min over 3 Å molecular sieves in DMF prior to the addition of the base, three unidentified products were formed in small yields (Table 53, entry 7). Increasing the stirring time over molecular sieves to 18 h, one compound was formed but the data collected did not correspond to lactam **561** or to the desired methylated bicyclic ketone (entry 8).

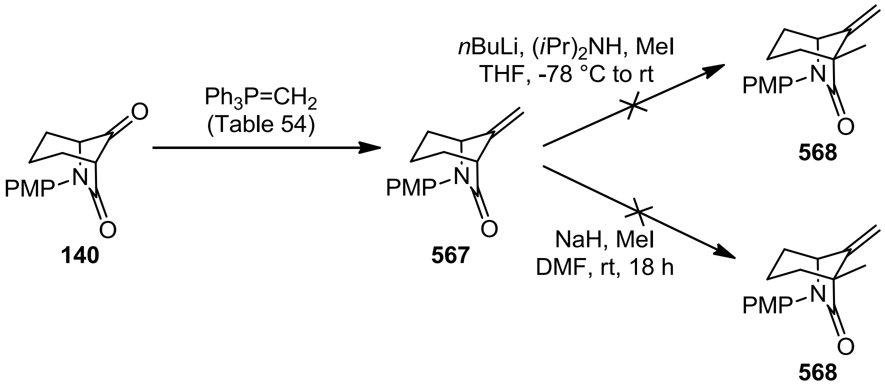
Alkylation was also attempted on freshly prepared *N*-C_8H_{17} bicyclic ketone **181** which was more soluble in organic solvents. Addition of 3 eq of NaH and 10 eq of MeI to a mixture of **181** in THF did not afford bridgehead methylated **565** but lactam **566** in 88% yield.



Scheme 244

The formation of the hydrate of **140** being an issue for the bridgehead methylation, it was decided to form alkene **567** prior to alkylation. Treatment of **140** with 1.6 eq of methyltriphenylphosphonium bromide and *n*BuLi in THF afforded alkene **567** in 40% yield after an aqueous work-up (Scheme 245 and Table 54, entry 1).[70] Using the same procedure, alkene **567** was obtained in 24% yield after a work-up with hexane and a filtration to remove the triphenylphosphine oxide by-product (entry 2). Direct purification of the concentrated reaction mixture gave **567** in an improved 60% yield (entry 3). Finally, the use of 2.1 eq of reagents afforded alkene **567** in 93% yield (entry 4).

Low-temperature methylation of the bridgehead position on alkene **567** was then attempted using 2.5 eq of LDA prepared *in situ* and 5 eq of MeI (Scheme 245). Only starting material was obtained, even after the reaction mixture was warmed to rt. Bridgehead alkylation was then carried out using 2 eq of NaH and an excess of MeI in DMF. No conversion was observed and the starting material **567** was recovered after 18 h at rt.

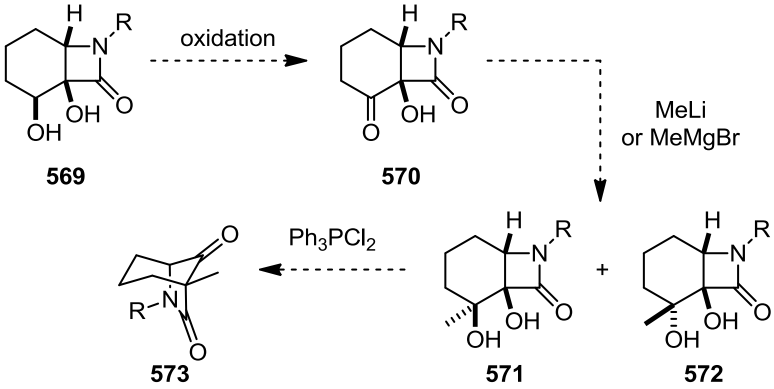


Scheme 245

Entry	Reagents in THF	work-up	T / time	Result
1	$Ph_3P^+CH_3,Br^-$, *n*BuLi (1.6 eq)	NH_4Cl, CH_2Cl_2	reflux / 18 h	**567** 40%
2	$Ph_3P^+CH_3,Br^-$, *n*BuLi (1.6 eq)	hexane filtration	reflux / 18 h	**567** 24%
3	$Ph_3P^+CH_3,Br^-$, *n*BuLi (1.6 eq)	concentration	reflux / 18 h	**567** 60%
4	$Ph_3P^+CH_3,Br^-$, *n*BuLi (2.1 eq)	concentration	reflux / 18 h	**567** 93%

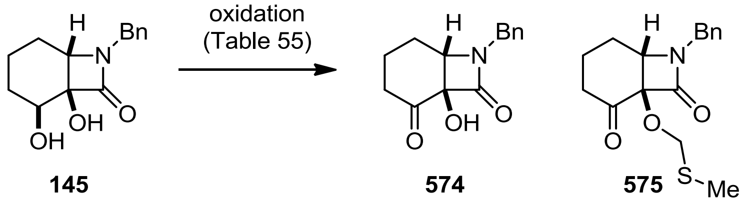
Table 54: Synthesis of alkene 567

Another option to incorporate a methyl at the bridgehead position of the 7,8-diketo-6-azabicyclo[3.2.1]octane structure would be to introduce it prior to the semipinacol rearrangement (Scheme 246). Oxidation of diol **569** would give α-hydroxyketone **570** which could then be reacted with MeLi or MeMgBr to give **571** and/or **572**. Semipinacol rearrangement of the *cis* diol **571** would then give the desired alkylated bicyclic ketone **573**.



Scheme 246

Oxidation of diol **145** was first attempted with 1.2 eq of PCC at rt and degradation of the reaction mixture was observed (Scheme 247 and Table 55, entry 1).[223] Using DMP in combination with pyridine or $NaHCO_3$ provided trace amounts of α-hydroxyketone **574** among products of degradation (entries 2 and 3).[224] Swern oxidation of diol **145** afforded protected ketone **575** in 35% yield (entry 4).[225-226] To avoid the formation of **575**, *i*PrOH was added in the same time as Et_3N. Unfortunately, tlc analysis showed that **575** was the main component after the work-up (entry 5). Finally, diol **145** was reacted with RuO_4 formed *in situ* from a mixture of $RuCl_3$, $NaHCO_3$ and Oxone® as described by Plietker in 2004 (entry 6).[227] α-Hydroxyketone **574** was formed in a moderate 38% yield and was contaminated with some degradation products even after an attempted purification by column chromatography.

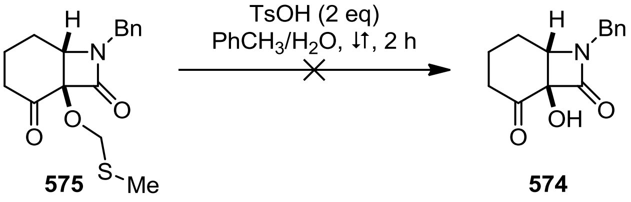


Scheme 247

Entry	Reagents	T / time	Result
1	PCC (1.2 eq), CH_2Cl_2	rt / 1.5 h	degradation
2	DMP (2 eq), pyridine (5 eq) CH_2Cl_2	0 °C to rt / 4.5 h	**574** traces
3	DMP (2 eq), $NaHCO_3$ (5 eq) CH_2Cl_2	0 °C to rt / 1 h	**574** traces
4	$(ClCO)_2$ (3 eq), DMSO (9 eq) Et_3N (20 eq), CH_2Cl_2	-78 °C / 2 h	**575** 35%
5	$(ClCO)_2$ (3 eq), DMSO (9 eq) Et_3N (20 eq), *i*PrOH (20 eq), CH_2Cl_2	-78 °C / 2 h	**575** 35%
6	$RuCl_3$ (10 mol%), $NaHCO_3$ (2.5 eq) Oxone® (5 eq), H_2O, CH_3CN, EtOAc	0 °C / 4 h	**574** 38% (impure)

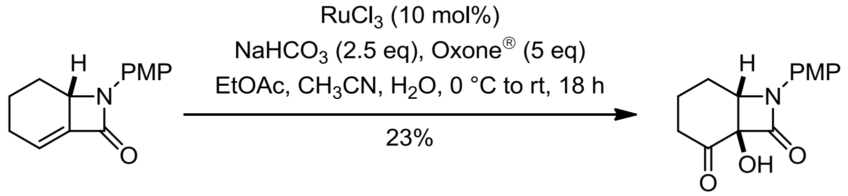
Table 55: Oxidation of diol 145

Deprotection of the methylthiomethyl group was attempted with TsOH in a refluxing 1:1 mixture of H_2O:toluene (Scheme 248).[228] No reaction occurred and the starting material was recovered.



Scheme 248

Plietker described the formation of α-hydroxyketones from oxidation of alkenes. Treatment of alkene **130** with 10 mol% RuO_4 gave **576** in 23% yield. Even if low-yielding, the product was obtained pure. Full conversion was observed by tlc analysis. Increasing the catalyst loading to 20 mol% did not improve the yield for this oxidation. Insufficient quantities of α-hydroxyketone **576** were formed and addition of a nucleophile could not be attempted.

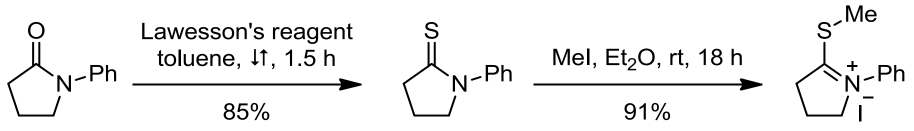


130 **576**

Scheme 249

5.7 Towards the synthesis of 546: nucleophilic addition to lactams and thiolactams

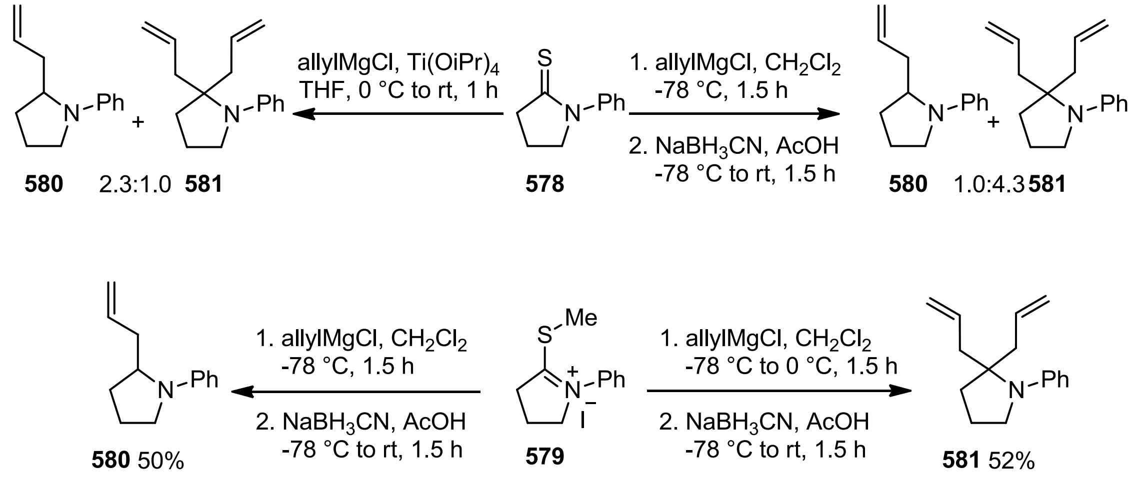
The addition of nucleophiles into lactam **567** was considered. However, before reacting **567**, the reactivity of a representative readily available substrate, 1-phenyl-2-pyrrolidinone **577**, was investigated. Formation of thiolactam **578** was achieved in 85% yield using 0.6 eq of Lawesson's reagent in refluxing toluene for 1.5 h (Scheme 250).[229] Treatment of **578** with an excess of MeI in Et_2O for 18 h at rt afforded *S*-alkylated thiolactam **579** in 91% yield.[70]



577 **578** **579**

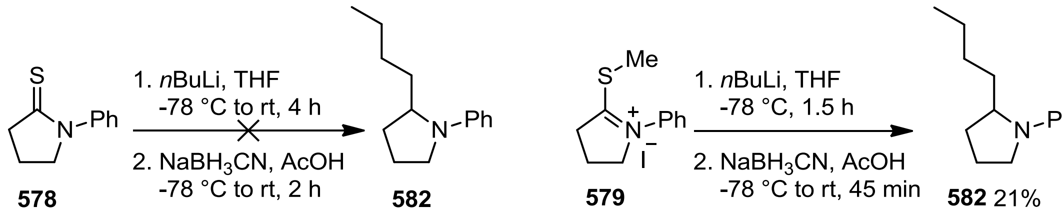
Scheme 250

Addition of a Grignard reagent, allylmagnesium chloride, in combination with $Ti(O\textit{i}Pr)_4$ to **578**, as recently described by Six and co-workers, afforded a 2.3:1.0 mixture of monoalkylated **580** and dialkylated **581** (Scheme 251).[230] Treatment of **578** with allylmagnesium chloride followed by *in situ* reduction with $NaBH_3CN$ gave a 1.0:4.3 mixture of **580:581**.[70] On the other hand, monoalkylated **580** was obtained in 50% yield as the sole product when **579** was treated at -78 °C with 1.5 eq of allylmagnesium chloride whereas dialkylated **581** was formed in 52% yield when the reaction mixture was warmed to 0 °C before the reduction.



Scheme 251

Addition of an organolithium species such as *n*BuLi was also considered (Scheme 252). Treatment of thiolactam **578** with 2 eq of *n*BuLi followed by reduction with NaBH$_3$CN afforded only starting material. On the other hand, the same procedure on alkylated thiolactam **579** gave pyrrolidine **582** in 21% yield.

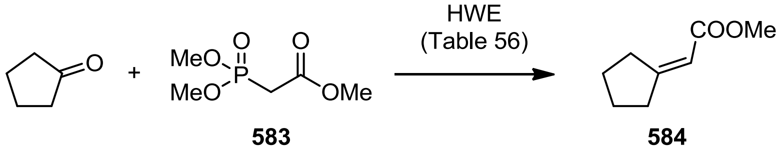


Scheme 252

In summary, addition of allylMgCl on thiolactam **578** gave a mixture of mono and dialkylated phenylpyrrolidines **580** and **581**. The addition was more selective on methylated thiolactam **579**. Indeed, dialkylation was observed when the reaction mixture was allowed to warm to 0 °C before reduction, whereas monoalkylated pyrrolidine **580** was formed in 50% yield when the mixture was kept at -78 °C. On the other hand, no reaction was observed when *n*BuLi was added into thiolactam **578** whereas butyl pyrrolidine **582** was formed in 21% yield with **579**.

As it was possible to selectively add commercially available nucleophiles on alkylated thiolactam **579**, it was decided to synthesize a nucleophile which upon addition to **567** would generate a suitable substrate to undergo the tandem radical cyclisation (Section 5.2, Scheme

198). Treatment of cyclopentanone with 1 eq of trimethylphosphonoacetate **583** and NaH in MeOH at rt for 18 h, as described by Brückner in 2006, gave methyl ester **584** in 29% yield after purification by distillation (Scheme 253 and Table 56, entry 1).[231] Using 1.5 eq of **583** and NaH, the Horner-Wadsworth-Emmons reaction did not go to completion. However, purification by column chromatography improved the isolated yield, giving 43% of **584** (entry 2). A similar yield was obtained when the reaction mixture was heated at reflux or when **583** was used as the limiting reagents (entries 3 and 4). Using Na instead of NaH to form NaOMe *in situ* afforded **584** in 68% yield (entry 5).

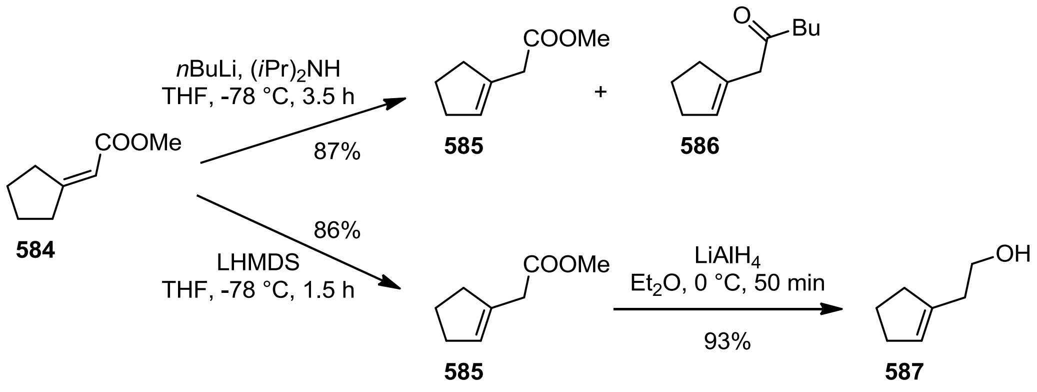


Scheme 253

Entry	Reagents in MeOH	T / time	Purification	Result
1	cyclopentanone (1 eq) **583** (1 eq), NaH (1.2 eq)	rt / 18 h	distillation	**584** 29%
2	cyclopentanone (1 eq) **583** (1.5 eq), NaH (1.5 eq)	rt / 18 h	chromatography	**584** 43%
3	cyclopentanone (1 eq) **583** (1.5 eq), NaH (1.5 eq)	reflux / 18 h	chromatography	**584** 38%
4	cyclopentanone (2 eq) **583** (1 eq), NaH (1 eq)	rt / 18 h	chromatography	**584** 37%
5	cyclopentanone (1 eq) **583** (1.5 eq), Na (1.5 eq)	rt / 18 h	chromatography	**584** 68%

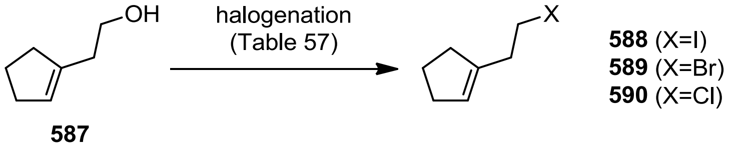
Table 56: Synthesis of methyl ester 584

Low-temperature isomerisation of the double bond was first achieved using 1.2 eq of LDA formed *in situ* as described in the literature.[231] The non-conjugated alkene **585** obtained in 86% was contaminated with a small amount (<10%) of ketone **586** which arose from attack of residual *n*BuLi onto the ester functional group. When conjugated ester **584** was reacted with 1.2 eq of LHMDS, ester **585** was isolated in 87% yield. Reduction of the ester functional group using 3 eq of $LiAlH_4$ in Et_2O at 0 °C gave alcohol **587** in 93% yield.



Scheme 254

Formation of different halogen derivatives from alcohol **587** was investigated (Scheme 255 and Table 57). Treatment of **587** with triphenylphosphine, iodine and imidazole gave iodide **588** in 59% yield (entry 1).[232-233] Using 2 eq of reagents afforded **588** in an improved 79% yield (entry 2).



Scheme 255

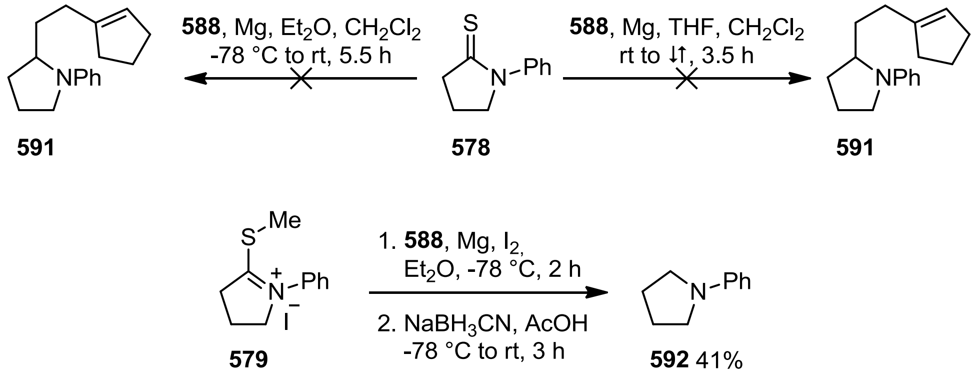
Entry	Halogen	Reagents	T / time	Result
1	I	PPh_3, I_2, Imid. (1.1 eq) Et_2O:CH_3CN	0 °C to rt / 2 h	**588** 59%
2		PPh_3, I_2, Imid. (2 eq) Et_2O:CH_3CN	rt / 3 h	**588** 79%
3	Br	PBr_3 (0.4 eq), Et_2O	0 °C / 1 h	degradation
4		PBr_3 (3 x 0.4 eq), Et_2O	-78 °C / 4.5 h	degradation
5	Cl	$SOCl_2$, pyridine, CH_2Cl_2	0 °C to rt / 9.5 h	degradation

Table 57: Halogenation of alcohol 587

Addition of PBr_3 to a solution of alcohol **587** in Et_2O at 0 °C afforded degradation of the reaction mixture (Table 57, entry 3).[234] When the reaction was carried out at -78 °C, a new component was seen by tlc analysis. However, it could not be isolated after the work-up (entry

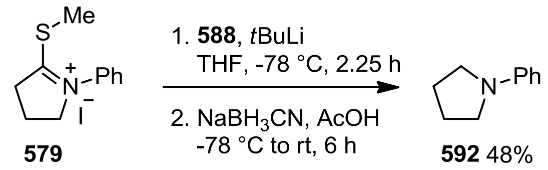
4). Isolation of chloride **590** was also impossible. Consumption of the starting material was observed when **587** was treated with thionyl chloride and pyridine.[235] However, ^{1}H-NMR spectroscopic analysis of the product obtained after purification showed only degradation (entry 5).

Treatment of **588** in Et_2O with Mg at rt and subsequent addition at low temperature of thiolactam **578** in CH_2Cl_2 did not afford the desired pyrrolidine derivative **591** (Scheme 256). Starting material **578** was also recovered when the procedure was repeated using THF and when the reaction mixture was refluxed. Finally, addition of alkylated thiolactam **579** into a solution of the Grignard in Et_2O afforded pyrrolidine **592** in 41% yield after reduction instead of **591**. The difficulty in forming the Grignard reagent *in situ* might explain the lack of reactivity. Indeed, the magnesium was not solubilised, even when iodine was used to activate the *in situ* formation.



Scheme 256

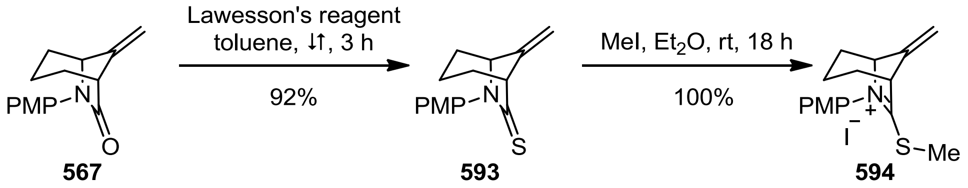
Addition of an organolithium species into **579** was then examined (Scheme 257). *t*BuLi was added to a solution of **588** in THF at -78 °C. After 30 min, the reaction mixture was warmed to 0 °C and cooled back to -78 °C after 15 min at 0 °C. Alkylated thiolactam **579** was added and the mixture was treated with $NaBH_3CN$ after 1.5 h at -78 °C. Unfortunately, pyrrolidine **592** was again the only isolated product, in 48% yield.



Scheme 257

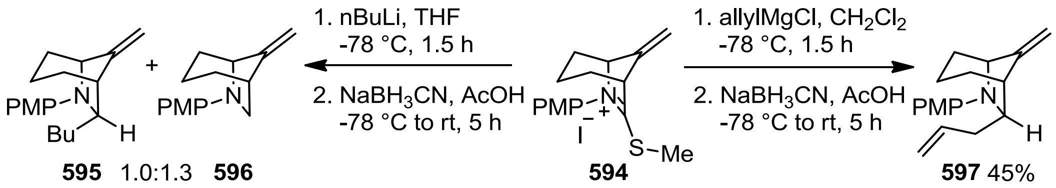
In summary, the addition of lithium or Grignard derivatives, *in situ* formed from **588**, on thiolactam **578** or methylated thiolactam **579** was not successful. Only reduction of the starting material was observed. It was therefore decided to only add allylMgCl and *n*BuLi to the bicyclic alkylated thiolactam to get an insight into the stereoselectivity of the reaction.

Formation of thiolactam **593** was achieved in 91% yield using 0.6 eq of Lawesson's reagent in refluxing toluene for 1.5 h (Scheme 258).[229] Treatment of **593** with an excess of MeI in Et_2O for 18 h at rt afforded *S*-alkylated thiolactam **594** in quantitative yield.[70]



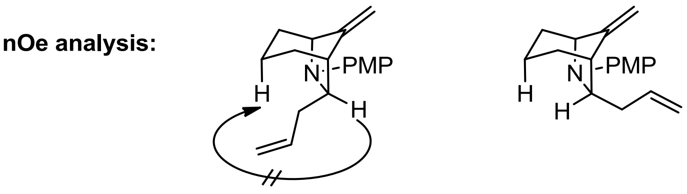
Scheme 258

Treatment of alkylated thiolactam **594** with *n*BuLi and subsequent reduction gave an inseparable 1.0:1.3 mixture of butylated amine **595** and amine **596** (Scheme 259). Addition of allylmagnesium chloride at low temperature followed by reduction with $NaBH_3CN$ afforded amine **597** in 45% yield as a single diastereomer.



Scheme 259

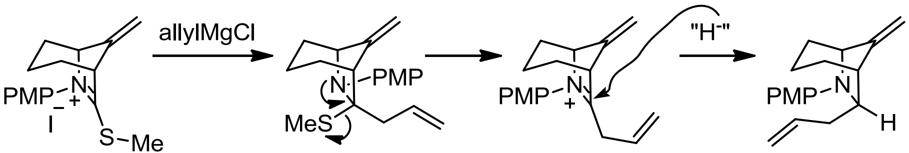
An nOe NMR experiment was conducted on **597** to determine which isomer was formed (Figure 30). When the proton next to the nitrogen and the allyl group was excited, an nOe enhancement to the axial proton was not observed whereas it would be expected for the desired isomer **598**. This tentatively suggested that the allyl group was located under the cyclohexyl ring. The stereochemistry of butylated amine **595** was assigned by analogy to **597**.



597 **598**

Figure 30

This stereoselectivity could be explained *via* the formation of intermediate **600**. Addition of hydride occurred from the presumably less hindered face to give **597** (Scheme 260). The opposite stereochemistry is desired for the tandem radical cyclisation to take place (Section 5.2, Scheme 198). It would therefore be necessary to reduce the thiolactam prior to the addition of a nucleophile.

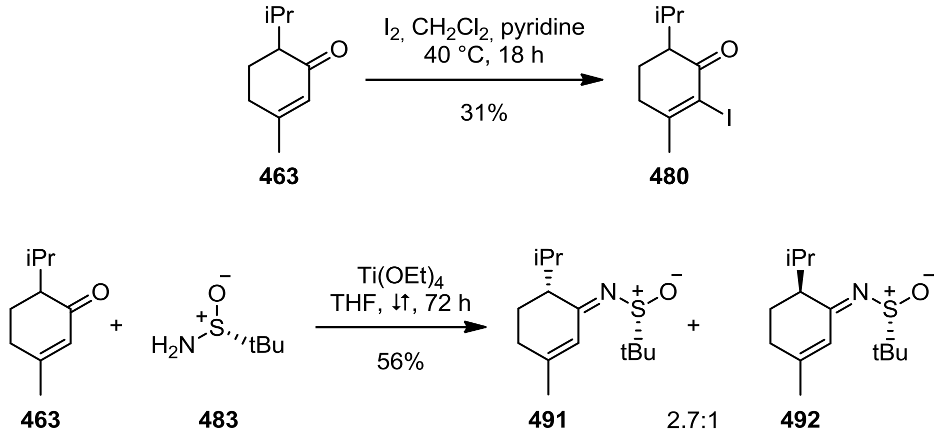


594 **599** **600** **597**

Scheme 260

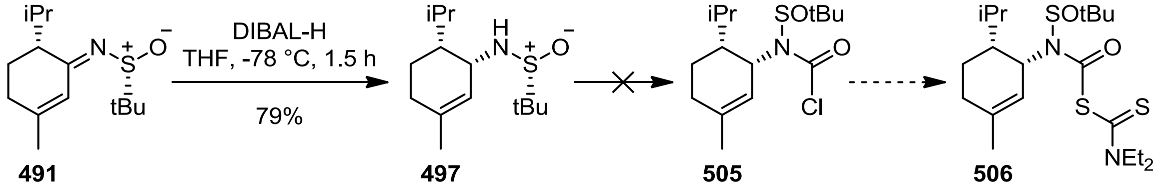
5.8 Conclusion and future work

The total synthesis of calyciphylline D, calyciphylline F and caldaphnidine M was attempted *via* transformation of piperitone **463**, a readily available terpene which possesses an isopropyl and methyl group in the same position as the natural products. Unfortunately, the reactivity of piperitone towards halogenation or reductive amination was quite poor (Scheme 261). The best yield was obtained with the formation of sulfinimines **491** and **492**.



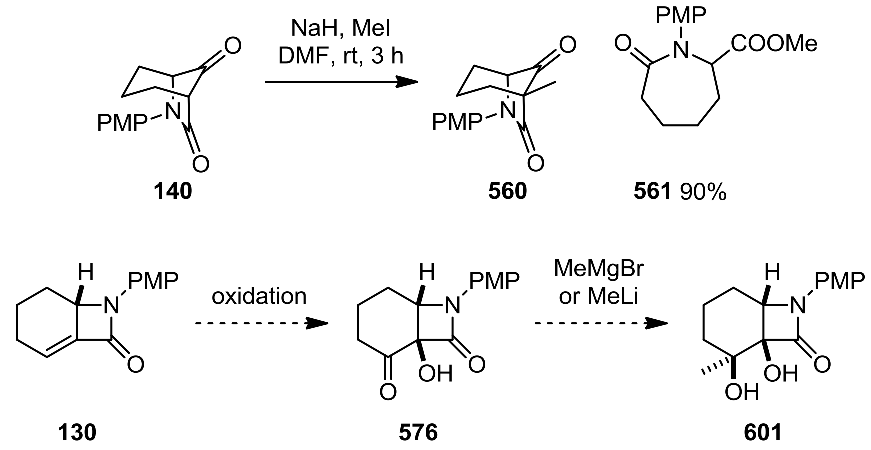
Scheme 261

Selective reduction of sulfinimine **491** to sulfinamide **497** was achieved in 79% yield with DIBAL-H (Scheme 262). However, further functional group transformation in order to synthesize dithiocarbamate **506** was not successful.



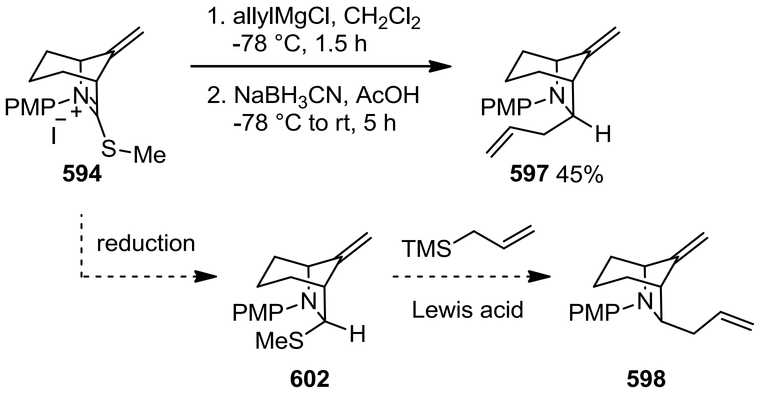
Scheme 262

The synthesis of the fused pentacyclic core structure from bicyclic ketone **140** was then investigated. Bridgehead methylation of bicyclic ketone **140** using NaH and MeI in DMF did not afford **560** but lactam **561** was formed in 90% yield (Scheme 263). Further investigation on the oxidation of alkene **130** towards α-hydroxyketone **576** and subsequent addition to stereoselectively form *cis* diol **601** will be required.



Scheme 263

Finally, addition of allylmagnesium chloride into methylated thiolactam **594** afforded the desired amine **597** but as the wrong isomer to pursue the synthesis (Scheme 264). It will therefore be necessary to examine the reduction of the thiolactam prior to the addition of a suitable nucleophile.



Scheme 264

Chapter six:

Experimental part

6.1 General experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker AVIII 300, Bruker AVIII 400 spectrometer. Spectra were recorded in D_2O referenced to residual H_2O (^1H, 4.79 ppm; ^{13}C, SR=161.3, corresponding to external TSP capillary set at 0 ppm), DMSO-d_6 referenced to residual DMSO (^1H, 2.50 ppm; ^{13}C, 39.4 ppm), MeOD-D_4 referenced to residual MeOH (^1H, 3.31 ppm; ^{13}C, 49.0 ppm) and deuterochloroform referenced to residual $CHCl_3$ (^1H, 7.26 ppm; ^{13}C, 77.2 ppm). Chemical shifts (δ) are reported in ppm and coupling constants (J) are reported in Hz. The following abbreviations are used to describe multiplicity; s-singlet, d-doublet, t-triplet, q-quartet, hept-heptet, m-multiplet, br-broad, ap. apparent. Mass spectra were recorded on a LCT spectrometer or on a LTQ Orbitrap spectrometer (NMSSC Swansea) utilising electrospray ionisation (recorded in the positive mode) with a methanol mobile phase, or electron impact ionisation, or chemical ionisation and are reported as (*m/z* (%)). HRMS were recorded on a LCT spectrometer or on a LTQ Orbitrap spectrometer (NMSSC Swansea) using lock mass incorporated into the mobile phase. IR spectra were recorded neat on Perkin Elmer 100-series FT-IR spectrometer. Melting points were determined using open glass capillaries on a Gallenkamp melting point apparatus and are uncorrected. Analytical t.l.c. was carried out on Merck 60 F245 aluminium-backed silica gel plates. Short-wave UV radiation (245 nm), $KMnO_4$ and vanillin were used to visualise components. Compounds were purified by flash column chromatography using Merck silica gel 60 (0.040-0.063 nm) or Merck alumina oxide 90 standardised. The following cooling baths were used; 0 °C (ice/water) and -78 °C (dry ice/acetone). All reactions in non-aqueous solvents were carried out under argon in oven-dried glassware. Solvents were degassed by bubbling argon through a needle immersed in the solvent for the stated length of time.

Solvents and reagents were purified as follows:

Pyridine and triethylamine were distilled from potassium hydroxide. NBS was recrystallised from H_2O, PPh_3 was recrystallised from conc. HCl and H_2O. Piperitone, $Ti(OEt)_4$ and $Ti(O\textit{i}Pr)_4$

were purified by bulb-to-bulb distillation under reduced pressure. THF, Et_2O, toluene, CH_3OH, CH_2Cl_2 and CH_3CN were dried by passing through activated alumina columns.

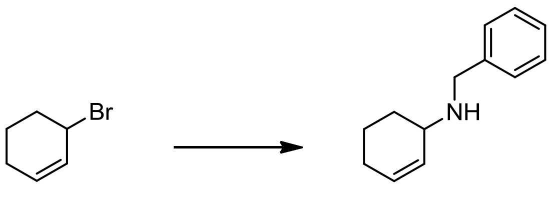
*n*BuLi was purchased as a 1.6 M solution in hexanes and the solution was titrated with menthol in the presence of 1-(biphenyl-4-yl)-3-phenyl-2-azapropene (“BLUE”).

*m*CPBA was purified by washing with a pH 7 phosphate buffer unless otherwise stated: A buffer solution was prepared from 0.1 M NaOH (154 mL) and 0.2 M KH_2PO_4 (94 mL) and made up to 376 mL with distilled water. *m*CPBA (77% w/w, 10 g) was dissolved in diethyl ether (100 mL) and washed four times with the buffer solution. The organic extract was dried over $MgSO_4$ and carefully evaporated under reduced pressure to yield pure *m*CPBA (7.3 g).

All other reagents and solvents were purchased from Aldrich, Alfa Aesar, Fisher Scientific, Merck or TCI Europe and were used as received. LHMDS in solution in THF was purchased only from Aldrich.

6.2 *Experimental procedures and analytical data for Chapter two*

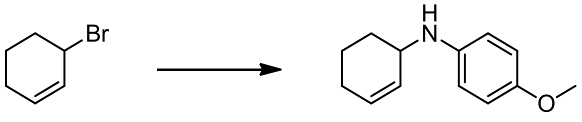
- *N*-Benzylcyclohex-2-enamine **123**



122 **123**

A known compound[236] prepared according to the literature procedure.[27] A solution of benzylamine (9.73 mL, 89.1 mmol) in CH_3CN (90 mL) was treated with 3-bromocyclohexene **122** (3.80 mL, 33.0 mmol) and K_2CO_3 (4.79 g, 34.7 mmol). After 2 h at rt, the reaction mixture was quenched with H_2O (50 mL) and extracted with EtOAc (2 x 75 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (CH_2Cl_2 to CH_2Cl_2:EtOH 9:1) to give amine **123** (6.18 g, 100%) as a colourless oil (lit. yield 76%). R_f 0.45 (CH_2Cl_2:EtOH 49:1); ν_{max} (neat)/cm^{-1}: 3063, 2926, 1452, 1106, 723, 696; δ_H (400 MHz, $CDCl_3$) 1.38 (1H, br s, NH), 1.47-1.63 (2H, m, CH_2), 1.73-1.81 (1H, m, CH_2), 1.89-1.97 (1H, m, CH_2), 1.99-2.06 (2H, m, CH_2), 3.20-3.26 (1H, m, NC*H*CH_2), 3.84, 3.88 (2H, ABq, *J* 13.0 Hz, NCH_2Ph), 5.75-5.82 (2H, m, CH=CH), 7.23-7.38 (5H, m, Ar H); δ_C (100 MHz, $CDCl_3$) 20.3 (CH_2), 25.5 (CH_2), 29.6 (CH_2), 51.1 (CH_2, $NHCH_2Ph$), 52.5 (CH, CH_2*C*HN), 126.9 (CH, Ar), 128.3 (2 x CH, Ar), 128.4 (2 x CH, Ar), 129.1 (CH, CH_2*C*H=CH), 130.1 (CH, CH=*C*HCHN), 140.9 (C, Ar); m/z (ES) 188 ($[M+H]^+$, 100%). *Literature data*:[236] δ_H (400 MHz, $CDCl_3$) 7.36-7.20 (m, 5H), 5.78-5.65 (m, 2H), 3.87 (d, *J* = 13.0 Hz, 1H), 3.83 (d, *J* = 13.0 Hz, 1H), 3.22 (m, 1H), 1.99 (m, 2H), 1.89 (m, 1H), 1.72 (m, 1H), 1.48 (m, 2H), 1.31 (br s, 1H); δ_C (100 MHz, $CDCl_3$) 140.87, 130.03, 129.03, 128.46, 128.24, 126.92, 52.48, 51.10, 29.59, 25.45, 20.33.

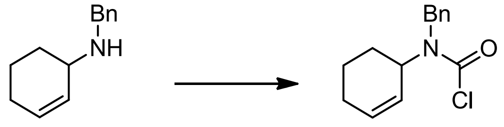
- *N*-(Cyclohex-2-en-1-yl)-4-methoxyaniline **124**



122 **124**

A known compound[237] prepared according to a literature procedure.[27] A solution of 4-methoxyaniline (2.89 g, 23.5 mmol) in CH_3CN (24 mL) was treated with 3-bromocyclohexene **122** (1.00 mL, 8.69 mmol) and K_2CO_3 (1.32 g, 9.56 mmol). After 6 h at rt, the reaction mixture was quenched with H_2O (25 mL) and extracted with Et_2O (2 x 25 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether:EtOAc 9:1) to give amine **124** (1.76 g, 99%) as a yellow oil. R_f 0.48 (Pet ether:EtOAc 9:1); ν_{max} (neat)/cm^{-1}: 3382, 2931, 1617, 1507, 1228, 815, 723; δ_H (400 MHz, $CDCl_3$) 1.55-1.76 (3H, m, CH_2), 1.87-1.94 (1H, m, CH_2), 2.01-2.05 (2H, m, CH_2), 3.31 (1H, br s, NH), 3.75 (3H, s, OCH_3), 3.89-3.96 (1H, m, NC*H*CH_2), 5.76 (1H, dd, *J* 2.7 and 9.9 Hz, CH_2C*H*=CH), 5.83 (1H, dtd, *J* 1.8, 3.3 and 9.9 Hz, CH=C*H*CHN), 6.60 (2H, d, *J* 9.0 Hz, Ar H), 6.77 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 19.9 (CH_2), 25.3 (CH_2), 29.2 (CH_2), 49.1 (CH, CH_2*C*HN), 56.0 (CH_3, OCH_3), 115.0 (2 x CH, Ar), 115.1 (2 x CH, Ar), 129.0 (CH, CH_2*C*H=CH), 130.0 (CH, CH=*C*HCHN), 141.5 (C, ArCN), 152.2 (C, ArCO); m/z (EI) 203.1306 (M^+ $C_{13}H_{17}NO$ requires 203.1310), 203 (M^+, 100%), 175 (39), 160 (22), 123 (56), 108 (57). *Literature data*:[237] δ_H ($CDCl_3$) 6.76 (m, 2H), 6.58 (m, 2H), 5.80 (m, 1H), 5.74 (m, 1H), 3.89 (br s, 1H, C*H*N), 3.73 (s, 3H, OC*H*$_3$), 3.26 (br s, 1H, N*H*), 2.01 (m, 2H), 1.88 (m, 1H), 1.69 (m, 1H), 1.57 (m, 2H); δ_C ($CDCl_3$) 152.1, 141.5, 130.0, 129.0, 115.1, 115.0, 55.9 (O*C*H_3), 49.1 (*C*HN), 29.1, 25.4, 19.9; m/z 203, 175, 160, 123, 108, 81.

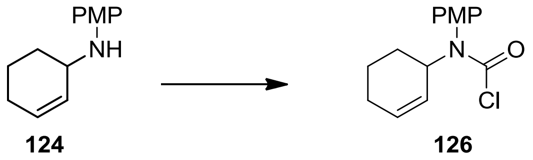
- Benzyl(cyclohex-2-enyl)carbamic chloride **125**



123 **125**

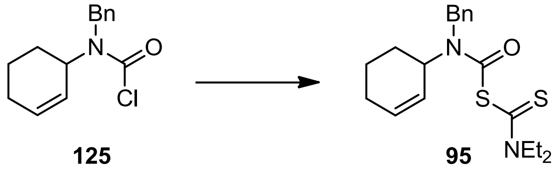
A known compound prepared according to a literature procedure.[27] A solution of triphosgene (0.852 g, 2.87 mmol) in toluene (50 mL) was treated with pyridine (0.750 mL, 9.30 mmol) and subsequently with a solution of amine **123** (1.46 g, 7.78 mmol) in toluene (5 mL). The reaction was stirred for 18 h at rt, quenched with $NaHCO_3$ (40 mL of a saturated aq. solution) and extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed sequentially with HCl (40 mL of a 0.25 M aq. solution), H_2O (40 mL) and brine (40 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give carbamoyl chloride **125** (1.85 g, 95%) as a white solid (lit. yield 74%). mp 73-75 °C; R_f 0.55 (Pet ether:EtOAc 85:15); ν_{max} (neat)/cm^{-1}: 2920, 1607, 1477, 1419, 727, 697; δ_H (400 MHz, $CDCl_3$) 1.57-1.71 (2H, m, CH_2), 1.80-1.92 (2H, m, CH_2), 2.02 (2H, br s, CH_2), 4.16-4.37 (2H, m, NCH_2Ph), 4.48-4.50 (1H, m, $NC\mathit{H}CH_2$), 5.52-5.54 (1H, m, $CH_2C\mathit{H}{=}CH$), 5.88-5.91 (1H, m, $CH{=}C\mathit{H}CHN$), 7.21-7.32 (5H, m, Ar H); δ_C (100 MHz, $CDCl_3$) (as a mixture of rotamers) 21.8, 22.0 (CH_2), 24.7 (CH_2), 28.0 (CH_2), 47.0 (CH_2, NCH_2Ph), 57.2 (CH, $CH_2\mathit{C}HN$), 126.6 (CH, Ar), 127.1, 127.2 (2 x CH, Ar), 128.2 (2 x CH, Ar), 129.0, 129.1 (CH, $CH_2\mathit{C}H{=}CH$), 131.5 (CH, $CH{=}\mathit{C}HCHN$), 140.3 (C, Ar), 164.9 (C, NC(O)Cl); m/z (ES) 423 (100%). *Literature data*:[27] δ_H (360 MHz, $CDCl_3$) 1.49-1.99 (6H, m, $CHC\mathit{H}_2C\mathit{H}_2C\mathit{H}_2CH{=}$), 4.46-4.75 (2H, m, $PhC\mathit{H}_2N$), 4.92-4.99 (1H, m, NCH), 5.46-5.51 (1H, m, $NCHC\mathit{H}{=}$), 5.87-5.95 (1H, $NCHCH{=}C\mathit{H}$), 7.24-3.36 (5H, m, Ph); δ_C (90 MHz, $CDCl_3$) (mixture of rotamers) 21.0 (t), 191 21.1 (t), 24.26 (t), 24.32 (t), 27.2 (t), 28.3 (t), 49.4 (t), 50.8 (t), 56.8 (d), 58.6 (d), 126.0 (d), 126.2 (d), 127.0 (d), 127.2 (d), 128.4 (d), 128.5 (d), 132.6 (d), 132.7 (d), 137.2 (s), 137.4 (s), 149.9 (s), 150.2 (s); m/z (EI) 249 (M^+; 11), 168 (16), 158 (60), 133 (22), 91 (100), 81 (78), 65 (17).

- Cyclohex-2-en-1-yl(4-methoxyphenyl)carbamic chloride **126**



A novel compound prepared according to a literature procedure.[27] A solution of triphosgene (2.16 g, 7.29 mmol) in toluene (100 mL) was treated with pyridine (1.91 mL, 23.7 mmol) and subsequently with a solution of amine **124** (4.01 g, 19.7 mmol) in toluene (30 mL). The reaction mixture was stirred for 18 h at rt, quenched with $NaHCO_3$ (100 mL of a saturated aq. solution) and extracted with Et_2O (2 x 100 mL). The combined organic extracts were washed sequentially with HCl (100 mL of a 0.25 M aq. solution), H_2O (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 85:15) to give carbamoyl chloride **126** (4.82 g, 92%) as a white solid. mp 68-70 °C (CH_2Cl_2); R_f 0.33 (Pet ether:EtOAc 9:1); ν_{max} (neat)/cm^{-1}: 2935, 1728, 1510, 1212, 739; δ_H (400 MHz, $CDCl_3$) 1.44-1.61 (3H, m, CH_2), 1.77-2.00 (3H, m, CH_2), 3.83 (3H, s, OCH_3), 5.04-5.10 (1H, m, CH_2C*H*N), 5.65-5.67 (1H, m, CH_2C*H*=CH), 5.76-5.81 (1H, m, CH=C*H*CHN), 6.88 (2H, d, *J* 8.8 Hz, Ar H), 7.06 (2H, d, *J* 8.8 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 21.0 (CH_2), 24.3 (CH_2), 27.6 (CH_2), 55.5 (CH_3, OCH_3), 57.1 (CH, CH_2*C*HN), 114.2 (2 x CH, Ar), 127.0 (CH, CH_2*C*H=CH), 130.9 (2 x CH, Ar), 131.5 (CH, CH=*C*HCHN), 131.9 (C, ArCN), 150.1 (C, ArCO), 159.7 (C, NC(O)Cl); m/z (ES) 288.0770 ($[M+Na]^+$ $C_{14}H_{16}{}^{35}ClNNaO_2$ requires 288.0767), 288 (100%).

- Diethylthiocarbamic acid-[benzyl(cyclohex-2-enyl)carbamic acid]-thioanhydride **95**

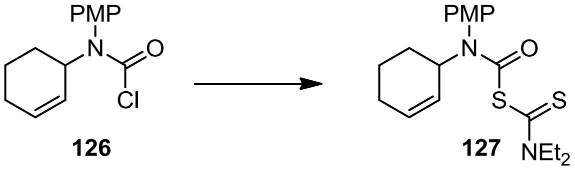


125 **95**

A known compound prepared according to the literature procedure.[27] A solution of carbamoyl chloride **125** (4.79 g, 19.2 mmol) in acetone (120 mL) was treated with sodium diethyldithiocarbamate trihydrate (17.3 g, 77.0 mmol). The solution was stirred at rt for 18 h quenched with H_2O (75 mL) and extracted with Et_2O (3 x 75 mL). The combined organic extracts were washed with brine (150 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether:EtOAc 95:5 to Pet ether:EtOAc 85:15) to give dithiocarbamate **95** (6.58 g, 95%) as a yellow oil (lit. yield 96%). R$_f$ 0.57 (Pet ether:EtOAc 85:15); ν$_{max}$ (neat)/cm^{-1}: 2931, 1663, 1492, 1418, 1271, 916, 725; δ$_H$ (400 MHz, $CDCl_3$) (as a mixture of rotamers) 1.19-1.34 (6H, m, CH$_2$C*H*$_3$), 1.42-1.74 (3H, m, CH$_2$), 1.90 (3H, br s, CH$_2$), 3.62-3.94 (4H, m, C*H*$_2$CH$_3$), 4.38-5.13 (3H, m, CH$_2$C*H*N and NCH$_2$Ph), 5.43-5.46 (1H, m, CH$_2$C*H*=CH), 5.80-5.82 (1H, m, CH=C*H*CHN), 7.08-7.33 (5H, m, Ar H); δ$_C$ (100 MHz, $CDCl_3$) (as a mixture of rotamers) 11.3 (CH$_3$, CH$_2$*C*H$_3$), 13.4 (CH$_3$, CH$_2$*C*H$_3$), 21.4 (CH$_2$), 24.5 (CH$_2$), 27.5 (CH$_2$), 48.9 (CH$_2$, NCH$_2$Ph), 50.0 (CH$_2$, *C*H$_2$CH$_3$), 52.1 (CH$_2$, *C*H$_2$CH$_3$), 54.8 (CH, CH$_2$*C*HN), 126.2 (3 x CH, Ar), 127.1 (2 x CH, Ar), 128.5 (CH, CH$_2$*C*H=CH), 132.5 (CH, CH=*C*HCHN), 138.4 (C, Ar), 163.0 (C, C(O)N), 185.3 (C, SC(S)); m/z (ES) 385 ([M+Na]$^+$, 100%). *Literature data*:[27] ν$_{max}$ (neat)/cm^{-1}: 2933, 1746, 1667, 1494, 1419, 1271, 916, 728; δ$_H$ (360 MHz, $CDCl_3$) 1.19-1.34 (6H, m, 2 × CH$_2$C*H*$_3$), 1.48-1.97 (6H, m, CHC*H*$_2$C*H*$_2$C*H*$_2$CH=), 3.69-3.83 (2H, br m, C*H*$_2$CH$_3$), 4.01 (2H, br s, C*H*$_2$CH$_3$), 4.51-5.13 (3H, m, PhC*H*$_2$N, NC*H*CH=), 5.52 (1H, d, *J* 10.1, NCHC*H*=), 5.88 (1H, d, *J* 7.8, NCHCH=C*H*), 7.26-7.30 (5H, m, Ph); δ$_C$ (125 MHz, $CDCl_3$) (mixture of rotamers) 11.1 (q), 13.2 (q), 21.2 (t), 24.4 (t), 27.5 (t), 28.6 (t), 47.9 (t), 48.7 (t), 49.1 (t), 49.8 (t), 54.65 (d), 57.1 (d), 126.0 (d), 126.9 (d), 128.4 (d), 132.4 (d), 138.2 (s), 163.0 (s), 184.7 (s), 185.5 (s); m/z (EI) 362

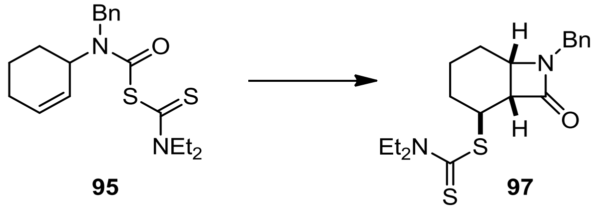
(M+; 8), 229 (29), 214 (19), 149 (75), 116 (58), 91 (32), 81 (100); HRMS (ESI): calcd for $C_{19}H_{26}N_2OS_2Na$ $[M+Na]^+$: 385.1379; found 385.1354.

- Diethyldithiocarbamic acid-[(4-methoxyphenyl)(cyclohex-2-enyl)carbamic acid]-thioanhydride **127**



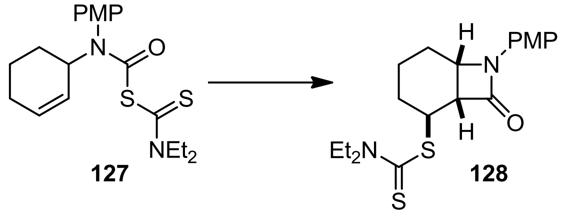
A novel compound prepared according to a literature procedure.[27] A solution of carbamoyl chloride **126** (4.60 g, 17.3 mmol) in acetone (120 mL) was treated with sodium diethyldithiocarbamate trihydrate (15.7 g, 69.4 mmol). The reaction mixture was heated at reflux for 18 h, quenched with H_2O (60 mL) and extracted with Et_2O (3 x 60 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 9:1) to give dithiocarbamate **127** (6.54 g, 100%) as a yellow oil. R_f 0.55 (Pet ether:EtOAc 3:1); ν_{max} (neat)/cm^{-1}: 2933, 1666, 1507, 1242, 1194, 740; δ_H (400 MHz, $CDCl_3$) 1.22 (3H, t, *J* 7.2 Hz, CH_2CH_3), 1.32 (3H, t, *J* 7.2 Hz, CH_2CH_3), 1.40-1.59 (3H, m, CH_2), 1.74-1.98 (3H, m, CH_2), 3.75-3.82 (5H, m, CH_2CH_3 and OCH_3), 3.99 (2H, q, *J* 7.2 Hz, CH_2CH_3), 5.22 (1H, br s, CHN), 5.62-5.65 (1H, m, CH_2CH=CH), 5.73-5.77 (1H, m, CH=C*H*CHN), 6.86 (2H, d, *J* 9.2 Hz, Ar H), 7.13 (2H, d, *J* 9.2 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 11.1 (CH_3, CH_2CH_3), 13.6 (CH_3, CH_2CH_3), 21.1 (CH_2), 24.4 (CH_2), 27.8 (CH_2), 48.7 (CH_2, CH_2CH_3), 50.4 (CH_2, CH_2CH_3), 54.5 (CH, CH_2CHN), 55.6 (CH_3, OCH_3), 114.3 (2 x CH, Ar), 127.7 (CH, CH_2CH=CH), 129.5 (C, ArCN), 131.1 (CH, CH=*C*HCHN), 132.4 (2 x CH, Ar), 160.3 (C, ArCO), 164.5 (C, C(O)N), 185.7 (C, SC(S)); m/z (ES) 401.1337 ($[M+Na]^+$ $C_{19}H_{26}N_2NaO_2S_2$ requires 401.1333), 417 (18%), 401 (100).

- (±)-(1*R,*2*S*,6*S*)-7-Benzyl-8-oxo-7-azabicyclo[4.2.0]octan-2-yl diethylcarbamodithioate **97**



A known compound prepared according to the literature procedure.[26] A solution of dithiocarbamate **95** (6.58 g, 18.2 mmol) in cyclohexane (180 mL) was degassed for 10 min and irradiated with a 500 W lamp which generated enough heat to bring the solution to reflux. After 5 h, the solvent was removed under reduced pressure and the crude product obtained was purified by column chromatography (Pet ether:EtOAc 9:1 to Pet ether:EtOAc 1:1) to give lactam **97** (5.63 g, 86%) as a light green solid (lit. yield 92%). mp 86-89 °C (CH_2Cl_2); R_f 0.38 (Pet ether:EtOAc 85:15); ν_{max} (neat)/cm^{-1}: 2926, 1729, 1208, 722; δ_H (400 MHz, $CDCl_3$) 1.27 (6H, t, *J* 7.2 Hz, CH_2CH_3), 1.41-1.61 (2H, m, CH_2), 1.71-1.84 (3H, m, CH_2), 2.26-2.35 (1H, m, CH_2), 3.60-3.63 (1H, m, C(O)C*H*CH), 3.68-3.76 (3H, m, CH_2CH_3 and CH_2CHS), 3.96-4.07 (2H, m, CH_2CH_3), 4.16, 4.60 (2H, ABq, *J* 15.0 Hz, NCH_2Ph), 4.52-4.54 (1H, m, $NCHCH_2$), 7.28-7.38 (5H, m, Ar H); δ_C (100 MHz, $CDCl_3$) 11.7 (CH_3, CH_2CH_3), 12.6 (CH_3, CH_2CH_3), 15.3 (CH_2), 22.2 (CH_2), 25.3 (CH_2), 44.4 (CH, *C*HC(O)), 44.6 (CH_2, NCH_2Ph), 46.7 (CH_2, CH_2CH_3), 49.2 (CH_2, CH_2CH_3), 50.3 (CH, CH_2CHN), 52.2 (CH, CH_2CHS), 127.7 (CH, Ar), 128.4 (2 x CH, Ar), 128.9 (2 x CH, Ar), 136.0 (C, Ar), 168.0 (C, C(O)N), 193.6 (C, SC(S)); m/z (ES) 385 ($[M+Na]^+$, 100%). *Literature data*:[26] ν_{max} (neat)/cm^{-1} 3434, 2931, 1746, 1486, 1415, 1267, 1206; δ_H (360 MHz; $CDCl_3$) 1.26 (6H, t, *J* = 7.1 Hz), 1.45-1.54 (2H, m), 1.65-1.83 (3H, m), 2.24-2.34 (1H, m), 3.59-3.61 (1H, m), 3.64-3.74 (3H, m), 3.92-4.06 (2H, m), 4.15 (1H, d, *J* = 15.1 Hz), 4.50-4.54 (1H, m), 4.59 (1H, d, *J* = 15.1 Hz), 7.23-7.36 (5H, m); δ_C (100 MHz; $CDCl_3$) 11.5 (CH_3), 12.4 (CH_3), 15.0 (CH_2), 21.9 (CH_2), 25.0 (CH_2), 44.1 (CH), 44.4 (CH_2), 46.5 (CH_2), 49.0 (CH_2), 50.1 (CH), 51.9 (CH), 127.6 (CH), 128.2 (CH), 128.6 (CH), 135.8 (C), 167.8 (C), 193.4 (C); m/z (EI) 362 (M^+; 13), 214 (100), 149 (27), 116 (57), 81 (62); HRMS (ESI): calcd for $C_{19}H_{26}N_2NaOS_2$ $[M+Na]^+$: 385.1379; found 385.1361.

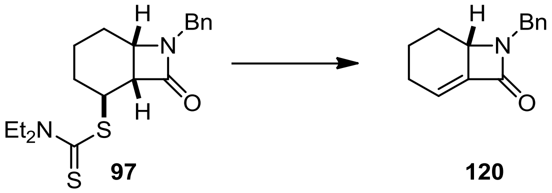
- (±)-(1*R,*2*S,*6*S*)-7-(4-Methoxyphenyl)-8-oxo-7-aza-bicyclo[4.2.0]octan-2-yl diethylcarbamodithioate **128**



127 **128**

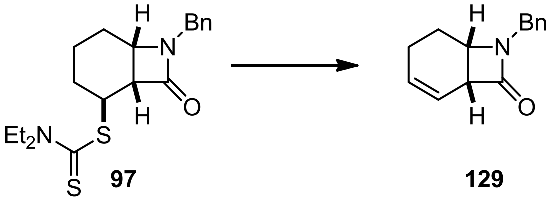
A novel compound prepared according to a literature procedure.[26] A solution of dithiocarbamate **127** (5.86 g, 15.5 mmol) in cyclohexane (155 mL) was degassed for 10 min and irradiated with a 500 W lamp which generated enough heat to bring the solution to reflux. After 4 h, the solvent was removed under reduced pressure and the crude product obtained was purified by column chromatography (Pet ether to Pet ether:EtOAc 1:1) to give lactam **128** (4.93 g, 84%) as a light green solid. mp 78-81 °C (CH_2Cl_2); R_f 0.41 (Pet ether:EtOAc 3:1); ν_{max} (neat)/cm^{-1}: 2929, 1721, 1508, 1243, 826; δ_H (400 MHz, $CDCl_3$) 1.25-1.31 (6H, m, $CH_2C\mathit{H}_3$), 1.57-1.64 (2H, m, CH_2), 1.83-2.03 (2H, m, CH_2), 2.09-2.16 (1H, m, CH_2), 2.30-2.39 (1H, m, CH_2), 3.70-3.81 (6H, m, $C\mathit{H}_2CH_3$, $CH_2C\mathit{H}S$ and OCH_3), 3.95-4.06 (2H, m, $C\mathit{H}_2CH_3$), 4.26-4.30 (1H, m, $CH_2C\mathit{H}N$), 4.60-4.63 (1H, m, CHC(O)), 6.86 (2H, d, *J* 8.8 Hz, Ar H), 7.33 (2H, d, *J* 8.8 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 11.7 (CH_3, $CH_2\mathit{C}H_3$), 12.7 (CH_3, $CH_2\mathit{C}H_3$), 15.2 (CH_2), 22.5 (CH_2), 25.5 (CH_2), 44.3 (CH, $CH_2\mathit{C}HC(O)$), 46.8 (CH_2, $\mathit{C}H_2CH_3$), 49.3 (CH_2, $\mathit{C}H_2CH_3$), 50.4 (CH, $CH_2\mathit{C}HN$), 51.8 (CH, $CH_2\mathit{C}HS$), 55.6 (CH_3, OCH_3), 114.6 (2 x CH, Ar), 118.4 (2 x CH, Ar), 131.2 (C, ArCN), 156.1 (C, ArCO), 164.9 (C, C(O)N), 193.5 (C, C(S)S); m/z (ES) 401.1329 ($[M+Na]^+$ $C_{19}H_{26}N_2NaO_2S_2$ requires 401.1333), 401 (100%).

- 7-Benzyl-7-azabicyclo[4.2.0]oct-1-en-8-one **120**



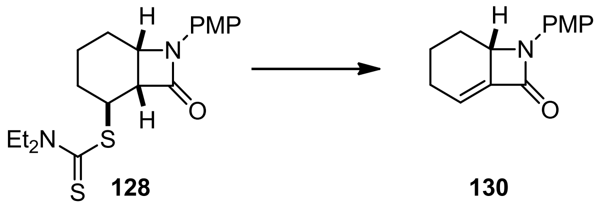
A novel compound prepared according to a modified literature procedure.[39] A solution of lactam **97** (1.00 g, 2.76 mmol) in THF (20 mL) was cooled to -78 °C and then treated with methyl iodide (189 µL, 3.04 mmol). The reaction mixture was stirred at -78 °C for 2.75 h, LHMDS (3.0 mL of a 1.0 M solution in THF, 3.0 mmol) was added over 2 min. After 5 h at -78 °C, the solvent was removed under reduced pressure and the crude product obtained was purified by column chromatography (Pet ether:EtOAc 95:5 to Pet ether:EtOAc 3:1) to give lactam **120** (0.544 g, 93%) as a yellow oil. R_f 0.36 (Pet ether:EtOAc 3:1); ν_{max} (neat)/cm^{-1}: 2942, 1735, 1495, 1454, 1374, 698; δ_H (400 MHz, CDCl$_3$) 0.88-0.98 (1H, m, CH$_2$), 1.30-1.42 (1H, m, CH$_2$), 1.82-1.90 (2H, m, CH$_2$), 2.04-2.17 (1H, m, CH$_2$), 2.29-2.36 (1H, m, CH$_2$), 3.62-3.66 (1H, m, NC*H*CH$_2$), 4.42, 4.52 (2H, ABq, *J* 14.8 Hz, NCH$_2$Ph), 6.23-6.25 (1H, m, CH$_2$C*H*=C), 7.27-7.36 (5H, m, Ar H); δ_C (100 MHz, CDCl$_3$) 20.2 (CH$_2$), 25.3 (CH$_2$), 28.0 (CH$_2$), 46.0 (CH$_2$, NCH$_2$Ph), 56.8 (CH, CH$_2$*C*HN), 124.8 (CH, CH$_2$*C*H=C), 127.8 (2 x CH, Ar), 128.5 (2 x CH, Ar), 128.8 (CH, Ar), 136.5 (C, Ar), 141.9 (C, CH=*C*C(O)), 163.9 (C, C(O)N); m/z (ES) 236.1041 ([M+Na]$^+$ C$_{14}$H$_{15}$NNaO requires 236.1051), 236 (100%).

- (±)-(1*S*,6*R*)-7-Benzyl-7-azabicyclo[4.2.0]oct-2-en-8-one **129**



A known compound prepared according to the literature procedure.[29] A solution of lactam **97** (0.200 g, 0.550 mmol) in Ph$_2$O (4 mL) was heated to reflux. After 4 h, the reaction mixture was directly purified by column chromatography (Pet ether to Pet ether:EtOAc 7:3) to give lactam **129** (95 mg, 48%) as a brown oil (lit. yield 79%). R_f 0.41 (Pet Ether:EtOAc 75:25); ν_{max} (neat)/cm^{-1}: 2927, 1733, 1383, 703; δ_H (400 MHz, $CDCl_3$) 1.21-1.36 (1H, m, CH_2), 1.80-1.89 (2H, m, CH_2), 1.96-2.04 (1H, m, CH_2), 3.64-3.66 (1H, m, CHC*H*C(O)), 3.86-3.88 (1H, m, CH_2C*H*N), 4.24, 4.53 (2H, ABq, *J* 15.0 Hz, NCH_2Ph), 5.82-5.87 (1H, m, CH_2C*H*=CH), 5.97-6.02 (1H, m, CH=C*H*CHN), 7.27-7.42 (5H, m, Ar H); δ_C (100 MHz, $CDCl_3$) 19.4 (CH_2), 22.5 (CH_2), 44.0 (CH_2, NCH_2Ph), 48.5 (CH, =CH*C*HC(O)), 51.0 (CH, CH_2*C*HN), 121.5 (CH, CH_2CH=CH), 127.7 (CH, Ar), 128.4 (2 x CH, Ar), 128.8 (2 x CH, Ar), 130.8 (CH, CH=*C*HCHN), 136.2 (C, Ar), 167.1 (C, C(O)N); m/z (ES) 236.1044 ($[M+Na]^+$, $C_{14}H_{15}NNaO$ requires 236.1051), 236 (100%). *Literature data*:[29] ν_{max} (neat)/cm^{-1}: 2927, 1744, 1384, 1243, 1153, 706; δ_H (360 MHz; $CDCl_3$) 1.30-1.35 (1H, m), 1.79-2.02 (3H, m), 3.63-3.66 (1H, m), 3.84-3.86 (1H, m), 4.22 (1H, d, *J* = 15.0), 5.53 (1H, d, *J* = 15.0), 5.81-5.86 (1H, m), 5.96-6.01 (1H, m), 7.27-3.37 (5H, m); δ_C (100 MHz; $CDCl_3$) 19.4 (CH_2), 22.5 (CH_2), 43.9 (CH_2), 48.5 (CH), 51.0 (CH), 121.5 (CH), 127.7 (CH), 128.4 (CH), 128.7 (CH), 130.8 (CH), 136.1 (C), 167.1 (C); m/z (EI) 214 ($[M+1]^+$; 12), 91 (82), 81 (99), 77 (100), 65 (84); m/z (ES) 236.1050 ($[M+Na]^+$, $C_{14}H_{15}NNaO$ requires 236.1051).

- 7-(4-Methoxyphenyl)-7-azabicyclo[4.2.0]oct-1-en-8-one **130**

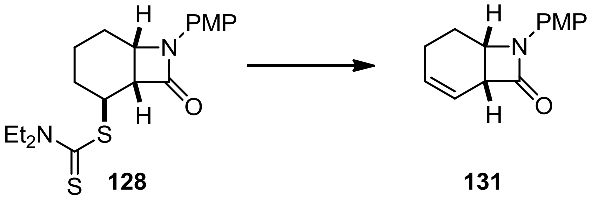


128 **130**

A novel compound prepared according to a modified literature procedure.[39] A solution of lactam **128** (0.864 g, 2.29 mmol) in THF (18 mL) was cooled to -78 °C and treated with methyl iodide (157 µL, 2.52 mmol). The reaction mixture was stirred at -78 °C for 1.5 h, LHMDS (2.5 mL of a 1.0 M solution in THF, 2.5 mmol) was added dropwise over 2 min. After 6.5 h at -78 °C, the solvent was removed under reduced pressure and the crude product obtained was purified by column chromatography (Pet ether to Pet ether:EtOAc 3:1) to give lactam **130** (0.519 g, 99%)

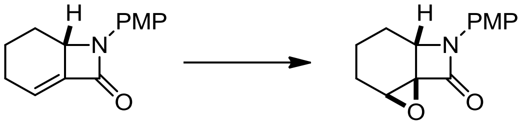
as a light yellow solid. mp 60-62 °C (CH_2Cl_2); R_f 0.29 (Pet ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1}: 2942, 1722, 1509, 1242, 1119, 811; δ_H (400 MHz, $CDCl_3$) 1.18-1.32 (1H, m, CH_2), 1.51-1.63 (1H, m, CH_2), 1.99-2.06 (1H, m, CH_2), 2.16-2.27 (1H, m, CH_2), 2.38-2.47 (2H, m, CH_2), 3.77 (3H, s, OCH_3), 4.11-4.15 (1H, m, CH_2C*H*N), 6.34-6.35 (1H, m, CH_2C*H*=C), 6.87 (2H, d, *J* 9.0 Hz, Ar H), 7.35 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 19.8 (CH_2), 25.3 (CH_2), 27.8 (CH_2), 55.3 (CH_3, OCH_3), 57.0 (CH, CH_2*C*HN), 114.3 (2 x CH, Ar), 117.2 (2 x CH, Ar), 125.7 (CH, CH_2*C*H=C), 132.5 (C, ArCN), 140.8 (C, CH=*C*C(O)), 155.6 (C, ArCO), 159.8 (C, C(O)N); m/z (EI) 229.1104 (M^+ $C_{14}H_{15}NO_2$ requires 229.1103), 229 (M^+, 100%), 214 (7), 201 (6), 186 (9), 173 (7), 107 (8).

- (±)-(1*R*,6*S*)-7-(4-Methoxyphenyl)-7-azabicyclo[4.2.0]oct-2-en-8-one **131**



A novel compound prepared according to a literature procedure.[29] A solution of lactam **128** (1.22 g, 3.23 mmol) in diphenyl ether (25 mL) was heated to reflux. After 4.5 h, the reaction mixture was directly purified by column chromatography (Hexane to Hexane:EtOAc 7:3) to give lactam **131** (0.593 g, 80%) as a brown solid. mp 72-75 °C; R_f 0.47 (Pet ether:EtOAc 3:1); ν_{max} (neat)/cm^{-1} : 2943, 1722, 1509, 1243, 1119, 1030, 842, 804; δ_H (400 MHz, $CDCl_3$) 1.48-1.57 (1H, m, CH_2), 1.93-2.10 (2H, m, CH_2), 2.28-2.32 (1H, m, CH_2), 3.78-3.83 (4H, m, CHC*H*C(O) and OCH_3), 4.42-4.44 (1H, m, CH_2C*H*N), 5.87-5.91 (1H, m, CH_2C*H*=CH), 6.04-6.09 (1H, m, CHC*H*=CH), 6.87 (2H, d, *J* 9.0 Hz, Ar H), 7.33 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 19.5 (CH_2), 22.8 (CH_2), 48.2 (CH, =CH*C*HC(O)), 51.3 (CH, CH_2*C*HN), 55.6 (CH_3, OCH_3), 114.6 (2 x CH, Ar), 118.8 (2 x CH, Ar), 121.3 (CH, CH_2*C*H=CH), 130.8 (C, ArCN), 131.5 (CH, CH=*C*HCH), 156.2 (C, ArCO), 164.4 (C, C(O)N); m/z (ES) 252.0989 ($[M+Na]^+$ $C_{14}H_{15}NNaO_2$ requires 252.1000), 284.2 (5%), 252 (100).

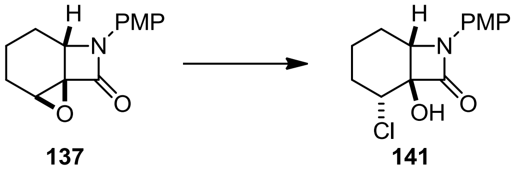
- (±)-(1*R,*3*S,*7*S*)-8-(4-Methoxyphenyl)-2-oxa-8-azatricyclo[5.2.0.0^{1,3}]nonan-9-one **137**



130 **137**

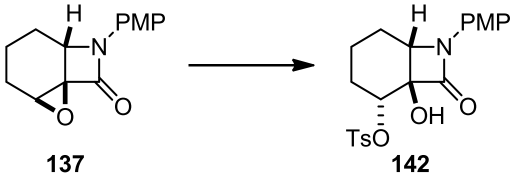
A novel compound prepared according to a literature procedure.[52] A solution of lactam **130** (0.300 g, 1.31 mmol) in CH_2Cl_2 (9 mL) was cooled to 0 °C, treated with recrystallised *m*CPBA (0.677 g, 3.93 mmol) and allowed to warm to rt over 1 h. After 4 h at rt, the reaction mixture was cooled to 0 °C, diluted with CH_2Cl_2 (9 mL) and treated with KF (0.686 g, 11.8 mmol). After stirring at 0 °C for 1 h, the reaction mixture was filtered through a pad of celite (eluent CH_2Cl_2), the filtrate was evaporated under reduced pressure and purified by column chromatography (Pet ether:EtOAc 9:1 to Pet ether:EtOAc 4:1) to give epoxy lactam **137** (0.224 g, 70%) as a white solid. mp 98-100 °C; R_f 0.43 (Pet ether:EtOAc 3:1); ν_{max} (neat)/cm^{-1} : 2923, 1740, 1514, 1242, 825; δ_H (300 MHz, $CDCl_3$) 1.21-1.30 (2H, m, CH_2), 1.64-1.72 (1H, m, CH_2), 1.76-1.88 (1H, m, CH_2), 2.19-2.26 (1H, m, CH_2), 2.32-2.39 (1H, m, CH_2), 3.68 (1H, d, *J* 2.4 Hz, $CH_2C\textit{H}O$), 3.79 (3H, s, OCH_3), 4.11-4.16 (1H, m, $CH_2C\textit{H}N$), 6.88 (2H, d, *J* 9.2 Hz, Ar H), 7.37 (2H, d, *J* 9.2 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 16.8 (CH_2), 25.1 (CH_2), 27.2 (CH_2), 54.0 (CH, $CH_2\textit{C}HO$), 55.6 (CH_3, OCH_3), 56.4 (CH, $CH_2\textit{C}HN$), 66.9 (C, CH*C*OC(O)), 114.7 (2 x CH, Ar), 118.3 (2 x CH, Ar), 131.6 (C, ArCN), 156.4 (C, ArCO), 164.2 (C, C(O)N); m/z (EI) 245.1048 (M^+ $C_{14}H_{15}NO_3$ requires 245.1052), 245 (100%), 217 (6), 189 (49), 174 (10), 149 (27), 134 (28).

- (±)-(1*S,*2*R*,6*S*)-2-Chloro-1-hydroxy-7-(4-methoxyphenyl)-7-azabicyclo[4.2.0]octan-8-one **141**



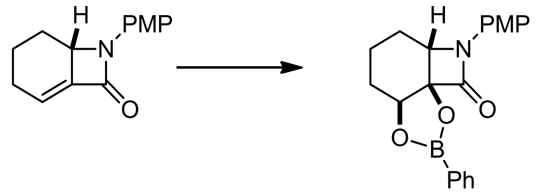
A novel compound prepared according to a modified literature procedure.[23] A solution of epoxy lactam **137** (30 mg, 0.12 mmol) in toluene (9 mL) was cooled to -78 °C and treated with $TiCl_4$ (14 µL, 0.13 mmol). After 1 h, the solution was carefully quenched with H_2O (4 mL) and extracted with EtOAc (2 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give chloro hydroxy lactam **141** (21 mg, 62%) as a yellow solid. mp 108-111 °C; R_f 0.24 (Pet ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1} : 3350, 2946, 1709, 1511, 1245, 832; δ_H (400 MHz, $CDCl_3$) 1.28 (1H, br s, OH), 1.55-1.66 (1H, m, CH_2), 1.68-1.79 (1H, m, CH_2), 1.83-2.02 (2H, m, CH_2), 2.12-2.19 (1H, m, CH_2), 2.23-2.32 (1H, m, CH_2), 3.78 (3H, s, OCH_3), 4.28 (1H, dd, *J* 5.2 and 9.6 Hz, CH_2C*H*Cl), 4.30-4.32 (1H, m, CH_2C*H*N), 6.87 (2H, d, *J* 9.0 Hz, Ar H), 7.31 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 16.4 (CH_2), 20.3 (CH_2), 28.0 (CH_2), 55.6 (CH_3, OCH_3), 60.3 (CH, CH_2*C*HN), 62.0 (CH, CH_2*C*HCl), 84.5 (C, CH*C*OH), 114.7 (2 x CH, Ar), 119.0 (2 x CH, Ar), 130.1 (C, ArCN), 156.8 (C, ArCO), 163.8 (C, C(O)N); m/z (ES) 304.0702 ($[M+Na]^+$ $C_{14}H_{16}{}^{35}ClNNaO_3$ requires 304.0716), 306 (24%), 304 (100).

- (±)-(1*R*,2*R*,6*S*)-1-Hydroxy-7-(4-methoxyphenyl)-8-oxo-7-azabicyclo[4.2.0]octan-2-yl 4-methyl benzene sulfonate **142**



A novel compound prepared according to a modified literature procedure.[23] A solution of epoxy lactam **137** (0.163 g, 0.665 mmol) in toluene (4 mL) was treated with PPTS (0.184 g, 0.733 mmol) and refluxed for 2.25 h. The reaction mixture was quenched with H_2O (4 mL) and extracted with EtOAc (2 x 4 mL). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether:EtOAc 4:1 to Pet ether:EtOAc 7:3) to give *trans* hydroxy tosyl lactam **142** (0.116 g, 42%) as a white solid. mp 121-123 °C; R_f 0.34 (Pet ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1} : 3433, 2949, 1730, 1512, 1172, 816; δ_H (400 MHz, $CDCl_3$) 1.59-1.72 (2H, m, CH_2), 1.77-1.92 (2H, m, CH_2), 2.02-2.11 (2H, m, CH_2), 2.44 (3H, s, $PhCH_3$), 3.78 (3H, s, OCH_3), 4.22 (1H, br s, OH), 4.24 (1H, t, *J* 3.0 Hz, CH_2C*H*N), 4.98 (1H, dd, *J* 5.8 and 11.8 Hz, CH_2C*H*OTs), 6.86 (2H, d, *J* 9.0 Hz, Ar H), 7.22 (2H, d, *J* 9.0 Hz, Ar H), 7.34 (2H, d, *J* 8.2 Hz, Ar H), 7.88 (2H, d, *J* 8.2 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 16.0 (CH_2), 20.7 (CH_2), 21.8 (CH_3, $PhCH_3$), 24.7 (CH_2), 55.6 (CH_3, OCH_3), 61.8 (CH, CH_2*C*HN), 80.9 (CH, CH_2*C*HOTs), 83.5 (C, CH*C*OH), 114.7 (2 x CH, Ar), 119.0 (2 x CH, Ar), 128.1 (2 x CH, Ar), 130.0 (2 x CH, Ar), 133.4 (C, ArCN), 145.3 (2 x C*,* Ar), 156.8 (C, ArCO), 163.1 (C, C(O)N); m/z (ES) 440.1147 ($[M+Na]^+$ $C_{21}H_{23}NNaO_6S$ requires 440.1144), 456 (18%), 440 (100), 423 (19), 268 (21).

- (±)-(3a*R*,5a*S*,8a*S*)-5-(4-Methoxyphenyl)-2-phenylhexahydro-4*H*-[1,3,2]dioxaborolo [4′,5′:2,3]benzo [1,2-*b*]azet-4-one **143**

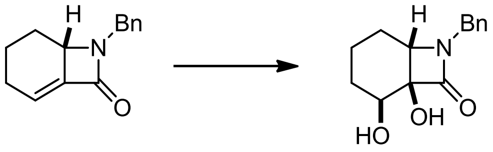


130 **143**

A novel compound prepared according to a literature procedure.[54] A solution of lactam **130** (0.100 g, 0.437 mmol) in CH_2Cl_2 (2 mL) was added dropwise over 2 min to a mixture of $PhB(OH)_2$ (59 mg, 0.48 mmol), NMO (56 mg, 0.48 mmol) and OsO_4 (2 mg, 0.09 mmol) in CH_2Cl_2 (4 mL). After 3 h at rt, Na_2SO_3 (2 mL of a 10% aq. solution) was added and the reaction mixture was stirred for 2 h. The organic layer was separated and the aqueous layer was extracted with

CH_2Cl_2 (2 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether:EtOAc 4:1 to Pet ether:EtOAc 7:3) to give boronic ester **143** (0.100 g, 65%) as a white solid. mp 78-81 °C; R_f 0.21 (Pet ether:EtOAc 3:2); ν_{max} (neat)/cm^{-1} : 2937, 1742, 1511, 1346, 1242, 701; δ_H (400 MHz, $CDCl_3$) 1.36-1.46 (1H, m, CH_2), 1.52-1.64 (2H, m, CH_2), 1.82-1.91 (1H, m, CH_2), 2.15-2.19 (1H, m, CH_2), 2.32-2.39 (1H, m, CH_2), 3.82 (3H, s, OCH_3), 4.50 (1H, dd, *J* 1.6 and 6.0 Hz, CH_2C*H*N), 4.96 (1H, dd, *J* 6.8 and 8.8 Hz, CH_2C*HO*), 6.93 (2H, d, *J* 8.8 Hz, Ar H), 7.35-7.43 (5H, m, Ar H), 7.85 (2H, d, *J* 6.8 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 15.8 (CH_2), 24.7 (CH_2), 30.6 (CH_2), 55.6 (CH_3, OCH_3), 60.4 (CH, CH_2*C*HN), 75.6 (CH, CH_2*C*HO), 87.5 (C, CH*C*O), 114.7 (2 x CH, Ar), 119.6 (2 x CH, Ar), 128.0 (2 x CH, Ar), 129.5 (C, ArCN), 132.0 (CH, Ar), 135.1 (2 x CH, Ar), 156.8 (C, ArCO), 164.9 (C, C(O)N); m/z (ES) 372.1377 ($[M+Na]^+$ $C_{20}H_{20}BNNaO_4$ requires 372.1383), 372 (59%), 286 (100).

- (±)-(1*R*,2*S*,6*S*)-7-Benzyl-1,2-dihydroxy-7-azabicyclo[4.2.0]octan-8-one **145**

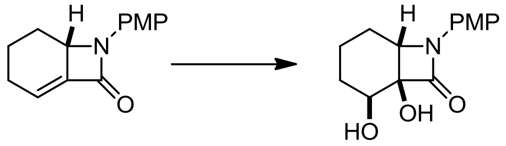


120 **145**

A novel compound prepared according to a literature procedure.[56] A solution of lactam **120** (84 mg, 0.39 mmol) in a 5:5:2 mixture of H_2O:acetone:*t*BuOH (2.2 mL) was treated with NMO (0.111 g, 0.945 mmol) and OsO_4 (2 µL of a 4 wt% aq. solution, cat). After 5 h at 40 °C, sodium bisulfite was added (0.225 g, 1.18 mmol) to quench the reaction. After 45 min at 40 °C, the reaction mixture was diluted with H_2O (2 mL) and extracted with Et_2O (2 x 3 mL). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether:EtOAc 1:1 to EtOAc) to give diol **145** (76 mg, 74%) as a white solid. mp 118-120 °C (CH_2Cl_2); R_f 0.65 (Pet ether:EtOAc 2:3); ν_{max} (neat)/cm^{-1}: 3486, 3216, 2914, 1710, 1350, 1108, 694; δ_H (400 MHz,

$CDCl_3$) 1.19-1.31 (1H, m, CH_2), 1.54-1.65 (2H, m, CH_2), 1.66-1.87 (3H, m, CH_2), 3.60 (1H, br s, OH), 3.70-3.72 (1H, m, NC*H*CH_2), 4.07-4.10 (1H, m, CH_2C*H*OH), 4.18, 4.56 (2H, ABq, *J* 14.8 Hz, NCH_2Ph), 4.92 (1H, br s, OH), 7.26-7.37 (5H, m, Ar H); δ_C (100 MHz, $CDCl_3$) 14.6 (CH_2), 21.6 (CH_2), 25.8 (CH_2), 44.5 (CH_2, NCH_2Ph), 61.2 (CH, CH_2*C*HN), 67.8 (CH, CH_2*C*HOH), 82.5 (C, CH*C*OH), 128.0 (CH, Ar), 128.5 (2 x CH, Ar), 129.0 (2 x CH, Ar), 135.3 (C, Ar), 171.2 (C, C(O)N); m/z (ES) 270.1100 ($[M+Na]^+$ $C_{14}H_{17}NNaO_3$ requires 270.1106), 270 (100%).

- (±)-(1*R,*2*S,*6*S*)-1,2-Dihydroxy-7-(4-methoxyphenyl)-7-azabicyclo[4.2.0]octan-8-one **146**

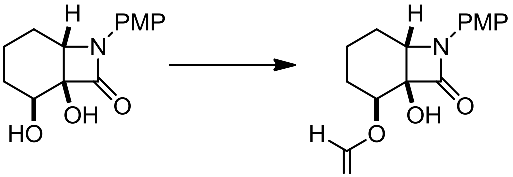


130 **146**

A novel compound prepared according to a literature procedure.[56] A solution of lactam **130** (1.27 g, 5.53 mmol) in a 5:5:2 mixture of H_2O:acetone:*t*BuOH (31 mL) was treated with NMO (1.56 g, 13.3 mmol) and OsO_4 (10 µL of a 4 wt% aq. solution, cat). After 18 h at 40 °C, sodium bisulfite (3.15 g, 16.6 mmol) was added to quench the reaction. After 2 h at 40 °C, the reaction mixture was diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (2 x 45 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether:EtOAc 7:3 to Pet ether:EtOAc 1:9) to give dihydroxy lactam **146** (1.18 g, 81%) as an off-white solid. mp 90-92 °C (CH_2Cl_2); R_f 0.13 (Pet ether:EtOAc 3:2); ν_{max} (neat)/cm^{-1}: 3314, 2936, 1713, 1512, 1246, 1163, 831; δ_H (400 MHz, $CDCl_3$) 1.36-1.47 (1H, m, CH_2), 1.61-1.71 (1H, m, CH_2), 1.79-1.85 (2H, m, CH_2), 1.97-2.04 (1H, m, CH_2), 2.09-2.18 (1H, m, CH_2), 3.26 (1H, br s, OH), 3.79 (3H, s, OCH_3), 4.17-4.20 (1H, m, CH_2C*H*N), 4.20-4.22 (1H, m, CH_2C*H*OH), 4.61 (1H, br s, OH), 6.86 (2H, d, *J* 9.0 Hz, Ar H), 7.29 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_2), 21.6 (CH_2), 25.4 (CH_2), 55.6 (CH_3, OCH_3), 61.8 (CH, CH_2*C*HN), 67.6 (CH, CH_2*C*HOH), 82.2 (C, CH*C*OH), 114.7 (2 x CH, Ar), 119.4 (2 x

CH, Ar), 130.2 (C, ArCN), 156.8 (C, ArCO), 167.4 (C, C(O)N); m/z (ES) 286.1046 ([M+Na]$^+$ $C_{14}H_{17}NNaO_4$ requires 286.1055), 286 (100%).

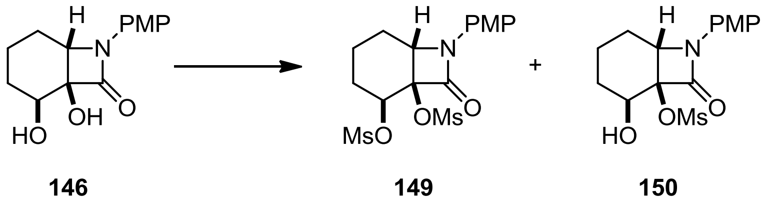
- (±)-(1*R*,2*S*,6*S*)-1-Hydroxy-7-(4-methoxyphenyl)-8-oxo-7-azabicyclo[4.2.0]octan-2-yl formate **147**



146 **147**

A novel compound prepared according to a literature procedure.[57] A solution of dihydroxy lactam **146** (0.100 g, 0.380 mmol) in CH_2Cl_2 (3 mL) at -35 °C was treated with trimethyl orthoformate (46 µL, 0.42 mmol) and $BF_3.Et_2O$ (53 µL, 0.42 mmol). The reaction mixture was progressively warmed to rt over 18 h. $NaHCO_3$ (3 mL of a saturated aq. solution) was then added to quench the reaction mixture and it was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether:EtOAc 4:1 to Pet ether:EtOAc 3:2) to give formate **147** (45 mg, 41%) as a yellow solid. mp 94-97 °C; R_f 0.19 (Pet ether:EtOAc 3:2); ν_{max} (neat)/cm^{-1} : 3336, 2956, 1708, 1512, 1439, 1160, 832; δ_H (400 MHz, $CDCl_3$) 1.39-1.50 (1H, m, CH_2), 1.58-1.68 (1H, m, CH_2), 1.86-1.99 (2H, m, CH_2), 2.12-2.17 (2H, m, CH_2), 3.78 (3H, s, OCH_3), 4.19 (1H, t, *J* 3.2 Hz, CH_2C*H*N), 4.37 (1H, br s, OH), 5.47 (1H, t, *J* 3.6 Hz, CH_2C*H*O), 6.86 (2H, d, *J* 9.0 Hz, Ar H), 7.30 (2H, d, *J* 9.0 Hz, Ar H), 8.18 (1H, s, HC(O)O); δ_C (100 MHz, $CDCl_3$) 12.6 (CH_2), 20.8 (CH_2), 22.8 (CH_2), 55.6 (CH_3, OCH_3), 61.3 (CH, CH_2*C*HN), 70.4 (CH, CH_2*C*HO), 82.4 (C, CH*C*OH), 114.7 (2 x CH, Ar), 119.1 (2 x CH, Ar), 130.2 (C, ArCN), 156.9 (C, ArCO), 161.1 (CH, HC(O)O), 164.8 (C, C(O)N); m/z (ES) 314.1000 ([M+Na]$^+$ $C_{15}H_{17}NNaO_5$ requires 314.1004), 314 (100%).

- (±)-(1*R*,2*S*,6*S*)-7-(4-methoxyphenyl)-8-oxo-7-azabicyclo[4.2.0]octan-1,2-diyl dimethanesulfonate **149** and (±)-(1*R*,2*S*,6*S*)-2-Hydroxy-7-(4-methoxyphenyl)-8-oxo-7-azabicyclo[4.2.0]octan-1-yl methane sulfonate **150**

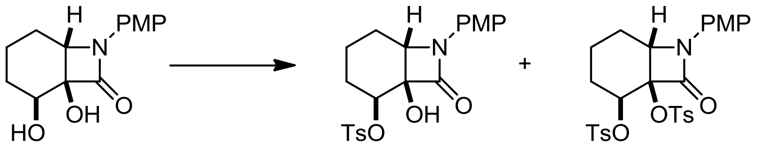


Novel compounds prepared according to a literature procedure.[238] A solution of dihydroxy lactam **146** (0.100 g, 0.380 mmol) in CH_2Cl_2 (1 mL) was treated with Et_3N (0.11 mL, 0.80 mmol) and MsCl (31 µL, 0.40 mmol). After 18 h at rt, further Et_3N (0.11 mL, 0.80 mmol) and MsCl (31 µL, 0.40 mmol) were added to drive the reaction to completion. After 3 h, the reaction mixture was quenched with HCl (2 mL of a 1 M aq. solution) and extracted with CH_2Cl_2 (2 x 3 mL). The combined organic extracts were washed with brine (4 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether:EtOAc 7:3 to Pet ether:EtOAc 3:7) to give dimesyl lactam **149** (93 mg, 58%) as a white solid and *cis* hydroxyl mesyl lactam **150** (11 mg, 9%) as a colourless oil.

149: mp 86-88 °C; R_f 0.50 (Pet ether:EtOAc 1:1); ν_{max} (neat)/cm^{-1} : 2963, 1736, 1513, 1358, 1252, 1171, 824; δ_H (400 MHz, $CDCl_3$) 1.41-1.52 (1H, m, CH_2), 1.73-1.84 (1H, m, CH_2), 1.94-2.03 (1H, m, CH_2), 2.17-2.33 (3H, m, CH_2), 3.15 (3H, s, SO_2CH_3), 3.33 (3H, s, SO_2CH_3), 3.80 (3H, s, OCH_3), 4.72-4.73 (1H, m, CH_2C*H*N), 5.28-5.30 (1H, m, CH_2C*H*OMs), 6.91 (2H, d, *J* 9.0 Hz, Ar H), 7.33 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 12.0 (CH_2), 20.2 (CH_2), 24.0 (CH_2), 39.1 (CH_3, SO_2CH_3), 40.9 (CH_3, SO_2CH_3), 55.7 (CH_3, OCH_3), 60.7 (CH, CH_2*C*HN), 77.0 (CH, CH_2*C*HOMs), 88.7 (C, CH*C*OMs), 114.9 (2 x CH, Ar), 119.6 (2 x CH, Ar), 129.1 (C, ArCN), 157.7 (C, ArCO), 158.4 (C, C(O)N); m/z (ES) 442.0601 ($[M+Na]^+$ $C_{16}H_{21}NNaO_8S_2$ requires 442.0606), 442 (100%), 229 (23), 197 (38).

150: R_f 0.22 (Pet ether:EtOAc 1:1); ν_{max} (neat)/cm^{-1} : 3485, 2937, 1741, 1511, 1357, 1245, 830; δ_H (400 MHz, $CDCl_3$) 1.34-1.45 (1H, m, CH_2), 1.68-1.76 (1H, m, CH_2), 1.79-1.88 (1H, m, CH_2), 1.98-2.13 (2H, m, CH_2), 2.28-2.37 (1H, m, CH_2), 2.65 (1H, br s, OH), 3.33 (3H, s, SO_2CH_3), 3.80 (3H, s, OCH_3), 4.39 (1H, br s, CH_2C*H*N), 4.66-4.67 (1H, m, CH_2C*H*OH), 6.90 (2H, d, *J* 9.0 Hz, Ar H), 7.34 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 12.4 (CH_2), 20.1 (CH_2), 20.9 (CH_2), 40.7 (CH_3, SO_2CH_3), 55.7 (CH_3, OCH_3), 60.8 (CH, CH_2*C*HN), 67.1 (CH, CH_2CHOH), 91.3 (C, CH*C*OMs), 114.8 (2 x CH, Ar), 119.5 (2 x CH, Ar), 129.6 (C, ArCN), 157.3 (C, ArCO), 160.4 (C, C(O)N); m/z (ES) 364.0826 ($[M+Na]^+$ $C_{15}H_{19}NNaO_6S$ requires 364.0831), 364 (100%), 268 (17).

- (±)-(1*R*,2*S*,6*S*)-1-Hydroxy-7-(4-methoxyphenyl)-8-oxo-7-azabicyclo[4.2.0]octan-2-yl methylbenzene sulfonate **151** and (±)-(1*R*,2*S*,6*S*)-7-(4-methoxyphenyl)-8-oxo-7-azabicyclo [4.2.0]octan-1,2-diyl bis(4-methylbenzenesulfonate) **152**



146 **151** **152**

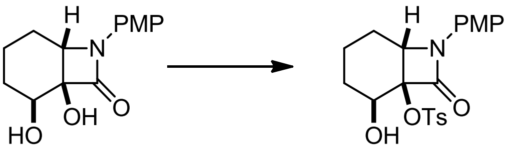
Novel compounds prepared according to a literature procedure.[14] A solution of dihydroxy lactam **146** (0.300 g, 1.14 mmol) in pyridine (6 mL) was treated with DMAP (28 mg, 0.23 mmol) and TsCl (0.652 g, 3.42 mmol). After 60 h at rt, the reaction mixture was quenched with H_2O (3 mL) and extracted with EtOAc (2 x 5 mL). The combined organic extracts were washed sequentially with HCl (5 mL of a 1 M aq. solution) and brine (5 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether:EtOAc 9:1 to Pet ether:EtOAc 1:1) to give *cis* hydroxyl tosyl lactam **151** (0.238 g, 50%) as a colourless oil and *cis* ditosyl lactam **152** (75 mg, 11%) as a white solid.

151: R_f 0.22 (Pet ether: EtOAc 1:1); ν_{max} (neat)/cm^{-1} : 3403, 2942, 1740, 1511, 1246, 871; δ_H (300 MHz, $CDCl_3$) 1.30-1.44 (1H, m, CH_2), 1.54-1.67 (1H, m, CH_2), 1.71-1.83 (1H, m, CH_2), 1.89-2.00 (1H, m, CH_2), 2.09-2.15 (2H, m, CH_2), 2.45 (3H, s, $PhCH_3$), 3.47 (1H, br s, OH), 3.78 (3H, s, OCH_3), 4.21-4.23 (1H, m, CH_2C*H*N), 4.94 (1H, t, *J* 3.3 Hz, CH_2C*H*OTs), 6.87 (2H, d, *J* 9.0 Hz, Ar H), 7.29 (2H, d, *J* 9.0 Hz, Ar H), 7.36 (2H, d, *J* 8.3 Hz, Ar H), 7.85 (2H, d, *J* 8.3 Hz, Ar H); δ_C (100 MHz,

$CDCl_3$) 12.1 (CH_2), 20.4 (CH_2), 21.8 (CH_3, $PhCH_3$), 23.5 (CH_2), 55.6 (CH_3, OCH_3), 61.6 (CH, CH_2*C*HN), 79.1 (CH, CH_2*C*HOTs), 82.3 (C, CH*C*OH), 114.7 (2 x CH, Ar), 119.0 (2 x CH, Ar), 128.1 (2 x CH, Ar), 130.1 (2 x CH, Ar), 133.3 (C, ArCN), 145.4 (2 x C, Ar), 156.9 (C, ArCO), 163.4 (C, C(O)N); m/z (ES) 440.1138 ($[M+Na]^+$ $C_{21}H_{23}NNaO_6S$ requires 440.1144), 440 (100%), 300.2 (3).

152: mp 126-129 °C; R_f 0.76 (Pet ether: EtOAc 1:1); ν_{max} (neat)/cm^{-1} : 2967, 1757, 1512, 1358, 1259, 1174, 855; δ_H (400 MHz, $CDCl_3$) 1.35-1.46 (1H, m, CH_2), 1.69-1.88 (2H, m, CH_2), 2.17-2.34 (3H, m, CH_2), 2.42 (3H, s, $PhCH_3$), 2.45 (3H, s, $PhCH_3$), 3.81 (3H, s, OCH_3), 4.84-4.87 (2H, m, CH_2C*H*N and CH_2C*H*OTs), 6.90 (2H, d, *J* 8.8 Hz, Ar H), 7.25-7.32 (6H, m, Ar H), 7.63 (2H, d, *J* 8.4 Hz, Ar H), 7.79 (2H, d, *J* 8.4 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 11.9 (CH_2), 20.1 (CH_2), 21.8 (2 x CH_3, $PhCH_3$), 23.2 (CH_2), 55.6 (CH_3, OCH_3), 60.3 (CH, CH_2*C*HN), 76.8 (CH, CH_2*C*HOTs), 88.7 (C, CH*C*OTs), 114.8 (2 x CH, Ar), 119.5 (2 x CH, Ar), 128.0 (2 x CH, Ar), 128.3 (2 x CH, Ar), 129.4 (C, Ar), 129.6 (2 x CH, Ar), 129.8 (2 x CH, Ar), 133.2 (C, ArCN), 134.3 (C, Ar), 144.9 (C, Ar), 145.2 (C, Ar), 157.4 (C, ArCO), 158.5 (C, C(O)N); m/z (ES) 594.1219 ($[M+Na]^+$ $C_{28}H_{29}NNaO_8S_2$ requires 594.1232), 594 (100%).

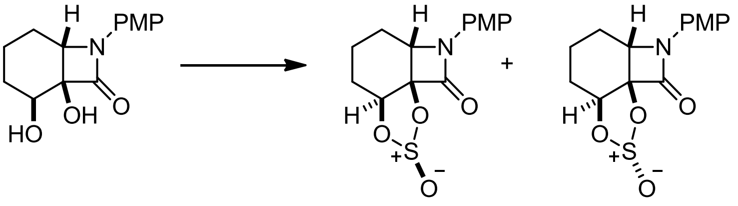
- (±)-(1*R*,2*S*,6*S*)-2-Hydroxy-7-(4-methoxyphenyl)-8-oxo-7-azabicyclo[4.2.0]octan-1-yl methylbenzene sulfonate **153**



146 **153**

A novel compound prepared according to a modified literature procedure.[238] A solution of dihydroxy lactam **146** (0.100 g, 0.380 mmol) in CH_2Cl_2 (2 mL) was treated with Et_3N (58 µL, 0.42 mmol), DMAP (10 mg, 0.082 mmol) and TsCl (78 mg, 0.42 mmol). After 18 h at rt, further Et_3N (58 µL, 0.42 mmol) and TsCl (78 mg, 0.42 mmol) were added to drive the reaction to completion. After 4 h, the reaction mixture was quenched with H_2O (2 mL) and extracted with Et_2O (2 x 3 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether:EtOAc 4:1 to Pet ether:EtOAc 3:2) to give *cis* hydroxyl tosyl lactam **153** (0.113 g, 71%) as a white solid. mp 84-86 °C; R_f 0.29 (Hexane:EtOAc 3:2); ν_{max} (neat)/cm^{-1} : 3524, 2968, 1746, 1512, 1172, 1048, 856; δ_H (300 MHz, $CDCl_3$) 1.32-1.42 (1H, m, CH_2), 1.62-2.15 (4H, m, CH_2), 2.28-2.38 (1H, m, CH_2), 2.43 (3H, s, $PhCH_3$), 2.88 (1H, br s, OH), 3.80 (3H, s, OCH_3), 4.30 (1H, t, *J* 3.3 Hz, CH_2CHN), 4.78 (1H, t, *J* 2.9 Hz, CH_2CHOH), 6.89 (2H, d, *J* 9.0 Hz, Ar H), 7.31-7.35 (4H, m, Ar H), 7.89 (2H, d, *J* 8.4 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 12.2 (CH_2), 20.1 (CH_2), 21.7 (CH_3, $PhCH_3$), 23.8 (CH_2), 55.5 (CH_3, OCH_3), 60.0 (CH, CH_2CHN), 66.9 (CH, CH_2CHOTs), 91.6 (C, CHCOH), 114.7 (2 x CH, Ar), 119.3 (2 x CH, Ar), 128.1 (2 x CH, Ar), 129.8 (2 x CH, Ar), 134.1 (C, ArCN), 145.4 (2 x C, Ar), 157.0 (C, ArCO), 160.2 (C, C(O)N); m/z (ES) 440.1141 ($[M+Na]^+$ $C_{21}H_{23}NNaO_6S$ requires 440.1144), 440 (100%).

- (±)-(3a*R*,5a*S*,8a*S*)-5-(4-Methoxyphenyl)hexahydro-4*H*-[1,3,2]dioxathiolo[4',5':2,3] benzo[1,2-*b*]azet-4-one 2-oxide **144a** and **144b**



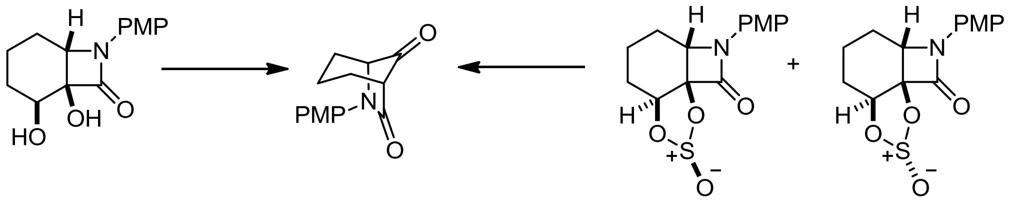
146 **144a** **144b**

Novel compounds prepared according to a literature procedure.[61] A solution of dihydroxy lactam **146** (0.100 g, 0.380 mmol) in CH_2Cl_2 (2 mL) at 0 °C was treated with pyridine (138 µL, 1.71 mmol) and $SOCl_2$ (55 µL, 0.76 mmol). The ice bath was removed after 25 min and stirring was continued for 3.5 h at rt. The reaction mixture was diluted with H_2O (2 mL) and extracted with CH_2Cl_2 (2 x 3 mL). The combined organic extracts were washed sequentially with HCl (3 mL of a 1 M aq. solution) and brine (3 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether:EtOAc 9:1 to Pet ether:EtOAc 65:35) to give **144a** (50 mg, 43%) and **144b** (50 mg, 43%) as white solids.

144a: mp 66-68 °C; R_f 0.90 (Pet ether:EtOAc 1:1); ν_{max} (neat)/cm^{-1}: 2933, 1749, 1511, 1198, 820, 653; δ_H (400 MHz, $CDCl_3$) 1.48-1.58 (1H, m, CH_2), 1.74-1.84 (1H, m, CH_2), 1.89-1.97 (1H, m, CH_2), 2.11-2.26 (3H, m, CH_2), 3.79 (3H, s, OCH_3), 4.58 (1H, dd, *J* 3.6 and 6.8 Hz, $CH_2C\mathit{H}N$), 5.04 (1H, t, *J* 5.8 Hz, $CH_2C\mathit{H}O$), 6.89 (2H, d, *J* 9.0 Hz, Ar H), 7.30 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 15.5 (CH_2), 25.4 (CH_2), 28.3 (CH_2), 55.6 (CH_3, OCH_3), 60.6 (CH, $CH_2\mathit{C}HN$), 81.8 (CH, $CH_2\mathit{C}HO$), 87.9 (C, $CH\mathit{C}OS$), 114.8 (2 x CH, Ar), 119.5 (2 x CH, Ar), 129.3 (C, ArCN), 157.2 (C, ArCO), 159.4 (C, C(O)N); m/z (ES) 332.0560 ($[M+Na]^+$ $C_{14}H_{15}NNaO_5S$ requires 332.0569), 332 (100%), 304 (9).

144b: mp 96-99 °C; R_f 0.74 (Pet ether:EtOAc 1:1); ν_{max} (neat)/cm^{-1}: 2947, 1738, 1511, 1206, 831, 655; δ_H (400 MHz, $CDCl_3$) 1.48-1.68 (2H, m, CH_2), 1.87-2.09 (3H, m, CH_2), 2.16-2.25 (1H, m, CH_2), 3.78 (3H, s, OCH_3), 4.37 (1H, dd, *J* 3.6 and 6.8 Hz, $CH_2C\mathit{H}N$), 5.41 (1H, t, *J* 5.8 Hz, $CH_2C\mathit{H}O$), 6.89 (2H, d, *J* 9.0 Hz, Ar H), 7.31 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 15.3 (CH_2), 25.1 (CH_2), 26.6 (CH_2), 55.6 (CH_3, OCH_3), 59.4 (CH, $CH_2\mathit{C}HN$), 77.1 (CH, $CH_2\mathit{C}HO$), 89.3 (C, $CH\mathit{C}OS$), 114.8 (2 x CH, Ar), 119.4 (2 x CH, Ar), 129.3 (C, ArCN), 157.1 (C, ArCO), 160.2 (C, C(O)N); m/z (ES) 332.0574 ($[M+Na]^+$ $C_{14}H_{15}NNaO_5S$ requires 332.0569), 364 (92%), 332 (100).

- (±)-(1*R*,5*S*)-6-(4-Methoxyphenyl)-6-azabicyclo[3.2.1]octane-7,8-dione **140**



146 **140** **144a** **144b**

A novel compound prepared according to a literature procedure.[19] A solution of PPh_3 (1.76 g, 6.70 mmol) and hexachloroethane (1.59 g, 6.70 mmol) in CH_3CN (10 mL) was stirred at rt for 30 min before being added dropwise to a solution of dihydroxylactam **146** (1.18 g, 4.47 mmol) in CH_3CN (20 mL). The reaction mixture was heated at reflux for 18 h, evaporated under reduced pressure and purified directly by column chromatography (Pet ether to Pet ether:EtOAc 1:1) to give bicyclic ketone **140** (1.03 mg, 94%) as a white solid.

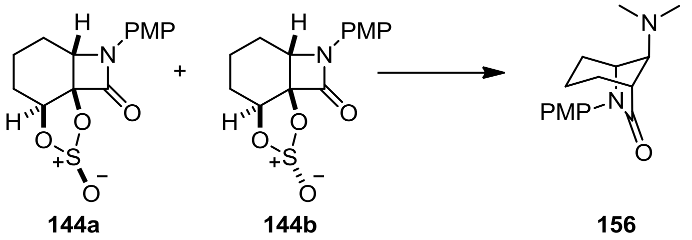
A solution of cyclic sulfites **144** (0.161 g, 0.520 mmol) in diphenyl ether (3 mL) was heated to 190 °C. After 2 h, the reaction mixture was directly purified by column chromatography (Pet ether to Pet ether:EtOAc 1:1) to give bicyclic ketone **140** (0.116 g, 91%) as a white solid.

A solution of cyclic sulfites **144a** (98 mg, 0.32 mmol) in diphenyl ether (1.9 mL) was heated to 190 °C. After 2.25 h, the reaction mixture was directly purified by column chromatography (Pet ether to Pet ether:EtOAc 1:1) to give bicyclic ketone **140** (68 g, 87%) as a white solid.

A solution of cyclic sulfites **144b** (98 mg, 0.32 mmol) in diphenyl ether (1.9 mL) was heated to 190 °C. After 0.75 h, the reaction mixture was directly purified by column chromatography (Pet ether to Pet ether:EtOAc 1:1) to give bicyclic ketone **140** (78 mg, 100%) as a white solid.

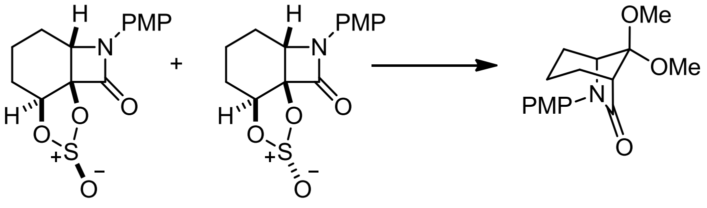
mp 61-63 °C; R_f 0.20 (Pet ether:EtOAc 1:1); ν_{max} (neat)/cm^{-1}: 2955, 1778, 1687, 1509, 1388, 1241, 824; δ_H (400 MHz, $CDCl_3$) 1.77-1.84 (2H, m, CH_2), 1.91-2.06 (2H, m, CH_2), 2.40-2.49 (2H, m, CH_2), 3.00-3.02 (1H, m, C(O)CHC(O)), 3.79 (3H, s, OCH_3), 4.27-4.28 (1H, m, C(O)CHN), 6.80 (2H, d, *J* 9.2 Hz, Ar H), 7.48 (2H, d, *J* 9.2 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 17.4 (CH_2), 31.9 (CH_2), 32.4 (CH_2), 54.1 (CH, C(O)*C*HC(O)), 55.6 (CH_3, OCH_3), 57.2 (CH, CH_2*C*HN), 114.6 (2 x CH, Ar), 122.9 (2 x CH, Ar), 129.9 (C, ArCN), 157.4 (C, ArCO), 169.1 (C, C(O)N), 208.3 (C, CH*C*(O)CH); m/z (ES) 268.0937 ([M+Na]$^+$ $C_{14}H_{15}NNaO_3$ requires 268.0950), 300 (61%), 286 (33), 268 (8), 246 (100).

- (±)-(1*R*,5*S*,8*S*)-8-(Dimethylamino)-6-(4-methoxyphenyl)-6-azabicyclo[3.2.1]octan-7-one **156**



A novel compound prepared according to a modified literature procedure.[16] A solution of cyclic sulfites **144** (47 mg, 0.19 mmol) in DMF (1 mL) was heated to reflux. After 6 h, the reaction mixture was evaporated under reduced pressure and purified by column chromatography (Pet ether:EtOAc 7:3 to Pet ether:EtOAc 2:3) to give dimethyl amine **156** (59 mg, 58%) as a light orange oil. R_f 0.11 (Pet ether:EtOAc 1:1); ν_{max} (neat)/cm^{-1} : 2954, 2877, 2827, 2781, 1692, 1509, 1243, 1033, 826; δ_H (400 MHz, $CDCl_3$) 1.60-1.71 (4H, m, CH_2), 1.85-1.94 (2H, m, CH_2), 2.21 (6H, s, $N(CH_3)_2$), 2.50 (1H, t, *J* 4.8 Hz, CHC*H*N$(CH_3)_2$), 2.57 (1H, br s, C(O)C*H*CH_2), 3.77 (3H, s, OCH_3), 4.05 (1H, t, *J* 4.4 Hz, CH_2C*H*N), 6.87 (2H, d, *J* 9.0 Hz, Ar H), 7.49 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 17.7 (CH_2), 18.7 (CH_2), 19.7 (CH_2), 42.7 (2 x CH_3, $N(CH_3)_2$), 44.8 (CH, CH_2*C*HC(O)), 55.6 (CH_3, OCH_3), 59.8 (CH, CH_2*C*HN), 66.8 (CH, *C*HN$(CH_3)_2$), 114.3 (2 x CH, Ar), 122.5 (2 x CH, Ar), 131.8 (C, ArCN), 156.7 (C, ArCO), 174.7 (C, C(O)N); m/z (ES) 297.1585 ($[M+Na]^+$ $C_{16}H_{22}N_2NaO_2$ requires 297.1579), 298 (18%), 297 (100), 275 (11).

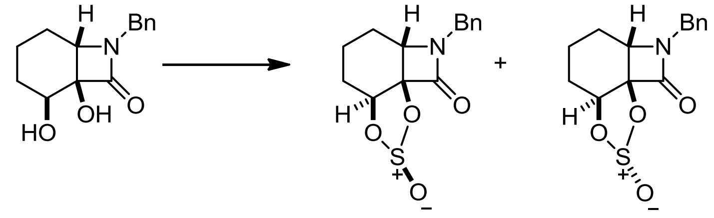
- (±)-(*1R,5S*)-8,8-Dimethoxy-6-(4-methoxyphenyl)-6-azabicyclo[3.2.1]octan-7-one **157**



A novel compound prepared according to a modified literature procedure.[16] A solution of cyclic sulfites **144** (0.113 g, 0.366 mmol) in toluene (2.2 mL) was treated with $BF_3.Et_2O$ dropwise over

2 min (99 µL, 0.78 mmol) and then refluxed. After 4 h, the reaction mixture was quenched with MeOH (2 mL), evaporated under reduced pressure and purified by column chromatography (Pet ether:EtOAc 7:3 to Pet ether:EtOAc 1:1) to give methoxy acetal **157** (54 mg, 50%) as a yellow oil. R_f 0.28 (Pet ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1} : 2941, 1697, 1509, 1241, 1120, 827; δ_H (400 MHz, $CDCl_3$) 1.44-1.55 (1H, m, CH_2), 1.57-1.66 (1H, m, CH_2), 1.70-1.79 (1H, m, CH_2), 1.84-1.92 (3H, m, CH_2), 2.69-2.71 (1H, m, $CH_2C\mathit{H}C(O)$), 3.26 (3H, s, OCH_3), 3.27 (3H, s, OCH_3), 3.77 (3H, s, $PhOCH_3$), 4.14-4.15 (1H, m, $CH_2C\mathit{H}N$), 6.87 (2H, d, *J* 9.0 Hz, Ar H), 7.45 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 16.7 (CH_2), 22.3 (CH_2), 23.4 (CH_2), 47.7 (CH, $CH_2\mathit{C}HC(O)$), 48.8 (CH_3, $C(O\mathit{C}H_3)_2$), 49.2 (CH_3, $C(O\mathit{C}H_3)_2$), 55.6 (CH_3, $PhOCH_3$), 61.1 (CH, $CH_2\mathit{C}HN$), 103.3 (C, $\mathit{C}(OCH_3)_2$), 114.4 (2 x CH, Ar), 122.7 (2 x CH, Ar), 131.6 (C, ArCN), 156.8 (C, ArCO), 173.0 (C, C(O)N); m/z (ES) 314.1375 ($[M+Na]^+$ $C_{16}H_{21}NNaO_4$ requires 314.1368), 315 (16%), 314 (100).

- (±)-(3a*R*,5a*S*,8a*S*)-5-Benzylhexahydro-4*H*-[1,3,2]dioxathiolo[4',5':2,3]benzo[1,2-*b*]azet-4-one 2-oxide **158a** and **158b**



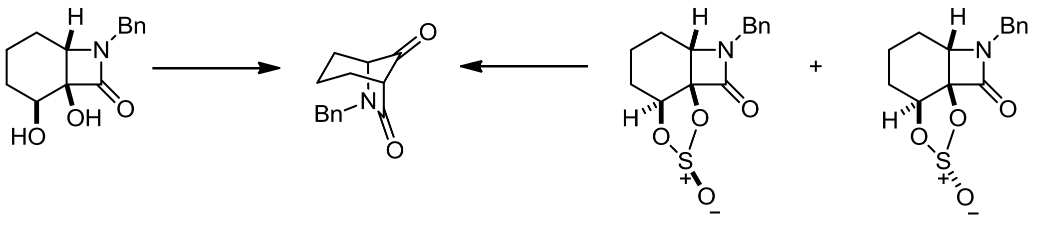
145 **158a** **158b**

Novel compounds prepared according to a literature procedure.[61] A solution of diol **145** (0.237 g, 0.960 mmol) in CH_2Cl_2 (5 mL) at 0 °C was treated with pyridine (349 µL, 4.32 mmol) and $SOCl_2$ (140 µL, 1.92 mmol). The reaction mixture was allowed to warm to rt over 18 h, diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were sequentially washed with HCl (10 mL of a 1 M aq. solution) and brine (10 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 7:3) to give **158a** (0.131 g, 47%) as a colourless oil and **158b** (0.127 g, 45%) as a white solid.

158a: R$_f$ 0.79 (Pet ether:EtOAc 1:1); ν$_{max}$ (neat)/cm^{-1}: 2946, 1762, 1405, 1204, 955, 699; δ$_H$ (400 MHz, CDCl$_3$) 1.32-1.43 (1H, m, CH$_2$), 1.62-1.85 (3H, m, CH$_2$), 1.90-1.99 (1H, m, CH$_2$), 2.21-2.29 (1H, m, CH$_2$), 4.06-4.14 (1H, m, CH$_2$C*H*N), 4.18, 4.68 (2H, ABq, *J* 15.2 Hz, NCH$_2$Ph), 4.96 (1H, dd, *J* 6.4 and 7.6 Hz, CH$_2$C*H*O), 7.27-7.40 (5H, m, Ar H); δ$_C$ (100 MHz, CDCl$_3$) 15.4 (CH$_2$), 24.3 (CH$_2$), 29.5 (CH$_2$), 44.6 (CH$_2$, NCH$_2$Ph), 60.2 (CH, CH$_2$*C*HN), 81.6 (CH, CH$_2$*C*HO), 88.3 (C, CH*C*OS(O)), 128.3 (3 x CH, Ar), 129.1 (2 x CH, Ar), 134.4 (C, Ar), 163.6 (C, C(O)N); m/z (ES) 316.0620 ([M+Na]$^+$ $C_{14}H_{15}NNaO_4S$ requires 316.0619), 348 ([M+Na+CH$_3$OH]$^+$, 33%), 317 (9), 316 (100), 301 (7).

158b: mp 56-57 °C (CH$_2$Cl$_2$); R$_f$ 0.63 (Pet ether:EtOAc 1:1); ν$_{max}$ (neat)/cm^{-1}: 2940, 1761, 1404, 1219, 1202, 954, 665; δ$_H$ (400 MHz, CDCl$_3$) 1.34-1.45 (1H, m, CH$_2$), 1.54-1.68 (3H, m, CH$_2$), 1.72-1.79 (1H, m, CH$_2$), 2.24-2.32 (1H, m, CH$_2$), 3.89 (1H, dd, *J* 2.4 and 5.6 Hz, CH$_2$C*H*N), 4.15, 4.72 (2H, ABq, *J* 15.2 Hz, NCH$_2$Ph), 5.31 (1H, t, *J* 7.0 Hz, CH$_2$C*H*O), 7.28-7.40 (5H, m, Ar H); δ$_C$ (100 MHz, CDCl$_3$) 15.0 (CH$_2$), 24.2 (CH$_2$), 27.2 (CH$_2$), 44.5 (CH$_2$, NCH$_2$Ph), 58.5 (CH, CH$_2$*C*HN), 76.9 (CH, CH$_2$*C*HO), 89.3 (C, CH*C*OS), 128.2 (CH, Ar), 128.3 (2 x CH, Ar), 129.1 (2 x CH, Ar), 134.5 (C, Ar), 164.2 (C, C(O)N); m/z (ES) 316.0620 ([M+Na]$^+$ $C_{14}H_{15}NNaO_4S$ requires 316.0619), 348 ([M+Na+CH$_3$OH]$^+$, 5%), 332 (17), 317 (14), 316 (100), 294 (6).

- (±)-(1*S*,5*R*)-6-Benzyl-6-azabicyclo[3.2.1]octane-7,8-dione **119**



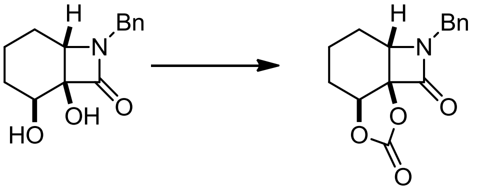
145 **119** **158a** **158b**

A novel compound prepared according to a literature procedure.[19] A solution of PPh$_3$ (0.162 g, 0.618 mmol) and hexachloroethane (0.145 g, 0.618 mmol) in CH$_3$CN (1.0 mL) was stirred at rt for 30 min before being added dropwise to a solution of diol **145** (0.102 g, 0.412 mmol) in CH$_3$CN (1.7 mL). The reaction mixture was heated at reflux for 18 h, concentrated under reduced pressure and purified directly by column chromatography (Pet ether to Pet ether:EtOAc 3:2) to give bicyclic ketone **119** (92 mg , 97%) as a white solid.

A solution of cyclic sulfites **158** (0.175 g, 0.597 mmol) in diphenyl ether (3.5 mL) was heated to 190 °C. After 2.25 h, the reaction mixture was directly purified by column chromatography (Pet ether to Pet ether:EtOAc 3:2) to give bicyclic ketone **119** (0.123 g, 90%) as a white solid.

mp 58-61 °C (CH_2Cl_2); R_f 0.30 (Pet ether:EtOAc 1:1); ν_{max} (neat)/cm^{-1}: 2943, 1780, 1686, 1448, 1252, 1033, 701; δ_H (400 MHz, $CDCl_3$) 1.51-1.78 (3H, m, CH_2), 1.88-1.97 (1H, m, CH_2), 1.98-2.04 (1H, m, CH_2), 2.34-2.41 (1H, m, CH_2), 2.91-2.93 (1H, m, C(O)CHC(O)), 3.67-3.69 (1H, d, *J* 4.8 Hz, C(O)CHN), 4.37, 4.89 (2H, ABq, *J* 14.8 Hz, NCH_2Ph), 7.27-7.37 (5H, m, Ar H); δ_C (100 MHz, $CDCl_3$) 17.5 (CH_2), 30.8 (CH_2), 31.9 (CH_2), 44.5 (CH_2, NCH_2Ph), 53.0 (CH, C(O)*C*HC(O)), 64.0 (CH, CH_2*C*HN), 128.2 (CH, Ar), 128.6 (2 x CH, Ar), 129.0 (2 x CH, Ar), 135.7 (C, Ar), 170.4 (C, C(O)N), 209.1 (C, CH*C*(O)CH); m/z (ES) 252.0992 ([M+Na]$^+$ $C_{14}H_{15}NNaO_2$ requires 252.1000), 284 (26%), 270 (100), 252 (10).

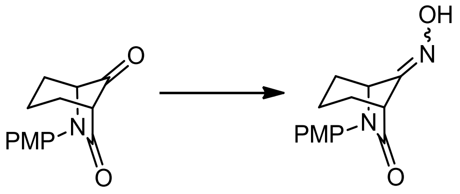
- (±)-(3a*R*,5a*S*,8a*S*)-5-Benzylhexahydro-4*H*-[1,3]dioxolo[4',5':2,3]benzo[1,2-*b*]azete-2,4-dione **160**



145 **160**

A novel compound prepared according to a literature procedure.[239] A solution of diol **145** (81 mg, 0.33 mmol) in CH_2Cl_2 (1.6 mL) at 0 °C was treated with pyridine (132 µL, 1.64 mmol) and triphosgene (79 mg, 0.27 mmol). The reaction mixture was allowed to warm to rt after 40 min at 0 °C, stirred at rt for 50 min, quenched with NH_4Cl (5 mL of a saturated aq. solution) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed sequentially with HCl (10 mL of a 1 M aq. solution) and brine (15 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 1:1) to give **160** (90 mg, 100%) as a white solid. mp 100-101 °C; R_f 0.52 (Pet ether:EtOAc 1:1); ν_{max} (neat)/cm^{-1}: 2955, 1812, 1766, 1362, 1165, 1067, 732; δ_H (400 MHz, $CDCl_3$) 1.19-1.38 (1H, m, CH_2), 1.45-1.84 (4H, m, CH_2), 2.20-2.35 (1H, m, CH_2), 3.92 (1H, dd, *J* 2.0 and 5.6 Hz, CH_2CHN), 4.15, 4.65 (2H, ABq, *J* 15.2 Hz, NCH_2Ph), 4.97 (1H, dd, *J* 7.0 and 8.7 Hz, CH_2CHO), 7.21-7.42 (5H, m, Ar H); δ_C (100 MHz, $CDCl_3$) 14.7 (CH_2), 24.2 (CH_2), 28.1 (CH_2), 44.4 (CH_2, NCH_2Ph), 57.9 (CH, CH_2CHN), 74.4 (CH, CH_2CHO), 85.0 (C, CH*C*OC(O)), 128.3 (2 x CH, Ar), 128.4 (CH, Ar), 129.2 (2 x CH, Ar), 134.2 (C, Ar), 152.6 (C, OC(O)O), 164.1 (C, C(O)N); m/z (ES) 274.1074 ($[M+H]^+$ $C_{15}H_{16}NO_4$ requires 274.1074), 292 (16%), 291 (100), 274 (51).

- (±)-(1*R*,5*S*)-8-(Hydroxyimino)-6-(4-methoxyphenyl)-6-azabicyclo[3.2.1]octan-7-one **162**

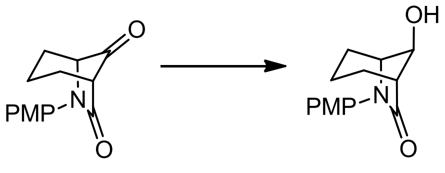


140 **162**

A novel compound prepared according to a literature procedure.[73] A solution of hydroxylamine hydrochloride (60 mg, 0.86 mmol) and sodium acetate (70 mg, 0.86 mmol) in H_2O (0.30 mL) was treated with a solution of bicyclic ketone **140** (30 mg, 0.12 mmol) in a 1:1 mixture of $H_2O:CH_3CN$ (0.30 mL). After 20 min at 100 °C, the reaction mixture was extracted with CH_2Cl_2 (2 x 1 mL). The combined organic extracts were washed with brine (1 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (CH_2Cl_2 to CH_2Cl_2:EtOH 98:2) to give a 1:1 mixture of *Z:E* oxime **162** (24 mg, 77%) as a colourless oil. R_f 0.18 (CH_2Cl_2:EtOH 98:2); ν_{max} (neat)/cm^{-1} : 3263, 2935, 1673, 1509, 1245, 826; δ_H (400 MHz, $CDCl_3$) (as a mixture of isomers) 1.72-1.97 (4H, m, CH_2), 2.17-2.35 (2H, m, CH_2), 3.18-3.21, 3.81-3.84 (1H, br s, C(O)C*H*C(N)OH), 3.80 (3H, s, OCH_3), 4.63, 5.26 (1H, d, *J* 4.0 Hz, NC*H*C(N)OH), 6.90 (2H, d, *J* 9.2 Hz, Ar H), 7.47-7.55 (2H, m, Ar H), 8.34, 8.51 (1H, br s, OH); δ_C (100 MHz,

$CDCl_3$) (as a mixture of isomers) 17.7 (CH_2), 28.2, 28.4 (CH_2), 30.6, 31.0 (CH_2), 43.7, 46.9 (CH, C(O)*C*HC(N)OH), 55.6 (CH_3, OCH_3), 57.1, 61.4 (CH, CH_2CHN), 114.5, 114.6 (2 x CH, Ar), 122.6, 122.7 (2 x CH, Ar), 130.3, 130.4 (C, ArCN), 157.1 (C, ArCO), 160.8, 161.0 (C, C(O)N), 171.1, 171.5 (C, C(N)OH); m/z (ES) 283.1056 ($[M+Na]^+$ $C_{14}H_{16}N_2NaO_3$ requires 283.1059), 315 (8%), 283 (100), 261 (5).

- (±)-(1*R*,5*S*,8*S*)-8-Hydroxy-6-(4-methoxyphenyl)-6-azabicyclo[3.2.1]octan-7-one **164**

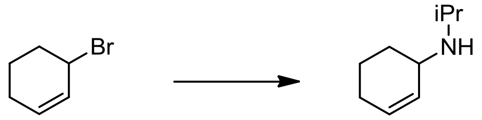


140 **164**

A novel compound prepared according to a modified literature procedure.[240] A solution of bicyclic ketone **140** (47 mg, 0.19 mmol) in THF (1 mL) was cooled to 0 °C and treated with L-selectride (0.29 mL of a 1.0 M solution in THF, 0.29 mmol). The reaction mixture was progressively allowed to warm to rt. After 6.25 h, the reaction mixture was quenched with H_2O (1 mL) and extracted with EtOAc (2 x 3 mL). The combined organic extract were washed with brine (2 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether:EtOAc 7:3) to give hydroxy lactam **164** (39 mg, 83%) as a white solid. mp 116-118 °C; R_f 0.33 (Pet ether:EtOAc 2:3); ν_{max} (neat)/cm^{-1} : 3327, 2947, 1661, 1511, 1245, 1113, 803; δ_H (400 MHz, $CDCl_3$) 1.46-1.59 (1H, m, CH_2), 1.62-1.73 (3H, m, CH_2), 1.92-2.04 (2H, m, CH_2), 2.55 (1H, br s, C(O)C*H*CH_2),3.43 (1H, br s, OH), 3.77 (3H, s, OCH_3), 3.97-4.00 (1H, m, CH_2C*H*N), 4.34-4.37 (1H, m, CHC*H*(OH)CH), 6.87 (2H, d, *J* 8.8 Hz, Ar H), 7.45 (2H, d, *J* 8.8 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 17.3 (CH_2), 18.5 (CH_2), 19.6 (CH_2), 46.4 (CH, C(O)*C*HCH_2), 55.6 (CH_3, OCH_3), 61.2 (CH, CH_2*C*HN), 68.2 (CH, CH*C*HOH), 114.4 (2 x CH, Ar), 122.9 (2 x CH, Ar), 131.3 (C, ArCN), 156.9 (C, ArCO), 174.3 (C, C(O)N); m/z (ES) 270.1111 ($[M+Na]^+$ $C_{14}H_{17}NNaO_3$ requires 270.1106), 270 (100%).

6.3 Experimental procedures and analytical data for chapter three

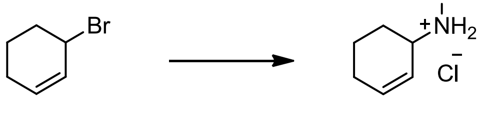
- *N*-isopropylcyclohex-2-enamine **166**



122 **166**

A novel compound prepared according to a literature procedure.[27] A solution of isopropylamine (2.56 mL, 30.0 mmol) in CH_3CN (30 mL) was treated with 3-bromocyclohexene **122** (1.29 mL, 11.2 mmol) and K_2CO_3 (1.63 g, 11.8 mmol). After 4 h at rt, the reaction was quenched with H_2O (30 mL) and extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with brine (60 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give amine **166** (1.48 g, 95%) as a light brown oil. R_f 0.26 (CH_2Cl_2:EtOH 49:1); ν_{max} (neat)/cm^{-1} : 3219, 2929, 1444, 1378, 1172, 723; δ_H (400 MHz, $CDCl_3$) 1.03-1.06 (6H, m, $CH(C\mathit{H}_3)_2$), 1.20 (1H, m, NH), 1.34-1.42 (1H, m, CH_2), 1.50-1.60 (1H, m, CH_2), 1.66-1.74 (1H, m, CH_2), 1.83-1.90 (1H, m, CH_2), 1.92-2.04 (2H, m, CH_2), 2.96-3.05 (1H, m, $NHC\mathit{H}(CH_3)_2$), 3.21 (1H, br s, $CH_2C\mathit{H}NH$), 5.67-5.74 (2H, m, CH=CH); δ_C (100 MHz, $CDCl_3$) 20.4 (CH_2), 23.2 (CH_3, $CH(\mathit{C}H_3)_2$), 23.6 (CH_3, $CH(\mathit{C}H_3)_2$), 25.4 (CH_2), 30.1 (CH_2), 45.1 (CH, $NH\mathit{C}H(CH_3)_2$), 49.9 (CH, $CH_2\mathit{C}HNH$), 128.7 (CH, $CH_2CH{=}CH$), 130.6 (CH, $CH{=}\mathit{C}HCHNH$); m/z (EI) 139.1358 (M^+, $C_9H_{17}N$ requires 139.1361), 139 (21%), 124 (20), 111 (77), 96 (100), 81 (14).

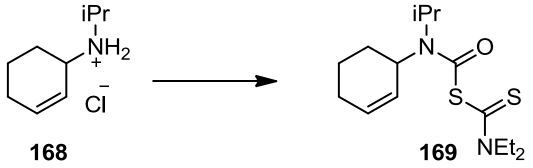
- *N*-Isopropylcyclohex-2-enaminium chloride **168**



122 **168**

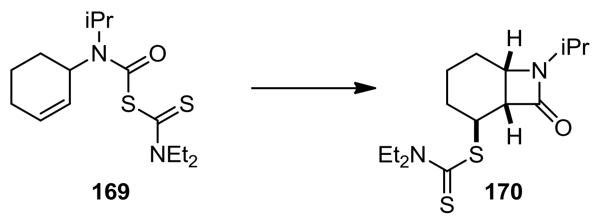
A novel compound prepared according to a modified literature procedure.[27] A solution of isopropylamine (2.50 mL, 108 mmol) in CH_3CN (110 mL) was treated with 3-bromocyclohexene **122** (5.00 mL, 40.1 mmol) and K_2CO_3 (6.10 g, 44.1 mmol). After 8 h at rt, the reaction was quenched with H_2O (110 mL) and extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with brine (150 mL), dried over $MgSO_4$, filtered and HCl (20 mL of a 4 M solution in dioxane, 80 mmol) was carefully added. The solvent was removed under reduced pressure to give amine hydrochloride **168** (6.54 g, 93%) as a white solid. δ_H (400 MHz, D_2O) 1.33 (6H, t, *J* 6.2 Hz, $CH(CH_3)_2$), 1.59-1.72 (2H, m, CH_2), 1.73-1.87 (1H, m, CH_2), 2.00-2.16 (3H, m, CH_2), 3.59 (1H, m, *J* 6.2 Hz, $NHCH(CH_3)_2$), 3.94 (1H, br s, CH_2CHN), 5.69 (1H, d, *J* 10.1 Hz, CH_2CH=CH), 6.16 (1H, d, *J* 10.1 Hz, CH=CHCHN); δ_C (100 MHz, $CDCl_3$) 18.2 (CH_3, $CH(CH_3)_2$), 18.6 (CH_2), 18.7 (CH_3, $CH(CH_3)_2$), 24.1 (CH_2), 25.2 (CH_2), 47.3 (CH, $NHCH(CH_3)_2$), 50.4 (CH, CH_2CHNH), 120.7 (CH, CH_2CH=CH), 135.8 (CH, CH=CHCHNH); m/z (EI) 139.135637 (M^+ $C_9H_{17}N$ requires 139.136100), 139 (41%), 124 (38), 111 (99), 96 (100), 81 (58), 44 (70).

- Diethyldithiocarbamic acid-[isopropyl(cyclohex-2-enyl)carbamic acid]-thioanhydride **169**



A novel compound prepared according to a modified literature procedure.[27] A solution of amine hydrochloride **168** (0.716 g, 4.08 mmol) in THF (27 mL) was cooled to -78 °C, *n*BuLi (9.07 mL of a 1.01 M solution in hexanes, 8.98 mmol), was added dropwise over 5 min. After 70 min at -78 °C, triphosgene (0.447 g, 1.51 mmol) was added and the reaction mixture was allowed to warm to rt. After 3 h, acetone (10 mL) and sodium diethyldithiocarbamate trihydrate (3.67 g, 16.3 mmol) were added. After 18 h at rt, the reaction mixture was quenched with H_2O (30 mL) and extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:Et_2O 4:1) to give dithiocarbamate **169** (0.562 g, 44%) as a yellow oil. R_f 0.36 (Pet ether:Et_2O 4:1); ν_{max} (neat)/cm^{-1} : 2933, 1741, 1671, 1487, 1415, 1247, 1196, 977, 808; δ_H (400 MHz, $CDCl_3$) (as a mixture of rotamers) 1.15-1.41 (12H, m, $CH(CH_3)_2$ and CH_2CH_3), 1.49-1.66 (2H, m, CH_2), 1.72-1.86 (1H, m, CH_2), 1.72-1.86 (3H, m, CH_2), 3.31-3.57 (1H, m, CH_2CHN), 3.76 (2H, q, *J* 7.2 Hz, CH_2CH_3), 3.87-4.07 (2H, m, CH_2CH_3), 4.30-4.49 (1H, m, $NCH(CH_3)_2$), 5.52 (1H, d, *J* 8.4 Hz, CH_2CH=CH), 5.86 (1H, br s, CH=C*H*CHN); δ_C (100 MHz, $CDCl_3$) (as a mixture of rotamers) 11.3 (CH_3, CH_2CH_3), 13.4 (CH_3, CH_2CH_3), 20.1 (2 x CH_3, $NCH(CH_3)_2$), 21.6 (CH_2), 24.3 (CH_2), 28.4 (CH_2), 48.8 (CH_2, CH_2CH_3), 49.8 (CH, CH_2CHN), 50.0 (CH_2, CH_2CH_3), 58.0 (CH, $NCH(CH_3)_2$), 127.3 (CH, CH_2CH=CH), 131.3 (CH, CH=*C*HCHN), 159.7 (C, C(O)N), 186.0 (C, SC(S)); m/z (ES) 337.1380 ($[M+Na]^+$ $C_{15}H_{26}N_2NaOS_2$ requires 337.1384), 353 (13%), 337 (100).

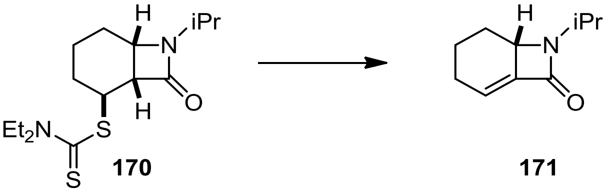
- (±)-(*1S,2R,6R*)-7-Isopropyl-8-oxo-7-azabicyclo[4.2.0]octan-2-yl diethylcarbamodithioate **170**



A novel compound prepared according to a literature procedure.[26] A solution of carbamoyl dithiocarbamate **169** (0.422 g, 1.34 mmol) in cyclohexane (13.5 mL) was degassed for 10 min and irradiated with a 500 W lamp which generated enough heat to bring the solvent to reflux. After 4.5 h, the solvent was removed under reduced pressure and the crude product obtained was purified by column chromatography (Pet ether to Pet ether:EtOAc 3:2) to give lactam **170** (0.293 g, 69%) as a pale yellow oil. R_f 0.27 (Pet Ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1} : 2933, 1733, 1486, 1414, 1266, 1205, 981, 916, 831; δ_H (400 MHz, $CDCl_3$) 1.20-1.28 (12H, m, CH_3CH_2 and $CH(CH_3)_2$), 1.58-1.88 (5H, m, CH_2), 2.25-2.34 (1H, m, CH_2), 3.44 (1H, app t, *J* 4.6 Hz, CHC*H*C(O)), 3.65-3.76 (2H, m, CH_2CH_3), 3.82-3.88 (2H, m, CH_2CH_3 and CH_2CHS), 3.91-4.07 (2H, m, $NCH(CH_3)_2$ and CH_2CH_3), 4.48 (1H, app dd, *J* 5.2 and 9.6 Hz, CH_2CHN); δ_C (100 MHz, $CDCl_3$) 11.7 (CH_3, CH_2CH_3), 12.7 (CH_3, CH_2CH_3), 15.5 (CH_2), 20.3 (CH_3, $NCH(CH_3)_2$), 21.7 (CH_3, $NCH(CH_3)_2$), 24.1

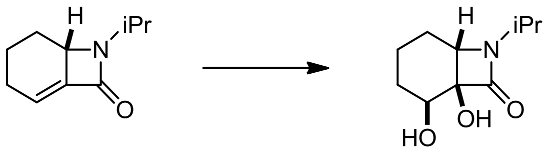
(CH_2), 25.2 (CH_2), 43.8 (CH, CH_2*C*HS), 44.6 (CH, CH_2*C*HN), 46.7 (CH_2, CH_2CH_3), 49.2 (CH_2, *C*H_2CH_3), 49.4 (CH, N*C*H$(CH_3)_2$), 51.2 (CH, CH_2*C*HC(O)), 167.4 (C, C(O)N), 193.8 (C, SC(S)); m/z (ES) 337.1387 ($[M+Na]^+$ $C_{15}H_{26}N_2NaOS_2$ requires 337.1384), 453 ($[M+Na+H_2O]^+$, 4%), 337 (100).

- 7-Isopropyl-7-azabicyclo[4.2.0]oct-1-en-8-one **171**



A novel compound prepared according to a modified literature procedure.[39] A solution of lactam **170** (0.291 g, 0.925 mmol) in THF (7.2 mL) was cooled to -78 °C and treated with methyl iodide (92.0 µL, 1.48 mmol). The reaction mixture was stirred at -78 °C for 1.5 h, then LHMDS (1.5 mL of a 1.0 M solution in THF, 1.5 mmol) was added dropwise over 2 min. The reaction mixture was allowed to warm to rt over 18 h. The solvent was removed under reduced pressure and the crude product obtained was purified by column chromatography (Pet ether to Pet ether:EtOAc 7:3) to give lactam **171** (88 mg, 56%) as a pale yellow oil. R_f 0.36 (Pet Ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1} : 2935, 1731, 1364, 1310, 1229, 812, 712; δ_H (400 MHz, $CDCl_3$) 1.05-1.16 (1H, m, CH_2), 1.19 (3H, d, *J* 6.7 Hz, CH(C*H*$_3$)$_2$), 1.22 (3H, d, *J* 6.7 Hz, CH(C*H*$_3$)$_2$), 1.39-1.55 (1H, m, CH_2), 1.89-2.00 (1H, m, CH_2), 2.06-2.19 (2H, m, CH_2), 2.28-2.40 (1H, m, CH_2), 3.74-3.80 (1H, m, CH_2C*H*N), 3.99 (1H, sept, *J* 6.7 Hz, NC*H*$(CH_3)_2$), 6.11-6.25 (1H, m, CH_2C*H*=C); δ_C (100 MHz, $CDCl_3$) 20.6 (CH_2), 20.9 (CH_3, NCH(*C*H_3)$_2$), 22.3 (CH_3, NCH(*C*H_3)$_2$), 25.4 (CH_2), 29.7 (CH_2), 44.2 (CH, CH_2*C*HN), 55.0 (CH, N*C*H$(CH_3)_2$), 124.0 (CH, CH_2*C*H=C), 141.4 (C, CH=*C*C(O)), 163.2 (C, C(O)N); m/z (ES) 166.1225 ($[M+H]^+$ $C_{10}H_{16}NO$ requires 166.1226), 167 (10%), 166 (100), 149 (10).

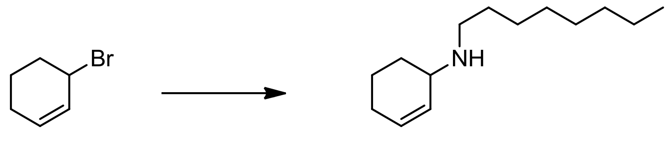
- (±)-(*1S,2R,6R*)-1,2-Dihydroxy-7-isopropyl-7-azabicyclo[4.2.0]octan-8-one **172**



171 **172**

A novel compound prepared according to a literature procedure.[56] A solution of lactam **171** (91 mg, 0.55 mmol) in a 5:5:2 mixture of H_2O:acetone:*t*BuOH (3.1 mL) was treated with NMO (0.155 g, 1.32 mmol) and OsO_4 (2 µL of 4 wt% aq. solution, cat). After 18 h at 40 °C, sodium bisulfite (0.314 g, 1.32 mmol) was added to quench the reaction. After 1.5 h at 40 °C, the reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Hexane:EtOAc 1:1 to EtOAc) to give dihydroxy lactam **172** (17 mg, 15%) as a white solid. mp 78-79 °C; R_f 0.13 (Pet Ether: EtOAc 2:3); ν_{max} (neat)/cm^{-1} : 3491, 3196, 2939, 1716, 1353, 1204, 1186, 1104, 828, 727; δ_H (400 MHz, $CDCl_3$) 1.22 (3H, d, *J* 6.8 Hz, $CH(CH_3)_2$), 1.28 (3H, d, *J* 6.8 Hz, $CH(CH_3)_2$), 1.46-1.60 (1H, m, CH_2), 1.63-1.83 (4H, m, CH_2), 1.29-2.04 (1H, m, CH_2), 3.32-3.90 (4H, m, CH_2CHN, $NCH(CH_3)_2$ and 2 x OH), 4.04 (1H, dd, *J* 4.3 and 6.1 Hz, CH_2CHOH); δ_C (100 MHz, $CDCl_3$) 15.0 (CH_2), 20.1 (CH_3, $NCH(CH_3)_2$), 21.6 (CH_3, $NCH(CH_3)_2$), 23.4 (CH_2), 25.6 (CH_2), 44.0 (CH, $NCH(CH_3)_2$), 60.3 (CH, CH_2CHN), 67.5 (CH, CH_2CHOH), 81.4 (C, CHCOH), 171.0 (C, C(O)N); m/z (ES) 200.1281 ($[M+H]^+$ $C_{10}H_{18}NO_3$ requires 200.1281), 222 (67%), 200 (100), 166 (11).

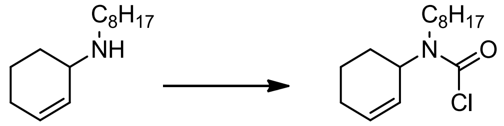
- *N*-octylcyclohex-2-enamine **173**



122 **173**

A novel compound prepared according to a literature procedure.[27] A solution of octylamine (23.3 mL, 141 mmol) in CH_3CN (140 mL) was treated with 3-bromocyclohexene **122** (6.00 mL, 52.2 mmol) and K_2CO_3 (7.94 g, 57.4 mmol). After 4.25 h at rt, the reaction mixture was quenched with H_2O (140 mL) and extracted with Et_2O (2 x 140 mL). The combined organic extracts were washed with brine (200 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Hexane:EtOAc 75:25 to EtOAc) to give amine **173** (8.34 g, 76%) as a golden oil. R_f 0.15 (Pet ether:EtOAc 9:1); ν_{max} (neat)/cm^{-1}: 3677, 2922, 1454, 1115, 722; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, *J* 7.0 Hz, $(CH_2)_8CH_3$), 1.03 (1H, br s, NH), 1.18-1.31 (10H, m, CH_2), 1.36-1.59 (4H, m, CH_2), 1.67-1.75 (1H, m, CH_2), 1.83-1.89 (1H, m, CH_2), 1.94-2.00 (2H, m, CH_2), 2.57-2.67 (2H, m, $NCH_2(CH_2)_7CH_3$), 3.10-3.15 (1H, m, $NCHCH_2$), 5.66-5.75 (2H, m, $CH_2CH{=}CHCHN$); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3, $(CH_2)_7CH_3$), 20.5 (CH_2), 22.8 (CH_2), 25.5 (CH_2), 27.7 (CH_2), 29.5 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 30.8 (CH_2), 32.0 (CH_2), 47.2 (CH_2, $NCH_2(CH_2)_6CH_3$), 53.3 (CH, CH_2CHN), 128.8 (CH, $CH_2CH{=}CH$), 130.4 (CH, $CH{=}CHCHN$); m/z (EI) 209.2141 (M^+ $C_{14}H_{27}N$ requires 209.2144), 209 ($[M+H]^+$, 13%), 181 (100), 110 (79), 81 (39).

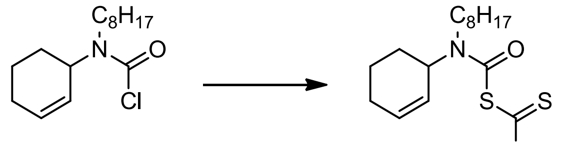
- Cyclohex-2-en-1-yl(octyl)carbamic chloride **174**



173 **174**

A novel compound prepared according to a literature procedure.[27] A solution of triphosgene (2.31 g, 7.79 mmol) in toluene (100 mL) was treated with pyridine (2.05 mL, 25.3 mmol) and subsequently with a solution of amine **173** (4.41 g, 21.1 mmol) in toluene (62 mL). The reaction was stirred for 18 h at rt, quenched with NH_4Cl (160 mL of a saturated aq. solution) and extracted with Et_2O (2 x 150 mL). The combined organic extracts were washed sequentially with HCl (150 mL of a 0.25 M aq. solution), H_2O (150 mL) and brine (150 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give carbamoyl chloride **174** (5.66 g, 97%) as a golden oil. R_f 0.76 (Pet ether:Et_2O 9:1); ν_{max} (neat)/cm^{-1}: 2925, 1730, 1458, 1398, 1236, 1104, 917, 726; δ_H (400 MHz, $CDCl_3$) 0.86-0.90 (3H, m, $(CH_2)_8CH_3$), 1.18-1.36 (10H, m, CH$_2$), 1.36-1.55 (4H, m, CH$_2$), 1.76-1.89 (1H, m, CH$_2$), 1.93-2.09 (3H, m, CH$_2$), 3.14-3.31 (2H, m, NC*H$_2$*(CH$_2$)$_7$CH$_3$), 4.71-4.89 (1H, m, NC*H*CH$_2$), 5.49-5.53 (1H, m, CH$_2$C*H*=CH), 5.89-5.98 (1H, m, CH=C*H*CHN); δ_C (100 MHz, CDCl$_3$) (as a mixture of rotamers) 14.3 (CH$_3$, (CH$_2$)$_7$*C*H$_3$), 21.4 (CH$_2$), 22.8 (CH$_2$), 24.5, 24.6 (CH$_2$), 27.1, 27.2 (CH$_2$), 27.6, 28.4 (CH$_2$), 28.9, 29.2 (CH$_2$), 29.4 (CH$_2$), 30.6 (CH$_2$), 31.9 (CH$_2$), 47.0, 47.9 (CH$_2$, N*C*H$_2$(CH$_2$)$_6$CH$_3$), 56.7, 58.4 (CH, CH$_2$*C*HN), 126.8, 127.0 (CH, CH$_2$*C*H=CH), 132.3, 132.4 (CH, CH=*C*HCHN), 161.7 (C, NC(O)Cl); m/z (EI) 271.1709 (M$^+$ C$_{15}$H$_{26}$^{35}ClNO requires 271.1703), 271 (2%), 236 (6), 126 (12), 112 (23), 99 (65), 79 (100).

- Diethyldithiocarbamic acid-[octyl(cyclohex-2-enyl)carbamic acid]-thioanhydride **175**

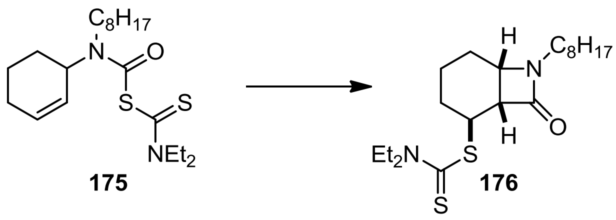


174 **175**

A novel compound prepared according to a literature procedure.[27] A solution of carbamoyl chloride **174** (5.04 g, 18.5 mmol) in acetone (140 mL) was treated with sodium diethyldithiocarbamate trihydrate (16.7 g, 74.1 mmol). The reaction mixture was stirred at rt for 18 h then heated at reflux for 1.5 h, quenched with H$_2$O (100 mL) and extracted with Et$_2$O (3 x 100 mL). The combined organic extracts were washed with brine (150 mL), dried over MgSO$_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether:CH$_2$Cl$_2$ 1:1 to CH$_2$Cl$_2$) to give dithiocarbamate **175** (5.83 g, 82%) as a green/yellow oil. R$_f$ 0.48 (Pet ether:CH$_2$Cl$_2$ 1:4); ν_{max} (neat)/cm^{-1}: 2926, 1663, 1487, 1417, 1268, 1199, 917, 751; δ_H (400 MHz, CDCl$_3$) (as a mixture of rotamers) 0.86 (3H, t, *J* 6.8 Hz, (CH$_2$)$_8$C*H$_3$*), 1.16-1.34 (17H, m, CH$_2$), 1.57-1.66 (3H, m, CH$_2$), 1.80 (1H, m, CH$_2$), 1.88-2.06 (3H, m, CH$_2$), 3.14-3.18 (2H, m, NC*H$_2$*(CH$_2$)$_7$CH$_3$), 3.79 (2H, q, *J* 7.0 Hz, C*H$_2$*CH$_3$), 4.01 (2H, q, *J* 7.0 Hz, C*H$_2$*CH$_3$), 4.43, 4.93 (1H, 2 x br s, NC*H*CH$_2$), 5.52 (1H, d, *J* 10.0 Hz, CH$_2$C*H*=CH), 5.83-5.95 (1H, m, CH=C*H*CH$_2$N); δ_C (100 MHz, CDCl$_3$) (as a mixture of rotamers) 11.3 (CH$_3$, CH$_2$*C*H$_3$), 13.5 (CH$_3$, CH$_2$*C*H$_3$), 14.2 (CH$_3$, (CH$_2$)$_7$*C*H$_3$), 21.6 (CH$_2$), 22.8 (CH$_2$), 24.5 (CH$_2$), 24.6 (CH$_2$), 27.7 (CH$_2$), 28.7 (CH$_2$), 29.4 (CH$_2$), 31.3 (CH$_2$), 31.9

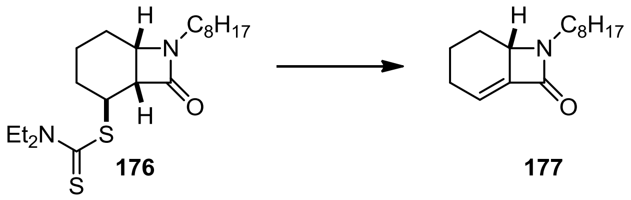
($\mathrm{CH_2}$), 45.7, 46.1 ($\mathrm{CH_2}$, $\mathrm{N}\mathit{C}\mathrm{H_2(CH_2)_6CH_3}$), 48.9 ($\mathrm{CH_2}$, $\mathit{C}\mathrm{H_2CH_3}$), 50.2 ($\mathrm{CH_2}$, $\mathit{C}\mathrm{H_2CH_3}$), 54.4, 57.0 (CH, $\mathrm{CH_2}\mathit{C}\mathrm{HN}$), 127.6 (CH, $\mathrm{CH_2}\mathit{C}\mathrm{H{=}CH}$), 131.8, 132.1 (CH, $\mathrm{CH{=}}\mathit{C}\mathrm{HCHN}$), 161.6, 162.4 (C, C(O)N), 185.4 (C, SC(S)); m/z (ES) 407.2162 ($[\mathrm{M+Na}]^+$ $\mathrm{C_{20}H_{36}N_2NaOS_2}$ requires 407.2167), 423 (9%), 408 (14), 407 (100), 210 (4).

- (±)-(1*S*,2*R*,6*R*)-7-Octyl-8-oxo-7-azabicyclo[4.2.0]octan-2-yl diethylcarbamodithioate **176**



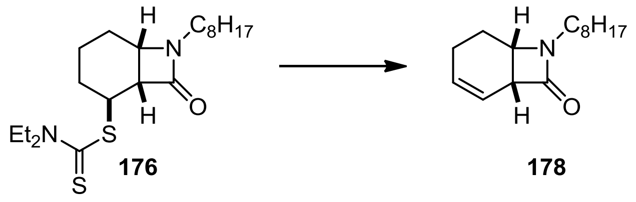
A novel compound prepared according to a literature procedure.[26] A solution of dithiocarbamate **175** (3.14 g, 8.16 mmol) in cyclohexane (82 mL) was degassed for 10 min and irradiated with a 500 W lamp which generated enough heat to bring the solution to reflux. After 4 h, the solvent was removed under reduced pressure and the crude product obtained was purified by column chromatography (Hexane to Hexane:EtOAc 3:2) to give lactam **176** (2.85 g, 91%) as a dark green oil. R_f 0.50 (Pet ether:EtOAc 7:3); ν_{max} (neat)/$\mathrm{cm^{-1}}$: 2925, 1740, 1486, 1413, 1266, 1206, 982, 916, 730; δ_H (400 MHz, $\mathrm{CDCl_3}$) 0.86 (3H, t, *J* 7.0 Hz, $\mathrm{(CH_2)_8C}\mathit{H_3}$), 1.21-1.30 (16H, m, $\mathrm{CH_2}$ and $\mathrm{CH_2C}\mathit{H_3}$), 1.44-1.64 (4H, m, $\mathrm{CH_2}$), 1.75-1.88 (3H, m, $\mathrm{CH_2}$), 2.24-2.33 (1H, m, $\mathrm{CH_2}$), 2.94 (1H, ddd, *J* 6.2, 7.6 and 13.8 Hz, $\mathrm{NC}\mathit{H_2}\mathrm{(CH_2)_7CH_3}$), 3.33 (1H, dt, *J* 7.6 and 13.8 Hz, $\mathrm{NC}\mathit{H_2}\mathrm{(CH_2)_7CH_3}$), 3.53 (1H, t, *J* 4.4 Hz, $\mathrm{CH_2C}\mathit{H}\mathrm{S}$), 3.70 (2H, septet, *J* 6.9 Hz, $\mathrm{C}\mathit{H_2}\mathrm{CH_3}$), 3.79 (1H, dt, *J* 3.4 and 5.4 Hz, $\mathrm{C(O)C}\mathit{H}\mathrm{CH}$), 3.99 (2H, d nonet, *J* 5.2 and 6.9 Hz, $\mathrm{C}\mathit{H_2}\mathrm{CH_3}$), 4.72 (1H, dt, *J* 3.8 and 5.4 Hz, $\mathrm{NC}\mathit{H}\mathrm{CH_2}$); δ_C (100 MHz, $\mathrm{CDCl_3}$) 11.7 ($\mathrm{CH_3}$, $\mathrm{CH_2}\mathit{C}\mathrm{H_3}$), 12.7 ($\mathrm{CH_3}$, $\mathrm{CH_2}\mathit{C}\mathrm{H_3}$), 14.2 ($\mathrm{CH_3}$, $\mathrm{(CH_2)_7}\mathit{C}\mathrm{H_3}$), 15.4 ($\mathrm{CH_2}$), 22.5 ($\mathrm{CH_2}$), 22.8 ($\mathrm{CH_2}$), 25.4 ($\mathrm{CH_2}$), 27.3 ($\mathrm{CH_2}$), 28.2 (2 x $\mathrm{CH_2}$), 29.3 ($\mathrm{CH_2}$), 31.9 ($\mathrm{CH_2}$), 40.4 (CH, $\mathrm{CH_2}\mathit{C}\mathrm{HN}$), 44.4 ($\mathrm{CH_2}$, $\mathrm{N}\mathit{C}\mathrm{H_2(CH_2)_6CH_3}$), 46.8 (CH, $\mathit{C}\mathrm{HC(O)}$), 49.2 (CH, $\mathrm{CH_2}\mathit{C}\mathrm{HS}$), 50.4 ($\mathrm{CH_2}$, $\mathit{C}\mathrm{H_2CH_3}$), 51.8 ($\mathrm{CH_2}$, $\mathit{C}\mathrm{H_2CH_3}$), 168.0 (C, C(O)N), 193.8 (C, SC(S)); m/z (ES) 407.2152 ($\mathrm{M^+}$ $\mathrm{C_{20}H_{36}N_2NaOS_2}$ requires 407.2167), 408 (16%), 407 (100).

▪ 7-Octyl-7-azabicyclo[4.2.0]oct-1-en-8-one **177**



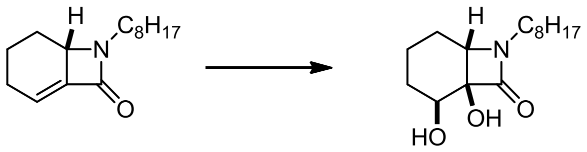
A novel compound prepared according to a modified literature procedure.[39] A solution of lactam **176** (0.143 g, 0.372 mmol) in THF (3.7 mL) was cooled to -78 °C and treated with methyl iodide (35 µL, 0.56 mmol) and LHMDS (0.56 mL of a 1.0 M solution in THF, 0.56 mmol). After 5.5 h at -78 °C, LHMDS (0.56 mL of a 1.0 M solution in THF, 0.56 mmol) was added to drive the reaction to completion. After a further 4.5 h, the solvent was removed under reduced pressure and the crude product obtained was purified by column chromatography (Pet ether to Pet ether:EtOAc 4:1) to give lactam **177** (59 mg, 67%) as a pale yellow oil. R_f 0.45 (Pet ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1}: 2924, 1741, 1697, 1376, 720; δ_H (400 MHz, $CDCl_3$) 0.83 (3H, t, *J* 6.8 Hz, $(CH_2)_8CH_3$), 0.98-1.08 (1H, m, CH_2), 1.16-1.32 (10H, m, CH_2), 1.36-1.55 (3H, m, CH_2), 1.89-1.96 (1H, m, CH_2), 2.04-2.14 (2H, m, CH_2), 2.31 (1H, tdd, *J* 1.2, 7.0 and 19.8 Hz, CH_2), 3.24 (2H, d septet, *J* 7.0 and 15.8 Hz, $NCH_2(CH_2)_7CH_3$), 3.66 (1H, ddd, *J* 1.2, 4.6 and 10.2 Hz, $NCHCH_2$), 6.15-6.16 (1H, m, $CH_2CH{=}C$); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3, $(CH_2)_7CH_3$), 20.3 (CH_2), 22.7 (CH_2), 25.2 (CH_2), 27.2 (CH_2), 28.4 (CH_2), 28.9 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 31.8 (CH_2), 41.8 (CH_2, $NCH_2(CH_2)_6CH_3$), 57.1 (CH, CH_2CHN), 123.9 (CH, $CH_2CH{=}C$), 141.9 (C, $CH{=}CC(O)$), 163.9 (C, C(O)N); m/z (EI) 235.1941 (M^+ $C_{15}H_{25}NO$ requires 235.1936), 235 (10), 206 (9), 192 (12), 179 (11), 164 (8), 150 (22), 136 (25), 107 (100), 79 (44).

- (±)-(1*R*,6*S*)-7-Octyl-7-azabicyclo[4.2.0]oct-2-en-8-one **178**



A novel compound prepared according to a modified literature procedure.[39] A solution of lactam **176** (1.15 g, 2.98 mmol) in THF (30 mL) was cooled to -78 °C and treated with methyl iodide (204 µL, 3.28 mmol). After 2 h at -78 °C, LHMDS (3.3 mL of a 1.0 M solution in THF, 3.3 mmol) was added dropwise over 2 min. After 4 h at -78 °C, another portion of LHMDS (1.5 mL of a 1.0 M solution in THF, 1.5 mmol) was added to drive the reaction to completion. After a further 3 h, LHMDS (3.3 mL of a 1.0 M solution in THF, 3.3 mmol) and methyl iodide (204 µL, 3.28 mmol) were added dropwise. The reaction mixture was allowed to warm to 10 °C over 18 h. The solvent was removed under reduced pressure and the crude product obtained was purified by column chromatography (Pet ether to Pet ether:EtOAc 7:3) to give a 1.00:0.58 mixture of lactams **177:178** (0.624 g, 89%) as a yellow oil. R_f 0.34 (Pet ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1}: 2924, 1742, 1505, 1385, 702; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J* 6.7 Hz, $(CH_2)_8CH_3$), 1.51-1.62 (14H, m, CH_2), 1.79-2.13 (3H, m, CH_2 and =CHC*H*C(O)), 3.00 (1H, ddd, *J* 6.3, 7.6 and 14.0 Hz, $NCH_2(CH_2)_7CH_3$), 3.27 (1H, dt, *J* 7.6 and 14.0 Hz, $NCH_2(CH_2)_7CH_3$), 3.52-3.58 (1H, m, NC*H*CH_2), 5.56 (1H, dd, *J* 2.8 and 10.1 Hz, CH_2C*H*=CH), 5.84-5.95 (1H, m, CH=C*H*CH); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3, $(CH_2)_7CH_3$), 19.5 (CH_2), 19.6 (CH, CH*C*HC(O)), 22.5 (CH_2), 22.7 (CH_2), 27.2 (CH_2), 28.4 (CH_2), 29.3 (CH_2), 31.9 (CH_2), 39.5 (CH_2), 52.6 (CH_2, $NCH_2(CH_2)_6CH_3$), 59.2 (CH, CH_2*C*HN), 127.9 (CH, CH_2*C*H=C), 129.4 (C, CH=*C*HCH), 170.6 (C, C(O)N).

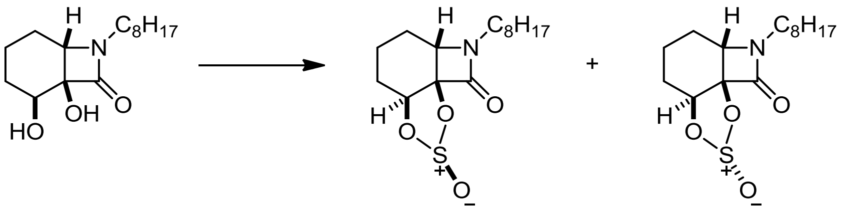
- (±)-(1*S,*2*R,*6*R*)-1,2-Dihydroxy-7-octyl-7-azabicyclo[4.2.0]octan-8-one **179**



177 **179**

A novel compound prepared according to a literature procedure.[56] A solution of lactam **177** (0.265 g, 1.13 mmol) in a 5:5:2 mixture of H_2O:acetone:*t*BuOH (6.2 mL) was treated with NMO (0.317 g, 2.70 mmol) and OsO_4 (2 µL of a 4 wt% aq. solution, cat). After 18 h at 40 °C, sodium bisulfite (0.644 g, 3.39 mmol) was added to quench the reaction. After 1 h at 40 °C, the reaction mixture was diluted with brine (6 mL) and extracted with EtOAc (2 x 6 mL). The combined organic extracts were dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether:EtOAc 1:1 to EtOAc) to give dihydroxy lactam **179** (0.243 g, 80%) as a colourless oil. R_f 0.25 (Pet ether:EtOAc 3:7); ν_{max} (neat)/cm^{-1}: 3354, 2925, 1723, 1107, 728; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.8 Hz, $(CH_2)_8CH_3$), 1.21-1.37 (10H, m, CH_2), 1.38-1.60 (3H, m, CH_2), 1.64-1.83 (4H, m, CH_2), 1.90-2.00 (1H, m, CH_2), 2.96 (1H, ddd, *J* 6.4, 7.6 and 14.0 Hz, $NCH_2(CH_2)_7CH_3$), 3.24 (1H, d, *J* 3.2 Hz, OH), 3.34 (1H, dt, *J* 7.6 and 14.0 Hz, $NCH_2(CH_2)_7CH_3$), 3.52 (1H, t, *J* 3.4 Hz, $NCHCH_2$), 4.03-4.06 (1H, m, CH_2CHOH), 4.53 (1H, s, OH); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3, $(CH_2)_7CH_3$), 14.5 (CH_2), 21.4 (CH_2), 22.7 (CH_2), 25.5 (CH_2), 27.1 (CH_2), 27.9 (CH_2), 29.2 (2 x CH_2), 31.8 (CH_2), 40.2 (CH_2, $NCH_2(CH_2)_6CH_3$), 61.1 (CH, CH_2CHN), 67.2 (CH, CH_2CHOH), 82.2 (C, CHCOH), 171.1 (C, C(O)N); m/z (ES) 292.1888 ($[M+Na]^+$ $C_{15}H_{27}NNaO_3$ requires 292.1889), 293 (11%), 292 (100).

- (±)-(3a*S,*5a*R,*8a*R*)-5-(Octyl)hexahydro-4*H*-[1,3,2]dioxathiolo[4',5':2,3]benzo[1,2-*b*]azet-4-one 2-oxide **180a** and **180b**



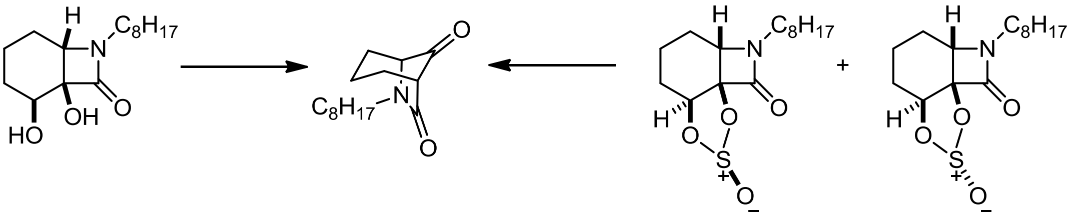
179 **180a** **180b**

Novel compounds prepared according to a literature procedure.[61] A solution of dihydroxy lactam **179** (68 mg, 0.25 mmol) in CH_2Cl_2 (1.3 mL) at 0 °C was treated with pyridine (92 μL, 1.1 mmol) and $SOCl_2$ (37 μL, 0.51 mmol). The ice bath was removed after 30 min and stirring continued at rt for 4 h. The reaction mixture was diluted with H_2O (1 mL) and extracted with CH_2Cl_2 (2 x 2 mL). The combined organic extracts were washed sequentially with HCl (3 mL of a 1 M aq. solution) and brine (3 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 7:3) to give **180a** (34 mg, 42%) and **180b** (33 mg, 41%) as colourless oils.

180a: R_f 0.64 (Pet ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1}: 2926, 1765, 1409, 1207, 956, 847; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J* 6.8 Hz, $(CH_2)_8CH_3$), 1.20-1.31 (10H, m, CH_2), 1.39-1.70 (3H, m, CH_2), 1.70-1.83 (2H, m, CH_2), 1.89-2.02 (2H, m, CH_2), 2.19-2.27 (1H, m, CH_2), 2.98 (1H, ddd, *J* 6.4, 7.6 and 14.2 Hz, $NCH_2(CH_2)_7CH_3$), 3.42 (1H, dt, *J* 7.6 and 14.2 Hz, $NCH_2(CH_2)_7CH_3$), 4.14 (1H, dd, *J* 2.6 and 5.8 Hz, NC*H*CH_2), 4.91 (1H, dd, *J* 6.4 and 7.2 Hz, CH_2C*H*OS); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3, $(CH_2)_7CH_3$), 15.6 (CH_2), 22.8 (CH_2), 24.7 (CH_2), 27.1 (CH_2), 27.8 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 29.5 (CH_2), 31.9 (CH_2), 40.4 (CH_2, $NCH_2(CH_2)_6CH_3$), 60.4 (CH, CH_2*C*HN), 81.6 (CH, CH_2*C*HOS), 88.1 (C, CH*C*OS), 163.6 (C, C(O)N); m/z (ES) 338.1393 ($[M+Na]^+$ $C_{15}H_{25}NNaO_4S$ requires 338.1402), 370 ($[M+Na+CH_3OH]^+$, 22%), 338 (100).

180b: R_f 0.40 (Pet ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1}: 2925, 1763, 1221, 1203, 958, 780, 665; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, *J* 7.8 Hz, $(CH_2)_8CH_3$), 1.21-1.36 (10H, m, CH_2), 1.40-1.85 (6H, m, CH_2), 2.22-2.30 (2H, m, CH_2), 2.94 (1H, ddd, *J* 6.0, 7.8 and 14.2 Hz, $NCH_2(CH_2)_7CH_3$), 2.94 (1H, dt, *J* 7.8 and 14.2 Hz, NC*H*$_2$(CH$_2$)$_7$CH$_3$), 3.94 (1H, dd, *J* 2.8 and 5.6 Hz, NC*H*CH$_2$), 5.25 (1H, t, J 6.8 Hz, CH$_2$C*H*OS); δ_C (100 MHz, CDCl$_3$) 14.2 (CH$_3$, (CH$_2$)$_7$*C*H$_3$), 15.0 (CH$_2$), 22.7 (CH$_2$), 24.5 (CH$_2$), 27.1 (CH$_2$), 27.3 (CH$_2$), 27.7 (CH$_2$), 29.2 (2 x CH$_2$), 31.8 (CH$_2$), 40.4 (CH$_2$, N*C*H$_2$(CH$_2$)$_6$CH$_3$), 58.8 (CH, CH$_2$*C*HN), 77.4 (CH, CH$_2$*C*HOS), 89.1 (C, CH*C*OS), 164.1 (C, C(O)N); m/z (ES) 338.1411 ([M+Na]$^+$ C$_{15}$H$_{25}$NNaO$_4$S requires 338.1402), 354 (14%), 338 (100).

- (±)-(1*R,*5*S*)-6-Octyl-6-azabicyclo[3.2.1]octane-7,8-dione **181**



179 **181** **180a** **180b**

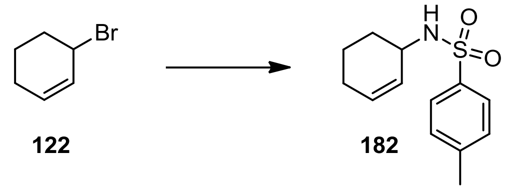
A novel compound prepared according to a literature procedure.[19] A solution of PPh$_3$ (0.147 g, 0.561 mmol) and hexachloroethane (0.133 g, 0.561 mmol) in CH$_3$CN (1.0 mL) was stirred at rt for 30 min before being added dropwise to a solution of dihydroxylactam **179** (0.101 g, 0.375 mmol) in CH$_3$CN (1.5 mL). The reaction mixture was heated at reflux for 18 h, concentrated under reduced pressure and purified directly by column chromatography (Pet ether:EtOAc 3:1 to Pet ether:EtOAc 1:1) to give bicyclic ketone **181** (75 mg, 80%) as a white solid.

A solution of cyclic sulfites **180** (72 mg, 0.23 mmol) in diphenyl ether (1.3 mL) was heated to 190 °C. After 2 h, the reaction mixture was directly purified by column chromatography (Pet ether:EtOAc 3:1 to Pet ether:EtOAc 1:3) to give bicyclic ketone **181** (53 mg, 93%) as a white solid.

mp 59-61 °C (CH$_2$Cl$_2$); R$_f$ 0.41 (Pet ether:EtOAc 1:1); ν_{max} (neat)/cm^{-1} (mixture with the hydrate): 3309, 3205, 2923, 1781, 1656, 1451, 1242, 1146, 1083, 955, 656; δ_H (400 MHz, CDCl$_3$) 0.82 (3H, t, *J* 6.8 Hz, (CH$_2$)$_8$C*H$_3$*), 1.15-1.30 (10H, m, CH$_2$), 1.42-1.90 (6H, m, CH$_2$), 2.18-2.31 (2H, m, CH$_2$), 2.78-2.80 (1H, m, C(O)CHC(O)), 3.08 (1H, ddd, *J* 5.4, 9.0 and 14.0 Hz, NC*H$_2$*(CH$_2$)$_7$CH$_3$), 3.64 (1H, ddd, *J* 7.0, 9.0 and 14.0 Hz, NC*H$_2$*(CH$_2$)$_7$CH$_3$), 3.73 (1H, d, *J* 4.8 Hz, NC*H*CH$_2$); δ_C (100 MHz, CDCl$_3$)

14.1 (CH_3, $(CH_2)_7$*C*H_3), 17.5 (CH_2), 22.7 (CH_2), 27.0 (CH_2), 28.0 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 31.1 (CH_2), 31.6 (CH_2), 31.8 (CH_2), 40.6 (CH_2, N*C*$H_2(CH_2)_6CH_3$), 52.9 (CH, C(O)*C*HC(O)), 64.5 (CH, CH_2*C*HN), 170.3 (C, C(O)N), 209.4 (C, CH*C*(O)CH); m/z (EI) 251.1883 (M^+ $C_{15}H_{25}NO_2$ requires 251.1885), 252 (16%), 223 (81), 195 (100), 152 (59), 97 (85).

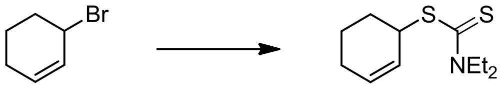
- *N*-(cyclohex-2-en-1-yl)-4-methylbenzenesulfonamide **182**



A known compound[241] prepared according to a literature procedure.[76] A solution of *para*-toluenesulfonamide (2.12 g, 11.3 mmol) in acetone (30 mL) was cooled to 0 °C, treated with K_2CO_3 (2.34 g, 17.0 mmol), stirred at 0 °C for 30 min, treated with 3-bromocyclohexene **122** (1.29 mL, 11.3 mmol), stirred at 0 °C for 5 min and then heated to reflux. After 18 h, the reaction mixture was quenched with H_2O (30 mL) and extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet Ether to Pet Ether:EtOAc 4:1) to give amine **182** (1.89 g, 67%) as white crystals. mp 98-100 °C; R_f 0.24 (Pet Ether:EtOAc 9:1); v_{max} (neat)/cm^{-1} : 3270, 3031, 2915, 1446, 1417, 1318, 1154, 1065, 889, 808, 669; δ_H (400 MHz, $CDCl_3$) 1.48-1.64 (3H, m, CH_2), 1.69-1.77 (1H, m, CH_2), 1.84-1.98 (2H, m, CH_2), 2.42 (3H, s, ArCH_3), 3.74-3.83 (1H, m, NC*H*CH_2), 4.68 (1H, d, *J* 8.0 Hz, NH), 5.34 (1H, m, CH_2C*H*=CH), 5.74 (1H, m, CH=C*H*CHN), 7.29 (2H, d, *J* 8.0, Ar H), 7.77 (2H, d, *J* 8.0, Ar H); δ_C (100 MHz, $CDCl_3$) 19.5 (CH_2), 21.7 (CH_3, Ar*C*H_3), 24.6 (CH_2), 30.4 (CH_2), 49.1 (CH, CH_2*C*HN), 127.1 (2 x CH, Ar), 127.2 (CH, CH_2CH=CH), 129.8 (2 x CH, Ar), 131.7 (CH, CH=*C*HCHN), 138.5 (C, Ar), 143.4 (C, ArC*S*); m/z (EI) 251.0992 (M^+ $C_{13}H_{17}NO_2S$ requires 251.0980), 251 (M^+, 7%), 223 (100), 187 (100), 155 (85), 96 (65), 91 (88). *Literature data*:[241] mp 98-100 °C; Rf 0.23 (Hexane:EtOAc 95:5); IR (neat)/cm^{-1} 3282, 2927, 1597, 1427, 1327, 1157, 1072; δ_H (400 MHz, $CDCl_3$) 7.79 (d, *J* = 7.6

Hz, 2H), 7.31 (d, *J* = 7.6 Hz, 2H), 5.76 (d, *J* = 10 Hz, 1H), 5.36 (d, *J* = 9.8 Hz, 1H), 4.66 (d, *J* = 8.4 Hz, 1H), 3.82 (s, 1H), 2.44 (s, 3H), 2.10–1.45 (6H); δ_C (100 MHz, $CDCl_3$) 143.2, 138.3, 131.5, 129.6, 127.06, 127.00, 48.9, 30.2, 24.4, 21.5, 19.3; m/z (ES) 274.0881 ($[M+Na]^+$ $C_{13}H_{17}NNaO_2S$ requires 274.0878).

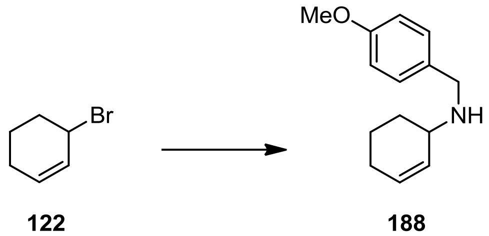
- Cyclohex-2-en-1-yl diethylcarbamodithioate **187**



122 **187**

A novel compound prepared according to a modified literature procedure.[27] A solution of 3-bromocyclohexene **122** (0.10 mL, 0.87 mmol) in CH_3CN (2.4 mL) was treated with K_2CO_3 (0.181 g, 1.31 mmol), tosylisocyanate **184** (0.200 mL, 1.31 mmol) and sodium diethyldithiocarbamate trihydrate (1.03 g, 3.48 mmol). After 18 h at rt, the reaction mixture was quenched with H_2O (3 mL) and extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet Ether to Pet Ether:EtOAc 85:15) to give dithiocarbamate **187** (0.199 g, 100%) as a light yellow oil. R_f 0.84 (Pet Ether:EtOAc 85:15); ν_{max} (neat)/cm^{-1} : 2931, 1482, 1412, 1265, 1207, 1139, 380, 916, 722; δ_H (300 MHz, $CDCl_3$) 1.27 (6H, td, *J* 1.8 and 7.1 Hz, CH_2CH_3), 1.67-1.77 (2H, m, CH_2), 1.94-2.13 (4H, m, CH_2), 3.74 (2H, qd, *J* 1.8 and 7.1 Hz, CH_2CH_3), 4.02 (2H, qd, *J* 1.8 and 7.1 Hz, CH_2CH_3), 4.60-4.78 (1H, m, CHS), 5.72-5.84 (1H, m, CH_2CH=), 5.84-5.96 (1H, m, =CHCHS); δ_C (100 MHz, $CDCl_3$) 11.8 (CH_3, CH_2CH_3), 12.7 (CH_3, CH_2CH_3), 20.1 (CH_2), 25.1 (CH_2), 29.3 (CH_2), 46.9 (CH_2, CH_2CH_3), 48.0 (CH, CHS), 49.4 (CH_2, CH_2CH_3), 126.3 (CH, CH_2CH=), 131.6 (CH, =CHCHS), 195.5 (C, C(S)S).

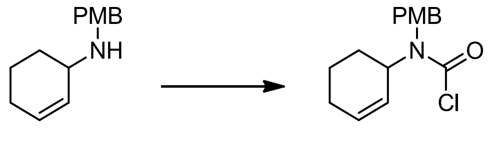
- *N*-(4-Methoxybenzyl)cyclohex-2-enamine **188**



122 **188**

A known compound[236] prepared according to a literature procedure.[27] A solution of 4-methoxybenzylamine (12.3 mL, 93.9 mmol) in CH_3CN (94 mL) was treated with 3-bromocyclohexene **122** (4.00 mL, 34.8 mmol) and K_2CO_3 (5.05 g, 36.5 mmol). After 8 h at rt, the reaction was quenched with H_2O (100 mL) and extracted with Et_2O (2 x 100 mL). The combined organic extracts were washed with brine (150 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Hexane:EtOAc 4:1 to Hexane:EtOAc 1:1) to give amine **188** (6.76 g, 89%) as a yellow oil. R_f 0.21 (Pet ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1}: 3019, 2929, 1611, 1509, 1242, 1035, 822, 722; δ_H (400 MHz, $CDCl_3$) 1.39 (1H, br s, NH), 1.45-1.62 (2H, m, CH_2), 1.72-1.80 (1H, m, CH_2), 1.87-2.04 (3H, m, CH_2), 3.18-3.24 (1H, m, NC*H*CH_2), 3.77, 3.82 (2H, ABq, *J* 12.8 Hz, NCH_2Ar), 3.80 (3H, s, OCH_3), 5.70-5.80 (2H, m, CH=CH), 6.86 (2H, d, *J* 8.6 Hz, Ar H), 7.27 (2H, d, *J* 8.6 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 20.4 (CH_2), 25.5 (CH_2), 29.7 (CH_2), 50.6 (CH_2, NCH_2Ar), 52.4 (CH, CH_2*C*HN), 55.4 (CH_3, OCH_3), 113.9 (2 x CH, Ar), 129.0 (CH, CH_2*C*H=CH), 129.4 (2 x CH, Ar), 130.1 (CH, CH=*C*HCHN), 133.1 (C, Ar*C*CH_2N), 158.7 (C, ArCO); m/z (EI) 217.1461 (M^+ $C_{14}H_{19}NO$ requires 217.1467), 218 ($[M+H]^+$, 5%), 217 (M^+, 50), 121 (100). *Literature data*:[236] δ_H (400 MHz, $CDCl_3$) 7.28 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.80-5.68 (m, 2H), 3.81 (d, *J* = 10.5 Hz, 1H), 3.77 (s, 3H), 3.70 (overlapped d, *J* = 10.5 Hz, 1H), 3.18 (m, 1H), 1.98 (m, 2H), 1.88 (m, 1H), 1.72 (m, 1H), 1.48 (m, 2H), 1.22 (br s, 1H); δ_C (100 MHz, $CDCl_3$) 158.71, 133.07, 130.13, 129.51, 129.11, 113.94, 55.47, 52.49, 50.59, 29.69, 25.54, 20.45; Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.57; H, 8.74; N, 6.38.

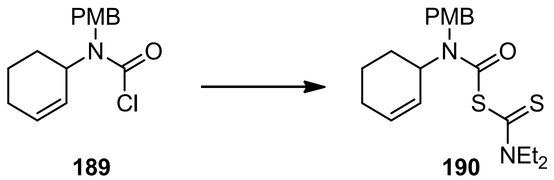
- Cyclohex-2-en-1-yl(4-methoxybenzyl)carbamic chloride **189**



188 **189**

A novel compound prepared according to a literature procedure.[27] A solution of triphosgene (1.33 g, 4.50 mmol) in toluene (65 mL) was treated with pyridine (1.17 mL, 14.5 mmol) and subsequently with a solution of amine **188** (2.64 g, 12.1 mmol) in toluene (15 mL). The reaction was stirred for 18 h at rt, quenched with H_2O (100 mL) and extracted with Et_2O (2 x 80 mL). The combined organic extracts were washed sequentially with HCl (50 mL of a 0.25 M aq. solution), H_2O (50 mL) and brine (75 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give carbamoyl chloride **189** (3.19 g, 95%) as a colorless oil. R_f 0.85 (Pet ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1}: 2938, 1724, 1618, 1512, 1245, 1175, 1146, 1032, 728, 666, 628; δ_H (400 MHz, $CDCl_3$) (as a mixture of rotamers) 1.52-1.64 (2H, m, CH_2), 1.70-1.79 (1H, m, CH_2), 1.89-2.01 (3H, m, CH_2), 3.80 (3H, d, *J* 6.4 Hz, OCH_3), 4.40-4.69 (2H, m, NC*H*$_2$Ar), 4.85, 4.96 (1H, 2 x br s, CH_2C*H*N), 5.48 (1H, t, *J* 12.8 Hz, CH_2C*H*=CH), 5.83-5.95 (1H, m, CH=C*H*CHN), 5.83-5.89 (2H, m, Ar H), 7.16-7.21 (2H, m, Ar H); δ_C (100 MHz, $CDCl_3$) (as a mixture of rotamers) 21.2 (CH_2), 24.4 (CH_2), 27.3, 28,4 (CH_2), 49.0, 50.7 (CH_2, NCH_2Ar), 55.3 (CH_3, OCH_3), 57.0, 58.7 (CH, CH_2*C*HN), 113.9, 114.0 (2 x CH, Ar), 126.5, 126.6 (CH, CH_2*C*H=CH), 127.6, 128.8 (2 x CH, Ar), 129.4, 129.5 (C, Ar*C*CH_2N), 132.5 (CH, CH=*C*HCHN), 150.0 (C, ArCO), 158.9 (C, C(O)Cl); m/z (ES) 302.0915 ($[M+Na]^+$ $C_{15}H_{18}{}^{35}ClNNaO_2$ requires 302.0924), 302 (18%), 298 (70), 239 (10), 219 (10), 218 (100).

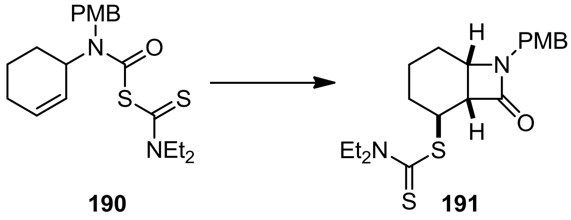
- Diethyldithiocarbamic acid-[(4-methoxybenzyl)(cyclohex-2-enyl)carbamic acid]-thioanhydride **190**



189 **190**

A novel compound prepared according to a literature procedure.[27] A solution of carbamoyl chloride **189** (3.19 g, 11.5 mmol) in acetone (72 mL) was treated with sodium diethyldithiocarbamate trihydrate (10.4 g, 46.0 mmol). The solution was stirred at rt for 18 h, quenched with H_2O (60 mL) and extracted with Et_2O (3 x 60 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 85:15) to give dithiocarbamate **190** (3.93 g, 87%) as a yellow oil. R_f 0.24 (Pet ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1}: 2935, 1662, 1511, 1418, 1243, 1174, 967, 726; δ_H (400 MHz, $CDCl_3$) (as a mixture of rotamers) 1.11-1.36 (6H, m, $CH_2C\mathit{H_3}$), 1.44-1.76 (3H, m, CH_2), 1.88-2.00 (3H, m, CH_2), 3.66-3.85 (5H, m, $C\mathit{H_2}CH_3$ and OCH_3), 3.90-4.04 (2H, m, $C\mathit{H_2}CH_3$), 4.29-4.56, 5.03 (3H, m and br s, NCH_2Ar and CHN), 5.47 (1H, d, *J* 10.4 Hz, $CH_2C\mathit{H}{=}CH$), 5.74-5.92 (1H, m, $CH{=}C\mathit{H}CHN$), 6.81 (2H, br s, Ar H), 7.15 (2H, br s, Ar H); δ_C (100 MHz, $CDCl_3$) (mixture of rotamers) 11.2 (CH_3, $CH_2\mathit{C}H_3$), 13.3 (CH_3, $CH_2\mathit{C}H_3$), 21.3 (CH_2), 24.4 (CH_2), 27.5 (CH_2), 47.4 (CH_2, NCH_2Ar), 48.8 (CH_2, $\mathit{C}H_2CH_3$), 50.1 (CH_2, $\mathit{C}H_2CH_3$), 54.7, 57.1 (CH, $CH_2\mathit{C}HN$), 55.2 (CH_3, OCH_3), 113.8 (2 x CH, Ar), 127.0 (2 x CH, Ar), 128.7 (CH, $CH_2\mathit{C}H{=}CH$), 130.1 (C, $Ar\mathit{C}CH_2N$), 132.2 (CH, $CH{=}\mathit{C}HCHN$), 158.6 (C, ArCO), 162.9 (C, C(O)N), 184.6, 185.3 (C, C(S)S); m/z (ES) 415.1480 ($[M+Na]^+$ $C_{20}H_{28}N_2NaO_2S_2$ requires 415.1490), 431 (6%), 416 (13), 415 (100), 292 (14).

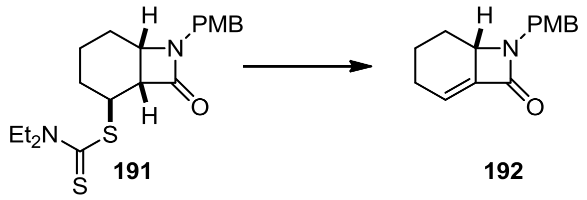
- (±)-(1*R,*2*S,*6*S*)-7-(4-Methoxybenzyl)-8-oxo-7-azabicyclo[4.2.0]octan-2-yl diethylcarbamodithioate **191**



190 **191**

A novel compound prepared according to a literature procedure.[26] A solution of dithiocarbamate **190** (1.12 g, 2.86 mmol) in cyclohexane (150 mL) was degassed for 10 min and irradiated with a 500 W lamp which generated enough heat to bring the solution to reflux. After 5 h, the solvent was removed under reduced pressure and the crude product obtained was purified by column chromatography (Pet ether to Pet ether:EtOAc 7:3) to give lactam **191** (0.899 g, 80%) as a white solid. mp 97-99 °C (CH_2Cl_2); R_f 0.35 (Pet ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1}: 2938, 1738, 1615, 1493, 1248, 1090, 832, 589; δ_H (400 MHz, $CDCl_3$) 1.23 (6H, t, *J* 7.2 Hz, $CH_2C\mathit{H_3}$), 1.36-1.79 (5H, m, CH_2), 2.19-2.29 (1H, m, CH_2), 3.53-3.57 (1H, m, $CH_2C\mathit{H}S$), 3.64-3.72 (3H, m, $C\mathit{H_2}CH_3$ and $CHC\mathit{H}C(O)$), 3.77 (3H, s, OCH_3), 3.91-4.10 (3H, m, $C\mathit{H_2}CH_3$ and NCH_2Ar), 4.45-4.51 (2H, m, $CH_2C\mathit{H}N$ and $C\mathit{H_2}CH_3$), 6.83 (2H, d, *J* 8.4 Hz, Ar H), 7.16 (2H, d, *J* 8.4 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 11.7 (CH_3, CH_2CH_3), 12.6 (CH_3, CH_2CH_3), 15.2 (CH_2), 22.2 (CH_2), 25.2 (CH_2), 44.0 (CH_2, NCH_2Ar), 44.4 (CH, $CH\mathit{C}HC(O)$), 46.7 (CH_2, $\mathit{C}H_2CH_3$), 49.2 (CH_2, $\mathit{C}H_2CH_3$), 50.2 (CH, $CH_2\mathit{C}HN$), 52.0 (CH, $CH_2\mathit{C}HS$), 55.4 (CH_3, OCH_3), 114.2 (2 x CH, Ar), 128.0 (C, $Ar\mathit{C}CH_2N$), 129.7 (2 x CH, Ar), 159.2 (C, ArCO), 167.9 (C, C(O)N), 193.6 (C, SC(S)); m/z (ES) 415.1498 ($[M+Na]^+$ $C_{20}H_{28}N_2NaO_2S_2$ requires 415.1490), 415 (100%).

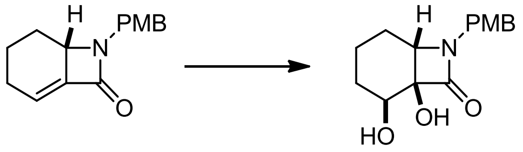
- 7-(4-Methoxybenzyl)-7-azabicyclo[4.2.0]oct-1-en-8-one **192**



191 **192**

A novel compound prepared according to a modified literature procedure.[39] A solution of lactam **191** (0.800 g, 2.04 mmol) in THF (17 mL) was cooled to -78 °C and treated with methyl iodide (139 µL, 2.24 mmol). The reaction mixture was stirred at -78 °C for 2 h, then LHMDS (2.2 mL of a 1.0 M solution in THF, 2.2 mmol) was added dropwise over 2 min. After 8 h at -78 °C, the solvent was removed under reduced pressure and the crude product obtained was purified by column chromatography (Pet ether to Pet ether:EtOAc 3:2) to give lactam **192** (0.408 g, 88%) as a white solid. mp 57-58 °C (CH_2Cl_2); R_f 0.22 (Pet ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1}: 3018, 2941, 1730, 1692, 1511, 1358, 1238, 1179, 1027, 816, 735; δ_H (400 MHz, $CDCl_3$) 0.82-0.92 (1H, m, CH_2), 1.25-1.38 (1H, m, CH_2), 1.77-1.86 (2H, m, CH_2), 2.00-2.11 (1H, m, CH_2), 2.24-2.31 (1H, m, CH_2), 3.56-3.60 (1H, m, CH_2C*H*N), 3.76 (3H, s, OCH_3), 4.32, 4.42 (2H, ABq, *J* 14.8 Hz, NCH_2Ar), 6.18-6.19 (1H, m, CH_2C*H*=C), 6.83 (2H, d, *J* 8.6 Hz, Ar H), 7.16 (2H, d, *J* 8.6 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 20.2 (CH_2), 25.3 (CH_2), 28.0 (CH_2), 45.3 (CH_2, NCH_2Ar), 55.3 (CH_3, OCH_3), 56.6 (CH, CH_2*C*HN), 114.1 (2 x CH, Ar), 124.5 (CH, CH_2*C*H=CH), 128.4 (C, Ar*C*CH_2N), 129.8 (2 x CH, Ar), 141.8 (C, CH=*C*C(O)), 159.2 (C, ArCO), 163.7 (C, C(O)N); m/z (ES) 266.1161 ($[M+Na]^+$ $C_{15}H_{17}NNaO_2$ requires 266.1157), 279 (10%), 266 ($[M+Na]^+$, 100), 244 (10), 218 (6).

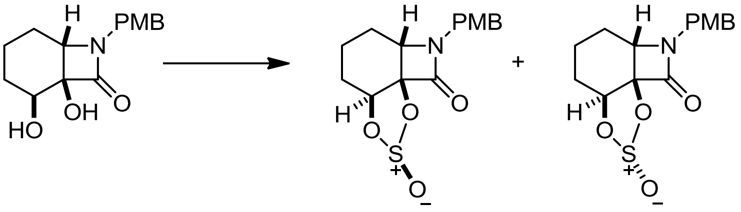
- (±)-(1*R*,2*S*,6*S*)-1,2-Dihydroxy-7-(4-methoxybenzyl)-7-azabicyclo[4.2.0]octan-8-one **193**



192 **193**

A novel compound prepared according to a literature procedure.[56] A solution of lactam **192** (0.498 g, 1.79 mmol) in a 5:5:2 mixture of H_2O:acetone:*t*BuOH (9.7 mL) was treated with NMO (0.505 g, 4.31 mmol) and OsO_4 (2 µL of a 4 wt% aq. solution, cat). After 23 h at 40 °C, sodium bisulfite (1.02 g, 5.37 mmol) was added to quench the reaction. After 30 min at 40 °C, the reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (2 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether:EtOAc 3:1 to EtOAc) to give dihydroxy lactam **193** (0.398 g, 80%) as a white solid. mp 98-100 °C (CH_2Cl_2); R_f 0.22 (Pet ether:EtOAc 2:3); ν_{max} (neat)/cm^{-1}: 3484, 3222, 2958, 2869, 1709, 1613, 1514, 1251, 1176, 1105, 1032, 628; δ_H (400 MHz, $CDCl_3$) 1.14-1.26 (1H, m, CH_2), 1.50-1.58 (2H, m, CH_2), 1.66-1.71 (2H, m, CH_2), 1.75-1.84 (1H, m, CH_2), 3.65 (1H, t, *J* 3.6 Hz, CH_2C*H*N), 3.76 (3H, s, OCH_3), 4.03-4.06 (1H, m, CH_2C*H*OH), 4.08-4.17 (2H, m, NCH_2Ar and OH), 4.45 (1H, d, *J* 14.8 Hz, NCH_2Ar), 5.37 (1H, br s, OH), 6.83 (2H, d, *J* 8.4 Hz, Ar H), 7.17 (2H, d, *J* 8.4 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 14.5 (CH_2), 21.5 (CH_2), 25.6 (CH_2), 43.9 (CH_2, NCH_2Ar), 55.3 (CH_3, OCH_3), 61.2 (CH, CH_2*C*HN), 67.4 (CH, CH_2*C*HOH), 82.5 (C, CH*C*OH), 114.3 (2 x CH, Ar), 127.3 (C, Ar*C*CH_2N), 129.7 (2 x CH, Ar), 159.3 (C, ArCO), 171.1 (C, C(O)N); m/z (ES) 300.1209 ([M+Na]$^+$ $C_{15}H_{19}NNaO_4$ requires 300.1212), 300 (100%).

- (±)-(3a*R*,5a*S*,8a*S*)-5-(4-Methoxybenzyl)hexahydro-4*H*-[1,3,2]dioxathiolo[4',5':2,3] benzo[1,2-*b*]azet-4-one 2-oxide **194a** and **194b**



193 **194a** **194b**

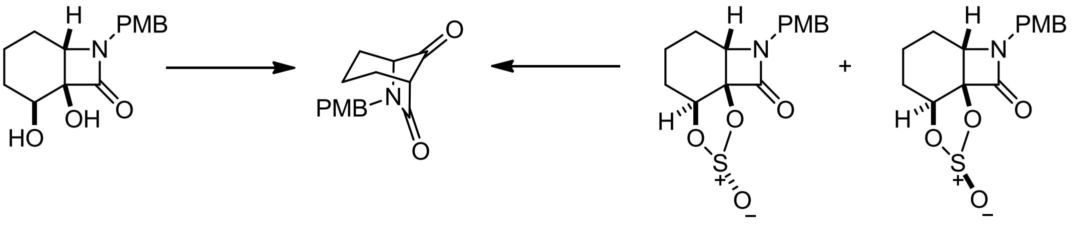
Novel compounds prepared according to a literature procedure.[61] A solution of dihydroxy lactam **193** (0.150 g, 0.542 mmol) in CH_2Cl_2 (2.8 mL) at 0 °C was treated with pyridine (196 µL, 2.35 mmol) and $SOCl_2$ (78.0 µL, 1.05 mmol). The ice bath was removed after 30 min and stirring continued at rt for 4.25 h. The reaction mixture was diluted with H_2O (3 mL) and extracted with CH_2Cl_2 (2 x 4 mL). The combined organic extracts were washed sequentially with HCl (5 mL of a 1 M aq. solution) and brine (5 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether:EtOAc 4:1 to Pet ether:EtOAc 1:1) to give **194a** (83 mg, 47%) and **194b** (82 mg, 46%) as colourless oils.

194a: R_f 0.71 (Pet ether:EtOAc 1:1); ν_{max} (neat)/cm^{-1}: 2946, 1761, 1612, 1512, 1204, 955, 850, 772, 648; δ_H (400 MHz, $CDCl_3$) 1.29-1.40 (1H, m, CH_2), 1.60-1.83 (3H, m, CH_2), 1.88-1.97 (1H, m, CH_2), 2.18-2.26 (1H, m, CH_2), 3.80 (3H, s, OCH_3), 4.02 (1H, dd, *J* 2.6 and 5.8 Hz, $CH_2C\mathit{H}N$), 4.10, 4.60 (2H, ABq, *J* 15.2 Hz, NCH_2Ar), 4.93 (1H, dd, *J* 6.4 and 7.6 Hz, $CH_2C\mathit{H}OS$), 6.87 (2H, d, *J* 8.8 Hz, Ar H), 7.17 (2H, d, *J* 8.8 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 15.5 (CH_2), 24.5 (CH_2), 29.5 (CH_2), 44.2 (CH_2, NCH_2Ar), 55.4 (CH_3, OCH_3), 60.1 (CH, $CH_2\mathit{C}HN$), 81.7 (CH, $CH_2\mathit{C}HOS$), 88.2 (C, $CH\mathit{C}OS$), 114.6 (2 x CH, Ar), 126.4 (C, $Ar\mathit{C}CH_2N$), 129.7 (2 x CH, Ar), 159.6 (C, ArCO), 163.6 (C, C(O)N); m/z (ES) 346.0721 ($[M+Na]^+$ $C_{15}H_{17}NNaO_5S$ requires 346.0725), 378 (92%), 346 (100), 282 (26).

194b: R_f 0.51 (Pet ether:EtOAc 1:1); ν_{max} (neat)/cm^{-1}: 2937, 1761, 1612, 1512, 1201, 954, 778, 664; δ_H (400 MHz, $CDCl_3$) 1.30-1.41 (1H, m, CH_2), 1.50-1.64 (3H, m, CH_2), 1.67-1.74 (1H, m, CH_2), 2.20-2.28 (1H, m, CH_2), 3.78 (3H, s, OCH_3), 3.83 (1H, dd, *J* 2.2 and 5.8 Hz, $CH_2C\mathit{H}N$), 4.05, 4.62 (2H, ABq, *J* 15.2 Hz, NCH_2Ar), 5.27 (1H, t, *J* 7.0 Hz, $CH_2C\mathit{H}OS$), 6.86 (2H, d, *J* 8.8 Hz, Ar H), 7.17

(2H, d, *J* 8.8 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 15.0 (CH_2), 24.3 (CH_2), 27.3 (CH_2), 44.0 (CH_2, NCH_2Ar), 55.4 (CH_3, OCH_3), 58.4 (CH, CH_2*C*HN), 77.6 (CH, CH_2*C*HOS), 89.3 (C, CH*C*OS), 114.4 (2 x CH, Ar), 126.4 (C, Ar*C*CH_2N), 129.7 (2 x CH, Ar), 159.5 (C, ArCO), 164.1 (C, C(O)N); m/z (ES) 346.0720 ($[M+Na]^+$ $C_{15}H_{17}NNaO_5S$ requires 346.0725), 362 (9%), 346 (100).

- (±)-(1*R,*5*S*)-6-(4-Methoxybenzyl)-6-azabicyclo[3.2.1]octane-7,8-dione **195**



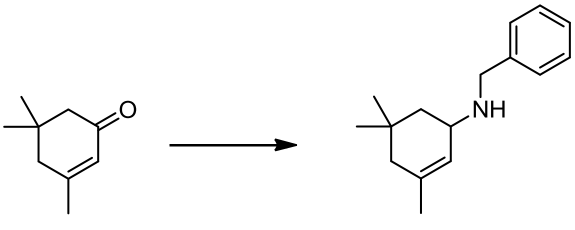
193 **195** **194a** **194b**

A novel compound prepared according to a literature procedure.[19] A solution of PPh_3 (0.312 g, 1.19 mmol) and hexachloroethane (0.282 g, 1.19 mmol) in CH_3CN (2.0 mL) was stirred at rt for 30 min before being added dropwise to a solution of dihydroxylactam **193** (0.220 g, 0.794 mmol) in CH_3CN (3.3 mL). The reaction mixture was heated at reflux for 18 h, concentrated under reduced pressure and purified directly by column chromatography (Pet ether:EtOAc 7:3 to Pet ether:EtOAc 3:7) to give bicyclic ketone **195** (0.206 g , 80%) as a white solid.

A solution of cyclic sulfites **194** (0.165 g, 0.510 mmol) in diphenyl ether (3 mL) was heated to 190 °C. After 2.25 h, the reaction mixture was directly purified by column chromatography (Pet ether to Pet ether:EtOAc 1:3) to give bicyclic ketone **195** (0.109 g, 83%) as a white solid.

mp 86-88 °C (CH_2Cl_2); R_f 0.21 (Pet ether:EtOAc 1:1); ν_{max} (neat)/cm^{-1} (mixture with the hydrate): 3290, 2946, 1778, 1661, 1512, 1417, 1236, 1081, 1031, 809; δ_H (400 MHz, $CDCl_3$) 1.43-1.71 (3H, m, CH_2), 1.86 (1H, dtd, *J* 2.0, 7.2 and 20.4 Hz, CH_2), 1.89-1.95 (1H, m, CH_2), 2.27-2.34 (1H, m, CH_2), 2.83-2.85 (1H, m, C(O)CHC(O)), 3.62 (1H, d, *J* 4.4 Hz, C(O)CHN), 3.75 (3H, s, OCH_3), 4.34, 4.70 (2H, ABq, *J* 14.6 Hz, NCH_2Ar), 6.82 (2H, d, *J* 8.4 Hz, Ar H), 7.19 (2H, d, *J* 8.4 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 17.4 (CH_2), 30.8 (CH_2), 31.8 (CH_2), 43.9 (CH_2, NCH_2Ar), 52.9 (CH, C(O)*C*HC(O)), 55.3 (CH_3, OCH_3), 64.0 (CH, CH_2*C*HN), 114.3 (2 x CH, Ar), 127.7 (C, Ar*C*CH_2N), 129.9 (2 x CH, Ar), 159.5 (C, Ar*C*O), 170.1 (C, C(O)N), 209.0 (C, CH*C*(O)CH); m/z (ES) (as the hydrate) 300.1219 ($[M+Na]^+$ $C_{15}H_{19}NNaO_4$ requires 300.1212), 314 (33%), 300 (100).

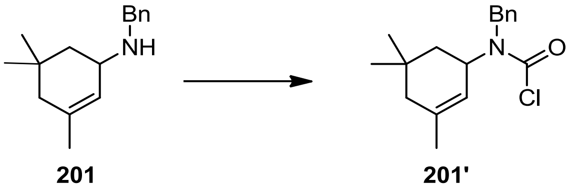
- *N*-Benzyl-3,5,5-trimethylcyclohex-2-enamine **201**


199 **201**

A known compound prepared according to a modified literature procedure.[242] A solution of benzylamine (14.2 mL, 130 mmol) in MeOH (100 mL) was treated with Ti(O*i*Pr)$_4$ (4.51 mL, 15.2 mmol) and isophorone **199** (2.17 mL, 14.5 mmol). After 7.5 h at reflux, the reaction mixture was cooled to rt, treated with $NaBH_4$ (2.19 g, 58.0 mmol) portionwise over 10 min and heated to reflux. After 18 h, the excess of $NaBH_4$ was carefully quenched with H_2O (40 mL) and the mixture was extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with NaOH (50 mL of a 5% aq. solution) and brine (50 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether:EtOAc 9:1 to Pet ether:EtOAc 4:1) to give amine **201** (1.90 g, 57%) as a light yellow oil. R_f 0.70 (CH_2Cl_2:EtOH 9:1); ν_{max} (neat)/cm^{-1} : 2949, 2865, 1453, 1363, 1101, 729, 696; δ_H (400 MHz, $CDCl_3$) 0.93 (3H, s, $C(CH_3)_2$), 1.05 (3H, s, $C(CH_3)_2$), 1.15-1.20 (1H, m, CH_2), 1.45 (1H, br s, NH), 1.65, 1.92 (2H, ABq, *J* 17.2 Hz, CH_2), 1.73 (3H, s, $=CCH_3$), 1.77 (1H, dd, *J* 5.6 and 12.4 Hz, CH_2), 3.26-3.38 (1H, m, NC*H*CH$_2$), 3.91 (2H, s, CH_2Ph), 5.50 (1H, br s, =CH), 7.27-7.42 (5H, m, Ar H); δ_C (100 MHz, $CDCl_3$) 23.9 (CH_3, C(*C*H$_3$)$_2$), 25.9 (CH_3, C(*C*H$_3$)$_2$), 30.8 (C, *C*(CH$_3$)$_2$), 31.0 (CH_3, =C*C*H$_3$), 43.4 (CH_2), 44.5 (CH_2), 51.2 (CH_2, NH*C*H$_2$Ph), 52.6 (CH, CH$_2$*C*HN), 122.3 (CH, =CH), 127.0 (CH, Ar), 128.4 (2 x CH, Ar), 128.5 (2 x CH, Ar), 134.8 (C, =*C*CH$_3$), 141.0 (C, Ar); m/z (ES) 229.1826 (M^+ $C_{16}H_{23}N$ requires 229.1830), 229 (M^+, 35%), 214 (100), 173 (21), 158 (43), 107 (15), 91 (28). *Literature data*:[242] ν_{max} (neat)/cm^{-1}: 1360, 1600, 1670, 3020, 3400; δ_H (300 MHz, $CDCl_3$) 0.86

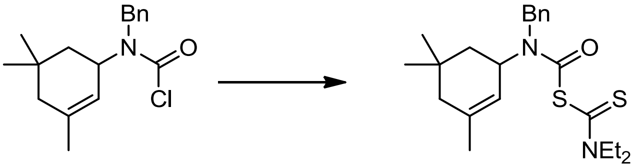
(3H, s), 0.98 (3H, s), 1.55-1.86 (4H, m), 1.66 (3H, s), 3.18-3.28 (1H, broad), 3.81 (2H, d, *J* = 12 Hz), 4.17-4.22 (1H, broad), 5.40-5.43 (1H, m), 7.25-7.36 (5H, m); δ_C (75 MHz, $CDCl_3$) 23.5 (CH_3), 26.1 (CH_3), 30.0 (C), 31.8 (CH_3), 44.2 (CH_2), 45.1 (CH_2), 53.0 (CH_2), 66.5 (CH), 122.5 (CH), 123.8 (2 CH), 126.9 (CH), 128.3 (2 CH), 134.7 (C), 140.4 (C). Anal. Calcd for $C_{16}H_{23}N$: C, 83.79; H, 10.11; N, 6.11. Found: C, 84.01; H, 10.21; N, 6.40.

- Benzyl(3,5,5-trimethylcyclohex-2-en-1-yl)carbamic chloride **201'**



A novel compound prepared according to a literature procedure.[27] A solution of triphosgene (0.907 g, 3.06 mmol) in toluene (45 mL) was treated with pyridine (0.800 mL, 9.91 mmol) and subsequently with a solution of amine **201** (1.90 g, 8.26 mmol) in toluene (10 mL). The reaction mixture was stirred for 18 h at rt, quenched with H_2O (30 mL) and extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed sequentially with HCl (50 mL of a 0.25 M aq. solution), H_2O (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give carbamoyl chloride **201'** (2.19 g, 91%) as a yellow oil. R_f 0.73 (Pet ether:EtOAc 95:5); ν_{max} (neat)/cm^{-1} : 2953, 1727, 1672, 1454, 1229, 1142, 969, 715, 694; δ_H (400 MHz, $CDCl_3$) 0.95 (6H, t, *J* 12.0 Hz, $C(CH_3)_2$), 1.28 (1H, q, *J* 11.4 Hz, CH_2), 1.54-1.73 (5H, m, $=CCH_3$ and CH_2), 1.81-1.96 (1H, m, CH_2), 4.38-4.71 (2H, m, CH_2Ph), 4.86-5.08 (1H, m, $NCHCH_2$), 5.14-5.27 (1H, m, =CH), 7.22-7.46 (5H, m, Ar H); δ_C (100 MHz, $CDCl_3$) (as a mixture of rotamers) 23.9 (CH_3, $=CCH_3$), 25.1, 25.2 (CH_3, $C(CH_3)_2$), 31.2, 31.3 (C, $C(CH_3)_2$), 31.8 (CH_3, $C(CH_3)_2$), 39.3, 40.1 (CH_2), 43.8 (CH_2), 49.7, 51.1 (CH_2, NCH_2Ph), 57.0, 58.6 (CH, CH_2CHN), 119.2 (CH, =CH), 126.4 (CH, Ar), 127.3, 127.4 (2 x CH, Ar), 128.6, 128.7 (2 x CH, Ar), 137.7, 137.8 (C, $=CCH_3$), 138.9, 139.0 (C, Ar), 150.1, 150.4 (C, NC(O)Cl); m/z (ES) 314.1282 ($[M+Na]^+$ $C_{17}H_{22}{}^{35}ClNNaO$requires 314.1282), 314 (4%), 282 (8), 230 (100).

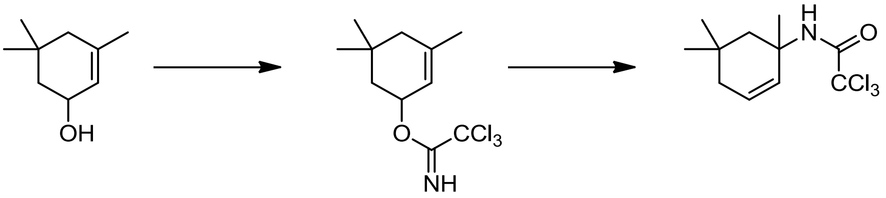
- Diethyldithiocarbamic acid-[benzyl(3,5,5-trimethylcyclohex-2-en-1-yl)carbamic acid]-thioanhydride **202**



201' **202**

A novel compound prepared according to a literature procedure.[27] A solution of carbamoyl chloride **201'** (2.19 g, 7.53 mmol) in acetone (47 mL) was treated with sodium diethyldithiocarbamate trihydrate (6.79 g, 30.1 mmol). The reaction mixture was stirred for 18 h at rt, quenched with H_2O (40 mL) and extracted with Et_2O (3 x 40 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 95:5) to give dithiocarbamate **202** (2.70 g, 89%) as a yellow oil. R_f 0.57 (Pet ether:EtOAc 85:15); ν_{max} (neat)/cm^{-1} : 2935, 1659, 1488, 1418, 1270, 1143, 962, 718, 695; δ_H (400 MHz, $CDCl_3$) (as a mixture of rotamers) 0.93 (3H, s, $C(CH_3)_2$), 0.95 (3H, s, $C(CH_3)_2$), 1.11-1.40 (8H, m, $CH_2C\mathit{H_3}$ and CH_2), 1.53-1.77 (4H, m, $=CCH_3$ and CH_2), 1.86 (1H, d, *J* 17.3 Hz, CH_2), 3.62-4.15 (4H, m, $C\mathit{H_2}CH_3$ and NCH_2Ph), 4.48-4.66 (3H, m, $C\mathit{H_2}CH_3$ and CHN), 5.22 (1H, br s, =CH), 7.29 (5H, br s, Ar H); δ_C (100 MHz, $CDCl_3$) (as a mixture of rotamers) 11.1 (CH_3, $CH_2\mathit{C}H_3$), 13.3 (CH_3, $CH_2\mathit{C}H_3$), 23.6 (CH_3, $=C\mathit{C}H_3$), 24.8 (CH_3, $C(\mathit{C}H_3)_2$), 30.9 (C, $\mathit{C}(CH_3)_2$), 31.6 (CH_3, $C(\mathit{C}H_3)_2$), 39.2, 40.3 (CH_2), 43.5 (CH_2), 48.7 (CH_2, NCH_2Ph), 49.9 (CH_2, $\mathit{C}H_2CH_3$), 50.3 (CH_2, $\mathit{C}H_2CH_3$), 54.4, 56.5 (CH, $CH_2\mathit{C}HN$), 119.5 (CH, =CH), 126.1 (CH, Ar), 126.9, 127.2 (2 x CH, Ar), 128.3 (2 x CH, Ar), 138.3 (C, Ar), 138.4 (C, $CH=\mathit{C}CH_3$), 162.9, 163.1 (C, C(O)N), 184.5, 185.3 (C, C(S)S); m/z (ES) 427.1847 ($[M+Na]^+$ $C_{22}H_{32}N_2NaOS_2$ requires 427.1854), 443 (22%), 427 (100).

- 3,5,5-Trimethylcyclohex-2-en-1-yl 2,2,2-trichloroacetimidate **213** and 2,2,2-trichloro-*N*-(1,5,5-trimethylcyclohex-2-en-1-yl)acetamide **214**

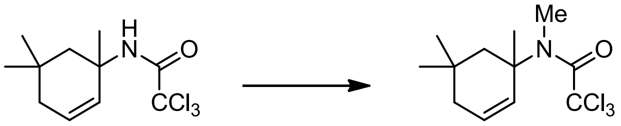


212 **213** **214**

A known compound[243] prepared according to a literature procedure.[89] A suspension of NaH (0.226 g of a 60% dispersion in mineral oil, 5.89 mmol), which had been previously washed with hexane (2 x 2 mL), in Et$_2$O (30 mL) was treated dropwise with a solution of 3,5,5-trimethyl-2-cyclohexen-1-ol **212** (9.00 mL, 58.9 mmol) in Et$_2$O (15 mL). After the evolution of hydrogen had ceased, the reaction mixture was cooled to -10 °C and trichloroacetonitrile (5.91 mL, 58.9 mmol) was added dropwise over 15 min. The reaction mixture was allowed to warm to rt over 1 h. After 5 h at rt, the solvent was evaporated under reduced pressure, pentane was added (55 mL) and the insoluble material was removed by gravity filtration. The filtrate was concentrated under reduced pressure to give crude imidate **213** as an orange oil which was used in the next step without further purification. R$_f$ 0.29 (Pet Ether:EtOAc 9:1); ν_{max} (neat)/cm^{-1} : 3306, 2954, 1692, 1514, 1446, 1365, 1278, 1156, 1066, 843, 817, 721; δ_H (400 MHz, CDCl$_3$) 0.97 (3H, s, C(CH$_3$)$_2$), 1.03 (3H, s, C(CH$_3$)$_2$), 1.57-1.67 (2H, m, CH$_2$), 1.72 (3H, s, =CCH$_3$), 1.83-1.93 (2H, m, CH$_2$), 5.42-5.51 (1H, m, OC*H*CH$_2$), 5.57 (1H, br s, =CH), 8.21 (1H, br s, =NH); δ_C (100 MHz, CDCl$_3$) 23.0 (CH$_3$, =C*C*H$_3$), 27.9 (CH$_3$, C(*C*H$_3$)$_2$), 30.1 (CH$_3$, C(*C*H$_3$)$_2$), 33.2 (C, *C*(CH$_3$)$_2$), 40.1 (CH$_2$), 44.4 (CH$_2$), 75.3 (CH, CH$_2$*C*HO), 92.2 (C, CCl$_3$), 118.3 (CH, =CH), 139.4 (C, =*C*CH$_3$), 162.7 (C, O*C*(NH)CCl$_3$); m/z (ES) 284.0375 ([M+H]$^+$ $C_{11}H_{17}{}^{35}Cl_3NO$ requires 284.0370), 305 (29%), 303 (99), 301 (100), 288 (27), 286 (29), 284 (92). *Literature data*:[243] δ_H (300 MHz, CDCl$_3$) 0.98 (3H, s), 1.04 (3H, s), 1.60 (1H, dd, *J* = 13, 7 Hz), 1.73 (3H, s), 1.74 (1H, br d, *J* = 18 Hz), 1.86 (1H, dd, *J* = 13, 6 Hz), 1.91 (1H, br d, *J* = 18 Hz), 5.46 (1H, m), 5.57 (1H, m), 8.22 (1H, br s).

A solution of imidate **213** in xylenes (540 mL) was refluxed for 1 h. The solvent was removed under reduced pressure and the crude residue obtained was purified by column chromatography (Pet ether to Pet ether:EtOAc 95:5) to give acetamide **214** (7.94 g, 47%) as a pale yellow oil (lit. yield 19%). R_f 0.76 (Pet ether:EtOAc 9:1); ν_{max} (neat)/cm^{-1} : 3304, 2954, 1692, 1514, 1446, 1365, 1278, 1156, 817, 721; δ_H (400 MHz, $CDCl_3$) 0.99 (3H, s, $C(CH_3)_2$), 1.01 (3H, s, $C(CH_3)_2$), 1.47 (1H, d, *J* 14.6 Hz, CCH_2C), 1.51 (3H, s, $=CCH_3$), 1.82-1.93 (2H, m, CH_2), 2.19 (1H, d, *J* 14.6 Hz, CCH_2C), 5.79-5.87 (2H, m, CH=CH), 6.53 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 27.5 (CH_3, $C(\textit{C}H_3)_2$), 27.6 (CH_3, $C(\textit{C}H_3)_2$), 29.4 (C, $\textit{C}(CH_3)_2$), 31.6 (CH_3, $NHC\textit{C}H_3$), 39.0 (CH_2), 46.0 (CH_2), 54.4 (C, $NH\textit{C}CH_3$), 93.6 (C, CCl_3), 128.9 (CH, $CH_2\textit{C}H=CH$), 129.6 (CH, $CH=\textit{C}HC$), 159.8 (C, $NH\textit{C}(O)CCl_3$); m/z (ES) 338 (9%), 310 (18), 308 (93), 306 (100), 184 (13). *Literature data*:[243] ν_{max} (KBr)/cm^{-1}: 3429, 3349, 2954, 1717, 1506; δ_H (300 MHz, $CDCl_3$) 0.99 (3H, s), 1.01 (3H, s), 1.48 (1H, d, *J* = 15 Hz), 1.52 (3H, s), 1.88 (2H, m), 2.21 (1H, br d, *J* = 15 Hz), 5.78-5.89 (2H, m), 6.54 (1H, br); δ_C (75 MHz, $CDCl_3$) 27.2, 27.3, 29.1, 31.3, 38.7, 45.7, 54.2, 93.4, 128.8, 129.4, 159.8; m/z (EI) 268 ($M-CH_3$), 248 (M-Cl), HR-MS (FAB) for $C_{10}H_{13}$-$ONCl_3$ ($M-CH_3$), calculated 268.0062, found 268.0060.

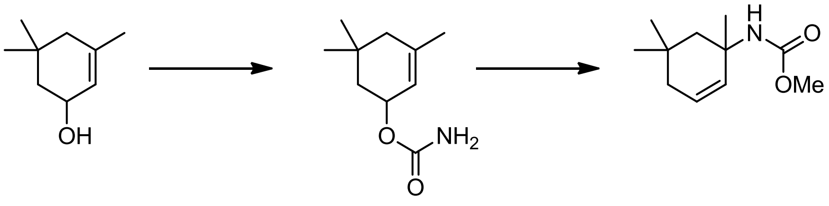
▪ 2,2,2-Trichloro-*N*-methyl-*N*-(1,5,5-trimethylcyclohex-2-en-1-yl)acetamide **219**



214 **219**

A novel compound prepared according to a modified literature procedure.[91] A solution of NaH (0.101 g of a 60% dispersion in mineral oil, 2.64 mmol) in THF (1.33 mL) was cooled to -15 °C, treated with acetamide **214** (0.150 g, 0.527 mmol), 18-crown-6 (cat.) and methyl iodide (0.328 mL, 5.27 mmol). The reaction mixture was allowed to warm to rt and after 5.5 h, it was carefully quenched with HCl (2 mL of a 1 M aq. solution) and extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed sequentially with $NaHCO_3$ (20 mL of a saturated aq. solution), and brine (20 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:Et_2O 96:4) to give acetamide **219** (30 mg, 19%) as a colourless oil. R_f 0.77 (Pet ether:EtOAc 9:1); ν_{max} (neat)/cm^{-1} : 2953, 1681, 1454, 1364, 1080, 832, 809, 669; δ_H (300 MHz, $CDCl_3$) 0.90 (3H, s, $C(CH_3)_2$), 0.95 (3H, s, $C(CH_3)_2$), 1.43-1.55 (4H, m, CH_2 and $=CCH_3$), 1.74-1.97 (2H, m, CH_2), 2.66 (1H, dt, *J* 1.1 and 14.7 Hz, CH_2), 3.22 (3H, s, NCH_3), 5.59 (1H, ddd, *J* 2.0, 3.3 and 10.2 Hz, $CH_2CH{=}CH$), 5.79-5.91 (1H, m, $CH{=}CHC$); δ_C (100 MHz, $CDCl_3$) 26.7 (CH_3, $C(CH_3)_2$), 28.0 (CH_3, $C(CH_3)_2$), 29.4 (C, $C(CH_3)_2$), 31.2 (CH_3, $NCCH_3$), 35.6 (CH_3, NCH_3), 39.2 (CH_2), 43.5 (CH_2), 62.2 (C, $NCCH_3$), 129.6 (CH, $CH_2CH{=}CH$), 129.8 (CH, $CH{=}CHC$), 159.4 (C, $NC(O)CCl_3$); m/z (ES) 320.03530 ($[M+Na]^+$ $C_{12}H_{18}{}^{35}Cl_3NNaO$ requires 320.0352), 324 (16%), 322 (98), 320 (100), 202 (11), 200 (85), 198 (99).

- Methyl (1,5,5-trimethylcyclohex-2-en-1-yl)carbamate **227**

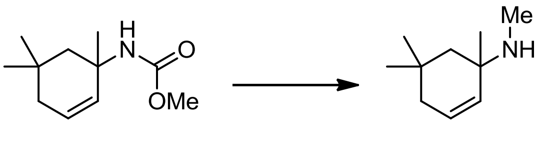


212 **226** **227**

A novel compound prepared according to a literature procedure.[97] A solution of 3,5,5-trimethyl-2-cyclohexen-1-ol **212** (2.00 mL, 13.1 mmol) in CH_2Cl_2 (66 mL) was cooled to 0 °C and treated with trichloroacetyl isocyanate (1.87 mL, 15.7 mmol). After 2 h at rt, the solvent was removed under reduced pressure and the residue was dissolved in MeOH (33 mL), cooled to 0 °C, treated with H_2O (33 mL) and K_2CO_3 (5.25 g, 37.9 mmol). After 3.5 h at rt, the reaction mixture was quenched with H_2O (70 mL) and extracted with CH_2Cl_2 (2 x 70 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give crude carbamate **226** as a white solid which was used in the next step without further purification.

A solution of carbamate **226** in CH_2Cl_2 (100 mL) was treated with Et_3N (7.30 mL, 52.4 mmol) and PPh_3 (8.59 g, 32.8 mmol), cooled to 0 °C and a solution of CBr_4 (12.2 g, 36.7 mmol) in CH_2Cl_2 (15 mL) was added dropwise over 15 min. After 1 h at rt, MeOH (26 mL) and Bu_3SnOMe (0.38 mL, 1.31 mmol) were added. After 18 h at rt, the reaction mixture was diluted with CH_2Cl_2 (100 mL), washed sequentially with HCl (100 mL of a 1 M aq. solution), $NaHCO_3$ (100 mL of a saturated aq. solution) and brine (150 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 3:2) to give carbamate **227** (1.60 g, 62%) as a colourless oil. R_f 0.46 (Hexane:EtOAc 2:1); ν_{max} (neat)/cm^{-1} : 3351, 2952, 1703, 1499, 1447, 1277, 1100, 1061, 738; δ_H (400 MHz, $CDCl_3$) 0.95 (3H, s, $C(CH_3)_2$), 0.98 (3H, s, $C(CH_3)_2$), 1.41 (1H, d, *J* 14.2 Hz, CCH_2C), 1.41 (3H, s, $=CCH_3$), 1.76-1.88 (2H, m, CH_2), 2.07 (1H, d, *J* 14.2 Hz, CCH_2C), 3.60 (3H, s, $C(O)OCH_3$), 4.62 (1H, br s, NH), 5.67-5.75 (2H, m, CH=CH); δ_C (100 MHz, $CDCl_3$) 28.1 (CH_3, $C(\mathit{C}H_3)_2$), 28.8 (CH_3, $C(\mathit{C}H_3)_2$), 29.6 (C, $\mathit{C}(CH_3)_2$), 31.3 (CH_3, $NHC\mathit{C}H_3$), 39.0 (CH_2, $=CH\mathit{C}H_2C$), 46.9 (CH_2, $C\mathit{C}H_2C$), 52.6 (CH_3, $C(O)O\mathit{C}H_3$), 52.0 (C, $NH\mathit{C}CH_3$), 127.7 (CH, $CH_2\mathit{C}H=CH$), 130.7 (CH, $CH=\mathit{C}HC$), 154.5 (C, $NH\mathit{C}(O)OCH_3$); m/z (EI) 197.1410 (M^+ $C_{11}H_{19}NO_2$ requires 197.1416), 197 (1%), 182 (100), 141 (19), 122 (24), 107 (31).

- *N*-1,5,5-Tetramethylcyclohex-2-enamine **228**

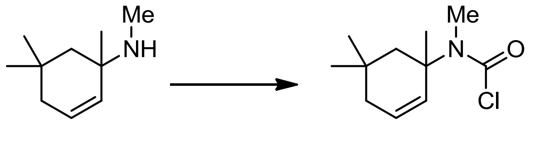


227 **228**

A novel compound prepared according to a literature procedure.[99] A solution of carbamate **227** (0.169 g, 0.860 mmol) in THF (8.6 mL) was treated with $LiAlH_4$ (0.130 g, 3.43 mmol) and heated at reflux for 18 h. The reaction mixture was cooled to 0 °C, carefully quenched with H_2O (1 mL) and filtered through a pad of celite (eluent Et_2O). The filtrate was dried over $MgSO_4$, filtered and evaporated under reduced pressure to give amine **228** (94 mg, 71%) as a light yellow oil. ν_{max} (neat)/cm^{-1} : 3293, 2951, 1458, 1364, 1154, 1099, 992, 723; δ_H (400 MHz, $CDCl_3$)

0.92 (3H, s, C(CH$_3$)$_2$), 0.93 (3H, s, C(CH$_3$)$_2$), 1.09 (3H, s, NHCC*H$_3$*), 1.20 (1H, br s, NH), 1.25, 1.58 (2H, ABq, *J* 13.8 Hz, CCH$_2$C), 1.65-1.78 (2H, m, =CHC*H$_2$*C), 2.23 (3H, s, NCH$_3$), 5.41 (1H, dt, *J* 1.6 and 10.2 Hz, CH$_2$C*H*=CH), 5.63 (1H, ddd, *J* 3.2, 4.4 and 10.2 Hz, CH=C*H*C); δ_C (100 MHz, CDCl$_3$) 28.2 (CH$_3$, C(CH$_3$)$_2$), 28.6 (CH$_3$, C(*C*H$_3$)$_2$), 29.1 (CH$_3$, NHC*C*H$_3$), 30.5 (C, *C*(CH$_3$)$_2$), 30.9 (CH$_3$, HNCH$_3$), 38.9 (CH$_2$, =CH*C*H$_2$C), 46.2 (CH$_2$, C*C*H$_2$C), 52.9 (C, NH*C*CH$_3$), 126.2 (CH, CH$_2$*C*H=CH), 133.2 (CH, CH=*C*HC); m/z (EI) 153.1520 (M$^+$ C$_{10}$H$_{19}$N requires 153.1517), 153 (1%), 138 (100), 122 (28), 107 (87), 97 (33), 91 (45), 82 (40), 79 (29).

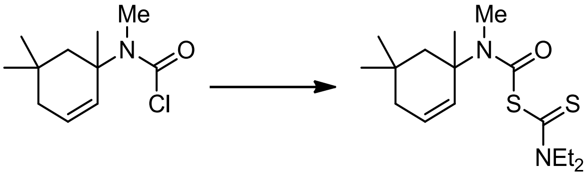
- Methyl(1,5,5-trimethylcyclohex-2-en-1-yl)carbamic chloride **229**



228 **229**

A novel compound prepared according to a literature procedure.[27] A solution of triphosgene (0.197 g, 0.664 mmol) in toluene (10 mL) was treated with pyridine (0.174 mL, 2.15 mmol) and subsequently with a solution of amine **228** (0.275 g, 1.79 mmol) in toluene (2 mL). The reaction mixture was stirred for 18 h at rt, quenched with H$_2$O (15 mL) and extracted with Et$_2$O (2 x 15 mL). The combined organic extracts were washed sequentially with HCl (15 mL of a 1 M aq. solution) and brine (50 mL), dried over MgSO$_4$, filtered and evaporated under reduced pressure to give carbamoyl chloride **229** (0.223 g, 58%) as a yellow oil. R$_f$ 0.60 (Pet ether:EtOAc 7:3); δ_H (400 MHz, CDCl$_3$) 0.92 (3H, s, C(CH$_3$)$_2$), 0.93 (3H, s, C(CH$_3$)$_2$), 1.39 (1H, d, *J* 14.7 Hz, CH$_2$), 1.47 (3H, s, NCCH$_3$), 1.74-1.93 (2H, m, CH$_2$), 2.54 (1H, dt, *J* 1.2 and 14.7 Hz, CH$_2$), 3.08 (3H, s, NCH$_3$), 5.56 (1H, ddd, *J* 2.1, 3.1 and 10.2 Hz, CH$_2$C*H*=CH), 5.78-5.90 (1H, m, CH=C*H*C); δ_C (100 MHz, CDCl$_3$) 27.2 (CH$_3$, C(*C*H$_3$)$_2$), 27.4 (CH$_3$, C(*C*H$_3$)$_2$), 29.2 (C, *C*(CH$_3$)$_2$), 31.2 (CH$_3$, NC*C*H$_3$), 37.0 (CH$_3$, NCH$_3$), 39.1 (CH$_2$), 44.1 (CH$_2$), 62.0 (C, N*C*CH$_3$), 129.5 (CH, CH$_2$*C*H=CH), 139.8 (CH, CH=*C*HC); 147.9 (C, NC(O)Cl).

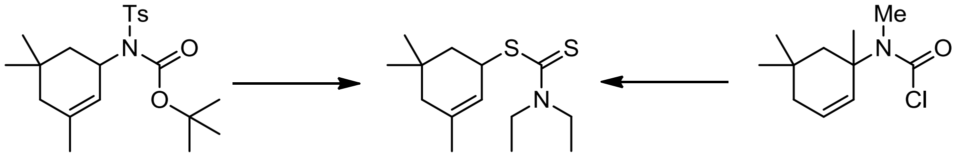
- Diethyldithiocarbamic acid-[(4-methyl)(cyclohex-2-enyl)carbamic acid]-thioanhydride **220**



229 **220**

A novel compound prepared according to a literature procedure.[27] A solution of carbamoyl chloride **229** (0.185 g, 0.856 mmol) in acetone (5.5 mL) was treated with sodium diethyldithiocarbamate trihydrate (0.773 g, 3.43 mmol). After 18 h at rt, the reaction mixture was quenched with H_2O (6 mL) and extracted with Et_2O (3 x 6 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 93:7) to give dithiocarbamate **220** (0.192 g, 68%) as a yellow oil. R_f 0.61 (Pet Ether: EtOAc 85:15); ν_{max} (neat)/cm^{-1} : 2973, 1670, 1486, 1416, 1268, 1199, 1052, 979, 916, 739; δ_H (400 MHz, $CDCl_3$) 0.85 (3H, s, $C(CH_3)_2$), 0.88 (3H, s, $C(CH_3)_2$), 1.26 (6H, dt, *J* 7.1 and 14.1 Hz, CH_2C*H_3*), 1.40 (1H, d, *J* 14.6 Hz, CH_2), 1.46 (3H, s, $NCCH_3$), 1.69-1.87 (2H, m, CH_2), 2.57 (1H, d, *J* 14.6 Hz, CH_2), 2.91 (3H, s, NCH_3), 3.76 (2H, q, *J* 7.1 Hz, C*H_2*CH_3), 3.98 (2H, q, *J* 7.1 Hz, C*H_2*CH_3), 5.52 (1H, dd, *J* 1.1 and 10.2 Hz, CH_2C*H*=CH), 5.76 (1H, dt, *J* 3.9 and 10.2 Hz, CH=C*H*C); δ_C (100 MHz, $CDCl_3$) 11.2 (CH_3, CH_2*C*H_3), 13.4 (CH_3, CH_2*C*H_3), 27.5 (2 x CH_3, C(*C*H_3)$_2$), 29.2 (C, *C*(CH_3)$_2$), 31.0 (CH_3, NC*C*H_3), 34.3 (CH_3, NCH_3), 38.9 (CH_2), 44.4 (CH_2), 48.6 (CH_2, *C*H_2CH_3), 50.0 (CH_2, *C*H_2CH_3), 61.1 (C, N*C*CH_3), 128.8 (CH, CH_2*C*H=CH), 130.1 (CH, CH=*C*HC); 161.1 (C, C(O)N), 185.7 (C, C(S)S); m/z (ES) 351.1543 ([M+Na]$^+$ $C_{16}H_{28}N_2NaOS_2$ requires 351.1541), 351 (100%).

- 3,5,5-Trimethylcyclohex-2-en-1-yl diethylcarbamodithioate **232**



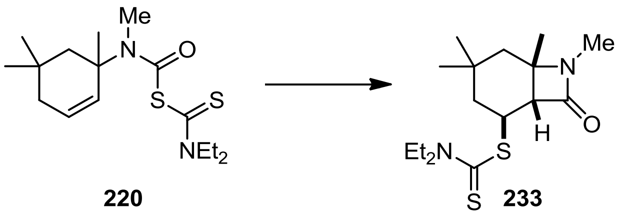
543 **232** **229**

A novel compound prepared according to a modified literature procedure.[27] A solution of carbamoyl chloride **229** (0.449 g, 2.08 mmol) in acetone (13 mL) was treated with sodium diethyldithiocarbamate trihydrate (1.88 g, 8.33 mmol) and heated to reflux. After 18 h, the reaction mixture was quenched with H_2O (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:Et_2OAc 4:1) to give thiocarbamate **232** (0.162 g, 29%) as a pale yellow oil.

A solution of Boc protected tosylamine **543** (52 mg, 0.13 mmol) in acetone (1.0 mL) was treated with sodium diethyldithiocarbamate trihydrate (89 mg, 0.40 mmol) and heated to reflux. After 18 h, the reaction mixture was quenched with H_2O (1.0 mL) and extracted with Et_2O (3 x 2 mL). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 9:1) to give thiocarbamate **232** (20 mg, 56%) as a pale yellow oil.

R_f 0.86 (Pet ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1} : 2930, 1483, 1412, 1264, 1206, 983, 917; δ_H (400 MHz, $CDCl_3$) 0.88 (6H, s, $C(CH_3)_2$), 1.27 (6H, t, *J* 7.0 Hz, $CH_2C\mathit{H}_3$), 1.45 (1H, dd, *J* 9.9 and 12.8 Hz, $CCH_2C=$), 1.60 (1H, d, *J* 16.7 Hz, $C\mathit{CH_2}CHS$), 1.68 (3H, s, $=CCH_3$), 1.85 (1H, d, *J* 16.7 Hz, $C\mathit{CH_2}CHS$), 1.97 (1H, dd, *J* 6.2 and 12.8 Hz, $CCH_2C=$), 3.72 (2H, q, *J* 7.0 Hz, $C\mathit{H_2}CH_3$), 3.81-4.15 (2H, m, $C\mathit{H_2}CH_3$), 4.66-4.80 (1H, m, CHS), 5.50 (1H, br s, CH=); δ_C (100 MHz, $CDCl_3$) 11.9 (CH_3, $CH_2\mathit{C}H_3$), 12.6 (CH_3, $CH_2\mathit{C}H_3$), 24.1 (CH_3, $=C\mathit{C}H_3$), 26.0 (CH_3, $C(\mathit{C}H_3)_2$), 31.0 (CH_3, $C(\mathit{C}H_3)_2$), 31.1 (C, $\mathit{C}(CH_3)_2$), 41.8 (CH_2, $C\mathit{C}H_2CHS$), 44.1 (CH_2, $C\mathit{C}H_2C=$), 46.8 (CH_2, $\mathit{C}H_2CH_3$), 48.1 (CH, CHS), 49.4 (CH_2, $\mathit{C}H_2CH_3$), 120.7 (CH, =CH), 136.5 (C, $=\mathit{C}CH_3$), 195.7 (C, SC(S)); m/z (ES) 272.1507 ($[M+H]^+$ $C_{14}H_{26}NS_2$ requires 272.1501), 297 (76%), 275 (100), 272 (67), 182 (20), 150 (92).

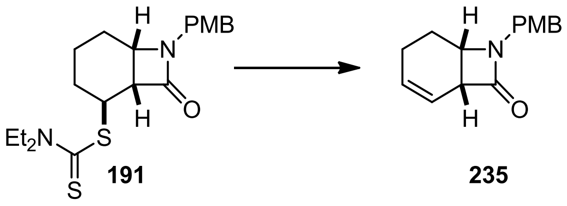
- (±)-(*1S,2R,6R*)-7-Methyl-8-oxo-7-azabicyclo[4.2.0]octan-2-yl diethylcarbamodithioate **233**



220 **233**

A novel compound prepared according to a literature procedure.[26] A solution of carbamoyl dithiocarbamate **220** (0.192 g, 0.584 mmol) in cyclohexane (5.8 mL) was degassed for 10 min and irradiated with a 500 W lamp which generated enough heat to bring the solvent to reflux. After 16 h, the solvent was removed under reduced pressure and the crude product obtained was purified by column chromatography (Pet ether to Pet ether:EtOAc 1:1) to give lactam **233** (74 mg, 39%) as a colourless oil. R_f 0.24 (Pet ether:EtOAc 3:2); ν_{max} (neat)/cm^{-1} : 2928, 1740, 1419, 1264, 1204, 978, 915, 828; δ_H (400 MHz, CDCl$_3$) 0.99 (6H, d, *J* 3.4 Hz, C(CH$_3$)$_2$), 1.17-1.27 (6H, m, C*H$_3$*CH$_2$), 1.30 (3H, s, NCCH$_3$), 1.49 (1H, d, *J* 15.2 Hz, CH$_2$), 1.60-1.73 (2H, m, CH$_2$), 2.03 (1H, dd, *J* 4.7 and 14.6 Hz, CH$_2$), 2.63 (3H, s, NCH$_3$), 3.10 (1H, d, *J* 4.7 Hz, CHS), 3.54-3.76 (2H, m, C*H$_2$*CH$_3$), 3.83-4.09 (2H, m, C*H$_2$*CH$_3$), 4.52 (1H, dt, J 4.7 and 7.3 Hz, CHC(O)); δ_C (100 MHz, CDCl$_3$) 11.6 (CH$_3$, CH$_2$CH$_3$), 12.6 (CH$_3$, CH$_2$*C*H$_3$), 23.6 (CH$_3$, NCH$_3$), 25.2 (CH$_3$, NC*C*H$_3$), 29.4 (C, *C*(CH$_3$)$_2$), 31.0 (CH$_3$, C(*C*H$_3$)$_2$), 34.0 (CH$_3$, C(*C*H$_3$)$_2$), 40.0 (CH$_2$), 42.4 (CH$_2$), 45.2 (CH, CH*C*HC(O)), 46.6 (CH$_2$, *C*H$_2$CH$_3$), 49.2 (CH$_2$, *C*H$_2$CH$_3$), 57.7 (C, N*C*CH$_3$), 58.3 (CH, CH$_2$*C*HS), 167.1 (C, C(O)N), 193.5 (C, C(S)S); m/z (ES) 329.1722 ([M+H]$^+$ $C_{16}H_{29}N_2OS_2$ requires 329.1716), 329 (100%).

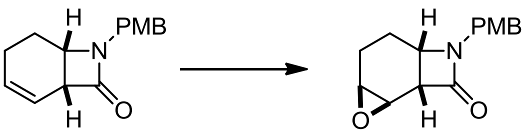
- (±)-(1*R*,6*S*)-7-(4-Methoxybenzyl)-7-azabicyclo[4.2.0]oct-2-en-8-one **235**



191 **235**

A novel compound prepared according to a literature procedure.[29] A solution of lactam **191** (3.10 g, 7.89 mmol) in diphenyl ether (61 mL) was heated to reflux. After 7 h, the reaction mixture was directly purified by column chromatography (Pet ether to Pet ether:EtOAc 3:1) to give lactam **235** (1.54 g, 80%) as a pale yellow oil. R_f 0.22 (Pet Ether: EtOAc 7:3); ν_{max} (neat)/cm^{-1}: 2930, 1734, 1611, 1511, 1241, 1175, 1030, 831, 693; δ_H (400 MHz, $CDCl_3$) 1.21-1.34 (1H, m, CH_2), 1.79-1.87 (2H, m, CH_2), 1.94-2.01 (1H, m, CH_2), 3.62 (1H, t, *J* 5.4 Hz, CHC*H*C(O)), 3.80-3.84 (4H, m, CH_2C*H*N and OCH_3), 4.17, 4.45 (2H, ABq, *J* 14.8 Hz, NCH_2Ar), 5.80-5.85 (1H, m, CH_2C*H*=CH), 5.95-6.00 (1H, m, CHC*H*=CH), 6.87 (2H, d, *J* 8.4 Hz, Ar H), 7.21 (2H, d, *J* 8.4 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 19.7 (CH_2), 22.8 (CH_2), 43.6 (CH_2, NCH_2Ar), 48.6 (CH, =CH*C*HC(O)), 51.1 (CH, CH_2*C*HN), 55.5 (CH_3, OCH_3), 114.3 (2 x CH, Ar), 121.7 (CH, CH_2*C*H=CH), 128.5 (C, Ar*C*CH_2N), 129.9 (2 x CH, Ar), 131.5 (CH, CH=*C*HCH), 159.3 (C, ArCO), 167.2 (C, C(O)N); m/z (ES) 266.1153 ($[M+Na]^+$ $C_{15}H_{17}NNaO_2$ requires 266.1157), 267 (10%), 266 (100).

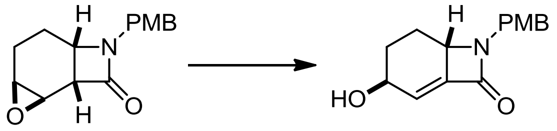
- (±)-(1*S*,2*R*,4*S*,7*S*)-8-(4-Methoxybenzyl)-3-oxa-8-azatricyclo[5.2.0.0^{2,4}]nonan-9-one **236**



235 **236**

A novel compound prepared according to a literature procedure.[52] A solution of lactam **235** (0.812 g, 3.34 mmol) in CH_2Cl_2 (22 mL) was cooled to 0 °C, treated with recrystallised *m*CPBA (1.73 g, 10.0 mmol) and allowed to warm to rt over 1 h. After 5 h at rt, the reaction mixture was cooled to 0 °C, diluted with CH_2Cl_2 (22 mL) and treated with KF (1.75 g, 30.1 mmol). After stirring at 0 °C for 1 h, the reaction mixture was filtered through a pad of celite, the filtrate was evaporated under reduced pressure and purified by column chromatography (Pet ether:EtOAc:Et$_3$N 75:25:5 to Pet ether:EtOAc:Et$_3$N 60:35:5) to give epoxy lactam **236** (0.627 g, 72%) as a colorless oil. R$_f$ 0.33 (Pet ether:EtOAc 3:2); ν$_{max}$ (neat)/cm^{-1} : 2935, 1736, 1611, 1512, 1242, 1175, 1029, 805, 731; δ$_H$ (400 MHz, CDCl$_3$) 1.42-1.48 (1H, m, CH$_2$), 1.60-1.78 (2H, m, CH$_2$), 1.85-1.91 (1H, m, CH$_2$), 3.17-3.19 (1H, m, CH$_2$C*H*O), 3.30-3.32 (1H, m, CHC*H*O), 3.52-3.56 (2H, m, CHC*H*C(O) and CH$_2$C*H*N), 3.77 (3H, s, OCH$_3$), 4.11, 4.39 (2H, ABq, *J* 14.8 Hz, NCH$_2$Ar), 6.84 (2H, d, *J* 8.8 Hz, Ar H), 7.16 (2H, d, *J* 8.8 Hz, Ar H); δ$_C$ (100 MHz, CDCl$_3$) 18.3 (CH$_2$), 18.4 (CH$_2$), 44.0 (CH$_2$, NCH$_2$Ar), 47.6 (CH, *C*HC(O)), 49.3 (CH, CH*C*HO), 49.5 (CH, CH$_2$*C*HN), 52.2 (CH, CH$_2$*C*HO), 55.4 (CH$_3$, O*C*H$_3$), 114.3 (2 x CH, Ar), 127.8 (C, Ar*C*CH$_2$N), 129.8 (2 x CH, Ar), 159.3 (C, ArCO), 166.3 (C, C(O)N); m/z (ES) 282.1108 ([M+Na]$^+$ C$_{15}$H$_{17}$NNaO$_3$ requires 282.1106), 282 (100%).

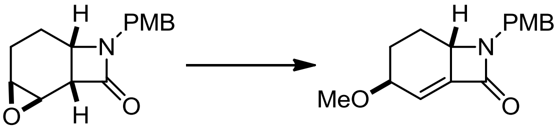
- (±)-(3*S*,6*S*)-3-Hydroxy-7-(4-methoxybenzyl)-7-azabicyclo[4.2.0]oct-1-en-8-one **237**



236 **237**

A novel compound prepared according to a modified literature procedure.[101] A solution of epoxy lactam **236** (0.123 g, 0.475 mmol) in THF (1.9 mL) was cooled to -78 °C, treated with LHMDS (0.76 mL of a 1.0 M solution in THF, 0.76 mmol) and allowed to warm progressively to rt. After 3 h, the reaction mixture was quenched with NH$_4$Cl (2 mL of a saturated aq. solution), and extracted with Et$_2$O (2 x 3 mL). The combined organic extracts were washed with brine (5 mL), dried over MgSO$_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether:EtOAc 2:3 to Pet ether:EtOAc 1:4) to give hydroxy lactam **237** (64 mg, 52%) as a white solid. mp 105-108 °C; R$_f$ 0.15 (Pet ether:EtOAc 1:1); ν$_{max}$ (neat)/cm^{-1} : 3351, 2956, 1722, 1688, 1513, 1392, 1245, 1173, 1028, 809, 552; δ$_H$ (400 MHz, CDCl$_3$) 1.11-1.38 (2H, m, CH$_2$), 1.76-1.82 (1H, m, CH$_2$), 2.12-2.18 (1H, m, CH$_2$), 2.92 (1H, s, OH), 3.75 (1H, ddt, *J* 1.4, 4.6 and 10.2 Hz, CH_2CHN), 3.78 (3H, s, OCH_3), 4.30-4.42 (3H, m, CH_2CHOH and NCH_2Ar), 6.12 (1H, d, *J* 3.6 Hz, CHC*H*=C), 6.84 (2H, d, *J* 8.8 Hz, Ar H), 7.15 (2H, d, *J* 8.8 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 29.1 (CH_2), 30.4 (CH_2), 45.6 (CH_2, NCH_2Ar), 55.4 (CH_3, OCH_3), 56.9 (CH, CH_2CHN), 68.1 (*C*H, CHOH), 114.3 (2 x CH, Ar), 124.7 (CH, CH*C*H=C), 127.7 (C, Ar*C*CH_2N), 129.9 (2 x CH, Ar), 145.4 (C, CH=*C*C(O)), 159.4 (C, ArCO), 163.5 (C, C(O)N); m/z (ES) 282.1107 ($[M+Na]^+$ $C_{15}H_{17}NNaO_3$ requires 282.1106), 282 (100%).

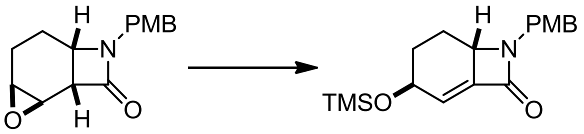
- (±)-(3*S*,6*S*)-3-Methoxy-7-(4-methoxybenzyl)-7-azabicyclo[4.2.0]oct-1-en-8-one **239**



236 **239**

A novel compound prepared according to a modified literature procedure.[244] A solution of epoxy lactam **236** (0.121 g, 0.467 mmol) in THF (1.9 mL) was cooled to -78 °C, treated with NaHMDS (1.2 mL of a 1.0 M solution in THF, 1.2 mmol) and allowed to warm progressively to 0 °C. After 1.5 h, the reaction mixture was cooled to -78 °C, treated with methyl iodide (32 µL, 0.51 mmol) and progressively allowed to warm to rt. After 18 h, it was quenched with water (2 mL) and extracted with Et_2O (2 x 3 mL). The combined organic extracts were washed with brine (5 mL) , dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether:EtOAc 3:2 to Pet ether:EtOAc 2:3) to give methoxy lactam **239** (29 mg, 23%) as a white solid. mp 87-90 °C; R_f 0.27 (Pet ether:EtOAc 1:1); ν_{max} (neat)/cm^{-1} : 2932, 1731, 1695, 1613, 1513, 1360, 1239, 1090, 1022, 948, 809, 743; δ_H (400 MHz, $CDCl_3$) 1.11-1.21 (1H, m, CH_2), 1.33-1.43 (1H, m, CH_2), 1.80-1.86 (1H, m, CH_2), 2.11-2.18 (1H, m, CH_2), 3.35 (3H, s, CHOC*H₃*), 3.75 (1H, ddt, *J* 1.4, 4.6 and 10.2 Hz, CH_2C*H*N), 3.79 (3H, s, ArOC*H₃*), 4.00-4.06 (1H, m, CH_2C*H*OCH_3), 4.34, 4.43 (2H, ABq, *J* 14.8 Hz, NCH_2Ar), 6.19 (1H, d, *J* 2.8 Hz, CHC*H*=C), 6.85 (2H, d, *J* 8.4 Hz, Ar H), 7.17 (2H, d, *J* 8.4 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 26.0 (CH_2), 28.9 (CH_2), 45.5 (CH_2, NCH_2Ar), 55.4 (CH_3, ArO*C*H_3), 56.1 (CH_3, CHO*C*H_3), 56.8 (CH, CH_2*C*HN), 76.4 (CH, *C*HOCH_3), 114.3 (2 x CH, Ar), 121.6 (CH, CH_2*C*H=CH), 127.9 (C, Ar*C*CH_2N), 129.9 (2 x CH, Ar), 147.0 (C, CH=*C*C(O)), 159.4 (C, ArCO), 163.2 (C, C(O)N); m/z (ES) 296.1256 ($[M+Na]^+$ $C_{16}H_{19}NNaO_3$ requires 296.1263), 296 (100%).

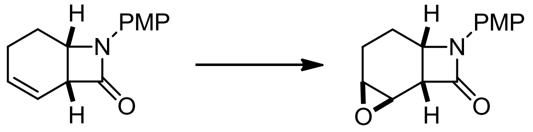
- (±)-(3*S*,6*S*)-7-(4-Methoxybenzyl)-3-((trimethylsilyl)oxy)-7-azabicyclo[4.2.0]oct-1-en-8-one **240**



236 **240**

A novel compound prepared according to a modified literature procedure.[244] A solution of epoxy lactam **236** (0.116 g, 0.447 mmol) in THF (1.8 mL) was cooled to -78 °C, treated with NaHMDS (1.1 mL of a 1.0 M solution in THF, 1.1 mmol) and allowed to warm progressively to 0 °C over 1.5 h. The reaction mixture was cooled to -40 °C and TMSOTf (74 µL, 0.49 mmol) was added. The reaction mixture was allowed to warm to rt over 3 h, quenched with H_2O (0.5 mL) and extracted with Et_2O (2 x 3 mL). The combined organic extracts were dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Hexane:EtOAc:Et_3N 5:4:1 to Hexane:EtOAc:Et_3N 4:5:1) to give TMS protected hydroxyl lactam **240** (42 mg, 28%) as a yellow oil. This compound is highly unstable and attempt to fully characterise it gave data corresponding to hydroxyl lactam **237**. δ_H (400 MHz, $CDCl_3$) 0.12 (9H, s, $Si(CH_3)_3$), 1.06-1.30 (1H, m, CH_2), 1.33-1.46 (1H, m, CH_2), 1.78 (1H, ddd, *J* 4.2, 7.0 and 11.5 Hz, CH_2), 1.96-2.09 (1H, m, CH_2), 3.72-4.83 (4H, m, CH_2C*H*N and OCH_3), 4.30-4.46 (3H, m, CH_2C*H*O and NCH_2Ar), 6.04 (1H, d, *J* 4.0 Hz, CHC*H*=C), 6.83 (2H, d, *J* 9.1 Hz, Ar H), 7.16 (2H, d, *J* 9.1 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 0.4 (3 x CH_3, $Si(CH_3)_3$), 29.3 (CH_2), 30.7 (CH_2), 45.6 (CH_2, NCH_2Ar), 55.4 (CH_3, O*C*H_3), 56.7 (CH, CH_2*C*HN), 68.9 (*C*H, *C*HOSi$(CH_3)_3$), 114.3 (2 x CH, Ar), 124.8 (CH, CH_2*C*H=CH), 128.0 (C, Ar*C*CH_2N), 129.9 (2 x CH, Ar), 145.4 (C, CH=*C*C(O)), 159.4 (C, ArCO), 163.4 (C, C(O)N).

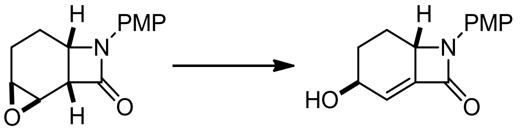
- (±)-(1*S*,2*R*,4*S*,7*S*)-8-(4-Methoxyphenyl)-3-oxa-8-azatricyclo[5.2.0.0^{2,4}]nonan-9-one **242**



131 **242**

A novel compound prepared according to a literature procedure.[52] A solution of lactam **131** (0.158 g, 0.690 mmol) in CH_2Cl_2 (4.6 mL) was cooled to 0 °C, treated with recrystallised *m*CPBA (0.357 g, 2.07 mmol) and allowed to warm to rt over 1 h. After 2 h at rt, the reaction mixture was cooled to 0 °C, diluted with CH_2Cl_2 (10 mL) and treated with KF (0.361 g, 6.21 mmol). After stirring at 0 °C for 2 h, the reaction mixture was filtered through a pad of celite (eluent CH_2Cl_2), the filtrate was evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 7:3) to give epoxy lactam **242** (0.156 g, 92%) as a yellow solid. mp 98-100 °C (CH_2Cl_2); R_f 0.43 (Pet ether:EtOAc 3:1); ν_{max} (neat)/cm^{-1} : 2955, 1725, 1513, 1398, 1243, 1226, 1028, 828; δ_H (400 MHz, $CDCl_3$) 1.90-2.02 (4H, m, CH_2), 3.29 (1H, t, *J* 3.6 Hz, CH_2CHO), 3.41 (1H, dd, *J* 3.2 and 4.0 Hz, CHC*H*O), 3.73 (1H, dd, *J* 2.8 and 5.2 Hz, CHC*H*C(O)), 3.79 (3H, s, OCH_3), 4.17-4.19 (1H, m, CH_2C*H*N), 6.89 (2H, d, *J* 9.0 Hz, Ar H), 7.30 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 18.0 (CH_2), 18.2 (CH_2), 47.1 (CH, *C*HC(O)), 49.2 (CH, CH*C*HO), 49.6 (CH, *C*HN), 51.9 (CH, CH_2*C*HO), 55.6 (CH_3, OCH_3), 114.6 (2 x CH, Ar), 118.8 (2 x CH, Ar), 130.4 (C, ArCN), 156.4 (C, ArCO), 163.2 (C, C(O)N); m/z (ES) 268.0938 ($[M+Na]^+$, $C_{14}H_{15}NNaO_3$ requires 258.0950), 314 (9%), 300 (8), 269 (7), 268 (100).

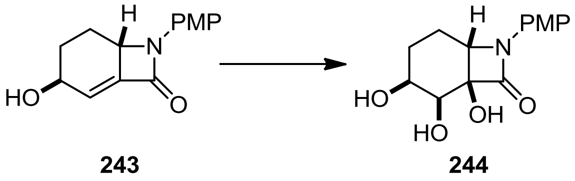
- (±)-(3*S*,6*S*)-3-Hydroxy-7-(4-methoxyphenyl)-7-azabicyclo[4.2.0]oct-1-en-8-one **243**



242 **243**

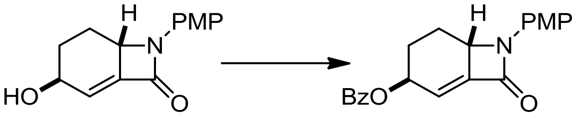
A novel compound prepared according to a modified literature procedure.[101] A solution of epoxy lactam **242** (0.496 g, 2.02 mmol) in THF (13 mL) was cooled to -78 °C and LHMDS (3.2 mL of a 1.0 M solution in THF, 3.2 mmol) was added dropwise over 2 min. The reaction mixture was allowed to warm to 0 °C over 2 h, quenched with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give hydroxyl lactam **243** (0.438 g, 88%) as a white solid. mp 164-165 °C (CH_2Cl_2); R_f 0.26 (Pet ether:EtOAc 3:1); ν_{max} (neat)/cm^{-1}: 3416, 2960, 1714, 1689, 1512, 1245, 1121, 984, 825; δ_H (300 MHz, $CDCl_3$) 1.47-1.69 (2H, m, CH_2), 1.84 (1H, d, *J* 6.7 Hz, OH), 2.30-2.55 (2H, m, CH_2), 3.79 (3H, s, OCH_3), 4.26-4.38 (1H, m, CH_2C*H*N), 4.47-4.61 (1H, m, CH_2C*H*OH), 6.29 (1H, dd, *J* 0.6 and 4.2 Hz, CHC*H*=C), 6.88 (2H, d, *J* 9.0 Hz, Ar H), 7.32 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 29.3 (CH_2), 30.8 (CH_2), 55.7 (CH_3, OCH_3), 57.5 (CH, CH_2*C*HN), 68.5 (CH, CH_2*C*HOH), 114.8 (2 x CH, Ar), 117.7 (2 x CH, Ar), 125.2 (CH, CH*C*H=C), 132.1 (C, ArCN), 145.2 (C, CH=*C*C(O)), 156.4 (C, ArCO), 159.6 (C, C(O)N); m/z (ES) 246.1128 ($[M+H]^+$ $C_{14}H_{16}NO_3$ requires 246.1125), 268 (M^+, 75%), 246 (100), 199 (19), 149 (56).

- (±)-(1*R*,2*S*,3*S*,6*S*)-1,2,3-Trihydroxy-7-(4-methoxyphenyl)-7-azabicyclo[4.2.0]octan-8-one **244**



A novel compound prepared according to a literature procedure.[56] A solution of hydroxyl lactam **243** (0.178 g, 0.728 mmol) in a 5:5:2: mixture of H_2O:acetone:*t*BuOH (3.0 mL) was treated with NMO (0.204 g, 1.74 mmol) and OsO_4 (2 µL of a 4 wt% aq. solution, cat). After 18 h at 40 °C, sodium bisulfite (0.416 g, 2.19 mmol) was added to quench the reaction. After 2 h at 40 °C, the reaction mixture was diluted with H_2O (3 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (8 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give trihydroxy lactam **244** (57 mg, 28%) as a white solid. mp 94-96 °C; R_f 0.38 (EtOAc); ν_{max} (neat)/cm^{-1}: 3277, 3180, 2862, 1727, 1454, 1170, 1055, 742, 700; δ_H (400 MHz, DMSO-d_6) 1.43-1.53 (2H, m, CH_2), 1.90-2.01 (1H, m, CH_2), 2.04-2.17 (1H, m, CH_2), 3.65 (1H, t, *J* 7.2 Hz, C*H*OH), 3.73 (3H, s, OCH_3), 3.77 (1H, br s, C*H*OH), 4.04 (1H, t, *J* 2.8 Hz, CH_2C*H*N), 4.65 (1H, br s, OH), 4.90 (1H, br s, OH), 6.18 (1H, br s, OH), 6.94 (2H, d, *J* 9.0 Hz, Ar H), 7.31 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, DMSO-d_6) 19.4 (CH_2), 23.8 (CH_2), 55.1 (CH_3, OCH_3), 60.5 (CH, CH_2CHN), 65.4 (CH, CHOH), 70.8 (CH, CHOH), 83.8 (C, CH*C*OH), 114.4 (2 x CH, Ar), 118.4 (2 x CH, Ar), 129.9 (C, ArCN), 155.6 (C, ArCO), 166.5 (C, C(O)N).

- (±)-(3*S*,6*S*)-7-(4-Methoxyphenyl)-8-oxo-7-azabicyclo[4.2.0]oct-1-en-3-yl benzoate **246**

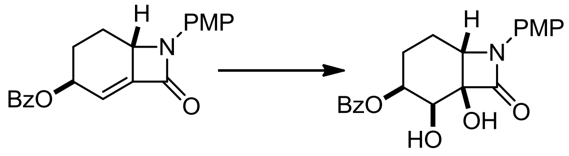


243 **246**

A novel compound prepared according to a literature procedure.[106] A solution of hydroxyl lactam **243** (0.109 g, 0.444 mmol) in CH_2Cl_2 (5.6 mL) was cooled to 0 °C and treated with BzCl (206 µL, 1.78 mmol) and pyridine (0.180 µL, 2.22 mmol). The reaction mixture was allowed to warm to rt over 18 h, quenched with $NaHCO_3$ (6 mL of a saturated aq. solution) and extracted with CH_2Cl_2 (3 x 6 mL). The combined organic extracts were dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 4:1) to give benzoyl protected lactam **246** (0.132 mg, 85%) as a white solid. mp 167-169 °C; R_f 0.48 (Pet ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1}: 2943, 1747, 1710, 1506, 1240, 1111, 1020, 947, 832, 705; δ_H (400 MHz, $CDCl_3$) 1.61-1.89 (2H, m, CH_2), 2.47-2.63 (2H, m, CH_2), 3.79 (3H, s, OCH_3), 4.34-4.45 (1H, m, CH_2C*H*N), 5.72-5.84 (1H, m, CH_2C*H*O), 6.38 (1H, dd, *J* 1.2 and 4.5 Hz, CHC*H*=C), 6.89 (2H, d, *J* 9.0 Hz, Ar H), 7.35 (2H, d, *J* 9.0 Hz, Ar H), 7.42-7.51 (2H, m, Ar H), 7.54-7.64 (1H, m, Ar H), 8.02-8.15 (2H, m, Ar H); δ_C (100 MHz, $CDCl_3$) 26.8 (CH_2), 29.1 (CH_2), 55.7 (CH_3, OCH_3), 57.1 (CH, CH_2*C*HN), 70.5 (CH, CH_2*C*HOBz), 114.8 (2 x CH, Ar), 117.8 (2 x CH, Ar), 121.6 (CH, CH*C*H=C), 128.6 (2 x CH, Ar), 129.9 (2 x CH, Ar), 130.0 (C, Ar), 132.1 (C, ArCN), 133.4 (CH, Ar), 147.4 (C, CH=*C*C(O)), 156.5 (C, ArCO), 159.0 (C, C(O)N), 166.3 (C, C(O)O);

m/z (ES) 372.1218 ([M+Na]$^+$ $C_{21}H_{19}NNaO_4$ requires 372.1212), 721 (100%), 404 (32), 372 (75), 228 (17).

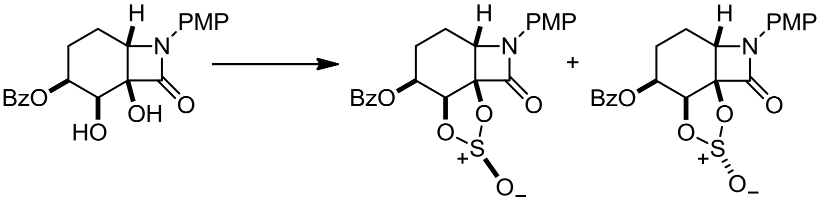
- (±)-(1*R*,2*S*,3*S*,6*S*)-1,2-Dihydroxy-7-(4-methoxyphenyl)-8-oxo-7-azabicyclo[4.2.0]octan-3-yl benzoate **247**



246 **247**

A novel compound prepared according to a literature procedure.[56] A solution of lactam **246** (0.162 g, 0.464 mmol) in a 5:5:2:2 mixture of H_2O:acetone:*t*BuOH:CH_2Cl_2 (3.0 mL) was treated with NMO (0.130 g, 1.11 mmol) and OsO_4 (2 µL of a 4 wt% aq. solution, cat). After 3 h at 40 °C, sodium bisulfite (0.264 g, 1.39 mmol) was added to quench the reaction. After 1 h at 40 °C, the reaction mixture was diluted with H_2O (3 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether:EtOAc 3:1 to Pet ether:EtOAc 1:3) to give dihydroxy lactam **247** (0.144 g, 81%) as a colourless oil. R_f 0.26 (Pet ether:EtOAc 1:3); ν_{max} (neat)/cm^{-1}: 3396, 2938, 1717, 1512, 1273, 1246, 1112, 905, 725; δ_H (400 MHz, $CDCl_3$) 1.71-1.97 (2H, m, CH_2), 1.99-2.13 (1H, m, CH_2), 2.17-2.34 (1H, m, CH_2), 3.75 (3H, s, OCH_3), 4.29 (1H, dd, *J* 2.3 and 4.0 Hz, CH_2C*H*N), 4.44 (1H, d, *J* 2.7 Hz, CHC*H*OH), 5.11 (2H, br s, OH), 5.30 (1H, td, *J* 2.7 and 6.5 Hz, CH_2C*H*OBz), 6.81 (2H, d, *J* 9.0 Hz, Ar H), 7.22 (2H, d, *J* 9.0 Hz, Ar H), 7.34 (2H, t, *J* 7.7 Hz, Ar H), 7.43-7.52 (1H, m, Ar H), 7.99-8.09 (2H, m, Ar H); δ_C (100 MHz, $CDCl_3$) 19.3 (CH_2), 21.8 (CH_2), 55.6 (CH_3, OCH_3), 61.0 (CH, CH_2*C*HN), 68.7 (CH, CH*C*HOH), 70.6 (CH, CH_2*C*HOBz), 82.4 (C, CH*C*OH), 114.6 (2 x CH, Ar), 119.6 (2 x CH, Ar), 128.4 (2 x CH, Ar), 129.5 (2 x CH, Ar), 129.9 (C, ArCN), 130.0 (C, Ar), 133.1 (CH, Ar), 156.9 (C, ArCO), 166.1 (C, C(O)O), 167.3 (C, C(O)N); m/z (ES) 406.1266 ([M+Na]$^+$ $C_{21}H_{21}NNaO_6$ requires 406.1267), 790 (48%), 789 (74), 407 (33), 406 (100), 384 (10).

- (±)-(3a*R*,5a*S*,8*S*,8a*S*)-5-(4-Methoxyphenyl)-2-oxido-4-oxohexahydro-4*H*-[1,3,2] dioxathiolo[4',5':2,3] benzo[1,2-*b*]azet-8-yl benzoate **248a** and **248b**



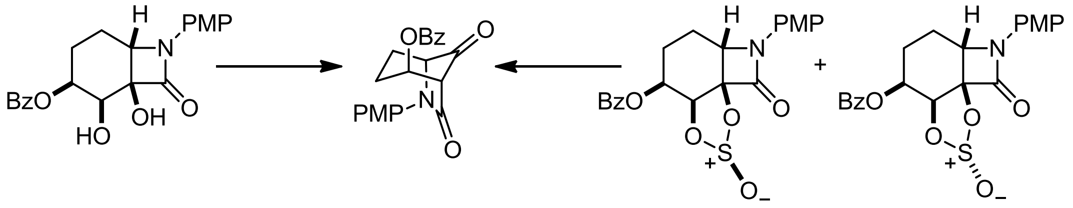
247 **248a** **248b**

Novel compounds prepared according to a literature procedure.[61] A solution of dihydroxy lactam **247** (93 mg, 0.26 mmol) in CH_2Cl_2 (1.4 mL) at 0 °C was treated with pyridine (93 µL, 1.2 mmol) and $SOCl_2$ (37 µL, 0.51 mmol). The ice bath was removed after 1 h and stirring continued for 30 min at rt. The reaction mixture was diluted with H_2O (2 mL) and extracted with CH_2Cl_2 (2 x 3 mL). The combined organic extracts were washed sequentially with HCl (3 mL of a 1 M aq. solution) and brine (3 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 7:3) to give **248a** (49 mg, 47%) as a white solid and **248b** (41 mg, 40%) as a colourless oil.

248a: mp 190-191 °C; R_f 0.59 (Pet ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1}: 2935, 1729, 1511, 1243, 1027, 834; δ_H (400 MHz, $CDCl_3$) 1.83-1.93 (1H, m, CH_2), 1.95-2.07 (1H, m, CH_2), 2.22-2.33 (1H, m, CH_2), 2.43-2.54 (1H, m, CH_2), 3.81 (3H, s, OCH_3), 4.61 (1H, dd, *J* 3.6 and 7.6 Hz, $CH_2C\mathit{H}N$), 5.19 (1H, d, *J* 3.9 Hz, $CHC\mathit{H}OS$), 5.53 (1H, ddd, *J* 2.4, 3.9 and 9.4 Hz, $CH_2C\mathit{H}OBz$), 6.93 (2H, d, *J* 9.0 Hz, Ar H), 7.32 (2H, d, *J* 9.0 Hz, Ar H), 7.46 (2H, t, *J* 7.7 Hz, Ar H), 7.59 (1H, tt, *J* 1.2 and 7.4 Hz, Ar H), 8.07-8.15 (2H, m, Ar H); δ_C (100 MHz, $CDCl_3$) 21.4 (CH_2), 21.4 (CH_2), 55.7 (CH_3, OCH_3), 59.5 (CH, $CH_2\mathit{C}HN$), 67.0 (CH, $CH_2\mathit{C}HOBz$), 81.4 (CH, $CH\mathit{C}HOS$), 90.3 (C, $CH\mathit{C}OS$), 115.0 (2 x CH, Ar), 119.6 (2 x CH, Ar), 128.6 (2 x CH, Ar), 129.1 (C, Ar), 129.4 (C, Ar), 130.2 (2 x CH, Ar), 133.7 (CH, Ar), 157.5 (C, ArCO), 158.5 (C, C(O)N), 165.6 (C, C(O)O); m/z (ES) 452.0781 ($[M+Na]^+$ $C_{21}H_{19}NNaO_7S$ requires 452.0780), 881 (13%), 453 (25), 452 (100), 258 (39), 212 (38).

248b: R_f 0.30 (Pet ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1}: 2935, 1754, 1728, 1511, 1245, 1027, 830, 820; δ_H (400 MHz, $CDCl_3$) 1.68-1.80 (1H, m, CH_2), 2.12-2.27 (3H, m, CH_2), 3.80 (3H, s, OCH_3), 4.67 (1H, t, *J* 3.9 Hz, $CH_2C\textit{H}N$), 5.40 (1H, d, *J* 3.9 Hz, $CHC\textit{H}OS$), 5.61-5.68 (1H, m, $CH_2C\textit{H}OBz$), 6.92 (2H, d, *J* 9.0 Hz, Ar H), 7.33 (2H, d, *J* 9.0 Hz, Ar H), 7.48 (2H, t, *J* 7.6 Hz, Ar H), 7.62 (1H, tt, *J* 1.2 and 7.6 Hz, Ar H), 7.95-8.04 (2H, m, Ar H); δ_C (100 MHz, $CDCl_3$) 18.0 (CH_2), 20.9 (CH_2), 55.7 (CH_3, OCH_3), 57.8 (CH, CH_2CHN), 66.3 (CH, CH_2CHOBz), 79.4 (CH, $CH\textit{C}HOS$), 89.7 (C, $CH\textit{C}OS$), 115.0 (2 x CH, Ar), 119.9 (2 x CH, Ar), 128.9 (2 x CH, Ar), 128.9 (C, Ar), 129.3 (C, Ar), 129.8 (2 x CH, Ar), 133.9 (CH, Ar), 157.4 (C, ArCO), 160.9 (C, C(O)N), 165.2 (C, C(O)O); m/z (ES) 452.0786 ($[M+Na]^+$ $C_{21}H_{19}NNaO_7S$ requires 452.0780), 484 (16%), 453 (25), 452 (100).

- (±)-(1*R*,2*S*,5*S*)-6-(4-Methoxyphenyl)-7,8-dioxo-6-azabicyclo[3.2.1]octan-2-yl benzoate **249**



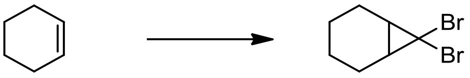
247 **249** **248a** **248b**

A novel compound prepared according to a literature procedure.[19] A solution of PPh_3 (50 mg, 0.19 mmol) and hexachloroethane (45 mg, 0.19 mmol) in CH_3CN (0.7 mL) was stirred at rt for 30 min before being added dropwise to a solution of diol **247** (49 mg, 0.13 mmol) in CH_3CN (0.3 mL). The reaction mixture was heated at reflux for 18 h, concentrated under reduced pressure and purified directly by column chromatography (Pet ether to Pet ether:EtOAc 4:1) to give bicyclic ketone **249** (36 mg, 77%) as a white solid.

A solution of cyclic sulfites **248** (66 mg, 0.15 mmol) in diphenyl ether (1.5 mL) was heated to 190 °C. After 5 h, the reaction mixture was directly purified by column chromatography (Pet ether to Pet ether:EtOAc 7:3) to give bicyclic ketone **249** (48 mg, 86%) as a white solid.

mp 163-164 °C (CH_2Cl_2); R_f 0.68 (Pet ether:EtOAc 1:1); ν_{max} (neat)/cm^{-1}: 2933, 1784, 1718, 1695, 1512, 1389, 1245, 1090, 816, 701; δ_H (400 MHz, $CDCl_3$) 2.08-2.36 (3H, m, CH_2), 2.43-2.54 (1H, m, CH_2), 3.49 (1H, dd, *J* 1.3 and 5.6 Hz, C(O)CHC(O)), 3.81 (3H, s, OCH_3), 4.42 (1H, m, C(O)CHN), 5.83-5.92 (1H, m, CH_2CHO), 6.94 (2H, d, *J* 9.1 Hz, Ar H), 7.42-7.53 (4H, m, Ar H), 7.58 (1H, tt, *J* 1.2 and 7.4 Hz, Ar H), 7.97-8.03 (2H, m, Ar H); δ_C (100 MHz, $CDCl_3$) 23.9 (CH_2), 27.6 (CH_2), 55.7 (CH_3, OCH_3), 57.9 (CH, C(O)*C*HC(O)), 67.1 (CH, CH_2*C*HN), 74.1 (CH, CH_2*C*HO), 114.8 (2 x CH, Ar), 123.0 (2 x CH, Ar), 128.7 (2 x CH, Ar), 129.5 (2 x C, ArCN and Ar), 129.9 (2 x CH, Ar), 133.7 (CH, Ar), 157.8 (C, ArCO), 165.2 (C, C(O)O), 165.7 (C, C(O)N), 202.6 (C, CH*C*(O)CH); m/z (ES) 388.1158 ($[M+Na]^+$ $C_{21}H_{19}NNaO_5$ requires 388.1161), 420 (15%), 389 (29), 388 (100).

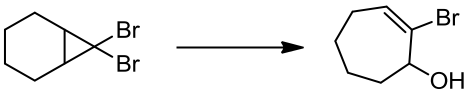
- 7,7-Dibromobicyclo[4.1.0]heptane **254**



254

A known compound[245] prepared according to a literature procedure.[109] A solution of cyclohexene (4.00 mL, 39.5 mmol) in cyclohexane (12 mL) was treated with *t*BuOK (13.3 g, 119 mmol), cooled to 0 °C and $CHBr_3$ (10.4 mL, 119 mmol) was added dropwise over 45 min. The reaction mixture was warmed to rt over 1 h. After a further 6 h, the reaction mixture was quenched with H_2O (100 mL) and extracted with hexane (2 x 100 mL). The combined organic extracts were washed with brine (150 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by fractional distillation to give dibromocyclopropane **254** (5.25 mg, 54%) as a colourless oil (lit. yield 35%). ν_{max} (neat)/cm^{-1} : 2938, 1461, 1443, 1333, 1164, 1019, 728; δ_H (300 MHz, $CDCl_3$) 1.10-1.27 (2H, m, CH_2), 1.29-1.44 (2H, m, CH_2), 1.50-1.64 (2H, m, CH_2), 1.77-1.88 (2H, m, CH_2), 1.92-2.09 (2H, m, $CHCBr_2$); *Literature data*:[245] Rf 0.72 (hexane); IR (neat)/cm^{-1}: 2936, 2852, 1462, 1444, 1334, 1165, 1020, 729 ; δ_H (300 MHz, $CDCl_3$) 1.00-1.25 (m, 2 H), 1.30-1.43 (m, 2H), 1.50-1.62 (m, 2H), 1.76-1.90 (m, 2H), 1.92-2.07 (m, 2H); δ_C (75.3 MHz, $CDCl_3$) 20.1, 20.6, 27.0, 40.7; Elemental analysis calcd (%) for $C_7H_{10}Br_2$: C 33.11, H 3.97; found: C 33.20, H 3.95.

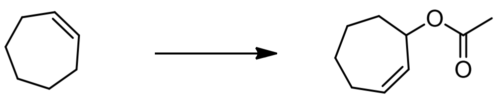
- 2-Bromocyclohept-2-enol **256**



254 **256**

A known compound[246] prepared according to a literature procedure.[110] A solution of dibromocyclopropane **254** (0.320 g, 1.31 mmol) in a 9:1 mixture of acetone:H_2O (2.3 mL) was treated with $AgClO_4.xH_2O$ (0.407 g, 1.97 mmol) which was previously dried between two pieces of filter paper. After 18 h at reflux, the reaction mixture was quenched with H_2O (5 mL), filtered through a pad of celite (eluent CH_2Cl_2). After removal of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 4:1) to give **256** (60 mg, 24%) as a yellow oil (lit. yield 80%). R_f 0.70 (Pet Ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1} : 3395, 2928, 1637, 1443, 1417, 1082, 997, 891; δ_H (400 MHz, $CDCl_3$) 1.56-1.69 (3H, m, CH_2), 1.80-1.96 (3H, m, CH_2), 2.02-2.11 (1H, m, CH_2), 2.16-2.24 (1H, m, CH_2), 2.34 (1H, br s, OH), 4.44 (1H, d, *J* 8.0 Hz, CHC*H*OH), 6.31 (1H, t, *J* 6.8 Hz, CH_2C*H*=C); δ_C (100 MHz, $CDCl_3$) 23.3 (CH_2), 25.0 (CH_2), 28.1 (CH_2), 32.5 (CH_2), 75.6 (CH, CH_2*C*HO), 129.0 (C, CH=*C*Br), 134.6 (CH, CH_2CH=CH). *Literature data*:[246] δ_H (60 MHz, CCl_4) 6.10 (t, *J* = 7 Hz, 1 H), 4.70 (s, 1 H), 4.30 (br t, *J* = 3 Hz, 1 H), 2.30-1.30 (m, 8 H); ν_{max} (neat)/cm^{-1} : 3400, 2940, 1720, 1240; m/z (EI) 192 ([M^++2], 5), 190 (M^+, 51), 174 (35), 172 (35), 150 (20), 148 (20), 111 (100), 93 (90).

- Cyclohept-2-en-1-yl acetate **258**

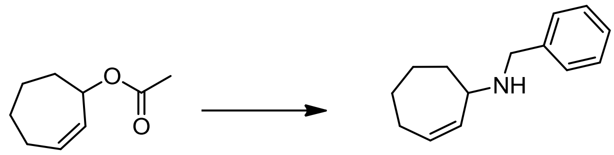


258

A known compound prepared according to the literature procedure.[112] A slurry of $Pd(OAc)_2$ (0.193 g, 0.860 mmol), *p*-benzoquinone (0.370 g, 3.42 mmol) and MnO_2 (1.78 g, 20.5 mmol) in

CH_3COOH (43 mL) was stirred at 60 °C. After 30 min, cycloheptene (2.00 mL, 17.1 mmol) was added. After 24 h at 60 °C, the reaction mixture was cooled to rt, diluted with a 1:1 mixture of pentane:Et_2O (25 mL), stirred for 30 min and filtered through a pad of celite which was washed with H_2O (2 x 25 mL) and a 1:1 mixture of pentane:Et_2O (2 x 25 mL). After separation of the organic layer, the aqueous layer was extracted with a 1:1 mixture of pentane:Et_2O (3 x 50 mL). The combined organic extracts were washed sequentially with NaOH (150 mL of a 1 M aq. solution), H_2O (150 mL) and brine (150 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:Et_2O 9:1) to give acetate **258** (1.93 g, 73%) as a pale yellow oil (lit. yield 73%). R_f 0.70 (Pet Ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1} : 2927, 1732, 1445, 1370, 1236, 1021, 677; δ_H (400 MHz, $CDCl_3$) 1.35-1.45 (1H, m, CH_2), 1.61-1.73 (3H, m, CH_2), 1.81-1.96 (2H, m, CH_2), 2.06 (3H, s, OC(O)CH_3), 2.07-2.13 (1H, m, CH_2), 2.16-2.24 (1H, m, CH_2), 5.40 (1H, d, *J* 8.8 Hz, CHC*H*O), 5.61-5.65 (1H, m, CH_2C*H*=CH), 5.78-5.85 (1H, m, CH=C*H*CHO); δ_C (100 MHz, $CDCl_3$) 21.6 (CH_3, OC(O)*C*H_3), 26.7 (CH_2), 26.8 (CH_2), 28.6 (CH_2), 33.0 (CH_2), 74.5 (CH, CH_2*C*HO), 131.7 (CH, CH_2*C*H=CH), 133.8 (CH, CH=*C*HCHO), 170.6 (C, *C*(O)O)CH_3); m/z (ES) 154 (M^+, 6%), 112 (26), 94 (26), 79 (100). *Literature data*:[112] δ_H (200 MHz, $CDCl_3$) 5.82 (m, 1 H), 5.65 (m, 1 H), 5.40 (m, 1 H), 2.05 (s, 3 H), 2.30-1.30 (m, 8 H); δ_C (100 MHz, $CDCl_3$) 170.24, 133.56, 131.38, 74.13, 32.70, 28.33, 26.48, 26.43, 21.20; Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15, Found: C, 70.18; H, 9.07.

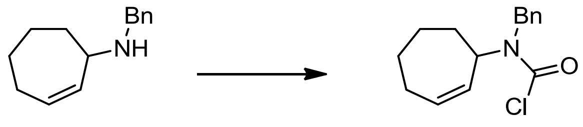
- *N*-Benzylcyclohept-2-enamine **259**



258 **259**

A known compound prepared according to a modified literature procedure.[113] A slurry of $Pd(OAc)_2$ (0.471 g, 2.10 mmol) and PPh_3 (2.75 g, 10.5 mmol) in THF (12 mL) was stirred at rt for 15 min. The slurry was treated with a solution of acetate **258** (1.62 g, 10.5 mmol) in THF (12 mL). The reaction mixture was cooled to 0 °C and benzylamine (1.71 mL, 15.7 mmol) was added over 5 min. After 10 min, the solution was heated to reflux. After 21 h, the reaction mixture was quenched with NH_4Cl (50 mL of a saturated aq. solution) and extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 1:3) to give amine **259** (0.977 g, 46%) as a yellow oil. ν_{max} (neat)/cm^{-1} : 3272, 2920, 1649, 1451, 1119, 731, 693; δ_H (400 MHz, $CDCl_3$) 1.25-1.40 (1H, m, CH_2), 1.45-1.74 (4H, m, CH_2 and NH), 1.75-1.85 (1H, m, CH_2), 1.93-2.25 (3H, m, CH_2), 3.38-3.44 (1H, m, NC*H*CH_2), 3.79, 3.84 (2H, ABq, *J* 13.0 Hz, NCH_2Ph), 5.70-5.78 (1H, m, CH_2C*H*=CH), 5.79-5.87 (1H, m, CH=C*H*CHN), 7.22-7.39 (5H, m, Ar H); δ_C (100 MHz, $CDCl_3$) 26.9 (CH_2), 28.7 (CH_2), 29.1 (CH_2), 34.2 (CH_2), 51.8 (CH_2, $NHCH_2Ph$), 58.4 (CH, CH_2*C*HN), 127.0 (CH, Ar), 128.4 (2 x CH, Ar), 128.6 (2 x CH, Ar), 131.2 (CH, CH_2CH=CH), 137.8 (CH, CH=*C*HCHN), 140.8 (C, Ar); m/z (EI) 201.1517 (M$^+$, $C_{14}H_{19}N$ requires 201.1517), 201 (36%), 172 (44), 91 (100), 79 (21). *Literature data*:[113] R_f 0.20 (Hexane:EtOAc 3:2); ν_{max} (neat)/cm^{-1} : 3315, 3085, 3062, 3024, 2922, 2850, 2802, 1944, 1869, 1734, 1652, 1605, 1495, 1453, 1394, 1351, 1310, 1267, 1200, 1123, 1074, 1028, 974, 906, 820, 788, 733, 697; δ_H (500 MHz, $CDCl_3$) 7.32 (m, 4H), 7.25 (m, 1H), 5.83 (m, 1H), 5.73 (m, 1H), 3.83 (d, 1H, *J* = 13.0 Hz), 3.77 (d, 1H, *J* = 13.0 Hz), 3.39 (m, 1H), 2.17 (m, 1H), 2.07 (m, 1H), 1.97 (m, 1H), 1.78 (m, 1H), 1.66 (m, 1H), 1.58 (m, 1H), 1.50 (m, 1H), 1.31 (m, 1H); δ_C (125 MHz, $CDCl_3$) 140.6, 137.6, 131.0, 128.4, 128.2, 126.8, 64.8, 58.2, 51.6, 46.1, 34.0, 29.0, 28.5, 26.6; m/z (EI) 201.1525 (M$^+$, $C_{14}H_{19}N$ requires 201.1517).

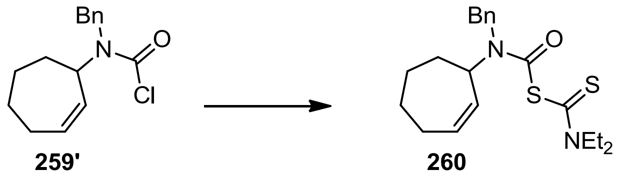
- Benzyl(cyclohept-2-en-1-yl)carbamic chloride **259’**



259 **259'**

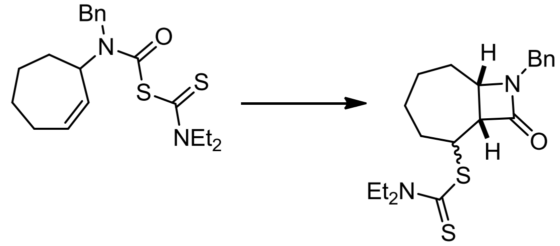
A novel compound prepared according to a literature procedure.[27] A solution of triphosgene (0.559 g, 1.88 mmol) in toluene (20 mL) was treated with pyridine (0.494 mL, 6.11 mmol) and subsequently with a solution of amine **259** (1.02 g, 5.09 mmol) in toluene (14 mL). The reaction mixture was stirred for 18 h at rt, quenched with $NaHCO_3$ (30 mL of a saturated aq. solution) and extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed sequentially with HCl (50 mL of a 0.25 M aq. solution), H_2O (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give carbamoyl chloride **259’** (1.13 g, 84%) as an orange oil. R_f 0.70 (Pet ether:EtOAc 9:1); ν_{max} (neat)/cm^{-1} : 2925, 1724, 1385, 1138, 963, 693; δ_H (400 MHz, $CDCl_3$) 1.27-1.42 (1H, m, CH_2), 1.45-1.61 (1H, m, CH_2), 1.66-2.14 (5H, m, CH_2), 2.20-2.32 (1H, m, CH_2), 4.53-5.04 (3H, m, CH_2Ph and NC*H*CH_2), 5.59-5.66 (1H, m, CH_2C*H*=CH), 5.80-5.89 (1H, m, CH=C*H*CHN), 7.27-7.41 (5H, m, Ar H); δ_C (100 MHz, $CDCl_3$) (mixture of rotamers) 26.3 (CH_2), 27.5, 27.8 (CH_2), 28.3 (CH_2), 32.4, 33.7 (CH_2), 50.4, 52.8 (CH_2, NCH_2Ph), 62.3, 63.4 (CH, CH_2*C*HN), 126.6 (2 x CH, Ar), 127.3, 127.5 (CH, Ar), 128.6, 128.7 (2 x CH, Ar), 132.1, 132.2 (CH, CH_2*C*H=CH), 132.6, 132.8 (CH, CH=*C*HCHN), 136.9, 137.23 (C*,* Ar), 149.6, 149.7 (C, NC(O)Cl); m/z (ES) 286.0952 ($[M+Na]^+$, $C_{15}H_{18}{}^{35}ClNNaO$ requires 286.0975), 288 (18%), 286 (88), 282 (100), 202 (11).

- Diethylthiocarbamic acid-[benzyl(cyclohept-2-enyl)carbamic acid]-thioanhydride **260**



A novel compound prepared according to a literature procedure.[27] A solution of carbamoyl chloride **259’** (0.971 g, 3.68 mmol) in acetone (23 mL) was treated with sodium diethyldithiocarbamate trihydrate (3.32 g, 14.7 mmol). The reaction mixture was stirred at rt for 18 h, quenched with H_2O (25 mL) and extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed with brine (40 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:Et_2O 9:1) to give carbamoyl dithiocarbamate **260** (1.21 g, 87%) as a yellow oil. R_f 0.33 (Pet ether:EtOAc 85:15); ν_{max} (neat)/cm^{-1} : 2929, 1664, 1488, 1418, 1269, 1188, 961, 725; δ_H (400 MHz, $CDCl_3$) (mixture of rotamers) 1.17-1.41 (7H, m, CH_2 and $CH_2C\mathit{H}_3$), 1.45-1.57 (1H, m, CH_2), 1.62-1.97 (4H, m, CH_2), 1.98-2.29 (2H, m, CH_2), 3.61-3.94 (2H, m, $C\mathit{H}_2CH_3$), 4.03 (2H, br s, $CH_2C\mathit{H}N$ and CH_2Ph), 4.42-5.03 (3H, m, $C\mathit{H}_2CH_3$ and CH_2Ph), 5.52-5.90 (2H, m, CH=CH), 7.31 (5H, br s, Ar H); δ_C (100 MHz, $CDCl_3$) (mixture of rotamers) 11.2 (CH_3, $CH_2\mathit{C}H_3$), 13.3 (CH_3, $CH_2\mathit{C}H_3$), 26.4 (CH_2), 27.7 (CH_2), 28.3 (CH_2), 32.4, 33.9 (CH_2), 48.7 (CH_2, CH_2Ph), 49.8 (CH_2, $\mathit{C}H_2CH_3$), 51.1 (CH_2, $\mathit{C}H_2CH_3$), 60.2, 61.7 (CH, $CH_2\mathit{C}HN$), 126.4 (CH, Ar), 127.2 (2 x CH, Ar), 128.5 (2 x CH, Ar), 132.2 (CH, $CH_2\mathit{C}H$=CH), 132.6 (CH, CH=CHCHN), 137.7, 138.3 (C, Ar), 162.2, 162.7 (C, C(O)N), 184.6, 185.6 (C, C(S)S); m/z (ES) 399.1546 ($[M+Na]^+$ $C_{20}H_{28}N_2NaOS_2$ requires 399.1541), 399 (100%).

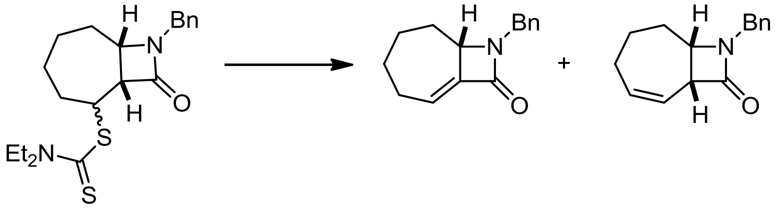
- (±)-(1*R*,7*S*)-8-Benzyl-9-oxo-8-aza-bicyclo[5.2.0]nonan-2-yl **261**



260 **261**

Novel compounds prepared according to a literature procedure.[26] A solution of carbamoyl dithiocarbamate **260** (0.872 g, 2.32 mmol) in cyclohexane (23 mL) was degassed for 10 min and irradiated with a 500 W lamp which generated enough heat to bring the solvent to reflux. After 5 h, the solvent was removed under reduced pressure and the crude product obtained was purified by column chromatography (Pet ether to Pet ether:EtOAc 3:2) to give lactam **261** (0.794 g, 91%) as a pale yellow oil. R_f 0.35 (Pet ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1} : 2924, 1737, 1413, 1265, 1205, 982, 698; δ_H (400 MHz, $CDCl_3$) (as a mixture of isomers) 1.22-1.31 (6H, m, $CH_2C\mathit{H}_3$), 1.32-2.21 (8H, m, CH_2), 3.63-3.86 (4H, m, $C\mathit{H}_2CH_3$, C(O)C*H*CH and $CH_2C\mathit{H}S$), 3.86-4.21 (4H, m, $C\mathit{H}_2CH_3$, CH_2Ph and NC*H*CH_2), 4.55-4.86 (1H, m, CH_2Ph), 7.21-7.37 (5H, m, Ar H); δ_C (100 MHz, $CDCl_3$) (as a mixture of isomers) 11.6 (CH_3, CH_2CH_3), 12.5 (CH_3, $CH_2\mathit{C}H_3$), 23.1 (CH_2), 28.6, 29.2 (CH_2), 30.1 (CH_2), 34.2 (CH_2), 44.1, 44.3 (CH_2, CH_2Ph), 46.8 (CH_2, $\mathit{C}H_2CH_3$), 49.3 (CH_2, $\mathit{C}H_2CH_3$), 49.8 (CH, $CH_2\mathit{C}HS$), 55.0, 55.6 (CH, $CH_2\mathit{C}HN$), 57.2, 58.1 (CH, CH*C*HC(O)), 127.6, 127.6 (CH, Ar), 128.2, 128.3 (2 x CH, Ar), 128.7 (2 x CH, Ar), 136.6, 136.7 (C, Ar), 167.3, 168.1 (C, C(O)N), 193.8, 194.5 (C, C(S)S); m/z (ES) 399.1558 ([M+Na]$^+$, $C_{20}H_{28}N_2NaOS_2$ requires 399.1541), 399 (100%).

- 8-Benzyl-8-azabicyclo[5.2.0]non-1-en-9-one **262** and (±)-(1*R*,7*S*)-8-benzyl-8-azabicyclo[5.2.0] non-2-en-9-one **263**



261 **262** **263**

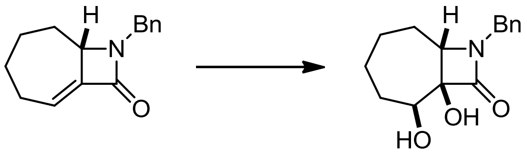
Novel compounds prepared according to a literature procedure.[29] A solution of lactam **261** (0.450 g, 1.19 mmol) in Ph$_2$O (9.2 mL) was heated to reflux. After 3 h, the reaction mixture was directly purified by column chromatography (Pet ether to Pet ether:EtOAc 9:1) to give conjugated lactam **262** (0.124 g, 46%) as a yellow solid and non-conjugated lactam **263** (75 mg, 28%) as a brown oil.

262: mp 49-53 °C; R$_f$ 0.34 (Pet Ether:Et$_2$O 2:3); ν_{max} (neat)/cm^{-1} : 2928, 1735, 1708, 1385, 1266, 1069, 694; δ_H (400 MHz, CDCl$_3$) 1.11-1.37 (3H, m, CH$_2$), 1.81-1.87 (1H, m, CH$_2$), 1.90-1.99 (2H, m, CH$_2$), 2.05-2.14 (1H, m, CH$_2$), 2.29-2.36 (1H, m, CH$_2$), 3.81-3.84 (1H, m, NC*H*CH$_2$), 4.30, 4.65 (2H, ABq, *J* 15.2 Hz, CH$_2$Ph), 6.40 (1H, ddd, *J* 1.4, 4.0 and 8.2 Hz, CH$_2$C*H*=C), 7.28-7.37 (5H, m, Ar H); δ_C (100 MHz, CDCl$_3$) 26.9 (CH$_2$), 27.5 (CH$_2$), 28.7 (CH$_2$), 31.5 (CH$_2$), 44.9 (CH$_2$, CH$_2$Ph), 60.4 (CH, CH$_2$*C*HN), 126.3 (CH, CH$_2$*C*H=C), 127.7 (2 x CH, Ar), 128.3 (2 x CH, Ar), 128.7 (CH, Ar), 136.3 (C, Ar), 145.6 (C, CH=*C*C(O)), 162.8 (C, C(O)N); m/z (ES) 228.1383 ([M+H]$^+$ C$_{15}$H$_{18}$NO requires 228.1383), 455 (14%), 279 (10), 228 (100).

263: R$_f$ 0.38 (Pet Ether:Et$_2$O 2:3); ν_{max} (neat)/cm^{-1} : 2929, 1735, 1397, 697; δ_H (400 MHz, CDCl$_3$) 1.36-1.45 (1H, m, CH$_2$), 1.51-1.62 (2H, m, CH$_2$), 1.82-1.89 (1H, m, CH$_2$), 2.11-2.16 (2H, m, CH$_2$), 3.59-3.65 (1H, m, CHC*H*C(O)), 3.95-4.00 (1H, m, CH$_2$C*H*N), 4.09, 4.59 (2H, ABq, *J* 15.1 Hz, CH$_2$Ph), 5.58-5.70 (2H, m, CH=CH), 7.25-7.37 (5H, m, Ar H); δ_C (100 MHz, CDCl$_3$) 19.2 (CH$_2$), 27.6 (CH$_2$), 28.1 (CH$_2$), 44.3 (CH$_2$, CH$_2$Ph), 53.3 (CH, CH$_2$*C*HN), 55.0 (CH, =CH*C*HC(O)), 121.4 (CH, CH$_2$*C*H=CH), 127.8 (CH, Ar), 128.4 (2 x CH, Ar), 128.5 (CH, CH=*C*HCHN), 128.9 (2 x CH, Ar), 136.2

(C, Ar), 168.6 (C, C(O)N); m/z (ES) 250.1215 ($[M+Na]^+$, $C_{15}H_{17}NNaO$ requires 250.1208), 251 (10%), 250 (100).

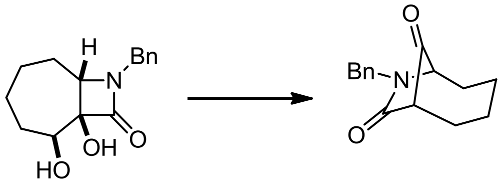
- (±)-(1*R*,2*S*,7*S*)-8-Benzyl-1,2-dihydroxy-8-azabicyclo[5.2.0]nonan-9-one **264**



262 **264**

A novel compound prepared according to a literature procedure.[56] A solution of lactam **262** (0.124 g, 0.55 mmol) in a 5:5:2 mixture of H_2O:acetone:*t*BuOH (3.1 mL) was treated with NMO (0.153 g, 1.31 mmol) and OsO_4 (3 mg, 0.01 mmol). After 18 h at 40 °C, sodium bisulfite was added (0.314 g, 1.65 mmol) to quench the reaction. After 45 min at 40 °C, the reaction mixture was diluted with brine (5 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether:EtOAc 3:1 to EtOAc) to give dihydroxy lactam **264** (0.106 g, 74%) as a colourless oil. R_f 0.15 (Pet Ether:EtOAc 1:1); ν_{max} (neat)/cm^{-1} : 3361, 2927, 1722, 1412, 1248, 1063, 981, 727, 697; δ_H (400 MHz, $CDCl_3$) 1.13-1.45 (3H, m, CH_2), 1.52-1.83 (3H, m, CH_2), 1.88-1.95 (1H, m, CH_2), 2.04-2.14 (1H, m, CH_2), 3.51-3.54 (1H, m, NC*H*CH_2), 4.12, 4.56 (2H, ABq, *J* 15.2 Hz, CH_2Ph), 4.17 (1H, d, *J* 10.0 Hz, CH_2C*H*OH), 4.37 (1H, br s, O*H*), 5.26 (1H, br s, O*H*), 7.28-7.37 (5H, m, Ar H); δ_C (100 MHz, $CDCl_3$) 23.8 (CH_2), 27.3 (CH_2), 29.7 (CH_2), 32.0 (CH_2), 44.2 (CH_2, CH_2Ph), 63.8 (CH, CH_2*C*HN), 71.5 (CH, CH_2*C*HOH), 87.5 (C, CH*C*OH), 127.8 (CH, Ar), 128.3 (2 x CH, Ar), 128.8 (2 x CH, Ar), 135.2 (C, Ar), 170.9 (C, C(O)N); m/z (ES) 284.1269 ($[M+Na]^+$ $C_{15}H_{19}NNaO_3$ requires 284.1263), 285 (6%), 284 (100).

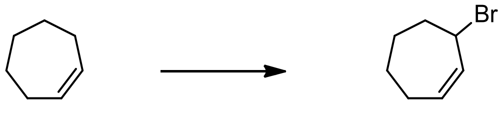
- (±)-(*1R,6S*)-7-Benzyl-7-azabicyclo[4.2.1]nonane-8,9-dione **265**



264 **265**

A novel compound prepared according to a literature procedure.[19] A solution of PPh_3 (0.158 g, 0.603 mmol) and C_2Cl_6 (0.143 g, 0.603 mmol) in CH_3CN (1 mL) was stirred at rt for 30 min and then added dropwise over 2 min onto a solution of dihydroxy lactam **264** (0.105 g, 0.402 mmol) in CH_3CN (1.7 mL). After heating to reflux for 18 h, the reaction mixture was concentrated under reduced pressure and directly purified by column chromatography (Pet ether to Pet ether:EtOAc 3:2) to give bicyclic ketone **265** (76 mg, 78%) as a colourless oil. R_f 0.53 (Pet Ether:EtOAc 3:2); ν_{max} (neat)/cm^{-1} : 2930, 1767, 1685, 1419, 1244, 699; δ_H (300 MHz, $CDCl_3$) 1.33-1.62 (4H, m, CH_2), 1.70-2.11 (4H, m, CH_2), 3.02 (1H, dd, *J* 2.9 and 7.0 Hz, C(O)CHC(O)), 3.85 (1H, app t, *J* 2.9 Hz, CH_2C*H*N), 4.04, 4.15 (2H, ABq, *J* 14.8 Hz, CH_2Ph), 7.20-7.40 (5H, m, Ar H); δ_C (100 MHz, $CDCl_3$) 22.9 (CH_2), 24.7 (CH_2), 27.2 (CH_2), 27.7 (CH_2), 43.8 (CH_2, CH_2Ph), 50.9 (CH, C(O)*C*HC(O)), 65.3 (CH, CH_2*C*HN), 128.2 (CH, Ar), 128.6 (2 x CH, Ar), 129.1 (2 x CH, Ar), 135.4 (C, Ar), 173.0 (C, C(O)N), 207.8 (C, CH*C*(O)CH); m/z (ES) 244.1330 ($[M+H]^+$ $C_{15}H_{18}NO_2$ requires 244.1332), 487 (65%), 244 (100).

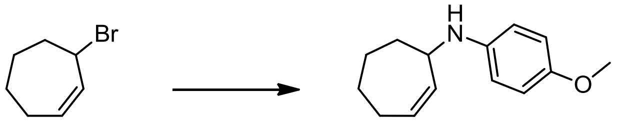
- 3-Bromocycloheptene **266**



266

A known compound[247] prepared according to the literature procedure.[115] A mixture of cycloheptene (10.3 g, 107 mmol), NBS (7.61 g, 42.7 mmol) and benzoyl peroxide (70%, 0.125 g, 0.52 mmol) in CCl_4 (36 mL) was heated to reflux. After 1.5 h, the reaction mixture was allowed to cool to rt and filtered (eluent CH_2Cl_2). The filtrate was concentrated under reduced pressure and purified *via* Kugelrohr distillation (0.8 mmHg, 115 °C) to give **266** (4.15 g, 56%) as a colourless oil (lit. yield 58%). δ_H (400 MHz, $CDCl_3$) 1.45-1.54 (1H, m, CH_2), 1.74-1.91 (2H, m, CH_2), 1.96-2.09 (2H, m, CH_2), 2.15-2.28 (3H, m, CH_2), 4.92-4.96 (1H, m, $CH_2C\textit{H}Br$), 5.73-5.96 (2H, m, CH=CH); δ_C (100 MHz, $CDCl_3$) 26.6 (CH_2), 26.8 (CH_2), 28.5 (CH_2), 36.5 (CH_2), 54.0 (CH, *C*HBr), 132.5 (CH, $CH_2C\textit{H}$=CH), 135.7 (CH, CH=C*H*CHBr). *Literature data*:[247] ν_{max} (neat)/cm^{-1}: 3025, 2928, 1642, 1444, 763; δ_H (300 MHz, $CDCl_3$) 5.92 (dd, *J* = 11.5, 6.0 Hz, 1H, H-2), 5.83 (dt, *J* = 11.4, 5.7 Hz, 1H, H-1), 4.93 (t (distorted), *J* = 6.0 Hz, 1 H, H-3), 2.27-1.40 (m, 8 H, allylic, homoallylic, and H-5); δ_C (75 MHz, $CDCl_3$) 135.27, 132.22, 53.56, 36.24, 28.22, 26.58, 26.36.

- *N*-(4-Methoxyphenyl)cyclohept-2-enamine **267**

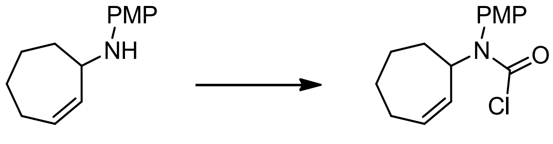


266 **267**

A novel compound prepared according to a literature procedure.[27] A solution of 4-methoxyaniline (7.35 g, 59.7 mmol) in CH_3CN (60 mL) was treated with 3-bromocycloheptene **266** (3.87 g, 22.1 mmol) and K_2CO_3 (3.36 g, 24.3 mmol). After 10 h at rt, the reaction mixture was quenched with H_2O (60 mL) and extracted with Et_2O (2 x 60 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Hexane to Hexane:EtOAc 96:4) to give amine **267** (3.57 g, 74%) as a brown oil. R_f 0.76 (Pet ether:EtOAc 9:1); ν_{max} (neat)/cm^{-1}: 3406, 2920, 1509, 1237, 1029, 812; δ_H (400 MHz, $CDCl_3$) 1.34-1.44 (1H, m, CH_2), 1.51-1.60 (1H, m, CH_2), 1.65-1.79 (2H, m, CH_2), 1.92-2.04 (2H, m, CH_2), 2.15-2.27 (2H, m, CH_2), 3.75 (3H, s, OCH_3), 3.80 (1H, br s, NH), 4.04 (1H, br d, *J* 10.0 Hz, $CH_2C\textit{H}N$), 5.69 (1H, d, *J* 11.6 Hz, $CH_2C\textit{H}$=CH), 5.82-5.88 (1H, m, CH=C*H*CHN), 6.61 (2H, d, *J* 9.0 Hz, Ar H), 6.79 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 26.7 (CH_2), 28.7 (CH_2), 28.8 (CH_2), 33.9 (CH_2), 55.2 (CH_3, OCH_3), 55.8 (CH, $CH_2\textit{C}HN$), 115.0 (2 x CH, Ar), 115.3 (2 x CH, Ar), 131.3 (CH, CH=*C*HCHN), 137.3 (CH,

CH_2*C*H=CH), 141.1 (C, ArCN), 152.3 (C, ArCO); m/z (EI) 217.1470 (M^+ $C_{14}H_{19}NO$ requires 217.1467), 218 ($[M+H]^+$, 13%), 217 (100), 188 (33), 123 (38), 108 (15).

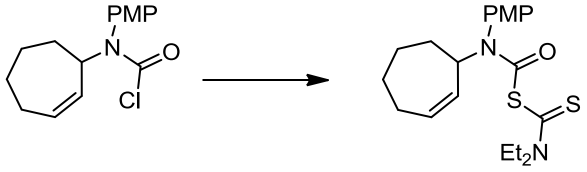
- Cyclohept-2-en-1-yl(4-methoxyphenyl)carbamic chloride **268**



267 **268**

A novel compound prepared according to a literature procedure.[27] A solution of triphosgene (1.79 g, 6.02 mmol) in toluene (100 mL) was treated with pyridine (1.58 mL, 19.6 mmol) and subsequently with a solution of amine **267** (3.53 g, 16.3 mmol) in toluene (25 mL). The reaction mixture was stirred for 18 h at rt, quenched with $NaHCO_3$ (100 mL of a saturated aq. solution) and extracted with Et_2O (2 x 100 mL). The combined organic extracts were washed sequentially with HCl (100 mL of a 0.25 M aq. solution), H_2O (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give carbamoyl chloride **268** (1.85 g, 100%) as a white solid. mp 49-51 °C; R_f 0.56 (Pet ether:EtOAc 9:1); ν_{max} (neat)/cm^{-1}: 2939, 1725, 1511, 1380, 1209, 1036, 834, 733; δ_H (400 MHz, $CDCl_3$) 1.21-1.31 (1H, m, CH_2), 1.52-1.73 (3H, m, CH_2), 1.89-2.07 (3H, m, CH_2), 2.08-2.16 (1H, m, CH_2), 3.81 (3H, s, OCH_3), 4.97 (1H, d, *J* 8.8 Hz, CH_2C*H*N), 5.75-5.83 (2H, m, CH=CH), 6.90 (2H, d, *J* 9.0 Hz, Ar H), 7.12 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 26.3 (CH_2), 27.9 (CH_2), 28.2 (CH_2), 33.2 (CH_2), 55.5 (CH_3, OCH_3), 62.6 (CH, CH_2*C*HN), 114.3 (2 x CH, Ar), 130.6 (2 x CH, Ar), 132.1 (CH, CH_2*C*H=CH), 132.6 (CH, CH=*C*HCHN), 132.9 (C, ArCN), 149.5 (C, ArCO), 159.6 (C, NC(O)Cl); m/z (EI) 279.1017 (M^+ $C_{15}H_{18}{}^{35}ClNO_2$ requires 279.1026), 185 (6%), 149 (100), 134 (70), 106 (32), 79 (35).

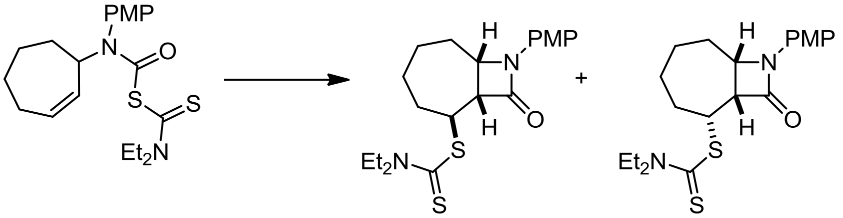
- Diethylthiocarbamic acid-[(4-methoxyphenyl)(cyclohept-2-enyl)carbamic acid]-thioanhydride **269**



268 **269**

A novel compound prepared according to a literature procedure.[27] A solution of carbamoyl chloride **268** (4.40 g, 15.7 mmol) in acetone (120 mL) was treated with sodium diethyldithiocarbamate trihydrate (14.2 g, 62.9 mmol). The reaction mixture was heated at reflux for 18 h quenched with H_2O (100 mL) and extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 4:1) to give dithiocarbamate **269** (5.21 g, 84%) as a pale yellow solid. mp 86-89 °C (CH_2Cl_2); R_f 0.54 (Pet ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1}: 2929, 1678, 1506, 1417, 1239, 1198, 839, 794, 734; δ_H (400 MHz, $CDCl_3$) 1.21 (3H, t, *J* 7.2 Hz, $CH_2C\mathit{H_3}$), 1.31 (3H, t, *J* 7.2 Hz, $CH_2C\mathit{H_3}$), 1.44-1.71 (4H, m, CH_2), 1.87-1.92 (2H, m, CH_2), 1.97-2.14 (2H, m, CH_2), 3.77 (2H, q, *J* 7.2 Hz, $C\mathit{H_2}CH_3$), 3.82 (3H, s, OCH_3), 3.99 (2H, q, *J* 7.2 Hz, $C\mathit{H_2}CH_3$), 5.17 (1H, d, *J* 11.2 Hz, $CH_2C\mathit{H}N$), 5.69-5.79 (2H, m, CH=CH), 6.88 (2H, d, *J* 8.6 Hz, Ar H), 7.19 (2H, d, *J* 8.6 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 11.3 (CH_3, $CH_2\mathit{C}H_3$), 13.6 (CH_3, $CH_2\mathit{C}H_3$), 26.4 (CH_2), 28.0 (CH_2), 28.4 (CH_2), 33.5 (CH_2), 46.8 (CH_2, $\mathit{C}H_2CH_3$), 50.4 (CH_2, $\mathit{C}H_2CH_3$), 55.6 (CH_3, OCH_3), 59.9 (CH, $CH_2\mathit{C}HN$), 114.5 (2 x CH, Ar), 130.3 (C, ArCN), 131.9 (2 x CH, Ar), 132.1 (CH, $CH_2\mathit{C}H$=CH), 133.3 (CH, CH=*C*HCHN), 160.1 (C, ArCO), 164.1 (C, C(O)N), 185.6 (C, SC(S)); m/z (ES) 415.1482 ($[M+Na]^+$ $C_{20}H_{28}N_2NaO_2S_2$ requires 415.1490), 416 (15%), 415 (100).

- 8-(4-Methoxyphenyl)-9-oxo-8-aza-bicyclo[5.2.0]nonan-2-yl diethyldithiocarbamate **270** and **271**



269 **270** **271**

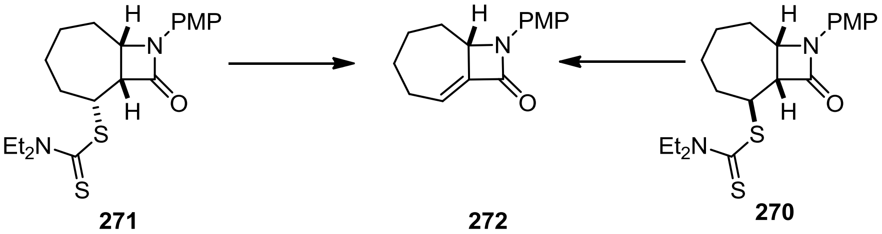
Novel compounds prepared according to a modified literature procedure.[26] A solution of dithiocarbamate **269** (2.02 g, 5.15 mmol) in chlorobenzene (52 mL) was degassed for 10 min and irradiated with a 500 W lamp which generated enough heat to bring the solution to reflux. After 2 h, the solvent was removed under reduced pressure and the crude product obtained was purified by column chromatography (Pet ether to Pet ether:EtOAc 9:1) to give (±)-(1*S*,2*R*,7*R*) lactam **270** (0.779 g, 39%) and (±)-(1*S*,2*R*,7*S*) lactam **271** (0.587 g, 29%) as off-white solids.

270: mp 113-115 °C (CH_2Cl_2); R_f 0.28 (Pet ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1}: 2929, 1728, 1513, 1298, 1247, 1196, 916, 818; δ_H (400 MHz, $CDCl_3$) 1.23-1.33 (6H, m, CH_3CH_2), 1.38-2.40 (8H, m, CH_2), 3.69-4.13 (8H, m, CH_2CH_3, OCH_3 and CHC*H*C(O)), 4.33 (1H, br s, CH_2CHS), 4.78 (1H, br s, CH_2CHN), 6.86 (2H, d, *J* 9.0 Hz, Ar H), 7.33 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 11.5 (CH_3, CH_2CH_3), 12.5 (CH_3, CH_2CH_3), 23.4 (CH_2), 28.5 (CH_2), 28.8 (2 x CH_2), 46.7 (CH_2, CH_2CH_3), 49.0 (CH, CH_2CHS), 49.3 (CH_2, CH_2CH_3), 55.3 (CH_3, OCH_3), 56.1 (CH, CH_2CHN), 56.5 (CH, CH*C*HC(O)), 114.2 (2 x CH, Ar), 118.4 (2 x CH, Ar), 130.9 (C, ArCN), 155.8 (C, ArCO), 164.4 (C, C(O)N), 193.4 (C, SC(S)); m/z (ES) 415.1482 ([M+Na]$^+$ $C_{20}H_{28}N_2NaO_2S_2$ requires 415.1490), 416 (12%), 415 (100), 266 (11).

271: mp 108-110 °C (CH_2Cl_2); R_f 0.35 (Pet ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1}: 2928, 1717, 1509, 1238, 1138, 828; δ_H (400 MHz, $CDCl_3$) 1.21-1.42 (7H, m, CH_3CH_2 and CH_2), 1.58-1.67 (2H, m, CH_2), 1.76-1.94 (3H, m, CH_2), 2.19 (1H, d, *J* 12.8 Hz, CH_2), 2.44-2.57 (1H, m, CH_2), 3.68-3.83 (5H, m, CH_2CH_3 and OCH_3), 3.94-4.12 (3H, m, CH_2CH_3 and CHC*H*C(O)), 4.26 (1H, d, *J* 11.6 Hz,

CH_2CHS), 4.41 (1H, t, *J* 4.8 Hz, CH_2CHN), 6.87 (2H, d, *J* 9.2 Hz, Ar H), 7.34 (2H, d, *J* 9.2 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 11.6 (CH_3, CH_2CH_3), 12.5 (CH_3, CH_2CH_3), 22.6 (CH_2), 28.4 (CH_2), 30.0 (CH_2), 34.2 (CH_2), 46.8 (CH_2, CH_2CH_3), 49.3 (CH_2, CH_2CH_3), 49.5 (CH, CH_2CHS), 55.4 (CH_3, OCH_3), 55.6 (CH, CH_2CHN), 57.4 (CH, CHCHC(O)), 114.4 (2 x CH, Ar), 118.4 (2 x CH, Ar), 131.3 (C, ArCN), 155.9 (C, ArCO), 165.3 (C, C(O)N), 194.3 (C, SC(S)); m/z (ES) 415.1495 ($[M+Na]^+$ $C_{20}H_{28}N_2NaO_2S_2$ requires 415.1490), 416 (18%), 415 (100), 266 (8), 244 (7).

- 8-(4-Methoxyphenyl)-8-azabicyclo[5.2.0]non-1-en-9-one **272**



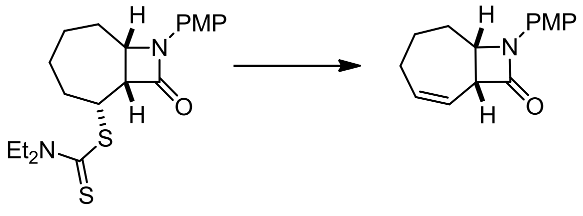
A novel compound prepared according to a modified literature procedure[39] and the literature procedure.[29]

A solution of lactam **271** (0.112 g, 0.285 mmol) in THF (2.9 mL) was cooled to -78 °C and treated with methyl iodide (20 µL, 0.31 mmol). The reaction mixture was stirred at -78 °C for 1.5 h, LHMDS (0.31 mL of a 1.0 M solution in THF, 0.31 mmol) was added over 2 min. After 7 h at -78 °C, the solvent was removed under reduced pressure and the crude product obtained was purified by column chromatography (Pet ether to Pet ether:EtOAc 7:3) to give lactam **272** (64 mg, 93%) as a white solid.

A solution of lactam **270** (0.412 g, 1.05 mmol) in diphenyl ether (10.5 mL) was heated to reflux. After 2.5 h, the reaction mixture was directly purified by column chromatography (Pet ether to Pet ether:EtOAc 4:1) to give lactam **272** (0.217 g, 85%) as a white solid and non-conjugated lactam **273** (26 mg, 10%) as a light green solid.

mp 112-114 °C (CH_2Cl_2); R_f 0.64 (Pet ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1}: 2930, 2840, 1731, 1712, 1509, 1242, 1126, 1028, 826, 809; δ_H (400 MHz, $CDCl_3$) 1.25-1.41 (2H, m, CH_2), 1.50-1.61 (1H, m, CH_2), 1.88-1.95 (1H, m, CH_2), 2.03-2.11 (1H, m, CH_2), 2.16-2.25 (1H, m, CH_2), 2.35-2.43 (1H, m, CH_2), 2.46-2.52 (1H, m, CH_2), 3.78 (3H, s, OCH_3), 4.34-4.37 (1H, m, CH_2CHN), 6.52 (1H, ddd, *J* 1.6, 4.2 and 8.2 Hz, $CH_2CH{=}C$), 6.86 (2H, d, *J* 8.8 Hz, Ar H), 7.35 (2H, d, *J* 8.8 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 27.2 (CH_2), 27.7 (CH_2), 29.0 (CH_2), 31.4 (CH_2), 55.7 (CH_3, OCH_3), 61.0 (CH, CH_2CHN), 114.6 (2 x CH, Ar), 118.0 (2 x CH, Ar), 127.9 (CH, $CH_2CH{=}C$), 132.1 (C, ArCN), 144.6 (C, $CH{=}CC(O)$), 156.0 (C, ArCO), 159.7 (C, C(O)N); m/z (ES) 266.1149 ($[M+Na]^+$ $C_{15}H_{17}NNaO_2$ requires 266.1157), 298 (7%), 282 (13), 267 (4), 266 (100), 244 (5).

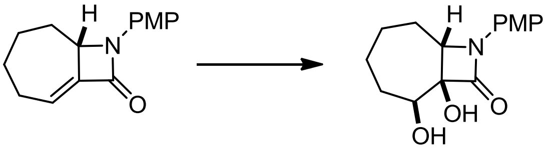
- (±)-(1*R*,7*S*)-8-(4-Methoxyphenyl)-8-azabicyclo[5.2.0]non-2-en-9-one **273**



271 **273**

A novel compound prepared according to a literature procedure.[29] A solution of lactam **271** (0.106 g, 0.270 mmol) in diphenyl ether (2.7 mL) was heated to reflux. After 2.5 h, the reaction mixture was directly purified by column chromatography (Pet ether to Pet ether:EtOAc 7:3) to give lactam **273** (59 mg, 89%) as a light green solid. mp 94-96 °C; R_f 0.54 (Pet ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1}: 2939, 1723, 1510, 1382, 1243, 1030, 825; δ_H (400 MHz, $CDCl_3$) 1.50-1.80 (3H, m, CH_2), 2.15-2.29 (3H, m, CH_2), 3.76 (3H, s, OCH_3), 4.05-4.08 (1H, m, $=CHCHC(O)$), 4.15-4.20 (1H, m, CH_2CHN), 5.64-5.72 (2H, m, $CH{=}CH$), 6.85 (2H, d, *J* 9.0 Hz, Ar H), 7.30 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 19.2 (CH_2), 27.2 (CH_2), 28.2 (CH_2), 52.7 (CH, $=CHCHC(O)$), 55.2 (CH, CH_2CHN), 55.6 (CH_3, OCH_3), 114.5 (2 x CH, Ar), 118.5 (2 x CH, Ar), 121.0 (CH, $CH_2CH{=}CH$), 128.9 (CH, $CH{=}CHCH$), 131.2 (C, ArCN), 156.0 (C, ArCO), 165.5 (C, C(O)N); m/z (ES) 266.1156 ($[M+Na]^+$ $C_{15}H_{17}NNaO_2$ requires 266.1157), 415 (17%), 298 (10), 267 (5), 266 (100).

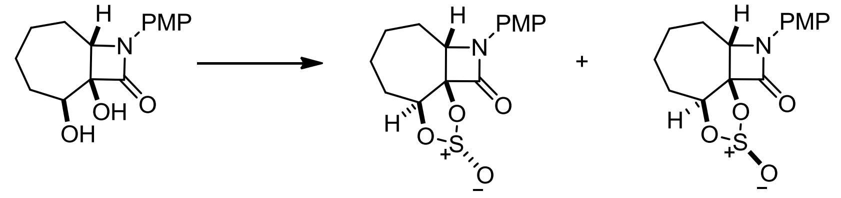
- (±)-(1*S,*2*R,*7*R*)-8-(4-Methoxyphenyl)-1,2-dihydroxy-8-azabicyclo[5.2.0]nonan-9-one **274**



272 **274**

A novel compound prepared according to a literature procedure.[56] A solution of lactam **272** (0.309 g, 1.27 mmol) in a 5:5:2 mixture of H_2O:acetone:*t*BuOH (7.0 mL) was treated with NMO (0.402 g, 3.43 mmol) and OsO_4 (10 µL of a 4 wt% aq. solution, cat). After 18 h at 40 °C, sodium bisulfite was added (0.0.724 g, 3.81 mmol) to quench the reaction. After 1.5 h at 40 °C, the reaction mixture was diluted with brine (10 mL) and extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether:EtOAc 3:1 to Pet ether:EtOAc 1:3) to give diol **274** (0.272 g, 77%) as a white solid. mp 168-170 °C (CH_2Cl_2); R_f 0.24 (Pet ether:EtOAc 2:3); ν_{max} (neat)/cm^{-1}: 3436, 3349, 2925, 2849, 1721, 1512, 1248, 1108, 973, 821; δ_H (400 MHz, $CDCl_3$) 1.30-1.49 (3H, m, CH_2), 1.70-1.90 (3H, m, CH_2), 2.04-2.14 (1H, m, CH_2), 2.43 (1H, br s, CH_2), 3.11 (1H, br s, OH), 3.78 (3H, s, OCH_3), 4.08 (1H, dd, *J* 4.8 and 10.8 Hz, $CH_2C\mathit{H}N$), 4.10-4.26 (2H, dd and br s, *J* 1.6 and 10.4 Hz, $CH_2C\mathit{H}OH$ and OH), 6.85 (2H, d, *J* 8.8 Hz, Ar H), 7.28 (2H, d, *J* 8.8 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 24.3 (CH_2), 27.3 (CH_2), 29.5 (CH_2), 31.7 (CH_2), 55.7 (CH_3, OCH_3), 64.4 (CH, CH_2CHN), 72.1 (CH, $CH_2\mathit{C}HOH$), 86.6 (C, $CH\mathit{C}OH$), 114.6 (2 x CH, Ar), 119.6 (2 x CH, Ar), 130.3 (C, ArCN), 156.7 (C, ArCO), 167.7 (C, C(O)N); m/z (ES) 300.1209 ([M+Na]$^+$ $C_{15}H_{19}NNaO_4$ requires 300.1212), 301 (10%), 300 (100).

- (±)-(3a*R,*5a*S,*9a*S*)-5-(4-Methoxyphenyl)hexahydro-[1,3,2]dioxathiolo[4',5':2,3] cyclohepta[1,2-*b*]azet-4(5H)-one 2-oxide **275a** and **275b**



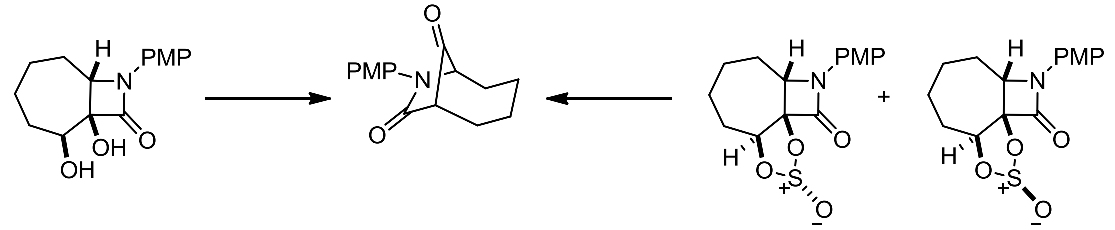
274 **275a** **275b**

Novel compounds prepared according to a literature procedure.[61] A solution of diol **274** (0.149 g, 0.537 mmol) in CH_2Cl_2 (2.8 mL) at 0 °C was treated with pyridine (195 µL, 2.42 mmol) and $SOCl_2$ (78 µL, 1.07 mmol). The ice bath was removed after 30 min and stirring continued at rt for 4 h. The reaction mixture was diluted with H_2O (2.5 mL) and extracted with CH_2Cl_2 (2 x 4 mL). The combined organic extracts were washed sequentially with HCl (5 mL of a 1 M aq. solution) and brine (5 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 7:3) to give **275a** (65 mg, 38%) and **275b** (86 mg, 49%) as white solids.

275a: mp 147-148 °C (CH_2Cl_2); R_f 0.48 (Pet ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1}: 2940, 1747, 1510, 1245, 1220, 948, 930, 836, 655; δ_H (300 MHz, $CDCl_3$) 1.46-1.68 (3H, m, CH_2), 1.75-1.96 (2H, m, CH_2), 2.02-2.27 (3H, m, CH_2), 3.79 (3H, s, OCH_3), 4.01 (1H, dd, *J* 3.9 and 7.8 Hz, CH_2C*H*N), 5.35 (1H, dd, *J* 3.6 and 7.2 Hz, CH_2C*H*OS), 6.88 (2H, d, *J* 9.0 Hz, Ar H), 7.33 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 22.4 (CH_2), 23.7 (CH_2), 27.6 (CH_2), 28.8 (CH_2), 55.6 (CH_3, OCH_3), 64.3 (CH, CH_2*C*HN), 82.1 (CH, CH_2*C*HOS), 95.6 (C, CH*C*OS), 114.7 (2 x CH, Ar), 119.6 (2 x CH, Ar), 129.6 (C, ArCN), 157.1 (C, ArCO), 160.5 (C, C(O)N); m/z (ES) 346.0736 ($[M+Na]^+$ $C_{15}H_{17}NNaO_5S$ requires 346.0725), 362 (29%), 346 (100).

275b: mp 128-130 °C (CH_2Cl_2); R_f 0.67 (Pet ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1}: 2934, 1740, 1513, 1396, 1204, 947, 928, 660; δ_H (300 MHz, $CDCl_3$) 1.49-1.68 (3H, m, CH_2), 1.81-1.98 (2H, m, CH_2), 2.05-2.14 (1H, m, CH_2), 2.33-2.44 (2H, m, CH_2), 3.79 (3H, s, OCH_3), 4.59 (1H, dd, *J* 3.8 and 9.8 Hz, CH_2C*H*N), 4.92 (1H, dd, *J* 2.7 and 9.0 Hz, CH_2C*H*OS), 6.90 (2H, d, *J* 9.3 Hz, Ar H), 7.31 (2H, d, *J* 9.3 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 22.8 (CH_2), 24.5 (CH_2), 27.9 (CH_2), 30.9 (CH_2), 55.6 (CH_3, OCH_3), 64.5 (CH, CH_2*C*HN), 83.9 (CH, CH_2*C*HOS), 94.9 (C, CH*C*OS), 114.8 (2 x CH, Ar), 119.9 (2 x CH, Ar), 129.4 (C, ArCN), 157.2 (C, ArCO), 160.5 (C, C(O)N); m/z (ES) 346.0723 ($[M+Na]^+$ $C_{15}H_{17}NNaO_5S$ requires 346.0725), 378 (29%), 346 (100).

- (±)-(1*R*,6*S*)-7-(4-Methoxyphenyl)-7-azabicyclo[4.2.1]nonane-8,9-dione **276**



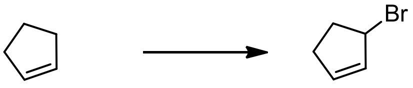
274 **276** **275a** **275b**

A novel compound prepared according to a literature procedure.[19] A solution of PPh_3 (0.157 g, 0.599 mmol) and hexachloroethane (0.142 g, 0.599 mmol) in CH_3CN (1 mL) was stirred at rt for 30 min and then added dropwise over 2 min onto a solution of diol **274** (0.111 g, 0.401 mmol) in CH_3CN (1.7 mL). After heating to reflux for 18 h, the reaction mixture was concentrated under reduced pressure and directly purified by column chromatography (Pet ether to Pet ether:EtOAc 3:2) to give bicyclic ketone **276** (0.102 g, 98%) as a yellow solid.

A solution of cyclic sulphites **275** (0.151 g, 0.467 mmol) in diphenyl ether was heated to 190 °C. After 2 h, the reaction mixture was directly purified by column chromatography (Pet ether:EtOAc 3:1 to Pet ether:EtOAc 1:3) to give bicyclic ketone **276** (0.113 g, 94%) as a yellow solid.

mp 116-119 °C; R_f 0.61 (Pet ether:EtOAc 1:1); ν_{max} (neat)/cm^{-1}: 2934, 1764, 1687, 1507, 1389, 1244, 1128, 1020, 827, 797; δ_H (400 MHz, $CDCl_3$) 1.47-1.68 (4H, m, CH_2), 1.78-1.88 (2H, m, CH_2), 1.93-2.01 (1H, m, CH_2), 2.07-2.15 (1H, m, CH_2), 3.08 (1H, dd, *J* 2.6 and 7.0 Hz, C(O)CHC(O)), 3.78 (3H, s, OCH_3), 4.52 (1H, t, *J* 3.0 Hz, C(O)CHN), 6.91 (2H, d, *J* 9.0 Hz, Ar H), 7.40 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 23.2 (CH_2), 24.6 (CH_2), 27.6 (CH_2), 28.4 (CH_2), 51.9 (CH, C(O)*C*HC(O)), 55.6 (CH_3, OCH_3), 68.7 (CH, CH_2*C*HN), 114.7 (2 x CH, Ar), 124.7 (2 x CH, Ar), 129.1 (C, ArCN), 157.8 (C, ArCO), 171.9 (C, C(O)N), 207.2 (C, CHC(O)CH); m/z (ES) 282.1100 ([M+Na]$^+$ $C_{15}H_{17}NNaO_3$ requires 282.1106), 314 (39%), 282 (100).

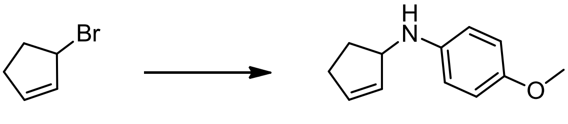
- 3-Bromocyclopentene **277**



277

A known compound[177] prepared according to the literature procedure.[115] A mixture of cyclopentene (13.3 mL, 150 mmol), NBS (10.7 g, 60.0 mmol) and benzoyl peroxide (70%, 0.150 g, 0.433 mmol) in CCl_4 (50 mL) was heated at reflux for 1.25 h. The reaction mixture was filtered (eluent CH_2Cl_2, 30 mL). The filtrate was concentrated under reduced pressure and purified *via* Kugelrohr distillation (0.8 mmHg, 60 °C) to give allyl bromide **277** (4.72 g, 53%) as a colourless oil (lit. yield 12%). δ_H (400 MHz, $CDCl_3$) 2.31-2.40 (3H, m, CH_2), 2.57-2.68 (1H, m, CH_2), 5.13-5.19 (1H, m, CH_2C*H*Br), 5.99-6.05 (2H, m, CH=CH); δ_C (100 MHz, $CDCl_3$) 31.2 (CH_2), 35.6 (CH_2), 58.3 (CH, CHBr), 133.5 (CH, CH_2C*H*=CH), 136.6 (CH, CH=C*H*CHBr); m/z (EI) 280 (5%), 278 (5), 211 (5), 213 (5), 199 (7), 133 (100). *Literature data*:[177] δ_H (400 MHz, $CDCl_3$) 2.38 (m, 3H), 2.62 (m, 1H), 5.16 (m, 1H), 6.04 (m, 2H); δ_C (100 MHz, $CDCl_3$) 31.1, 35.5, 58.4, 133.3, 136.6.

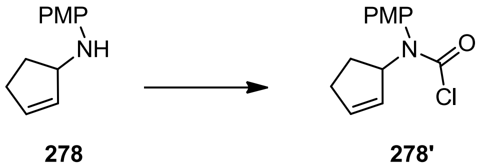
- *N*-(Cyclopent-2-en-1-yl)-4-methoxyaniline **278**



277 **278**

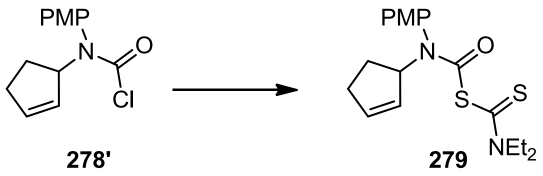
A novel compound prepared according to a literature procedure.[27] A solution of 4-methoxyaniline (1.50 g, 12.2 mmol) in CH_3CN (12 mL) was treated with allyl bromide **277** (0.662 g, 4.50 mmol) and K_2CO_3 (0.684 g, 4.95 mmol). After 8.5 h at rt, the reaction mixture was quenched with NH_4Cl (10 mL of a saturated aq. solution) and extracted with Et_2O (2 x 15 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Hexane to Hexane:EtOAc 96:4) to give amine **278** (0.601 g, 71%) as an orange oil. R$_f$ 0.52 (Pet ether:EtOAc 9:1); ν_{max} (neat)/cm^{-1}: 3375, 2933, 1507, 1229, 1034, 816, 722; δ_H (400 MHz, $CDCl_3$) 1.61-1.70 (1H, m, CH_2), 2.28-2.40 (2H, m, CH_2), 2.43-2.53 (1H, m, CH_2), 3.26 (1H, br s, NH), 3.76 (3H, s, OCH_3), 4.46-4.54 (1H, m, $CH_2C\mathit{H}N$), 5.85 (1H, dq, *J* 2.2 and 5.8 Hz, $CH_2C\mathit{H}$=CH), 5.94-5.97 (1H, m, CH=C*H*CHN), 6.62 (2H, d, *J* 9.0 Hz, Ar H), 6.79 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 31.3 (2 x CH_2), 55.9 (CH_3, OCH_3), 60.6 (CH, $CH_2\mathit{C}HN$), 115.0 (2 x CH, Ar), 115.1 (2 x CH, Ar), 132.3 (CH, $CH_2\mathit{C}H$=CH), 134.0 (CH, CH=*C*HCHN), 142.0 (C, ArCN), 152.3 (C, ArCO); m/z (ES) 190.1225 ($[M+H]^+$ $C_{12}H_{16}NO$ requires 190.1226), 190 (100%).

- Cyclopent-2-en-1-yl(4-methoxyphenyl)carbamic chloride **278’**



A novel compound prepared according to a literature procedure.[27] A solution of triphosgene (1.20 g, 4.04 mmol) in toluene (74 mL) was treated with pyridine (1.06 mL, 13.1 mmol) and subsequently with a solution of amine **278** (2.06 g, 10.9 mmol) in toluene (10 mL). The reaction mixture was stirred for 18 h at rt, quenched with NH_4Cl (70 mL of a saturated aq. solution) and extracted with Et_2O (2 x 70 mL). The combined organic extracts were washed sequentially with HCl (100 mL of a 0.25 M aq. solution), H_2O (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give carbamoyl chloride **278’** (2.36 g, 86%) as a yellow solid. mp 66-69 °C; R$_f$ 0.76 (Pet ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1}: 2933, 1727, 1509, 1458, 1394, 1212, 1030, 930, 739; δ_H (400 MHz, $CDCl_3$) (as a mixture of rotamers) 1.80-1.96 (2H, m, CH_2), 2.07-2.19 (1H, m, CH_2), 2.21-2.30 (1H, m, CH_2), 3.81 (3H, s, OCH_3), 5.46-5.59 (1H, m, $CH_2C\mathit{H}N$), 5.65-5.68 (1H, m, $CH_2C\mathit{H}$=CH), 5.81-5.86 (1H, m, CH=C*H*CHN), 6.85 (2H, d, *J* 8.0 Hz, Ar H), 6.92-7.13 (2H, m, Ar H); δ_C (100 MHz, $CDCl_3$) 28.3 (CH_2), 31.4 (CH_2), 55.5 (CH_3, OCH_3), 66.6 (CH, CH_2*C*HN), 114.1 (2 x CH, Ar), 129.2 (CH, CH_2*C*H=CH), 131.1 (2 x CH, Ar), 131.8 (C, ArCN), 136.7 (CH, CH=*C*HCHN), 149.8 (C, ArCO), 159.6 (C, NC(O)Cl); m/z (ES) 274.0608 ($[M+Na]^+$ $C_{13}H_{14}{}^{35}ClNNaO_2$ requires 274.0605), 276 (33%), 274 (100), 252 (22), 186 (17), 172 (38).

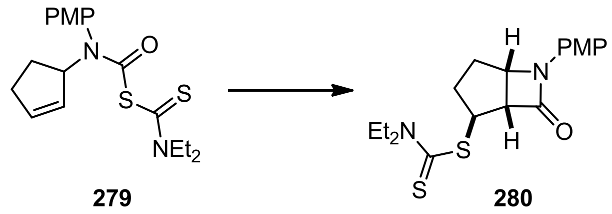
- Diethylthiocarbamic acid-[(4-methoxyphenyl)(cyclopent-2-enyl)carbamic acid]-thioanhydride **279**



278' **279**

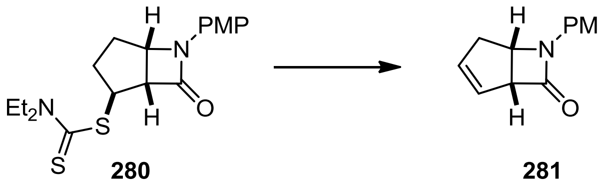
A novel compound prepared according to a literature procedure.[27] A solution of carbamoyl chloride **278’** (0.658 g, 2.61 mmol) in acetone (20 mL) was treated with sodium diethyldithiocarbamate trihydrate (2.36 g, 10.5 mmol). The solution was heated at reflux for 18 h, quenched with H_2O (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (70 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 7:3) to give dithiocarbamate **279** (0.885 g, 93%) as a yellow oil. R_f 0.32 (Pet ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1}: 2933, 1742, 1667, 1508, 1417, 1242, 1028, 916, 741; δ_H (400 MHz, $CDCl_3$) (as a mixture of rotamers) 1.21 (3H, t, *J* 7.0 Hz, CH_2*CH_3*), 1.31 (3H, t, *J* 7.0 Hz, CH_2*CH_3*), 1.74-1.81 (1H, m, CH_2), 1.85-1.93 (1H, m, CH_2), 2.08-2.15 (1H, m, CH_2), 2.17-2.27 (1H, m, CH_2), 3.77 (2H, q, *J* 7.0 Hz, C*H_2*CH_3), 3.80 (3H, s, OCH_3), 3.99 (2H, q, *J* 7.0 Hz, C*H_2*CH_3), 5.62-5.72 (2H, m, CH_2C*H*N and CH_2C*H*=CH), 5.79-5.82 (1H, m, CH=C*H*CHN), 6.83 (2H, d, *J* 8.4 Hz, Ar H), 7.04-7.13 (2H, m, Ar H); δ_C (100 MHz, $CDCl_3$) 11.1 (CH_3, $CH_2$$CH_3$), 13.6 ($CH_3$, CH_2*C*H_3), 28.3 (CH_2), 31.4 (CH_2), 48.7 (CH_2, *C*$H_2$$CH_3$), 50.4 ($CH_2$, *C*$H_2$$CH_3$), 55.5 ($CH_3$, O$CH_3$), 64.0 (CH, CH_2*C*HN), 114.2 (2 x CH, Ar), 129.3 (C, ArCN), 129.8 (CH, CH_2CH=CH), 132.4 (2 x CH, Ar), 136.1 (CH, CH=*C*HCHN), 160.2 (C, ArCO), 164.1 (C, C(O)N), 185.7 (C, SC(S)); m/z (ES) 365.1356 ([M+H]$^+$ $C_{18}H_{25}N_2O_2S_2$ requires 365.1352), 397 (34%), 365 (100), 289 (53), 150 (10).

- (±)-(1*R*,2*S*,5*S*)-6-(4-Methoxyphenyl)-7-oxo-6-azabicyclo[3.2.0]heptan-2-yl diethylcarbamodithioate **280**



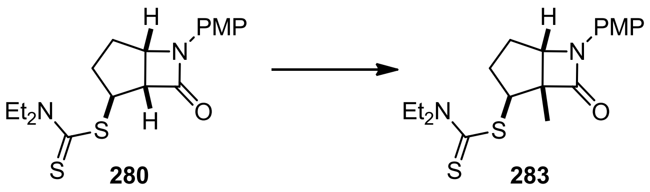
A novel compound prepared according to a literature procedure.[26] A solution of dithiocarbamate **279** (2.87 g, 7.86 mmol) in cyclohexane (79 mL) was degassed for 10 min and irradiated with a 500 W lamp which generated enough heat to bring the solution to reflux. After 4 h, the solvent was removed under reduced pressure and the crude product obtained was purified by column chromatography (Pet ether to Pet ether:EtOAc 1:1) to give lactam **280** (2.62 g, 92%) as a beige solid. mp 117-119 °C; R_f 0.45 (Pet ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1}: 2929, 1721, 1509, 1398, 1206, 1031, 914, 830, 800; δ_H (300 MHz, $CDCl_3$) 1.27 (6H, dt, *J* 2.6 and 7.1 Hz, CH_2CH_3), 1.71-1.84 (1H, m, CH_2), 2.12-2.35 (3H, m, CH_2), 3.70 (2H, q, *J* 7.1 Hz, CH_2CH_3), 3.78 (3H, s, OCH_3), 3.80-3.85 (1H, m, CHC*H*C(O)), 4.01 (2H, q, *J* 7.1 Hz, CH_2CH_3), 4.48 (1H, t, *J* 4.2 Hz, CH_2CHS), 4.61 (1H, d, *J* 5.4 Hz, CH_2CHN), 6.88 (2H, d, *J* 9.0 Hz, Ar H), 7.35 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 11.7 (CH_3, CH_2CH_3), 12.7 (CH_3, CH_2CH_3), 25.8 (CH_2), 30.2 (CH_2), 46.8 (CH_2, CH_2CH_3), 49.1 (CH_2, CH_2CH_3), 49.2 (CH, CH*C*HC(O)), 55.6 (CH_3, OCH_3), 57.1 (CH, CH_2CHS), 59.9 (CH, CH_2CHN), 114.6 (2 x CH, Ar), 118.1 (2 x CH, Ar), 130.9 (C, ArCN), 156.2 (C, ArCO), 163.2 (C, C(O)N), 193.5 (C, SC(S)); m/z (ES) 365.1356 ([M+H]$^+$ $C_{18}H_{25}N_2O_2S_2$ requires 365.1352), 365 (100%).

- (±)-(1*R*,5*S*)-8-(4-Methoxyphenyl)-6-azabicyclo[3.2.0]hept-2-en-7-one **281**



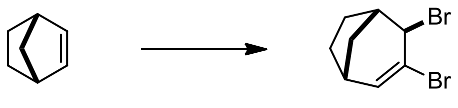
A novel compound prepared according to a literature procedure.[29] A solution of lactam **280** (73 mg, 0.20 mmol) in diphenyl ether (2.0 mL) was heated to reflux. After 1 h, the reaction mixture was directly purified by column chromatography (Pet ether to Pet ether:EtOAc 7:3) to give lactam **281** (33 mg, 77%) as a green solid. mp 89-91 °C (CH_2Cl_2); R_f 0.54 (Pet ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1}: 2937, 1732, 1511, 1297, 1231, 1031, 826, 806, 691; δ_H (400 MHz, $CDCl_3$) 2.51-2.58 (2H, m, CH_2), 3.77 (3H, s, OCH_3), 4.15-4.24 (1H, m, CH_2C*H*N), 4.55 (1H, t, *J* 5.4 Hz, CHC*H*C(O)), 5.85-5.87 (1H, m, CH_2C*H*=CH), 5.92-5.95 (1H, m, CH=C*H*C(O)), 6.85 (2H, d, *J* 9.2 Hz, Ar H), 7.29 (2H, d, *J* 9.2 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 33.7 (CH_2), 54.3 (CH, =CH*C*HC(O)), 55.6 (CH_3, OCH_3), 62.7 (CH, CH_2*C*HN), 114.6 (2 x CH, Ar), 118.0 (2 x CH, Ar), 126.4 (CH, CH_2*C*H=CH), 130.9 (C, ArCN), 133.3 (C, HC=*C*HCHC(O)), 156.0 (C, ArCO), 167.1 (C, C(O)N); m/z (EI) 215.0943 (M^+ $C_{13}H_{13}NO_2$ requires 215.0946), 215 (8%), 149 (100), 134 (25).

- (±)-(1*R*,2*S*,5*S*)-6-(4-Methoxyphenyl)-1-methyl-7-oxo-6-azabicyclo[3.2.0]heptan-2-yl diethylcarbamodithioate **283**



A novel compound prepared according to a modified literature procedure.[39] A solution of lactam **280** (99 mg, 0.27 mmol) in THF (2.7 mL) was cooled to -78 °C and treated with methyl iodide (85 μL, 1.4 mmol) and LHMDS (1.4 mL of a 1.0 M solution in THF, 1.4 mmol). After 3 h at -78 °C, the reaction mixture was allowed to warm to rt. After 4.5 h at rt, the solvent was removed under reduced pressure and the crude product obtained was purified by column chromatography (Pet ether to Pet ether:EtOAc 4:1) to give methyl lactam **283** (9 mg, 9%) as a colourless oil. R_f 0.27 (Pet ether:EtOAc 4:1); δ_H (400 MHz, $CDCl_3$) 1.23-1.33 (6H, m, 2 x $\mathrm{CH_2C}H_3$), 1.53 (3H, s, CH_3), 1.74-1.86 (1H, m, CH_2), 2.06-2.21 (2H, m, CH_2), 2.30-2.42 (1H, m, CH_2), 3.75 (2H, q, *J* 6.9 Hz, $\mathrm{C}H_2\mathrm{CH_3}$), 3.79 (3H, s, OCH_3), 4.02 (2H, q, *J* 6.9 Hz, $\mathrm{C}H_2\mathrm{CH_3}$), 4.08 (1H, d, *J* 4.4 Hz, $\mathrm{CH_2C}H\mathrm{S}$), 4.78 (1H, d, *J* 5.6 Hz, $\mathrm{CH_2C}H\mathrm{N}$), 6.88 (2H, d, *J* 9.0 Hz, Ar H), 7.35 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 11.8 (CH_3, $\mathrm{CH_2}C\mathrm{H_3}$), 12.8 ($CH_3$, $\mathrm{CH_2}C\mathrm{H_3}$), 15.2 ($CH_3$, $\mathrm{C}C\mathrm{H_3}$), 26.1 (CH_2), 33.0 (CH_2), 46.9 (CH_2, $C\mathrm{H_2CH_3}$), 49.6 (CH_2, $C\mathrm{H_2CH_3}$), 53.9 (CH, $\mathrm{CH_2}C\mathrm{HN}$), 55.7 ($CH_3$, OCH_3), 63.9 (CH, $\mathrm{CH_2}C\mathrm{HS}$), 64.1 (C, $\mathrm{CH}C\mathrm{(CH_3)C(O)}$), 114.7 (2 x CH, Ar), 118.4 (2 x CH, Ar), 131.0 (C, ArCN), 156.2 (C, ArCO), 167.3 (C, C(O)N), 194.1 (C, SC(S)); m/z (ES) 379.1507 ($[M+H]^+$ $C_{19}H_{27}N_2O_2S_2$ requires 379.1508), 379 (27), 366 (21), 365 (100).

- (±)-(1*S*,5*R*)-3,4-Dibromobicyclo[3.2.1]oct-2-ene **287**

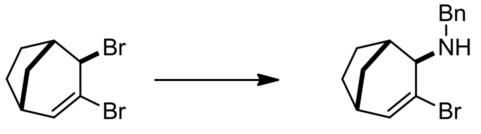


287

A known compound prepared according to a literature procedure.[116] A solution of norbornene (10.0 g, 106 mmol) and *t*BuOK (16.7 g, 149 mmol) in pentane (70 mL) at -30 °C was treated with a solution of $CHBr_3$ (12.1 mL, 138 mL) in pentane (12 mL) over 30 min. The reaction mixture was allowed to warm to rt and quenched with H_2O (80 mL) after 2 h. The organic layer was washed sequentially with H_2O (2 x 80 mL), brine (80 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The solvent and excess of $CHBr_3$ were removed under reduced pressure. The residual crude product obtained was purified by column chromatography (Hexane) to give dibromo bicycle **287** (7.04 g, 25%) as a pale yellow oil. R_f 0.81 (Hexane:Et_2O 95:5); ν_{max} (neat)/cm^{-1} : 2951, 2867, 1719, 1445, 1299, 1153, 1042, 859, 695, 622; δ_H (400 MHz, $CDCl_3$) 1.44-1.52 (2H, m, CH_2), 1.70-1.75 (2H, m, $\mathrm{CHC}H_2\mathrm{CH}$), 1.95-2.04 (1H, m, CH_2), 2.19 (1H, d, *J* 12.0 Hz, CH_2), 2.58-2.67 (1H, m, $\mathrm{=CHC}H\mathrm{CH_2}$), 2.81-2.91 (1H, m, $\mathrm{CH_2C}H\mathrm{CHBr}$), 4.53 (1H, d, *J* 2.8 Hz, $\mathrm{CHC}H\mathrm{Br}$), 6.33 (1H, dd, *J* 1.0 and 7.0 Hz, $\mathrm{C}H\mathrm{=CBr}$); δ_C (100 MHz, $CDCl_3$) 23.8

(CH_2), 27.4 (CH_2), 30.9 (CH_2, CH*C*H$_2$CH), 37.8 (CH, =CH*C*HCH$_2$), 43.7 (CH, CH$_2$*C*HCHBr), 61.3 (CH, CH*C*HBr), 121.0 (C, =CBr), 139.2 (CH, CH*C*H=); m/z (EI) 266 (M^+, 5%), 264 (3), 187 (68), 185 (74), 159 (99), 157 (100), 105 (44), 78 (41), 77 (64).

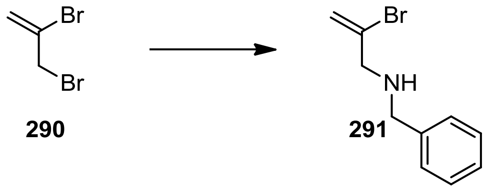
- (±)-(2*R*,5*S*)-*N*-Benzyl-3-bromobicyclo[3.2.1]oct-3-en-2-amine **288**



287 **288**

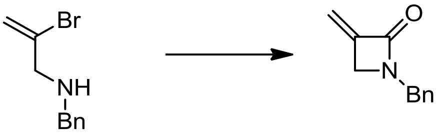
A novel compound prepared according to a literature procedure.[27] A solution of benzylamine (7.81 mL, 71.5 mmol) in CH_3CN (72 mL) was treated with dibromo bicycle **287** (7.04 g, 26.5 mmol) and K_2CO_3 (4.03 g, 29.1 mmol). After 6.5 h at rt, the reaction was quenched with H_2O (70 mL) and extracted with Et_2O (2 x 70 mL). The combined organic extracts were washed with brine (90 mL), dried over $MgSO_4$, filtered, concentrated under reduced pressure and purified by column chromatography (Hexane:Et_2O 98:2 to Hexane:Et_2O 9:1) to give amine **288** (6.98 g, 90%) as a pale yellow oil. R_f 0.32 (Pet ether:Et_2O 95:5); ν_{max} (neat)/cm^{-1} : 3332, 2940, 1630, 1452, 1331, 1107, 1027, 882; δ_H (400 MHz, $CDCl_3$) 1.28-1.40 (2H, m, CH_2), 1.60-1.69 (1H, m, CH_2), 1.73-1.79 (2H, m, CH_2 and NH), 1.86-1.95 (2H, m, CH_2), 2.51-2.59 (2H, m, CH$_2$C*H*CHN and CH$_2$C*H*CH=), 2.96 (1H, d, *J* 2.4 Hz, CHC*H*N), 3.88, 3.98 (2H, ABq, *J* 13.2 Hz, NCH$_2$Ph), 6.31 (1H, d, *J* 6.8 Hz, C*H*=CBr), 7.26-7.44 (5H, m, Ar H); δ_C (100 MHz, $CDCl_3$) 26.5 (CH_2), 30.7 (CH_2), 32.6 (CH_2), 38.2 (CH), 38.3 (CH), 52.3 (CH_2, NCH$_2$Ph), 68.5 (CH, CH*C*HN), 124.3 (C, =CBr), 127.0 (CH, Ar), 128.3 (2 x CH, Ar), 128.5 (2 x CH, Ar), 138.1 (CH, CH*C*H=CBr), 140.6 (C, Ar); m/z (ES) 292.0704 (M^+, $C_{15}H_{19}{}^{79}BrN$ requires 292.0701), 294 (89%), 292 (100), 187 (33), 185 (28).

- *N*-Benzyl-2-bromoprop-2-en-1-amine **291**



A known compound prepared according to a literature procedure.[108] A solution of benzylamine (4.75 mL, 43.5 mmol) and K_2CO_3 (2.20 g, 16.0 mmol) in DMF (36 mL) was cooled to 0 °C and treated with 2,3-dibromopropene **290** (1.50 g, 14.5 mmol). The reaction mixture was allowed to warm progressively to rt over 18 h, diluted with Et_2O (40 mL) and washed with brine (2 x 40 mL). The combined organic extracts were dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 4:1) to give amine **291** (3.28 g, 100%) as a pale yellow oil (lit. yield 92%). R_f 0.47 (Pet ether:Et_2O 3:2); ν_{max} (neat)/cm^{-1} : 3356, 3027, 2829, 1625, 1453, 1105, 892, 732; δ_H (400 MHz, $CDCl_3$) 1.76 (1H, br s, NH), 3.48 (2H, s, $NCH_2C=$), 3.75 (2H, s, NCH_2Ph), 5.61 (1H, d, *J* 1.8 Hz, $CH_2=C$), 5.80 (1H, d, *J* 1.8 Hz, $CH_2=C$), 7.24-7.39 (5H, m, Ar H); δ_C (100 MHz, $CDCl_3$) 51.7 (CH_2, NCH_2Ph), 56.8 (CH_2, N*C*$H_2C=$), 118.1 (CH_2, *C*$H_2=C$), 127.3 (CH, Ar), 128.5 (2 x CH, Ar), 128.6 (2 x CH, Ar), 133.7 (C, $CH_2=$*C*Br), 139.9 (C, Ar); m/z (EI) 226 (5%), 224 (5), 146 (13), 120 (18), 91 (100). *Literature data*:[108] ν_{max} (neat)/cm^{-1} : 3320 (NH), 1625 (C=C); δ_H (60 MHz, $CDCl_3$) 1.80 (s, 1 H, NH), 3.45 (s, 2H, NCH_2CBr), 3.72 (s, 2H, $PhCH_2N$), 5.60 (d, 1H, *J* = 1 Hz, vinyl), 5.80 (d, 1H, *J* = 1 Hz, vinyl), 7.28-7.45 (m, 5H, aromatic); m/z 227, 225 (M^+), 146 ($[M-Br]^+$).

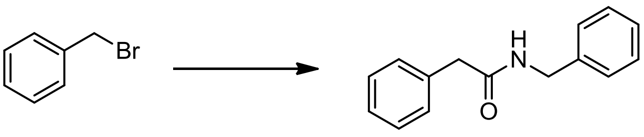
- 1-Benzyl-3-methyleneazetidin-2-one **292**



291 **292**

A known compound prepared according to a literature procedure.[108] A solution of amine **291** (0.207 g, 0.880 mmol) in HMPA (1.7 mL) was treated with *n*Bu_3N (0.422 mL, 1.77 mmol), $Pd(OAc)_2$ (20 mg, 0.088 mmol) and PPh_3 (92 mg, 0.35 mmol). The reaction mixture was saturated with CO (1 atm) for 5 min and heated to 100 °C under CO (1 atm). After 4.5 h, the reaction mixture was quenched with H_2O (2 mL) and extracted with Et_2O (2 x 4 mL). The combined organic extracts were washed sequentially with HCl (5 mL of a 1 M aq. solution) and brine (50 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether:EtOAC 9:1 to Pet ether:EtOAc 3:2) to give lactam **292** (59 mg, 37%) as a yellow oil (lit. yield 62%). R_f 0.57 (Pet ether:EtOAc 1:1); ν_{max} (neat)/cm^{-1} : 2960, 1735, 1396, 1355, 1216, 928, 696; δ_H (400 MHz, $CDCl_3$) 3.65 (2H, t, *J* 1.4 Hz, NCH_2C=), 4.52 (2H, s, NCH_2Ph), 5.16 (1H, d, *J* 1.4 Hz, CH_2=C), 5.74 (1H, d, *J* 1.4 Hz, CH_2=C), 7.25-7.38 (5H, m, Ar H); δ_C (100 MHz, $CDCl_3$) 46.2 (CH_2, NCH_2Ph), 48.0 (CH_2, N*C*H_2C=), 109.8 (CH_2, *C*H_2=C), 128.0 (CH, Ar), 128.3 (2 x CH, Ar), 129.0 (2 x CH, Ar), 135.5 (C, Ar), 145.3 (C, CH_2=*C*C(O)), 163.7 (C, C(O)N); m/z (EI) 173 (28%), 172 (36), 133 (32), 105 (29), 91 (100), 65 (16). *Literature data*:[108] ν_{max} (neat)/cm^{-1} : 1740(C=O); δ_H (60 MHz, $CDCl_3$) 3,65 (t, *J* = 1 Hz, 2H, H-4), 4.54 (s, 2H, NCH_2Ph), 5.17 (dd, *J* = 3,1 Hz, 1H, vinyl), 5.75 (dd, *J* = 3,1 Hz, 1H, vinyl), 7.20-7.50 (m, 5H, aromatic); δ_C (15 MHz, $CDCl_3$) 45.9, 47.7, 109.2, 127.8, 135.1, 144.9, 163.0; m/z (EI) 173 (M^+), 172, 133, 91 (Found: C, 76.44; H, 6.42; N, 8.07. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09%).

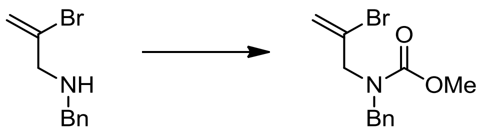
- *N*-Benzyl-2-phenylacetamide **297**



297

A known compound prepared according to the literature procedure.[122] A solution of benzyl bromide (71 µL, 0.60 mmol), benzylamine (55 µL, 0.50 mmol), $Mo(CO)_6$ (26 mg, 0.10 mmol), Et_4NCl (18 mg, 0.10 mmol) and $n$$Bu_3N$ (131 µL) in diglyme (6.0 mL) was heated to 150 °C. After 5.5 h, the reaction mixture was concentrated under reduced pressure and the crude residue obtained was purified by column chromatography (Pet ether to Pet ether:EtOAc 3:2) to give amide **297** (47 mg, 42%) as a white solid (lit. yield 52%). mp 114-115 °C (CH_2Cl_2); R_f 0.13 (Pet ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1} : 3284, 2925, 1636, 1547, 1453, 1026, 691; δ_H (400 MHz, $CDCl_3$) 3.64 (2H, s, $CH_2C(O)$), 4.43 (2H, d, *J* 5.8 Hz, NCH_2Ph), 5.87 (1H, br s, NH), 7.18-7.23 (2H, m, Ar H), 7.24-7.41 (8H, m, Ar H); δ_C (100 MHz, $CDCl_3$) 43.7 (CH_2, $NHCH_2Ph$), 43.9 (CH_2, $\mathit{C}H_2C(O)$), 127.5 (CH, Ar), 127.5 (CH, Ar), 127.6 (2 x CH, Ar), 128.8 (2 x CH, Ar), 129.2 (2 x CH, Ar), 129.6 (2 x CH, Ar), 135.0 (C, Ar*C*$CH_2C(O)$), 138.2 (C, Ar*C*CH_2N), 171.0 (C, C(O)N); m/z (ES) 226.1228 ($[M+H]^+$ $C_{15}H_{16}NO$ requires 226.1226), 226 (100%). *Literature data*:[248] Rf 0.35 (Hexane :EtOAc 1:1); δ_H (400 MHz, $CDCl_3$) 7.30 (m, 10H), 5.90 (s, 1H), 4.43 (d, *J*=5.8 Hz, 2H), 3.64 (s, 2H); δ_C (100 MHz, $CDCl_3$) 171.0, 138.2, 134.9, 129.5, 129.1, 128.7, 127.5, 127.4, 127.4, 60.4, 43.8, 43.6; ν_{max} (NaCl)/cm^{-1} : 3320, 3100, 1660, 1070; m/z (ES) 226.1 ($[M+H]^+$); HRMS calcd for $C_{15}H_{16}NO$ ($[M+H]^+$) 226.1232, found 226.1245.

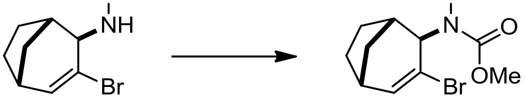
- Methyl benzyl(2-bromoallyl)carbamate **301**



291 **301**

A novel compound prepared according to a literature procedure.[123] A solution of amine **291** (0.609 g, 2.69 mmol) and Et_3N (3.00 mL, 21.5 mmol) in CH_2Cl_2 (38 mL) was cooled to 0 °C and treated with methylchloroformate (1.56 mL, 20.2 mmol). After 5 min at 0 °C, the solution was allowed to warm to rt. After 18 h, the reaction mixture was diluted with CH_2Cl_2 (30 mL), washed sequentially with H_2O (40 mL) and brine (40 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:Et_2O 4:1) to give carbamate **301** (0.666 g, 87%) as a colorless oil. R_f 0.48 (Pet ether:Et_2O 4:1); ν_{max} (neat)/cm^{-1} : 2955, 1700, 1466, 1453, 1235, 1121, 947, 895, 734; δ_H (400 MHz, $CDCl_3$) (mixture of rotamers) 4.06 (3H, s, OCH_3), 4.29, 4.40 (2H, s, NCH_2C=), 4.79, 4.81 (2H, s, NCH_2Ph), 5.87 (1H, br s, CH_2=C), 5.96-6.01 (1H, m, CH_2=C), 7.47-7.64 (5H, m, Ar H); δ_C (100 MHz, $CDCl_3$) (mixture of rotamers) 49.4, 49.8 (CH_2, NCH_2Ph), 53.3 (CH_3, OCH_3), 56.7 (CH_2, N*C*H$_2$C=), 117.6, 118.6 (CH_2, *C*H$_2$=C), 127.6, 128,3 (CH, Ar), 127.7 (2 x CH, Ar), 128.8 (2 x CH, Ar), 129.0 (C, CH_2=*C*Br), 137.1 (C, Ar), 157.1 (C, C(O)N); m/z (ES) 284.0286 ([M+H]$^+$ $C_{12}H_{15}{}^{79}BrNO_2$ requires 284.0281), 287 (14%), 286 (99), 285 (14), 284 (100).

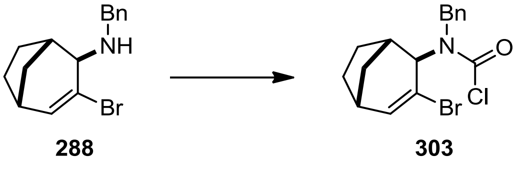
- (±)-Methyl benzyl((1*S*,2*R*,5*R*)-bromobicyclo[3.2.1]oct-3-en-2-yl)carbamate **302**



288 **302**

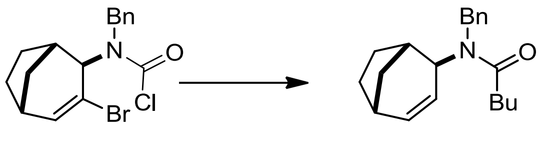
A novel compound prepared according to a literature procedure.[123] A solution of amine **288** (0.372 g, 1.27 mmol) and Et_3N (1.42 mL, 10.2 mmol) in CH_2Cl_2 (18 mL) was cooled to 0 °C and treated with methylchloroformate (0.511 mL, 6.62 mmol). After 5 min at 0 °C, the solution was allowed to warm to rt. After 18 h, the reaction mixture was cooled to 0 °C, methylchloroformate (0.785 mL, 7.62 mmol) and Et_3N (0.354 mL, 2.54 mmol) were added to drive the reaction to completion. After 18 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL). The organic layer was washed sequentially with H_2O (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, concentrated under reduced pressure and purified by column chromatography to give carbamate **302** (0.380 g, 85%) as a white solid. mp 149-151 °C; R_f 0.44 (Pet ether:EtOAc 95:5); ν_{max} (neat)/cm^{-1} : 2953, 1687, 1449, 1398, 1261, 1202, 1116, 742; δ_H (400 MHz, $CDCl_3$) (mixture of rotamers) 0.99-1.03 (1H, m, CH_2), 1.26-1.60 (3H, m, CH_2), 1.65-1.74 (1H, m, CH_2), 1.88-1.97 (1H, m, CH_2), 2.42-2.64 (2H, m, $CH_2C\mathit{H}CHN$ and $CH_2C\mathit{H}CH$=), 3.66, 3.79 (CH_3, s, OCH_3), 4.14-4.22 (1H, m, NCH_2Ph), 4.48-4.68 (1H, m, $CHC\mathit{H}N$), 4.79-4.94 (1H, m, $N\mathit{CH_2}Ph$), 6.45-6.59 (1H, m, $C\mathit{H}$=CBr), 7.17-7.32 (5H, m, Ar H); δ_C (100 MHz, $CDCl_3$) (mixture of rotamers) 28.3, 28.4 (CH_2), 30.3 (CH_2), 32.3 (CH_2), 37.6 (CH, $CH_2\mathit{C}HCHN$), 40.7, 41.0 (CH, $CH_2\mathit{C}HCH$=), 47.6 (CH_2, $N\mathit{C}H_2Ph$), 53.0, 53.1 (CH_3, OCH_3), 66.1 (CH, $CH_2\mathit{C}HN$), 120.3 (C, =CBr), 125.9 (CH, Ar), 126.3, 126.5 (2 x CH, Ar), 128.4 (2 x CH, Ar), 139.2, 139.5 (C, Ar), 141.6 (CH, $CH\mathit{C}H$=CBr), 157.2, 157.7 (C, C(O)N); m/z (ES) 372.0564 ($[M+Na]^+$, $C_{17}H_{20}{}^{79}BrNNaO_2$ requires 372.0575), 374 (100%), 372 (85).

- (±)-Benzyl((1*R*,2*R*,5*S*)-bromobicyclo[3.2.1]oct-3-en-2-yl)carbamic chloride **303**



A novel compound prepared according to a literature procedure.[27] A solution of triphosgene (0.102 g, 0.343 mmol) in toluene (3.2 mL) was treated with pyridine (90 µL, 1.1 mmol) and subsequently with a solution of amine **288** (0.272 g, 0.931 mmol) in toluene (3 mL). After 36 h at rt, triphosgene (0.102 g, 0.343 mmol) and pyridine (90 µL, 1.1 mmol) were added to drive the reaction to completion. After 3 h, the reaction was quenched with H_2O (7 mL) and extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed sequentially with HCl (15 mL of a 0.25 M aq. solution) and brine (15 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give carbamoyl chloride **303** (0.299 g, 91%) as a yellow oil. R_f 0.51 (Pet ether:EtOAc 95:5); ν_{max} (neat)/cm^{-1} : 2945, 1722, 1453, 1390, 1324, 1235, 1138, 966, 719; δ_H (400 MHz, $CDCl_3$) (mixture of rotamers) 0.88-0.98 (1H, m, CH_2), 1.10-1.19 (1H, m, CH_2), 1.26-1.35 (1H, m, CH_2), 1.39-1.50 (1H, m, CH_2), 1.54-1.63 (1H, m, CH_2), 1.77-1.90 (1H, m, CH_2), 2.35-2.54 (2H, m, $CH_2C\mathit{H}CHN$ and $CH_2C\mathit{H}CH$=), 4.16-4.34 (1H, m, NCH_2Ph), 4.51-4.63 (1H, m, $CHC\mathit{H}N$), 4.81-4.91 (1H, m, NCH_2Ph), 6.44-6.47 (1H, m, CH=CBr), 7.06-7.23 (5H, m, Ar H); δ_C (100 MHz, $CDCl_3$) (mixture of rotamers) 28.4 (CH_2), 30.2, 30.3 (CH_2), 32.1 (CH_2), 37.6 (CH, $CH_2\mathit{C}HCHN$), 40.0, 41.1 (CH, $CH_2\mathit{C}HCH$=), 50.3, 51.2 (CH_2, $N\mathit{C}H_2Ph$), 68.3, 70.2 (CH, $CH_2\mathit{C}HN$), 118.2, 118.3 (C, =CBr), 125.9, 126.0 (2 x CH, Ar), 127.1, 127.2 (CH, Ar), 128.7 (2 x CH, Ar), 136.6, 137.2 (C, Ar), 142.7, 142.8 (CH, $CH\mathit{C}H$=CBr), 150.0, 151.6 (C, NC(O)Cl); m/z (ES) 371.0527 ($[M+NH_4]^+$, $C_{16}H_{21}{}^{79}Br^{35}ClN_2O$ requires 371.0520), 373 (62%), 371 (47), 352 (97), 350 (100).

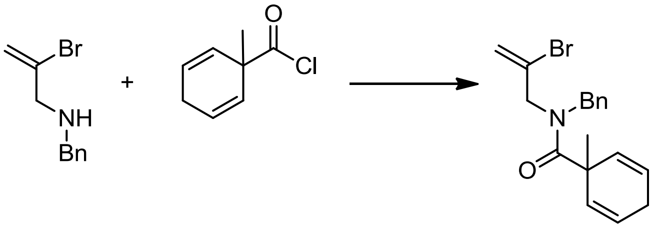
(±)-*N*-Benzyl-*N*-((1*S*,2*R*,5*R*)-3-bromobicyclo[3.2.1]oct-3-en-2-yl)pentanamide **304**



303 **304**

A novel compound prepared according to a literature procedure.[125] A solution of *n*BuLi (0.90 mL of a 1.1 M solution in hexanes, 0.96 mmol) in THF (4.6 mL) was cooled to -78 °C and treated with carbamoyl chloride **303** (0.113 g, 0.319 mmol). After 1.5 h at -78 °C, the reaction mixture was quenched with NH_4Cl (5 mL of a saturated aq. solution) and extracted with Et_2O (2 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, concentrated under reduced pressure and purified by column chromatography to give amide **304** (24 mg, 25%) as a colorless oil. R_f 0.48 (Pet ether:EtOAc 9:1); ν_{max} (neat)/cm^{-1} : 2952, 1641, 1406, 1195, 1170, 728; δ_H (400 MHz, $CDCl_3$) 0.81 (3H, t, *J* 7.2 Hz, $(CH_2)_3CH_3$), 1.17-1.98 (11H, m, CH_2), 2.06-2.24 (1H, m, CH_2), 2.37-2.61 (2H, m, CH_2CHCHN and CH_2CHCH=), 4.58-4.75 (3H, m, NCH_2Ph and CHC*H*N), 5.24-5.33 (1H, m, CH_2CHCH=), 6.11-6.18 (1H, m, CH=CHCHN), 7.13-7.34 (5H, m, Ar H); δ_C (100 MHz, $CDCl_3$) (mixture of rotamers) 14.0 (CH_3, $(CH_2)_3CH_3$), 22.6 (CH_2), 27.5 (CH_2), 28.2 (CH_2), 30.1 (CH_2), 32.7(CH_2), 33.9 (CH_2), 35.0, 35.6 (CH, CH_2CHCHN), 39.2, 41.1 (CH, CH_2CHCH=), 47.3, 48.9 (CH_2, NCH_2Ph), 58.4, 59.1 (CH, CH_2CHN), 122.6, 122.7 (CH, CHCH=CH), 125.6 (2 x CH, Ar), 126.6, 127.0 (CH, Ar), 128.4, 128.8 (2 x CH, Ar), 139.3, 140.1 (CH, CH=CHCHN), 139.8 (C, Ar), 174.3 (C, C(O)N); m/z (ES) 298.2171 ($[M+H]^+$, $C_{20}H_{28}NO$ requires 298.2165), 320 (14%), 300 (25), 298 (100).

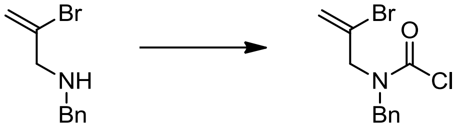
- *N*-Benzyl-*N*-(2-bromoallyl)-1-methylcyclohexa-2,5-dienecarboxamide **309**



291 **308** **309**

A novel compound prepared according to a literature procedure.[127] To solution of amine **291** (0.128 g, 0.566 mmol), Et_3N (86 µL, 0.63 mmol) and DMAP (cat) in CH_2Cl_2 (1.7 mL) was added acyl chloride **308** (0.115 g, 0.734 mmol) dropwise over 1 min. The reaction mixture was heated at reflux for 18 h, quenched with H_2O (2 mL) and extracted with CH_2Cl_2 (2 x 3 mL). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give amide **309** (0.131 g, 67%) as a colourless oil. R_f 0.50 (Pet ether:Et_2O 4:1); ν_{max} (neat)/cm^{-1} : 2931, 1639, 1397, 1223, 866, 697; δ_H (400 MHz, $CDCl_3$) (mixture of rotamers) 1.40 (3H, s, CH_3), 2.57-2.77 (2H, m, =CHC*H*$_2$CH=), 4.13, 4.25 (2H, s, NCH_2C=), 4.62, 4.79 (2H, s, NCH_2Ph), 5.58-5.86 (6H, m, CH_2=C and CH=CH), 7.13-7.36 (5H, m, Ar H); δ_C (100 MHz, $CDCl_3$) (mixture of rotamers) 25.7 (CH_2, CH=CH_2CH=), 28.7 (CH_3, =CHCCH_3), 45.2 (C, =CH*C*CH_3), 49.4, 50.7 (CH_2, NCH_2Ph), 52.7, 54.4 (CH_2, N*C*H_2C=), 116.1, 117.9 (CH_2, *C*H_2=C), 123.4 (2 x CH, CH=CH), 127.1, 127.8 (CH, Ar), 127.4 (2 x CH, Ar), 128.7 (2 x CH, Ar), 128.8 (C, CH_2=*C*Br), 129.9, 130.2 (2 x CH, CH=CH), 136.9, 137.3 (C, Ar), 174.0, 174.1 (C, C(O)N); m/z (ES) 368.0615 ($[M+Na]^+$ $C_{18}H_{20}{}^{79}BrNNaO$ requires 368.0626), 371 (12%), 370 (89), 368 (100).

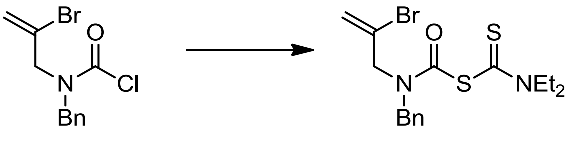
- Benzyl(2-bromoallyl)carbamic chloride **291'**



291 **291'**

A novel compound prepared according to a literature procedure.[27] A solution of triphosgene (0.726 g, 2.45 mmol) in toluene (30 mL) was treated with pyridine (0.632 mL, 7.93 mmol) and subsequently with a solution of amine **291** (1.50 g, 6.61 mmol) in toluene (14 mL). After 18 h at rt, the reaction mixture was quenched with H_2O (30 mL) and extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed sequentially with HCl (30 mL of a 0.25 M aq. solution) and brine (45 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give carbamoyl chloride **291'** (1.80 g, 94%) as a yellow oil. R_f 0.65 (Pet ether:Et_2O 4:1); ν_{max} (neat)/cm^{-1} : 2934, 1726, 1391, 1188, 1166, 981, 905, 698; δ_H (400 MHz, $CDCl_3$) (mixture of rotamers) 4.19, 4.24 (2H, s, NCH_2C=), 4.63, 4.78 (2H, s, NCH_2Ph), 5.70-5.72 (1H, m, CH_2=C), 5.79 (1H, br s, CH_2=C), 7.26-7.41 (5H, m, Ar H); δ_C (100 MHz, $CDCl_3$) (mixture of rotamers) 51.8, 53.5 (CH_2, NCH_2Ph), 55.1, 56.8 (CH_2, N*C*H_2C=), 119.2, 120.4 (CH_2, *C*H_2=C), 126.3, 126.7 (C, CH_2=*C*Br), 127.5 (CH, Ar), 128.5 (2 x CH, Ar), 129.2 (2 x CH, Ar), 134.9, 135.1 (C, Ar), 150.2, 150.6 (C, NC(O)Cl); m/z (EI) 286.9724 (M^+ $C_{11}H_{11}{}^{79}Br^{35}ClNO$ requires 286.9713), 210 (7%), 208 (35), 125 (7), 91 (100).

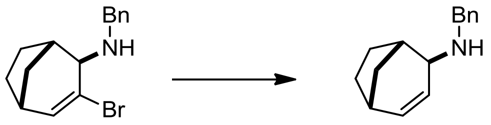
- Diethyltiocarbamic acid-[benzyl(2-bromoallyl)carbamic acid]-thioanhydride **310**



291' **310**

A novel compound prepared according to a literature procedure.[27] A solution of carbamoyl chloride **291'** (1.62 g, 5.61 mmol) in acetone (35 mL) was treated with sodium diethyldithiocarbamate trihydrate (5.05 g, 22.4 mmol). The solution was stirred at rt for 18 h, quenched with H_2O (30 mL) and extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 7:3) to give dithiocarbamate **310** (2.16 g, 100%) as a yellow solid. mp 76-78 °C; R_f 0.51 (Pet ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1} : 2977, 1666, 1488, 1272, 1139, 976, 902, 699; δ_H (400 MHz, $CDCl_3$) (mixture of rotamers) 1.28-1.37 (6H, m, CH_2CH_3), 3.82 (2H, q, *J* 7.0 Hz, CH_2CH_3), 4.04 (2H, q, *J* 7.0 Hz, CH_2CH_3), 4.18 (2H, br s, NCH_2C=), 4.77 (2H, br s, NCH_2Ph), 5.68-5.92 (2H, m, CH_2=C), 7.36 (5H, br s, Ar H); δ_C (100 MHz, $CDCl_3$) (mixture of rotamers) 11.1 (CH_3, CH_2CH_3), 13.4 (CH_3, CH_2CH_3), 48.8 (CH_2, NCH_2Ph), 49.6, 50.0 (CH_2, CH_2CH_3), 50.2, 51.8 (CH_2, CH_2CH_3), 53.2, 55.4 (CH_2, NCH_2C=), 119.3 (CH_2, CH_2=C), 126.4 (C, CH_2=CBr), 127.3 (CH, Ar), 127.9 (2 x CH, Ar), 128.7 (2 x CH, Ar), 134.9, 135.2 (C, Ar), 162.9 (C, C(O)N), 183.7, 184.6 (C, C(S)S); m/z (ES) 401.0352 ($[M+H]^+$ $C_{16}H_{22}{}^{79}BrN_2OS_2$ requires 401.0351), 403 (100%), 401 (96), 371 (41), 176 (53).

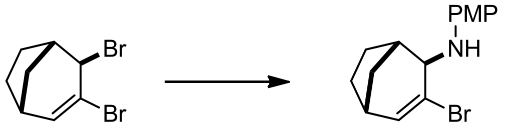
- (±)-(1*S*,2*R*,5*S*)-*N*-Benzylbicyclo[3.2.1]oct-3-en-2-amine **311**



288 **311**

A novel compound prepared according to a literature procedure.[249] A solution of amine **288** (0.150 g, 0.510 mmol) in THF (5.1 mL) was cooled to -78 °C. *n*BuLi (1.45 mL of a 1.06 M solution in hexane, 1.54 mmol) was added dropwise over 2 min. The reaction mixture was allowed to warm to rt over 8 h, quenched with NH_4Cl (10 mL of a saturated aq. solution) and extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether:Et_3N 97:3 to Pet ether:EtOAc:Et_3N 77:20:3) to give amine **311** (0.101 g, 93%) as a yellow oil. R_f 0.42 (Pet ether:EtOAc 85:15); ν_{max} (neat)/cm^{-1} : 3024, 2933, 1453, 1102, 756, 732; δ_H (300 MHz, $CDCl_3$) 0.77-2.05 (7H, m, CH_2), 2.33-2.78 (2H, m, CH_2C*H*CHN and CH_2C*H*CH=), 2.79-2.94 (1H, m, CHC*H*N), 3.85, 3.97 (2H, ABq, *J* 13.2 Hz, NCH_2Ph), 5.50 (1H, ddd, *J* 1.7, 3.9 and 9.5 Hz, CHC*H*=CH), 5.97-6.10 (1H, m, CH=C*H*CHN), 7.21-7.51 (5H, m, Ar H); δ_C (100 MHz, $CDCl_3$) 27.3 (CH_2), 31.2 (CH_2), 32.8 (CH_2), 36.0 (CH, CH_2*C*HCH=), 37.0 (CH, CH_2*C*HCHN), 51.5 (CH_2, N*C*H_2Ph), 61.0 (CH, CH_2*C*HN), 125.8 (CH, CH*C*H=CH), 127.1 (CH, Ar), 128.3 (2 x CH, Ar), 128.6 (2 x CH, Ar), 136.8 (CH, CH=*C*HCHN), 140.8 (C, Ar); m/z (ES) 214.1592 ($[M+H]^+$, $C_{15}H_{20}N$ requires 214.1590), 425 (16%), 326 (26), 270 (82), 214 (100).

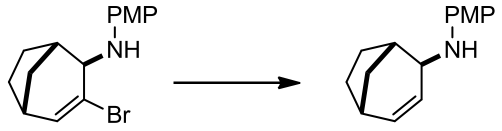
- (±)- (2*R*,5*S*)-3-Bromo-*N*-(4-methoxyphenyl)bicyclo[3.2.1]oct-3-en-2-amine **312**



287 **312**

A novel compound prepared according to a literature procedure.[27] A solution of 4-methoxyaniline (6.28 g, 38.9 mmol) in CH_3CN (51 mL) was treated with dibromo octene **287** (5.02 g, 18.9 mmol) and K_2CO_3 (2.87 g, 20.8 mmol). After 7 h at rt, the reaction mixture was quenched with H_2O (50 mL) and extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with brine (75 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:Et_2O 4:1) to give amine **312** (5.11 g, 88%) as a beige solid. mp 105-108 °C; R_f 0.59 (Pet ether:Et_2O 4:1); ν_{max} (neat)/cm^{-1} : 3381, 2935, 1509, 1229, 1032, 815, 761; δ_H (400 MHz, $CDCl_3$) 1.28-1.35 (1H, m, CH$_2$), 1.41-1.51 (1H, m, CH$_2$), 1.60-1.73 (2H, m, CH$_2$), 1.79 (1H, ddt, *J* 2.3, 9.0 and 11.6 Hz, CH$_2$), 1.94 (1H, dddd, *J* 2.6, 7.9, 10.6 and 13.5 Hz, CH$_2$), 2.54-2.60 (1H, m, CH$_2$C*H*CH=), 2.63 (1H, t, *J* 6.3 Hz, CH$_2$C*H*CHN), 3.61 (1H, d, *J* 2.0 Hz, CHC*H*N), 3.70 (1H, br s, NH), 3.75 (3H, s, OCH$_3$), 6.39 (1H, d, *J* 7.1 Hz, CH=CBr), 6.62 (2H, d, *J* 8.9 Hz, Ar H), 6.80 (2H, d, *J* 8.9 Hz, Ar H); δ_C (100 MHz, CDCl$_3$) 26.0 (CH$_2$), 31.0 (CH$_2$), 32.4 (CH$_2$), 38.1 (CH, CH$_2$*C*HCH=), 38.9 (CH, CH$_2$CHCHN), 56.0 (CH$_3$, OCH$_3$), 65.5 (CH, CH*C*HN), 114.8 (2 x CH, Ar), 115.2 (2 x CH, Ar), 122.3 (C, =CBr), 139.3 (CH, CH*C*H=CBr), 141.4 (C, ArCN), 152.5 (C, ArCO); m/z (ES) 330.0453 ([M+Na]$^+$ $C_{15}H_{18}{}^{79}BrNNaO$ requires 330.0469), 332 (100%), 330 (100), 310 (43),308 (43).

- (±)-(2*R*,5*S*)-*N*-(4-Methoxyphenyl)bicyclo[3.2.1]oct-3-en-2-amine **313**

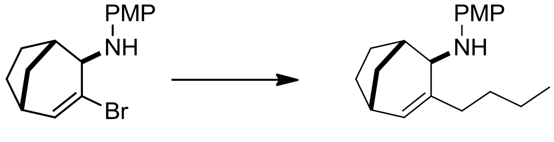


312 **313**

A novel compound prepared according to a literature procedure.[249] A solution of amine **312** (1.46 g, 4.73 mmol) in THF (47 mL) was cooled to -78 °C. *n*BuLi (12.7 mL of a 1.12 M solution in hexane, 14.2 mmol) was added dropwise over 10 min. The reaction mixture was allowed to warm to 10 °C over 4.5 h, quenched with NH$_4$Cl (50 mL of a saturated aq. solution) and extracted with Et$_2$O (2 x 50 mL). The combined organic extracts were washed with brine (75 mL), dried over MgSO$_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:Et$_2$O 9:1) to give amine **313** (0.958 g, 88%) as a yellow solid. mp 78-79 °C; R$_f$ 0.54 (Pet ether:Et$_2$O 4:1); ν_{max} (neat)/cm^{-1} : 3369, 2932, 2867, 1616, 1507, 1225, 1034, 814, 770; δ_H (400 MHz, CDCl$_3$) 1.22-1.30 (1H, m, CH$_2$), 1.30-1.41 (1H, m, CH$_2$), 1.59 (1H, d, *J* 11.1 Hz, CH$_2$), 1.62-1.75 (2H, m, CH$_2$), 1.85-1.97 (1H, m, CH$_2$), 2.46-2.57 (2H, m, CH$_2$C*H*CHN and CH$_2$C*H*CH=), 3.45 (1H, br s, NH), 3.52-3.57 (1H, m, CHC*H*N), 3.76 (3H, s, OCH$_3$), 5.47 (1H, ddd, *J* 1.7, 4.0 and 9.4 Hz, CHC*H*=CH), 6.09 (1H, ddt, *J* 1.2, 6.7 and 9.4 Hz, NCHC*H*=CH), 6.60 (2H, d, *J* 8.9 Hz, Ar H), 6.80 (2H, d, *J* 8.9 Hz, Ar H); δ_C (100 MHz, CDCl$_3$) 26.7

(CH_2), 31.4 (CH_2), 32.7 (CH_2), 35.8 (CH, CH_2*C*HCH=), 36.7 (CH, CH_2*C*HCHN), 56.0 (CH_3, OCH_3), 57.6 (CH, CH*C*HN), 114.6 (2 x CH, Ar), 115.2 (2 x CH, Ar), 124.8 (CH, CH*C*H=CH), 137.9 (CH, NCH*C*H=CH), 141.4 (C, ArCN), 152.0 (C, ArCO); m/z (ES) 230.1542 ($[M+H]^+$, $C_{15}H_{20}NO$ requires 230.1539), 532 (16%), 445 (15), 371 (52), 355 (16), 230 (100), 149 (11).

- (±)-(2*R*,5*S*)-3-Butyl-*N*-(4-methoxyphenyl)bicyclo[3.2.1]oct-3-en-2-amine **314**

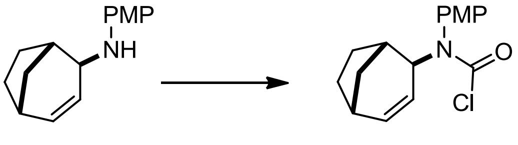


312 **314**

A novel compound prepared according to a literature procedure.[249] A solution of amine **312** (0.150 g, 0.487 mmol) in THF (4.9 mL) was cooled to -78 °C. *n*BuLi (1.00 mL of a 1.46 M solution in hexane, 1.46 mmol) was added dropwise over 1 min. The reaction mixture was stirred at -78 °C for 1 h then warmed to rt. After 3 h at rt, the reaction mixture was quenched with NH_4Cl (5 mL of a saturated aq. solution) and extracted with Et_2O (2 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:Et_2O 9:1) to give amine **313** (55 mg, 49%) as a yellow solid and alkylated amine **314** (25 mg, 18%) as a yellow oil. R_f 0.75 (Pet ether:Et_2O 4:1); ν_{max} (neat)/cm^{-1} : 3395, 2929, 2862, 1617, 1508, 1228, 1038, 815; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.1 Hz, $(CH_2)_3$C*H₃*), 1.17-1.48 (6H, m, CH_2), 1.58-1.67 (3H, m, CH_2), 1.79-1.98 (2H, m, CH_2), 2.02-2.04 (1H, m, CH_2), 2.43 (1H, d, *J* 3.7 Hz, CH_2C*H*CH=), 2.50 (1H, t, *J* 5.5 Hz, CH_2C*H*CHN), 3.41 (1H, d, *J* 1.7 Hz, CHC*H*N), 3.49 (1H, br s, NH), 3.76 (3H, s, OCH_3), 5.76 (1H, d, *J* 6.7 Hz, =CH), 6.59 (2H, d, *J* 8.9 Hz, Ar H), 6.79 (2H, d, *J* 8.9 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3, $(CH_2)_3CH_3$), 22.5 (CH_2), 26.3 (CH_2), 30.7 (CH_2), 31.6 (CH_2), 33.1 (CH_2), 33.3 (CH_2), 35.4 (CH, CH_2*C*HCH=), 36.7 (CH, CH_2*C*HCHN), 56.1 (CH_3, OCH_3), 59.5 (CH, CH*C*HN), 114.3 (2 x CH, Ar), 115.3 (2 x CH, Ar), 131.9 (CH, =CH), 135.6 (C, =*C*$(CH_2)_3CH_3$), 142.2

(C, ArCN), 151.8 (C, ArCO); m/z (ES) 286.2170 ($[M+H]^+$, $C_{19}H_{28}NO$ requires 286.2165), 532 (10%), 445 (13), 388 (10), 371 (42), 355 (11), 286 (100), 163 (96).

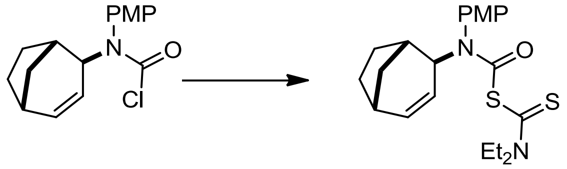
- (±)-(2*R*,5*S*)-Bicyclo[3.2.1]oct-3-en-2-yl(4-methoxyphenyl)carbamic chloride **313'**



313 **313'**

A novel compound prepared according to a literature procedure.[27] A solution of triphosgene (0.556 g, 1.87 mmol) in toluene (10 mL) was treated with pyridine (0.492 mL, 6.08 mmol) and subsequently with a solution of amine **313** (1.16 g, 5.07 mmol) in toluene (20 mL). The reaction mixture was stirred for 18 h at rt, quenched with NH_4Cl (20 mL of a saturated aq. solution) and extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed sequentially with HCl (50 mL of a 0.25 M aq. solution) and brine (50 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give carbamoyl chloride **313'** (1.46 g, 99%) as a brown solid. mp 73-74 °C; R_f 0.54 (Pet ether:Et_2O 4:1); ν_{max} (neat)/cm^{-1}: 2940, 1723, 1509, 1246, 1203, 1033, 735; δ_H (400 MHz, $CDCl_3$) 0.36 (1H, d, *J* 11.2 Hz, CH_2), 0.98 (1H, dddd, *J* 1.1, 3.8, 4.8 and 11.2 Hz, CH_2), 1.36-1.43 (1H, m, CH_2), 1.57-1.62 (2H, m, CH_2), 1.88-2.01 (1H, m, CH_2), 2.28-2.32 (1H, m, CH_2C*H*CH=), 2.58 (1H, t, *J* 6.1 Hz, CH_2C*H*CHN), 3.81 (3H, s, OCH_3), 4.61-4.69 (1H, m, CHC*H*N), 5.43 (1H, ddd, *J* 1.7, 3.6 and 9.5 Hz, CHC*H*=CH), 6.06 (1H, tdd, *J* 1.4, 6.9 and 16.4 Hz, NCHC*H*=CH), 6.83-7.19 (4H, m, Ar H); δ_C (100 MHz, $CDCl_3$) (as a mixture of rotamers) 29.3 (CH_2), 30.3 (CH_2), 32.8 (CH_2), 34.7 (CH, CH_2*C*HCH=), 38.8 (CH, CH_2*C*HCHN), 55.6 (CH_3, OCH_3), 62.6 (CH, CH*C*HN), 113.9, 114.2 (2 x CH, Ar), 122.3 (CH, CH*C*H=CH), 131.2, 132.0 (2 x CH, Ar), 132.6 (C, ArCN), 139.5 (CH, NCH*C*H=CH), 150.1 (C, ArCO), 159.7 (C, NC(O)Cl); m/z (ES) 314.0934 ($[M+Na]^+$, $C_{16}H_{18}{}^{35}ClNNaO_2$ requires 314.0934), 316 (13%), 314 (76), 310 (26), 241 (18), 239 (100).

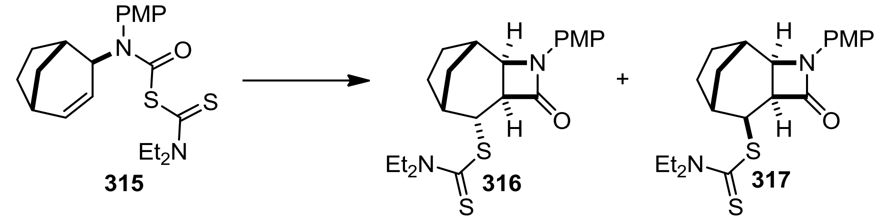
- (±)-(2*R*,5*S*)-Diethyldithiocarbamic acid-[(4-methoxyphenyl)(bicyclo[3.2.1]oct-3-en-2-yl)carbamic acid]-thioanhydride **315**



313' **315**

A novel compound prepared according to a literature procedure.[27] A solution of carbamoyl chloride **313’** (0.223 g, 0.764 mmol) in acetone (5.9 mL) was treated with sodium diethyldithiocarbamate trihydrate (0.517 g, 2.29 mmol). The reaction mixture was heated at reflux for 18 h, quenched with H_2O (6 mL) and extracted with Et_2O (3 x 6 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 4:1) to give dithiocarbamate **315** (0.285 g, 92%) as a yellow solid. mp 131-132 °C (CH_2Cl_2); R_f 0.37 (Pet ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1}: 2946, 1673, 1507, 1486, 1424, 1228, 1191, 821; δ_H (400 MHz, $CDCl_3$) (as a mixture of rotamers) 0.86 (1H, d, *J* 11.2 Hz, CH_2), 0.92-1.00 (1H, m, CH_2), 1.20 (3H, t, *J* 7.1 Hz, CH_2CH_3), 1.29 (3H, t, *J* 7.1 Hz, CH_2CH_3), 1.32-1.40 (1H, m, CH_2), 1.49-1.57 (2H, m, CH_2), 1.82-1.94 (1H, m, CH_2), 2.17-2.29 (1H, m, $CH_2C\mathit{H}CH=$), 2.53 (1H, t, *J* 6.0 Hz, $CH_2C\mathit{H}CHN$), 3.76 (2H, q, *J* 7.1 Hz, $C\mathit{H}_2CH_3$), 3.79 (3H, s, OCH_3), 3.97 (2H, q, *J* 7.1 Hz, $C\mathit{H}_2CH_3$), 4.76 (1H, br s, CHC*H*N), 5.36 (1H, ddd, *J* 1.7, 3.7 and 9.5 Hz, CHC*H*=CH), 6.00 (1H, t, *J* 8.2 Hz, NCHC*H*=CH), 6.83 (2H, t, *J* 6.8 Hz, Ar H), 7.03 (1H, d, *J* 8.4 Hz, Ar H), 7.21 (1H, d, *J* 8.4 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) (as a mixture of rotamers) 11.1 (CH_3, CH_2CH_3), 13.6 (CH_3, CH_2CH_3), 29.1 (CH_2), 30.4 (CH_2), 32.7 (CH_2), 34.7 (CH, $CH_2CHCH=$), 38.9 (CH, $CH_2\mathit{C}HCHN$), 48.7 (CH_2, $\mathit{C}H_2CH_3$), 50.4 (CH_2, $\mathit{C}H_2CH_3$), 55.5 (CH_3, OCH_3), 60.0 (CH, CH*C*HN), 114.1 (2 x CH, Ar), 122.7 (CH, CH*C*H=CH), 130.0 (C, ArCN), 132.5, 133.1 (2 x CH, Ar), 139.1 (CH, NCH*C*H=CH), 160.2 (C, ArCO), 164.3 (C, C(O)N), 185.7 (C, C(S)S); m/z (ES) 427.1491 ($[M+Na]^+$, $C_{21}H_{28}N_2NaO_2S_2$ requires 427.1490), 854 (28%), 833 (42), 832 (74), 831 (100), 690 (11), 506 (56), 450 (45), 427 (46), 405 (17), 256 (19).

- (±)-(1*S*,2*R*,5*S*,6*R*,7*R*)-3-(4-Methoxyphenyl)-4-oxo-3-azatricyclo[5.2.1.0^{2,5}]decan-6-yl diethyldithiocarbamate **316** and (±)-(1*S*,2*R*,5*S*,6*S*,7*R*)-3-(4-methoxyphenyl)-4-oxo-3-azatricyclo[5.2.1.0^{2,5}]decan-6-yl diethyldithiocarbamate **317**

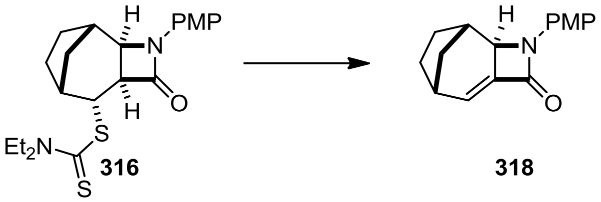


Novel compounds prepared according to a literature procedure.[26] A solution of dithiocarbamate **315** (1.65 g, 4.07 mmol) in cyclohexane (41 mL) was degassed for 10 min and irradiated with a 500 W lamp which generated enough heat to bring the solution to reflux. After 3.5 h, the solvent was removed under reduced pressure and the crude product obtained was purified by column chromatography (Pet ether to Pet ether:EtOAc 85:15) to give *cis*-lactam **316** (1.07 g, 65%) and *trans*-lactam **317** (0.265 g, 16%) as pale yellow solids.

316: mp 160-162 °C; R_f 0.50 (Pet ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1}: 2932, 1739, 1512, 1243, 825; δ_H (400 MHz, CDCl$_3$) 1.19-1.33 (6H, m, CH$_2$C*H$_3$*), 1.43-1.56 (2H, m, CH$_2$), 1.64-1.91 (4H, m, CH$_2$), 2.71 (1H, t, *J* 5.2 Hz, CH$_2$C*H*CHS), 2.79 (1H, q, *J* 5.6 Hz, CH$_2$C*H*CHN), 3.19 (1H, t, *J* 5.1 Hz, CHC*H*C(O)), 3.70 (2H, q, *J* 7.0 Hz, C*H$_2$*CH$_3$), 3.75 (3H, s, OCH$_3$), 3.83-4.12 (3H, m, C*H$_2$*CH$_3$ and CHC*H*S), 4.71 (1H, t, *J* 4.8 Hz, CHC*H*N), 6.84 (2H, d, *J* 9.0 Hz, Ar H), 7.33 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, CDCl$_3$) 11.6 (CH$_3$, CH$_2$*C*H$_3$), 12.6 (CH$_3$, CH$_2$*C*H$_3$), 24.7 (CH$_2$), 27.5 (CH$_2$), 31.1 (CH$_2$), 34.5 (CH, CH$_2$*C*HCHS), 37.1 (CH, CH$_2$*C*HCHN), 46.7 (CH$_2$, *C*H$_2$CH$_3$), 48.2 (CH, CH*C*HC(O)), 49.2 (CH$_2$, *C*H$_2$CH$_3$), 50.8 (CH, CH*C*HN), 55.6 (CH$_3$, OCH$_3$), 57.9 (CH, CH*C*HS), 114.5 (2 x CH, Ar), 118.6 (2 x CH, Ar), 130.9 (C, ArCN), 156.1 (C, ArCO), 166.0 (C, C(O)N), 193.4 (C, C(S)S); m/z (ES) 427.1485 ([M+Na]$^+$ $C_{21}H_{28}N_2NaO_2S_2$ requires 427.1490), 833 (19%), 832 (37), 831 (59), 428 (27), 427 (100), 405 (34).

317: mp 134-136 °C; R_f 0.70 (Pet ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1}: 2935, 1729, 1511, 1242, 1027, 835; δ_H (400 MHz, CDCl$_3$) 1.27 (3H, t, *J* 7.1 Hz, CH$_2$C*H$_3$*), 1.33 (3H, t, *J* 7.1 Hz, CH$_2$C*H$_3$*), 1.53-1.63 (1H, m, CH$_2$), 1.75-2.03 (5H, m, CH$_2$), 2.50 (1H, t, *J* 6.1 Hz, CH$_2$C*H*CHN), 2.73 (1H, t, *J* 5.7 Hz, CH$_2$C*H*CHS), 3.71-4.14 (6H, m, C*H$_2$*CH$_3$, CHC*H*C(O) and CHC*H*S), 3.77 (3H, s, OCH$_3$), 4.32 (1H, d, *J* 10.7 Hz, CHC*H*N), 6.86 (2H, d, *J* 9.0 Hz, Ar H), 7.35 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, CDCl$_3$) 11.7 (CH$_3$, CH$_2$*C*H$_3$), 12.8 (CH$_3$, CH$_2$*C*H$_3$), 26.7 (CH$_2$), 27.6 (CH$_2$), 31.9 (CH$_2$), 35.0 (CH, CH$_2$*C*HCHS), 41.9 (CH, CH$_2$CHCHN), 45.1 (CH, CH*C*HC(O)), 47.2 (CH$_2$, *C*H$_2$CH$_3$), 49.6 (CH$_2$, *C*H$_2$CH$_3$), 51.1 (CH, CH*C*HN), 55.7 (CH$_3$, OCH$_3$), 57.4 (CH, CH*C*HS), 114.6 (2 x CH, Ar), 118.6 (2 x CH, Ar), 130.9 (C, ArCN), 156.1 (C, ArCO), 165.2 (C, C(O)N), 195.2 (C, C(S)S); m/z (ES) 427.1485 ([M+Na]$^+$ C$_{21}$H$_{28}$N$_2$NaO$_2$S$_2$ requires 427.1490), 428 (18), 427 (100), 405 (15).

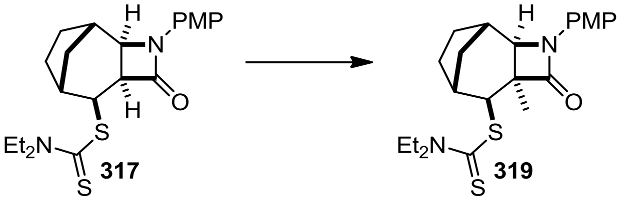
- (±)-(1*S*,2*R*,7*R*)-3-(4-Methoxyphenyl)-3-azatricyclo[5.2.1.0^{2,5}]decan-5-en-4-one **318**



316 **318**

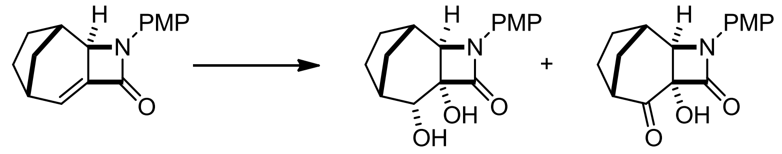
A novel compound prepared according to a modified literature procedure.[39] A solution of lactam **316** (0.139 g, 0.344 mmol) in THF (3.4 mL) was cooled to -78 °C and treated with methyl iodide (32 μL, 0.52 mmol). The reaction mixture was stirred at -78 °C for 30 min, LHMDS (0.52 mL of a 1.0 M solution in THF, 0.52 mmol) was added over 2 min. After 5.5 h at -78 °C, the solvent was removed under reduced pressure and the crude product obtained was purified by column chromatography (Pet ether to Pet ether:EtOAc 9:1) to give lactam **318** (69 mg, 78%) as a white solid. mp 120-121 °C; R$_f$ 0.69 (Pet ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1}: 2942, 1738, 1507, 1370, 1235, 833; δ_H (400 MHz, CDCl$_3$) 1.42 (1H, d, *J* 11.6 Hz, CH$_2$), 1.51 (1H, ddd, *J* 3.1, 4.4 and 11.6 Hz, CH$_2$), 1.60-1.75 (2H, m, CH$_2$), 1.75-1.88 (1H, m, CH$_2$), 1.94-2.07 (1H, m, CH$_2$), 2.72-2.82 (2H, m, CH$_2$C*H*CH= and CH$_2$C*H*CHN), 3.78 (3H, s, OCH$_3$), 4.18 (1H, d, *J* 1.4 Hz, CHC*H*N), 6.87 (2H, d, *J* 9.0 Hz, Ar H), 6.95 (1H, dd, *J* 1.4 and 7.5 Hz, CHC*H*=C), 7.31 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, CDCl$_3$) 30.1 (CH$_2$), 31.8 (CH$_2$), 34.2 (CH), 34.6 (CH), 35.8 (CH$_2$), 55.7 (CH$_3$, OCH$_3$), 65.5 (CH, CH*C*HN), 114.7 (2 x CH, Ar), 117.4 (2 x CH, Ar), 132.9 (C, ArCN), 137.2 (C, =C), 140.4 (CH, =CH), 155.8 (C, ArCO), 162.1 (C, C(O)N); m/z (ES) 278.1154 ($[M+Na]^+$, $C_{16}H_{17}NNaO_2$ requires 278.1154), 279 (12%), 278 (100).

- (±)-(1*S*,2*R*,5*S*,6*S*,7*R*)-3-(4-Methoxyphenyl)-5-methyl-4-oxo-3-azatricyclo[5.2.1.0^{2,5}] decan-6-yl diethyldithiocarbamate **319**



A novel compound prepared according to a modified literature procedure.[39] A solution of lactam **317** (64 mg, 0.16 mmol) in THF (1.6 mL) was cooled to -78 °C, treated with methyl iodide (4.9 µL, 0.79 mmol) and LHMDS (0.79 mL of a 1.0 M solution in THF, 0.79 mmol). After 6.5 h at -78 °C, the solvent was removed under reduced pressure and the crude product obtained was purified by column chromatography (Pet ether to Pet ether:EtOAc 7:3) to give lactam **319** (54 mg, 82%) as a yellow solid. mp 150-151 °C; R_f 0.39 (Pet ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1}: 2931, 1733, 1514, 1487, 1250, 829; δ_H (400 MHz, CDCl$_3$) 1.17-1.37 (7H, m, CH$_2$ and CH$_2$C*H*$_3$), 1.53 (3H, s, CH$_3$CC(O)), 1.55-1.61 (1H, m, CH$_2$), 1.76-2.01 (4H, m, CH$_2$), 2.45 (1H, t, *J* 5.9 Hz, CH$_2$C*H*CHN), 2.71 (1H, t, *J* 5.2 Hz, CH$_2$C*H*CHS), 3.76 (1H, s, CHC*H*S), 3.78 (3H, s, OCH$_3$), 3.76-4.10 (4H, m, C*H*$_2$CH$_3$), 4.12 (1H, s, CHC*H*N), 6.87 (2H, d, *J* 8.9 Hz, Ar H), 7.35 (2H, d, *J* 8.9 Hz, Ar H); δ_C (100 MHz, CDCl$_3$) 11.8 (CH$_3$, CH$_2$*C*H$_3$), 12.8 (CH$_3$, CH$_2$*C*H$_3$), 24.6 (CH$_3$, *C*H$_3$CC(O)), 26.5 (CH$_2$), 26.7 (CH$_2$), 31.6 (CH$_2$), 35.1 (CH, CH$_2$*C*HCHS), 42.7 (CH, CH$_2$*C*HCHN), 47.0 (CH$_2$, *C*H$_2$CH$_3$), 49.6 (CH$_2$, *C*H$_2$CH$_3$), 51.1 (C, CH$_3$*C*C(O)), 55.7 (CH$_3$, OCH$_3$), 59.1 (CH, CH*C*HN), 65.5 (CH, CH*C*HS), 114.6 (2 x CH, Ar), 118.9 (2 x CH, Ar), 130.9 (C, ArCN), 156.2 (C, ArCO), 168.2 (C, C(O)N), 195.8 (C, C(S)S); m/z (ES) 419.1823 ($[M+H]^+$, $C_{22}H_{31}N_2O_2S_2$ requires 419.1821), 854 (18%), 441 (12), 419 (100).

- (±)-(1*S*,2*R*,5*S*,6*R*,7*R*)-5,6-Dihydroxy-3-(4-methoxyphenyl)-3-azatricyclo[5.2.1.$0^{2,5}$] decan-4-one **320** and (±)-(1*S*,2*R*,5*S*,7*R*)-5-Hydroxy-3-(4-methoxyphenyl)-3-azatricyclo[5.2.1.$0^{2,5}$] decane-4,6-dione **321**



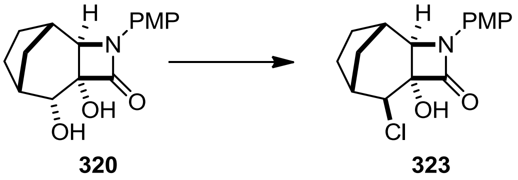
318 **320** **321**

Novel compounds prepared according to a literature procedure.[56] A solution of lactam **318** (95 mg, 0.37 mmol) in a 5:5:2 mixture of H_2O:acetone:*t*BuOH (2.1 mL) was treated with NMO (0.105 g, 0.893 mmol) and OsO_4 (2 µL of a 4 wt% aq. solution, cat). After 18 h at 40 °C, sodium bisulfite (0.212 g, 1.12 mmol) was added to quench the reaction. After 1 h at 40 °C, the reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (2 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether:EtOAc 3:1 to Pet ether:EtOAc 1:1) to give diol **320** (0.100 g, 93%) as a yellow solid contaminated with 16% of hydroxyl ketone **321**.

320: mp 162-165 °C; R_f 0.35 (Pet ether:EtOAc 1:1); ν_{max} (neat)/cm^{-1}: 3492, 3274, 2925, 1702, 1515, 1399, 1251, 1082, 1021, 827, 816; δ_H (400 MHz, $CDCl_3$) 1.35-1.47 (1H, m, CH_2), 1.54 (1H, d, *J* 13.0 Hz, CH_2), 1.57-1.71 (2H, m, CH_2), 1.72-1.93 (2H, m, CH_2), 2.45 (1H, dd, *J* 6.4 and 11.6 Hz, CH_2C*H*CHOH), 2.67 (1H, t, *J* 4.4 Hz, CH_2C*H*CHN), 3.78 (3H, s, OCH_3), 4.02 (1H, t, *J* 1.6 Hz, CHC*H*N), 4.23 (1H, s, C*H*OH), 4.99 (2H, br s, OH), 6.87 (2H, d, *J* 9.0 Hz, Ar H), 7.32 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 20.5 (CH_2), 24.9 (CH_2), 27.7 (CH_2), 29.6 (CH, CH_2*C*HCHO), 33.9 (CH, CH_2*C*HCHN), 55.7 (CH_3, OCH_3), 68.3 (CH, CH*C*HOH), 69.2 (CH, CH*C*HN), 79.4 (C, CH*C*OH), 114.6 (2 x CH, Ar), 119.8 (2 x CH, Ar), 130.1 (C, ArCN), 156.9 (C, ArCO), 170.6 (C, C(O)N); m/z (ES) 290.1389 ($[M+H]^+$, $C_{16}H_{20}NO_4$ requires 290.1387), 312 (24%), 307 (20), 305 (16), 291 (17),290 (100).

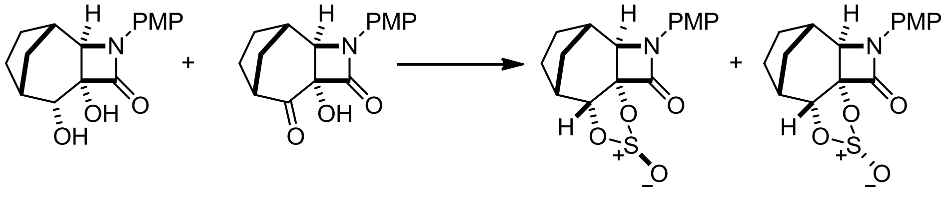
321: mp 149-150 °C; R_f 0.41 (Pet ether:EtOAc 1:1); ν_{max} (neat)/cm^{-1}: 3308, 1753, 1687, 1514, 1251, 1151, 1015, 833; δ_H (300 MHz, $CDCl_3$) 1.52-1.87 (3H, m, CH_2), 2.00-2.19 (3H, m, CH_2), 2.91-3.06 (2H, m, CH_2C*H*CHN and CH_2C*H*C(O)), 3.80 (3H, s, OCH_3), 3.96-4.28 (2H, m, CHC*H*N and OH), 6.91 (2H, d, *J* 9.0 Hz, Ar H), 7.38 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 24.9 (CH_2), 27.7 (CH_2), 29.6 (CH_2), 34.1 (CH), 48.8 (CH), 55.7 (CH_3, OCH_3), 63.2 (CH, CH*C*HN), 85.8 (C, CH*C*OH), 114.9 (2 x CH, Ar), 119.5 (2 x CH, Ar), 129.9 (C, ArCN), 157.1 (C, ArCO), 161.4 (C, C(O)N), 207.3 (C, CH*C*(O)C); m/z (ES) 305.1503 ($[M+NH_4]^+$ $C_{16}H_{21}N_2O_4$ requires 305.1496), 371 (19%), 305 (100), 139 (68).

- (±)-(1*S*,2*R*,5*S*,6*S*,7*R*)-6-Chloro-5-hydroxy-3-(4-methoxyphenyl)-3-azatricyclo[5.2.1.0^{2,5}] decan-4-one **323**



A novel compound prepared according to a literature procedure.[19] A solution of PPh_3 (0.111 g, 0.425 mmol) and hexachloroethane (0.100 g, 0.425 mmol) in CH_3CN (1.0 mL) was stirred at rt for 20 min before being added dropwise to a solution of diol **320** (82 mg, 0.28 mmol) in CH_3CN (0.9 mL). The reaction mixture was heated at reflux for 18 h, evaporated under reduced pressure and purified directly by column chromatography (Pet ether to Pet ether:EtOAc 1:1) to give chloro hydroxyl lactam **323** (26 mg, 30%) as a white solid. mp 224-225 °C; R_f 0.67 (Pet ether:EtOAc 3:2); ν_{max} (neat)/cm^{-1}: 3294, 2936, 1696, 1513, 1248, 1159, 1026, 819; δ_H (400 MHz, $CDCl_3$) 1.50-1.66 (2H, m, CH_2), 1.86 (1H, dd, *J* 5.3 and 15.4 Hz, CH_2), 2.05 (1H, tdd, *J* 2.6, 5.6 and 13.4 Hz, CH_2), 2.18-2.36 (2H, m, CH_2), 2.42 (1H, d, *J* 3.1 Hz, CH_2C*H*CHCl), 2.54 (1H, t, *J* 4.2 Hz, CH_2C*H*CHN), 3.51 (1H, br s, OH), 3.78 (3H, s, OCH_3), 4.02 (1H, d, *J* 1.2 Hz, CHC*H*N), 4.64 (1H, s, CHC*H*Cl), 6.83 (2H, d, *J* 9.0 Hz, Ar H), 7.28 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 24.5 (CH_2), 27.8 (CH_2), 27.8 (CH_2), 33.8 (CH, CH_2*C*HCHCl), 43.4 (CH, CH_2*C*HCHN), 55.8 (CH_3, OCH_3), 59.0 (CH, CH*C*HCl), 67.3 (CH, CH*C*HN), 91.4 (C, CH*C*OH), 114.7 (2 x CH, Ar), 119.0 (2 x CH, Ar), 130.0 (C, ArCN), 156.9 (C, ArCO), 165.8 (C, C(O)N); m/z (ES) 330.0867 ($[M+Na]^+$, $C_{16}H_{18}{}^{35}ClNNaO_3$ requires 330.0873), 364 (13%), 362 (59), 332 (42), 330 (100), 308 (8), 294 (7).

- (±)-(3a*S*,5a*R*,6*S*,9*R*,9a*S*)-5-(4-Methoxyphenyl)hexahydro-6,9-methanol[1,3,2] dioxathiolo[4',5':2,3] cyclohepta[1,2-*b*]azet-4(5H)-one 2-oxide **325a** and **325b**



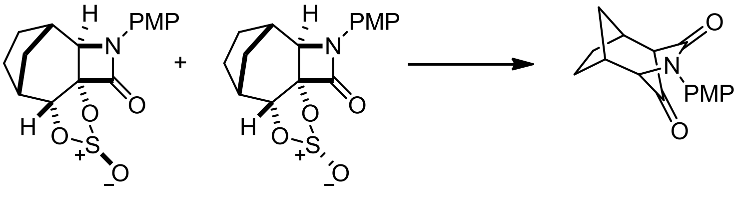
320 **321** **325a** **325b**

Novel compounds prepared according to a literature procedure.[61] A solution of diol **320** (65 mg, 0.23 mmol) in CH_2Cl_2 (1.2 mL) at 0 °C was treated with pyridine (82 µL, 1.0 mmol) and $SOCl_2$ (33 µL, 0.45 mmol). The ice bath was removed after 30 min and stirring continued at rt for 6.5 h. The reaction mixture was diluted with H_2O (2 mL) and extracted with CH_2Cl_2 (2 x 3 mL). The combined organic extracts were washed sequentially with HCl (3 mL of a 1 M aq. solution) and brine (3 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 3:2) to give **325a** (31 mg, 41%) and **325b** (26 mg, 35%) as white solids and hydroxyl ketone **321** (9 mg, 14% based on recovered SM), an impurity from the dihydroxylation reaction, as a colourless oil.

325a: mp 170-173 °C; R_f 0.37 (Pet ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1}: 2957, 1745, 1510, 1244, 971, 798, 660; δ_H (300 MHz, $CDCl_3$) 1.51-1.75 (5H, m, CH_2), 1.83-1.97 (1H, m, CH_2), 2.67-2.75 (1H, m, CH_2C*H*CHO), 2.78 (1H, t, *J* 5.5 Hz, CH_2C*H*CHN), 3.79 (3H, s, OCH_3), 4.16-4.19 (1H, m, CHC*H*N), 5.33 (1H, d, *J* 5.8 Hz, CHC*H*O), 6.90 (2H, d, *J* 9.0 Hz, Ar H), 7.37 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 21.1 (CH_2), 26.8 (CH_2), 27.9 (CH_2), 33.6 (CH, CH_2*C*HCHO), 35.1 (CH, CH_2*C*HCHN), 55.6 (CH_3, OCH_3), 66.1 (CH, CH*C*HN), 81.6 (CH, CH*C*HOS), 88.3 (C, CH*C*OS), 114.8 (2 x CH, Ar), 119.5 (2 x CH, Ar), 129.6 (C, ArCN), 157.1 (C, ArCO), 161.6 (C, C(O)N); m/z (ES) 336.0906 ([M+H]$^+$ $C_{16}H_{18}NO_5S$ requires 336.0900), 371 (17%), 353 (45), 336 (100).

325b: mp 152-153 °C; R_f 0.62 (Pet ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1}: 2943, 1749, 1511, 1206, 974, 823, 791, 649; δ_H (300 MHz, $CDCl_3$) 1.50-1.78 (4H, m, CH_2), 1.87-1.99 (1H, m, CH_2), 2.14-2.30 (1H, m, CH_2), 2.71 (1H, q, *J* 6.2 Hz, CH_2C*H*CHO), 2.78 (1H, t, *J* 6.0 Hz, CH_2C*H*CHN), 3.80 (3H, s, OCH_3), 4.25-4.30 (1H, m, CHC*H*N), 5.12 (1H, d, *J* 6.8 Hz, CHC*H*O), 6.91 (2H, d, *J* 9.0 Hz, Ar H), 7.36 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 23.8 (CH_2), 25.5 (CH_2), 27.4 (CH_2), 34.0 (CH, CH_2*C*HCHO), 35.5 (CH, CH_2*C*HCHN), 55.7 (CH_3, OCH_3), 68.1 (CH, CH*C*HN), 85.8 (CH, CH*C*HOS), 88.1 (C, CH*C*OS), 114.8 (2 x CH, Ar), 119.7 (2 x CH, Ar), 129.4 (C, ArCN), 157.3 (C, ArCO), 160.9 (C, C(O)N); m/z (ES) 336.0906 ([M+H]$^+$ $C_{16}H_{18}NO_5S$ requires 336.0900), 532 (14%), 445 (12), 353 (35), 336 (100).

- (±)-(1*S*,2*R*,6*R*)-3-(4-Methoxyphenyl)-3-azatricyclo[4.2.1.1^{2,5}]decan-4,10-dione **322**

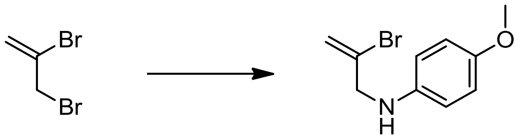


325a **325b** **322**

A novel compound prepared according to a modified literature procedure.[16] A solution of cyclic sulphites **325** (59 mg, 0.18 mmol) in diphenyl ether (1.8 mL) were heated to reflux. After 2 h, the reaction mixture was directly purified by column chromatography (Pet ether to Pet ether:EtOAc 4:1) to give tricyclic ketone **322** (43 mg, 90%) as pale yellow crystals. mp 112-114 °C; R_f 0.35 (Pet ether:EtOAc 7:3); ν_{max} (neat)/ cm^{-1}: 2959, 1774, 1692, 1510, 1375, 1215, 1027, 831; δ_H (400 MHz, $CDCl_3$) 1.45 (1H, dt, *J* 3.2 and 12.7 Hz, CH_2), 1.64-1.90 (4H, m, CH_2), 1.93 (1H, d, *J* 12.7 Hz, CH_2), 2.77-2.85 (1H, m, CH_2C*H*CHN), 2.97-3.03 (1H, m, CH_2C*H*CHC(O)), 3.05 (1H, dd, *J* 2.3 and 7.1 Hz, CHC*H*C(O)), 3.79 (3H, s, OCH_3), 4.08 (1H, dd, *J* 2.3 and 6.2 Hz, CHC*H*N), 6.89 (2H, d, *J* 9.1 Hz, Ar H), 7.44 (2H, d, *J* 9.1 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 27.0 (CH_2), 27.7 (CH_2),

31.7 (CH_2), 40.4 (CH, CH_2*C*HCHC(O)), 41.8 (CH, CH_2*C*HCHN), 55.6 (CH_3, OCH_3), 60.1 (CH, CH*C*HC(O)), 69.9 (CH, CH*C*HN), 114.5 (2 x CH, Ar), 122.2 (2 x CH, Ar), 130.5 (C, ArCN), 157.1 (C, ArCO), 168.0 (C, C(O)N), 201.3 (C, CH*C*(O)CH); m/z (ES) 272.1283 ($[M+H]^+$, $C_{16}H_{18}NO_3$ requires 272.1281), 565 (10%), 543 (56), 272 (100).

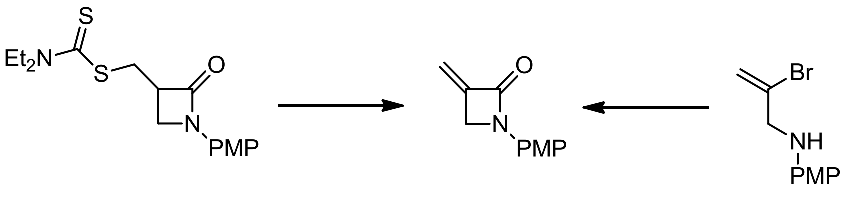
- *N*-(2-Bromoallyl)-4-methoxyaniline **326**



290 **326**

A known compound prepared according to the literature procedure.[108] A solution of 4-methoxyaniline (3.08 g, 25.0 mmol) and K_2CO_3 (1.27 g, 9.16 mmol) in DMF (21 mL) was cooled to 0 °C and treated with 2,3-dibromopropene **290** (1.67 g, 8.33 mmol). The reaction mixture was allowed to warm progressively to rt over 18 h, diluted with Et_2O (20 mL) and washed with brine (2 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:Et_2O 9:1) to give amine **326** (1.66 g, 83%) as a yellow oil (lit. yield 76%). R_f 0.24 (Pet ether:Et_2O 9:1); ν_{max} (neat)/cm^{-1} : 3408, 2933, 1636, 1509, 1230, 1033, 890, 816; δ_H (300 MHz, $CDCl_3$) 3.75 (3H, s, OCH_3), 3.95 (3H, br s and t, *J* 1.4 Hz, NH and CH_2N), 5.55 (1H, m, CH_2=C), 5.85 (1H, dd, *J* 1.4 and 3.5 Hz, CH_2=C), 6.59 (2H, d, *J* 9.0 Hz, Ar H), 6.79 (2H, d, *J* 9.0 Hz, Ar H); δ_C (75 MHz, $CDCl_3$) 53.1 (CH_2, NCH_2), 55.9 (CH_3, OCH_3), 114.6 (2 x CH, Ar), 115.0 (2 x CH, Ar), 117.0 (CH_2, *C*H_2=C), 131.7 (C, CH_2=*C*Br), 140.8 (C, ArCN), 152.7 (C, ArCO); m/z (ES) 242.0176 ($[M+H]^+$ $C_{10}H_{13}{}^{79}BrNO$ requires 242.0175), 245 (12%), 244 (100), 243 (11), 242 (95), 240 (20). *Literature data*:[108] ν_{max} (neat)/cm^{-1}: 3410 (NH), 1630 (C=C); δ_H (60 MHz, $CDCl_3$) 3.71 (1H, s, NH), 3.73 (s, 3H, OCH_3), 3.94 (t, *J* = 1.5 Hz, 2H, NCH_2), 5.54 (m, 1H, vinyl), 5.83 (m, 1H, vinyl), 6.52-6.83 (m, 4H, aromatic); m/z (EI) 243, 241 (M^+), 228, 226, 162 ($[M-Br]^+$), 122.

- 1-(4-Methoxyphenyl)-3-methyleneazetidin-2-one **327**



331 **327** **326**

A known compound prepared according to a modified literature procedure[39] and according to the literature procedure.[108]

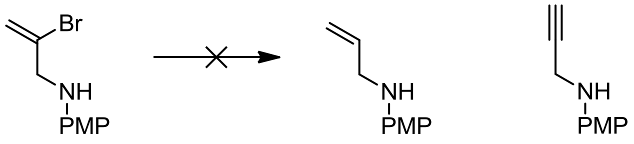
A solution of amine **326** (0.365 g, 1.51 mmol) in DMF (3.0 mL) was treated with Pd(OAc)$_2$ (34 mg, 0.15 mmol), *n*Bu$_3$N (0.719 mL, 3.02 mmol) and PPh$_3$ (0.158 g, 0.604 mmol). The reaction mixture was saturated with CO (1 atm) for 5 min and heated to 85 °C under CO (1 atm). After 5 h, the reaction mixture was diluted with EtOAc (15 mL), washed sequentially with HCl (2 x 5 mL of a 1 M aq. solution), brine (10 mL), dried over MgSO$_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 4:1) to give lactam **327** (86 mg, 30%) as a pale yellow solid.

A solution of lactam **331** (0.312 g, 0.922 mmol) in THF (9.2 mL) was cooled to -78 °C and treated with methyl iodide (86 µL, 1.4 mmol) and LHMDS (1.4 mL of a 1.0 M solution in THF, 1.4 mmol). After 4.5 h at -78 °C, the solvent was removed under reduced pressure and the crude product obtained was purified by column chromatography (Pet ether to Pet ether:EtOAc 7:3) to give lactam **327** (0.173 g, 99%) as a pale yellow solid.

mp 87-90 °C; R$_f$ 0.64 (Pet ether:EtOAc 1:1); ν_{max} (neat)/cm^{-1} : 2951, 1720, 1510, 1383, 1239, 1144, 1030, 933, 824; δ_H (300 MHz, CDCl$_3$) 3.79 (3H, s, OCH$_3$), 4.09 (2H, t, *J* 1.4 Hz, CH$_2$N), 5.31 (1H, dd, *J* 1.4 and 3.2 Hz, CH$_2$=C), 5.83 (1H, dd, *J* 1.4 and 3.2 Hz, CH$_2$=C), 6.89 (2H, d, *J* 9.0 Hz, Ar H), 7.34 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, CDCl$_3$) 48.0 (CH$_2$, NCH$_2$), 55.7 (CH$_3$, OCH$_3$), 110.7 (CH$_2$, *C*H$_2$=C), 114.6 (2 x CH, Ar), 117.8 (2 x CH, Ar), 132.1 (C, CH$_2$=*C*), 143.7 (C, ArCN), 156.4 (C, ArCO), 159.9 (C, C(O)N); m/z (ES) 190.0862 ([M+H]$^+$ $C_{11}H_{12}NO_2$ requires 190.0863), 190 (100%). *Literature data*:[250] ν_{max} (CHCl$_3$)/cm^{-1} : 1738 (CO); δ_H (300 MHz, CDCl$_3$) 3.77 (3 H, s, OMe), 4.08 (2

H, dd, *J* = 1.5 and 2 Hz, C_4-H_2), 5.28 (1 H, dd, *J* = 1.5 and 2 Hz, =CH*H*), 5.80 (1 H, dd, *J* = 2 and 2 Hz, =CH*H*), 6.84 (2 H, d, *J* = 9 Hz, 2 x Ar H), 7.30 (2 H, d, *J* = 9 Hz, 2 x Ar H); m/z (EI) 189 (M^+) (Found: C, 69.52; H, 5.77; N, 7.37. Calc for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40%).

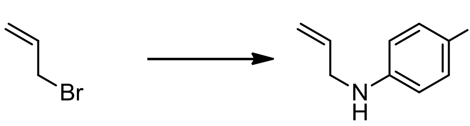
- *N*-(4-Methoxyphenyl)prop-2-yn-1-amine **329**



326 **328** **329**

A known compound[251] prepared according to a modified literature procedure.[129] A solution of amine **328** (0.671 g, 2.77 mmol) in THF (28 mL) was cooled to -78 °C. *n*BuLi (6.87 mL of a 1.21 M solution in hexane, 8.31 mmol) was added dropwise over 5 min. After 2 h at -78 °C, the reaction mixture was quenched with NH_4Cl (20 mL of a saturated aq. solution) and extracted with Et_2O (2 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 9:1) to give propynamine **329** (0.355 g, 80%) as a yellow oil. R_f 0.29 (Pet ether:Et_2O 9:1); ν_{max} (neat)/cm^{-1} : 3675, 3261, 2918, 2109, 1506, 1233, 1031, 824, 686; δ_H (400 MHz, $CDCl_3$) 2.76 (1H, t, *J* 2.4 Hz, HC≡C), 3.52 (1H, br s, NH), 3.76 (3H, s, OCH_3), 3.95 (2H, d, *J* 2.4 Hz, CH_2N), 6.68 (2H, d, *J* 8.9 Hz, Ar H), 6.82 (2H, d, *J* 8.9 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 34.8 (CH_2, NCH_2), 55.9 (CH_3, OCH_3), 71.4 (CH, H*C*≡C), 81.5 (C, HC≡*C*), 115.0 (2 x CH, Ar), 115.3 (2 x CH, Ar), 141.0 (C, ArCN), 153.2 (C, ArCO); m/z (CI) 162.0912 ($[M+H]^+$ $C_{10}H_{12}NO$ requires 162.0913), 162 (100%). *Literature data*:[251] ν_{max} (neat)/cm^{-1} : 3378, 2160, 1514; δ_H (90 MHz, $CDCl_3$) 2.11 (1H, t, *J* 2.0 Hz), 3.71 (3H, s), 3.91 (2H, d, *J* 2.0 Hz), 6.60-6.98 (5H, m); m/z (EI) 161 (100), 146 (57), 122 (94).

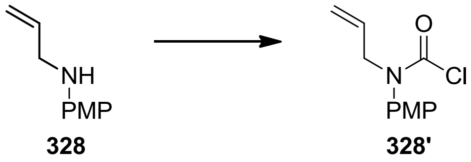
- *N*-Allyl-4-methoxyaniline **328**



328

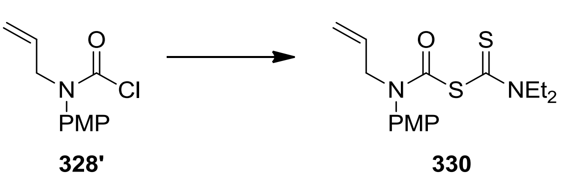
A known compound[252] prepared according to a literature procedure.[27] A solution of 4-methoxyaniline (3.21 g, 26.0 mmol) and K_2CO_3 (1.89 g, 13.6 mmol) in DMF (28 mL) was treated with allyl bromide (1.50 g, 12.4 mmol). After 18 h at 80 °C, the reaction mixture was quenched with H_2O (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 4:1) to give amine **328** (1.45 g, 72%) as a yellow oil. R_f 0.41 (Pet ether:Et_2O 9:1); ν_{max} (neat)/cm^{-1} : 3394, 2934, 1509, 1229, 1034, 816; δ_H (300 MHz, $CDCl_3$) 3.46 (1H, br s, NH), 3.74 (2H, dt, *J* 1.6 and 5.5 Hz, CH_2N), 3.75 (3H, s, OCH_3), 5.15 (1H, dq, *J* 1.6 and 10.3 Hz, CH_2=CH), 5.85 (1H, dq, *J* 1.6 and 17.2 Hz, CH_2=CH), 5.88-6.06 (1H, m, CH_2=C*H*), 6.61 (2H, d, *J* 9.0 Hz, Ar H), 6.79 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 47.7 (CH_2, NCH_2), 56.0 (CH_3, OCH_3), 114.5 (2 x CH, Ar), 115.0 (2 x CH, Ar), 116.3 (CH_2, *C*H_2=CH), 135.9 (CH, CH_2=*C*H), 142.4 (C, ArCN), 152.4 (C, ArCO); m/z (ES) 165 (13%), 164 (100), 163 (84). *Literature data*:[252] ν_{max} (neat)/cm^{-1} : 1643; δ_H (300 MHz, $CDCl_3$) 6.80-6.75 (m, 2H), 6.62-6.58 (m, 2H), 6.00-5.91 (m, 1H), 5.30-5.24 (m, 1H), 5.17-5.12 (m, 1H), 3.73-3.70 (m with a singlet at 3.73, total 6H); δ_C (75 MHz, $CDCl_3$) 152.6, 142.6, 136.2, 116.5, 115.2 (2), 114.7 (2), 56.1, 49.9; Anal. Calcd for $C_{10}H_{13}NO$: C, 73.62; H, 7.97. Found: C, 73.37; H, 7.77.

- Allyl(4-methoxyphenyl)carbamic chloride **328’**



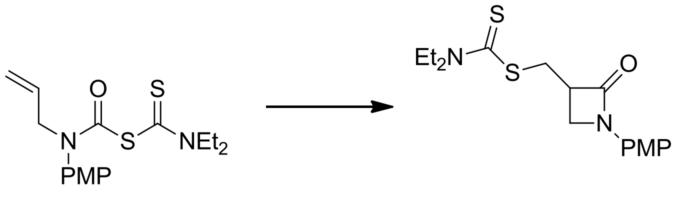
A novel compound prepared according to a literature procedure.[27] A solution of triphosgene (0.686 g, 2.31 mmol) in toluene (35 mL) was treated with pyridine (0.607 mL, 7.50 mmol) and subsequently with a solution of amine **328** (1.01 g, 6.25 mmol) in toluene (13 mL). After 18 h at rt, the reaction mixture was quenched with H_2O (40 mL) and extracted with Et_2O (2 x 40 mL). The combined organic extracts were washed sequentially with HCl (40 mL of a 0.25 M aq. solution) and brine (50 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 4:1) to give carbamoyl chloride **328’** (1.23 g, 87%) as a pale orange oil. R_f 0.49 (Pet ether:EtOAc 9:1); ν_{max} (neat)/cm^{-1} : 2936, 1728, 1510, 1217, 1034, 834, 787; δ_H (300 MHz, $CDCl_3$) (mixture of rotamers) 3.82 (3H, s, OCH_3), 4.14-4.34, 4.39 (2H, m, CH_2N), 5.09-5.32 (2H, m, C*H₂*=CH), 5.79-6.01 (1H, m, CH_2=C*H*), 6.90 (2H, d, *J* 8.9 Hz, Ar H), 7.07-7.24 (2H, m, Ar H); δ_C (100 MHz, $CDCl_3$) (mixture of rotamers) 54.3, 55.9 (CH_2, NCH_2), 55.6 (CH_3, OCH_3), 114.5, 114.7 (2 x CH, Ar), 119.2, 119.7 (CH_2, *C*H_2=CH), 128.4, 128.6 (2 x CH, Ar), 131.4, 131.9 (CH, CH_2=*C*H), 132.7, 134.8 (C, ArCN), 148.4, 149.7 (C, ArCO), 159.0, 159.6 (C, NC(O)Cl); m/z (ES) 248.0447 ($[M+H]^+$ $C_{11}H_{12}{}^{35}ClNNaO_2$ requires 248.0449), 250 (31%), 248 (100).

- Diethylthiocarbamic acid-[allyl(4-methoxyphenyl)carbamic acid]thioanhydride **330**



A novel compound prepared according to a literature procedure.[27] A solution of carbamoyl chloride **328’** (1.06 g, 4.68 mmol) in acetone (36 mL) was treated with sodium diethyldithiocarbamate trihydrate (3.17 g, 14.1 mmol). The solution was heated at reflux for 18 h, quenched with H_2O (30 mL). Acetone was removed under reduced pressure. The aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 4:1) to give dithiocarbamate **330** (1.52 g, 96%) as a bright yellow oil. R_f 0.27 (Pet ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1} : 2974, 1668, 1509, 1419, 1245, 1196, 918, 833, 730; δ_H (400 MHz, $CDCl_3$) 1.23 (3H, t, *J* 7.1 Hz, CH_2CH_3), 1.32 (3H, t, *J* 7.1 Hz, CH_2CH_3), 3.78 (2H, q, *J* 7.1 Hz, CH_2CH_3), 3.82 (3H, s, OCH_3), 4.00 (2H, q, *J* 7.1 Hz, CH_2CH_3), 4.27 (2H, d, *J* 6.4 Hz, $NCH_2CH=$), 4.99-5.21 (2H, m, $CH_2=CH$), 5.85 (1H, ddt, *J* 6.4, 10.2 and 16.7 Hz, $CH_2=CH$), 6.88 (2H, d, *J* 8.9 Hz, Ar H), 7.18 (2H, d, *J* 8.9 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 11.2 (CH_3, CH_2CH_3), 13.7 (CH_3, CH_2CH_3), 48.9 (CH_2, CH_2CH_3), 50.5 (CH_2, CH_2CH_3), 54.1 (CH_2, $NCH_2CH=$), 55.7 (CH_3, OCH_3), 114.8 (2 x CH, Ar), 119.1 (CH_2, $CH_2=CH$), 130.8 (2 x CH, Ar), 132.4 (CH, $CH_2=CH$), 133.6 (C, ArCN), 153.8 (C, ArCO), 160.1 (C, C(O)N), 185.3 (C, C(S)S); m/z (ES) 339.1197 ($[M+H]^+$ $C_{16}H_{23}N_2O_2S_2$ requires 339.1195), 341 (9%), 340 (18), 339 (100).

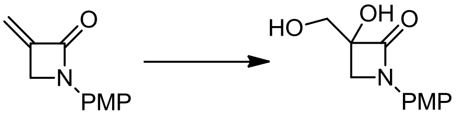
- 1-(4-Methoxyphenyl)-2-oxoazetidin-3-yl)methyl diethylcarbamodithioate **331**



330 **331**

A novel compound prepared according to a literature procedure.[26] A solution of dithiocarbamate **330** (0.961 g, 2.84 mmol) in cyclohexane (28 mL) was degassed for 10 min and irradiated with a 500 W lamp which generated enough heat to bring the solution to reflux. After 2 h, the solvent was removed under reduced pressure and the crude product obtained was purified by column chromatography (Pet ether to Pet ether:EtOAc 4:1) to give lactam **331** (0.823 g, 86%) as a dark orange oil. R_f 0.27 (Pet ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1} : 2974, 1735, 1510, 1241, 1143, 826; δ_H (400 MHz, $CDCl_3$) 1.23-1.29 (6H, m, CH_2CH_3), 3.50 (1H, dd, *J* 1.9 and 5.7 Hz, SCH_2CH), 3.68-4.16 (11H, m, CH_2CH_3, NCH_2CH, SCH_2CH, $CH_2CHC(O)$), 6.86 (2H, d, *J* 9.0 Hz, Ar H), 7.29 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 11.7 (CH_3, CH_2CH_3), 12.7 (CH_3, CH_2CH_3), 35.2 (CH_2), 44.0 (CH_2), 47.0 (CH_2), 48.3 (CH, CHC(O)), 50.1 (CH_2), 55.7 (CH_3, OCH_3), 114.5 (2 x CH, Ar), 117.8 (2 x CH, Ar), 132.0 (C, ArCN), 156.3 (C, ArCO), 165.0 (C, C(O)N), 194.7 (C, C(S)S); m/z (ES) 339.1196 ($[M+H]^+$ $C_{16}H_{23}N_2O_2S_2$ requires 339.1195), 341 (8%), 340 (17), 339 (100).

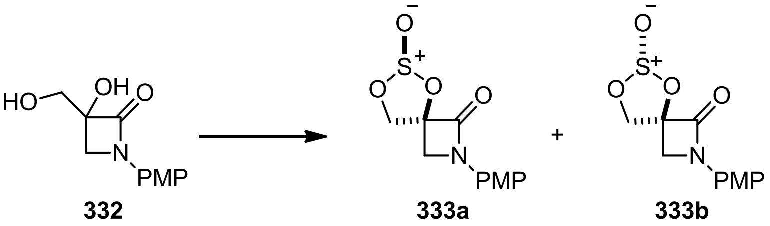
- 3-Hydroxy-3-(hydroxymethyl)-1-(4-methoxyphenyl)azetidin-2-one **332**



327 **332**

A novel compound prepared according to a literature procedure.[56] A solution of lactam **327** (0.152 g, 0.803 mmol) in a 5:5:2 mixture of H_2O:acetone:*t*BuOH (4.5 mL) was treated with NMO (0.226 g, 1.93 mmol) and OsO_4 (2 µL of a 4 wt% aq. solution, cat). After 18 h at 40 °C, sodium bisulfite (0.456 g, 2.41 mmol) was added to quench the reaction. After 70 min at 40 °C, the reaction mixture was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether:EtOAc 1:1 to Pet ether:EtOAc 1:3) to give dihydroxy lactam **332** (0.104 g, 58%) as a white solid. mp 138-140 °C; R_f 0.19 (Pet ether:EtOAc 1:3); ν_{max} (neat)/cm^{-1} : 3352, 3294, 2969, 2488, 2447, 1713, 1513, 1233, 1044, 825; δ_H (400 MHz, CD_3OD) 3.54, 3.92 (2H, ABq, *J* 5.8 Hz, CH_2N), 3.72, 3.82 (2H, ABq, *J* 11.4 Hz, CH_2OH), 3.77 (3H, s, OCH_3), 4.87 (2H, br s, OH), 6.92 (2H, d, *J* 9.0 Hz, Ar H), 7.35 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, CD_3OD) 53.0 (CH_2, NCH_2), 55.9 (CH_3, OCH_3), 63.3 (CH_2, CH_2OH), 85.0 (C, COH), 115.4 (2 x CH, Ar), 119.3 (2 x CH, Ar), 132.8 (C, ArCN), 158.1 (C, ArCO), 168.7 (C, C(O)N); m/z (ES) 224.0915 ($[M+H]^+$ $C_{11}H_{14}NO_4$ requires 224.0917), 246 (55%), 241 (18), 224 (100), 199 (17).

- (±)-(4*S*)-2-(4-Methoxyphenyl)-5,7-dioxa-6-thia-2-azaspiro[3.4]octan-1-one 6-oxide **333a** and **333b**



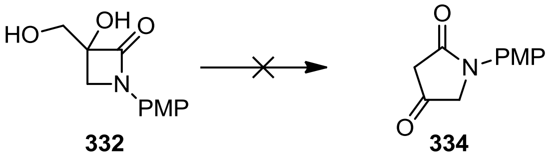
Novel compounds prepared according to a literature procedure.[61] A solution of dihydroxy lactam **332** (52 mg, 0.23 mmol) in CH_2Cl_2 (1.2 mL) at 0 °C was treated with pyridine (85 µL, 1.1 mmol) and $SOCl_2$ (34 µL, 0.47 mmol). The ice bath was removed after 1 h and stirring was continued for 1.75 h at rt. The reaction mixture was diluted with H_2O (2 mL) and extracted with CH_2Cl_2 (2 x 3 mL). The combined organic extracts were washed sequentially with HCl (3 mL of a 1 M aq. solution) and brine (3 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 4:1) to give **333a** (19 mg, 30%) and **333b** (24 mg, 38%) as white solids.

333a: mp 157-159 °C; R_f 0.19 (Pet ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1} : 2953, 1744, 1511, 1216, 948, 828, 766; δ_H (400 MHz, $CDCl_3$) 3.80 (3H, s, OCH_3), 3.89, 3.91 (2H, ABq, *J* 6.5 Hz, CH_2N), 4.84, 5.05 (2H, ABq, *J* 9.6 Hz, CH_2OS), 6.90 (2H, d, *J* 9.0 Hz, Ar H), 7.31 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 52.4 (CH_2, NCH_2), 55.7 (CH_3, OCH_3), 70.3 (CH_2, CH_2OS), 90.5 (C, COS), 114.8 (2 x CH, Ar), 118.5 (2 x CH, Ar), 130.8 (C, ArCN), 157.3 (C, ArCO), 159.0 (C, C(O)N); m/z (CI) 287.0694 ($[M+NH_4]^+$ $C_{11}H_{15}N_2O_5S$ requires 287.0696), 287 (100%), 207 (49).

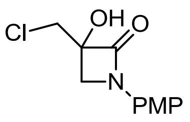
333b: mp 147-148 °C; R_f 0.38 (Pet ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1} : 2953, 1744, 1511, 1216, 948, 828, 766; δ_H (400 MHz, $CDCl_3$) 3.81 (3H, s, OCH_3), 4.03, 4.18 (2H, ABq, *J* 6.8 Hz, CH_2N), 4.75, 5.02 (2H, ABq, *J* 9.1 Hz, CH_2OS), 6.91 (2H, d, *J* 9.0 Hz, Ar H), 7.31 (2H, d, *J* 9.0 Hz, Ar H); δ_C

(100 MHz, $CDCl_3$) 52.4 (CH_2, NCH_2), 55.7 (CH_3, OCH_3), 71.5 (CH_2, CH_2OS), 88.8 (C, COS), 114.8 (2 x CH, Ar), 118.6 (2 x CH, Ar), 130.7 (C, ArCN), 157.4 (C, ArCO), 158.9 (C, C(O)N); m/z (CI) 287.0694 ($[M+NH_4]^+$ $C_{11}H_{15}N_2O_5S$ requires 287.0696), 287 (100%), 207 (58).

- 3-(Chloromethyl)-3-hydroxy-1-(4-methoxyphenyl)azetidin-2-one **335**



332 **334**

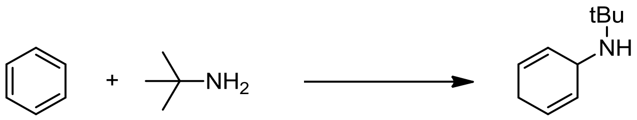


335

A novel compound prepared according to a literature procedure.[19] A solution of PPh_3 (65 mg, 0.25 mmol) and hexachloroethane (59 mg, 0.25 mmol) in CH_3CN (0.71 mL) was stirred at rt for 30 min before being added dropwise to a solution of diol **332** (37 mg, 0.17 mmol) in CH_3CN (0.40 mL). The reaction mixture was heated at reflux for 18 h, concentrated under reduced pressure and purified directly by column chromatography (Pet ether to Pet ether:EtOAc 7:3) to give chloro hydroxyl lactam **335** (34 mg, 85%) as pale yellow crystals. mp 117-118 °C; R_f 0.54 (Pet ether:EtOAc 1:1); ν_{max} (neat)/cm^{-1} : 3192, 2958, 1705, 1510, 1242, 1167, 1025, 822; δ_H (400 MHz, $CDCl_3$) 3.71, 3.90 (2H, ABq, *J* 6.0 Hz, CH_2N), 3.79 (3H, s, OCH_3), 3.88 (2H, s, CH_2Cl), 5.04 (1H, br s, OH), 6.86 (2H, d, *J* 9.0 Hz, Ar H), 7.27 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 45.3 (CH_2, CH_2Cl), 52.6 (CH_2, NCH_2), 55.7 (CH_3, OCH_3), 83.1 (C, COH), 114.6 (2 x CH, Ar), 118.5 (2 x CH, Ar), 130.8 (C, ArCN), 157.0 (C, ArCO), 165.0 (C, C(O)N); m/z (ES) 242.0579 ($[M+H]^+$ $C_{11}H_{13}{}^{35}ClNO_3$ requires 242.0578), 264 (39%), 244 (32), 242 (100).

6.4 Experimental procedures and analytical data for chapter four

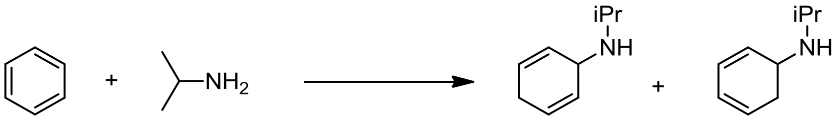
- *N*-(*tert*-butyl)cyclohexa-2,5-dienamine **408**



408

A known compound prepared according to a modified literature procedure.[146] A solution of benzene (150 mL) and *t*BuNH$_2$ (150 mL) was degassed under argon for 30 min, before irradiating with a low pressure mercury lamp for 21 h. A few crystals of 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide were added and the solvent was removed under reduced pressure. An orange oil was obtained and purification by Kugelrohr distillation gave amine **408** (1.46 g) as a yellow oil. δ_H (300 MHz, CDCl$_3$) 0.12 (9H, s, C(CH$_3$)$_3$), 1.82 (1H, d, *J* 7.1 Hz, NH), 2.51-2.64 (2H, m, =CHC*H*$_2$CH=), 3.55-3.71 (1H, m, CHN), 5.61-5.83 (4H, m, =CH). *Literature data*:[146] ν_{max} (neat)/cm^{-1}: 3029, 2964, 2866, 2814 (=C-H stretch), 1230 (C-N stretch); δ_H (250 MHz, CDCl$_3$) 1.06 (10H, s, C(CH$_3$)$_3$, NH), 2.48-2.54 (2H, m, CH$_2$), 3.54-3.58 (CHN), 5.61-5.72 (4H, m, =CH); δ_C (63 MHz, CDCl$_3$) 26.25 (CH$_2$, =CH*C*H$_2$CH=), 30.22 (CH$_3$ C(*C*H$_3$)$_3$), 44.97 (CH, CHN), 51.67 (C, *C*(CH$_3$)$_3$), 124.84 (2 x CH), 130.21 (2 x CH).

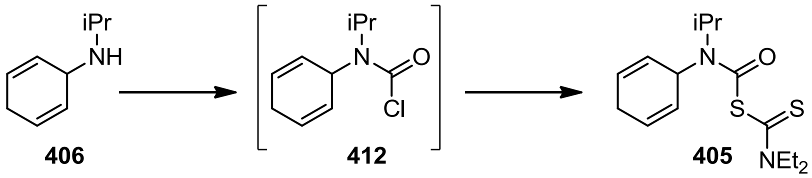
- *N*-Isopropylcyclohexa-2,5-dienamine **406**



406 **411**

A novel compound prepared according to a modified literature procedure.[146] A solution of benzene (170 mL) and *i*PrNH$_2$ (170 mL) was degassed under argon for 30 min, before irradiating with a low pressure mercury lamp for 87 h. A few crystals of 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide were added and the solvent was removed under reduced pressure. A brown oil was obtained and purification by Kugelrohr distillation gave a mixture of amines **406** and **411** (2.81 g) as a yellow oil. δ_H (400 MHz, $CDCl_3$) (mixture of **406** and **411**) 1.00 (6H, t, *J* 6.1 Hz, CH(C*H*$_3$)$_2$ for **411**), 1.03 (6H, d, *J* 6.2 Hz, CH(C*H*$_3$)$_2$ for **406**), 2.32 (2H, qddd, *J* 1.6, 4.4, 7.9 and 17.7 Hz, =CHC*H*$_2$CHN for **411**), 2.50-2.70 (2H, m, =CHCH$_2$CH= for **406**), 2.95 (1H, hept, *J* 6.1 Hz, C*H*(CH$_3$)$_2$ for **411**), 3.07 (1H, hept, *J* 6.2 Hz, C*H*(CH$_3$)$_2$ for **406**), 3.29-3.40 (1H, m, CHN for **411**), 3.59-3.72 (1H, m, CHN for **406**), 5.73-5.95 (8H, m, =CH); δ_C (100 MHz, $CDCl_3$) (mixture of **406:411**) 23.2 (CH$_3$, CH(*C*H$_3$)$_2$ for **411**), 23.4 (CH$_3$, CH(*C*H$_3$)$_2$ for **411**), 23.7 (2 x CH$_3$, CH(*C*H$_3$)$_2$ for **406**), 26.6 (CH$_2$, =CH*C*H$_2$CH= for **406**), 30.0 (CH$_2$, =CH*C*H$_2$CHN for **411**), 44.8 (CH, *C*H(CH$_3$)$_2$ for **411**), 45.1 (CH, *C*H(CH$_3$)$_2$ for **406**), 47.2 (CH, CH$_2$*C*HN for **411**), 47.8 (CH, CH$_2$*C*HN for **406**), 124.1 (CH, =CH for **411**), 124.3 (CH, =CH for **411**), 125.5 (2 x CH, =CH for **406**), 128.3 (2 x CH, =CH for **406**), 129.8 (2 x CH, =CH for **411**).

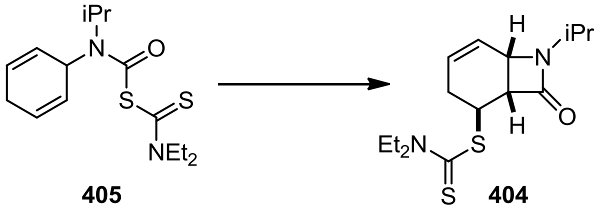
- Diethyldithiocarbamic acid-[isopropyl(cyclohexa-2,5-dien-1-yl)carbamic acid]-thioanhydride **405**



A novel compound prepared according to a literature procedure.[27] A solution of triphosgene (1.20 g, 4.03 mmol) in toluene (68 mL) was treated with pyridine (1.82 mL, 13.1 mmol) and subsequently with a solution of amines **406** and **411** (1.49 g, 10.9 mmol) in toluene (15 mL). The reaction mixture was stirred for 18 h at rt, quenched with NH_4Cl (50 mL of a saturated aq. solution) and extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed sequentially with HCl (75 mL of a 0.5 M aq. solution) and brine (50 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give carbamoyl chloride **412** and **413** (1.58 g, 73%) as a brown oil.

A solution of carbamoyl chloride **412** and **413** (1.58 g, 7.92 mmol) in acetone (61 mL) was treated with sodium diethyldithiocarbamate trihydrate (7.13 g, 31.7 mmol). The reaction mixture was stirred at rt for 18 h, quenched with H_2O (60 mL) and extracted with Et_2O (3 x 60 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 9:1) to give carbamoyl dithiocarbamate **405** (1.63 g, 66%) as a yellow solid. mp 108-111 °C; R_f 0.50 (Pet ether:Et_2O 4:1); ν_{max} (neat)/cm^{-1}: 2969, 1682, 1673, 1486, 1414, 1250, 1198, 1183, 1071, 912, 812, 772; δ_H (400 MHz, $CDCl_3$) 1.25-1.38 (12H, m, $CH(C\mathit{H_3})_2$ and $CH_2C\mathit{H_3}$), 2.53-2.83 (2H, m, $=CHC\mathit{H_2}CH=$), 3.46 (1H, s, $C\mathit{H}(CH_3)_2$), 3.77 (2H, q, *J* 7.1 Hz, $C\mathit{H_2}CH_3$), 4.00 (2H, q, *J* 7.1 Hz, $C\mathit{H_2}CH_3$), 4.98 (1H, s, $=CHC\mathit{H}N$), 5.67 (2H, d, *J* 9.2 Hz, =CH), 5.99 (2H, d, *J* 8.6 Hz, =CH); δ_C (100 MHz, $CDCl_3$) 11.4 (CH_3, $CH_2\mathit{C}H_3$), 13.4 (CH_3, $CH_2\mathit{C}H_3$), 20.4 (2 x CH_3, $CH(\mathit{C}H_3)_2$), 26.0 (CH_2, $=CH\mathit{C}H_2CH=$), 48.9 (CH_2, $\mathit{C}H_2CH_3$), 49.6 (2 x CH, CHN), 50.0 (CH_2, $\mathit{C}H_2CH_3$), 124.8 (2 x CH, =CH), 128.9 (2 x CH, =CH), 186.4 (C, C(S)S); m/z (ES) 335.1221 ($[M+H]^+$ $C_{15}H_{25}N_2NaOS_2$ requires 335.1228), 394 (17%), 384 (10), 335 (100).

- (±)-(1R,2S,6S)-7-Isopropyl-8-oxo-7-azabicyclo[4.2.0]oct-4-en-2-yl diethylcarbamodithioate **404**

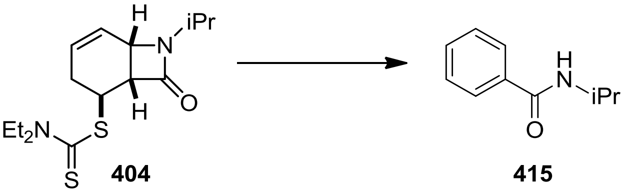


405 **404**

A novel compound prepared according to a literature procedure.[26] A solution of carbamoyl dithiocarbamate **405** (1.60 g, 5.10 mmol) in cyclohexane (51 mL) was degassed for 10 min and irradiated with a 500 W lamp which generated enough heat to bring the solvent to reflux. After 5 h, the solvent was removed under reduced pressure and the crude product obtained was purified by column chromatography (Hexane to Hexane:EtOAc 7:3) to give lactam **404** (0.877 g, 55%) as as a yellow brown oil. R_f 0.56 (Pet ether:Et_2O 7:3); ν_{max} (neat)/cm^{-1}: 2972, 1732, 1486, 1415, 1267, 1205, 1005, 982; δ_H (400 MHz, $CDCl_3$) 1.16 (3H, d, *J* 6.7 Hz, $C\mathit{H_2}CH_3$), 1.18-1.28 (9H, m, $CH_2C\mathit{H_3}$ and $CH(C\mathit{H_3})_2$), 2.50-2.71 (2H, m, $=CHC\mathit{H_2}CHS$), 3.66 (2H, q, *J* 7.0 Hz, $C\mathit{H_2}CH_3$), 3.70-

3.72 (1H, m, CHS), 3.87 (1H, hept, *J* 6.7 Hz, C*H*(CH_3)$_2$), 3.93-4.07 (3H, m, CH_2C*H*$_3$ and CHC(O)), 4.67-4.79 (1H, m, =CHC*H*N), 6.00-6.15 (2H, m, =CH); δ_C (100 MHz, $CDCl_3$) 11.7 (CH_3, CH_2*C*H_3), 12.7 (CH_3, CH_2*C*H_3), 20.5 (CH_3, CH(*C*H_3)$_2$), 22.0 (CH_3, CH(*C*H_3)$_2$), 28.2 (CH_2, =CH*C*H_2CH=), 44.4 (CH, *C*H(CH_3)$_2$), 46.5 (2 x CH, CHN, *C*HC(O)), 46.8 (CH_2, *C*$H_2$$CH_3$), 49.3 ($CH_2$, *C*$H_2$$CH_3$), 53.3 (CH, CHS), 127.6 (CH, =CH), 132.7 (CH, =CH), 167.1 (C, C(O)N), 186.4 (C, C(S)S); m/z (ES) 313.1408 ($[M+H]^+$ $C_{15}H_{25}N_2OS_2$ requires 313.1403), 313 (100%).

- *N*-Isopropylbenzamide **415**

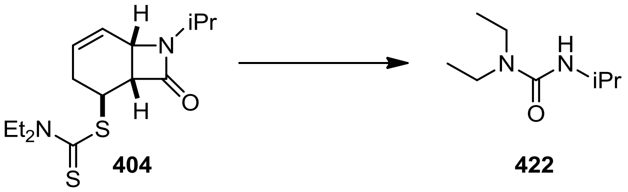


404 **415**

A known compound[253] prepared according to a modified literature procedure.[43] A solution of β-lactam **404** (35 mg, 0.11 mmol) in THF (1.1 mL) was cooled to 0 °C and LHMDS (0.17 mL of a 1.0 M solution in THF, 0.17 mmol) was added dropwise over 1 min. After 1 h at 0 °C, Davis oxaziridine (44 mg, 0.17 mmol) was added. The reaction mixture was allowed to warm to rt and after 18 h, it was evaporated under reduced pressure. The crude material obtained was purified by column chromatography (Pet ether to Pet ether:EtOAc 3:2) to give amide **415** (16 mg, 89%) as a white solid. mp 101-103 °C; R_f 0.58 (Pet ether:EtOAc 65:35); ν_{max} (neat)/cm^{-1}: 3295, 2971, 1630, 1531, 1346, 1288, 1168, 1137, 692; δ_H (400 MHz, $CDCl_3$) 1.25 (6H, d, *J* 6.6 Hz, CH(C*H*$_3$)$_2$), 4.18-4.73 (1H, m, C*H*(CH_3)$_2$), 6.04 (1H, br s, NH), 7.36-7.43 (2H, m, Ar H), 7.44-7.49 (1H, m, Ar H), 7.71-7.77 (2H, m, Ar H); δ_C (100 MHz, $CDCl_3$) 23.0 (2 x CH_3, CH(*C*H_3)$_2$), 42.0 (CH, *C*H(CH_3)$_2$), 127.0 (2 x CH, Ar), 128.6 (2 x CH, Ar), 131.4 (CH, Ar), 135.1 (C, Ar), 166.9 (C, C(O)N). *Literature data*:[253] Light yellow solid. mp 101-103 °C ; ν_{max} (KBr)/cm^{-1}: 3299, 3064, 2972, 2929, 1633, 1542, 1492, 1461, 1352, 1289, 1169, 931, 884, 702 ; δ_H (400 MHz, $CDCl_3$) 7.74 (d, *J* = 8.4 Hz, 2H), 7.48-7.37 (m, 3H), 6.12 (br. s, 1H), 4.33-4.21 (m, 1H), 1.24 (d, *J* = 6.4 Hz, 6H) ; δ_C (100

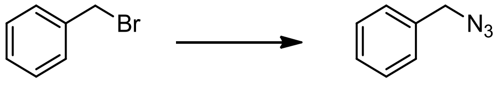
MHz, $CDCl_3$) 166.7, 134.9, 131.2, 128.4, 126.8, 41.8, 22.7 ; m/z (EI): 28, 51, 77, 105, 117, 148, 163.

- 1,1-Diethyl-3-isopropylurea **422**



A novel compound prepared according to a literature procedure.[27] A solution of lactam **404** (86 mg, 0.28 mmol) in Ph_2O (2.8 mL) was heated to reflux. After 1 h, the reaction mixture was directly purified by column chromatography (Pet ether to Pet ether:EtOAc 85:15) to give urea **422** (15 mg, 33%) as a white crystal. mp 54-57 °C; R_f 0.18 (Pet ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1}: 3390, 2972, 1609, 1529, 1491, 1268, 1200, 1079, 765; δ_H (400 MHz, $CDCl_3$) 1.06-1.17 (12H, m, CH_2CH_3 and $CH(CH_3)_2$), 3.22 (4H, q, *J* 7.1 Hz, CH_2CH_3), 3.98 (1H, hept, *J* 6.7 Hz, $CH(CH_3)_2$), 4.04 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 14.0 (2 x CH_3, CH_2CH_3), 23.8 (2 x CH_3, $CH(CH_3)_2$), 41.2 (2 x CH_2, CH_2CH_3), 42.5 (CH, $CH(CH_3)_2$), 156.8 (C, C(O)N); m/z (EI) 158.1412 (M^+ $C_8H_{18}N_2O$ requires 158.1419), 158 (73%), 100 (90), 72 (39), 70 (47), 58 (100).

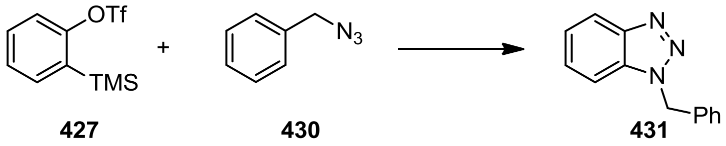
- (Azidomethyl)benzene **430**



430

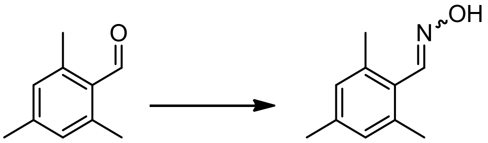
A known compound[254] prepared according to a literature procedure.[149] A solution of benzyl bromide (0.238 mL, 2.00 mmol) and sodium azide (0.325 g, 5.00 mmol) in H_2O (4 mL) was heated at 120 °C with microwave irradiation for 30 min. The reaction mixture was extracted with Et_2O (3 x 5 mL), washed with brine (10 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give (azidomethyl)benzene **430** (0.266 g, 100%) as a colourless oil (lit. yield 100%). R_f 0.85 (Pet ether:EtOAc 9:1); ν_{max} (neat)/cm^{-1}: 3032, 2090, 1496, 1454, 1252, 875, 735, 695; δ_H (400 MHz, CDCl$_3$) 4.35 (2H, s, CH$_2$N$_3$), 7.31-7.44 (5H, m, Ar H); δ_C (100 MHz, CDCl$_3$) 55.0 (CH$_2$, CH$_2$N$_3$), 128.4 (2 x CH, Ar), 128.5 (CH, Ar), 129.0 (2 x CH, Ar), 135.5 (C, Ar); m/z (EI) 133 (8%), 105 (69), 104 (100), 91 (29), 77 (39). *Literature data*:[254] δ_H (400 MHz, CDCl$_3$) 7.25-7.43 (m, 5H), 4.35 (s, 2H); δ_C (100.59 MHz, CDCl$_3$) 135.5, 129.3, 128.3, 128.2, 54.8.

- 1-Benzyl-1*H*-benzo[*d*][1,2,3]triazole **431**



A known compound[254] prepared according to a literature procedure.[148] A solution of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **427** (0.260 g, 0.871 mmol) in CH$_3$CN (12.5 mL) was treated with (azidomethyl)benzene **430** (0.116 g, 0.871 mmol) and cesium fluoride (0.265 g, 1.74 mmol). After 4.5 h at rt, the reaction mixture was diluted with EtOAc (15 mL), washed with brine (30 mL), dried over MgSO$_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 7:3) to give triazole **431** (71 mg, 39%) as a colourless oil (lit. yield 82%). R_f 0.17 (Pet ether:EtOAc 9:1); ν_{max} (neat)/cm^{-1}: 2921, 1496, 1456, 1224, 1095, 1060, 946, 744, 718; δ_H (400 MHz, CDCl$_3$) 5.85 (2H, s, NCH$_2$Ph), 7.26-7.45 (8H, m, Ar H), 8.09 (1H, d, *J* 8.2 Hz, Ar H); δ_C (100 MHz, CDCl$_3$) 52.3 (CH$_2$, NCH$_2$Ph), 109.8 (CH, Ar), 120.1 (CH, Ar), 124.0 (CH, Ar), 127.4 (CH, Ar), 127.6 (2 x CH, Ar), 128.5 (CH, Ar), 129.0 (2 x CH, Ar), 132.9 (C, Ar), 134.8 (C, ArCN), 146.4 (C, ArCN); m/z (ES) 301 (13%), 264 (16), 232 (100), 210 (30). *Literature data*:[254] mp 114-115 °C; δ_H NMR (400 MHz, CDCl$_3$) 8.07 (d, *J* = 8.0 Hz, 1H), 7.26-7.41 (m, 8H), 5.85 (s, 2H); δ_C (100.59 MHz, CDCl$_3$) 146.3, 134.7, 132.8, 129.0, 128.4, 127.6, 127.4, 123.9, 120.0, 109.7, 52.2; m/z (EI) 209.0945 (M$^+$ C$_{13}$H$_{11}$N$_3$ requires 209.0953).

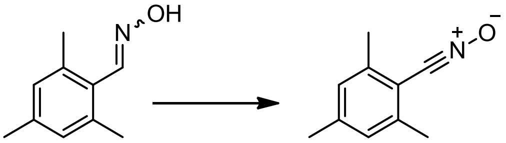
- Mesitaldehyde oxime **435**



434 **435**

A known compound[255] prepared according to a literature procedure.[152] A solution of aldehyde **434** (0.519 g, 3.50 mmol) in EtOH (27 mL) was treated with a solution of $H_2NOH.HCl$ (0.365 g, 5.25 mmol) in pyridine (27 mL). After 2 h at rt, the solvent was evaporated under reduced pressure. The reaction mixture was quenched with H_2O (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (60 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give oxime **435** (0.519 g, 92%) as a white solid. mp 119-122 °C; R_f 0.56 (Pet ether:EtOAc 9:1); ν_{max} (neat)/cm^{-1}: 3208, 2918, 1610, 1438, 1298, 943, 842, 722; δ_H (300 MHz, $CDCl_3$) 2.29 (3H, s, CH_3), 2.40 (6H, s, CH_3), 6.89 (2H, s, Ar H), 8.43 (1H, s, C(N)H), 8.56 (1H, br s, OH); δ_C (100 MHz, $CDCl_3$) 21.2 (3 x CH_3), 126.5 (C, *C*C(N)OH), 129.5 (2 x CH, Ar), 137.7 (2 x C, Ar), 139.1 (C, Ar), 150.0 (CH, C(N)H); m/z (ES) 164.1069 ($[M+H]^+$ $C_{10}H_{14}NO$ requires 164.1070), 594 (36%), 445 (26), 371 (52), 164 (100). *Literature data*:[255] mp 124-127 °C (lit. 124 °C); ν_{max} (CH_2Cl_2)/cm^{-1}: ν_{OH} = 3600, 3560-3100; δ_H (200 MHz, $CDCl_3$) 7.91 (s, 1H), 6.72 (s, 2H), 4.58 (bs, 1H exchange with D_2O), 2.31 (s, 6H), 2.20 (s, 3H).

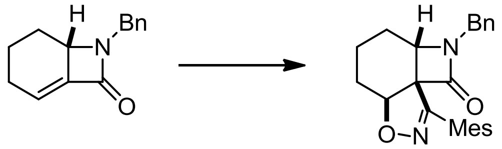
- Mesityl nitrile oxide **432**



435 **432**

A known compound prepared according to the literature procedure.[153] A solution of oxime **435** (0.178 g, 1.09 mmol) and Et_3N (0.167 mL, 1.20 mmol) in CH_2Cl_2 (9 mL) was stirred at rt for 30 min. *N*-Chlorosuccinimide (0.153 g, 1.15 mmol) in solution in CH_2Cl_2 (2 mL) was added portionwise every 5 min over 30 min. After 2 h at rt, another portion of *N*-chlorosuccinimide (73 mg, 0.54 mmol) was added to drive the reaction to completion. After 1 h at rt, the reaction mixture was evaporated under reduced pressure, diluted with Et_2O (10 mL) and the white precipitate formed was filtered through celite (eluent Et_2O). The filtrate was evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 95:5) to give nitrile oxide **432** (113 mg, 64%) as a white solid (lit. yield 99%). mp 83-88 °C; R_f 0.80 (Pet ether:EtOAc 9:1); ν_{max} (neat)/cm^{-1}: 2918, 2290, 1607, 1376, 1329, 1175, 1066, 867; δ_H (300 MHz, $CDCl_3$) 2.30 (3H, s, CH_3), 2.41 (6H, s, 2 x CH_3), 6.90 (2H, s, Ar H); δ_C (100 MHz, $CDCl_3$) 20.9 (2 x CH_3), 21.6 (CH_3), 111.2 (C, $C{\equiv}N^+{-}O^-$), 128.5 (2 x CH, Ar), 141.1 (C, Ar), 141.9 (2 x C, Ar); m/z (ES) 162.0914 ($[M+H]^+$ $C_{10}H_{12}NO$ requires 162.0913), 179 (34%), 162 (100). *Literature data*:[256] m.p. 112-113 °C (from methanol); ν_{max} (paste)/cm^{-1}: 2285; δ_H (220 MHz, $CDCl_3$) 2.30 (3 H, s,) 2.39 (6 H, s), 6.90 (2 H, s); δ_C (55 MHz, $CDCl_3$) 20.7 (q), 21.4 (q), 110.9 (s), 128.3 (d), 140.9 (s), and 141.5 (s).

- (±)-(3a*R*,5a*S*,8a*S*)-5-Benzyl-3-mesityl-5,5a,6,7,8,8a-hexahydro-4*H*-azeto[3',2':1,6] benzo[1,2-*d*] isoxazol-4-onemesitaldehyde oxime **436**

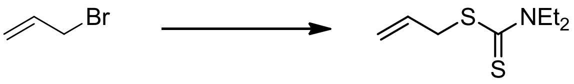


120 **436**

A novel compound prepared according to a literature procedure.[152] A solution of conjugated lactam **120** (66 mg, 0.31 mmol) in CH_2Cl_2 (3.1 mL) was treated with nitrile oxide **432** (55 mg, 0.34 mmol) and heated to reflux. After 5 h, the reaction mixture was evaporated under reduced pressure and the crude residue obtained was purified by column chromatography (Pet ether to Pet ether:EtOAc 7:3) to give oxazoline **436** (96 mg, 83%) as a white solid. mp 123-127 °C; R_f 0.55 (Pet ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1}: 2921, 1751, 1450, 1407, 871, 851, 734, 700; δ_H (400 MHz, $CDCl_3$) 1.33-1.65 (4H, m, CH_2), 1.79-1.90 (1H, m, CH_2), 2.10 (3H, s, CH_3), 2.26-2.36

(1H, m, CH_2), 2.38 (3H, s, CH_3), 2.43 (3H, s, CH_3), 3.56 (1H, dd, *J* 1.5 and 5.7 Hz, CHN), 3.89, 4.65 (2H, ABq, *J* 15.9 Hz, NCH_2Ph), 5.13 (1H, dd, *J* 7.1 and 9.2 Hz, CHO), 6.69 (2H, d, *J* 7.4 Hz, Ar H), 6.89 (1H, s, Ar H), 7.01 (1H, s, Ar H), 7.09 (2H, t, *J* 7.5 Hz, Ar H), 7.19 (1H, t, *J* 7.4 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 15.0 (CH_2), 20.1 (CH_3), 20.3 (CH_3), 21.2 (CH_3), 24.9 (CH_2), 28.2 (CH_2), 43.5 (CH_2, NCH_2Ph), 52.9 (CH, CH_2*C*HN), 71.8 (C, *C*C(O)), 79.6 (CH, CH_2*C*HO), 123.9 (C, Ar), 127.1 (2 x CH, Ar), 127.5 (CH, Ar), 128.4 (CH, Ar), 128.7 (2 x CH, Ar), 129.0 (CH, Ar), 134.4 (C, Ar), 137.1 (C, Ar), 138.6 (C, Ar), 139.2 (C, Ar), 154.1 (C, C(N)), 165.9 (C, C(O)N); m/z (ES) 375.2071 ($[M+H]^+$ $C_{24}H_{27}N_2O_2$ requires 375.2067), 771 (10%), 749 (33), 397 (26), 375 (100), 242 (47).

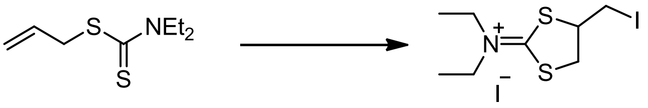
- Allyl diethylcarbamodithioate **449**



449

A known compound[257] prepared according to a literature procedure.[154] A solution of allyl bromide (0.173 mL, 2.00 mmol) in acetone (12.5 mL) was treated with sodium diethyldithiocarbamate trihydrate (1.80 g, 8.00 mmol). After 1.5 h at rt, the reaction mixture was quenched with H_2O (15 mL) and extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:Et_2O 9:1) to give dithiocarbamate **449** (0.379 g, 100%) as a brown yellow oil. R_f 0.67 (Pet ether:Et_2O 9:1); ν_{max} (neat)/cm^{-1}: 2976, 1635, 1484, 1413, 1266, 1203, 1141, 983, 915, 830; δ_H (400 MHz, $CDCl_3$) 1.27 (6H, q, *J* 7.0 Hz, CH_2CH_3), 3.74 (2H, q, *J* 7.0 Hz, CH_2CH_3), 3.95-4.10 (4H, m, CH_2CH_3, $=CHCH_2S$), 5.14 (1H, d, *J* 10.0 Hz, $=CH_2$), 5.30 (1H, dd, *J* 1.3 and 17.0 Hz, $=CH_2$), 5.93 (1H, ddt, *J* 7.0, 10.0 and 17.0 Hz, =CH); δ_C (100 MHz, $CDCl_3$) 11.7 (CH_3, CH_2CH_3), 12.6 (CH_3, CH_2CH_3), 40.5 (CH_2, $=CHCH_2S$), 46.9 (CH_2, CH_2CH_3), 49.7 (CH_2, CH_2CH_3), 118.6 (CH_2, $=CH_2$), 132.9 (CH, =CH), 195.2 (C, C(S)S); m/z (EI) 189.0651 (M^+ $C_8H_{15}NS_2$ requires 189.0646), 189 (44%), 148 (39), 116 (100), 88 (75), 76 -46), 72 (51), 60 (29).

- *N*-Ethyl-*N*-(4-(iodomethyl)-1,3-dithiolan-2-ylidene)ethanaminium iodide **450**

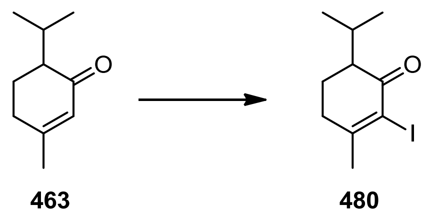


449 **450**

A known compound prepared according to the literature procedure.[154] A solution of dithiocarbamate **449** (0.193 g, 1.02 mmol) in CH_2Cl_2 (10 mL) was treated with iodine (0.388 g, 1.53 mmol). After 2.5 h at rt, the reaction mixture was concentrated under reduced pressure. The residue was triturated with a 1:3 mixture of CH_2Cl_2:Et_2O. Filtration of the precipitate (eluent: Et_2O) gave 1,3-dithiolane **450** (0.431 g, 95%) as a yellow solid. mp 171-173 °C; ν_{max} (neat)/cm^{-1}: 2937, 1566, 1513, 1461, 1265, 1191, 1172, 908, 779, 730; δ_H (400 MHz, MeOD) 1.43 (6H, td, *J* 5.2 and 7.3 Hz, CH_2CH_3), 3.76 (1H, dd, *J* 6.1 and 10.5 Hz, CH_2I), 3.82 (1H, dd, *J* 9.0 and 10.5 Hz, CH_2I), 3.89-3.98 (4H, m, CH_2CH_3), 4.24 (2H, q, *J* 4.9 and 12.6 Hz, CH_2S), 4.87-4.97 (1H, m, CHS); δ_C (100 MHz, MeOD) 2.7 (CH_2, CH_2I), 11.9 (CH_3, CH_2CH_3), 12.0 (CH_3, CH_2CH_3), 45.5 (CH_2, CH_2S), 56.0 (CH_2, CH_2CH_3), 56.2 (CH_2, CH_2CH_3), 60.0 (CH, CHS), 194.7 (C, SC(N)S); m/z (ES) 315.9686 ($[M-I]^+$ $C_8H_{15}{}^{127}INS_2$ requires 316.9691), 316 (100%).

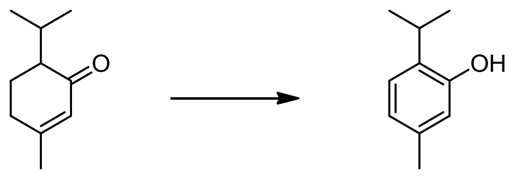
6.5 *Experimental procedures and analytical data for chapter five*

- 2-Iodo-6-isopropyl-3-methylcyclohex-2-enone **480**



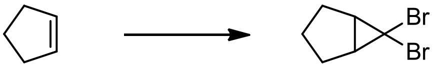
A novel compound prepared according to a modified literature procedure.[172] Iodine (0.501 g, 1.97 mmol) was dissolved slowly in a 1:1 mixture of pyridine:CH_2Cl_2 (1.4 mL). The reaction mixture was wrapped in foil to keep away from the light and piperitone **463** (0.143 g, 0.939 mmol) was added dropwise. After 19 h at 40 °C, the reaction mixture was diluted with EtOAc (10 mL) and washed with $Na_2S_2O_3$ (2 x 10 mL of a saturated aq. solution). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered, evaporated under reduced pressure and purified by column chromatography (Hexane to Hexane:EtOAc 9:1) to give iodo ketone **480** (82 mg, 31%) as a yellow solid. mp 33-35 °C; R_f 0.75 (Pet ether:Et_2O 4:1); ν_{max} (neat)/cm^{-1}: 2958, 1665, 1595, 1367, 1215, 777, 711; δ_H (300 MHz, $CDCl_3$) 0.83 (3H, d, *J* 6.8 Hz, CH(C*H*$_3$)$_2$), 0.91 (3H, d, *J* 6.8 Hz, CH(C*H*$_3$)$_2$), 1.72-1.88 (1H, m, CH_2), 1.89-2.01 (1H, m, CH_2), 2.20 (3H, s, =CCH_3), 2.22-2.66 (4H, m, CH_2, C*H*(CH_3)$_2$ and CHC(O)); δ_C (100 MHz, $CDCl_3$) 18.6 (CH_3, CH(*C*H$_3$)$_2$, 20.8 (CH_3, CH(*C*H$_3$)$_2$, 22.8 (CH_2, CH*C*H$_2$CH$_2$C=), 26.9 (CH, *C*H(CH_3)$_2$, 31.6 (CH_3, =C*C*H$_3$), 33.6 (CH_2, CHCH$_2$*C*H$_2$C=), 51.8 (CH, *C*HC(O)), 107.5 (C, I*C*=CCH$_3$), 165.0 (C, IC=*C*CH$_3$), 193.9 (C, C(O)); m/z (ES) 279.0243 ($[M+H]^+$ $C_{10}H_{16}{}^{127}IO$ requires 279.0240), 279 (100%), 151 (44), 109 (12).

- Thymol **481**


463 **481**

A known compound[258] prepared according to a modified literature procedure.[172] A solution of piperitone **463** (2.00 g, 13.1 mmol) in a 1:1 mixture of pyridine:CCl_4 (50 mL) was cooled to 0 °C and a solution of iodine (6.67 g, 26.3 mmol) in a 1:1 mixture of pyridine:CCl_4 (50 mL) was added dropwise. The reaction mixture was allowed to warm to rt over 1 h. After 20 h at rt, the reaction mixture was heated to 96 °C to drive the reaction to completion. After 24 h at 96 °C, the brown solution was diluted with Et_2O (100 mL), washed sequentially with H_2O (100 mL), HCl (2 x 100 mL of a 1 M aq. solution), Na_2SO_3 (100 mL of a 20% aq. solution) and brine (100 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:Et_2O 4:1) to give thymol **481** (1.21 g, 61%) as a colourless oil. Rf 0.45 (Pet ether:Et_2O 4:1); ν_{max} (neat)/cm^{-1}: 3383, 2961, 1617, 1585, 1418, 1289, 1152, 1088, 945, 808; δ_H (300 MHz, $CDCl_3$) 1.25 (6H, d, *J* 6.9 Hz, $CH(CH_3)_2$), 2.28 (3H, s, $=CCH_3$), 3.17 (1H, sept, *J* 6.9 Hz, $CH(CH_3)_2$), 4.71 (1H, s, OH), 6.59 (1H, d, *J* 0.7 Hz, Ar H), 6.75 (1H, dd, *J* 0.7 and 7.7 Hz, Ar H), 7.10 (1H, d, *J* 7.7 Hz, Ar H); m/z (EI) 150 (28%), 136 (9), 135 (100), 117 (9), 115 (11), 91 (11). *Literature data*:[258] ν_{max} (CH_2Cl_2)/cm^{-1}: 3586 (OH), 2965, 2933, 2869, 1671, 1606; δ_H (400 MHz, $CDCl_3$) 7.22 (dd, 1H, J_1 = 8.4 Hz), 7.08 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 6.93 (td, 1H, J_1 = 7.5 Hz, J_2 = 1.1 Hz), 6.76 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.2 Hz), 4.79 (s, 1H, OH), 3.23 (septet, 1H, *J* = 6.96), 1.27 (d, 6H, *J* = 6.8 Hz); δ_C (100.6 MHz, $CDCl_3$) 152.9, 134.6, 126.9, 126.6, 121.2, 115.4, 27.2, 22.8; m/z (EI) 135.9025 (M^+ $C_9H_{12}O$ requires 136.0888), 121 (100), 103 (20), 77 (18).

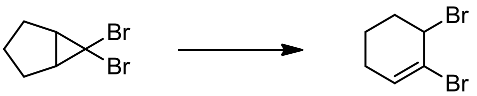
- 6,6-Dibromobicyclo[3.1.0]hexane **486**



486

A known compound[259] prepared according to a literature procedure.[116] A solution of cyclopentene (4.63 g, 67.9 mmol) and *t*BuOK (10.7 g, 95.1 mmol) in pentane (40 mL) was cooled to -30 °C and a solution of bromoform (8.50 mL, 88.4 mmol) in pentane (12 mL) was added dropwise. The reaction mixture was allowed to warm to rt over 18 h, washed with H_2O (3 x 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by Kugelrohr distillation (90 °C, 0.8 mmHg) to give dibromo hexane **486** (7.75 g, 48%) as a colourless liquid. R_f 0.85 (Pet ether); δ_H (300 MHz, $CDCl_3$) 1.67-1.78 (2H, m, $CH_2C\textit{H}_2CH_2$), 1.82-1.93 (2H, m, $CHC\textit{H}_2CH_2$), 1.97-2.17 (2H, m, $CHC\textit{H}_2CH_2$), 2.20-2.29 (2H, m, $BrCC\textit{H}CH_2$); *Literature data*:[259] δ_H (300 MHz, $CDCl_3$) 2.23 (m, 2 H), 2.11-1.97 (complex m, 2 H), 1.93-1.81 (complex m, 2 H), 1.78-1.64 (complex m, 2 H); δ_C (75 MHz, $CDCl_3$) 40.8 (C), 39.9 (CH), 29.5 (CH_2), 25.9 (CH_2); ν_{max} (KBr)/cm^{-1}: 2930, 2860, 1467, 1441, 1318, 1285, 1074, 1005, 969, 890, 746; m/z (EI) 237.8982 ($M^{+\cdot}$ $C_6H_8{}^{79}Br_2$ requires 237.8993), 241.8954 ($M^{+\cdot}$ $C_6H_8{}^{81}Br_2$ requires 241.8952242), 240 and 238 ($M^{+\cdot}$ 6 and 3%), 201, 199 and 197 (5, 10 and 6), 161 and 159 (36 and 35), 79 (100), 57 (42).

- 1,6-Dibromocyclohex-1-ene **487**

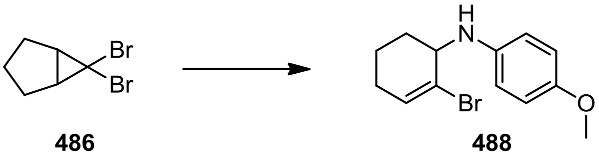


486 **487**

A known compound[260] prepared according to a modified literature procedure.[176] A solution of dibromohexane **486** (0.118 g, 0.492 mmol) in CH_3CN (4.9 mL) was heated to reflux. After 4 h, the reaction mixture was concentrated under reduced pressure to give dibromocyclohexene **487** (32 mg, 27%) as a pale yellow oil. R_f 0.73 (Pet ether:EtOAc 9:1); δ_H (300 MHz, $CDCl_3$) 1.71-

1.81 (1H, m, $CH_2CH_2CH_2$), 1.93-2.07 (1H, m, $CH_2CH_2CH_2$), 2.10-2.37 (4H, m, CH_2), 4.78 (1H, br s, CHBr), 6.19 (1H, dd, *J* 3.1 and 5.0 Hz, =CH); δ_C (100 MHz, $CDCl_3$) 16.5 (CH_2, $CH_2CH_2CH_2$), 27.6 (CH_2), 33.9 (CH_2), 54.1 (CH, CHBr), 122.5 (C, =CBr), 134.0 (CH, =CH). *Literature data*:[260] ν_{max} (neat)/cm^{-1}: 2953 (w), 2935 (w), 2832 (w), 1634 (w), 1437 (w), 1319 (w), 1191 (m), 996 (w), 943 (w), 907 (s), 889 (m), 847 (w), 730 (s), 638 (m). δ_H (400 MHz, $CDCl_3$) 6.19 (m, 1H; alkene-H), 4.78 (m, 1H; CHBr), 2.09-2.38 (m, 6H; CH_2), 2.00 (m, 1H; CH_2), 1.76 (m, 1H; CH_2); δ_C (100 MHz, $CDCl_3$) 133.7, 122.2, 53.9, 33.6, 27.4, 16.3.

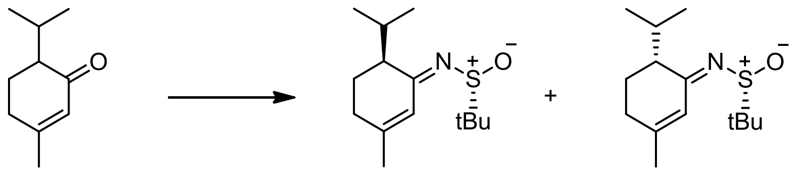
- *N*-(2-Bromocyclohex-2-en-1-yl)-4-methoxyaniline **488**



A novel compound prepared according to a modified literature procedure.[27,176] A solution of dibromohexane **486** (2.57 g, 10.7 mmol) in CH_3CN (29 mL) was heated at reflux for 1 h. The reaction mixture was allowed to cool to rt, treated with K_2CO_3 (1.63 g, 11.8 mmol) and 4-methoxyaniline (3.56 g, 28.9 mmol). After 6.5 h at rt, the reaction mixture was quenched with NH_4Cl (30 mL of a saturated aq. solution and extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Hexane to Hexane:EtOAc 95:5) to give bromo amine **488** (2.74 g, 91%) as a yellow oil. R_f 0.65 (Pet ether:EtOAc 9:1); ν_{max} (neat)/cm^{-1}: 3393, 2932, 1507, 1229, 1177, 1035, 986, 815, 725; δ_H (300 MHz, $CDCl_3$) 1.59-1.70 (2H, m, $CH_2CH_2CH_2$), 1.74-1.90 (1H, m, CH_2), 1.97-2.25 (3H, m, CH_2), 3.62 (1H, br s, NH), 3.76 (3H, s, OCH_3), 4.00 (1H, br s, CHN), 6.26 (1H, t, *J* 4.0 Hz, =CH), 6.64 (2H, d, *J* 9.0 Hz, Ar H), 6.81 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 17.1 (CH_2, $CH_2CH_2CH_2$), 27.8 (CH_2), 29.9 (CH_2), 55.8 (CH_3, OCH_3), 56.1 (CH, CHN), 114.9 (2 x CH, Ar), 115.0 (2 x CH, Ar), 123.9 (C, ArCN), 133.1 (CH,

=CH), 141.4 (C, ArCO), 152.4 (C, =CBr); m/z (ES) 282.0487 ([M+H]$^+$ $C_{13}H_{17}{}^{79}BrNO$ requires 282.0488), 284 (98%), 282 (100).

- (*R*,*Z*)-*N*-((*S*)-6-Isopropyl-3-methylcyclohex-2-en-1-ylidene)-2-methylpropane-2-sulfinamide **492** and (*R*,*Z*)-*N*-((*R*)-6-isopropyl-3-methylcyclohex-2-en-1-ylidene)-2-methyl propane-2-sulfinamide **491**



463 **492** **491**

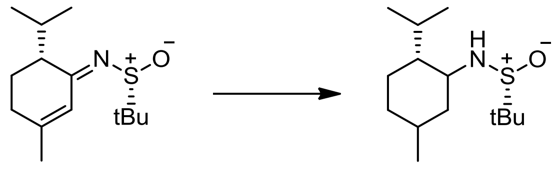
Novel compounds prepared according to a literature procedure.[175] A solution of piperitone **463** (0.110 g, 0.723 mmol) and $Ti(OEt)_4$ (0.621 mL, 2.96 mmol) in THF (1.0 mL) was treated with sulphonamide **483** (0.184 g, 1.52 mmol) and heated to reflux. After 72 h, the reaction mixture was concentrated under reduced pressure and directly purified by column chromatography (Pet ether to Pet ether:EtOAc 4:1) to give sulfinyl ketimine **492** (27 mg, 15%) and **491** (76 mg, 41%) as yellow oils.

492: Rf 0.36 (Pet ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1}: 2956, 1627, 1568, 1456, 1360, 1068; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, d, *J* 6.8 Hz, CH(C$\mathit{H_3}$)$_2$), 0.95 (3H, d, *J* 6.8 Hz, CH(C$\mathit{H_3}$)$_2$), 1.24 (9H, s, $SC(CH_3)_3$), 1.72-1.93 (5H, m, $=CCH_3$ and CH_2), 2.08-2.21 (2H, m, CH_2 and CHC(N)), 2.21-2.34 (2H, m, CH_2 and C*H*$(CH_3)_2$), 6.91 (1H, s, =CH); δ_C (100 MHz, $CDCl_3$) 19.0 (CH_3, CH(*C*H_3)$_2$), 21.5 (CH_3, CH(*C*H_3)$_2$), 22.7 (3 x CH_3, SC(*C*H_3)$_3$), 23.2 (CH_2, CH*C*H_2CH_2C=), 24.6 (CH_3, =C*C*H_3), 26.7 (CH, *C*H$(CH_3)_2$), 30.1 (CH_2, $CHCH_2$*C*H_2C=), 50.1 (CH, *C*HC(N)), 56.9 (C, S*C*$(CH_3)_3$), 130.1 (CH, H*C*=CCH_3), 156.1 (C, HC=*C*CH_3), 178.7 (C, C(N)); m/z (ES) 278.1557 ([M+Na]$^+$ $C_{14}H_{25}NNaOS$ requires 278.1555), 278 (100%), 256 (20), 222 (28), 200 (45); $[\alpha]^{20}_D$ -346.5° (c 0.86, $CHCl_3$), -390.6° (c 0.43, $CHCl_3$).

491: Rf 0.25 (Pet ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1}: 2956, 1628, 1567, 1383, 1360, 1069; δ_H (400 MHz, $CDCl_3$) 0.85 (3H, d, *J* 6.9 Hz, CH(C$\mathit{H_3}$)$_2$), 0.90 (3H, d, *J* 6.9 Hz, CH(C$\mathit{H_3}$)$_2$), 1.20 (9H, s,

$SC(CH_3)_3$), 1.68-1.81 (1H, m, CH_2), 1.83-1.94 (4H, m, $=CCH_3$ and CH_2), 2.08-2.20 (2H, m, CH_2 and CHC(N)), 2.20-2.34 (2H, m, CH_2 and C*H*$(CH_3)_2$), 6.75 (1H, s, =CH); δ_C (100 MHz, $CDCl_3$) 18.9 (CH_3, $CH(\mathit{C}H_3)_2$), 21.3 (CH_3, $CH(\mathit{C}H_3)_2$), 22.3 (3 x CH_3, $SC(\mathit{C}H_3)_3$), 23.1 (CH_2, $CH\mathit{C}H_2CH_2C=$), 24.6 (CH_3, $=C\mathit{C}H_3$), 26.7 (CH, $\mathit{C}H(CH_3)_2$), 29.9 (CH_2, $CHCH_2\mathit{C}H_2C=$), 49.9 (CH, *C*HC(N)), 56.2 (C, $S\mathit{C}(CH_3)_3$), 119.8 (CH, $H\mathit{C}=CCH_3$), 156.7 (C, $HC=\mathit{C}CH_3$), 179.3 (C, C(N)); m/z (ES) 278.1558 ($[M+Na]^+$ $C_{14}H_{25}NNaOS$ requires 278.1555), 278 (100%), 256 (22), 222 (32), 200 (33); $[\alpha]^{20}_D$ -131.0° (c 1.05, $CHCl_3$).

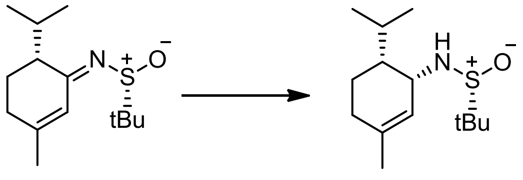
- (*R*)-*N*-((2*R*)-2-Isopropyl-5-methylcyclohexyl)-2-methylpropane-2-sulfinamide **495**



A novel compound prepared according to a literature procedure.[180] A solution of (*R*,*Z*)-*N*-(*R*)-sulfinyl ketimine **491** (59 mg, 0.23 mmol) in THF (0.58 mL) was cooled to 0 °C and treated with L-Selectride (0.69 mL of a 1.0 M solution in THF, 0.69 mmol). The reaction mixture was allowed to warm to rt over 3.5 h, quenched with NH_4Cl (3 mL of a saturated aq. solution) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Hexane to Hexane:EtOAc 7:3) to give sulfinamide **495** (18 mg, 30%) as a white solid. R_f 0.52 (Pet ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1}: 3330, 2914, 1455, 1371, 1159, 1060, 941; δ_H (400 MHz, $CDCl_3$) 0.85 (3H, d, *J* 6.5 Hz, $CH(C\mathit{H}_3)_2$), 0.93 (3H, d, *J* 6.5 Hz, $CH(C\mathit{H}_3)_2$), 0.98 (3H, d, *J* 6.6 Hz, $CHC\mathit{H}_3$), 1.00-1.12 (4H, m, CH_2, $CH_2C\mathit{H}CHN$ and $C\mathit{H}_2CHN$), 1.21 (9H, s, $SC(CH_3)_3$), 1.34-1.44 (1H, m, $C\mathit{H}(CH_3)_2$), 1.56-1.77 (3H, m, CH_2 and $C\mathit{H}CH_3$), 1.98 (1H, ddd, *J* 3.3, 5.6 and 13.8 Hz, $C\mathit{H}_2CHN$), 3.07 (1H, br s, NH), 3.67-3.77 (1H, m, CHN); δ_C (100 MHz, $CDCl_3$) 20.5 (CH_3, $CH\mathit{C}H_3$), 21.5 (CH_3, $CH(\mathit{C}H_3)_2$), 22.4 (CH_3, $CH(\mathit{C}H_3)_2$), 22.8 (3 x CH_3, $SC(\mathit{C}H_3)_3$), 24.8 (CH_2), 25.7

(CH, *C*HCH$_3$), 29.0 (CH, *C*H(CH$_3$)$_2$), 35.3 (CH$_2$), 40.3 (CH$_2$, *C*H$_2$CHN), 47.9 (CH, CH$_2$*C*HCHN), 50.8 (CH, CHN), 55.4 (C, S*C*(CH$_3$)$_3$).

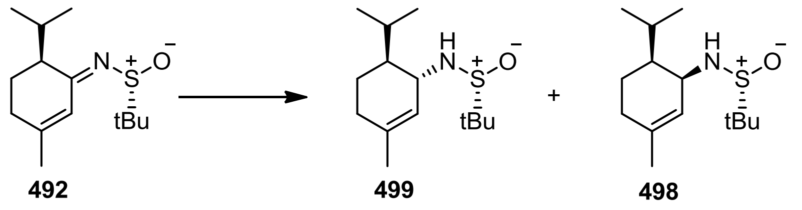
- (*R*)-*N*-((1*S*,6*R*)-6-Isopropyl-3-methylcyclohex-2-en-1-yl)-2-methylpropane-2-sulfinamide **497**



491 **497**

A novel compound prepared according to a literature procedure.[181] A solution of (*R*,*Z*)-*N*-(*R*)-sulfinyl ketimine **491** (0.144 g, 0.564 mmol) in Et$_2$O (5.6 mL) was cooled to -78 °C and treated with DIBAL-H (1.7 mL of a 1.0 M solution in hexanes, 1.7 mmol). After 1.5 h, the reaction mixture was quenched with NH$_4$Cl (10 mL of a saturated aq. solution) and extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic extracts were washed sequentially with H$_2$O (15 mL), brine (15 mL), dried over MgSO$_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Hexane to Hexane:EtOAc 7:3) to give *cis* sulfinamide **497** (0.114 g, 79%) as a colourless oil. R$_f$ 0.19 (Pet ether:EtOAc 7:3); ν$_{max}$ (neat)/cm^{-1}: 3435, 3223, 2955, 1473, 1363, 1048, 969; δ$_H$ (400 MHz, CDCl$_3$) 0.94 (3H, d, *J* 6.6 Hz, CH(C*H$_3$*)$_2$), 0.98 (3H, d, *J* 6.6 Hz, CH(C*H$_3$*)$_2$), 1.03-1.12 (1H, m, CH$_2$), 1.18 (9H, s, SC(CH$_3$)$_3$), 1.22-1.35 (1H, m, CH$_2$), 1.53-1.61 (1H, m, C*H*(CH$_3$)$_2$), 1.67-1.76 (4H, m, =CCH$_3$ and CH$_2$C*H*CHN), 1.86-2.04 (2H, m, CH$_2$), 3.26 (1H, d, *J* 6.1 Hz, NH), 3.86-3.97 (1H, m, CHN), 5.57-5.66 (1H, m, =CH); δ$_C$ (100 MHz, CDCl$_3$) 20.6 (CH$_2$, CH*C*H$_2$CH$_2$C=), 21.2 (2 x CH$_3$, CH(*C*H$_3$)$_2$), 23.0 (3 x CH$_3$, SC(*C*H$_3$)$_3$), 23.5 (CH$_3$, =C*C*H$_3$), 28.0 (CH, *C*H(CH$_3$)$_2$), 31.6 (CH$_2$, CHCH$_2$*C*H$_2$C=), 46.5 (CH, CH$_2$*C*HCHN), 51.0 (CH, CHN), 55.9 (C, S*C*(CH$_3$)$_3$), 121.8 (CH, H*C*=CCH$_3$), 139.3 (C, HC=*C*CH$_3$); m/z (ES) 280.1708 ([M+Na]$^+$ $C_{14}H_{27}NNaOS$ requires 280.1711), 280 (100%); $[\alpha]^{20}_D$ -194.3° (c 0.97, CHCl$_3$).

- (*R*)-*N*-((1*S*,6*S*)-6-Isopropyl-3-methylcyclohex-2-en-1-yl)-2-methylpropane-2-sulfinamide **499** and (*R*)-*N*-((1*R*,6*S*)-6-isopropyl-3-methylcyclohex-2-en-1-yl)-2-methylpropane-2-sulfinamide **498**



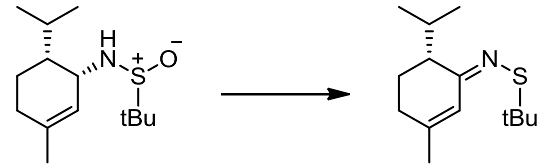
Novel compounds prepared according to a literature procedure.[181] A solution of (*R*,*Z*)-*N*-(*S*)-sulfinyl ketimine **492** (45 mg, 0.18 mmol) in THF (1.8 mL) was cooled to -78 °C and treated with DIBAL-H (0.53 mL of a 1.0 M solution in hexanes, 0.53 mmol). After 1 h, the reaction mixture was quenched with NH_4Cl (5 mL of a saturated aq. solution) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 4:1) to give *trans* sulfinamide **499** (21 mg, 47%) as a yellow solid and *cis* sulfinamide **498** (11 mg, 25%) as a yellow oil.

trans sulfinamide **499** : mp 46-50 °C; R_f 0.24 (Pet ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1}: 3478, 3114, 1455, 1364, 1023, 1011; δ_H (400 MHz, $CDCl_3$) 0.84 (3H, d, *J* 6.8 Hz, $CH(CH_3)_2$), 0.96 (3H, d, *J* 6.8 Hz, $CH(CH_3)_2$), 1.20 (9H, s, $SC(CH_3)_3$), 1.30-1.48 (2H, m, CH_2), 1.67 (3H, s, $=CCH_3$), 1.68-1.78 (1H, m, CH_2), 1.91 (2H, m, CH_2 and CH_2CHCHN), 1.94-2.06 (1H, m, $CH(CH_3)_2$), 3.15 (1H, d, *J* 7.6 Hz, NH), 3.62-3.76 (1H, m, CHN), 5.35 (1H, dd, *J* 1.5 and 3.0 Hz, =CH); δ_C (100 MHz, $CDCl_3$) 17.7 (CH_3, $CH(CH_3)_2$), 20.7 (CH_2, $CHCH_2CH_2C=$), 21.6 (CH_3, $CH(CH_3)_2$), 22.8 (3 x CH_3, $SC(CH_3)_3$), 23.6 (CH_3, $=CCH_3$), 26.0 (CH, $CH(CH_3)_2$), 29.2 (CH_2, $CHCH_2CH_2C=$), 46.6 (CH, CH_2CHCHN), 55.5 (CH, CHN), 55.8 (C, $SC(CH_3)_3$), 123.6 (CH, $HC=CCH_3$), 137.9 (C, $HC=CCH_3$); $[\alpha]^{20}_D$ -69.5° (c 1.0, $CHCl_3$).

cis sulfinamide **498**: R_f 0.33 (Pet ether:EtOAc 7:3); δ_H (400 MHz, $CDCl_3$) 0.93 (6H, dd, *J* 4.6 and 6.6 Hz, $CH(CH_3)_2$), 1.02-1.16 (2H, m, CH_2), 1.20 (9H, s, $SC(CH_3)_3$), 1.47-1.61 (1H, m, $CH(CH_3)_2$), 1.65 (3H, s, $=CCH_3$), 1.77-1.86 (1H, m, CH_2), 1.89-1.98 (2H, m, CH_2 and CH_2CHCHN), 2.85 (1H, d, *J* 9.3 Hz, NH), 3.72-3.88 (1H, m, CHN), 5.63-5.79 (1H, m, =CH); δ_C (100 MHz, $CDCl_3$) 21.0 (CH_3,

CH(*C*H$_3$)$_2$), 21.1 (CH$_3$, CH(*C*H$_3$)$_2$), 21.7 (CH$_2$, CH*C*H$_2$CH$_2$C=), 23.1 (3 x CH$_3$, SC(*C*H$_3$)$_3$), 23.5 (CH$_3$, =C*C*H$_3$), 28.3 (CH, *C*H(CH$_3$)$_2$), 31.2 (CH$_2$, CHCH$_2$*C*H$_2$C=), 46.3 (CH, CH$_2$*C*HCHN), 53.4 (CH, CHN), 56.3 (C, S*C*(CH$_3$)$_3$), 125.0 (CH, H*C*=CCH$_3$), 137.4 (C, HC=*C*CH$_3$).

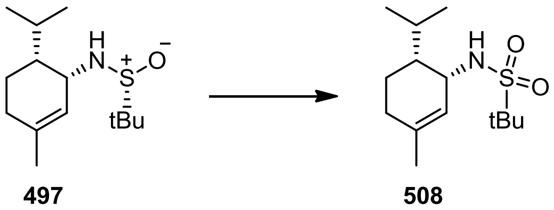
- (*R*,*Z*)-*S*-(tert-Butyl)-*N*-(6-isopropyl-3-methylcyclohex-2-en-1-ylidene)thiohydroxylamine **507**



497 **507**

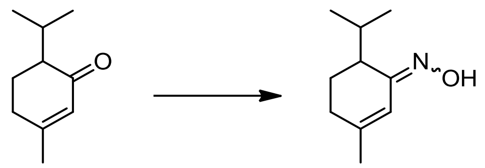
A novel compound prepared according to a literature procedure.[27] A solution of (*R*)-*N*-((1*S*,6*R*)-sulfinamide **497** (0.104 g, 0.404 mmol) in toluene (1.1 mL) was added dropwise to a solution of triphosgene (44 mg, 0.15 mmol) and pyridine (39 µL, 0.49 mmol) in toluene (2.0 mL). After 18 h at rt, the reaction mixture was quenched with NH$_4$Cl (3 mL of a saturated aq. solution) and extracted with Et$_2$O (3 x 5 mL). The combined organic extracts were washed sequentially with HCl (10 mL of a 0.25 M aq. solution) and brine (10 mL), dried over MgSO$_4$, filtered and evaporated under reduced pressure to give a 3.2:1 mixture of *Z:E* imine **507** (97 mg, 80%) as a colourless oil. R$_f$ 0.49 (Pet ether:CH$_2$Cl$_2$ 9:1); ν$_{max}$ (neat)/cm^{-1}: 2957, 1634, 1568, 1454, 1379, 1359, 1167, 724; δ$_H$ (400 MHz, CDCl$_3$) (as a mixture of isomers) 0.89, 0.94 (3H, d, *J* 6.7 Hz, CH(C*H$_3$*)$_2$), 0.91, 0.97 (3H, d, *J* 6.7 Hz, CH(C*H$_3$*)$_2$), 1.36, 1.38 (9H, s, SC(CH$_3$)$_3$), 1.68-2.00 (5H, m, CH$_2$ and =CCH$_3$), 2.02-2.24, 2.39-2.46 (4H, m, CH$_2$, CH$_2$C*H*C(N) and C*H*(CH$_3$)$_2$), 5.91, 6.09 (1H, dd, *J* 1.4 and 2.9 Hz, =CH); δ$_C$ (100 MHz, CDCl$_3$) (as a mixture of isomers) 19.4, 20.7 (CH$_3$, CH(*C*H$_3$)$_2$), 21.4, 21.5 (CH$_3$, CH(*C*H$_3$)$_2$), 23.6, 24.0 (CH$_3$, =C*C*H$_3$), 23.9, 24.4 (CH$_2$, CH*C*H$_2$CH$_2$C=), 26.9 (CH, *C*H(CH$_3$)$_2$), 27.1, 29.5 (CH$_2$, CHCH$_2$*C*H$_2$C=), 29.2, 29.3 (3 x CH$_3$, SC(*C*H$_3$)$_3$), 45.5, 49.8 (CH, CH$_2$*C*HC(N)), 45.9, 46.1 (C, S*C*(CH$_3$)$_3$), 119.1, 125.6 (CH, H*C*=CCH$_3$), 142.3, 148.9 (C, HC=*C*CH$_3$), 162.2, 166.5 (C, C(N)); m/z (ES) 240.1787 ([M+H]$^+$ C$_{14}$H$_{26}$NS requires 240.1786), 241 (65%), 240 (100), 184 (25); $[\alpha]^{20}_D$ +177.2° (c 1.03, CHCl$_3$).

- *N*-((1*S*,6*R*)-6-Isopropyl-3-methylcyclohex-2-en-1-yl)-2-methylpropane-2-sulfonamide **508**



A novel compound prepared according to a literature procedure.[184] A solution of (*R*)-*N*-((1*S*,6*R*)-sulfinamide **497** (55 mg, 0.21 mmol) in CH_2Cl_2 (3.1 mL) was treated with *m*CPBA (48 mg, 0.28 mmol). After 2.5 h at rt, the reaction mixture was quenched with Na_2SO_3 (5 mL of a saturated aq. solution), $NaHCO_3$ (5 mL of a saturated aq. solution) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:Et_2O 9:1) to give sulfonamide **508** (30 mg, 52%) as a colourless oil. R_f 0.38 (Pet ether:Et_2O 7:3); ν_{max} (neat)/cm^{-1}: 3282, 2957, 1430, 1296, 1125, 985, 910, 823, 689; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, d, *J* 6.6 Hz, $CH(CH_3)_2$), 0.99 (3H, d, *J* 6.6 Hz, $CH(CH_3)_2$), 1.05-1.26 (2H, m, CH_2CHCHN and CH_2), 1.40 (9H, s, $SC(CH_3)_3$), 1.66 (3H, s, $=CCH_3$), 1.70-1.86 (2H, m, $CH(CH_3)_2$ and CH_2), 1.88-2.04 (2H, m, CH_2), 3.48 (1H, d, *J* 9.6 Hz, NH), 4.02 (1H, dt, *J* 4.4 and 9.1 Hz, CHN), 5.59-5.76 (1H, m, =CH); δ_C (100 MHz, $CDCl_3$) 20.5 (CH_3, $CH(CH_3)_2$), 20.8 (CH_2, $CHCH_2CH_2C=$), 21.9 (CH_3, $CH(CH_3)_2$), 23.5 (CH_3, $=CCH_3$), 24.6 (3 x CH_3, $SC(CH_3)_3$), 27.9 (CH, $CH(CH_3)_2$), 31.2 (CH_2, $CHCH_2CH_2C=$), 45.5 (CH, CH_2CHCHN), 50.7 (CH, CHN), 59.9 (C, $SC(CH_3)_3$), 123.6 (CH, $HC=CCH_3$), 138.2 (C, $HC=CCH_3$); m/z (ES) 296.1653 ($[M+Na]^+$ $C_{14}H_{27}NNaO_2S$ requires 296.1660), 296 (100%); $[\alpha]^{20}_D$ -164.9° (c 0.65, $CHCl_3$).

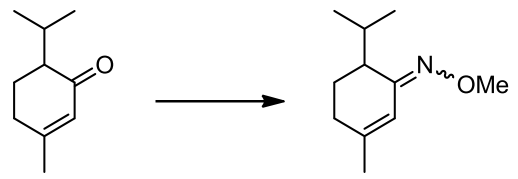
- 6-Isopropyl-3-methylcyclohex-2-enone oxime **512**



463 **512**

A novel compound prepared according to a literature procedure.[73] A solution of piperitone **463** (0.157 g, 1.03 mmol) in CH_3CN (2.6 mL) was added onto a solution of hydroxylamine hydrochloride (0.501 g, 7.21 mmol) and sodium acetate (0.591 g, 7.21 mmol) in H_2O (2.6 mL). The reaction mixture was heated to reflux. After 4.5 h, hydroxylamine hydrochloride (72 mg, 1.0 mmol) and sodium acetate (84 mg, 1.0 mmol) were added to drive the reaction to completion. After 18 h, the reaction mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 9:1) to give a 3:1 mixture of *Z:E* oxime **512** (0.124 g, 72%) as an orange oily solid. R_f 0.58 (Pet ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1}: 3186, 2956, 1639, 1431, 1379, 1366, 1150, 939, 886, 857; δ_H (400 MHz, $CDCl_3$) (as a mixture of isomers) 0.90, 0.91 (3H, d, *J* 6.7 Hz, $CH(CH_3)_2$), 0.93, 0.98 (3H, d, *J* 6.7 Hz, $CH(CH_3)_2$), 1.59-1.97 (2H, m, CH_2), 1.77, 1.84 (3H, s, $=CCH_3$), 1.97-2.07, 2.98 (2H, m, CH_2 and CHC(N)), 2.13-2.26 (2H, m, CH_2 and $CH(CH_3)_2$), 5.83, 6.53 (1H, d, *J* 0.7 Hz, =CH), 9.66 (1H, br s, OH); δ_C (100 MHz, $CDCl_3$) (as a mixture of isomers) 20.1, 20.9 (CH_3, $CH(CH_3)_2$), 21.5, 21.6 (CH_3, $CH(CH_3)_2$), 23.9, 24.2 (CH_3, $=CCH_3$), 24.1, 24.3 (CH_2, $CHCH_2CH_2C=$), 26.9, 27.1 (CH, $CH(CH_3)_2$), 27.6, 28.6 (CH_2, $CHCH_2CH_2C=$), 36.9, 44.1 (CH, CHC(N)), 112.9, 119.4 (CH, $HC=CCH_3$), 144.4, 148.8 (C, $HC=CCH_3$), 156.1, 159.8 (C, C(N)); m/z (ES) 168.1389 ($[M+H]^+$ $C_{10}H_{18}NO$ requires 169.1388), 232 (100%), 190 (31), 168 (23).

- 6-Isopropyl-3-methylcyclohex-2-enone *O*-methyl oxime **513**

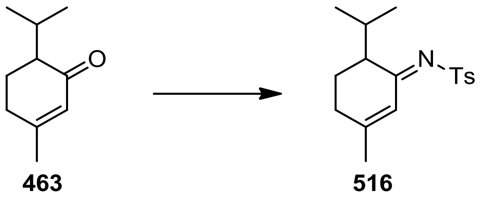


463 **513**

A novel compound prepared according to a literature procedure.[187] A solution of piperitone **463** (0.150 g, 0.985 mmol) in a 5:1 mixture of CH_3OH:H_2O (1.0 mL) was treated with methoxylamine hydrochloride (0.720 mL of a 25% wt aq. solution, 4.93 mmol) and sodium acetate (0.684 g, 5.02 mmol). The reaction mixture was heated at reflux for 18 h and MeOH was evaporated under reduced pressure. The aqueous reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:Et_2O 9:1) to give a 3.5:1.0 mixture of *Z:E* oxime **513** (0.105 g, 59%) as a pale yellow oil. R_f 0.62 (Pet ether:Et_2O 9:1); ν_{max} (neat)/cm^{-1}: 2955, 1639, 1435, 1054, 902, 865; δ_H (400 MHz, $CDCl_3$) (as a mixture of isomers) 0.85, 0.91 (3H, d, *J* 6.7 Hz, $CH(CH_3)_2$), 0.94, 0.97 (3H, d, *J* 6.7 Hz, $CH(CH_3)_2$), 1.57-1.85 (6H, m, CH_2, $=CCH_3$ and $CH(CH_3)_2$), 1.86-2.06, 2.83-2.93 (2H, m, CH_2 and CHC(N)), 2.12-2.27 (1H, m, CH_2), 3.81, 3.85 (3H, s, OCH_3), 5.81, 6.40 (1H, d, *J* 0.9 Hz, =CH); δ_C (100 MHz, $CDCl_3$) (as a mixture of isomers) 20.4, 20.9 (CH_3, $CH(CH_3)_2$), 21.4, 21.5 (CH_3, $CH(CH_3)_2$), 24.0, 24.2 (CH_3, $=CCH_3$), 24.5 (CH_2, $CHCH_2CH_2C=$), 26.9, 27.4 (CH, $CH(CH_3)_2$), 27.1, 28.5 (CH_2, $CHCH_2CH_2C=$), 37.6, 44.0 (CH, *C*HC(N)), 61.2, 61.5 (CH_3, OCH_3), 113.2, 119.3 (CH, $HC=CCH_3$), 144.7, 148.9 (C, $HC=CCH_3$), 156.2, 159.8 (C, C(N)); m/z (ES) 182.1535 ($[M+H]^+$ $C_{11}H_{20}NO$ requires 182.1539), 182 (100%).

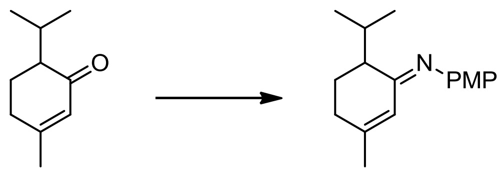
- (*Z*)-*N*-(6-Isopropyl-3-methylcyclohex-2-en-1-ylidene)-4-methylbenzenesulfonamide

516



A novel compound prepared according to a modified literature procedure.[175] A solution of piperitone **463** (0.114 g, 0.749 mmol) and $TsNH_2$ (0.141 g, 0.824 mmol) in THF (1.0 mL) was treated with $Ti(OEt)_4$ (0.528 mL, 1.65 mmol) and heated to reflux. After 36 h, the reaction mixture was quenched with H_2O (25 µL) and filtered through a pad of celite (eluent EtOAc). The filtrate was concentrated under reduced pressure and the crude product obtained was purified by column chromatography (Pet ether to Pet ether:EtOAc 4:1) to give tosyl imine **516** (24 mg, 10%) as a colourless oil. Rf 0.49 (Pet ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1}: 2952, 1728, 1438, 1367, 1237, 1018, 940; δ_H (400 MHz, $CDCl_3$) 0.88 (6H, t, *J* 6.9 Hz, CH(C*H*$_3$)$_2$), 1.82-1.99 (2H, m, CH_2), 2.00 (3H, s, =CCH_3), 2.05-2.40 (4H, m, CH_2, CHC(N) and C*H*(CH_3)$_2$), 2.41 (3H, s, $ArCH_3$), 7.06 (1H, s, =CH), 7.29 (2H, d, *J* 8.1 Hz, Ar H), 7.85 (2H, d, *J* 8.1 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 19.4 (CH_3, CH(*C*H$_3$)$_2$), 21.1 (CH_3, CH(*C*H$_3$)$_2$), 21.7 (CH_3, $ArCH_3$), 23.2 (CH_2, CH*C*H$_2$CH$_2$C=), 25.1 (CH_3, =C*C*H$_3$), 27.5 (CH, *C*H(CH_3)$_2$), 29.7 (CH_2, CHCH$_2$*C*H$_2$C=), 49.4 (CH, *C*HC(N)), 121.0 (CH, H*C*=CCH$_3$), 126.9 (2 x CH, Ar), 129.5 (2 x CH, Ar), 139.5 (C, Ar*C*CH$_3$), 143.1 (C, ArCS), 163.0 (C, HC=*C*CH$_3$), 181.1 (C, C(N)); m/z (ES) 306.1523 ([M+H]$^+$ $C_{17}H_{24}NO_2S$ requires 306.1522), 306 (100%), 258 (50), 249 (83), 195 (72), 137 (48), 123 (60), 95 (84).

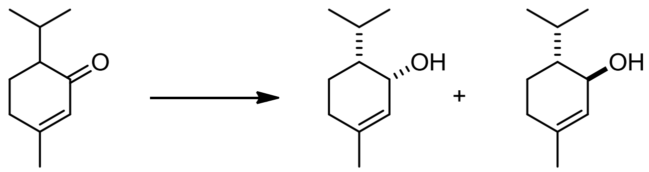
- (*Z*)-*N*-(6-Isopropyl-3-methylcyclohex-2-en-1-ylidene)-4-methoxyaniline **517**



463 **517**

A novel compound prepared according to a modified literature procedure.[175] A solution of piperitone **463** (0.114 g, 0.749 mmol) and 4-methoxyaniline (0.101 g, 0.824 mmol) in THF (1.0 mL) was treated with $Ti(OEt)_4$ (0.528 mL, 1.65 mmol) and heated to reflux. After 36 h, the reaction mixture was quenched with H_2O (25 µL) and filtered through a pad of celite (eluent EtOAc). The filtrate was concentrated under reduced pressure and the crude product obtained was purified by column chromatography (Pet ether to Pet ether:EtOAc 9:1) to give a 1.0:7.6 mixture of *E:Z* aniline imine **517** (77 mg, 41%) as a golden oil. Rf 0.58 (Pet ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1}: 2956, 1634, 1605, 1500, 1237, 1034, 827; δ_H (300 MHz, $CDCl_3$) (Z isomer) 0.97 (3H, d, *J* 6.4 Hz, $CH(CH_3)_2$), 1.03 (3H, d, *J* 6.4 Hz, $CH(CH_3)_2$), 1.73 (3H, s, $=CCH_3$), 1.89-2.33 (6H, m, CH_2, CHC(N) and $CH(CH_3)_2$), 3.77 (3H, s, OCH_3), 5.78 (1H, s, =CH), 6.70 (2H, d, *J* 8.9 Hz, Ar H), 6.83 (2H, d, *J* 8.9 Hz, Ar H); m/z (ES) 258.1851 ($[M+H]^+$ $C_{17}H_{24}NO$ requires 258.1852), 258 (23%), 169 (100), 151 (30), 124 (78).

- (±)-(1*S*,6*R*)-6-Isopropyl-3-methylcyclohex-2-enol or *cis* piperitol **521** and (±)-(1*R*,6*R*)-6-isopropyl-3-methylcyclohex-2-enol or *trans* piperitol **519**



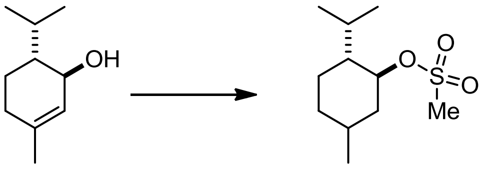
463 **521** **519**

Known compounds prepared according to the literature procedure.[196] A slurry of $LiAlH_4$ (50 mg, 1.3 mmol) in Et_2O (2.1 mL) was cooled to 0 °C and a solution of piperitone **463** (0.200 g, 1.31 mmol) in Et_2O (0.5 mL) was added dropwise over 3 min. After 3 h at 0 °C, the reaction mixture was carefully quenched with H_2O (3 mL) and extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Hexane to Hexane:Et_2O 4:1) to give *cis* piperitol **521** (38 mg, 19%) as a white solid and *trans* piperitol **519** (0.111 g, 55%) as a colourless oil.

cis piperitol **521**: mp 29-30 °C; R_f 0.65 (Pet ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1}: 3336, 2910, 1669, 1390, 953, 904; δ_H (400 MHz, $CDCl_3$) 0.92-1.02 (7H, m and 2 x d, *J* 6.7 Hz, $CH(CH_3)_2$ and $CH_2CHCHOH$), 1.11 (1H, br s, OH), 1.32 (1H, tdd, *J* 6.3, 11.3 and 13.6 Hz, CH_2), 1.58-1.77 (5H, m, $CH(CH_3)_2$, CH_2 and $=CCH_3$), 1.87-2.05 (2H, m, CH_2), 4.12 (1H, br s, CHOH), 5.55-5.58 (1H, m, =CH); δ_C (100 MHz, $CDCl_3$) 20.8 (CH_2, $CHCH_2CH_2C=$), 21.0 (CH_3, $CH(CH_3)_2$), 21.2 (CH_3, $CH(CH_3)_2$), 23.6 (CH_3, $=CCH_3$), 28.6 (CH, $CH(CH_3)_2$), 31.7 (CH_2, $CHCH_2CH_2C=$), 46.4 (CH, $CH_2CHCHOH$), 65.2 (CH, CHOH), 123.9 (CH, $HC=CCH_3$), 139.8 (C, $HC=CCH_3$); m/z (ES) 153.1270 ($[M-H]^+$ $C_{10}H_{17}O$ requires 153.1274), 154 (10%), 138 (12), 137 (100). *Literature data*:[196] δ_H (300 MHz, $CDCl_3$) 5.6 (d, *J* = 6 Hz, 1H, H-2), 4.1 (m, 1H, H-3), 1.9 (m, 2H, H-6), 1.7 (s, 3H, CH_3), 1.8–1.6 (m, 2H, H-4 + $(CH_3)_2CH$), 1.3 (m, 2H, H-5), 1.0 and 0.9 (d+d, *J* = 7 Hz, 6H, $(CH_3)_2CH$); δ_C (75 MHz, $CDCl_3$) 139.5 (C_1), 123.6 (C_2), 64.9 (C_3), 46.1 (C_4), 31.4 (C_6), 28.3 $(CH_3)_2CH$), 23.3, 20.9, 20.7 ($3\times CH_3$) and 20.4 (C_5); m/z 154 (M^+, 7.0), 139 (69), 121 (10), 112 (27), 111 (21), 95 (14), 93 (28), 91 (20), 84 (100), 83 (74), 79 (18), 77 (17), 69 (18), 55 (33) and 41 (64).

trans piperitol **519**: R_f 0.58 (Pet ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1}: 3307, 2928, 1434, 1367, 1026, 984, 898; δ_H (400 MHz, $CDCl_3$) 0.83 (3H, d, *J* 6.9 Hz, $CH(CH_3)_2$), 0.96 (3H, d, *J* 6.9 Hz, $CH(CH_3)_2$), 1.18-135 (2H, m, CH_2 and $CH_2CHCHOH$), 1.38 (1H, br s, OH), 1.63-1.71 (4H, m, CH_2 and $=CCH_3$), 1.83-2.07 (3H, m, $CH(CH_3)_2$ and CH_2), 4.00 (1H, br s, CHOH), 5.32-5.44 (1H, m, =CH); δ_C (100 MHz, $CDCl_3$) 17.8 (CH_3, $CH(CH_3)_2$), 21.1 (CH_2, $CHCH_2CH_2C=$), 21.4 (CH_3, $CH(CH_3)_2$), 23.3 (CH_3, $=CCH_3$), 26.7 (CH, $CH(CH_3)_2$), 30.3 (CH_2, $CHCH_2CH_2C=$), 48.2 (CH, $CH_2CHCHOH$), 69.3 (CH, CHOH), 125.4 (CH, $HC=CCH_3$), 137.8 (C, $HC=CCH_3$); m/z (ES) 153.1270 ($[M-H]^+$ $C_{10}H_{17}O$ requires 153.1274), 138 (12), 137 (100), 81 (32). *Literature data*:[196] δ_H (300 MHz, $CDCl_3$) 5.4 (br s, 1H, H-2), 4.0 (m, 1H, H-3), 2.1–1.9 (m, 4H, H-4 + H-6 + $(\mathrm{CH_3})_2\mathrm{C}\mathit{H}$), 1.6 (s, 3H, $\mathrm{CH_3}$), 1.2 (m, 2H, H-5), 0.9 and 0.8 (d+d, *J* = 7 Hz, 6H, $(\mathrm{C}\mathit{H}_3)_2\mathrm{CH}$); δ_C (75 MHz, $\mathrm{CDCl_3}$) 137.2 (C_1), 125.4 (C_2), 68.8 (C_3), 47.6 (C_4), 30.0 (C_6), 26.3 $(\mathrm{CH_3})_2\mathit{C}\mathrm{H}$), 23.0, 21.1, 17.1 (3×$\mathit{C}\mathrm{H_3}$) and 20.7 ($C_5$); m/z 154 ($M^+$, 7), 139 (61), 121 (7), 112 (24), 111 (24), 93 (30), 91 (22), 84 (100), 83 (73), 81 (18), 79 (17), 77 (18), 69 (16), 55 (34) and 41 (65).

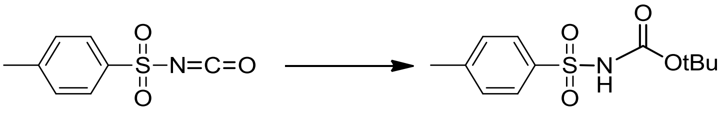
- (±)-(1*S*,2*R*)-2-Isopropyl-5-methylcyclohexyl methanesulfonate **523**



519 **523**

A known compound[261] prepared according to a literature procedure.[203] A solution of *trans*-piperitol **519** (67 mg, 0.43 mmol) in pyridine (4.3 mL) was treated with MsCl (50 µL, 0.65 mmol). After 3 h at rt, the reaction mixture was quenched with H_2O (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with H_2O (3 x 10 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure to give mesylated piperitol **523** (6 mg, 6%) as a yellow oil. R_f 0.53 (Pet ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1}: 2928, 1456, 1351, 1332, 1171, 938, 911; δ_H (300 MHz, $\mathrm{CDCl_3}$) 0.83 (3H, d, *J* 7.0 Hz, $\mathrm{CHC}\mathit{H_3}$), 0.96 (6H, dd, *J* 2.5 and 6.8 Hz, $\mathrm{CH(C}\mathit{H_3})_2$), 0.96-1.64 (5H, m, $\mathrm{CH_2}$, $\mathrm{CH_2C}\mathit{H}\mathrm{CH_3}$ and $\mathrm{CH_2C}\mathit{H}\mathrm{CHO}$), 1.62-1.68 (2H, m, $\mathrm{CH_2}$), 2.07 (1H, dtd, *J* 2.5, 6.8 and 9.4 Hz, $\mathrm{C}\mathit{H}(\mathrm{CH_3})_2$), 2.22-2.31 (1H, m, $\mathrm{CH_2}$), 3.01 (3H, s, $\mathrm{SCH_3}$), 4.55 (1H, dt, *J* 4.6 and 10.9 Hz, CHOMs); δ_C (100 MHz, $\mathrm{CDCl_3}$) 15.9 ($\mathrm{CH_3}$, $\mathrm{CH}\mathit{C}\mathrm{H_3}$), 21.0 ($\mathrm{CH_3}$, $\mathrm{CH(}\mathit{C}\mathrm{H_3})_2$), 22.0 ($\mathrm{CH_3}$, $\mathrm{CH(}\mathit{C}\mathrm{H_3})_2$), 23.3 ($\mathrm{CH_2}$), 26.1 (CH, $\mathit{C}\mathrm{HCH_3}$), 31.8 (CH, $\mathit{C}\mathrm{H(CH_3)_2}$), 34.0 ($\mathrm{CH_2}$), 39.3 ($\mathrm{CH_3}$, $\mathrm{SCH_3}$), 42.4 (CH, $\mathrm{CH_2}\mathit{C}\mathrm{HCHO}$), 47.6 ($\mathrm{CH_2}$, $\mathit{C}\mathrm{H_2CHO}$), 83.6 (CH, CHOMs). *Literature data*:[261] ν_{max} (neat)/cm^{-1}: 2960, 2875, 1460, 1350, 1175, 920, 865, 750, 536. δ_H (500 MHz, $\mathrm{CDCl_3}$) 0.84 (d, *J* = 6.9 Hz, 3H), 0.85–0.90 (m, 1H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 1.02–1.11 (m, 1H), 1.23–1.30 (m, 1H), 1.39–1.50 (m, 2H), 1.67–1.75 (m, 2H), 2.06–2.09 (m, 1H), 2.24–2.28 (m, 1H), 3.01 (s, 3H), 4.51–4.57 (m, 1H); m/z 234 (M^+), 132, 78.

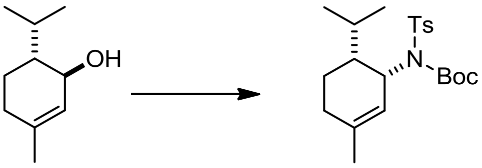
- *tert*-Butyl tosylcarbamate **527**



184 **527**

A known compound[262] prepared according to a literature procedure.[209] Tosylisocyanate **184** (1.00 mL, 6.72 mmol) in *t*BuOH (6.7 mL) was stirred at rt. After 18 h, the excess of solvent was removed under reduced pressure and TsNHBoc **527** (1.82 g, 100%) was obtained as a white solid. mp 87-89 °C; R$_f$ 0.65 (Pet ether:EtOAc 1:1); ν$_{max}$ (neat)/cm^{-1}: 3257, 2935, 1748, 1509, 1438, 1230, 1125, 1033, 816; δ$_H$ (400 MHz, CDCl$_3$) 1.39 (9H, s, C(CH$_3$)$_3$), 2.44 (3H, s, ArCH$_3$), 7.32 (2H, d, *J* 8.3 Hz, Ar H), 7.66 (1H, s, NH), 7.89 (2H, d, *J* 8.3 Hz, Ar H); δ$_C$ (100 MHz, CDCl$_3$) 21.8 (CH$_3$, ArCH$_3$), 28.0 (3 x CH$_3$, C(*C*H$_3$)$_3$), 84.2 (C, O*C*(CH$_3$)$_3$), 128.4 (2 x CH, Ar), 129.6 (2 x CH, Ar), 136.1 (C, Ar*C*CH$_3$), 144.9 (C, ArCS), 149.4 (C, C(O)); m/z (ES) 272.0955 ([M+H]$^+$ $C_{12}H_{18}NO_4S$ requires 272.0951), 316 (53%), 289 (98), 272 (17), 238 (31), 216 (100), 155 (24). *Literature data*:[262] mp 115-116 °C; ν$_{max}$ (KBr)/cm^{-1}: 3225, 1750, 1439, 1340, 1234, 1149; δ$_H$ (200 MHz, CDCl$_3$) 1.47 (s, 9H), 2.46 (s, 3H), 7.30 (s, 1H), 7.38 (AA' part of the AA'BB' system, *J* = 8.2 Hz, 2H), 7.93 (BB' part of the AA'BB' system, *J* = 8.2 Hz, 2H); δ$_C$ (50 MHz, CDCl$_3$) 21.6, 27.7, 84.0, 128.1, 129.4, 135.9, 144.6, 149.4; m/z (EI) 171 ([M-COO*t*Bu]$^+$, 85%), 155 (80), 91 (100).

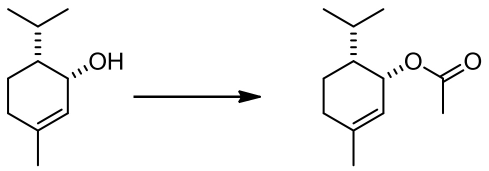
- (±)-*tert*-Butyl ((1*S*,6*R*)-6-Isopropyl-3-methylcyclohex-2-en-1-yl)(tosyl)carbamate **528**



519 **528**

A novel compound prepared according to a modified literature procedure.[208] A solution of *trans*-piperitol **519** (80 mg, 0.52 mmol), TsNHBoc **527** (0.211 g, 0.778 mmol) and PPh$_3$ (0.408 g, 1.56 mmol) in THF (7.4 mL) was wrapped in foil and treated with DIAD (0.204 mL, 1.04 mmol). After 52 h at rt, the reaction mixture was concentrated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:$\mathrm{Et_2O}$ 9:1) to give Boc-protected tosylamine **528** (56 mg, 26%) as a yellow oil. R_f 0.50 (Pet ether:EtOAc 9:1); ν_{max} (neat)/cm^{-1}: 2958, 1723, 1349, 1250, 1147, 1087, 994; δ_H (400 MHz, $\mathrm{CDCl_3}$) (as a mixture of rotamers) 0.87, 0.91 (3H, d, *J* 6.8 Hz, $\mathrm{CH(C}H_3)_2$), 0.94, 1.04 (3H, d, *J* 6.8 Hz, $\mathrm{CH(C}H_3)_2$), 1.28, 1.32 (9H, s, $\mathrm{C(CH_3)_3}$), 1.44 (1H, dd, *J* 6.6 and 14.9 Hz, $\mathrm{CH_2}$), 1.66, 1.71 (3H, s, $\mathrm{=CCH_3}$), 1.73-1.80 (1H, m, $\mathrm{CH_2}$), 1.85-2.10 (3H, m, $\mathrm{CH_2}$ and $\mathrm{C}H\mathrm{(CH_3)_2}$), 2.10-2.21 (1H, m, $\mathrm{CH_2C}H\mathrm{CHN}$), 2.43 (3H, s, $\mathrm{ArCH_3}$), 4.90-4.99 (1H, m, CHN), 5.16, 5.25 (1H, s, =CH), 7.30 (2H, d, *J* 8.3 Hz, Ar H), 7.81, 7.84 (2H, d, *J* 8.3 Hz, Ar H); δ_C (100 MHz, $\mathrm{CDCl_3}$) (as a mixture of rotamers) 15.9, 18.7 ($\mathrm{CH_3}$, $\mathrm{CH(}C\mathrm{H_3)_2}$), 19.4, 22.4 ($\mathrm{CH_2}$, $\mathrm{CH}C\mathrm{H_2CH_2C{=}}$), 21.6, 23.3 ($\mathrm{CH_3}$, $\mathrm{CH(}C\mathrm{H_3)_2}$), 21.8, 23.9 ($\mathrm{CH_3}$, $\mathrm{=C}C\mathrm{H_3}$), 23.2 ($\mathrm{CH_3}$, $\mathrm{ArCH_3}$), 26.5 (CH, $C\mathrm{H(CH_3)_2}$), 28.1 (3 x $\mathrm{CH_3}$, $\mathrm{C(}C\mathrm{H_3)_3}$), 30.7 ($\mathrm{CH_2}$, $\mathrm{CHCH_2}C\mathrm{H_2C{=}}$), 42.3, 44.3 (CH, $\mathrm{CH_2}C\mathrm{HCHN}$), 57.1, 60.2 (CH, CHN), 83.6, 83.8 (C, $\mathrm{O}C\mathrm{(CH_3)_3}$), 120.2, 123.6 (CH, $\mathrm{H}C\mathrm{{=}CCH_3}$), 128.1, 128.4 (2 x CH, Ar), 129.3 (2 x CH, Ar), 136.5 (C, $\mathrm{HC{=}}C\mathrm{CH_3}$), 138.0, 138.6 (C, $\mathrm{Ar}C\mathrm{CH_3}$), 143.7, 143.9 (C, ArCS), 151.2, 151.7 (C, C(O)); m/z (ES) 430.2022 ($\mathrm{[M+Na]^+}$ $\mathrm{C_{22}H_{33}NNaO_4S}$ requires 430.2028), 430 (50%), 294 (100), 238 (80).

- (±)-(1*S*,6*R*)-6-Isopropyl-3-methylcyclohex-2-en-1-yl acetate **533**

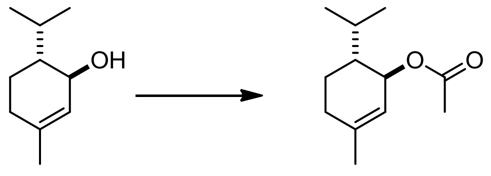


521 **533**

A known compound[196] prepared according to a literature procedure.[213] A solution of *cis* piperitol **521** (0.402 g, 2.61 mmol) in pyridine (2.6 mL) was treated with $\mathrm{Ac_2O}$ (0.492 mL, 5.21 mmol). After 18 h at rt, the reaction mixture was heated at reflux for 1 h, poured onto $\mathrm{H_2O}$ (15 mL) and extracted with $\mathrm{Et_2O}$ (3 x 20 mL). The combined organic extracts were washed sequentially with HCl (30 mL of a 1 M aq. solution) and brine (30 mL), dried over $\mathrm{MgSO_4}$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:$\mathrm{Et_2O}$ 96:4) to give allylic acetate **533** (0.401 g, 78%) as a colourless oil. R_f

0.68 (Pet ether:EtOAc 9:1); ν_{max} (neat)/cm^{-1}: 2959, 1727, 1369, 1238, 1015, 950, 900; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, d, *J* 6.6 Hz, $CH(CH_3)_2$), 0.93 (3H, d, *J* 6.6 Hz, $CH(CH_3)_2$), 1.08-1.18 (1H, m, CH_2CHCHO), 1.38-1.63 (2H, m, CH_2 and $CH(CH_3)_2$), 1.70 (3H, s, $=CCH_3$), 1.72-1.80 (1H, m, CH_2), 1.89-2.08 (5H, m, CH_2 and $CH_3C(O)O$), 5.21 (1H, br s, CHOAc), 5.63 (1H, dd, *J* 1.3 and 3.2 Hz, =CH); δ_C (100 MHz, $CDCl_3$) 20.9 (CH_3, $CH(CH_3)_2$), 21.0 (CH_3, $CH(CH_3)_2$), 21.4 (CH_2, $CHCH_2CH_2C=$), 21.6 (CH_3, $CH_3C(O)O$), 23.5 (CH_3, $=CCH_3$), 28.6 (CH, $CH(CH_3)_2$), 31.4 (CH_2, $CHCH_2CH_2C=$), 44.6 (CH_2, CH_2CHCHO), 68.8 (CH, CHOAc), 120.0 (CH, $HC=CCH_3$), 141.6 (C, $HC=CCH_3$), 171.1 (C, C(O)); m/z (ES) 219.1369 ($[M+Na]^+$ $C_{12}H_{20}NaO_2$ requires 219.1361), 251 (26%), 219 (100), 170 (27). *Literature data*:[196] δ_H (300 MHz, $CDCl_3$) 5.6 (d, *J* = 7 Hz, 1H, H-2), 5.2 (m, 1H, H-3), 2.0–1.8 (m, 2H, H-4), 1.9 (s, 3H, CH_3CO), 1.8–1.7 (m, 2H, H-6 + $(CH_3)_2CH$), 1.6 (s, 3H, CH_3), 1.6–1.3 (m, 2H, H-5), 0.9 and 0.8 (d+d, *J* = 7 Hz, 6H, $(CH_3)_2CH$); δ_C (75 MHz, $CDCl_3$) 170.8 (CO), 141.4 (C_1), 119.8 (C_2), 68.5 (C_3), 44.3 (C_4), 31.2 (C_6), 28.3 $(CH_3)_2CH$), 23.3 (CH_3), 21.3 (C_5), 20.7 and 20.6 ($CH_3)_2CH$); m/z 154 (11), 137 (76), 136 (94), 121 (100), 93 (59), 81 (42), 43 (80) and 41 (39).

- (±)-(1*R*,6*R*)-6-Isopropyl-3-methylcyclohex-2-en-1-yl acetate **534**

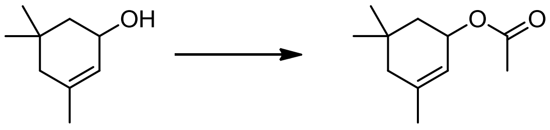


519 **534**

A known compound[196] prepared according to a literature procedure.[213] A solution of *trans* piperitol **519** (45 mg, 0.29 mmol) in pyridine (0.29 mL) was treated with Ac_2O (50 µL, 0.52 mmol). After 18 h at rt, the reaction mixture was poured onto H_2O (1.5 mL) and extracted with Et_2O (3 x 2 mL). The combined organic extracts were washed sequentially with HCl (3 mL of a 1 M aq. solution) and brine (3 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:Et_2O 92:8) to give allylic acetate **534** (38 mg, 67%) as a colourless oil. R_f 0.64 (Pet ether:EtOAc 9:1); ν_{max} (neat)/cm^{-1}: 2959, 1729, 1369, 1235, 1016, 903; δ_H (400 MHz, $CDCl_3$) 0.83 (3H, d, *J* 6.9 Hz,

$CH(C\mathit{H}_3)_2$), 0.94 (3H, d, *J* 6.9 Hz, $CH(C\mathit{H}_3)_2$), 1.34-1.52 (2H, m, CH_2 and $CH_2C\mathit{H}CHOAc$), 1.67 (3H, s, $=CCH_3$), 1.68-1.76 (2H, m, CH_2 and $C\mathit{H}(CH_3)_2$), 1.88-2.00 (2H, m, CH_2), 2.04 (3H, s, $CH_3C(O)O$), 5.21-5.28 (1H, m, CHOAc), 5.28-5.34 (1H, m, =CH); δ_C (100 MHz, $CDCl_3$) 18.1 (CH_3, $CH(\mathit{C}H_3)_2$), 21.0 (CH_3, $CH(\mathit{C}H_3)_2$), 21.3 (CH_2, $CH\mathit{C}H_2CH_2C=$), 21.6 (CH_3, $\mathit{C}H_3C(O)O$), 23.4 (CH_3, $=C\mathit{C}H_3$), 27.0 (CH, $\mathit{C}H(CH_3)_2$), 29.7 (CH_2, $CHCH_2\mathit{C}H_2C=$), 44.1 (CH, $CH_2\mathit{C}HCHOAc$), 72.2 (CH, CHOAc), 121.0 (CH, $H\mathit{C}=CCH_3$), 139.9 (C, $HC=\mathit{C}CH_3$), 171.3 (C, C(O)); m/z (ES) 219.1370 ($[M+Na]^+$ $C_{12}H_{20}NaO_2$ requires 219.1361), 251 (12%), 219 (100), 170 (26). *Literature data*:[196] δ_H (300 MHz, $CDCl_3$) 5.2 (br s, 1H, H-2), 5.1 (m, 1H, H-3), 1.9 (s, 3H, $C\mathit{H}_3CO$), 1.8 (m, 2H, H-6), 1.7-1.5 (m, 2H, H-4 + $(CH_3)_2C\mathit{H}$), 1.5 (s, 3H, $C\mathit{H}_3$), 1.4–1.2 (m, 2H, H-5), 0.8 and 0.7 (d+d, *J* = 7 Hz, 6H, $(C\mathit{H}_3)_2CH$); δ_C (75 MHz, $CDCl_3$) 170.5 (CO), 139.1 (C_1), 120.6 (C_2), 71.5 (C_3), 43.5 (C_4), 29.1 (C_6), 26.4 $(CH_3)_2\mathit{C}H$), 22.7 (CH_3), 20.8 (C_5), 20.9, 20.4 and 17.5 ($3\times CH_3$); m/z 154 (11), 139 (10), 137 (4), 136 (25), 121 (85), 93 (100), 91 (40), 84 (85), 81 (35), 79 (38), 77 (37), 43 (85), and 41 (40).

3,5,5-Trimethylcyclohex-2-en-1-yl acetate **212**

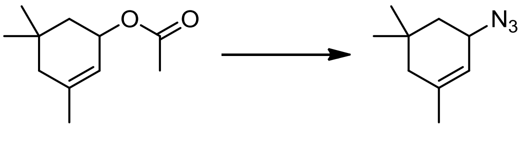


212 **535**

A known compound[263] prepared according to a literature procedure.[213] A solution of 3,5,5-trimethylcyclohex-2-enol **212** (1.96 g, 14.4 mmol) in pyridine (14 mL) was treated with Ac_2O (3.94 mL, 42.0 mmol). After 18 h at rt, the reaction mixture was poured onto H_2O (20 mL) and extracted with Et_2O (3 x 40 mL). The combined organic extracts were washed sequentially with HCl (70 mL of 1 M aq. solution), $NaHCO_3$ (70 mL of a saturated aq. solution) and brine (70 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:Et_2O 9:1) to give allyl acetate **535** (2.07 g, 81%) as a colourless oil. R_f 0.87 (Pet ether:Et_2O 4:1); ν_{max} (neat)/cm^{-1} : 2952, 1728, 1438, 1373, 1235, 1018, 940; δ_H (400 MHz, $CDCl_3$) 0.93 (3H, s, $C(CH_3)_2$), 0.99 (3H, s, $C(CH_3)_2$), 1.38 (1H, dd, *J* 8.1

and 12.8 Hz, CCH$_2$C=), 1.61-1.71 (4H, m, CH$_3$C= and CC*H*$_2$CHOAc), 1.74 (1H, dd, *J* 6.1 and 12.8 Hz, CCH$_2$C=), 1.87 (1H, d, *J* 17.7 Hz, CC*H*$_2$CHOAc), 2.03 (3H, s, C(O)CH$_3$), 5.29-5.36 (1H, m, CHOAc), 5.37 (1H, br s, CH=); δ_C (100 MHz, CDCl$_3$) 21.6 (CH$_3$, *C*H$_3$C(O)O), 23.8 (CH$_3$, =C*C*H$_3$), 27.0 (CH$_3$, C(*C*H$_3$)$_2$), 30.6 (CH$_3$, C(*C*H$_3$)$_2$), 30.8 (C, *C*(CH$_3$)$_2$), 40.8 (CH$_2$, C*C*H$_2$CHOAc), 44.2 (CH$_2$, C*C*H$_2$C=), 70.3 (CH, CHOAc), 119.4 (CH, =CH), 138.6 (C, =*C*CH$_3$), 171.1 (C, C(O)O); m/z (EI) 182.1316 (M$^+$ $C_{11}H_{18}O_2$ requires 182.1307), 140 (5%), 122 (39), 107 (100), 91 (44), 79 (21). *Literature data*:[263] δ_H (90 MHz, CDCl$_3$) 0.96 and 1.01 (two s, CH$_3$ at C-5), 1.72 (m, CH$_3$ at C-1), 2.06 (s, OCOCH$_3$), 5.45 (m, H-3), 5.53 (m, H-2); δ_C (22.5 MHz, CCl$_4$) 20.6, 23.2, 26.7, 30.1, 30.1, 40.4, 43.8, 68.8, 119.8, 136.7, 168.7; m/z 182 (M$^+$).

- 3-Azido-1,5,5-trimethylcyclohex-1-ene **536**

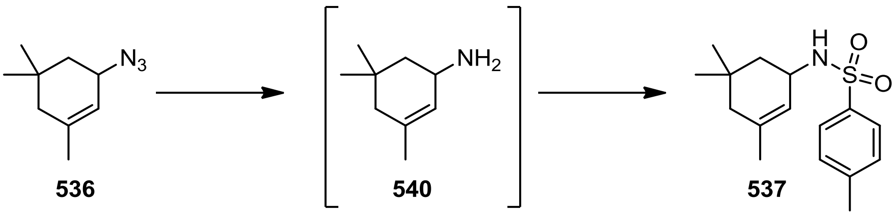


535 **536**

A known compound[264] prepared according to a literature procedure.[214] A solution of allylic acetate **535** (2.04 g, 11.2 mmol) and TMSN$_3$ (4.45 mL, 33.5 mmol) in Et$_2$O (41 mL) was cooled to 0 °C and treated with LiClO$_4$ (13.1 g, 123 mmol). The reaction mixture was allowed to warm to rt after 10 min. After 6 h at rt, the reaction mixture was quenched with H$_2$O (40 mL) and extracted with Et$_2$O (3 x 40 mL). The combined organic extracts were washed with brine (60 mL), dried over MgSO$_4$, filtered and evaporated under reduced pressure to give allylic azide **536** (1.85 g, 100%) as a colourless oil. R$_f$ 0.93 (Pet ether:Et$_2$O 85:15); ν_{max} (neat)/cm^{-1} : 2955, 2086, 1244, 906; δ_H (400 MHz, CDCl$_3$) 0.89 (3H, s, C(CH$_3$)$_2$), 1.00 (3H, s, C(CH$_3$)$_2$), 1.33 (1H, dd, *J* 9.7 and 12.7 Hz, CCH$_2$C=), 1.58-1.76 (5H, m, CC*H*$_2$CHN$_3$, CCH$_2$C= and CH$_3$C=), 1.87 (1H, d, *J* 17.4 Hz, CC*H*$_2$CHN$_3$), 3.83-3.97 (1H, m, CHN$_3$), 5.37-5.39 (1H, m, CH=); δ_C (100 MHz, CDCl$_3$) 23.8 (CH$_3$, =C*C*H$_3$), 26.0 (CH$_3$, C(*C*H$_3$)$_2$), 30.8 (C, *C*(CH$_3$)$_2$), 31.1 (CH$_3$, C(*C*H$_3$)$_2$), 40.9 (CH$_2$, C*C*H$_2$CHN$_3$), 44.0 (CH$_2$, C*C*H$_2$C=), 57.3 (CH, CHN$_3$), 118.6 (CH, =CH), 138.6 (C, =*C*CH$_3$); m/z (EI) 137.1210 ([M-N$_2$]$^+$

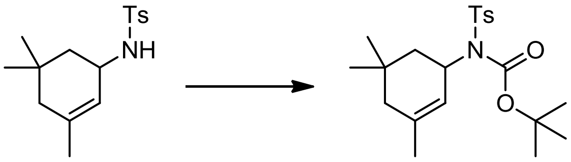
$C_9H_{15}N$ requires 137.1204), 137 (6%), 123 (63), 122 (50), 107 (100), 91 (53), 81 (28), 79 (28). *Literature data*:[264] δ_H (250 MHz, $CDCl_3$) 0.89 (s, 3 H), 1.01 (s, 2 H), 1.26-1.38 (m, 1 H), 1.60-1.92 (m, 1 H), 1.70 (s, 6 H), 3.90 (br m, 1 H), 5.38 (d, *J* 0.93 Hz, 1 H); δ_C (62.9 MHz, $CDCl_3$) 24.0 (q), 26.2 (q), 31.0 (s), 31.3 (q), 41.1 (t), 44.2 (t), 57.6 (d), 118.9 (d), 138.8 (s); ν_{max} (neat)/cm^{-1} : 2100 (N_3); m/z (CI) 166 ($M^{\cdot+}$, 6), 138 ($(M+H-N_2]^{\cdot+}$, 14), 123 ($[M-N_3]^+$, 100).

- 4-Methyl-*N*-(3,5,5-trimethylcyclohex-2-en-1-yl)benzenesulfonamide **537**



A novel compound prepared according to a literature procedure.[215] A solution of allylic azide **536** (1.92 g, 11.6 mmol) in Et_2O (116 mL) was treated with $LiAlH_4$ (0.486 g, 12.8 mmol). After 3.5 h at rt, the reaction mixture was cooled to 0 °C and quenched with dropwise addition of H_2O (0.496 mL), NaOH (0.496 mL of a 15% aq. solution) and H_2O (1.46 mL). The white precipitate formed was filtered and the filtrate was concentrated under reduced pressure to give allyl amine **540**. A solution of amine **540** in Et_2O (40 mL) was treated with NaH (0.408 g of a 60% dispersion in mineral oil, 12.1 mmol) and a solution of TsCl (2.31 g, 12.1 mmol) in Et_2O (21 mL) was added dropwise over 30 min. After 18 h at rt, the reaction mixture was carefully quenched with H_2O (3 mL), diluted with H_2O (40 mL) and extracted with EtOAc (3 x 40 mL). The combined organic extracts were washed with brine (80 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Hexane to Hexane:EtOAc 4:1) to give tosylamine **537** (1.21 g, 35% over 2 steps) as a white solid. mp 97-100 °C; R_f 0.59 (Pet ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1} : 3256, 2913, 1432, 1320, 1157, 1092, 1064, 808, 659; δ_H (400 MHz, $CDCl_3$) 0.80 (3H, s, $C(CH_3)_2$), 0.89 (3H, s, $C(CH_3)_2$), 1.11 (1H, dd, *J* 10.0 and 12.6 Hz, CCH_2C=), 1.48-1.61 (5H, m, CCH_2CHNTs, CCH_2C= and CH_3C=), 1.74 (1H, d, *J* 16.5 Hz, CCH_2CHNTs), 2.42 (3H, s, $ArCH_3$), 3.72-3.88 (1H, m, CHNTs), 4.59 (1H, d, *J* 8.9 Hz, NH), 5.04 (1H, d, *J* 0.8 Hz, CH=), 7.29 (2H, d, *J* 8.2 Hz, Ar H), 7.77 (2H, d, *J* 8.2 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 21.7 (CH_3, $ArCH_3$), 23.7 (CH_3, =C*C*H_3), 25.7 (CH_3, C(*C*H_3)$_2$), 30.8 (C, *C*(CH_3)$_2$), 31.1 (CH_3, C(*C*H_3)$_2$), 43.6 (CH_2), 43.7 (CH_2), 50.0 (CH, CHNTs), 120.9 (CH, =CH), 127.1 (2 x CH, Ar), 129.8 (2 x CH, Ar), 137.3 (C, Ar*C*CH_3), 138.6 (C, =*C*CH_3), 143.3 (C, $ArCSO_2$); m/z (ES) 316.1357 ($[M+Na]^+$ $C_{16}H_{23}NNaO_2S$ requires 316.1347), 317 (15%), 316 (100), 194 (30).

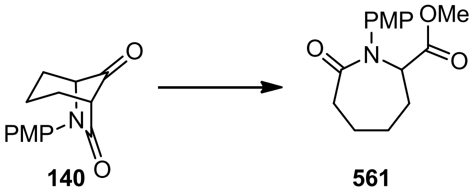
- t-Butyl tosyl(3,5,5-trimethylcyclohex-2-en-1-yl)carbamate **543**



537 **543**

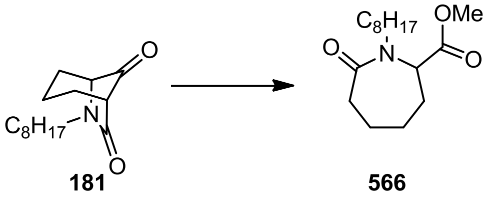
A novel compound prepared according to a literature procedure.[217] A solution of tosylamine **537** (0.326 g, 1.11 mmol) in CH_3CN (22 mL) was treated with Boc_2O (0.291 g, 1.33 mmol) and DMAP (27 mg, 0.22 mmol). After 18 h at rt, the reaction mixture was concentrated under reduced pressure and purified directly by column chromatography (Pet ether to Pet ether:Et_2O 4:1) to give Boc protected tosylamine **543** (0.426 g, 97%) as a white solid. mp 81-83 °C; R_f 0.73 (Pet ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1} : 2954, 1726, 1351, 1245, 1148, 1088, 812, 726; δ_H (400 MHz, $CDCl_3$) 0.96 (3H, s, C(CH_3)$_2$), 0.99 (3H, s, C(CH_3)$_2$), 1.31 (9H, s, C(CH_3)$_3$), 1.44-1.73 (5H, m, CH_2 and CH_3C=), 1.81-2.01 (2H, m, CH_2), 2.42 (3H, s, $ArCH_3$), 4.96-5.12 (1H, m, CHN), 5.17 (1H, br s, CH=), 7.30 (2H, d, *J* 8.2 Hz, Ar H), 7.81 (2H, d, *J* 8.2 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 21.7 (CH_3, $ArCH_3$), 23.7 (CH_3, =C*C*H_3), 25.5 (CH_3, C(*C*H_3)$_2$), 28.0 (3 x CH_3, C(*C*H_3)$_3$), 31.8 (C, *C*(CH_3)$_2$), 31.9 (CH_3, C(*C*H_3)$_2$), 40.7 (CH_2), 43.6 (CH_2), 55.9 (CH, CHN), 83.5 (C, O*C*(CH_3)$_3$), 121.1 (CH, =CH), 127.9 (2 x CH, Ar), 129.4 (2 x CH, Ar), 134.6 (C, Ar*C*CH_3), 138.1 (C, =*C*CH_3), 143.9 (C, $ArCSO_2$), 151.1 (C, NC(O)O); m/z (ES) 394.2048 ($[M+H]^+$ $C_{21}H_{32}NO_4S$ requires 394.2047), 416 (13%), 394 (6), 338 (36), 294 (16), 238 (8), 216 (28).

- Methyl 1-(4-methoxyphenyl)-7-oxoazepane-2-carboxylate **561**



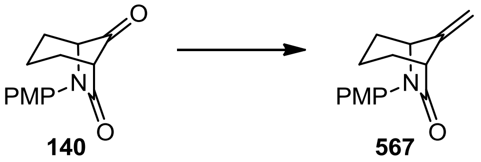
A novel compound prepared according to a literature procedure.[222] A solution of rearranged product **140** (54 mg, 0.22 mmol) in DMF (2.2 mL) was treated with NaH (15 mg, 0.44 mmol). After 1 h at rt, iodomethane (0.137 mL, 2.20 mmol) was added. After 3 h at rt, the reaction mixture was quenched with brine (2 mL) and extracted with EtOAc (2 x 4 mL). The combined organic extract were washed with brine (5 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether:EtOAc 3:1 to Pet ether:EtOAc 1:3) to give lactam **561** (55 mg, 90%) as a colourless oil. R_f 0.36 (Pet ether:EtOAc 3:2); ν_{max} (neat)/cm^{-1} : 2935, 1737, 1655, 1508, 1423, 1240, 1030, 826, 727; δ_H (400 MHz, $CDCl_3$) 1.55-1.66 (2H, m, CH_2), 1.80-2.03 (3H, m, CH_2), 2.40-2.55 (2H, m, CH_2), 2.72 (1H, dd, *J* 7.6 and 14.8 Hz, CH_2), 3.78 (3H, s, $PhOCH_3$), 3.81 (3H, s, $C(O)OCH_3$), 4.40 (1H, dd, *J* 3.2 and 5.6 Hz, $CH_2C\mathit{H}N$), 6.87 (2H, d, *J* 8.8 Hz, Ar H), 7.14 (2H, d, *J* 8.8 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 22.8 (CH_2), 26.2 (CH_2), 31.2 (CH_2), 38.2 (CH_2), 52.6 (CH_3, $C(O)O\mathit{C}H_3$), 55.5 (CH_3, $PhOCH_3$), 64.8 (CH, $CH_2\mathit{C}HN$), 114.6 (2 x CH, Ar), 127.8 (2 x CH, Ar), 138.6 (C, ArCN), 158.4 (C, ArCO), 171.3 (C, C(O)N), 176.0 (C, C(O)O); m/z (ES) 300.1217 ($[M+Na]^+$ $C_{15}H_{19}NNaO_4$ requires 300.1212), 301 ($[M+Na+H]^+$, 6%), 300 (100), 278 (14).

- Methyl 1-octyl-7-oxoazepane-2-carboxylate **181**



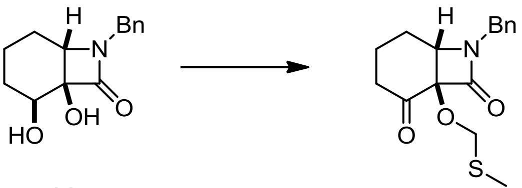
A novel compound prepared according to a literature procedure.[222] A solution of rearranged product **181** (30 mg, 0.12 mmol) in THF (1.2 mL) was treated with NaH (15 mg, 0.37 mmol). After 1 h at rt, iodomethane (76 µL, 1.2 mmol) was added and the solution was refluxed. After 18 h, the reaction mixture was quenched with brine (2 mL) and extracted with EtOAc (2 x 2 mL). The combined organic extract were washed with brine (5 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give **566** (30 mg, 88%) as a colorless oil. R_f 0.61 (Pet ether:EtOAc 1:1); ν_{max} (neat)/cm^{-1} : 2924, 1742, 1639, 1426, 1171, 1085, 992, 708; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, *J* 6.8 Hz, $(CH_2)_8CH_3$), 1.17-1.32 (10H, m, CH_2), 1.37-1.57 (4H, m, CH_2), 1.65-1.86 (3H, m, CH_2), 2.27 (1H, ddd, *J* 1.8, 12.6 and 14.8 Hz, CH_2), 2.44-2.50 (1H, m, CH_2), 2.59 (1H, dd, *J* 7.0 and 14.6 Hz, CH_2), 3.20 (1H, ddd, *J* 6.2, 9.0 and 13.4 Hz, $NCH_2(CH_2)_7CH_3$), 3.57 (1H, ddd, *J* 6.6, 9.0 and 13.4 Hz, $NCH_2(CH_2)_7CH_3$), 3.77 (3H, s, OCH_3), 4.09 (1H, dd, *J* 3.6 and 5.6 Hz, $NCHCH_2$); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3, $(CH_2)_7CH_3$), 22.9 (CH_2), 26.1 (CH_2), 27.1 (CH_2), 28.1 (CH_2), 29.4 (CH_2), 29.6 (CH_2), 29.9 (CH_2), 31.1 (CH_2), 32.0 (CH_2), 38.1 (CH_2), 50.3 (CH_2, $NCH_2(CH_2)_6CH_3$), 52.6 (CH_3, OCH_3), 61.3 (CH, CH_2CHN), 171.5 (C, C(O)N), 175.7 (C, C(O)O); m/z (ES) 384.2224 ($[M+H]^+$ $C_{16}H_{30}NO_3$ requires 284.2220), 306 (17%), 284 (100).

- (±)-(1*R*,5*S*)-6-(4-Methoxyphenyl)-8-methylene-6-azabicyclo[3.2.1]octane-7-one **567**



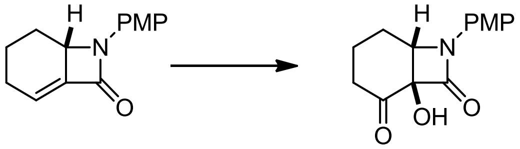
A novel compound prepared according to a modified literature procedure.[70] A solution of $Ph_3P^+{-}CH_3,Br^-$ (0.291 g, 0.816 mmol) in THF (1.0 mL) was cooled to 0 °C, *n*BuLi (0.51 mL of a 1.6 M solution in hexane, 0.82 mmol) was added dropwise over 2 min. The reaction mixture was stirred for 25 min at rt and a solution of rearranged product **140** (95 mg, 0.39 mmol) in THF (1.6 mL) was added. The reaction mixture was heated at reflux for 18 h, evaporated under reduced pressure and purified directly by column chromatography (Pet ether to Pet ether:EtOAc 7:3) to give lactam **567** (87 mg, 93%) as a pale yellow solid. mp 105-107 °C; R_f 0.78 (Pet ether:EtOAc 1:1); ν_{max} (neat)/cm^{-1}: 2934, 1676, 1610, 1509, 1381, 1243, 1031, 817, 829; δ_H (300 MHz, $CDCl_3$) 1.62-1.81 (4H, m, CH_2), 2.04-2.23 (2H, m, CH_2), 3.02 (1H, m, CCHC(O)), 3.76 (3H, s, OCH_3), 4.49 (1H, d, *J* 3.7 Hz, CH_2C*H*N), 4.76 (1H, s, $=CH_2$), 4.84 (1H, s, $=CH_2$), 6.87 (2H, d, *J* 9.1 Hz, Ar H), 7.52 (2H, d, *J* 9.1 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 18.4 (CH_2), 30.3 (CH_2), 30.6 (CH_2), 50.1 (CH, C*C*HC(O)), 55.7 (CH_3, OCH_3), 64.4 (CH, CH_2*C*HN), 101.1 (CH_2, $=CH_2$), 114.5 (2 x CH, Ar), 122.2 (2 x CH, Ar), 131.4 (C, ArCN), 151.0 (C, =C), 156.7 (C, ArCO), 173.8 (C, C(O)N); m/z (ES) 266.1145 ($[M+Na]^+$ $C_{15}H_{17}NNaO_2$ requires 266.1157), 266 (100%).

- (±)-(1*R*,6*S*)-7-Benzyl-1-((methylthio)methoxy)-7-azabicyclo[4.2.0]octane-2,8-dione **575**



A novel compound prepared according to a literature procedure.[225] A solution of oxalyl chloride (64 µL, 0.76 mmol) in CH_2Cl_2 (2.4 mL) was cooled to -60 °C and treated with a solution of DMSO (0.164 mL, 2.28 mmol) in CH_2Cl_2 (0.6 mL). The reaction mixture was stirred for 30 min at -60 °C and diol **145** (63 mg, 0.25 mmol) was added. After 25 min, Et_3N (0.705 mL, 5.06 mmol) was added. The reaction mixture was stirred for 5 min at -60 °C and 40 min at rt. It was quenched with H_2O (3 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 3:1) to give lactam **575** (27 mg, 35%) as a pale yellow oil. R_f 0.51 (Pet ether:EtOAc 1:1); ν_{max} (neat)/cm^{-1}: 2923, 1754, 1706, 1404, 1239, 1074, 982, 699; δ_H (400 MHz, $CDCl_3$) 1.71-1.88 (3H, m, CH_2), 1.92-2.02 (1H, m, CH_2), 2.14 (3H, s, SCH_3), 2.33-2.46 (1H, m, CH_2), 2.58-2.68 (1H, m, CH_2), 4.03 (1H, t, *J* 2.4 Hz, NC*H*CH_2), 4.11, 4.77 (2H, ABq, *J* 15.1 Hz, NCH_2Ph), 4.87-4.96 (2H, m, OCH_2S), 7.28-7.40 (5H, m, Ar H); δ_C (100 MHz, $CDCl_3$) 14.8 (CH_3, SCH_3), 16.5 (CH_2), 23.8 (CH_2), 38.9 (CH_2), 45.0 (CH_2, NCH_2Ph), 60.1 (CH, CH_2*C*HN), 73.3 (CH_2, OCH_2S), 90.8 (C, C(O)*C*OCH_2), 128.4 (CH, Ar), 128.6 (2 x CH, Ar), 129.2 (2 x CH, Ar), 134.5 (C, Ar), 161.6 (C, C(O)N), 202.8 (C, CH_2*C*(O)C); m/z (ES) 328.0979 ($[M+Na]^+$ $C_{16}H_{19}NNaO_3S$ requires 328.0983), 344 (50%), 329 (36), 328 (100).

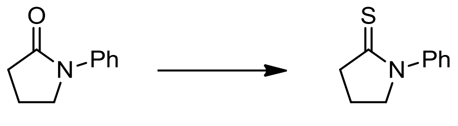
- (±)-(1*R*,6*S*)-1-Hydroxy-7-(4-methoxyphenyl)-7-azabicyclo[4.2.0]octan-2,8-dione **576**



130 **576**

A novel compound prepared according to a literature procedure.[227] $NaHCO_3$ (53 mg, 0.63 mmol) and $RuCl_3$ (25 µL of a 0.1 M aq. solution, $2.5.10^{-3}$ mmol) were dissolved in a 1:2:2 mixture of H_2O:CH_3CN:EtOAc (3.2 mL). Oxone® (0.389 g, 1.27 mmol) was added and the bright yellow reaction mixture was cooled to 0 °C. Lactam **130** (58 mg, 0.25 mmol) was added. After 1.5 h, the reaction mixture was allowed to warm to rt. After 1.5 h at rt, $RuCl_3$ (0.25 mL of a 0.1 M aq. solution, 0.025 mmol) was added to drive the reaction to completion and stirring was continued for 18 h. The reaction mixture was diluted with EtOAc (5 mL), filtered, washed with Na_2SO_3 (5 mL of a saturated aq. solution), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether:EtOAc 3:1 to Pet ether:EtOAc 1:1) to give keto hydroxy lactam **576** (15 mg, 23%) as a brown oil. R_f 0.27 (Pet ether:EtOAc 3:2); δ_H (300 MHz, $CDCl_3$) 1.48-2.12 (3H, m, CH_2), 2.39 (1H, dq, *J* 3.0 and 14.8 Hz, CH_2), 2.48-2.64 (1H, m, CH_2), 2.70-2.86 (1H, m, CH_2), 3.81 (3H, s, OCH_3), 4.49 (1H, br s, OH), 4.51-4.60 (1H, m, $CH_2C\mathit{H}N$), 6.93 (2H, d, *J* 9.1 Hz, Ar H), 7.38 (2H, d, *J* 9.1 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 16.5 (CH_2), 23.2 (CH_2), 35.9 (CH_2, $\mathit{C}H_2C(O)$), 55.7 (CH_3, OCH_3), 62.8 (CH, $CH_2\mathit{C}HN$), 88.2 (C, COH), 114.9 (2 x CH, Ar), 119.4 (2 x CH, Ar), 129.7 (C, ArCN), 157.2 (C, ArCO), 160.4 (C, C(O)N), 205.3 (C, $CH\mathit{C}(O)C$); m/z (ES) 262.1076 ($[M+H]^+$ $C_{14}H_{16}NO_4$ requires 262.1074), 316 (14%), 300 (25), 294 (66), 278 (100), 262 (35).

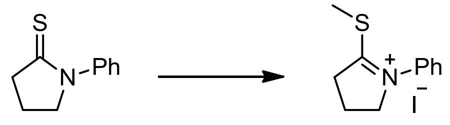
- 1-Phenylpyrrolidine-2-thione **578**



577 **578**

A novel compound prepared according to a literature procedure.[229] A solution of Lawesson's reagent (3.02 g, 7.48 mmol) and 1-phenyl-2-pyrrolidinone **577** (2.01 g, 7.48 mmol) in toluene (125 mL) was heated to reflux. After 75 min, the reaction mixture was concentrated under reduced pressure. The precipitate that appeared upon addition of CH_2Cl_2 (30 mL) was filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:EtOAc 9:1) to give thiolactam **578** (1.86 g, 85%) as a pale yellow solid. mp 81-83 °C; R_f 0.49 (Pet ether:Et_2O 7:3); ν_{max} (neat)/cm^{-1}: 2948, 1594, 1494, 1438, 1252, 1140, 1041, 760, 689; δ_H (300 MHz, $CDCl_3$) 2.13-2.32 (2H, m, $CH_2C\mathit{H_2}CH_2$), 3.22 (2H, t, *J* 7.9 Hz, $CH_2C(S)$), 4.21 (2H, t, *J* 7.3 Hz, CH_2N), 7.28-7.36 (1H, m, Ar H), 7.40-7.54 (4H, m, Ar H); δ_C (100 MHz, $CDCl_3$) 20.8 (CH_2, $CH_2\mathit{C}H_2CH_2$), 46.5 (CH_2, $\mathit{C}H_2C(S)$), 58.9 (CH_2, CH_2N), 125.1 (2 x CH, Ar), 127.9 (CH, Ar), 129.2 (2 x CH, Ar), 140.7 (C, Ar), 202.9 (C, C(S)N); m/z (EI) 177.0603 (M^+ $C_{10}H_{11}NS$ requires 177.0612), 178 (8%), 177 (46), 176 (100), 148 (8).

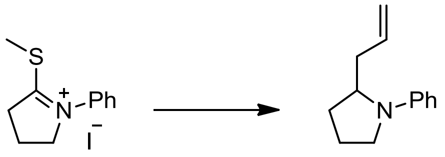
- 5-(Methylthio)-1-phenyl-3,4-dihydro-2H-pyrrol-1-ium iodide **579**



578 **579**

A novel compound prepared according to a literature procedure.[70] A solution of thiolactam **578** (0.499 g, 2.81 mmol) and iodomethane (2.97 mL, 47.8 mmol) in Et_2O (6.0 mL) was stirred at rt. After 18 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and concentrated under reduced pressure (3 times) to give iminium salt **579** (0.815 g, 91%) as a yellow solid. mp 181-183 °C; ν_{max} (neat)/cm^{-1}: 2973, 1581, 1297, 1148, 1032, 766, 692; δ_H (300 MHz, $CDCl_3$) 2.64 (2H, quint, *J* 7.8 Hz, $CH_2\mathit{CH_2}CH_2$), 2.79 (3H, s, SCH_3), 3.93 (2H, t, *J* 7.8 Hz, $C\mathit{H_2}C(SCH_3)=N$), 4.56 (2H, t, *J* 7.8 Hz, CH_2N), 7.39-7.57 (3H, m, Ar H), 7.64-7.76 (2H, m, Ar H); δ_C (100 MHz, $CDCl_3$) 17.7 (CH_3, SCH_3), 20.0 (CH_2, $CH_2\mathit{C}H_2CH_2$), 42.0 (CH_2, $\mathit{C}H_2C(SCH_3)=N$), 65.2 (CH_2, CH_2N), 124.6 (2 x CH, Ar), 130.5 (2 x CH, Ar), 131.2 (CH, Ar), 136.5 (C, Ar), 197.5 (C, $=\mathit{C}SCH_3$); m/z (ES) 210.0949 ($[M-I+H_2O]^+$ $C_{11}H_{14}NOS$ requires 210.0947), 239 (14%), 232 (21), 210 (29), 184 (42), 162 (68), 161 (100).

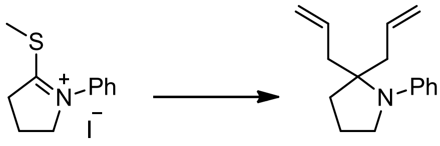
- 2-Allyl-1-phenylpyrrolidine **580**



579 **580**

A novel compound prepared according to a literature procedure.[265] A solution of iminium salt **579** (96 mg, 0.30 mmol) in CH_2Cl_2 (3.3 mL) was cooled to -78 °C, allylmagnesium chloride (0.23 mL of a 2.0 M solution in THF, 0.46 mmol) was added dropwise over 1 min. After 1.5 h at -78 °C, $NaBH_3CN$ (0.60 mL of a 1.0 M solution in THF, 0.60 mmol) and CH_3COOH (1.7 mL) were added and the reaction mixture was allowed to warm to rt. After 1.5 h, NaOH (10 mL of a 10% aq. solution) was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:CH_2Cl_2 95:5) to give allyl amine **580** (23 mg, 50%) as a colourless oil. ν_{max} (neat)/cm^{-1}: 2967, 1595, 1503, 1361, 1157, 990, 911, 743, 690; δ_H (400 MHz, $CDCl_3$) 1.86-2.17 (5H, m, $\mathrm{CH_2C}\mathit{H_2}\mathrm{CH_2}$, $\mathrm{NCHC}\mathit{H_2}\mathrm{CH_2}$ and $\mathrm{C}\mathit{H_2}\mathrm{CH{=}CH_2}$), 2.49-2.59 (1H, m, $\mathrm{C}\mathit{H_2}\mathrm{CH{=}CH_2}$), 3.20 (1H, td, *J* 6.9 and 9.0 Hz, CH_2N), 3.40-3.53 (1H, m, CH_2N), 3.73-3.85 (1H, m, $\mathrm{CH_2C}\mathit{H}\mathrm{N}$), 5.07-5.20 (2H, m, $\mathrm{CH{=}C}\mathit{H_2}$), 5.78-5.94 (1H, m, $\mathrm{C}\mathit{H}\mathrm{{=}CH_2}$), 6.62 (2H, d, *J* 8.0 Hz, Ar H), 6.69 (1H, d, *J* 7.3 Hz, Ar H), 7.22-7.32 (2H, m, Ar H); δ_C (100 MHz, $CDCl_3$) 23.4 (CH_2), 29.9 (CH_2), 37.5 (CH_2, $\mathit{C}\mathrm{H_2CH{=}CH_2}$), 48.5 ($CH_2$, CH_2N), 58.2 (CH, $\mathrm{CH_2}\mathit{C}\mathrm{HN}$), 112.0 (2 x CH, Ar), 115.5 (CH, Ar), 117.1 (CH_2, $\mathrm{CH{=}}\mathit{C}\mathrm{H_2}$), 129.4 (2 x CH, Ar), 135.8 (CH, $\mathit{C}\mathrm{H{=}CH_2}$), 147.2 (C, Ar); m/z (EI) 187.1363 (M^+ $C_{13}H_{17}N$ requires 187.1361), 187 (10%), 147 (11), 146 (100), 104 (12), 77 (16).

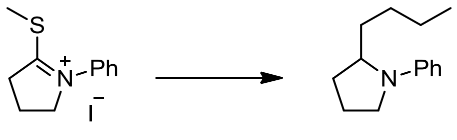
- 2,2-Diallyl-1-phenylpyrrolidine **581**



579 **581**

A novel compound prepared according to a literature procedure.[265] A solution of iminium salt **579** (98 mg, 0.30 mmol) in CH_2Cl_2 (3.4 mL) was cooled to -78 °C, allylmagnesium chloride (0.23 mL of a 2.0 M solution in THF, 0.46 mmol) was added dropwise over 1 min. The reaction mixture was allowed to warm to 0 °C over 35 min, stirred at 0 °C for 35 min and warmed to rt. After 75 min at rt, $NaBH_3CN$ (0.60 mL of a 1.0 M solution in THF, 0.60 mmol) and CH_3COOH (1.7 mL) were added. After 1.75 h, NaOH (15 mL of a 10% aq. solution) was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 6 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:CH_2Cl_2 9:1) to give diallyl amine **581** (36 mg, 52%) as a colourless oil. ν_{max} (neat)/cm^{-1}: 2972, 1597, 1502, 1342, 992, 910, 744, 691; δ_H (400 MHz, $CDCl_3$) 1.84-1.93 (2H, m, $CH_2CH_2CH_2$), 2.02 (2H, t, *J* 7.4 Hz, CCH_2CH_2), 2.46 (2H, dd, *J* 8.6 and 14.2 Hz, $CH_2CH{=}CH_2$), 2.82 (2H, ddt, *J* 1.1, 5.9 and 14.2 Hz, $CH_2CH{=}CH_2$), 3.34 (2H, t, *J* 6.6 Hz, CH_2N), 5.00-5.09 (4H, m, $CH{=}CH_2$), 5.62-5.74 (2H, m, $CH{=}CH_2$), 6.69 (1H, t, *J* 7.2 Hz, Ar H), 6.81 (2H, d, *J* 8.1 Hz, Ar H), 7.18-7.26 (2H, m, Ar H); δ_C (100 MHz, $CDCl_3$) 22.4 (CH_2, $CH_2CH_2CH_2$), 37.1 (CH_2, CCH_2CH_2), 42.7 (2 x CH_2, $CH_2CH{=}CH_2$), 51.4 (CH_2, CH_2N), 65.9 (C, CH_2CN), 113.7 (2 x CH, Ar), 115.9 (CH, Ar), 117.7 (2 x CH_2, $CH{=}CH_2$), 129.1 (2 x CH, Ar), 134.9 (2 x CH, $CH{=}CH_2$), 146.7 (C, Ar); m/z (ES) 228.1751 ($[M+H]^+$ $C_{16}H_{22}N$ requires 228.1747), 228 (100%).

- 2-Butyl-1-phenylpyrrolidine **582**

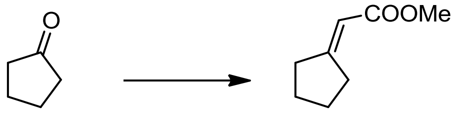


579 **582**

A novel compound prepared according to a modified literature procedure.[265] A solution of iminium salt **579** (0.115 g, 0.360 mmol) in THF (4.0 mL) was cooled to -78 °C, *n*BuLi (0.340 mL of a 1.59 M solution in THF, 0.540 mmol) was added dropwise over 1 min. After 1.5 h at -78 °C, $NaBH_3CN$ (0.72 mL of a 1.0 M solution in THF, 0.72 mmol) and CH_3COOH (2.0 mL) were added and the reaction mixture was allowed to warm to rt. After 45 min, NaOH (10 mL of a 10% aq. solution) was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:CH_2Cl_2 9:1) to give pyrrolidine **582** (15 mg, 21%) as a colourless oil. ν_{max} (neat)/cm^{-1}: 2927, 1595, 1503, 1362, 1157, 990, 742, 690; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.0 Hz, $(CH_2)_3CH_3$), 1.20-1.47 (5H, m, CH_2), 1.65-1.79 (1H, m, CH_2), 1.80-1.89 (1H, m, CH_2), 1.89-2.12 (3H, m, CH_2), 3.11-3.21 (1H, m, CH_2N), 3.38-3.47 (1H, m, CH_2N), 3.59-3.71 (1H, m, CH_2CHN), 6.58 (2H, d, *J* 8.0 Hz, Ar H), 6.66 (1H, d, *J* 7.3 Hz, Ar H), 7.18-7.30 (2H, m, Ar H); δ_C (100 MHz, $CDCl_3$) 14.4 (CH_3, $(CH_2)_3CH_3$), 23.1 (CH_2), 23.7 (CH_2), 29.1 (CH_2), 30.5 (CH_2), 33.0 (CH_2), 48.4 (CH_2,

CH_2N), 58.8 (CH, CH_2*C*HN), 111.9 (2 x CH, Ar), 115.3 (CH, Ar), 129.3 (2 x CH, Ar), 147.5 (C, Ar); m/z (ES) 204.1749 ($[M+H]^+$ $C_{14}H_{22}N$ requires 204.1747), 204 (100%).

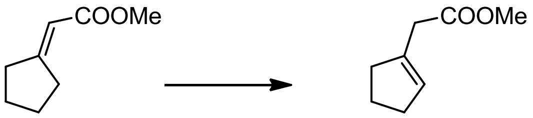
- Methyl 2-cyclopentylideneacetate **584**



584

A known compound[266] prepared according to a modified literature procedure.[231] Sodium (0.449 g, 19.6 mmol) was added portionwise to MeOH (10 mL). After complete dissolution, the NaOMe solution was treated with trimethyl phosphonoacetate **583** (2.83 mL, 19.6 mmol). After 50 min at rt, cyclopentanone (1.10 g, 13.1 mmol) was added and vigorous stirring was applied for 18 h. The reaction mixture was concentrated under reduced pressure, carefully diluted with H_2O (10 mL) and Et_2O (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:Et_2O 95:5) to give conjugated ester **584** (1.25 g, 68%) as a colourless oil. R_f 0.61 (Pet ether:Et_2O 95:5); ν_{max} (neat)/cm^{-1}: 2952, 1713, 1653, 1197, 1120, 1030, 856; δ_H (300 MHz, $CDCl_3$) 1.59-1.81 (4H, m, CH_2*C*H_2*C*H_2CH_2), 2.38-2.49 (2H, m, $=CCH_2$), 2.69-2.82 (2H, m, $=CCH_2$), 3.67 (3H, s, OCH_3), 5.76-5.83 (1H, m, =CH); δ_C (100 MHz, $CDCl_3$) 25.7 (CH_2, $=CCH_2CH_2$), 26.6 (CH_2, $=CCH_2$*C*H_2), 32.8 (CH_2, =*C*CH_2), 36.1 (CH_2, =*C*CH_2), 50.9 (CH_3, OCH_3), 111.4 (CH, =CH), 167.5 (C, =C), 169.6 (C, *C*(O)OCH_3); m/z (EI) 140.0835 (M^+ $C_8H_{12}O_2$ requires 140.0837), 140 (100%), 109 (29), 79 (36). *Literature data*:[266] ν_{max} (neat)/cm^{-1}: 1714.3, 1651.7; δ_H (300 MHz, $CDCl_3$) 5.78 (m, 1H), 3.66 (s, 3H), 2.74 (m, 2H), 2.41 (m, 2H), 1.75-1.61 (m, 4H); δ_C (100 MHz, $CDCl_3$) 169.51, 167.31, 111.18, 50.76, 35.94, 32.64, 26.39, 25.49; m/z (EI) 140.0832 (calcd for $C_8H_{12}O_2$ 140.0837), 140 (100), 109 (77), 105 (52), 79 (13), 57 (22), 41 (31), 32 (22), 28 (100).

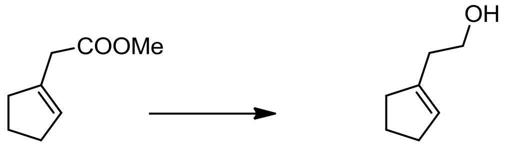
- Methyl 2-(cyclopent-1-en-1-yl)acetate **585**



584 **585**

A known compound[267] prepared according to a modified literature procedure.[231] A solution of conjugated ester **584** (1.86 g, 13.3 mmol) in THF (20 mL) was cooled to -78 °C and treated with LHMDS (16 mL of a 1.0 M solution in THF, 16 mmol). After 1.5 h at -78 °C, the reaction mixture was carefully quenched with NH_4Cl (20 mL of a saturated aq. solution) and extracted with Et_2O (2 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:Et_2O 95:5) to give unconjugated ester **585** (1.60 g, 86%) as a colourless oil. R_f 0.61 (Pet ether:Et_2O 95:5); ν_{max} (neat)/cm^{-1}: 2952, 1737, 1435, 1156, 1013; δ_H (400 MHz, $CDCl_3$) 1.84-1.95 (2H, m, $CH_2C\textit{H}_2CH_2$), 2.27-2.38 (4H, m, $=CCH_2$ and $=CHC\textit{H}_2$), 3.12 (2H, s, $=CCH_2C(O)$), 3.68 (3H, s, OCH_3), 5.44-5.61 (1H, m, =CH); δ_C (100 MHz, $CDCl_3$) 23.6 (CH_2, $CH_2\textit{C}H_2CH_2$), 32.7 (CH_2), 35.3 (CH_2), 37.0 (CH_2, $\textit{C}H_2C(O)$), 51.9 (CH_3, OCH_3), 128.5 (CH, =CH), 136.7 (C, =C), 172.1 (C, $\textit{C}(O)OCH_3$); m/z (EI) 140.0833 (M^+ $C_8H_{12}O_2$ requires 140.0837), 140 (100%), 108 (39), 80 (93), 67 (31). *Literature data*:[267] δ_H ($CDCl_3$, 90 MHz) 5.48 (br s, 1 H, CH), 3.62 (s, 3 H, CH_3), 3.07 (s, 2 H, CH_2), 2.74-2.13 (m, 4 H, C_3' and C_5'), 2.03-1.72 (m, 2 H, C_4'); δ_C ($CDCl_3$, 25 MHz) 23.4 (C_4'), 32.4 (C_3'), 35.0 (C_5'), 36.7 (CH_2), 51.6 (CH_3), 128.2 (C_2'), 136.4 (C_1'), 171.7 (C=O).

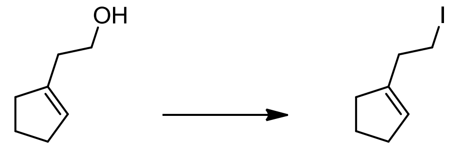
- 2-(Cyclopent-1-en-1yl)ethanol **587**



585 **587**

A known compound[268] prepared according to a modified literature procedure.[196] A solution of unconjugated ester **585** (1.68 g, 12.0 mmol) in THF (120 mL) was added dropwise over 30 min onto a slurry of $LiAlH_4$ (1.36 g, 35.9 mmol) in Et_2O (120 mL) at 0 °C. After a further 20 min at 0 °C, the reaction mixture was quenched with H_2O (1.36 mL), NaOH (1.36 mL of a 15% aq. solution) and H_2O (4.09 mL). The reaction mixture was allowed to warm to rt and the white precipitate formed was filtered. The filtrate was dried over $MgSO_4$, filtered and evaporated under reduced pressure to give alcohol **587** (1.25 g, 93%) as a colourless oil. R_f 0.40 (Pet ether:EtOAc 4:1); ν_{max} (neat)/cm^{-1}: 3321, 2844, 1441, 1045, 1019; δ_H (400 MHz, $CDCl_3$) 1.67 (1H, br s, OH), 1.81-1.93 (2H, m, $CH_2CH_2CH_2$), 2.26 (2H, t, *J* 7.3 Hz, CH_2), 2.29-2.39 (4H, m, CH_2), 3.70 (2H, td, *J* 1.7 and 6.3 Hz, CH_2OH), 5.40-5.54 (1H, m, =CH); δ_C (100 MHz, $CDCl_3$) 23.5 (CH_2, $CH_2CH_2CH_2$), 32.7 (CH_2), 34.6 (CH_2), 35.1 (CH_2), 60.7 (CH_2, CH_2OH), 126.4 (CH, =CH), 141.0 (C, =C); m/z (EI) 112.0891 (M^+ $C_7H_{12}O$ requires 112.0888), 112 (18%), 94 (14), 79 (100), 67 (15). *Literature data*:[268] ν_{max} (liquid film)/cm^{-1}: 3337 (OH), 3046, 2950, 2894, 2847, 1445, 1048, 1022; δ_H ($CDCl_3$) 5.49 (1H, m, CH=), 3.73 (2H, t , *J* = 6.2 Hz, CH_2O), 1.50-2.48 (9H, m, (CH_2)) and OH); Anal. Calcd for $C_7H_{12}O$: C, 74.96; H, 10.78. Found: C, 74.94; H, 11.03.

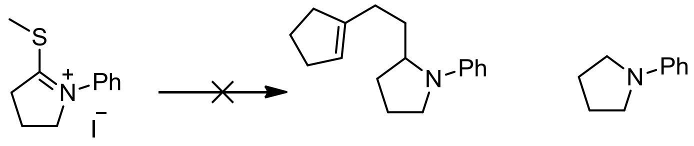
- 1-(2-Iodoethyl)cyclopent-1-ene **588**



587 **588**

A known compound prepared according to a modified literature procedure.[232] A solution of PPh_3 (2.56 g, 9.77 mmol) and imidazole (0.665 g, 9.77 mmol) in a 3:1 mixture of Et_2O:CH_3CN (20 mL) was cooled to 0 °C. I_2 (2.48 g, 9.77 mmol) was added with vigorous stirring in 4 portions over 20 min. The reaction mixture was warmed to rt, stirred for 30 min, cooled to 0 °C, treated with alcohol **587** (0.548 g, 4.89 mmol) over 3 min and warmed to rt. After 2 h at rt, the slurry was cooled to 0 °C, diluted with pentane (30 mL) and stirred vigorously for 5 min. The top layer was decanted. $NaHCO_3$ (30 mL of a 5% aq. solution) was added and the aqueous layer was extracted with pentane (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether) to give iodocyclopentene **588** (0.856 g, 79%) as a colourless oil. R_f 0.78 (Pet ether); ν_{max} (neat)/cm^{-1}: 2949, 2842, 1440, 1232, 1167, 1037, 949, 819; δ_H (300 MHz, $CDCl_3$) 1.81-1.95 (2H, m, $CH_2CH_2CH_2$), 2.20-2.36 (4H, m, CH_2), 2.66 (2H, t, *J* 7.5 Hz, $=CCH_2CH_2I$), 3.25 (2H, t, *J* 7.5 Hz, $=CCH_2CH_2I$), 5.40-5.49 (1H, m, =CH); δ_C (100 MHz, $CDCl_3$) 3.9 (CH_2, CH_2I), 23.3 (CH_2, $CH_2CH_2CH_2$), 32.4 (CH_2), 34.4 (CH_2), 35.7 (CH_2, $=CCH_2CH_2I$), 125.9 (CH, =CH), 142.8 (C, =C); m/z (ES) 222.9975 ($[M+H]^+$ $C_7H_{12}{}^{127}I$ requires 222.9972), 317 (64%), 222 (100). *Literature data*:[232] δ_H ($CDCl_3$) 5.44 (s, 1H), 3.25 (t, 2H), 2.68 (t, 2H), 2.26 (m, 4H), 1.89 (m, 2H).

- 1-Phenylpyrrolidine **592**

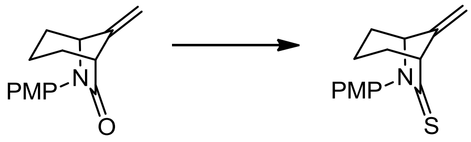


579 **591** **592**

A known compound[269] prepared according to a modified literature procedure.[70] A solution of iodocyclopentene **588** (0.140 g, 0.630 mmol) in THF (4.7 mL) was cooled to -78 °C, *t*BuLi (0.37 mL of a 1.7 M solution in THF, 0.63 mmol) was added dropwise over 1 min. After 35 min, the iminium salt **579** (0.134 g, 0.420 mmol) was added in one portion. After 35 min at -78 °C, $NaBH_3CN$ (0.84 mL of a 1.0 M solution in THF, 0.84 mmol) and CH_3COOH (2.3 mL) were added and the reaction mixture was allowed to warm to rt. After 40 min, NaOH (15 mL of a 10% aq. solution) was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:CH_2Cl_2 9:1) to give pyrrolidine **592** (30 mg, 48%) as a colourless oil. ν_{max} (neat)/cm^{-1}: 2965, 2828, 1593, 1504, 1365, 1183, 1156, 991, 742, 688; δ_H (300 MHz, $CDCl_3$) 1.95-2.10 (4H, m, NCH_2CH_2), 3.25-3.37 (4H, m, NCH_2CH_2), 6.60 (2H, d, *J* 6.6 Hz, Ar H), 6.69 (1H, d, *J* 7.3 Hz, Ar

H), 7.20-7.33 (2H, m, Ar H); δ_C (75 MHz, $CDCl_3$) 25.6 (2 x CH_2, NCH_2CH_2), 47.7 (2 x CH_2, NCH_2CH_2), 111.8 (2 x CH, Ar), 115.5 (CH, Ar), 129.3 (2 x CH, Ar), 148.1 (C, Ar); m/z (ES) 148.1118 ($[M+H]^+$ $C_{10}H_{14}N$ requires 148.1121), 148 (100%). *Literature data*:[269] δ_H (270 MHz, C_6D_6) 1.45–1.50 (m, 4H), 2.91 (t, *J* = 6.5 Hz, 4H), 6.53 (d, *J* = 8.1 Hz, 2H), 6.81 (t, *J* = 7.0 Hz, 1H), 7.31 (t, *J* = 7.0 Hz, 2H); δ_C (67.5 MHz, C_6D_6) 25.4, 47.4, 112.1, 115.9, 129.3, 148.3; m/z (EI) calcd for $C_{10}H_{13}N$: 147.1048, found 147.1037.

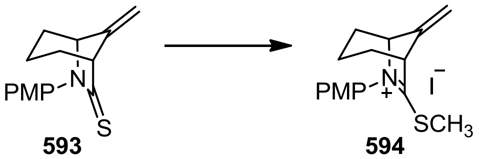
- (±)-(1*R*,5*S*)-6-(4-Methoxyphenyl)-8-methylene-6-azabicyclo[3.2.1]octane-7-thione **593**



567 **593**

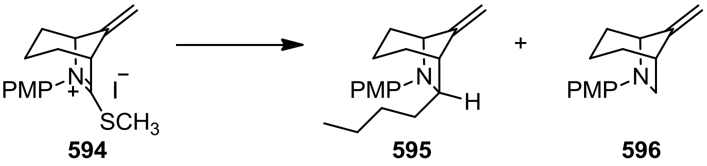
A novel compound prepared according to a literature procedure.[229] A solution of Lawesson's reagent (48 mg, 0.12 mmol) and lactam **567** (48 mg, 0.20 mmol) in toluene (2.0 mL) was heated to reflux. After 3 h, the reaction mixture was concentrated under reduced pressure and purified directly by column chromatography (Pet ether to Pet ether:EtOAc 9:1) to give thiolactam **593** (47 mg, 92%) as a pale yellow solid. mp 76-78 °C; R_f 0.76 (Pet ether:EtOAc 7:3); ν_{max} (neat)/cm^{-1}: 2941, 1685, 1606, 1584, 1510, 1431, 1250, 1021, 890, 827, 738; δ_H (400 MHz, $CDCl_3$) 1.67-1.88 (4H, m, CH_2), 2.01-2.12 (1H, m, CH_2), 2.17-2.31 (1H, m, CH_2), 3.53 (1H, br s, CCHC(S)), 3.81 (3H, s, OCH_3), 4.50 (1H, d, *J* 4.0 Hz, CH_2CHN), 4.83 (1H, s, $=CH_2$), 4.86 (1H, s, $=CH_2$), 6.95 (2H, d, *J* 9.0 Hz, Ar H), 7.44 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 18.3 (CH_2), 29.6 (CH_2), 32.1 (CH_2), 55.6 (CH_3, OCH_3), 61.0 (CH, CCHC(S)), 72.0 (CH, CH_2CHN), 101.4 (CH_2, $=CH_2$), 114.6 (2 x CH, Ar), 126.8 (2 x CH, Ar), 132.1 (C, ArCN), 152.0 (C, =C), 158.8 (C, ArCO), 203.8 (C, C(S)N); m/z (ES) 282.0922 ($[M+Na]^+$ $C_{15}H_{17}NNaOS$ requires 282.0929), 283 (12%), 282 (100).

- (±)-(1*R,*5*S*)-6-(4-Methoxyphenyl)-8-methylene-7-(methylthio)-6-azabicyclo[3.2.1] octan-6-en-6-ium iodide **594**



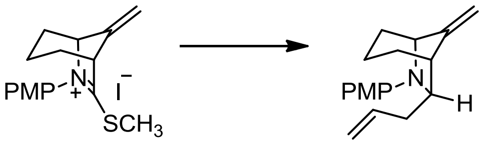
A novel compound prepared according to a literature procedure.[70] A solution of thiolactam **593** (94 mg, 0.36 mmol) and iodomethane (0.383 mL, 6.15 mmol) in Et_2O (0.77 mL) was stirred at rt. After 18 h, the reaction mixture was diluted with CH_2Cl_2 (1.0 mL) and concentrated under reduced pressure (3 times) to give iminium salt **594** (0.145 g, 100%) as a bright yellow foam. mp: degradation above 60 °C; ν_{max} (neat)/cm^{-1}: 3434, 2949, 1602, 1505, 1255, 1019, 845, 827; δ_H (400 MHz, $CDCl_3$) 1.66-1.84 (1H, m, CH_2), 1.85-1.97 (1H, m, CH_2), 1.99-2.18 (3H, m, CH_2), 2.24-2.36 (1H, m, CH_2), 3.06 (3H, s, SCH_3), 3.83 (3H, s, OCH_3), 4.80 (1H, br s, C*CH*$CSCH_3$)), 4.99 (1H, d, *J* 3.7 Hz, CH_2C*H*N), 5.28 (1H, s, =CH_2), 5.39 (1H, s, =CH_2), 7.04 (2H, d, *J* 9.0 Hz, Ar H), 7.47 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 18.3 (CH_3, SCH_3), 18.6 (CH_2), 28.4 (CH_2), 29.2 (CH_2), 54.0 (CH, C*C*H$CSCH_3$), 56.0 (CH_3, OCH_3), 76.8 (CH, CH_2*C*HN), 107.9 (CH_2, =CH_2), 116.1 (2 x CH, Ar), 125.8 (2 x CH, Ar), 127.5 (C, ArCN), 145.6 (C, =C), 161.6 (C, ArCO), 196.9 (C, =*C*SCH_3); m/z (ES) 292.1369 ($[M-I+H_2O]^+$ $C_{16}H_{22}NO_2S$ requires 292.1366), 314 (52%), 298 (100), 292 (40), 282 (39), 276 (72), 244 (56), 216 (62).

- (±)-(1*R,*5*S*,7*R*)-7-Butyl-6-(4-methoxyphenyl)-8-methylene-6-azabicyclo[3.2.1] **595** and (±)-(1*R*,5*S*)-6-(4-methoxyphenyl)-8-methylene-6-azabicyclo[3.2.1]octane **596**



Novel compounds prepared according to a modified literature procedure.[70] A solution of iminium salt **594** (73 mg, 0.18 mmol) in THF (2.0 mL) was cooled to -78 °C and *n*BuLi (0.40 mL of a 0.69 M solution in THF, 0.27 mmol) was added dropwise over 1 min. After 1.75 h at -78 °C, $NaBH_3CN$ (0.36 mL of a 1.0 M solution in THF, 0.36 mmol) and CH_3COOH (1.0 mL) were added and the reaction mixture was allowed to warm to rt. After 5 h, NaOH (5 mL of a 10% aq. solution) was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 2 mL). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:Et_2O 96:4) to give a 1.3:1.0 mixture of butyl amine **595** : bicyclic amine **596** (33 mg) as a colourless oil. ν_{max} (neat)/cm^{-1}: 2933, 1508, 1236, 1040, 883, 809; δ_H (400 MHz, $CDCl_3$) (mixture of **595:596**) 0.96 (3H, m, $(CH_2)_3CH_3$ for **595**), 1.24-2.02 (17H, m, CH_2), 2.05-2.23 (1H, m, CH_2), 2.24-2.34 (1H, m, CH_2), 2.68 (1H, d, *J* 2.8 Hz, C*H*C=CH_2 for **595**), 2.2.81-2.90 (1H, m, C*H*C=CH_2 for **596**), 3.17 (1H, d, *J* 8.4 Hz, NC*H*$_2$CH for **596**), 3.41-3.51 (2H, m, NC*H*$_2$CH for **596** and $NCH(CH_2)_3CH_3$ for **595**), 3.73-3.80 (6H, s, OCH_3), 3.98 (1H, d, *J* 4.0 Hz, CH_2C*H*N for **595**), 4.20 (1H, d, *J* 3.8 Hz, CH_2C*H*N for **596**), 4.56 (1H, s, =CH_2), 4.64 (1H, s, =CH_2 for **595**), 4.75 (1H, s, =CH_2 for **596**), 4.79 (1H, s, =CH_2 for **596**), 6.51 (2H, d, *J* 9.0 Hz, Ar H for **596**), 6.58 (2H, d, *J* 9.0 Hz, Ar H for **595**), 6.77-6.89 (4H, m, Ar H); δ_C (100 MHz, $CDCl_3$) (mixture of **595:596**) 14.4 (CH_3, $(CH_2)_3$*C*H_3 for **595**), 18.7 (CH_2), 19.9 (CH_2), 23.2 (CH_2 for **595**), 26.6 (CH_2), 29.1 (CH_2), 29.3 (CH_2 for **595**), 32.0 (CH_2), 34.7 (CH_2), 35.9 (CH_2), 41.9 (CH, CH_2=C*C*H for **596**), 44.0 (CH, CH_2=C*C*H for **595**), 52.8 (CH_2, CH*C*H_2N for **596**), 56.1 (CH_3, OCH_3 for **595**), 56.2 (CH_3, OCH_3 for **596**), 60.1 (CH, CH*C*HN for **596**), 68.1 (CH, CH*C*HN for **595**), 62.3 (CH, N*C*H$(CH_2)_3CH_3$ for **595**), 98.8 (CH_2, C=*C*H_2 for **595**), 99.5 (CH_2, C=*C*H_2 for **596**), 111.5 (2 x CH, Ar for **596**), 114.4 (2 x CH, Ar for **595**), 114.9 (2 x CH, Ar for **595**), 115.4 (2 x CH, Ar for **596**), 140.9 (C, Ar*C*N for **596**), 143.3 (C, Ar*C*N for **595**), 150.4 (C, Ar*C*O for **596**), 151.5 (C, Ar*C*O for **595**), 154.7 (C, =C), 155.0 (C, =C); m/z (ES) 230.1535 ($[M+H]^+$ $C_{15}H_{17}NO$ requires 230.1539), 286.2161 ($[M+H]^+$ $C_{19}H_{28}NO$ requires 286.2165), 286 (29%), 230 (100).

- (±)-(1*R*,5*S*,7*R*)-7-Allyl-6-(4-methoxyphenyl)-8-methylene-6-azabicyclo[3.2.1]octane **597**



594 **597**

A novel compound prepared according to a literature procedure.[70] A solution of iminium salt **594** (73 mg, 0.18 mmol) in CH_2Cl_2 (2.0 mL) was cooled to -78 °C, allylmagnesium chloride (0.14 mL of a 2.0 M solution in THF, 0.28 mmol) was added dropwise over 1 min. After 1.75 h at -78 °C, $NaBH_3CN$ (0.36 mL of a 1.0 M solution in THF, 0.36 mmol) and CH_3COOH (1.0 mL) were added and the reaction mixture was allowed to warm to rt. After 5 h, NaOH (5 mL of a 10% aq. solution) was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 2 mL). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (Pet ether to Pet ether:Et_2O 9:1) to give bicyclic amine **597** (22 mg, 45%) as a colourless oil. R_f 0.68 (Pet ether:EtOAc 9:1); ν_{max} (neat)/cm^{-1}: 2941, 1506, 1236, 1040, 815; δ_H (400 MHz, $CDCl_3$) 1.62-1.79 (3H, m, CH_2), 1.84-1.97 (1H, m, CH_2), 1.99-2.15 (2H, m, CH_2), 2.32 (1H, ddd, *J* 7.5, 10.9 and 14.6 Hz, $CHCH_2CH{=}CH_2$), 2.65-2.78 (2H, m, $CH_2CHC{=}CH_2$ and $CHCH_2CH{=}CH_2$), 3.52-3.62 (1H, m, CHC*H*N), 3.77 (3H, s, OCH_3), 4.00 (1H, d, *J* 4.2 Hz, CH_2CHN), 4.57 (1H, s, $=CH_2$), 4.64 (1H, s, $=CH_2$), 5.09-5.26 (2H, m, $CH{=}CH_2$), 5.87 (1H, ddt, *J* 7.1, 10.2 and 17.1 Hz, $CH{=}CH_2$), 6.61 (2H, d, *J* 9.0 Hz, Ar H), 6.85 (2H, d, *J* 9.0 Hz, Ar H); δ_C (100 MHz, $CDCl_3$) 19.8 (CH_2), 29.4 (CH_2), 31.6 (CH_2, $CH_2CH{=}CH_2$), 35.7 (CH_2), 44.2 (CH, $CHC{=}CH_2$), 56.1 (CH_3, OCH_3), 61.6 (CH, CHCHN), 68.2 (CH, CH_2CHN), 99.1 (CH_2, $C{=}CH_2$), 114.6 (2 x CH, Ar), 115.0 (2 x CH, Ar), 116.9 (CH_2, $CH{=}CH_2$), 135.6 (CH, $CH{=}CH_2$), 143.0 (C, Ar*C*N), 151.7 (C, Ar*C*O), 154.3 (C, =C); m/z (ES) 270.1853 ($[M+H]^+$ $C_{18}H_{24}NO$ requires 270.1852), 270 (100%), 228 (37), 199 (97).

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Appendices

X-ray data for **130**

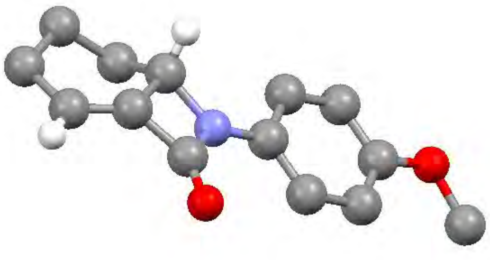

Table 1: Crystal data and structure refinement for **130**

Identification code	**130**	
Empirical formula	$C_{14}H_{15}NO_2$	
Formula weight	229.27	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 2(1)/n	
Unit cell dimensions	a = 9.0675(3) Å	α= 90°.
	b = 6.0052(2) Å	β= 98.657(2)°.
	c = 21.3783(8) Å	γ = 90°.
Volume	1150.83(7) Å^3	
Z	4	
Density (calculated)	1.323 Mg/m^3	
Absorption coefficient	0.089 mm^{-1}	
F(000)	488	
Crystal size	0.56 x 0.28 x 0.09 mm^3	
Theta range for data collection	3.40 to 27.48°.	
Index ranges	-11<=h<=11, -7<=k<=7, -27<=l<=27	
Reflections collected	12191	
Independent reflections	2628 [R(int) = 0.0413]	
Completeness to theta = 27.48°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9921 and 0.9520	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2628 / 0 / 155	
Goodness-of-fit on F^2	1.015	
Final R indices [I>2sigma(I)]	R1 = 0.0435, wR2 = 0.1219	
R indices (all data)	R1 = 0.0563, wR2 = 0.1314	
Largest diff. peak and hole	0.287 and -0.263 e.Å^{-3}	

X-ray data for **144a**

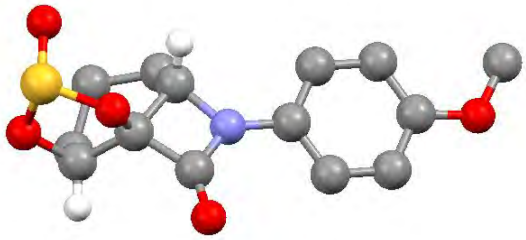

Table 1. Crystal data and structure refinement for **144a**.

Identification code	**144a**	
Empirical formula	$C_{14} H_{15} N O_5 S$	
Formula weight	309.33	
Temperature	120(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P bca	
Unit cell dimensions	a = 11.0852(2) Å	α= 90°.
	b = 7.98040(10) Å	β= 90°.
	c = 31.3518(5) Å	γ = 90°.
Volume	2773.52(8) Å^3	
Z	8	
Density (calculated)	1.482 Mg/m^3	
Absorption coefficient	2.288 mm^{-1}	
F(000)	1296	
Crystal size	0.24 x 0.22 x 0.20 mm^3	
Theta range for data collection	6.92 to 68.24°.	
Index ranges	-13<=h<=12, -9<=k<=8, -32<=l<=36	
Reflections collected	20175	
Independent reflections	2528 [R(int) = 0.0212]	
Completeness to theta = 68.24°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.6576 and 0.6097	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2528 / 0 / 191	
Goodness-of-fit on F^2	1.068	
Final R indices [I>2sigma(I)]	R1 = 0.0281, wR2 = 0.0752	
R indices (all data)	R1 = 0.0285, wR2 = 0.0755	
Largest diff. peak and hole	0.241 and -0.310 e.Å^{-3}	

X-ray data for **144b**

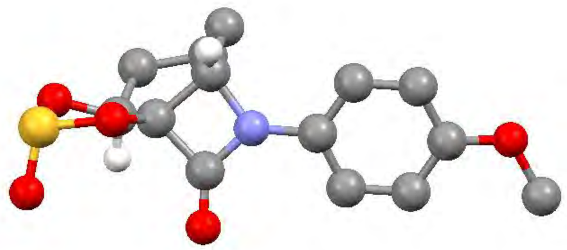

Table 1. Crystal data and structure refinement for **144b**.

Identification code	**144b**	
Empirical formula	$C_{14} H_{15} N O_5 S$	
Formula weight	309.33	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C 2/c	
Unit cell dimensions	a = 16.1951(4) Å	α= 90°.
	b = 7.5226(3) Å	β= 107.623(2)°.
	c = 23.5755(9) Å	γ= 90°.
Volume	2737.39(17) Å^3	
Z	8	
Density (calculated)	1.501 Mg/m^3	
Absorption coefficient	0.258 mm^{-1}	
F(000)	1296	
Crystal size	0.32 x 0.30 x 0.22 mm^3	
Theta range for data collection	3.01 to 27.48°.	
Index ranges	-20<=h<=20, -9<=k<=9, -30<=l<=30	
Reflections collected	14480	
Independent reflections	3120 [R(int) = 0.0371]	
Completeness to theta = 27.48°	99.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9453 and 0.9219	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3120 / 0 / 191	
Goodness-of-fit on F^2	1.029	
Final R indices [I>2sigma(I)]	R1 = 0.0384, wR2 = 0.1129	
R indices (all data)	R1 = 0.0474, wR2 = 0.1213	
Largest diff. peak and hole	0.274 and -0.404 e.Å^{-3}	

X-ray data for **140**

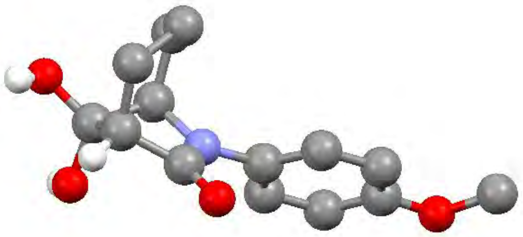

Table 1. Crystal data and structure refinement for **140**.

Identification code	**140**	
Empirical formula	$C_{14} H_{17} N O_4$	
Formula weight	263.29	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 2_1/c	
Unit cell dimensions	a = 6.0349(17) Å	α= 90°.
	b = 6.944(2) Å	β= 95.570(11)°.
	c = 29.781(9) Å	γ = 90°.
Volume	1242.0(6) $Å^3$	
Z	4	
Density (calculated)	1.408 Mg/m^3	
Absorption coefficient	0.103 mm^{-1}	
F(000)	560	
Crystal size	0.24 x 0.09 x 0.02 mm^3	
Theta range for data collection	3.01 to 25.03°.	
Index ranges	-7<=h<=7, 0<=k<=8, 0<=l<=35	
Reflections collected	2187	
Independent reflections	2187 [R(int) = 0.0000]	
Completeness to theta = 25.03°	94.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9979 and 0.9756	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2187 / 0 / 176	
Goodness-of-fit on F^2	1.188	
Final R indices [I>2sigma(I)]	R1 = 0.1102, wR2 = 0.3248	
R indices (all data)	R1 = 0.1170, wR2 = 0.3347	
Largest diff. peak and hole	0.566 and -0.591 e.$Å^{-3}$	

X-ray data for **262**

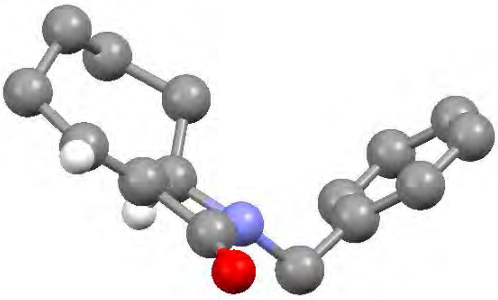

Table 1. Crystal data and structure refinement for **262**.

Identification code	**262**	
Empirical formula	$C_{15}H_{17}NO$	
Formula weight	227.30	
Temperature	100(2) K	
Wavelength	0.71075 Å	
Crystal system	Monoclinic	
Space group	$P\ 2_1/c$	
Unit cell dimensions	a = 12.953(15) Å	α= 90°.
	b = 5.736(7) Å	β= 90.89(2)°.
	c = 16.756(18) Å	γ = 90°.
Volume	1245(2) Å^3	
Z	4	
Density (calculated)	1.213 Mg/m^3	
Absorption coefficient	0.076 mm^{-1}	
F(000)	488	
Crystal size	0.08 x 0.01 x 0.01 mm^3	
Theta range for data collection	2.92 to 25.02°.	
Index ranges	-14<=h<=15, -6<=k<=6, -19<=l<=19	
Reflections collected	8486	
Independent reflections	2164 [R(int) = 0.0989]	
Completeness to theta = 25.02°	98.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.000 and 0.615	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2164 / 0 / 154	
Goodness-of-fit on F^2	1.130	
Final R indices [I>2sigma(I)]	R1 = 0.0983, wR2 = 0.2413	
R indices (all data)	R1 = 0.1399, wR2 = 0.2760	
Largest diff. peak and hole	0.341 and -0.333 e.Å^{-3}	

X-ray data for **270**

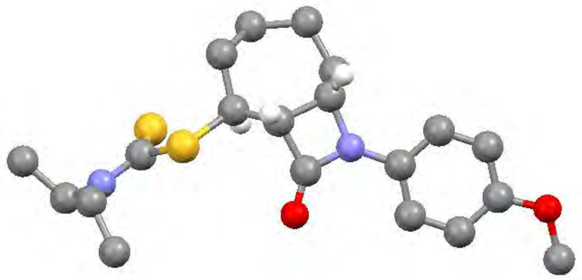

Table 1. Crystal data and structure refinement for **270**.

Identification code	**270**	
Empirical formula	$C_{20}H_{28}N_2O_2S_2$	
Formula weight	392.56	
Temperature	100(2) K	
Wavelength	1.54187 Å	
Crystal system	Triclinic	
Space group	*P*–1	
Unit cell dimensions	*a* = 6.3563(16) Å	α = 87.759(12)°
	b = 7.9604(13) Å	β = 89.300(18)°
	c = 20.414(4) Å	γ = 74.762(18)°
Volume	995.8(4) $Å^3$	
Z	2	
Density (calculated)	1.309 Mg / m^3	
Absorption coefficient	2.553 mm^{-1}	
F(000)	420	
Crystal	Block; Colourless	
Crystal size	0.10 × 0.10 × 0.08 mm^3	
θ range for data collection	2.17 – 66.43°	
Index ranges	$-7 \leq h \leq 6$, $-9 \leq k \leq 9$, $-24 \leq l \leq 24$	
Reflections collected	10836	
Independent reflections	3410 [R_{int} = 0.0555]	
Completeness to θ = 66.43°	96.7 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.8218 and 0.7844	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3410 / 0 / 239	
Goodness-of-fit on F^2	0.986	
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0408, *wR2* = 0.1029	
R indices (all data)	*R1* = 0.0441, *wR2* = 0.1057	
Extinction coefficient	0.0320(16)	
Largest diff. peak and hole	0.380 and –0.355 e $Å^{-3}$	

X-ray data for **319**

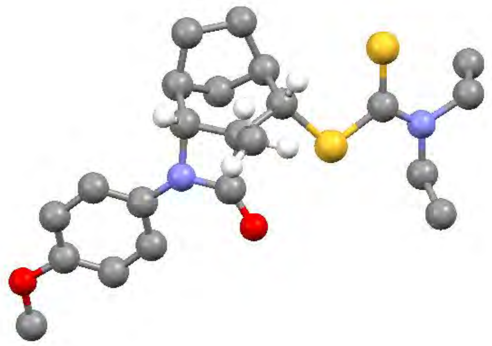

Table 1. Crystal data and structure refinement for **319**.

Identification code	**319**	
Empirical formula	$C_{22}H_{30}N_2O_2S_2$	
Formula weight	418.60	
Temperature	100(2) K	
Wavelength	1.54187 Å	
Crystal system	Orthorhombic	
Space group	P $na2_1$	
Unit cell dimensions	a = 45.85(7) Å	= 90°.
	b = 6.260(11) Å	= 90°.
	c = 7.640(13) Å	= 90°.
Volume	2193(6) $Å^3$	
Z	4	
Density (calculated)	1.268 Mg/m^3	
Absorption coefficient	2.351 mm^{-1}	
F(000)	896	
Crystal size	0.28 x 0.18 x 0.02 mm^3	
Theta range for data collection	6.97 to 66.60°.	
Index ranges	-34<=h<=54, -5<=k<=7, -8<=l<=9	
Reflections collected	13394	
Independent reflections	3417 [R(int) = 0.1247]	
Completeness to theta = 66.60°	95.2 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9545 and 0.5589	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3417 / 1 / 259	
Goodness-of-fit on F^2	1.455	
Final R indices [I>2sigma(I)]	R1 = 0.1215, wR2 = 0.3230	
R indices (all data)	R1 = 0.1435, wR2 = 0.3709	
Absolute structure parameter	0.00(6)	
Extinction coefficient	0.010(2)	
Largest diff. peak and hole	1.078 and -0.618 e.$Å^{-3}$	

X-ray data for **498**

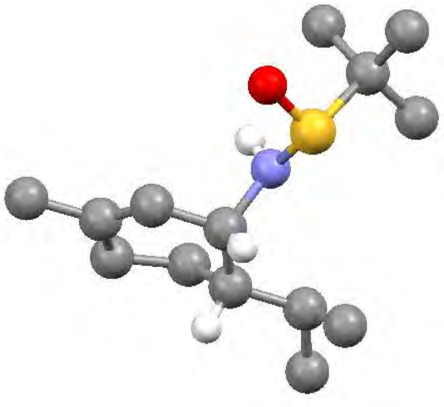

Table 1. Crystal data and structure refinement for **498**.

Identification code	**498**	
Empirical formula	$C_{14}H_{27}NOS$	
Formula weight	257.43	
Temperature	150(2) K	
Wavelength	0.71075 Å	
Crystal system	Orthorhombic	
Space group	*P*212121	
Unit cell dimensions	a = 5.970(3) Å	α = 90°
	b = 13.234(7) Å	β = 90°
	c = 19.291(9) Å	γ = 90°
Volume	1524.1(13) $Å^3$	
Z	4	
Density (calculated)	1.122 Mg / m^3	
Absorption coefficient	0.200 mm^{-1}	
F(000)	568	
Crystal	Needle; yellow	
Crystal size	0.30 × 0.03 × 0.02 mm^3	
θ range for data collection	3.25 – 25.00°	
Index ranges	$-4 \le h \le 7$, $-15 \le k \le 14$, $-22 \le l \le 22$	
Reflections collected	6541	
Independent reflections	2657 [R_{int} = 0.0501]	
Completeness to θ = 25.00°	99.5 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9960 and 0.9424	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2657 / 0 / 164	
Goodness-of-fit on F^2	1.124	
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0563, *wR2* = 0.0890	
R indices (all data)	*R1* = 0.0679, *wR2* = 0.0932	
Absolute structure parameter	–0.10(11)	
Largest diff. peak and hole	0.193 and –0.247 e $Å^{-3}$	