Total Synthesis of Ferrugine and Synthetic Studies Towards Ferruginine and Stemofoline

by

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Abstract

Tropane alkaloids, containing the 8-azabicyclo[3.2.1]octane ring system, are widespread in Nature. This thesis describes the total synthesis of the tropane alkaloid *ferrugine*, isolated from the arboreal species *Darlingiana ferruginea* and attempted synthesis of *ferruginine*, isolated from the arboreal species *D. darlingiana*. Formation of a bridged 6-azabicyclic-[3.2.2]-ring system was achieved using a transannular photomediated cyclisation of a carbamoyl radical, generated from a carbamoyl diethyldithiocarbamate, onto an unactivated pendant alkene, followed by group transfer of the dithiocarbamate moiety. The carbamoyl radical cyclisation precursor was synthesised from a known seven-membered ring carboxylic acid. The diastereomeric dithiocarbamates converged to a single alkene upon thermal elimination. Addition of phenyllithium to the amide followed by base-mediated skeletal rearrangement resulted in the total synthesis of the natural product *ferrugine*, and using a similar strategy the core structure of *ferruginine* was secured.

The stemona alkaloid *stemofoline* is characterised by a complex azatricyclic ring system unique to this class of natural products. Synthetic efforts have been made toward the synthesis of a cyclisation precursor required for the assembly of this azatricyclic framework, *via* a proposed tandem *7-endo-trig/5-exo-trig* carbamoyl radical cyclisation. The synthesis commenced with the commercially available dimethyl 3,3-thiodipropanoate which was further elaborated and coupled with 5-hepten-2-one to provide an advanced intermediate enone. Addition of ammonia gave a pyrroline which was condensed with triphosgene followed by sodium diethyldithiocarbamate to produce a carbamoyl radical precursor. Unfortunately, efforts towards oxidation and elimination of the sulfide to obtain an α,β-unsaturated ketone proved ineffective.

Attempted carbamoyl radical cyclisation-dithiocarbamate group transfer onto enones and nitriles are also presented.

ABBREVIATIONS

Ac	acetyl
Bn	benzyl
Boc	*t*-butoxycarbonyl
Bu	butyl
CI	chemical ionisation
°C	degrees centigrade
cat.	catalytic
cm^3	cubic centimetres
DBU	1,8-diazabicyclo[5.4.0] undecene
DIBAH	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DPPA	diphenylphosphorylazide
DMAP	4-dimethylamino pyridine
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethylsulfoxide
DMF	*N*,*N*-dimethylformamide
de	diastereomeric excess
ee	enantiomeric excess
EI	electron impact
ESI	electron spray ionisation
Et	ethyl
g	grams
GC	gas chromatography
h	hours
Hz	hertz
HMPA	hexamethylphosphoramide
i-	*iso*-
IBX	2-Iodoxybenzoic acid
IR	infrared spectrometry
J	coupling constant (Hz)

LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
M	molar
Me	methyl
min.	minutes
mL	millilitres
mp	melting point
Ms	methanesulfonyl
MS	mass spectrometry
MPO	4-methoxypyridine-*N*-oxide
n-	*normal*-
NMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
p-	*para*-
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	parts per million
Pr	propyl
R_f	retention factor
rt	room temperature
s-	*secondary*-
sat.	saturated
t-	*tertiary*-
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*t*-butyldimethylsilyl
TIPS	tri-isopropylsilyl
Tf	trifluoromethanesulfonyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*para*-toluenesulfonyl

CONTENTS

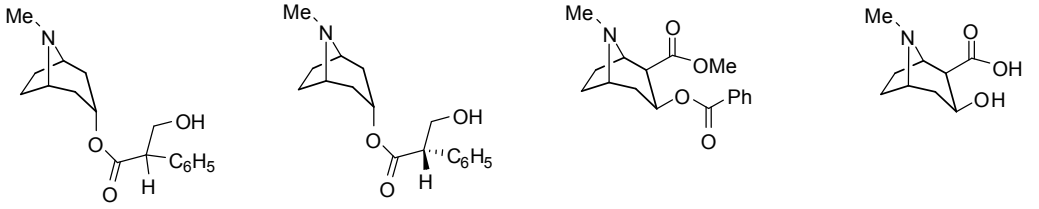
1. *FERRUGININE*: BACKGROUND AND SIGNIFICANCE

Tropane alkaloids

Tropane alkaloids are nitrogenous bicyclic organic compounds which have the 8-azabicyclo[3.2.1]octane skeleton. The nitrogen bridge is between C1 and C5, two asymmetric carbons but tropane is optically inactive due to symmetry (fig 1).

Fig 1

Currently there are over two hundred tropane alkaloids known to occur in natural sources.[1] They are naturally found in many members of the plant families including *Solanaceae*, *Erythroxylaceae*, *Con*-V*ol*V*ulaceae*, *Proteaceae*, *Rhizophoraceae*, *Brassicaceae*, and *Euphorbiaceae*. They are known for their toxic and important medicinal properties.[2-5] Atropine, the racemic form of (-)-hyoscyamine, was first isolated from *atropa belladonna* in 1833, while (-)-hyoscyamine was also isolated in the same year from *hyoscyamus niger*.[1] These tropane alkaloids are muscarinic receptor agonist that are involved in constriction of the pupil and vasodilation. They are also responsible for moderating the heartbeat and stimulating secretions. While the notorious cocaine, isolated from the dried leaves of *erythroxylum coca*, can be used for its anaesthetic properties and can also be prepared from its precursor and metabolite, ecogonine (fig 2).[2,3]

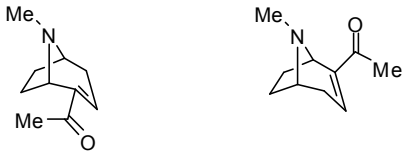


atropine **(-)-hyoscyamine** **(-)-cocaine** **(-)-ecogonine**

Fig 2

Ferrugine: isolation and biological activity

The tropane alkaloid (+)-*ferruginine* **(1)** was isolated from the arboreal species *Darlingiana ferruginea*[6] and *D. darlingiana*,[7] and its unnatural isomer (-)-*ferruginine* **(2)** has been prepared from cocaine.[6] *Ferruginine* is found to be a good agonist for the nicotine acetylcholine receptor (nAchR). Due to its biological activity coupled with an interesting molecular architecture, it has generated considerable synthetic interest culminating in several racemic and enantiospecific syntheses.[7-15]

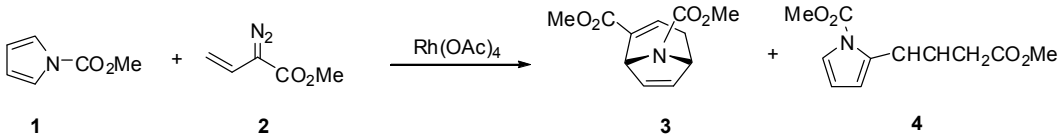


(+)-ferruginine (-)-ferruginine

From hereon, a comprehensive review of the syntheses of *ferruginine* will be presented outlining the key chemical transformations involved.

Davies synthesis of *ferruginine*.[8]

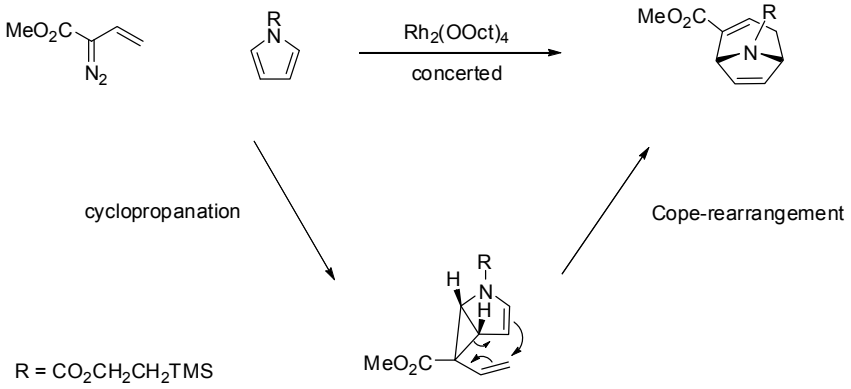
Davies and co-workers successfully constructed the tropane alkaloid skeleton, 8-azabicyclo[3.2.1]octa-2,6-diene **(3)**, by rhodium acetate-catalysed decomposition of vinyldiazomethane **(2)**, a precursor to vinylcarbenoids, in the presence of *N*-(alkoxy-carbonyl)pyrroles **(1)** (scheme 1).[16-18] Initially when the reaction was performed under normal conditions, azabicyclic diene **(3)** along with the unexpected side product **(4)** were isolated in a 55:45 ratio respectively.



1 **2** **3** **4**

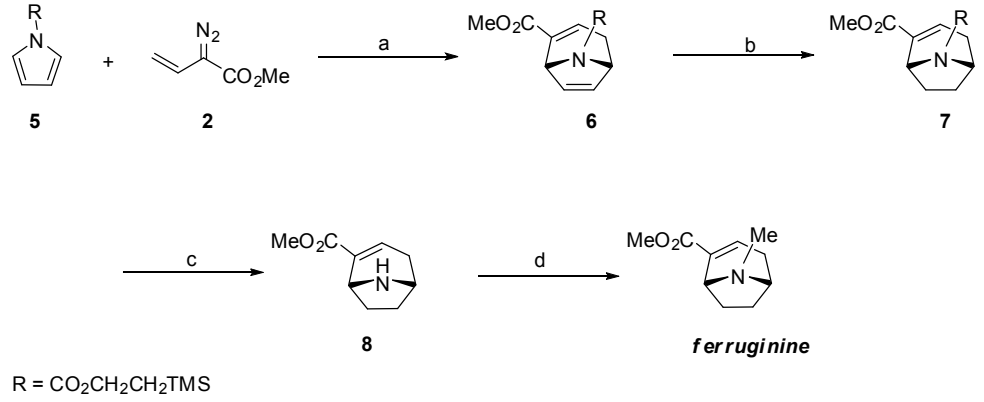
Scheme 1

It was later discovered that the reactivity could be controlled, and ultimately the formation of alkylated pyrrole **(4)** could be suppressed by choosing the appropriate solvent and catalyst.[19] Therefore, using rhodium hexanoate in a non polar solvent such as hexane, smoothly provided the desired azabicyclic diene **(3)** in 75% isolated yield. Alternatively, the formation of alkylated pyrrole **(4)** was preferred when an electron-withdrawing ligand such as trifluoroacetate was used in polar solvents. The hypothesised mechanism of this transformation is believed to occur *via* a [4+3] cycloaddition between pyrroles and vinylcarbenoids, either *via* a concerted pathway or tandem cyclopropanation-Cope rearrangement, the latter being more acceptable (scheme 2).[17]



Scheme 2

Equipped with suitable conditions for the construction of azabicyclic motifs, the Davies group embarked on the synthesis of the tropane alkaloid *ferruginine* utilising this methodology. Hence, the synthesis began with the decomposition of mono functionalised vinyldiazoethane **(2)** with rhodium acetate to form the reactive carbenoid intermediate which was reacted *in situ* with excess *N*-((2-(trimethyl-silyl)ethoxy)carbonyl)pyrrole **(5)** in refluxing toluene to form the bicyclic system **(6)**. Efficient regioselective catalytic hydrogenation of the less polar double bond of the azabicyclic diene furnished **(7)**. This advanced intermediate **(7)** was uneventfully converted to the natural product *ferruginine* in racemic form, firstly by deprotection with TBAF to give **(8)**, and finally a reductive methylation with aqueous formaldehyde in the presence of sodium cyanoborohydride (scheme 3).



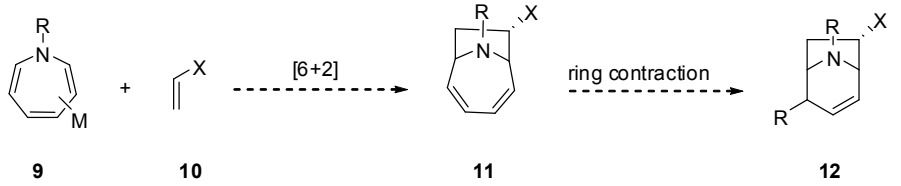
Scheme 3

Reagents & conditions: a) $Rh_2(OOct)_4$, toluene, reflux, 24 h, 73%; b) $RhCl(PPh_3)_3$ (cat), H_2, EtOH, 12 h, 96%; c) TBAF, THF, 12 h, 75%; d) aq CH_2O, $NaBH_3CN$, MeCN, 97%.

In summary, a racemic synthesis of *ferruginine* has been accomplished utilising rhodium(II) acetate-catalysed decomposition of vinyldiazomethanes in the presence of *N*-(alkoxy-carbonyl)pyrroles.

Rigby's synthesis of (+)-*ferruginine.*[9]

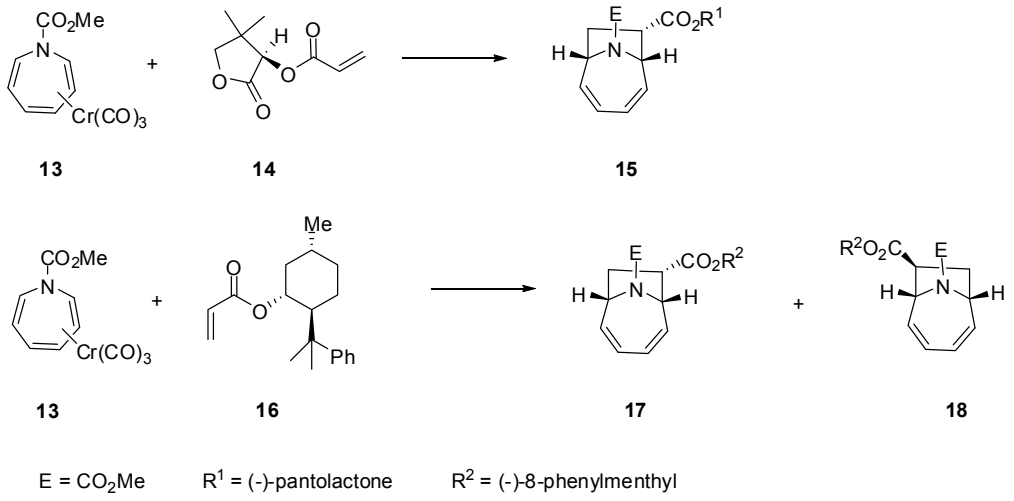
Rigby and co-workers embarked on a journey to synthesise (+)-*ferruginine* using asymmetric induction in the metal promoted higher order [6+2] cycloaddition methodology, previously developed in their laboratories.[20] They proposed that cycloaddition of azepines **(9)** with a suitable auxiliary-based dienophile **(10)** would provide the non racemic adduct **(11)**. Adduct **(11)** would then be subjected to a suitable ring contraction to furnish the bicyclic tropane alkaloid skeleton **(12)** of *ferruginine* (scheme 4).[21-23]



9 **10** **11** **12**

Scheme 4

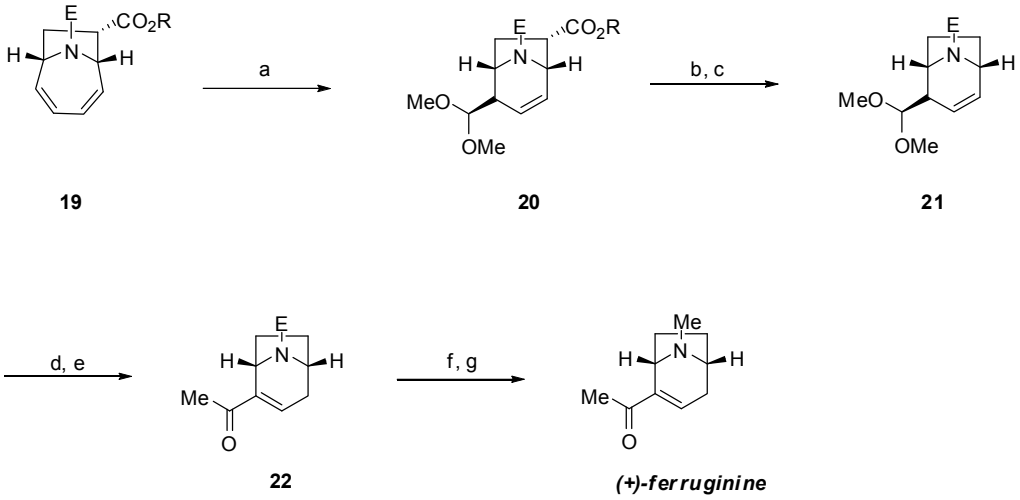
Cycloaddition of azepine complex **(13)** with the acrylate derivative of (*R*)-(-)-pentolactone **(14)** proceeded smoothly to afford exclusively the *endo*-adduct **(15)**. However, cycloaddition of azepine complex **(13)** with an alternative acrylate derivative, (-)-8-phenylmenthyl **(16)**, provided the much anticipated *endo* adduct **(17)**, accompanied by the minor *exo* adduct **(18)**. A general observation from Rigby's earlier work in this field showed the formation of *exo* adducts are very rare from these high order cycloadditon pathways, presumably *via* an epimerisation on the initially formed *endo* adduct **(17)** leading to the less favoured *exo* product **(18)** (scheme 5).



Scheme 5

Reagents & conditions: a) hν, (**15**, 59%, 53% de), (**17**, 58%, 98% de) and (**18**, 15%, 98% de)

The enantiomerically pure *endo*-cycloadduct **(19)** was then subjected to oxidative rearrangement[24] conditions using thallium trinitrate in methanol to yield exclusively a single enantiomer of tropane alkaloid **(20)** in excellent yield. Saponification of **(20)** with LiOH followed by Barton thiohydroxymate ester decarboxylation gave methyl carbamate **(21)**, which was subjected to further chemical transformations to install the α,β-unsaturated moiety, and complete the synthesis of (+)-*ferruginine* (scheme 6).



Scheme 6

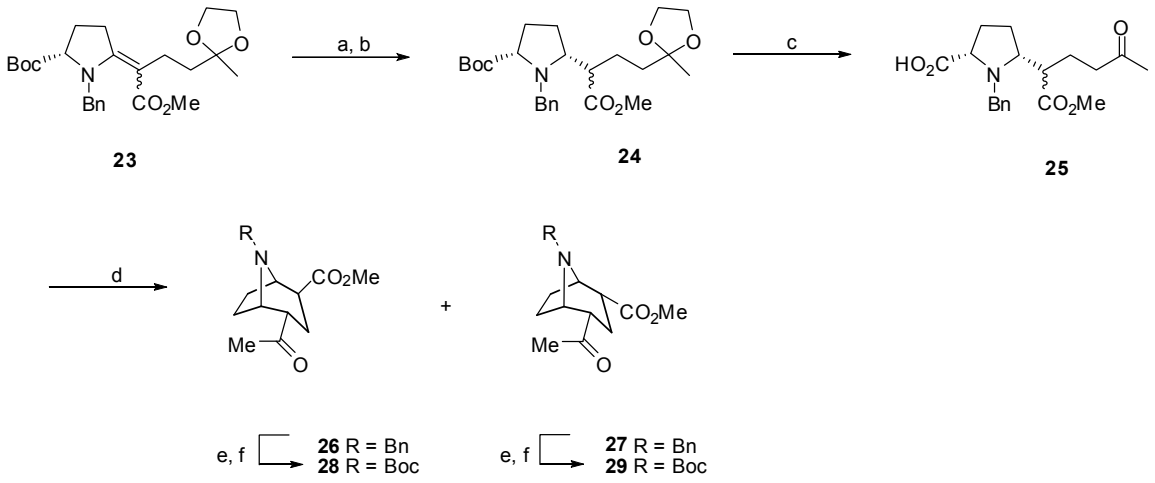
Reagents & conditions: a) $Ti(ONO_2)_3.H_2O$, MeOH, 85%; b) LiOH, MeOH/H_2O, 84%; c) *i*-$BuCO_2Cl$, NMO, *N*-hydroxypyridine-2-thione, Et_3N, *t*-BuSH, hν 49%; d) TFA, H_2O/acetone; e) MeMgBr, Et_2O; f) $LiAlH_4$, Et_2O; g) Dess-Martin periodinane, CH_2Cl_2, 28%.

In conclusion, Rigby and co-workers have successfully completed the asymmetric synthesis of (+)-*ferruginine* utilising a chromium promoted higher order [6+2] cycloaddition, followed by thallium mediated oxidative rearrangement. This is an attractive approach for the synthesis of enantiomerically pure tropane alkaloid skeletons starting from azepine complex **(13)**.

Rapoport's synthesis of (+)-*ferruginine* & (-)-*ferruginine.*[10]

Rapoport and co-workers expanded on their earlier work on *anatoxin*[25, 26] and *epibatimine*[27] by targeting the syntheses of (+)-*ferruginine* and its unnatural isomer (-)-*ferruginine via* intramolecular iminium ion cyclisation of keto-acid derivatives, derived from L-glutamic acid.

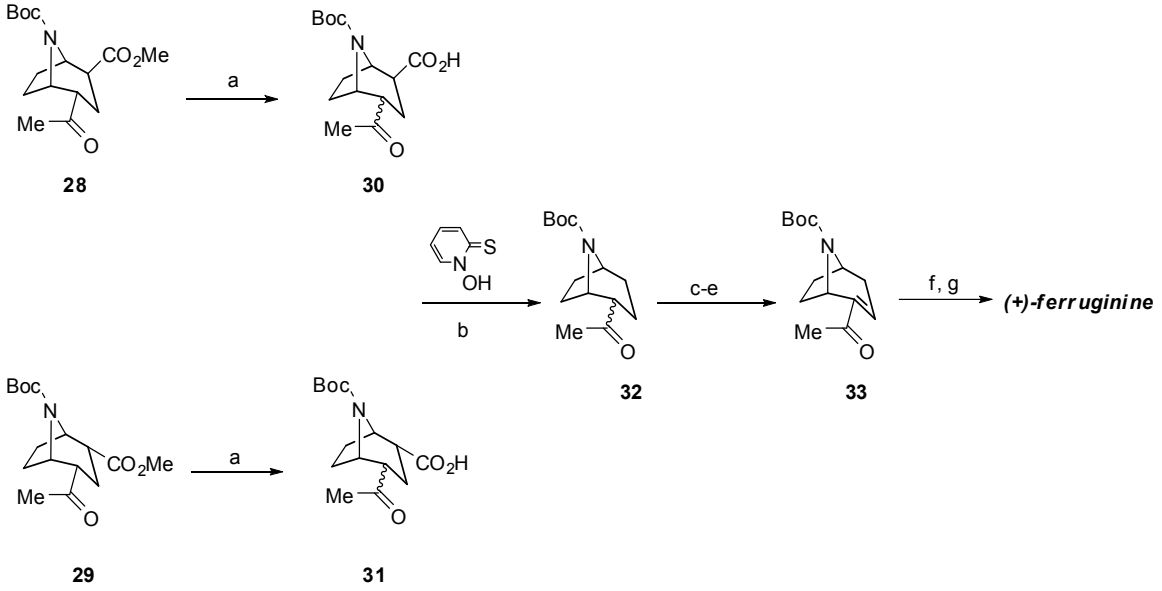
The key vinylogous carbamate intermediate **(23)** was subjected to an *exo*-face hydrogenation using Pd/C followed by rebenzylation of pyrrole using benzyl bromide afforded *cis* pyrrolidine **(24)** in 82% over two steps. Acidic cleavage of the tertiary butyl ester provided the prerequisite keto acid species **(25)** in 95% as a 7:3 mixture of diastereomers. Decarbonylation and iminium ion cyclisation gave the azabicyclic systems **(26)** and **(27)** in a 2:1 ratio, respectively, which were unambiguously assigned by extensive spectroscopic analysis. It is noteworthy that under the cyclisation conditions, the stereocentre at C2 did not epimerise, thus, each diastereomer of the keto acid **(3)** will only lead to one diastereomer **(4)** or **(5)**. Therefore, the intramolecular iminium ion cyclisation proceeded with high levels of stereoselectivity, and an opportunity to pursue an enantiospecific synthesis of *ferruginine* had arisen. A change in protecting group strategy was employed by hydrogenation of benzyl groups and reprotection as butyl carbamates **(28)** and **(29)**, respectively (scheme 7).



Scheme 7

Reagents & conditions: a) H_2, Pd/C, MeOH; b) BnBr, K_2CO_3, 82% over two steps; c) HCl/H_2O, 95%, 7:3 mixture of diastereomers; d) $(COCl)_2$, 1,2 DCE/ toluene, **(26)**, 62%, **(27)**, 27%; e) H_2, Pd/C; f) $(Boc)_2O$, **(28)**, 93%, **(29)**, 97%.

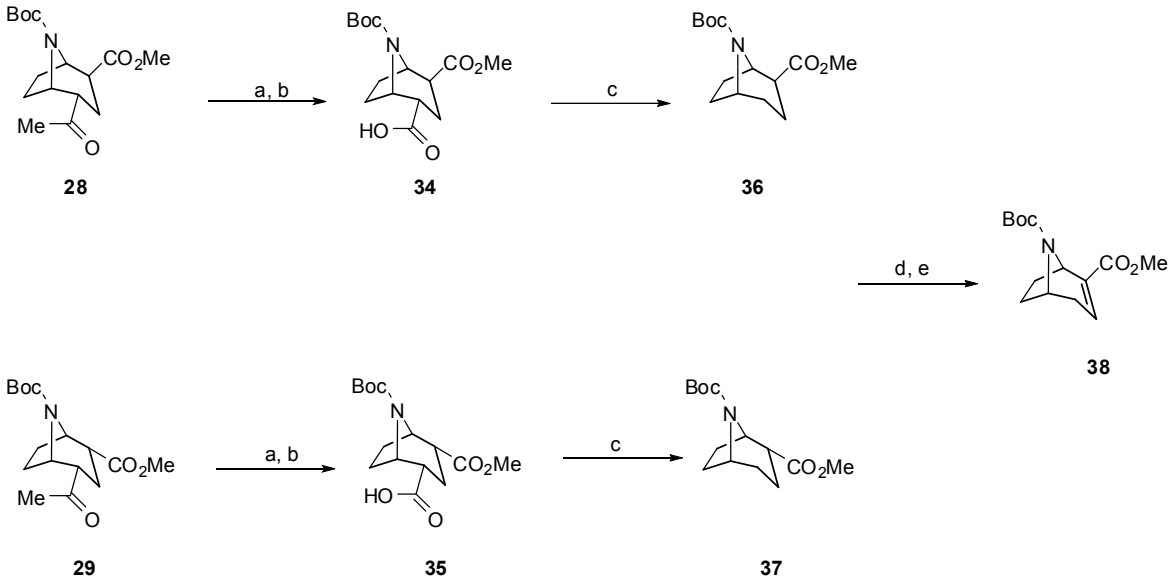
Hydrolysis of bicyclic ester **(28)** and **(29)** delivered epimeric mixtures of acids **(30)** and **(31)** as a 7:1 and 2:1 ratio of *S* and *R*, respectively. Reductive decarboxylation of acids **(30)** and **(31)** was best achieved by photolysis of the corresponding thioxamate esters to furnish epimeric methyl ketones **(32)** as a 9:1 and 2:1 ratio, respectively. Conjugated methyl ketone **(33)** was obtained *via* formation of the thermodynamic silyl enol ether using TBSCl, alpha selenation with phenyl selenyl chloride, oxidation to the selenoxide with *m*CPBA and elimination. Finally, acidic deprotection of butyl carbamate followed by reductive methylation of the resultant free amine furnished the desired (+)-*ferruginine* (scheme 8).



Scheme 8

Reagents & conditions: a) KOH, H_2O, *i*-PrOH, **(30)**, 93%, **(31)**, 100%; b) *t*-BuOCOCl, hν, *t*-BuSH, 79% from **(30)**, 81% from **(31)**; c) NaH, TBSCl; d) PhSeCl; e) *m*CPBA, K_2CO_3; f) TFA, 93%; g) $NaBH_3CN$, CH_2O.

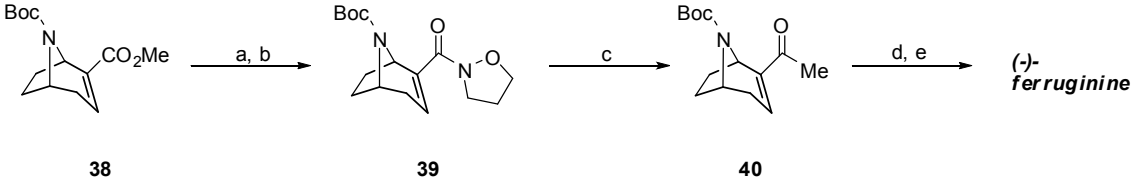
Having completed the total synthesis of (+)-*ferruginine*, the group envisaged the synthesis of its unnatural enantiomeric fom (-)-*ferruginine* using similar strategy. Carboxylic acids **(34)** and **(35)** were obtained *via* selective enolisation of methyl ketones **(28)** and **(29)** by treatment with KHMDS and TMSCl, followed by oxidative cleavage of the resultant enol ethers. Radical decarboxylation[28, 29] of carboxylic acid groups furnished the corresponding methyl esters **(36)** and **(37)**, which were transformed into α,β-unsaturated methyl ester **(38)** *via* kinetic selenation, oxidation and subsequent elimination (scheme 9).



Scheme 9

Reagents & conditions: a) KHMDS, TMSCl; b) O_3, Me_2S, **(34)**, 79%, **(35)**, 84%; c) *t*-$BuCO_2Cl$, hν, *t*-BuSH, **(36)**, 66%, **(37)**, 70% ; d) LDA, PhSeCl; e) $NaIO_4$, 84% from **(36)**, 88% from **(37)**.

The concluding steps involved the conversion of conjugated methyl ester **(38)** to methyl ketone **(40)** *via* hydrolysis and formation of isoxazolidine **(39)**, which was subsequently displaced by methyllithium to deliver **(40)**. The synthesis was completed by acidic deprotection of the carbamate group of **(40)** followed by a reductive methylation to yield the unnatural (-)-*ferruginine* (scheme 10).



38 **39** **40**

Scheme 10

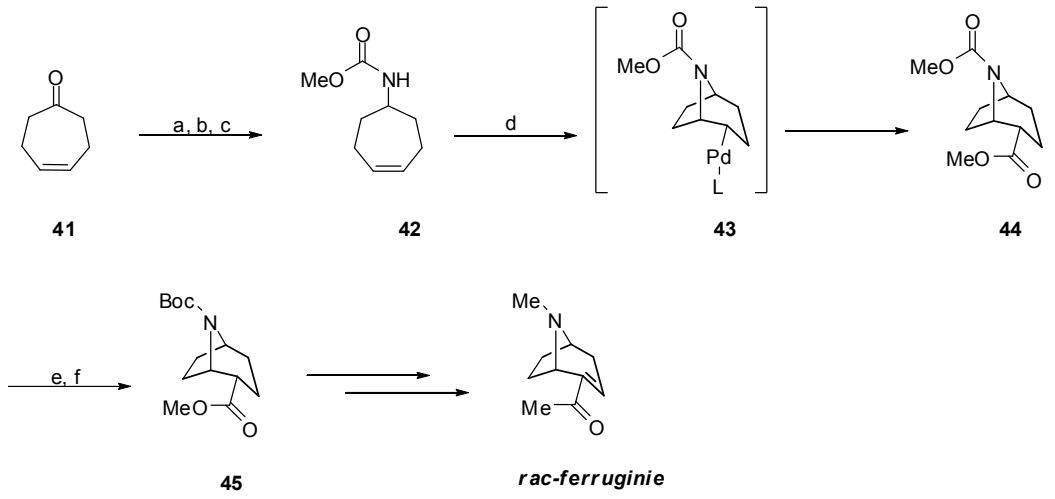
Reagents & conditions: a) KOH, H_2O, *i*-PrOH, 100%; b) isoxazolidine, 87%; c) MeLi, 92%; d) TFA, 93%; e) $NaBH_3CN$, CH_2O, 73%.

In conclusion, Rapport and co-workers have successfully completed enantioselective syntheses of (+)-*ferrugine* and (-)-*ferruginine*. They effectively utilised an iminium ion cyclisation methodology to acquire the tropane alkaloid framework in a stereospecific manner.

Ham's formal synthesis of (*rac*)-*ferruginine.*[11]

Intramolecular aminocarbonylation has been a valuable tool for the construction of biologically important alkaloids and related products.[30-33] Ham and co-workers have successfully applied this methodology in the formal synthesis of the tropane alkaloid *ferruginine*.

Their synthesis began with the treatment of known heptenone **(41)** with hydroxylamine to give an oxime, which was reduced with lithium aluminium hydride to afford the free amine and subsequently protected as the methyl carbamate **(42)** with methyl chloroformate (scheme 11). Palladium catalysed intramolecular aminocarbonylation of **(42)** in the presence of palladium chloride, copper chloride and carbon monoxide under 1 atmosphere pressure furnished the azabicyclic skeleton of *ferruginine* as a single product **(43)** *via* the intermediate **(44)**. Acidic deprotection of methyl carbamate with 30% hydrogen bromide followed by Boc protection of the free amine delivered the known azabicycle **(45)**, whose conversion to *ferruginine* was earlier reported by Rapoport.[34]



Scheme 11

Reagents & conditions: a) $NH_2OH.HCl$, Na_2CO_3, MeOH, reflux, 85%; b) $LiAlH_4$, THF, reflux, 89%; c) methyl chloroformate, CH_2Cl_2, 39%; d) $PdCl_2$ (0.1 eq), $CuCl_2$, CO (1atm), MeOH, rt, 49%; e) 30% HBr.HOAc, rt; f) $(Boc)_2O$, dioxane, rt, 69% from **(44)**.

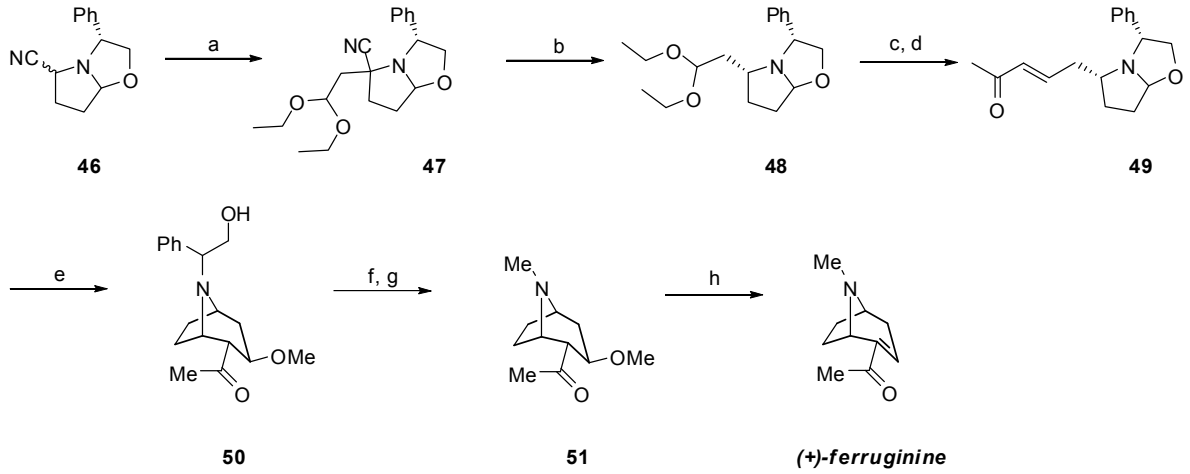
In conclusion, a formal synthesis of (*rac*)-*ferruginine* has been achieved through palladium catalysed intramolecular aminocarbonylation of methyl carbamate **(42)** to provide the tropane alkaloid **(44)**, which was transformed to the known azabicycle **(45)**.

Husson's synthesis of (+)-*ferruginine.*[12]

Husson and co-workers envisaged an asymmetric synthesis of (+)-*ferruginine* based on an intramolecular α,β-unsaturated ketone cyclisation onto an acyl iminium species derived from non-racemic 2-cyano-5-oxazolopyrrolidine to obtain the functionalised azabicycle.

The synthesis of *ferruginine* began with alkylation of **(46)** with bromoacetaldehyde diethyl acetal in the presence of LDA and HMPA to afford a diastereomeric mixture of cyano-oxazolopyrrolidines **(47)** (scheme 12). Removal of the cyano functionality was best achieved using lithium in ammonia, where previous investigations into this reduction step proceeded with

complete stereoselectivity to furnish oxazolopyrrolidine **(48)**.[35, 36] Removal of the acetal protecting group followed by a Horner-Wandsworth-Emmons olefination[37] provided the *trans* enone **(49)**, the precursor to the iminium ion cyclisation. Cyclisation of **(49)** delivered bicyclic adduct **(50)** as a single stereoisomer, which was confirmed by extensive spectroscopic analysis. Hydrogenolysis released the free amine which was immediately methylated with formaldehyde and sodium cyanoborohydride to give methyl amine **(51)**. The synthesis was completed through regioselective elimination of methanol using *p*-toluenesulfonic acid in benzene to install the enone.



Scheme 12

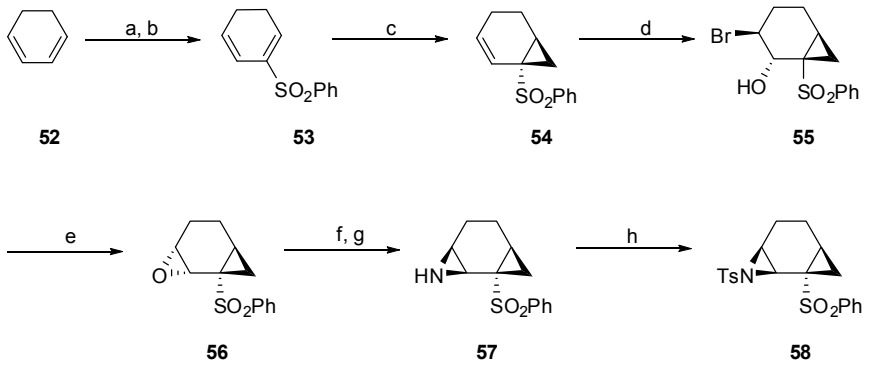
Reagents & conditions: a) LDA, $BrCH_2CH(OEt)_2$, HMPA, 86%; b) Li/NH_3, 66%; c) (10%) HCl; d) $(MeO)_2P(O)CH_2COCH_3$, 86%; e) H_2SO_4, MeOH, 60 °C, 84%; f) $H_2/Pd(OH)_2$; g) CH_2O, $NaBH_3CN$, 62%; h; TsOH, C_6H_6, 68%.

In summary, (+)-*ferruginine* was synthesised in seven steps with an overall yield of 20% starting from a chiral substrate. The azabicyclic motif of the tropane alkaloid natural product was constructed utilising an intramolecular α,β-unsaturated ketone cyclisation onto an acyl iminium species with complete stereoselectivity.

Bäckvall's synthesis of (*rac*)-*ferruginine.*[13]

Backvall and co-workers envisioned the tropane alkaloid skeleton of *ferruginine* could be obtained by means of Lewis-acid induced rearrangement of aziridino cyclopropanes, derived from 2-phenylsulfonyl 1,3-dienes. Preliminary studies from the group had demonstrated Lewis acid catalysed rearrangement of some 3,4-epoxy-1,2-methylene-2-(phenylsulfonyl)cycloalkanes[38] and their 3,4-aziridines analogues[39] to bicyclic compounds. In the case of aziridine analogues, acid catalysed rearrangement led to the tropane alkaloid motif.

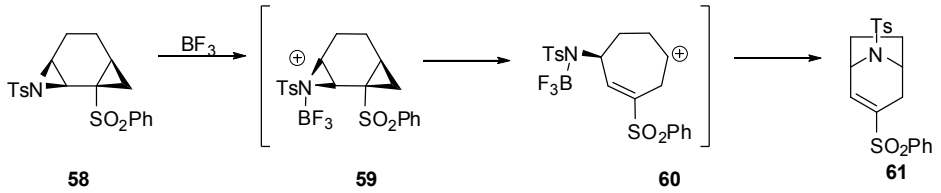
Their synthesis of *ferruginine* began with the readily available 2-(phenylsulfonyl)-1,3-cyclohexadiene **(53)**, prepared from cyclohexadiene **(52)** according to previous literature methods.[40, 41] Regioselective cyclopropanation of the electron deficient double bond of **(53)** proceeded smoothly using a nucleophilic cyclopropanating agent[38] to give **(54)**, which was transformed to the *anti*-epoxy cyclopropane **(56)** with complete stereoselectivity *via* bromohydrin **(55)**. Epoxide **(5)** was converted to aziridine **(57)** *via* ring opening with sodium azide followed by treatment with triphenylphosphine, which was subsequently protected as the sulfonamide **(58)** (scheme 13).



Scheme 13

Reagents and conditions: a) $HgCl_2$, $NaSO_2Ph$, 97%; b) Na_2CO_3, 2 M NaOH, 86%; c) Me_3SOI, NaH, 95%, d) NBS, H_2O, 98% (crude); e) 2 M NaOH, 75% from **(54)**; f) NaN_3, NH_4Cl; g) PPh_3, h) TsCl, NEt_3, 51% from **(56)**.

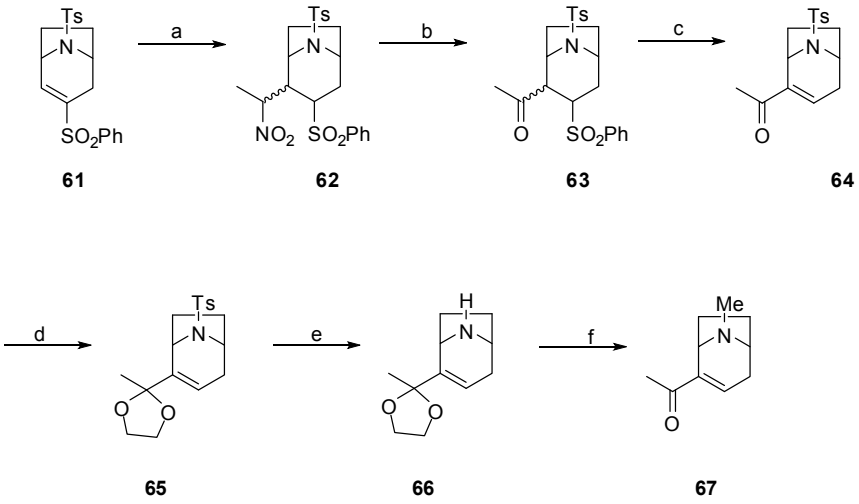
Aziridino cyclopropane **(58)** was subjected to Lewis acid catalysed rearrangement conditions using boron trifluoroetherate which resulted in the formation of the tropane alkaloid skeleton **61**, *via* the postulated intermediates **(59)** and **(60)** (scheme 14).[38, 39] For successful Lewis acid induced rearrangement to occur, a *syn* relationship between aziridine and the cyclopropane is crucial as an *anti* relationship fails to deliver any desired products.



Scheme 14

A Michael addition of nitroethane in the presence of DBU onto the tropane skeleton **(61)** led to nitrosulfone **(62)** as an inseperable 2:1 mixture of diastereomers, which were consequently transformed into ketosulfone **(63)** using a Nef reaction. Elimination of sulfone **(63)** was achieved

with potassium *tert*-butoxide to furnish enone **(64)**. The final few steps in this synthetic sequence involved an acetal protection using Noyori's reagent[42] to give **(65)**, which was essential for the de-tosylation of **(65)** with magnesium in methanol to afford free amine **(66)**, and finally reductive methylation with formaldehyde and sodium cyanoborohydride successfully delivered the racemic natural product *ferruginine*, while acid-base extraction cleaved the acetal protecting group in the subsequent work (scheme 15).



Scheme 15

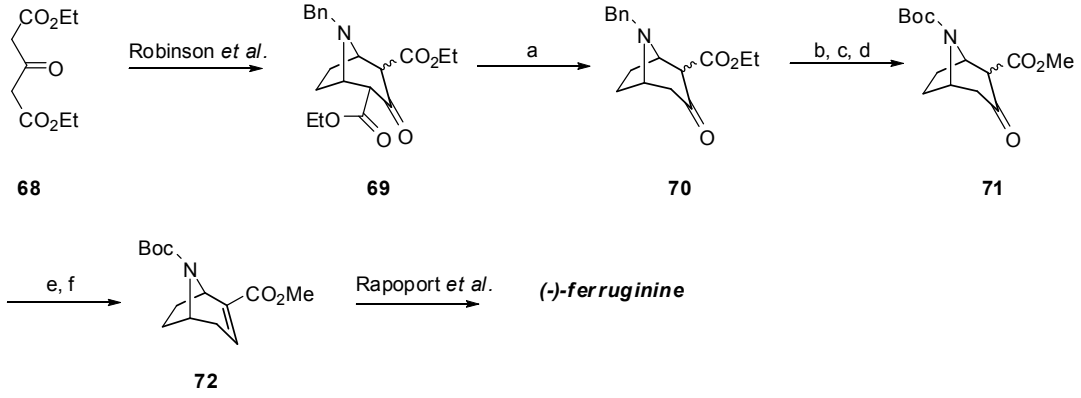
Reagents & conditions: a) $EtNO_2$, DBU, 91%; b) H_2O_2, K_2CO_3, 98%; c) *t*-BuOK, THF, 87%; d) Me_3SiOTf, 1,2-bis-((trimethylsilyl)oxy)ethane, 63%; e) Mg, MeOH, ultrasound; f) CH_2O, $NaCNBH_3$, 75% from **(65)**.

In conclusion, Bäckvall's group have demonstrated the scope of the Lewis acid promoted rearrangement of aziridino cyclopropanes **(58)** derived from 2-phenylsulfonyl 1,3-dienes **(53)** to the synthesis of *ferruginine*. Critical to the success of this transformation was the *syn* relationship between aziridine and the cyclopropane species; an *anti* relationship proved totally

ineffective. This methodology has the potential to assemble a range of tropane alkaloid analogues.

Node's synthesis of (+)-*ferruginine* & (-)-*ferruginine.* [14]

Node and co-workers utilised Robinson's tropinone synthesis[43] for the construction of azabicyclic diester **(69)** with the potential for a divergent asymmetric syntheses of both enantiomers of *ferruginine*, utilising a porcine liver esterase (PLE) catalysed asymmetric dealkoxycarbonylation strategy.[44-47] PLE catalysed dealkoxycarbonylation of tropinone diester **(69)** selectively removed the ethylester functionality to furnish β-azabicyclic keto ester **(70)** in excellent enantiomeric excess of 96%, albeit in poor yield (scheme 16). Methyl ester exchange was achieved with sodium and methanol, followed by hydrogenolysis of the benzyl group to the free amine, which was subsequently protected as *tert*-butyl carbamate **(71)**. Selective reduction of ketone **(71)** with tetrabutylammonium borohydride followed by acetylation and subsequent elimination of the resultant alcohol with trifluoroacetic anhydride and triethylamine furnished the known α,β-methyl enonoate **(72)**,[48, 10] hence accomplishing a formal synthesis of the unnatural isomer (-)-*ferruginine*.

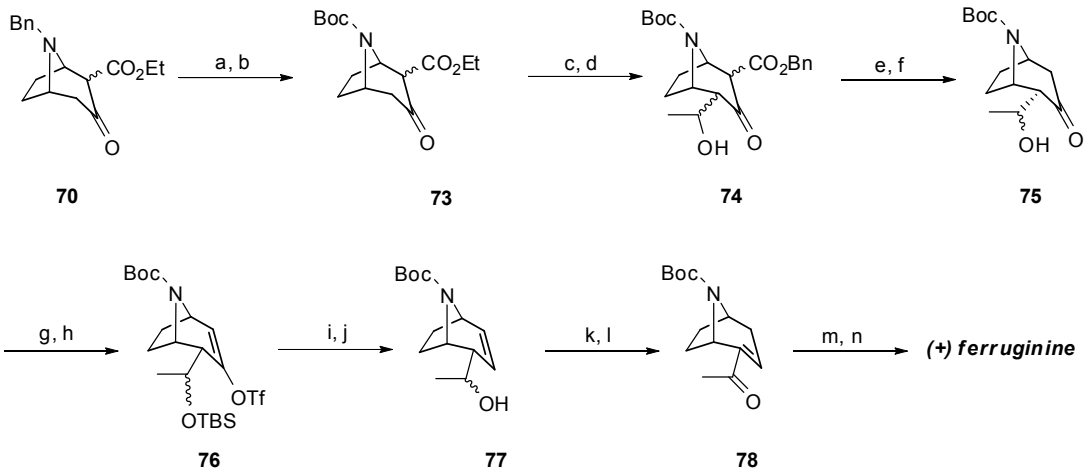


Scheme 16

Reagents & conditions: a) PLE (500 units), 1 M phosphate buffer, pH 8, DMSO, 24 h, rt, 38%, 96% ee; b) Na, MeOH, 95%, c) 10% Pd/C, H_2; d) $(Boc)_2O$, Et_3N, 95% over two steps; e) Bu_4NBH_4, 85%; f) $(CF_3CO)_2O$, Et_3N, DMAP, $CHCl_3$, 94%.

Having successfully completed the formal synthesis of (-)-*ferruginine*, their next step was to complete the total synthesis of the natural (+)-*ferruginine* from azabicyclic β-keto ester **(70)**. The benzyl protecting group of **(70)** was exchanged for butyl carbamate *via* hydrogenolysis and carbamoylation, which was followed by ester exchange with benzyl alcohol and DMAP to deliver **(73)** (scheme 17). Regioselective alkylation of ketone **(73)** with acetaldehyde provided **(74)**, which was followed by hydrogenolysis and decarboxylation with catalytic hydrochloric acid furnished β-hydroxyl ketone **(75)** as a single diastereomer. Silylation of the secondary alcohol was followed by formation of enol triflate **(76)** using *N*-phenyl trifluoromethanesulfonimide. Palladium catalysed reduction of the enol triflate was achieved with palladium acetate and formic acid, which was directly followed by desilylation upon treatment with TBAF to furnish the homoallylic alcohol **(77)**. The construction of the methyl enone moiety of *ferruginine* was achieved by PCC oxidation of alcohol **(77)** and subsequent double bond migration with DBU. Finally, the asymmetric synthesis of (+)-*ferruginine* was completed *via* deprotection of **(78)** using

trifluoroacetic acid, followed by reductive methylation using sodium cyanoborohydride and formaldehyde.



Scheme 17

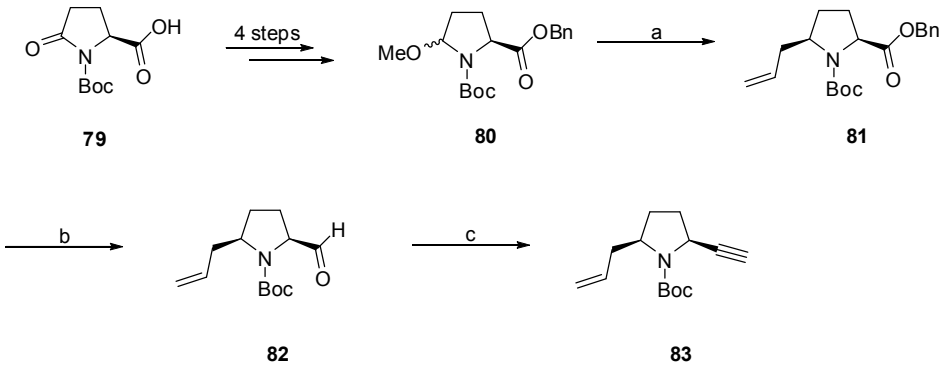
Reagents & conditions: a) Pd/C, H_2; b) $(Boc)_2O$, 83% over two steps; c) BnOH, DMAP, toluene, reflux, 98%; d) NaH, LDA, MeCHO, THF, 56%; e) Pd/C, H_2; f) HCl (cat), 85% over two steps; g) TBSCl, imidazole, DMF, 95%; h) *t*-BuOK, $PhNTf_2$, THF, 73%; i) $Pd(OAc)_2$, PPh_3, Et_3N, HCO_2H; j) TBAF, 66% over two steps; k) PCC; l) DBU, 83% over two steps; m) TFA; n) HCHO, $NaBH_3CN$, 94% over two steps.

In conclusion, Node and co-workers have developed divergent synthetic routes to (+)-*ferruginine* and its unnatural isomer (-)-*ferruginine* utilising a PLE catalysed asymmetric dealkoxycarbonylation of the readily available tropinone diester **(69)**, to deliver azabicyclic β-keto ester **(70)** in optically pure form.

Aggarwal's synthesis of (+)-*ferruginine.*[15]

Ring-closing metathesis is a very powerful tool in organic synthesis and has been successfully employed for the construction of cyclic and fused bicyclic systems.[49-53] However, there is less precedent for the construction of bridged bicycles using this methodology.[54] In light of this knowledge, Aggarwal and co-workers devised an enyne ring closing metathesis tactic for the construction of azabicycle system, derived from chiral Boc protected pyrrole. The added advantage of this approach is the incorporation of the double bond within the bicycle required for the natural product *ferruginine*, thus avoiding tedious chemistry for its insertion.

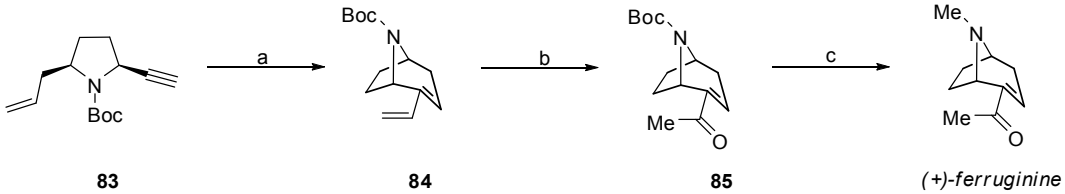
The synthesis began with the commercially available non racemic L-pyroglutamic acid **(79)** which was converted into aminal **(80)** in a 95:5 ratio of *cis/trans* isomers over four steps using previously described literature procedures.[55] Aminal **(80)** was treated with boron trifluoroetherate in the presence of allyltrimethylsilane to furnish the desired *cis* allylated pyrrole **(81)**. Chemoselective reduction of the benzyl ester with lithium aluminium hydride gave aldehyde **(82)**, which was subsequently homologated with the modified Gilbert reagent[56] to give the required enyne **(83)**, setting the stage for the key ring-closing metathesis (scheme 18).



Scheme 18

Reagents & conditions: a) $BF_3.OEt_2$, allyltrimethylsilane, -78 °C to rt, Et_2O, 15 h, 93% (8:2, *cis: trans*); b) $LiAlH_4$, THF, 0 °C, 78%; c) $CH_3COCN_2PO(OEt)_2$, K_2CO_3, MeOH, 1.5 h, rt, 93%.

Ring-closing metathesis was initially attempted with the more active Grubbs second generation catalyst, but this gave very low yields of the desired bicycle **(84)**, accompanied by a major by-product. Therefore, the group decided to monitor the progress of the metathesis by GC-MS and found after an initial build of the required product, there was a steady decline. This indicated that the active catalyst was destroying the product, and thus the alternative, less active Grubbs first generation catalyst was employed to furnish the desired azabicyclic compound **(84)** in high yield. Finally, a Wacker oxidation of **(84)** to the methyl ketone **(85)** followed by reductive methylation furnished the tropane alkaloid (+)-*ferruginine* (scheme 19).



83 **84** **85** *(+)-ferruginine*

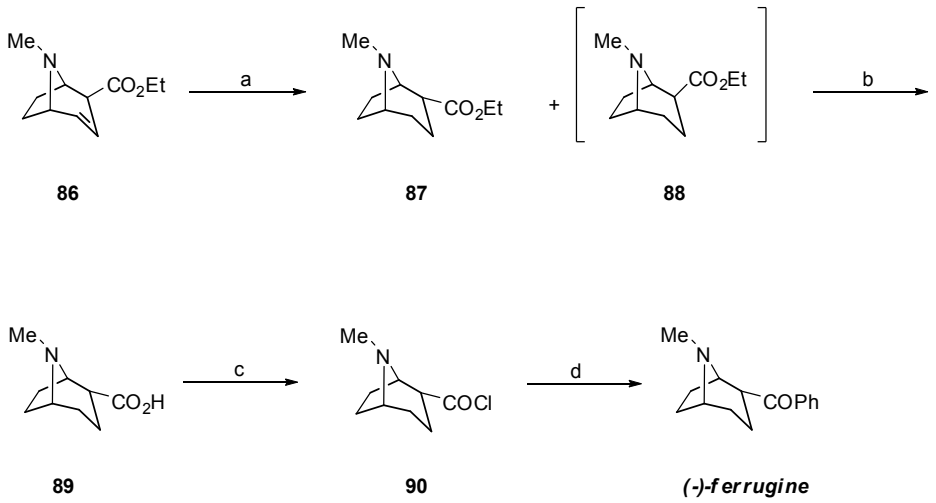
Scheme 19

Reagents & conditions: a) Grubbs I (10 mol%), CH_2Cl_2, 50 °C, 10 h, 86%; b) $PdCl_2$, $CuCl_2$, H_2O, DMF, 6 h, 81%; c) TFA, CH_2Cl_2, rt, 3 h, then K_2CO_3, 93%; d) CH_2O, $NaBH_3CN$, MeCN, 15 min, 97%.

In conclusion, Aggarwal and co-workers have developed an asymmetric synthesis of (+)-*ferruginine* in 12 steps with an overall yield of 27% beginning with the inexpensive commercially available L-pyroglutamic acid. Enyne metathesis was achieved with the less active Grubbs 1st generation catalyst as the more active 2nd generation catalyst decomposed the desired product. Although there is less precedent for the construction of fused bridged bicycles using this approach, this enyne strategy could be applied in obtaining alternative enones, which are found in many bridged azabicyclic systems and natural products.

Bick's synthesis of (-)-*ferrugine*.[7]

Having established the stereochemistry of (-)-*ferrugine*, Bick and co-workers confirmed the stereochemistry synthetically to eliminate any ambiguity. Hydrogentaion of the electron deficient double bond of anhydroecgonine ethyl ester **(86)**, prepared from cocaine[6] was achieved using Pd/C to deliver the hydroecgonine ethyl ester **(87)** accompanied by the undesirable isomer **(88)** (scheme 20). Ester hydrolysis of **(87)** followed by subsequent treatment with oxalylchloride provided hydroecgonine acid chloride **(90)**. Finally, synthesis of (-)-*ferrugine* was accomplished upon treatment with Ph_2Cd in a 23.6% overall isolated yield from **(86)**.



Scheme 20

Reagents & conditions: a) H_2, Pd/C (10 mol%), EtOH, rt, 3 h.; b) H_2O, reflux, 8 h; c) oxalylchloride, DCM, 0 °C-rt, 30 min; d) Ph_2Cd, DCM, 0 °C-rt, 30 min, 26% from **(86)**

2. AIMS AND OBJECTIVES

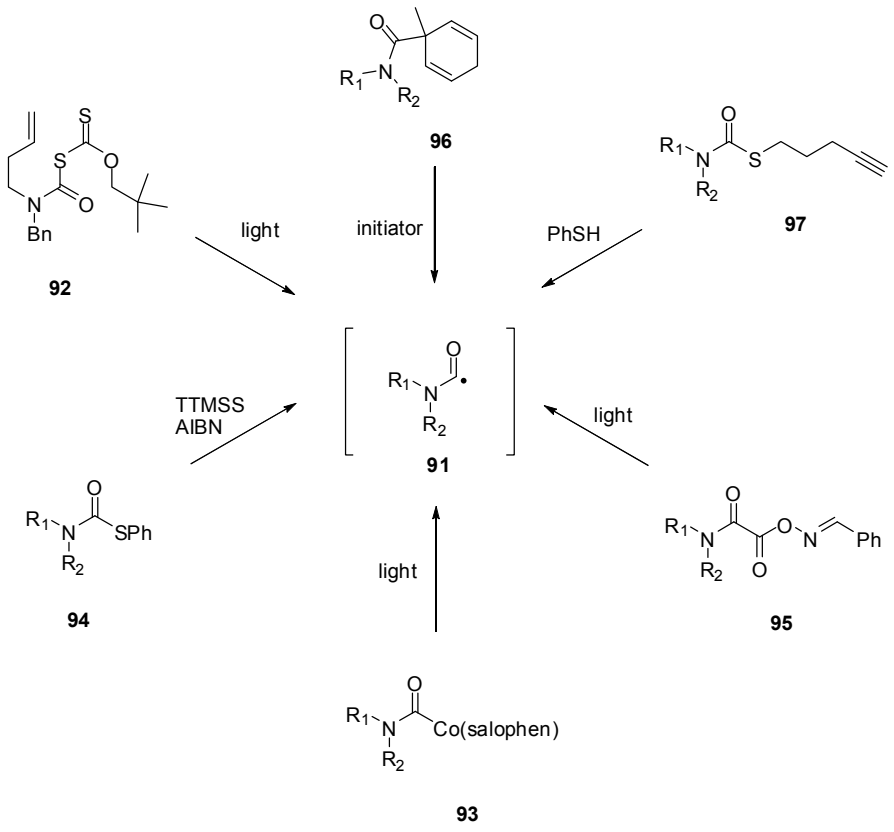
Carbamoyl radical chemistry

The application of radicals in organic synthesis has become increasingly popular over the last forty years. Radicals have numerous advantages over ionic based processes in synthesis, such as, their lower propensity for rearrangement, relatively fast reactions rates under mild conditions, they can also operate under polar and hindered environment, and their tolerance to a wide range of functional groups.[57] Despite the many well documented advantages of free radical reactions in organic chemistry, the majority of examples still rely on the use of highly toxic tributyl tin hydride (Bu_3SnH) in stoichiometric amounts. Furthermore, the products can be difficult to completely free from tin side products. Also a common problem with Bu_3SnH reactions is the premature reduction of radical internediates by the reagent prior to cyclisation. Consequently, such reactions require high dilutions along with slow addition of tributyltin reagents to reaction mixtures to prevent competing reduction.[58]

A major area of current research is the development of processes which seek to either alleviate the problems associated with toxic tin residues, or remove the need for tin completely.[59, 60] The Grainger group is involved in this field and is developing tin free radical methodology and applying it in natural product synthesis.[61] One of the modern pioneers in the development of tin free radical methodology is Zard and co-workers who have extensively developed the generation of a variety of radicals from xanthates,[62, 63] which are precursors to acyl,[64, 65] alkoxycarbonyl,[66] and a variety of carbon[66-71] and nitrogen-centred[57-73] radicals that have found numerous synthetic applications.[65-78]

Carbamoyl radicals **(91)** or aminoacyl radicals are reactive intermediates that have been generated under tin free conditions from xanthates **(92)**,[62, 63] cobaltsalophens **(93)**,[80] selenium carbamates **(94)**, and oxime oxalate amides **(95)** (scheme 21),[83] along with systems with a

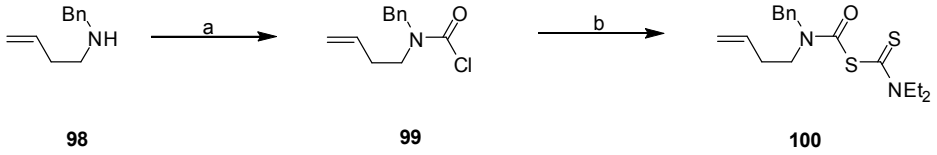
tendency for aromatisation **(96)**[86] and *S*-4 pentynyl carbamothioates **(97)**.[87] Such reactions have found limited application in natural product synthesis. However, Myers and co-workers utilised a carbamoyl radical generated from carbamoylcyclohexadienyl system as a key step in the synthesis of *stephacedin* B.[88]



Scheme 21

Previous work within the Grainger group sought to generate carbamoyl radicals from xanthate precursors, but unfortunately such precursors could only be isolated in poor yields, despite successful carbamoyl radical cyclisations. This study prompted research into an alternative carbamoyl radical precursor and eventually dithiocarbamates were employed as a suitable source of carbamoyl radicals.[88] Carbamoyl dithiocarbamates are easy to synthesise in two high yielding steps from secondary amines, such as **(98)**, firstly by treatment with triphosgene and pyridine to

provide carbamoyl chloride **(99)**, which was immediately converted to the corresponding carbamoyl dithiocarbamate **(100)** upon treatment with commercially available and inexpensive sodium diethyldithiocarbamate trihydrate salt (scheme 22).[88]

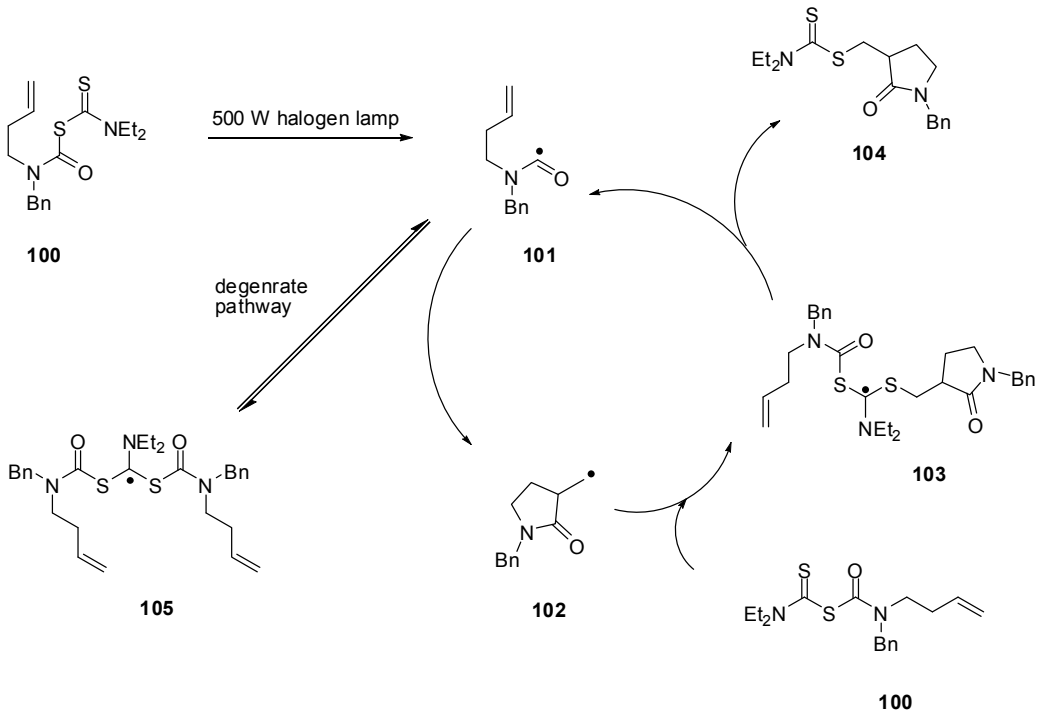


98 **99** **100**

Scheme 22

Reagents & conditions: (a) triphosgene (0.33 eq), pyridine (1.5 eq), toluene, rt, 1 h; (b) sodium diethyldithiocarbamate trihydrate (4 eq), acetone, > 95%.

Irradiation of carbamoyl dithiocarbamate **(100)** with 500 W halogen lamp generated carbamoyl radical **(101)** which underwent a *5-exo-trig* cyclisation onto a pendant alkene to give a primary radical **(102)** (scheme 23). Dithiocarbamate group transfer onto radical **(102)** afforded a stable tertiary radical **(103)**, which upon fragmentation furnished the desired functionalised lactam **(104)** and regenerated carbamoyl radical **(101)** to continue the chain process. An alternative competing pathway for carbamoyl radical is the reaction with **(100)** prior to cyclisation to give a new tertiary carbon-centred radical **(105)**. However, this route is degenerative and thus fragments back to give carbamoyl radical **(101)** along with the carbamoyl dithiocarbamate **(100)**. As a consequence, this degenerative pathway increases the lifetime of radical **(101)** which can preferentially cyclise to the desired product, and also allowing more difficult intramolecular radical cyclisations to take place such as seven and eight-membered rings, *cis* fused β-lactams, and spirobicyclic γ-lactams in good to excellent yields.[88]



Scheme 23

This methodology was successfully applied by the Grainger group in the formal synthesis of (-)-*aphanorphine*, a biologically active benzazepine alkaloid isolated from the freshwater blue-green alga *aphanizomenon flos-aquae*,[89] and similar in structure to natural and non-natural analgesics such as morphine, *eptazocine* and *pentazocine* (fig 3). [61]

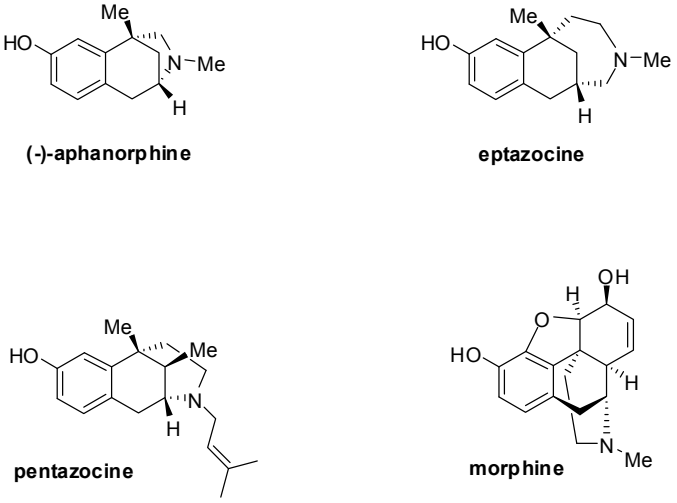
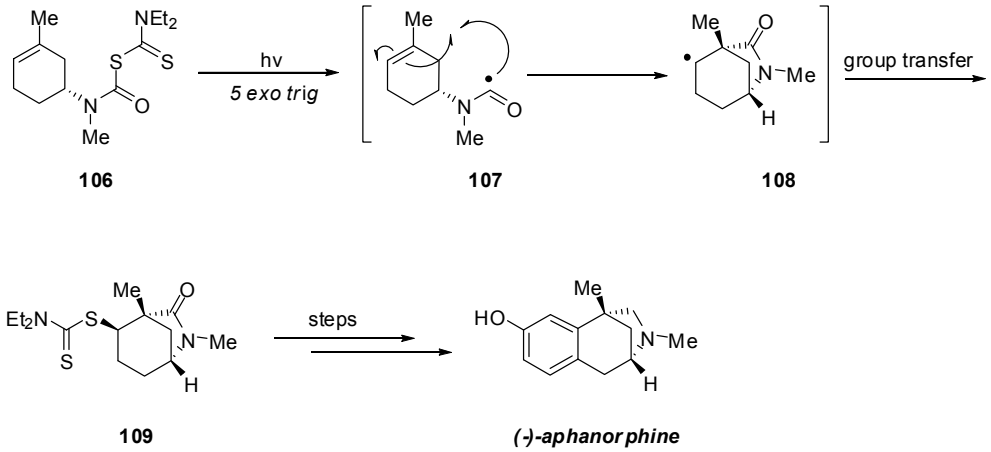


Fig 3

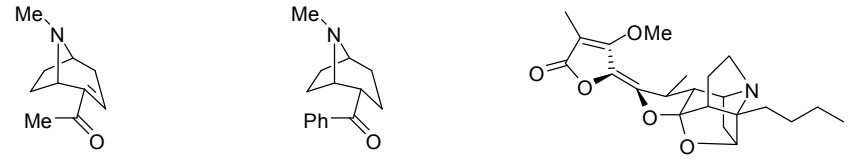
Irradiation of the cyclisation precursor **(106)** using 500 W halogen lamp generated the reactive carbamoyl radical **(107)**, which underwent a regioselective *5-exo-trig* cyclisation onto the alkene to form a new carbon centred radical **(108)**. Subsequent dithiocarbamate group transfer furnished the desired lactam **(109)** as a single regio and stereoisomer in 71% isolated yield. Further manipulations led to the synthesis of the benzazepine alkaloid *aphanorphine* (scheme 24). [61]



Scheme 24

Proposed synthesis of *ferrugine* and *ferruginine*

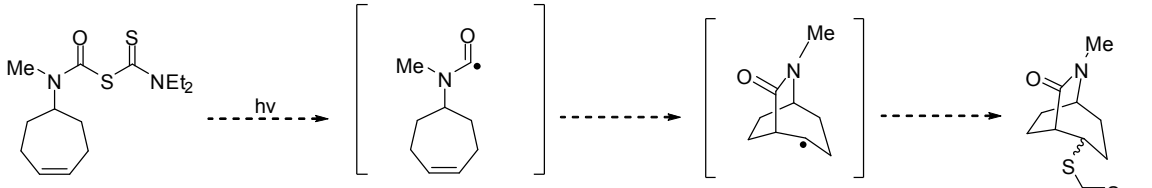
The primary aim of this project is to build upon the Grainger group's early work on dithiocarbamate group transfer carbamoyl radical cyclisation and apply this methodology to the syntheses of the tropane alkaloids *ferruginine* and *ferrugine*, and the more complex *stemofoline* (fig 4).



ferruginine **ferrugine** **stemofoline**

Fig 4

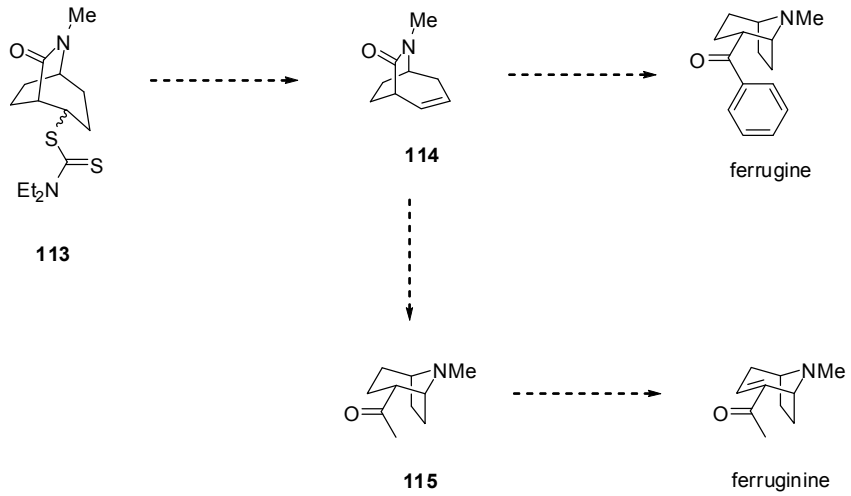
Syntheses of the tropane alkaloid framework of the two natural products *ferruginine* and *ferrugine* are proposed based upon carbamoyl radical cyclisation followed by group transfer of the dithiocarbamate functionality. It is envisaged that irradiation of dithiocarbamate **(110)**, will generate carbamoyl radical **(111)**, which will cyclise onto the pendant alkene to give a new carbon centred radical **(112)**. Radical **(112)** will then undergo a dithiocarbamate group transfer with **(110)** to furnish the lactam **(113)** (scheme 25).



110 **111** **112** **113**

Scheme 25

Thermal elimination of dithiocarbamate **(113)** with diphenyl ether will result in bicyclic amide **(114)** which will be subsequently treated with phenyllithium to deliver the tropane alkaloid *ferrugine via* a proposed one pot multistep transformation (scheme 26). Finally, the synthesis of *ferruginine* is envisioned using a similar one pot multistep transformation to deliver the tropane alkaloid framework **(115)**, by treatment of **(114)** with methyllithium, which will be subsequently oxidised to deliver the desired natural product.



Scheme 26

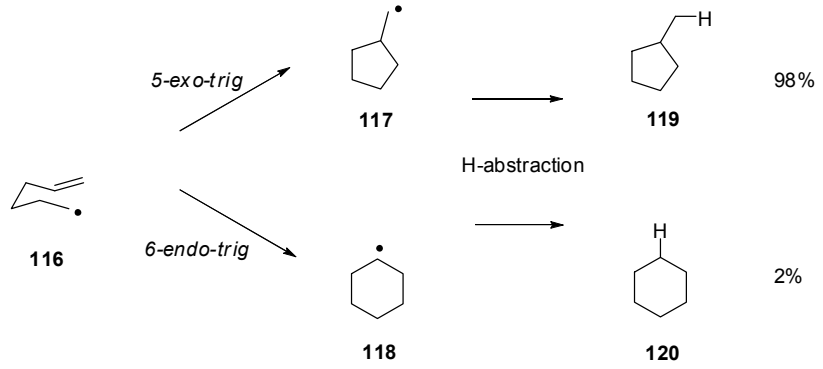
Preliminary investigations into the feasibility of the proposed radical cyclisation have been previously carried out in the Grainger group.[205]

The structurally intricate stemona alkaloid, *stemofoline* would provide the ultimate test to showcase the group's carbamoyl radical cyclisation dithiocarbamate group transfer methodology.

Radical Cyclisations

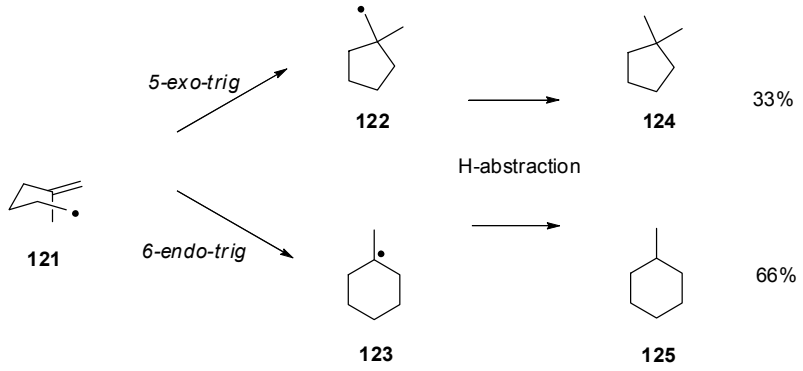
Radical cyclisation reactions are dominated by the *5-exo-trig* pathway to provide kinetic primary radicals rather than the more stable secondary radicals obtained *via 6-endo-trig* pathway in the absence of other factors.[90, 91] For example, the primary radical in **(116)** cyclises at a much faster

rate *via 5-exo-trig* to form a new primary radical **(117)**, which is thermodynamically less stable than the secondary radical **(118)**, formed *via* a *6-endo-trig* cyclisation. This observation is rationalised on stereoelectronic grounds as the singly occupied molecular orbital (SOMO) interacts more favourably with the lowest unoccupied molecular orbital (LUMO) of alkenes (scheme 27).[92]



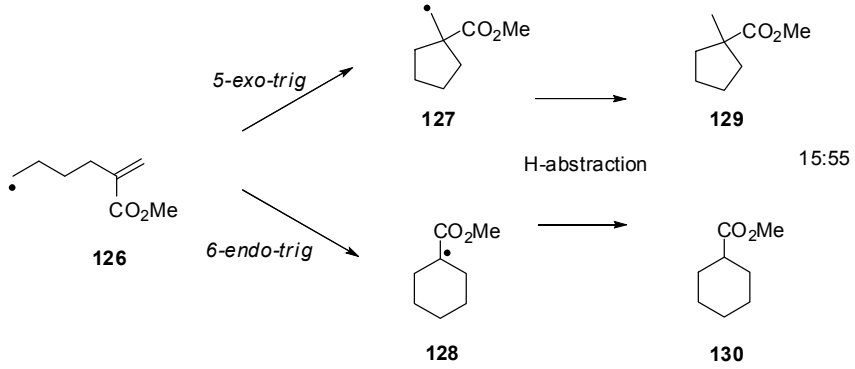
Scheme 27

However, depending on the steric and electronics properties of the system, *6-endo-trig* pathway can be favoured. For example, an alkyl substituent on alkene **(121)** would hinder the formation of primary radical **(122)** due to unfavourable steric interactions with the methyl substituent, and therefore, would favour the stable tertiary radical **(123)** (scheme 28).[91, 92]



Scheme 28

Also, the incorporation of electron withdrawing groups can enhance the formation of larger ring systems for example in the ester-substituted double bond in **(126)**. The net effect of the ester group will make the terminal double bond electron deficient and thus more electrophilic. Therefore, *6-endo-trig* cyclisation is predominantly favoured due to the polar effect of the ester group over *5-exo-trig* to give **(128)** by lowering the LUMO of the alkene.[92] The ester substituent substantially hinders the formation of the primary radical **(127)** *via 5-exo-trig* mode and thus, leads to the formation of a tertiary radical **(128)** which is also stabilised by the electron withdrawing nature of the ester group (scheme 29).[93, 94]

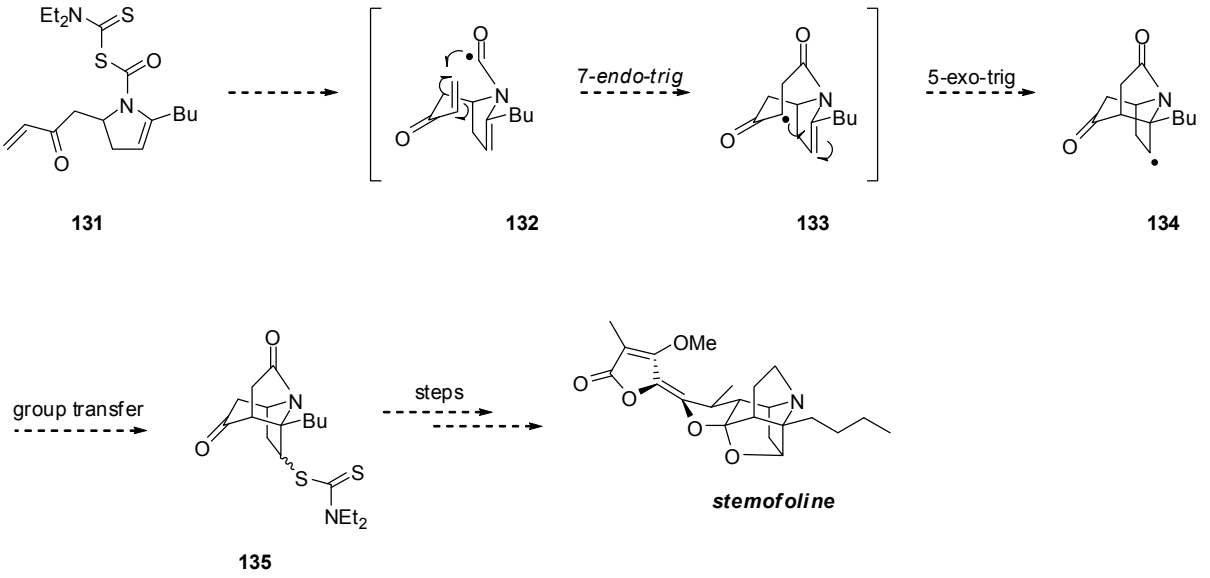


Scheme 29

Proposed synthesis of *stemofoline*

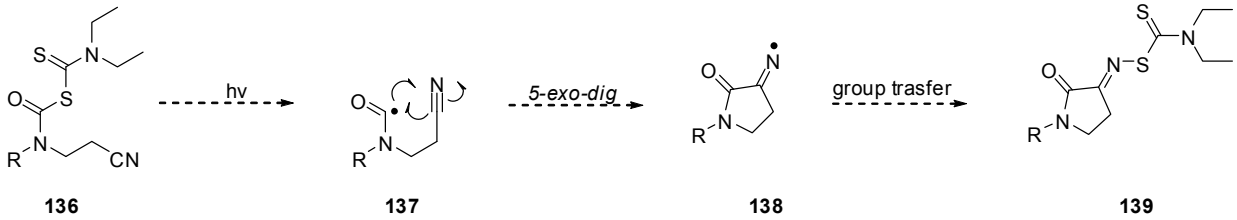
It is hypothesised that the core skeleton of *stemofoline* will be obtained *via* a tandem *7-endo-trig* cyclisation/transannular *5-exo-trig* cyclisation/intermolecular group transfer strategy. Carbamoyl radical species **(132)** could be generated by irradiating the cyclisation precursor **(131)** using a 500 W halogen lamp. Electronics of the electron deficient alkene should dictate a *7-endo-trig* cyclisation mode rather than *6-exo-trig*, as it is anticipated the nucleophilic carbamoyl radical will preferentially add to the less hindered terminus of the electron deficient double bond. This should lead to a stabilised secondary radical **(133)** which should undergo *5-exo-trig* cyclisation to

generate a new carbon centred radical **(134)**, which should finally undergo a dithiocarbamate group transfer to furnish the tricyclic core of *stemofoline* **(135)**. Furthermore, if the tandem cyclisation and group transfer is successful, the correct functionality would be present in the tricyclic core for further elaboration *en route* to the synthesis of the complex stemona alkaloid, *stemofoline* (scheme 30). Therefore, the primary aim of this project is to synthesise the cyclisation precursor **(131)** in racemic form to investigate this tandem cyclisation strategy.



Scheme 30

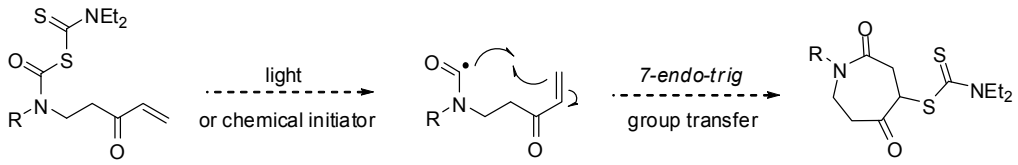
Carbamoyl radical cyclisation-dithiocarbamate group transfer onto nitriles will also be investigated. Upon generation of carbamoyl radical **(137)** by irradiating carbamoyl dithiocarbamate **(136)**, it is anticipated this reactive intermediate will cyclise onto the nitrile, *via* a *5-exo-dig* pathway, to give nitrogen-centred radical **(138)**. This new radical **(138)** will then be captured *via* dithiocarbamate group transfer to furnish the desired product **(139)**, regenerating the carbamoyl radical **(136)** to continue the chain process (scheme 31).



136 **137** **138** **139**

Scheme 31

Using a similar approach, study of carbamoyl radical cyclisations onto enone species will be investigated. Photo or chemical induced initiation of carbamoyl dithiocarbamate enone **(140)** will generate carbamoyl radical **(141)** (scheme 32). This species will undergo an intramolecular cyclisation onto the terminal enone through a *7-endo-trig* mode to produce a new radical, which will be captured by the dithiocarbamate group to provide the functionalised lactam **(142)**, along with the regeneration of carbamoyl radical **(141)** to continue the chain process.



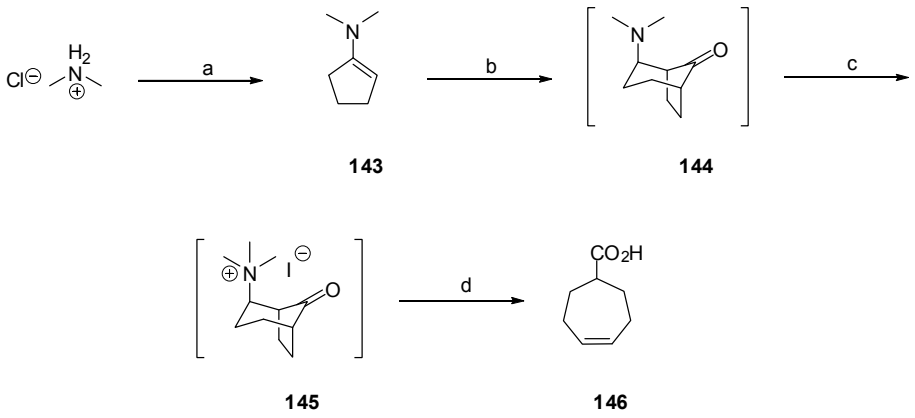
140 **141** **142**

Scheme 32

3. TOTAL SYNTHESIS OF *FERRUGINE* AND ATTEMPTED SYNTHESIS OF *FERRUGININE*

Synthesis of cyclisation precursor *via* carbamoyl chloride.

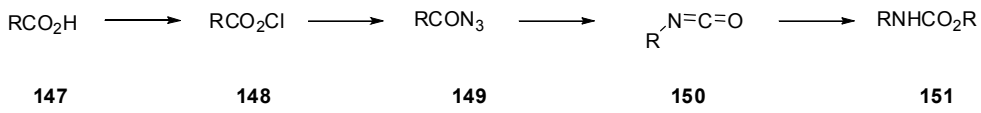
The synthesis of the radical cyclisation precursor **(110)** began with preparation of the known seven-membered ring carboxylic acid **(146)**.[95] Deprotection of dimethylamine hydrochloride with aqueous sodium hydroxide released the volatile amine, which was immediately condensed and reacted with cyclopentanone to afford enamine **(143)** in 86% after distillation (scheme 33). A Michael addition of enamine **(143)** onto acrolein followed by an intramolecular Mannich reaction resulted in the bicyclic ketoamine intermediate **(144)**. Treatment of ketoamine **(144)** with iodomethane in acetonitrile furnished ammonium salt **(145)**. Basic reflux in aqueous sodium hydroxide followed by acidification with concentrated hydrochloric acid furnished the desired carboxylic acid **(146)** *via* a nucleophilic addition Grob fragmentation sequence, unfortunately in poor yields, compared with the 56% reported in literature.[95] Disappointingly, attempts made towards increasing the yield by varying conditions proved unsuccessful.



Scheme 33

Reagents & conditions: (a) NaOH, H_2O -78 °C then cyclopentanone, 81%; (b) acrolein, 0 °C; (c) MeI, MeCN; (d) aq (20%) NaOH, 23%.

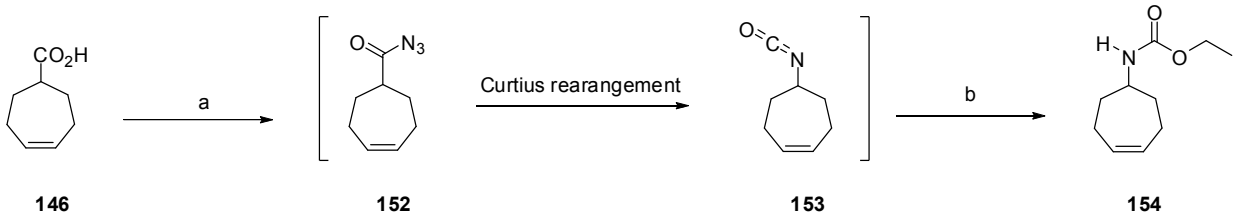
The Curtius rearrangement is a powerful reaction for the construction of carbamates form carboxylic acid derivatives. The classical route entails the formation of an acid chloride **(148)** from carboxylic acid **(147)**, which is converted into an acyl azide **(149)**. Curtius rearrangement of azide **(149)** gives an isocyanate **(150)**, which is subsequently trapped by an alcohol to furnish a carbamate **(151)** (scheme 34). [95, 96]



Scheme 34

More recently, Yamada et *al.* reported the synthesis of carbamates from carboxylic acids in a one pot transformation using diphenylphosphory azide (DPPA).[97] This route was synthetically more appealing and this transformation was investigated using compound **(146)** (scheme 35).[98-101] Initially, carboxylic acid **(146)** was dissolved in 1,2-dichloroethane and treated with Hünig's base followed by addition of DPPA. The reaction mixture was then heated to reflux for 20 min, ethanol added and further refluxed for five hours. Unfortunately, the desired carbamate was only isolated in very low yields since purification proved problematic. Since monitoring by TLC was difficult, infra-red (IR) spectroscopy was used to observe the formation and disappearance of the C-N acyl azide **(152)** stretch (2130 cm^{-1}). Gratifyingly, after two hours in refluxing 1,2-dichloroethane complete disappearance of the acyl azide peak was observed with formation of an isocyanate peak **(153)**. At this point solvent was removed in *vacuo* to leave the crude isocyanate **(153)** which was then dissolved in ethanol and the resultant mixture heated to reflux for 3.5 days to afford the desired carbamate **(154)** in 77% isolated yield. Duggan *et al.* reported the formation of carbamates from isocyanates under mild reaction conditions by using copper salts to accelerate this transformation.[102] However, employing two equivalents of copper (II) chloride with ethanol

at ambient temperature for 16 hours resulted in the formation of carbamate **(154)** in a lower overall yield (50% at best).



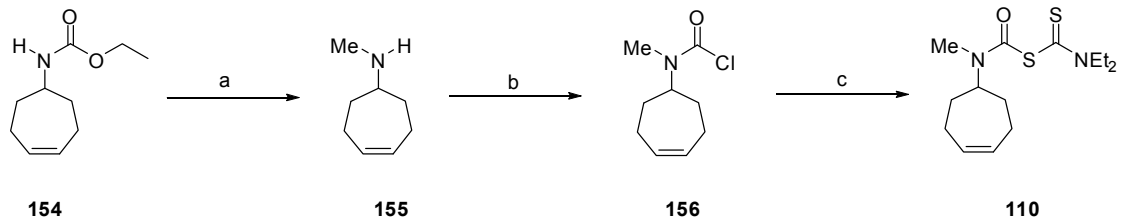
146 **152** **153** **154**

Scheme 35

Reagents & conditions: a) DIPEA (2 eq), DPPA (2 eq), 1,2-DCE, reflux, 2 h; b) EtOH, rt, 3.5 d, 77%.

Chemoselective reduction of carbamate **(154)** with excess lithium aluminium hydride in refluxing diethyl ether furnished the volatile amine **(155)**. Treatment of amine **(155)** with sub-stoichiometric amounts of triphosgene and a slight excess of pyridine under typical reaction conditions previously developed in the Grainger group[88] yielded the crude carbamoyl chloride **(156)**, which was used directly in the next synthetic step without further purification. Subsequent displacement of carbamoyl chloride **(156)** with sodium diethyldithiocarbamate trihydrate provided the desired cyclisation precursor, carbamoyl dithiocarbamate **(110)** in less than 30% isolated yield over two steps. Careful analysis of the reaction progress by TLC showed amine **(155)** was only partially consumed to carbamoyl chloride **(156)**, and also the subsequent displacement reaction of **(156)** with sodium diethyldithiocarbamate trihydrate resulted in incomplete consumption of the carbamoyl chloride species. These intriguing observations suggest intermediates **(155)** and **(156)** are not as reactive as typical amines and carbamoyl chlorides previously studied in the Grainger group. On that basis, the standard conditions employed by the Grainger group had to be modified in order to optimise this particular synthetic sequence. After careful optimisation of the reaction conditions, the cyclisation precursor **(110)** was obtained in a

modest 63% over two steps. This was achieved by treatment of amine **(155)** with sub-stoichiometric amounts of triphosgene and slight excess of pyridine in refluxing THF. After 16 hours, amine **(155)** was completely consumed and the crude carbamoyl chloride **(156)** was then treated with sodium diethyldithiocarbamate trihydrate in refluxing acetone overnight to furnish the desired carbamoyl dithiocarbamate **(110)** in 63% isolated yield over two steps (scheme 36).



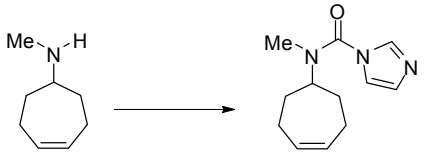
154 **155** **156** **110**

Scheme 36

Reagents & conditions: a) $LiAlH_4$, Et_2O, reflux, 4 h, quant; b) triphosgene (0.33 eq), pyridine (1.5 eq), THF, reflux, 16 h; c) sodium diethyldithiocarbamate trihydrate (4 eq), acetone, 16 h, 63% over two steps.

Route to cyclisation precursor *via* imidazolide

Given the modest yield of carbamoyl dithiocarbamate **(110)** achieved, an alternative route to the cyclisation precursor was considered. Batey *et al*. reported that carbamoyl imidazolium salts can be used as useful alternatives to carbamoyl chlorides.[103] Initial treatment of amine **(155)** with slight excess of carbonyldiimidazole (CDI) in dichloromethane failed to produce any imidazolide **(20)** (table 1, entry 1). The use of a basic catalyst also proved unsuccessful. However, the use of two equivalents of CDI and potassium carbonate in refluxing dichloromethane provided the desired imadazolide **(157)** in 55% yield after column chromatography (table 1, entry 2). The optimal conditions for this conversion required a large excess of CDI and potassium carbonate in a higher boiling solvent, THF, to provide imidazolide **(157)** in 80% yield (table 1, entry 5).

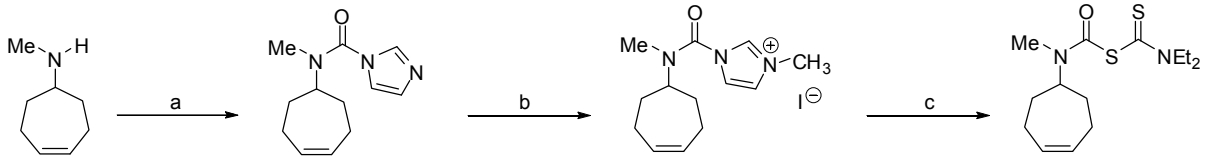


155 **157**

Entry	Reagents	Temperature	Time (h)	Yield (%)
1	CDI (1.1 eq), DCM	Rt	16	No reaction
2	CDI (1.1 eq), DMAP (10%), DCM	Rt	16	No reaction
3	CDI (2 eq), K_2CO_3 (2 eq), DCM	Reflux	16	55
4	CDI (2 eq), THF	Reflux	16	61
5	CDI (5 eq), K_2CO_3 (5 eq) THF	Reflux	16	80

Table 1: conversion of amine **(155)** to imidazolide **(157)**

Imidazolide **(157)** was activated with a large excess of iodomethane to provide imidazolium salt **(158)**. Subsequent treatment with sodium diethyldithiocarbamate in refluxing acetone furnished the cyclisation precursor, carbamoyl dithiocarbamate **(110)** in 75% isolated yield (scheme 36).



155 157 158 110

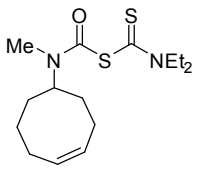
Scheme 36

Reagents & conditions: a) CDI (5 eq), K_2CO_3 (5 eq), THF, reflux, 16 h, 80%; b) MeI (50 eq), 85%; c) sodium diethyldithiocarbamate trihydrate (2 eq), acetone, reflux, 5 h, 75%.

Disappointingly, this alternative approach to the cyclisation precursor **(110)** *via* the imidazolium salt **(158)** was lower yielding (51%), 12% lower than the initial approach *via* the carbamoyl chloride. Therefore on that basis, cyclisation precursor **(110)** would be synthesised *via* carbamoyl chloride **(156)**.

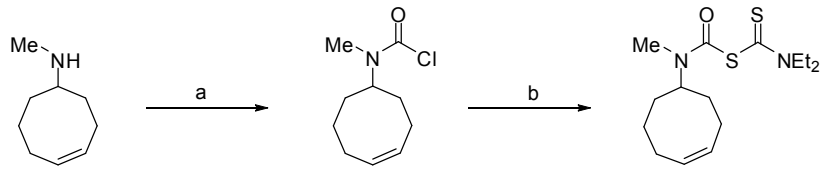
Synthesis of an eight-membered ring cyclisation precursor

During the synthesis of the cyclisation precursor **(110)** *en route* to the natural products *ferruginine* and *ferrugine*, it was decided to broaden the investigation of the photocyclisation-group transfer reaction by increasing the size of the ring system. This required synthesis of a new cyclisation precursor **(159)**, an eight-membered ring system with the potential to provide a mixture of regio-and stereoisomers from carbamoyl radical cyclisation-dithiocarbamate group transfer.



159

Synthesis of carbamoyl dithiocarbamate cyclisation precursor **(159)** began with amine **(160)**, synthesised according to literature procedures.[104] Treatment of amine **(160)** with sub-stoichiometric amounts of triphosgene and excess of pyridine afforded carbamoyl chloride **(161)**, which was used in the next step without further purification. Subsequent displacement of chloride with sodium diethyldithiocarbamate trihydrate provided the prerequisite cyclisation precursor **(159)** in moderate yield (scheme 37).



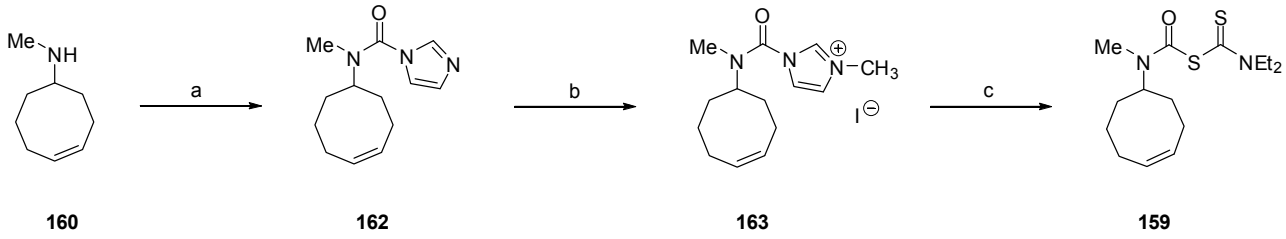
160 **161** **159**

Scheme 37

Reagents & conditions: a) triphosgene (0.33 eq), pyridine (1.5 eq), toluene, rt, 1 h; b) sodium diethyldithiocarbamate trihydrate (4 eq), acetone, rt, 16 h 39% over two steps.

The poor reaction yields once again prompted us to consider a substitute to carbamoyl chlorides, and as before, the use of carbonyldiimidazole (CDI) species was examined.[103] Amine **(160)** was therefore submitted to the optimum reaction conditions for the preparation of carbamoyl dithiocarbamate cyclisation precursor **(159)**, which furnished the desired imidazolide **(162)** in 75% isolated yield. Activation of imidazolide **(162)** with excess iodomethane furnished the imidazolium salt **(163)** in excellent yield, and subsequent displacement with sodium diethyldithiocarbamate in refluxing acetone provided the required cyclisation precursor **(159)** in 68% yield after column chromatography (scheme 38). The overall yield for this transformation was a moderate 50% over three steps, an improvement of 11% over the previous carbamoyl

chloride route. Therefore, for the purpose of this study, the alternative imidazolium approach was adopted for the synthesis of carbamoyl dithiocarbamate **(159)**.



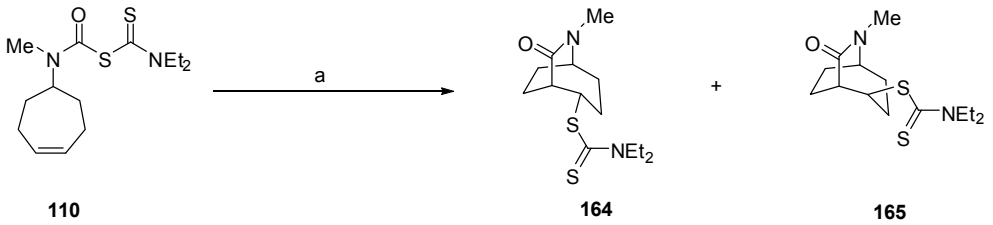
160 **162** **163** **159**

Scheme 38

Reagents & conditions: a) CDI (5 eq), K_2CO_3 (5 eq), THF, reflux, 16 h, 75%; b) MeI (50 eq), 97%; c) sodium diethyldithiocarbamate trihydrate (2 eq), acetone, reflux, 16 h, 68%, (50% from amine **160**).

Carbamoyl radical cyclisation

Having established a route to the cyclisation precursors **(110)** and **(159)**, photocyclisations were attempted. Irradiation of a solution of carbamoyl dithiocarbamate **(110)** in cyclohexane with a 500 W halogen lamp[88] (which generated enough heat to bring the mixture to reflux) afforded the desired cyclised dithiocarbamates **(164)** and **(165)** in 64% and 10% isolated yields, respectively (scheme 39). The relative stereochemistry of the major diastereomer **(164)** was confirmed by X-Ray crystallography (fig 5).[105]



110 164 165

Scheme 39

Reagents & conditions: a) 500 W halogen lamp, cyclohexane, reflux, 5 h, **(164)** 64% and **(165)** 10%.

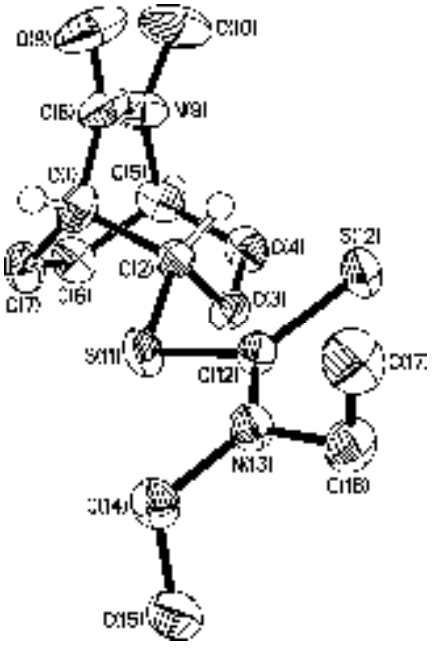
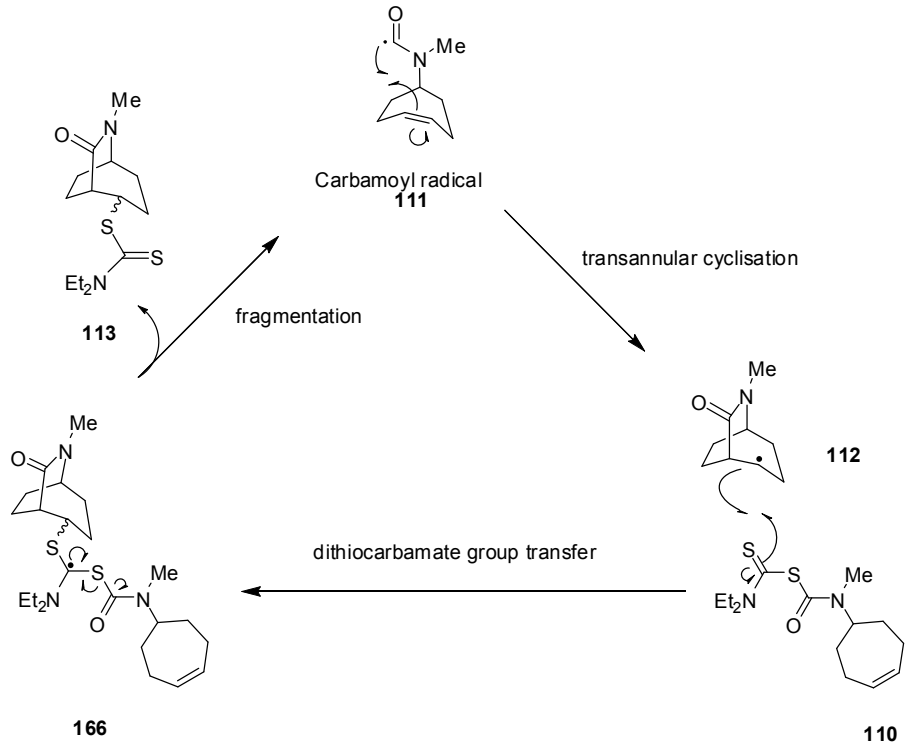


Fig 5: X-Ray crystal structure of major diastereomer **(164)** (30% probability ellipsoids)

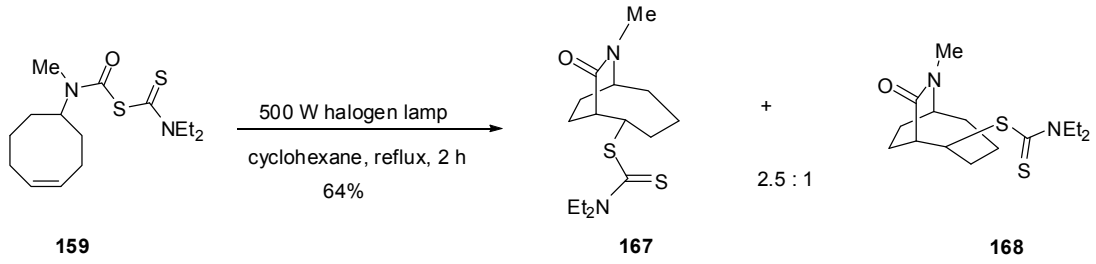
Irradiation of the carbamoyl diethyldithiocarbamate **(110)** using the halogen lamp homolytically cleaves the carbon-sulfur bond to generate carbamoyl radical **(111)** which undergoes a transannular cyclisation onto the pendant alkene, to generate a new carbon-centred radical **(112)**. The newly formed species is functionalised by a group transfer of the dithiocarbamate **(110)**, to furnish a tertiary radical **(166)**, which fragments to provide the dithiocarbamate diastereomers

(113), and in turn regenerates the carbamoyl radical **(111)** to continue the chain process (scheme 40).



Scheme 40

In similar fashion, irradiation of a solution of carbamoyl diethydithiocarbamate **(159)** in cyclohexane with a 500 W halogen lamp proceeded to provide diastereomers **(167)** and **(168)** in 46% and 18% yields respectively (scheme 41).



Scheme 41

This particular transannular cyclisation was highly regioselective but only moderately stereoselective. X-Ray crystallographic analysis on the minor diastereomer **(168)** confirmed the regio- and stereochemistry, which also shows the dithiocarbamate group on the same side as the amide junction (fig 6). This can be attributed to the preferential formation a six-membered rings, which occurs at a much faster rate than seven- membered ring formation. Cyclisation to form larger ring sizes usually results in poor orbital overlap and increased ring strain.

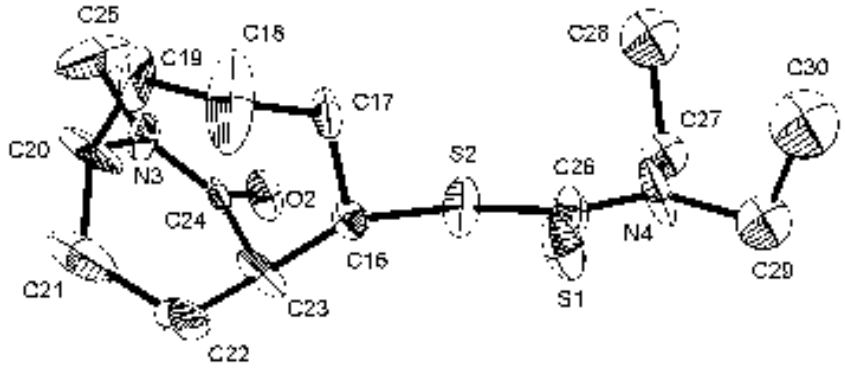
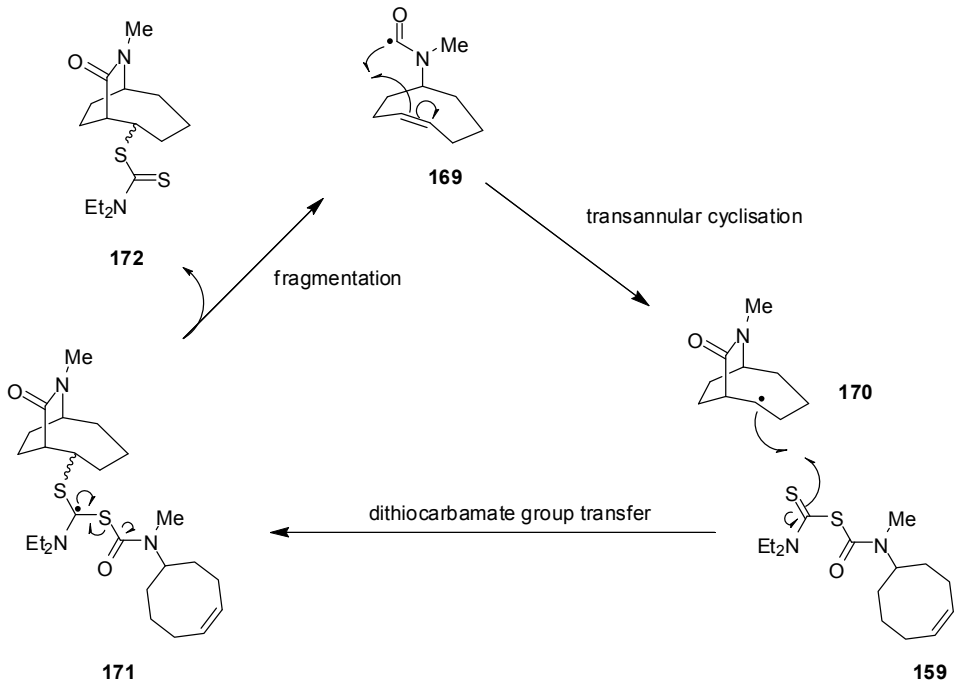


Fig 6: X-Ray crystal structure of minor diastereomer **(168)** (30% probability ellipsoids)

Irradiation of a solution of carbamoyl dithiocarbamate **(159)** generated carbamoyl radical **(169)** which cyclised onto the alkene to generate a secondary radical **(170)**. Radical **(170)** was further functionalised and captured by dithiocarbamate group transfer to form a tertiary radical **(171)**. Fragmentation of radical **(171)** proceeded to provide the diastereomers **(172)**, which also regenerated the carbamoyl radical **(169)** to continue the chain process (scheme 42).



Scheme 42

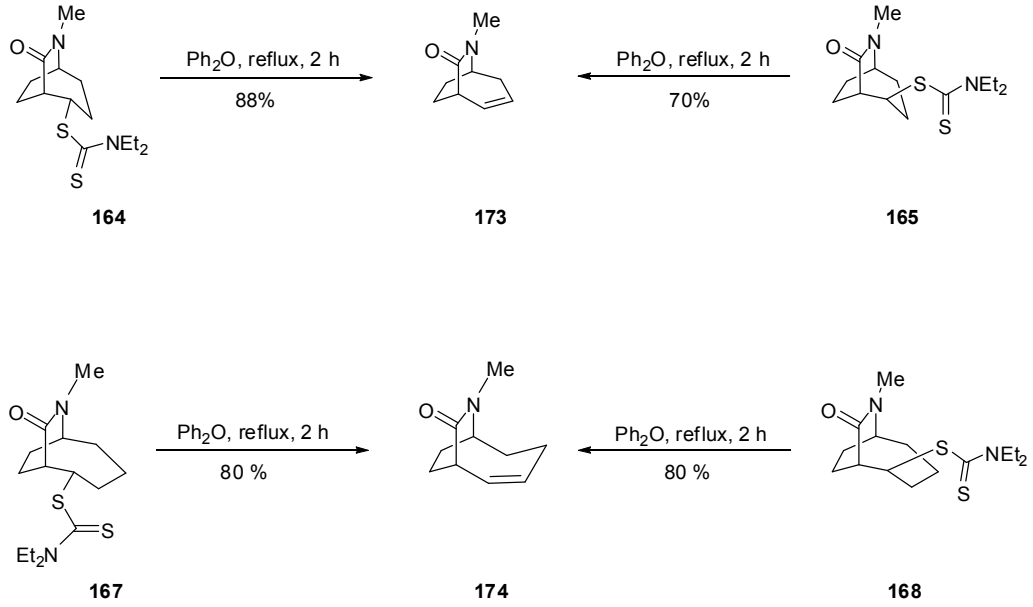
Thermal elimination of dithiocarbamates

Previously in the group, thermal elimination of dithiocarbamate groups were carried out by refluxing a solution of dithiocarbamates in diphenyl ether (bp 259 °C).[61, 88] Therefore, in a similar fashion, a solution of dithiocarbamate **(164)** in diphenyl ether was heated at reflux for 2 hours to provide the bicyclic alkene **(173)** in 88% yield after column chromatography.

Upon completion of the reaction, the mixture was allowed to cool to room temperature and subjected directly to column chromatography. The non-polar diphenyl ether was firstly removed by eluting with petrol, before increasing the polarity of the eluent system (petrol/EtOAc) to afford the desired alkene **(173)**. Similarly, thermal elimination of dithiocarbamate **(165)** also proceeded smoothly to afford alkene **(173)** in 70% isolated yield after purification. Once the individual yields were obtained from the thermal elimination reactions, a mixture of diastereomers **(164)**

and **(165)** (6:1) were subjected to thermal elimination conditions which converged to alkene **(173)** in 86% yield after column chromatography.

Thermal elimination of dithiocarbamate groups of diastereomers **(167)** and **(168)** in refluxing diphenyl ether resulted in alkene **(174)** in an identical 80% yield. The structure of **(174)** was elucidated by X-Ray crystallographic analysis (fig 7), and also confirms the regio-and stereochemical assignment of major diastereoisomer **(167)**. Also a mixture of diastereomers (2.5:1), in refluxing diphenyl ether converged to alkene **(174)** in 73% isolated yield after purification (scheme 43).



Scheme 43

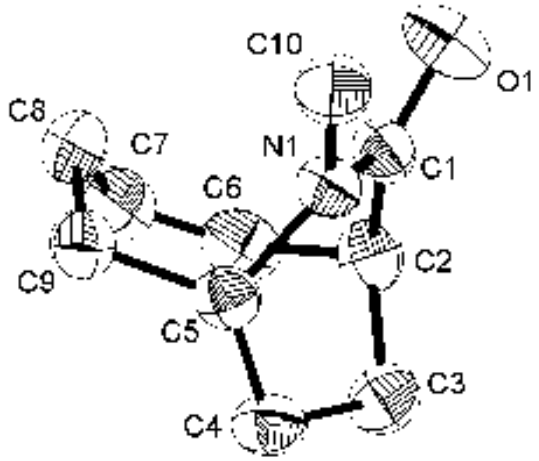


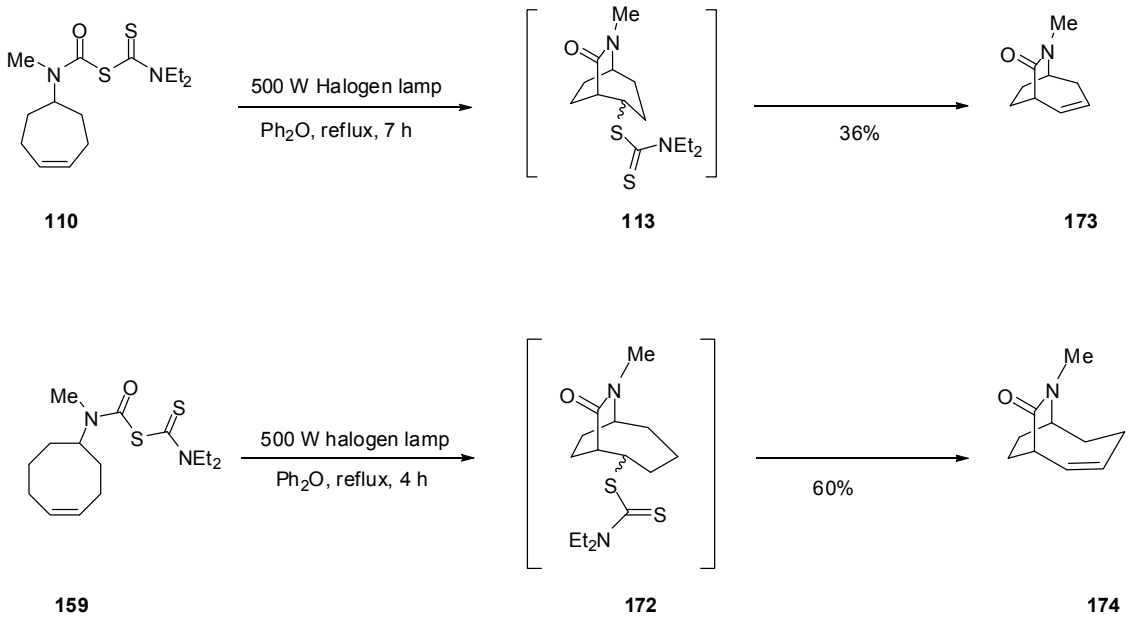
Fig 7: X-Ray crystal structure of alkene **(174)** from thermal elimination (30% probability ellipsoids)

Tandem carbamoyl radical cyclisation-thermal elimination

The possibility of achieving a tandem carbamoyl radical cyclisation- thermal elimination pathway to obtain the bicyclic alkene **(173)** was investigated. This could be achieved by irradiating a solution of cyclisation precursor in diphenyl ether with a 500 W halogen lamp. The anticipated thermal elimination of dithiocarbamate group should proceed after radical cyclisation has occurred to furnish the required alkene species. This was conditional on the 500 W halogen lamps generating enough heat to bring the high boiling diphenyl ether to reflux, which was indeed the case. The reaction progress was carefully monitored by TLC, and was completed after seven hours. Purification by column chromatography proved slightly more difficult than before as unwanted byproducts from the carbamoyl radical cyclisation reaction were carried through. However, the desired alkene **(173)** was ultimately obtained in a relatively poor isolated yield of 36% after column chromatography. Equally, the tandem carbamoyl radical cyclisation- thermal elimination reaction was carried out on the eight-membered cyclisation precursor **(159)** in

refluxing diphenyl ether, which proceeded smoothly in four hours to deliver alkene **(174)** in a much better 60% isolated yield after column chromatography (scheme 44).

Overall, this one pot transformation to obtain alkene **(173)** from cyclisation precursors **(110)** proved less efficient, with a lower overall yield of 36% compared with 64% from two steps, a decrease of 27%. However, the overall yield for alkene **(174)** from cyclisation precursor **(159)** was higher at 60%, an increase of 9% from 51% over the two step sequence.

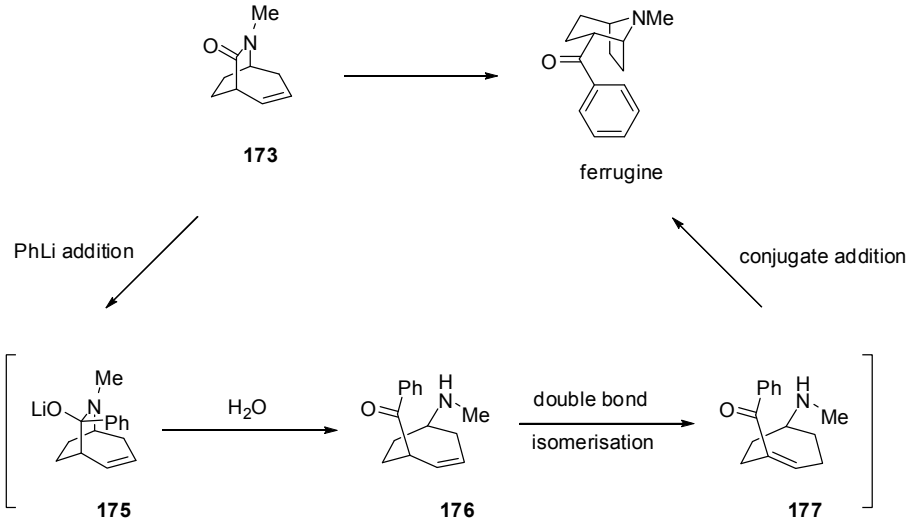


Scheme 44

Completion of the synthesis of *ferrugine*

The synthesis of *ferrugine* was completed through treatment of 6-azabicyclo[3.2.2]non-2-ene **(173)** using a large excess of phenyllithium followed by quenching with an aqueous solution of sodium hydroxide. This directly led to the formation of the 8-azabicyclo[3.2.1] octane ring system, *ferrugine*, as a single diastereomer, in a one-pot, multistep transformation, with no byproducts being observed from the over addition of phenyllithium. This conversion is believed

to occur through an initial nucleophilc attack of phenyllithium onto the amide which presumably led to hemiaminal **(175)**, which upon aqueous work-up liberated the intermediate amino ketone **(176)**. Treatment of amino ketone **(176)** with 5% sodium hydroxide shifted the double bond into conjugation with the phenyl ketone to give **(177)**, and finally an intramolecular conjugate addition proceeded to furnish the tropane alkaloid *ferrugine* (scheme 45), whose structure and relative stereochemistry was confirmed by X-Ray crystallography of the corresponding perchlorate salt (fig 8).[106] Initial comparison with literature data showed discrepancies in ^{1}H NMR chemical shift values, which suggested the incorrect relative stereochemistry was obtained.[6, 7] This inconsistency with literature values prompted the growth of the corresponding perchlorate crystal to be unambiguously assigned by X-Ray analysis.



Scheme 45

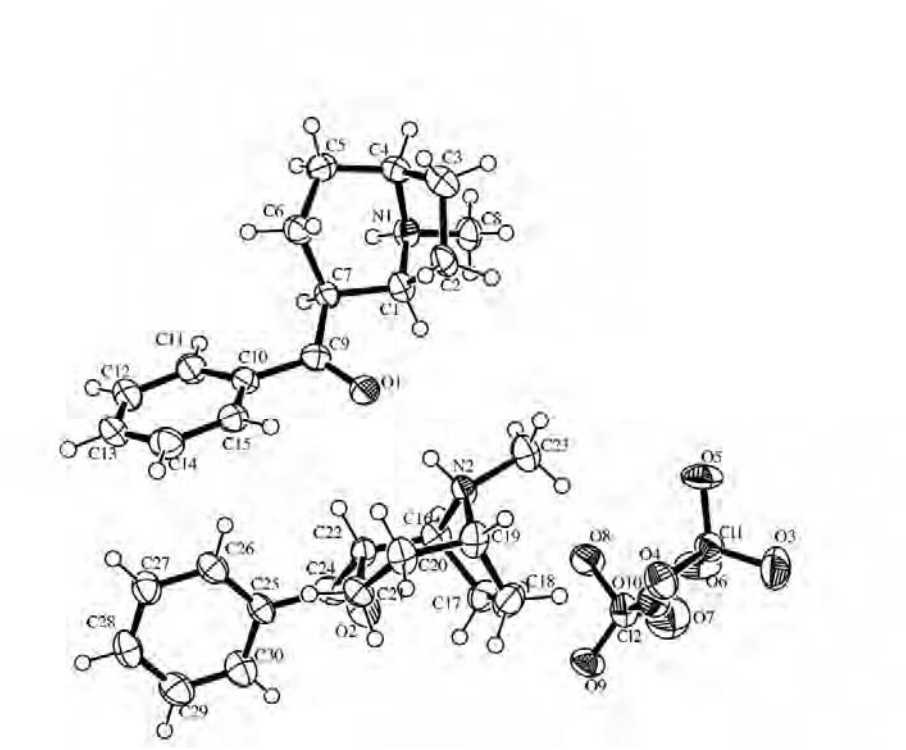
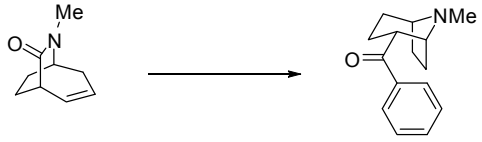


Fig 8: X-Ray of *ferrugine perchlorate salt* (30% probability ellipsoids)

Initially, this multistep transformation was attempted using a combination of phenyllithium and phenylmagnesium chloride with a Lewis acid, cerium chloride.[107, 108] It was hoped that activation of the amide ring with cerium chloride would lead to a successful phenyl addition to the bicyclic amide junction. However, this combination proved ineffective with starting material being recovered on each occasion (table 2, entries 1-4). Attention then turned to adding a large excess of phenyllithium and phenylmagnesium chloride to a solution of amide **(173)** in THF. Unfortunately even with up to 5 eq of both reagents, the reaction was again unsuccessful with the starting material being recovered (table 2, entries 5-6). Only when 10 eq of phenyllithium was added drop-wise to a solution of amide **(173)** in THF at 0 °C resulted in the disappearance of amide **(173)** by TLC after 1 hour. This was an encouraging indication of phenyl group insertion onto the amide **(173)**. At this point, the reaction mixture was quenched with water and

immediately basified with an aqueous solution of sodium hydroxide until a pH of 14 was reached. The resultant mixture was stirred overnight at room temperature to deliver the tropane alkaloid natural product, *ferrugine*. Purification proved slightly difficult at first due to the polar nature of the amine. To alleviate this problem, purification was carried out on basified neutral alumina which resulted in a 66% isolated yield (table 2, entry 8).[106]



173 ferrugine

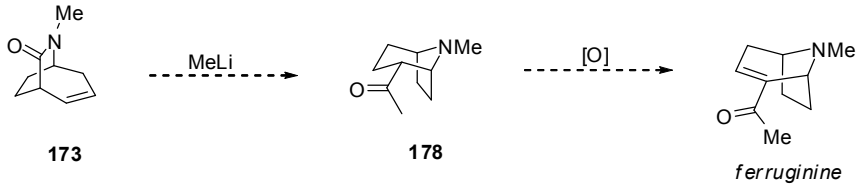
Entry	Reagents	Temperature	Time (h)	Yield (%)
1	PhLi/$CeCl_3$ (1.5 eq), THF	0 °C to reflux	16	No reaction
2	PhMgCl/$CeCl_3$ (1.5 eq), THF	0 °C to reflux	16	No reaction
3	PhLi/$CeCl_3$ (2 eq), THF	0 °C to reflux	16	No reaction
4	PhMgCl/$CeCl_3$ (2 eq), THF	0 °C to reflux	16	No reaction
5	PhLi (5 eq), THF	0 °C to rt	16	No reaction
6	PhMgCl (5 eq), THF	0 °C to rt	16	No reaction
7	PhMgCl (10 eq), THF	0 °C to rt	16	No reaction
8	PhLi (10 eq), THF, then H_2O, NaOH (5%)	0 °C to rt	16	66

Table 2: attempted conversion of **173** to *ferrugine*

Attempted synthesis of *ferruginine*

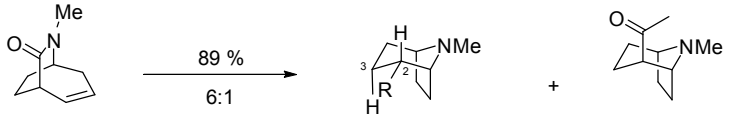
Having successfully completed the synthesis of *ferrugine*, attention turned to the related natural product, *ferruginine*. Preparation of the tropane framework **(178)** of *ferruginine* was envisaged from amide **(173)** *via* the already established one pot multistep sequence using methyllithium in

place of phenyllithium.[106] Finally, completion of the synthesis would require an oxidation step to introduce the conjugated enone system found in the natural product (scheme 46).



Scheme 46

Amide **(173)** was treated with methyllithium at 0 °C as the synthesis of the tropane alkaloid skeleton **(178)** was carefully monitored by TLC which showed complete consumption of starting amide **(173)** after one hour. The reaction mixture was subsequently quenched with water and basified with aqueous sodium hydroxide. The resultant mixture was slowly warmed to room temperature and stirred for six hours to furnish a 6:1 mixture of stereoisomers **(178)** and **(179)**, separable by column chromatography in combined 89% yield (scheme 47).[106] This transformation presumably occurs *via* a similar mechanistic pathway described earlier (scheme 14). Stereochemical assignment of the major isomer was confirmed by the ^{1}H NMR coupling constant between the di-axial hydrogens of C2 and C3 in **(178)** of 11 Hz, which is in the typical range for an axial-axial coupling constant (9-13 Hz). Unfortunately, the minor isomer **(179)** could not be isolated in a pure form, with impurities observed in the ^{1}H NMR spectrum. However, upon treatment with aqueous sodium hydroxide, the minor stereoisomer **(179)** epimerised to the original 6:1 mixture, thus indicating a clear thermodynamic preference for stereoisomer **(178)**.



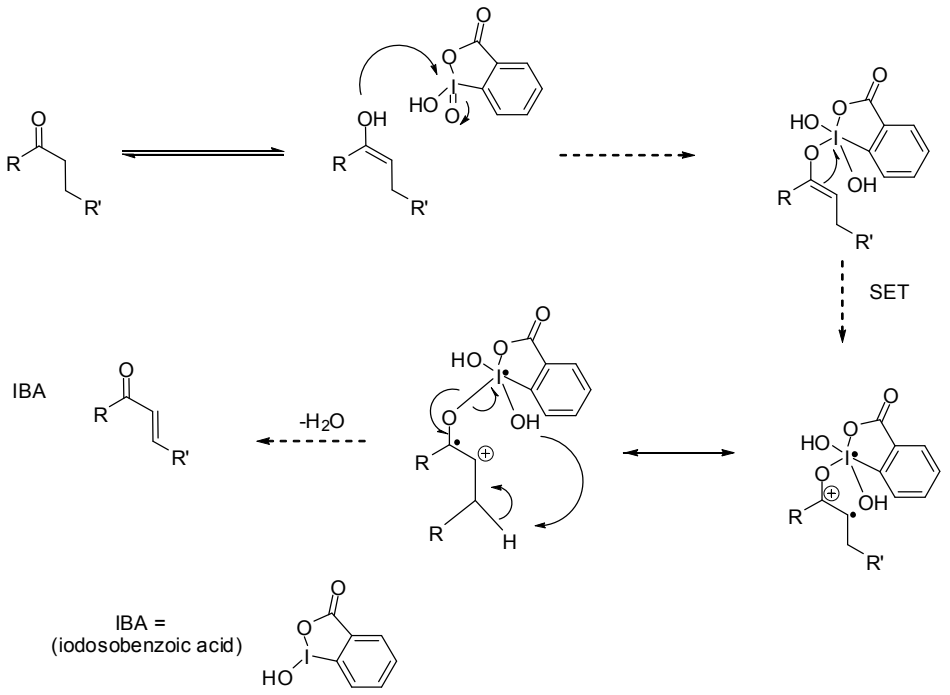
173 **178 R= COMe** **179**

Scheme 47

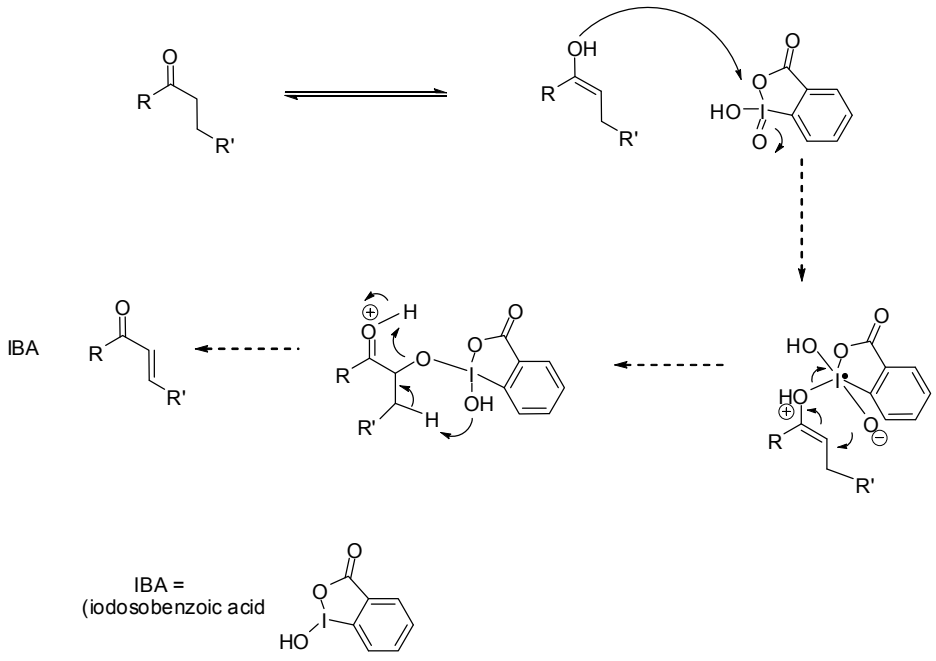
Reagents & conditions: MeLi (2 eq) THF, 0 °C, 1 h; then H_2O, aq NaOH (5%), 6 h, rt.

The synthesis of an α,β-unsaturated carbonyl moiety from a carbonyl compound is often a challenging transformation. Traditionally this particular transformation relies heavily upon one of the following two methods; 1) the palladium catalysed oxidation of a silyl enol ether,[109] or 2) treatment of carbonyl compounds with highly toxic selenium reagents such as PhSeCl followed by oxidation and spontaneous elimination of the corresponding sulfoxide to deliver α,β-unsaturated carbonyl systems.[110]

Nicolaou and co-workers have reported the use of non-toxic hypervalent iodine (V) complexes to produce α,β-unsaturated carbonyl systems in a one step conversion, without the need for prior silyl enol ether formation.[111] The use of iodosobenzoic acid (IBX) has been reported to promote the oxidation of alcohols into carbonyls, and further oxidation results in α,β-unsaturated system.[112] IBX is also used for the oxidation of secondary amines and hydroxylamines to produce imines and oximes respectively,[113] and also in the oxidation of benzylic carbon atoms under mild conditions with DMSO as a solvent.[111] Complexation of IBX with ligands such as *N*-oxides, in particular MPO,[114] can dramatically affect the reaction profile, and is heavily used. The hypothesised mode of action involving IBX proceeds *via* a single electron transfer mechanism (scheme 48) as opposed to an ionic process (scheme 49).[111]

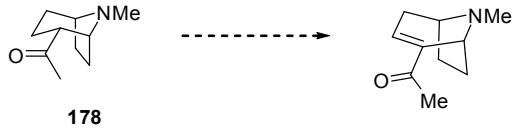


Scheme 48



Scheme 49

Although this was encouraging precedent for the one-pot transformation of ketones into α,β-unsaturated carbonyl motifs, there is only one report of such an oxidation occurring in a molecule containing a nitrogen atom.[115] With this in mind, tropane alkaloid skeleton **(178)** was treated with a pre-complexed mixture of IBX and MPO in DMSO at room temperature (table 3, entry 1). Unfortunately, even after seven days at room temperature, this failed to yield any of the desired α,β-unsaturated ketone, *ferruginine*. Pre-complexation of IBX and NMO were also attempted but once again failed to deliver the natural product (table 3, entry 2). Due to the lack of reactivity at room temperature, reactions were then performed at elevated temperatures ranging from 50 °C to 80 °C. Once again, these reactions failed to deliver the desired compound (table 3, entries 3 and 4), whereas using excess NMO or MPO at 80 °C to force reactivity only led to decomposition (table 3, entries 5 and 6).

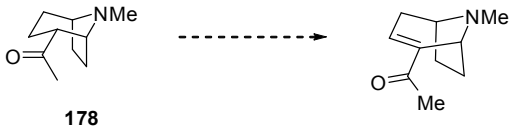


178 *ferruginine*

Entry	Reagents	Solvent	Conditions	Outcome
1	2.4 equiv IBX/MPO	DMSO (0.6M)	r.t up to 7 d	No reaction
2	2.4 equiv IBX/NMO	DMSO (0.6 M)	r.t up to 7 d	No reaction
3	2.4 equiv IBX/MPO	DMSO (0.6M)	50 °C 2 d to 60 °C 2 d	No reaction
4	2.4 equiv IBX/NMO	DMSO (0.6M)	50° C 2 d to 60 °C 2 d.	No reaction
5	4.8 equiv IBX/MPO	DMSO (0.6M)	80 °C 6 h	decomposition
6	4.8 equiv IBX/MPO	DMSO (0.6M)	80 °C 6 h	decomposition

Table 3: attempted oxidation of ketone **(178)**

With very little to no reaction at all, it was then decided to try a slightly different approach by protecting the nitrogen lone pair as this might be hindering the reaction. Investigation began with *in situ* amine protection using sub-stoichiometric amounts of acetic acid followed by treatment with IBX pre-complexed with MPO or NMO. Disappointingly, this approach also proved unsuccessful following similar reactivity trends as before, with up to 4.8 equivalents of reagents at 80 °C led to decomposition (table 4, entries 1-5). The free amine was also protected *in situ* with boron trifluoroetherate and subjected to the usual reaction conditions, which again failed to provide the natural product (table 4, entries 6 and 7).



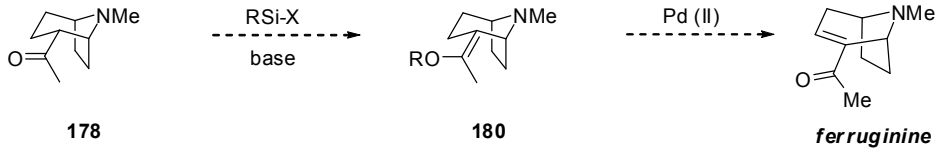
178 *ferruginine*

Entry	Reagents	Solvent	Conditions	Outcome
1	2.4 equiv IBX/ AcOH (10 mol%)	DMSO (0.6M)	r.t 7 d	No reaction
2	2.4 equiv IBX/ AcOH (10 mol%)	DMSO (0.6M)	50 °C 2 d to 60 °C 2 d	No reaction
3	4.8 equiv IBX, AcOH (10 mol%)	DMSO (0.6M)	80 °C 6 h	decomposition
4	2.4 equiv IBX/ MPO, AcOH (10 mol%)	DMSO (0.6M)	r.t to 60 °C	No reaction
5	2.4 equiv IBX/NMO, AcOH (10 mol%)	DMSO (0.6M)	r.t to 60 °C	No reaction
6	2.4 equiv IBX/ MPO, BF_3.OEt	DMSO (0.6M)	rt to 60 °C, 2 d	No reaction-decomposition
7	2.4 equiv IBX/NMO, BF_3.OEt	DMSO (0.6M)	rt to 60 °C, 2 d	No reaction-decomposition

Table 4: attempted oxidation of ketone **(178)**

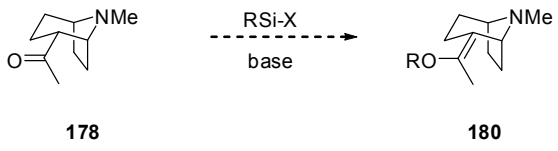
Having exhausted all possible methods for this one pot transformation to form the desired α,β-unsaturated ketone, attention then turned to the traditional two-step procedure.

Investigation began with the intention of functionalising the tropane alkaloid skeleton **(178)** by formation of a silyl enol ether **(180)**,[116-123] which upon palladium mediated oxidation would result in *ferruginine* (scheme 50).



Scheme 50

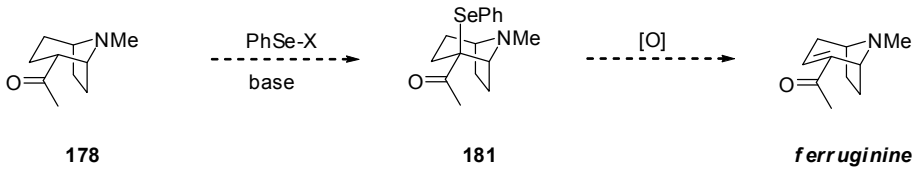
Treatment of tropane alkaloid **(178)** with trimethylsilyl chloride (TMSCl) and triethylamine in DMF, classical conditions for the formation of thermodynamic silyl enol ethers, gave no reaction at ambient temperatures, and complete decomposition of starting material upon raising the temperature slowly up to 100 °C (table 5, entry 1).[123] The use of slight excess of alkaloid **(178)** with lithium diisopropylamine (LDA) and TMSCl resulted in the formation of multiple spots by TLC. Encouragingly, a new clean spot emerged by TLC from the use of excess LDA and TMSCl (table 5, entry 3). Disappointingly however, isolation proved tricky and spectroscopic data from the impure product indicated the incorrect silyl enol ether was formed (methylene protons were observed in the ^{1}H NMR spectrum). At this point with this particular outcome, further progress was halted.[116, 118-121] Variation of bases and silylating agents under various conditions also proved unsuccessful as the desired outcome was not achieved, mostly leading to multiple spots by TLC or complete decomposition of starting material (table 5, entries 4-8).[117, 122, 123]



Entry	Reagents	Solvent	Conditions	Outcome
1	Et_3N (2.5 eq), TMSCl (1.3 eq)	DMF	rt to 100 °C	Decomposition
2	LDA (0.9 eq), TMSCl (3 eq)	THF	-78 °C, 30 min to rt, 30 min	Multiple spots
3	LDA (2 eq), TMSCl (3 eq)	THF	-78 °C, 30 min to rt, 30 min	product not observed by ^1H NMR spectra
4	NaHMDS (2.5 eq), TMSI (2 eq)	DCM	-20 °C to rt, o/n	Multiple spots
5	TBDMSCl (3 eq), NaH (3 eq)	THF	rt, 7 h	Multiple spots
6	TBDMSCl (1.1 eq), NaHMDS (1.05 eq)	THF	-78 °C to rt, o/n	No product observed by ^1H NMR spectra
7	TBDMSCl (5.1 eq), NaH (5 eq)	THF	rt, o/n	Multiple spots
8	^tBuOK (1.5 eq), Me_2SO_4 (1.5 eq)	DMSO	rt, 2 h	Decomposition
9	^tBuOK (1.05-2.10 eq), allyl chloroformate (1.2-2.4 eq)	DMF	0 °C to 125 °C	No reaction to decomposition

Table 5: attempted enolisation of ketone **(178)**

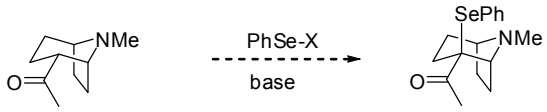
An alternative approach to this transformation is the use of highly toxic selenium reagents to give selenide **(181)**, which would be oxidised to selenoxide with *m*CPBA followed by a spontaneous elimination to furnish the natural product, *ferruginine* (scheme 51).[109, 124, 125]



178 **181** ***ferruginine***

Scheme 51

Treatment of alkaloid **(178)** with excess triethylamine and phenylselenium chloride in various solvents failed to deliver any encouraging results.[109, 124] This reaction proved unsuccessful due to the observed lack of reactivity to complete degradation (table 6, entries 1-3). Changing from phenylselenium chloride to phenylselenium bromide also proved unsuccessful with no reactivity observed in refluxing THF (table 6, entry 4).[125]

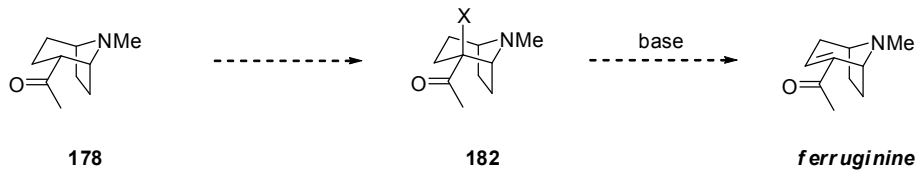


178 **181**

Entry	Reagents	Solvent	Conditions	Outcome
1	Et_3N (4 eq) PhSeCl (3 eq)	THF	rt to reflux, 2 d	No reaction
2	Et_3N (4 eq) PhSeCl (3 eq)	DMF	rt to reflux, 6 h	decomposition
3	Et_3N (4 eq) PhSeCl (3 eq)	EtOAc	reflux, 3 d	No reaction
4	Et_3N (2.5 eq), PhSeBr (1.2 eq)	THF	reflux, 2 d	No reaction

Table 6: attempted functionalisation of ketone **(178)**

A different strategy to form the required α,β-unsaturated system is *via* functionalisation of the tropane alkaloid **(178**) to incorporate a leaving group X adjacent to the ketone. This functionalised species **(182)** would then be subjected to base-promoted elimination to furnish the desired compound (scheme 52). Introduction of a halogen group α to the ketone was attempted by firstly treating **(178)** with thionyl chloride in carbon tetrachloride.[126] Unfortunately after two days at room temperature, there was no reaction and starting material was recovered (table 7, entry 1). Attempted bromination with molecular bromine was also unproductive with only starting material recovered (table 7, entries 2 and 3), while reactions with *N*-bromo-succinimide resulted in a complicated mixture and eventual decomposition of **(178)** (table 7, entries 4 and 5).[127]



178 **182** ***ferruginine***

Scheme 52

Entry	Reagents	Solvent	Conditions	Yield [%]
1	$SOCl_2$	CCl_4	rt, 2 d	No reaction
2	Br_2, AcOH	CCl_4	rt, 2 d	No reaction
3	Br_2, HBr, AcOH	$CHCl_3$	rt, o/n	No reaction
4	NBS (1.56 eq),	CCl_4	Reflux, 25 min	Multiple spots
5	NBS (1.56 eq), $PhCO_3H$ (30%)	CCl_4	70 °C, 2 h	decomposition

Table 7: attempted functionalisation of ketone **(178)**

Conclusion and future work

In summary, the synthesis of the tropane alkaloid *ferrugine* was accomplished in 7 steps from the known carboxylic acid **(146)** in 21% overall yield. The synthesis of *ferrugine* has demonstrated, and extended the synthetic utility of carbamoyl radical cyclisation-dithiocarbamate group transfer reactions. Carbamoyl radical cyclisation precursors **(110)** and **(159)** were synthesised in good yields *via* carbamoyl chloride and imidazolium salts, respectively. Carbamoyl radical cyclisation-group transfer proceeded with moderate selectivity to give diastereomers **(164)** and **(165)** which converged into bicyclic alkene **(173)** upon thermal elimination in diphenyl ether. Similarly irradiation of the eight-membered cyclisation precursor **(159)** resulted in the formation of diastereoisomers **(167)** and **(168)**, which also converged to a single bicyclic alkene **(174)**. Finally, an *in situ* multistep transformation of amide **(173)** with phenyllithium furnished *ferrugine*.

Unfortunately, efforts towards the synthesis of *ferruginine* from the tropane alkaloid skeleton **(178)** proved unsuccessful, as attempted oxidation to the α,β-unsaturated carbonyl system of the natural product using various reagents and conditions failed. The inability to functionalise

alkaloid **(178)** could be attributed to the exposed lone pair of the free amine having a detrimental outcome to the reaction progress.

Previous work toward the syntheses of *ferruginine* showed that the nitrogen lone pair remained fully protected as the Boc group throughout the synthesis, eliminating the possibility of unfavourable lone-pair interactions. Once the *ferruginine* framework has been accomplished (including the double bond), subsequent Boc deprotection and reductive methylation completed the synthesis. With the attempted synthesis of *ferruginine*, there may have been an alternative outcome had we protected the nitrogen lone pair as the Boc group earlier in the synthesis before attempting to install the α,β-unsaturated carbonyl motif, and hence, completing a formal synthesis.

4. *STEMOFOLINE*: BACKGROUND & SIGNIFICANCE

Stemona alkaloids

The extracts of several plants from the *stemonaceae* family are known as a rich source of structurally complex stemona alkaloids. Traditionally they have been used in Asian countries such as China, Japan and Thailand for treatment of respiratory diseases, antihelminits and also as domestic insecticides.[128] Currently there are around one hundred stemona alkaloids known in the literature of which around thirty have been fully elucidated by X-Ray crystallographic analyses, with the remainder analysed according to their spectroscopic data.[128] The complex structure of the stemona alkaloids consist of polycyclic saturated ring systems with a common pyrrolo[1,2-a]azepine core, with the majority consisting of at least one α-methyl-γ-butyralactone substructure attached to the azabicyclic unit. Due to their structural diversity and complexity, they have been recently classified into eight sub-categories and their basic skeletal structure along with the most representitive member of the stemona alkaloids are shown in figure 9.[129] The central pyrrolo[1,2-a]azepine core structure is present in the *stenine*, *stemoamide*, *tuberrostemopironine*, *stemonamine*, *parvistemoline* and *stemofoline* groups, while *stemocurtisine* contains the less common pyrrolo[1,2-a]azepine structure. The final group of the stemona alkaloids are categorised in the miscellaneous group, where the pyrrolo[1,2-a]azepine systems are hidden or completely lacking the azabicyclic constituent.

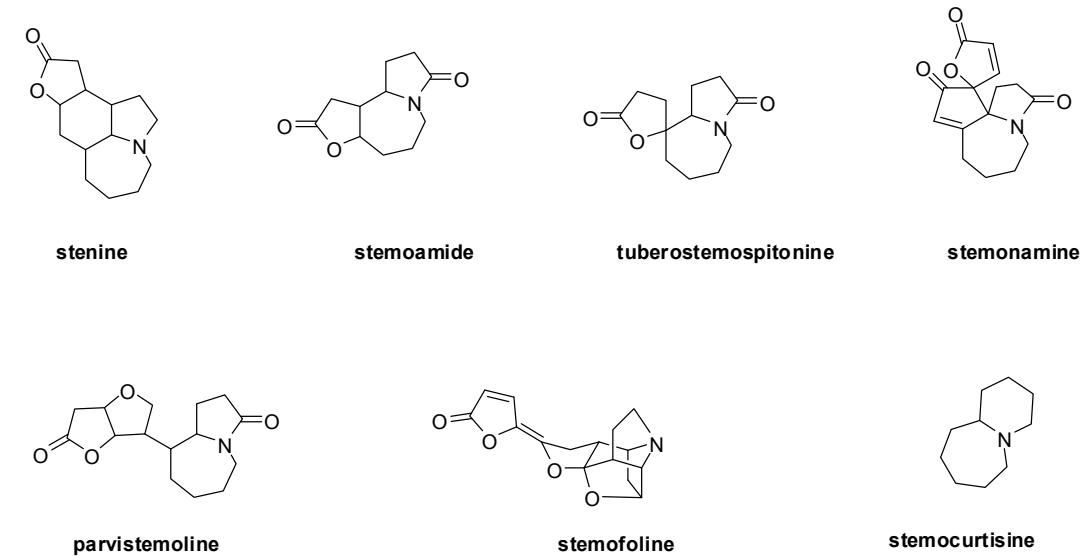


Fig 9

Due to their intricate molecular architecture coupled with their biological importance, the stemona alkaloids have attracted and motivated the synthetic community to develop novel

strategies for the construction of their molecular framework culminating in a number of completed total syntheses.[129-169]

***Stemofoline*: isolation and biological activity**

Stemofoline was isolated by Irie and co-workers from *stemona japonica*,[170] and its structure and absolute configuration was fully elucidated by X-Ray crystallography of its hydrobromide monohydrate which revealed a rigid pentacyclic core system along with α-methyl-γ-butyralactone substructure attached to the azabicyclic unit.[170] *Stemofoline* has shown insecticidal activity against *Plutella xylostella* larvae and against neonate larvae of *Spodopera litteralis*.[171] Additionally, *stemofoline* has antifeedant activity against the larvae of the diamondback moth, a vegetable crop pest.[172]

Owing to their captivating, rigid cage like structures and interesting biological activities, the structurally complex family of stemona alkaloids (fig 10) has attracted considerable synthetic interest over the last decade.[168, 169, 173-183] Kende *et al.* were the first group to report the synthesis of a member of this class of compounds, by achieving the total synthesis of *isostemofoline* in 1999.[168] Since then, Overman *et al.* have successfully reported the syntheses of *asparagamine* A (*didehydrostemofoline*) and its geometrical isomer *isodidehydrostemofoline*.[169]

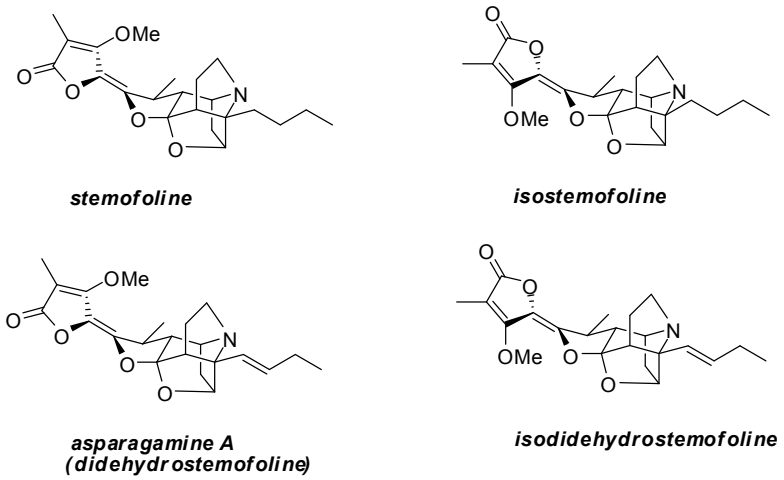


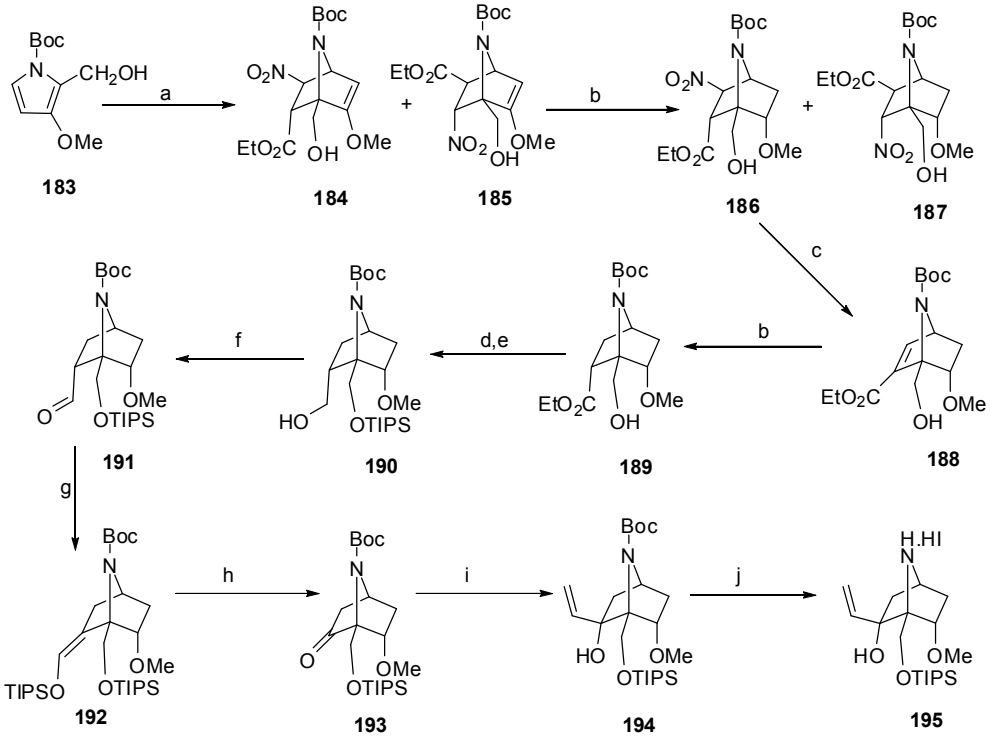
Fig 10

From hereon, the total syntheses and synthetic efforts toward this sub class of stemona alkaloids will discussed, outlining the key chemical transformations involved.

Overman's synthesis of *asparagamine* A.[169]

The synthesis of *asparagamine* A, isolated by Irie and co-workers from *S.collinase,*[170] began with a [4+2] Diels-Alder cycloaddition between the activated Boc-protected pyrrole **(183)** as the diene and ethyl *(E)*-3-nitroacrylate as the dienophile to deliver the regioisomeric adducts **(184)** and **(185)** in a 6:1 ratio (Scheme 52). Attempted purification of the cycloadducts on silica gel resulted in retro-Diels-Alder reaction back to starting materials; therefore the cycloadducts were directly subjected to an *exo*-face Pd/C-catalysed hydrogenation which resulted in the azabicycloheptanes **(186)** and **(187)**. The nitro group of the dienophile, which was crucial in facilitating the cycloaddition by minimising the energy levels of the HOMO and LUMO of the diene and the dienophile, respectivley, was subsequently eliminated from the major cycloadduct **(186)** by treatment with DBU to provide an α,β-unsaturated ester **(188)**. Hydrogenation from the less-hindered face yielded the axial ethyl ester **(189)**. Silylation of the primary alcohol using TIPSOTf followed by DIBALH reduction of the ester furnished alcohol **(190)**. Oxidation to the aldehyde

(191), formation of the enolsilane, and ozonolysis gave ketone **(193)**. Stereoselective addition of vinyl Grignard to the top face of the ketone using Luche conditions gave allylic alcohol **(194)**. Chemoselective deprotection of the Boc group upon treatment with TMSI provided the ammonium hydroiodide salt **(195)**, required for the crucial transformation in obtaining the core structure of stemona alkaloids.

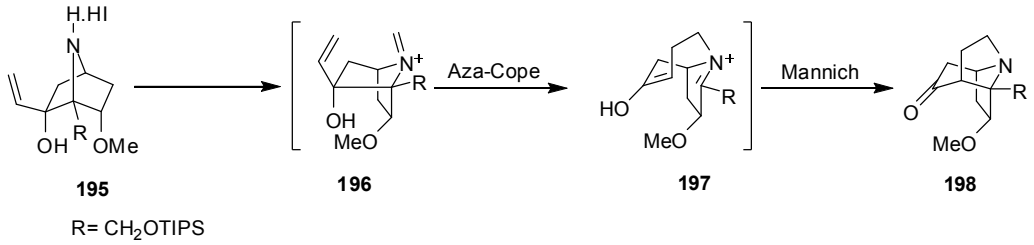


Scheme 52

Reagents & conditions: (a) (*E*)-$O_2NCHCHCO_2Et$, rt; (b) H_2, Pd/C, EtOAc, rt, **(8)**, 73% & **(9)**, 13%; (c) DBU, CH_2Cl_2, rt; (d) TIPSOTf, 2,6-lutidine, CH_2Cl_2, rt; (e) DIBALH, MePh, -78 °C, 51% (f) DMP, CH_2Cl_2, rt; (g) TIPSOTf, Et_3N, CH_2Cl_2, -78 °C; (h) O_3, MeOH, CH_2Cl_2, -78 °C; 72%; (i) $CH_2CHMgBr$, $CeCl_3$, THF, -78 °C; (j) TMSI, 2,6-lutidine, 0 °C- rt, MeOH; 85%.

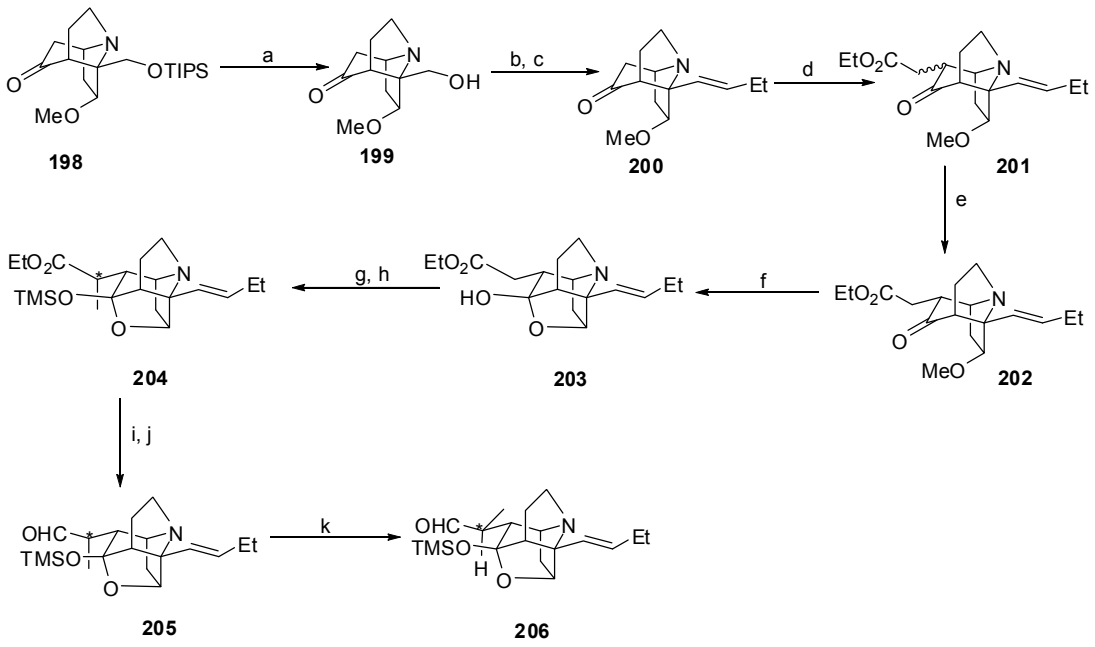
The key step in the synthesis of the core structure of *asparagamine* A is an Aza-Cope Mannich rearrangement (scheme 53).[184] The core structure **(198)** was obtained by heating the iodide salt

(195) in excess paraformaldehyde which resulted in the formation of the formaldiminium ion derivative **(196)**. A [3,3]-sigmatropic rearrangement between the two termini of the vinyl and iminium ion motifs of **(196)** furnished enol-iminium species **(197)**. Finally an intramolecular Mannich cyclisation of **(197)** afforded azatricyclodecanone **(198)** in almost quantitative yield.



Scheme 53

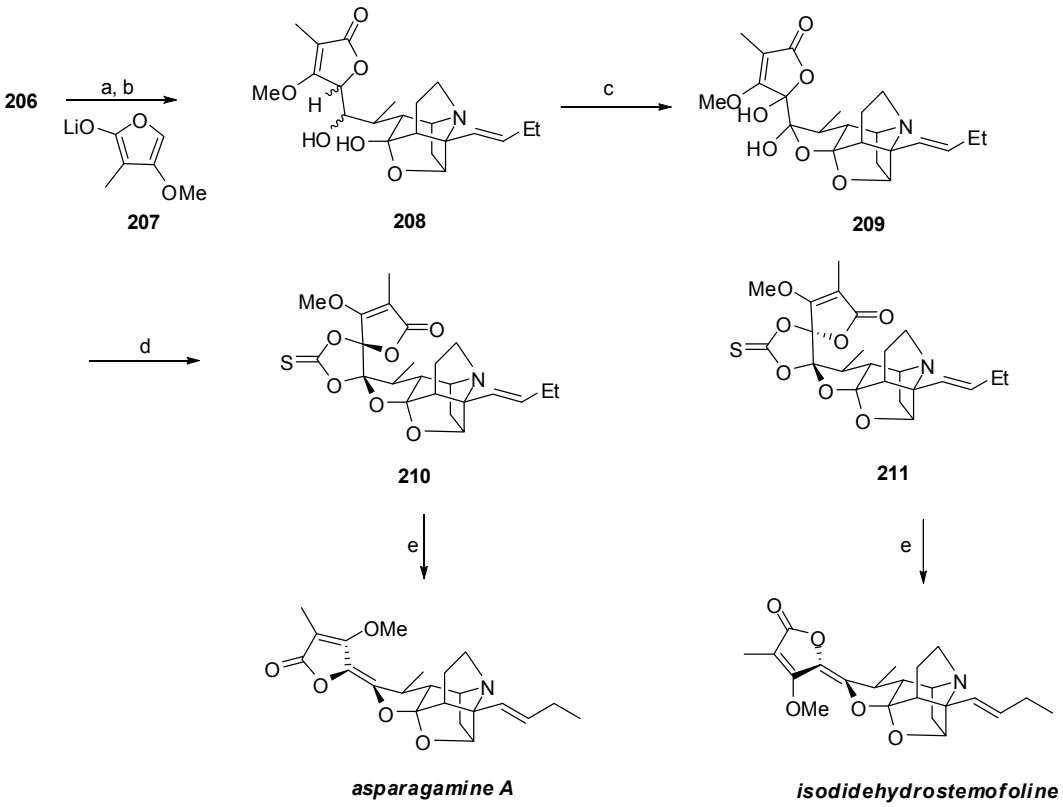
Desilylation of **(198)** using TBAF, followed by an activated DMSO oxidation of the primary alcohol **(199)**, and treatment of the resulting aldehyde under modified Julia olefination conditions[185] afforded the more thermodynamically stable *E* isomer **(200)** exclusively (scheme 54). Kinetically controlled alkylation of **(200)** with LDA and ethyl 2-iodoacetate resulted in a mixture of stereoisomers **(201)**. The stereoisomers were epimerised under basic conditions with DBU to give the more energetically preferred equatorial keto-ester configuration **(202)**. Deprotection of the methyl ether of **(202)** with BBr_3, silylation of the resulting lactol, followed by methylation of the lithium ester enolate of **(203)** furnished α-methyl ester **(204)**, which had the incorrect configuration at C* required for the natural product. This particular setback was overcome by the reduction of ester **(204)** to the corresponding primary alcohol, followed by Dess-Martin oxidation to the aldehyde **(205)**. This was subsequently epimerised under basic conditions to yield a 94:6 mixture of stereoisomers separable by chromatography, to obtain the major epimer **(206)**.



Scheme 54

Reagents & conditions: (a) TBAF, THF, rt; (b) SO_3Py, NEt_3, DMSO, rt; (c) $C_7H_5N_4SO_2$*n*-Pr, KHMDS, DME, -55 °C, 70%; (d) LDA, THF, ICH_2CO_2Et, -10 °C; (e) DBU, MePh, 130 °C, 67%; (f) BBr_3, CH_2Cl_2, -78 °C to -10 °C, aq NaOH; (g) TMS-imid., 130 °C; (h) LDA. MeI, THF-DMPU, -45 °C, 54%; (i) DIBALH, CH_2Cl_2, -78 °C; (j) DMP, rt; (k) DBU, $CHCl_3$, rt, 54%.

Introduction of the tetrahydrofuranylidene butenolide unit was achieved by nucleophilic attack of the lithiated form of 4-methoxy-3-methyl-2(5H) furanone **(207)** upon aldehyde **(206)**, followed by cleavage of the silyl protecting group to furnish hemiacetal **(208)** (scheme 55). Hypervalent iodine (V) oxidation of **(208)** using IBX[186] provided diol **(209)**, which was condensed with thiophosgene to form thiocarbonate derivatives **(210)** and **(211)**. These were subsequently transformed into *asparagamine* A, along with its geometrical isomer *isodidehydrostemofoline* by desulfurisation-decarboxylation, upon heating in excess trimethyl phosphite at 120 ºC



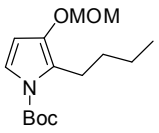
Scheme 55

Reagents & conditions: (a) **(207)**, *n*-BuLi, THF, -78 °C; (b), aq HCl, $CHCl_3$, MeOH, rt, 93%; (c) IBX, DMSO, 55 °C, 55%; (d) $CSCl_2$, DMAP, CH_2Cl_2, -50 °C, 68%; (e) $(MeO)_3P$, 120 °C, (*asparagamine* A, 66%), (*isodidehydrostemofoline*, 64%).

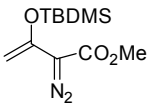
In conclusion, *asparagamine* A was synthesised in an overall yield of 3% over 27 steps starting from the Boc protected pyrrole **(183)**. Undoubtedly the strategy adopted in this total synthetic route to obtain the skeleton of stemona alkaloids was based on a key disconnection of azatricyclodecanone **(195)**. This was derived *via* a number of intermediates from formaldiminium derivative **(193)**, by an aza-Cope-Mannich rearrangement. Although the product is racemic, there is scope for it to be rendered asymmetric. A Diels-Alder cycloaddition under the influence of a chiral Lewis acid/auxiliary at the beginning of the synthesis could be used to set the stereochemistry in **(185)** and **(186)**, and hence lead to an asymmetric synthesis.

Kende's total synthesis of *Isostemofoline.* [168]

Kende and co-workers were the first to report the synthesis of this class of stemona alkaloids, utilising a [4+3] cycloaddition reaction between the activated Boc-protected pyrrole **(212)** and vinyl diazoester **(213)** to assemble the core structure. This was later followed by a triple tandem cyclisation to deliver the pentacyclic framework of the pyrrolizidine stemofoline alkaloids.

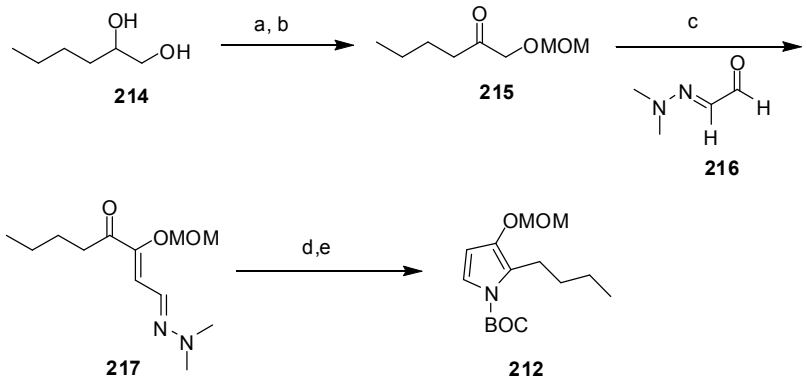


212



213

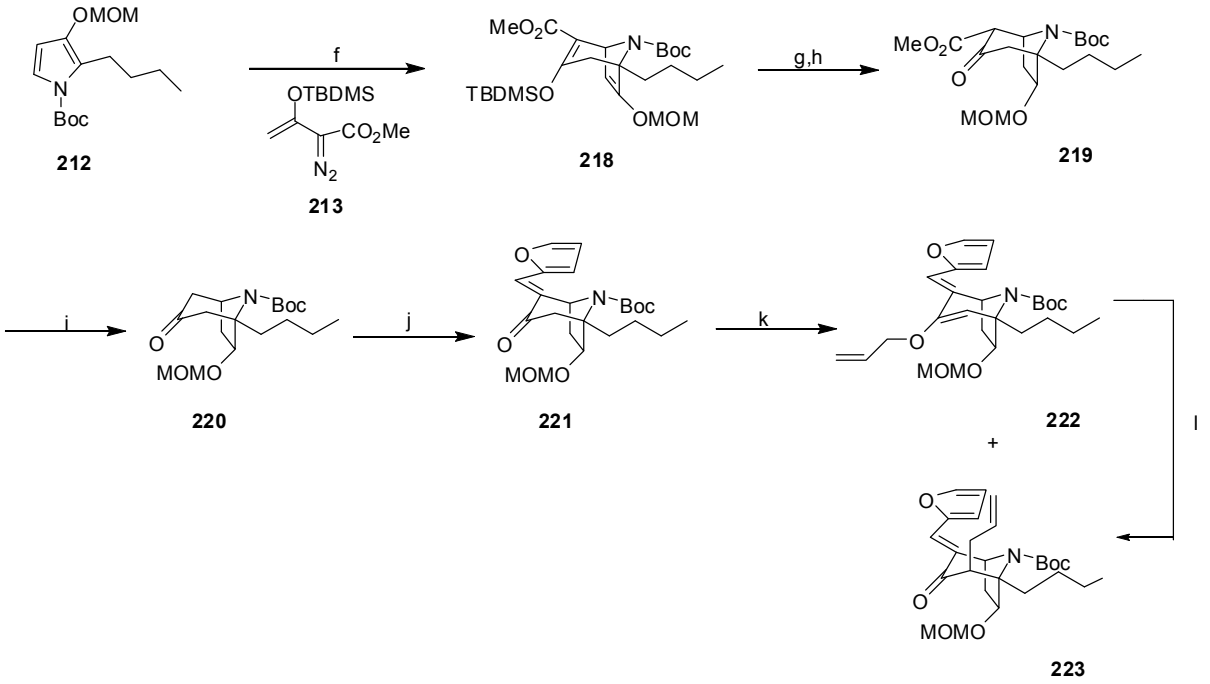
The synthesis was initiated with a selective oxidation of 1,2-hexanediol **(214)**, where the secondary alcohol is coverted to a ketone in the presence of a less sterically hindered primary alcohol followed by a MOM ether protection of the hydroxyl group to afford the MOM protected ketone **(215)**.[187] Regiospecific condensation of ketone **(215)** with dimethylhydrazone **(216)** in the presence of potassium ethoxide resulted in dienone **(217)**.[188] Boc protected pyrrole **(212)** was formed *via* a reductive cyclisation of dieneone **(217)** with sodium hydrosulfite in refluxing aqueous ethanol followed by a *tert*-butyl carbamate protection of the pyrrole using catalytic amounts of DMAP (scheme 56).



Scheme 56

Reagents & conditions: (a) 13% aq NaOCl, HOAc, 65%; (b) MOMCl, (*i*-Pr)$_2$NEt, CH_2Cl_2, 0 °C – rt, 93%, (c) KOEt, 80%; (d) $Na_2S_2O_4$, EtOH, H_2O, 90 °C, 35%; (e) $(Boc)_2O$, 4-DMAP, CH_3CN, 72%.

Synthesis of the core structure of the intricate alkaloid *isostemofoline* was accomplished *via* an elegant [4+3] cycloaddition between the Boc-protected pyrrole **(212)** and vinyl diazoester **(213)**, in the presence of catalytic rhodium octanoate dimer, to furnish the bicyclic adduct **(218)**.[189] Removal of the silicon protecting group with TBAF resulted in the enol methyl ester, which was subjected to hydrogenation over Pd/C from the less hindered *exo* face to form **(219)**. This was followed by a nucleophilic decarbomethoxylation using water and DMSO at 150 °C to yield nortropinone **(220)**.[190] Nortropinone **(220)** was then subjected to a stereoselective base catalysed condensation with furfural using NaOMe in methanol to give the thermodynamically stable *(E)* α,β-unsaturated ketone **(221)**. Alkylation of **(221)** using a lithium base in the presence of DMPU with allyl iodide yielded an undesirable 2.4:1 mixture of **(222)** and **(223)**. However, the unfavourable allyl enol ether **(222)** was converted into the desired α-allyl ketone **(223)** *via* an additional stereoselective Claisen rearrangement in refluxing toluene (scheme 57).[191]

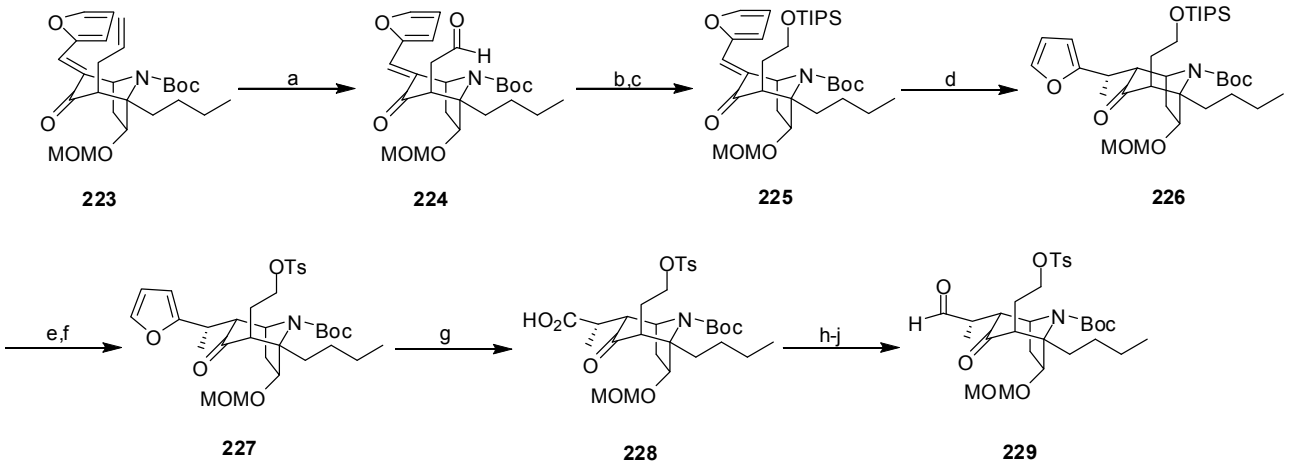


Scheme 57

Reagents & conditions: (f) rhodium octanoate dimer (10 mol%), pentane, reflux, 90%; (g) Bu_4NF, THF, 65%; (h) H_2, 5% Pd/C, MeOH, 90%; (i) H_2O, DMSO, 150 °C, 90%, (j) furfural, NaOH, MeOH, H_2O, reflux, 90%; (k) LiHMDS, 1.1 eq DMPU, THF, 0° C, allyl iodide, rt, 91%; (l) toluene, reflux, 86%.

Selective oxidative cleavage of the terminal alkene in **(223)** using potassium osmate and sodium periodate followed by chemoselective reduction of the resultant aldehyde **(224)** using zinc borohydride[192] and subsequent silicon protection of the primary alcohol resulted in the TIPS-protected keto alcohol **(225)**. The introduction of the methyl group with the correct stereochemistry was successfully achieved using a 1,4-Michael addition strategy with methyllithium in the presence of DMPU under very mild conditions to yield the 1,4-adduct **(226)**.[193] At this stage of the synthesis, the TIPS-protection was removed and replaced with a tosyl group to give **(227)** in order to serve as an excellent leaving group later in the synthesis as part of the triple cascade cyclisation. Ozonolysis of the α-methyl aldehyde **(227)** furnished

carboxylic acid **(228)**. The next step in this synthesis was the conversion of **(228)** to aldehyde **(229)** which was achieved in three overall transformations through the formation of anhydride, chemoselective sodium borohydride reduction to the primary alcohol and Dess-Martin oxidation (scheme 58).

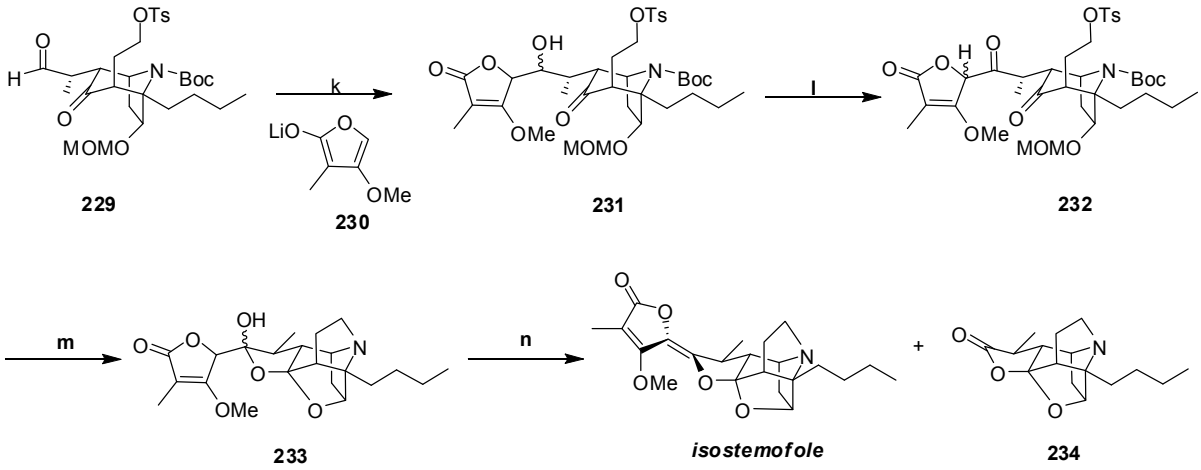


Scheme 58

Reagents & conditions: (a) K_2OsO_4, $NaIO_4$, Et_2O, H_2O, rt; (b) $Zn(BH_4)_2$, THF, -10 °C, 52%; (c) TIPSCl, imidazole, DMF, 93%; (d) 2.2 eq MeLi, 1.1 eq DMPU, Et_2O, -40 °C, 85%; (e) Bu_4NF, THF, 90%; (f) TsCl, pyridine, $CHCl_3$, 90%; (g) O_3, CH_2Cl_2; Me_2S, 65%; (h) *i*-BuOCOCl, *N*-methyl-morpholine, THF, 0 °C; (i) $NaBH_4$, MeOH; (j) Dess-Martin periodinane, CH_2Cl_2, 30% overall.

The final synthetic steps included the 1,2 addition of the lithium anion of 4-methoxy-3methyl-(5)-furanone **(230)** to aldehyde **(229)** to install the butenolide functionality as a 2:1 mixture of seperable diasteromeric alcohols **(231)**, which were oxidised with the Dess-Martin oxidant to give a 2:1 mixture of diastereomeric ketones **(232)**. The ketone mixtures were treated with trifluoroacetic acid that led to a rigid cage-like hemiacetal structure **(233)** *via* a tandem triple

cyclisation. Dehydration of **(233)** with triflic anhydride proceeded to furnish the *trans* isomer *isostemofoline*, over the *cis* isomer *asparagamine* A, albeit in low yield owing to the formation of the retro-aldol adduct **(234)** (scheme 59).



Scheme 59

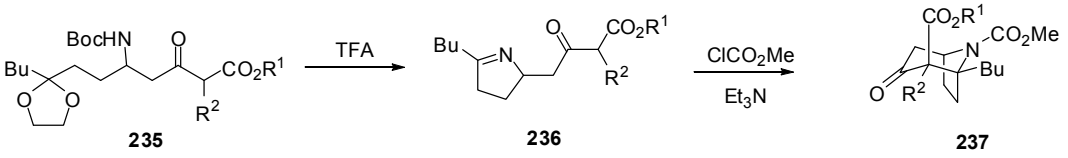
Reagents & conditions: (k) THF, -78 °C, 56%; (l) Dess-Martin periodinane, CH_2Cl_2, 61%; (m) (i) CF_3CO_2H; (ii) saturated aq $NaHCO_3$, 67%; (n) Tf_2O, CH_2Cl_2, *isostemofoline*: 12%, **(234)** 14%.

In conclusion, the synthesis of *isostemofoline* was accomplished in 26 steps with an overall yield of 3% starting from 1,2 hexanediol. Kende and co-workers were the first to synthesise a member of the stemona alkaloid natural products utilising an elegant [4+3] cycloaddition strategy between pyrrole **(212)** and vinyl diazoester **(213)** to furnish the bicyclic adduct **(214)** motif of *isostemofoline*. Another highlight of this synthetic sequence was the triple cascade cyclisation of diastereomeric ketone **(232)** to hemiacetal **(233)** using trifluoroacetic acid. Although this was a remarkable effort by Kende to accomplish the first synthesis of these classes of stemona alkaloids, albeit in racemic form, there is an opportunity for this endeavour to be rendered

asymmetric by means of a chiral reagent in the highlighted [4+3] cycloaddition between pyrrole **(212)** and vinyl diazoester **(213)**.

Thomas's efforts towards *stemofoline.* [178]

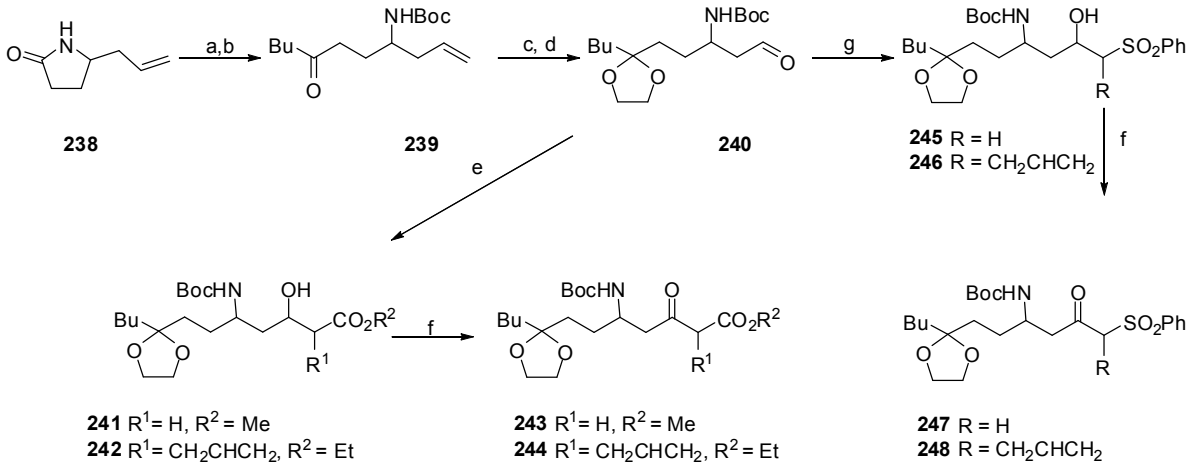
Thomas and co-workers proposed a synthesis for the alkaloid *stemofoline* highlighting the use of iminium ion cyclisation methodology to obtain the azabicyclic skeleton **(237)**. Deprotection of the acetyl and butyl carbamate groups of **(235)** was predicted to give rise to a spontaneous cyclisation to form the cyclisation precursor butyl imine **(236)**. Sequential treatment of imine **(236)** with methyl chlororformate followed by triethylamine would provide the azabicyclic core of *stemofoline* **(237)** (scheme 60).



235 **236** **237**

Scheme 60

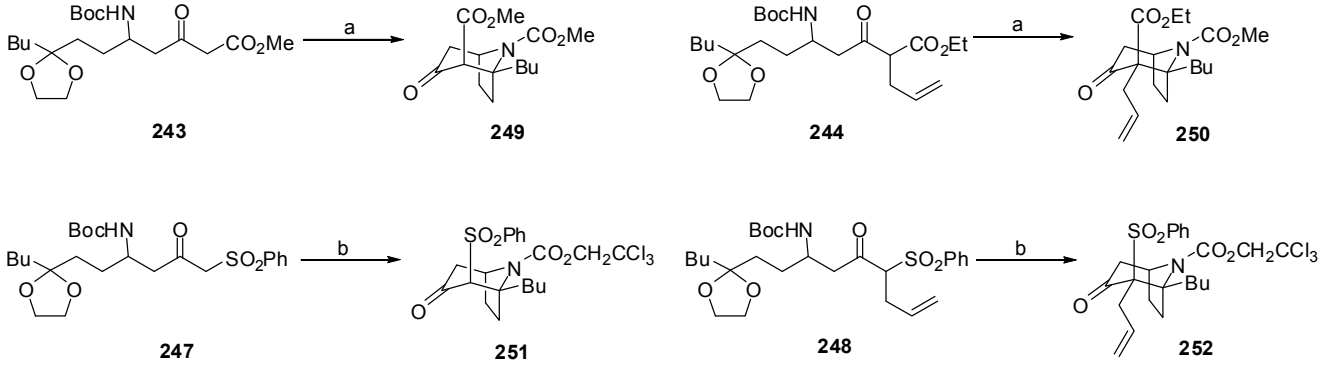
Synthesis of cyclisation substrates began with racemic pyrrolidinone **(238)**. Protection of the amine functionality as the butyl carbamate followed by treatment with butylmagnesium bromide gave butyl ketone **(239)**. Acetal protection of ketone **(239)** and ozonolysis furnished aldehyde **(240)**, which was transformed into ketoester **(243)** *via* an aldol condensation and oxidation. Ketosulfone **(247)** was similarly prepared by the addition of lithiated methyl phenylsulfone to aldehyde **(240)** followed by oxidation. Access to the allylated analogues **(244)** and **(248)**, were also achieved using this approach (scheme 61).



Scheme 61

Reagenets and conditions: (a) $(Boc)_2O$, DMAP, Et_3N, 76%; 9b) BuMgBr, THF, 91%; (c) $(CH_2OH)_2$, pyH-OTs, benzene 81%; (d) O_3, MeOH, then Ph_3P, 90%; (e) $MeCO_2Me$, LDA, -78 °C, (**241**, 95%) or ethyl pent-4-enoate, LDA, -78 °C (**242**, 92%); (f) PDC (**243**, 73%) or Dess-Martin (**244**, 59%; **247**, 72%; **248**, 66%); (g) $PhSO_2Me$, LDA, -78 °C (**245**, 58%) or but-3-enyl phenylsulfone, LDA, -78 °C (**246**, 80%).

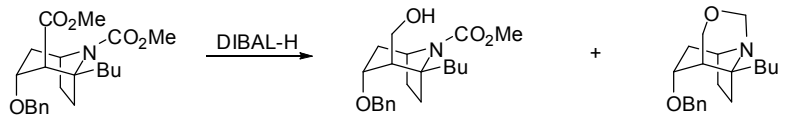
With the cyclisation precursors in hand, the next step in the synthesis was to assemble the azabicyclic framework of *stemofoline*. This was successfully accomplished in modest yields firstly *via* a double deprotection of acetal and butyl carbamate groups with TFA, followed by sequential addition of acetylating agent and triethylamine to provide stereoselectively the azabicyclic species **(249)**, **(250)**, **(251)** and **(252)** (scheme 62). Unfortunately the unfavourable equatorially disposed allyl unit in **(250)** and **(252)** could not be further elaborated to build the third ring of *stemofoline*. In light of this knowledge, the group decided to make further elaboration to ketoester **(249)** with a view of modifying the axial substituent to install the third ring of *stemofoline*.



Scheme 62

Reagents and conditions: (a) i) TFA, ii) $ClCO_2Me$, Et_3N, 71%; (b) i) TFA, ii) $ClCO_2CH_2CCl_3$, Et_3N, (**249**, 71%), (**250**, 42%), (**251**, 51%), (**252**, 40%).

A chemoselective DIBAL-H reduction of ketoester **(253)**, obtained from reduction of **(249)** with sodium cyanoborohydride, produced the desired primary alcohol **(254)**, along with the unexpected tricyclic aminoacetal **(255)**, albeit in poor yield. This serendipitous discovery prompted the group's investigation towards the construction the third ring of the alkaloid utilising the carbonyl carbon of the carbamate (scheme 63).

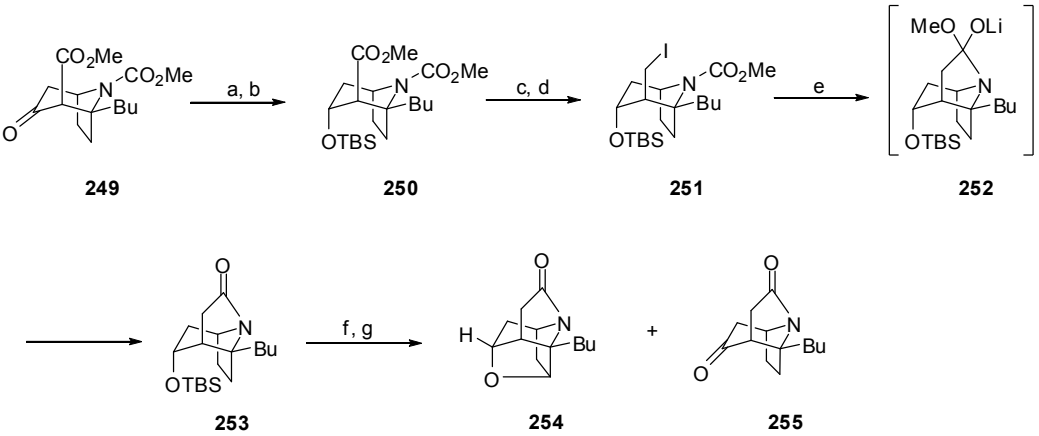


253 **254,** 59 % **255,** 18 %

Scheme 63

Construction of the third ring began with the selective reduction of ketoester **(249)** with zinc cyanoborohydride to give a 3:1 mixture of epimers in favour of the axial configuration. The axial alcohol was protected as the silyl ether **(250)**, which was followed by chemoselective DIBAL-H reduction of the methyl ester. The resultant primary alcohol was treated with I_2/PPh_3 to furnish

the primary iodide **(251)**, required for the installation of the third ring. A lithium-halogen exchange of iodide **(251)** with excess *n*-butyllithium led to the formation of lactam **(253)**, *via* intermediate adduct **(252)**, with loss of lithium methoxide. This lithium halogen exchange tactic provided a useful means of introducing the third ring of *stemofoline* by incorporating the carbamate functionality, albeit fortuitously. Lactam **(253)** was desilylated and a regioselective remote oxidisation using excess lead(IV) acetate to delivered the tetracyclic core **(254)** of the pyrrolizidine alkaloid *stemofoline*, together with ketone **(255)** as the minor product (scheme 64).

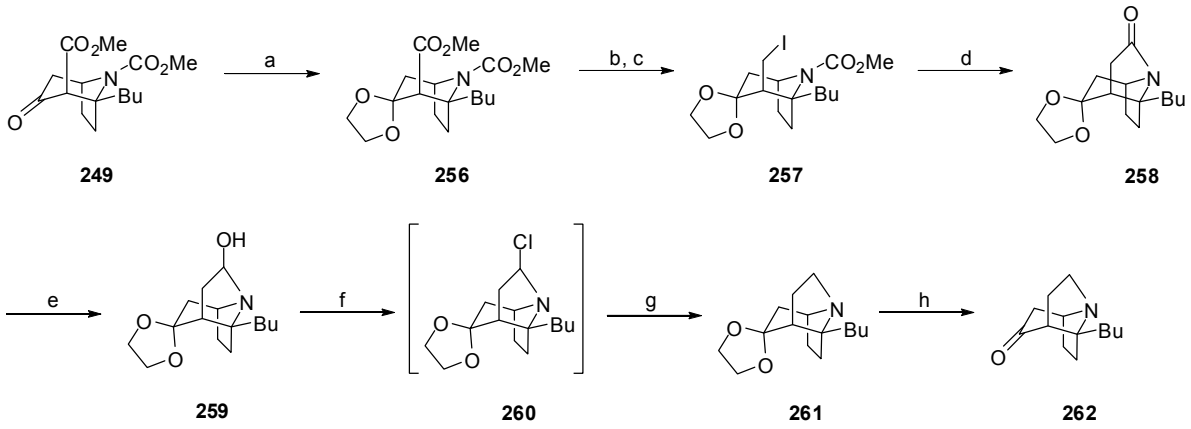


Scheme 64

Reagents and conditions: (a) $ZnCl_2$, $NaBH_3CN$, Et_2O 91% 75:25 mixture of epimers; (b) TBSOTf, 2,6 lutidine, 86%; (c) DIBAL-H, hexane, -78 °C to rt, 81%; (d) I_2, PPh_3, imid, 83%; (e) *n*-BuLi, -78 °C to rt, 81%; (f) TBAF, THF, rt, 99%; (g) $Pb(OAc)_4$, benzene, reflux, **(254)**, 35%, **(255)**, 16%, **(253)**, 12%.

At some stage during the synthesis of *stemofoline*, lactam **(255)** would have to be reduced to the tricyclic ketoamine **(262)**, therefore a procedure was developed for this transformation (scheme 65). This was best achieved starting with acetal protection of ketoester **(249)** using 2-methoxy-1,3-dioxolane and sub-stoichiometric amounts of *p*-toluene sulfonic acid to furnish ester **(256)**.

Ester **(256)** was then converted to the tricyclic lactam **(258)** using previously developed chemistry *via* cyclisation of the primary iodide **(257)** with excess *t*-butyllithium. Lithium aluminium hydride reduction of **(258)** provided aminol **(259)** and attempts to deoxygenate the hydroxyl group using radical chemistry proved unsuccessful. This problem was overcome by treatment with thionyl chloride followed by subsequent reduction, presumably of the chloride intermediate **(260)**, using lithium aluminium hydride to furnish the tricyclic amine **(261)**, and a final hydrolysis of the acetal functionality with aqueous sulfuric acid resulted in the desired ketoamine **(262)**.

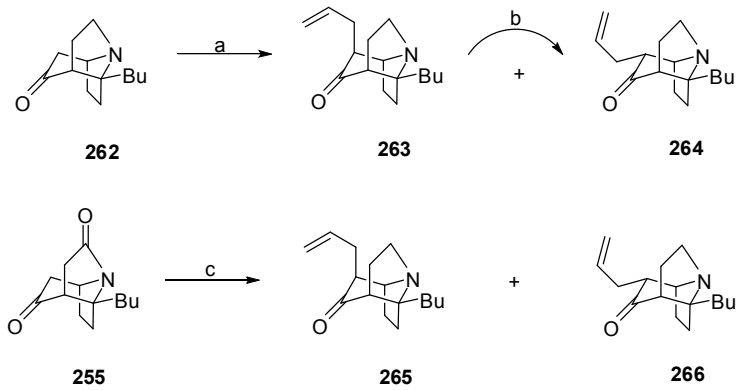


Scheme 65

Reagents and conditions: (a) 2-methoxy-1,3-dioxolane, TsOH, MeOH, toluene, 50 °C, 87%; (b) DIBAL-H, 55%; (c) I_2, PPh_3, imid, 78%; (d) *t*-BuLi, THF, -78 °C, 74%; (e) $LiAlH_4$, Et_2O, 83%; (f) $SOCl_2$; (g) $LiAlH_4$, 75%; h) 1% aq H_2SO_4, 90%.

At this advanced stage of the synthesis of *stemofoline*, the group turned their attention on the assembly of the essential pentacyclic nucleus of the natural product. Their initial attempts were focused on allylating the ketoamine **(262)** and ketolactam **(255)** with a combination of allyl iodide/bromide with various bases. Allylation of ketoamine **(255)** with allyl iodide and potassium

hexamethyldisilazide resulted in an undesirable epimeric 8:2 mixture of **(263)** and **(264)** in modest yields. However, the desired epimer **(264)** was easily made available in good yields by epimerisation of **(263)** with potassium *tert*-butoxide. Alternatively, allylation of ketolactam **(255)** with allylbromide and lithium diisopropylamine proved less efficient (scheme 66). However, attempts to elaborate the terminal double bond *via* oxidative cleavage were unsuccessful along with alkylation of the aminoketone **(262)** using methyl bromoacetate. Thus, this approach was abandoned. With this setback in mind, the group decided to assemble the pentacyclic core of *stemofoline* by alkylating the azabicyclic ketone intermediates synthesised earlier.

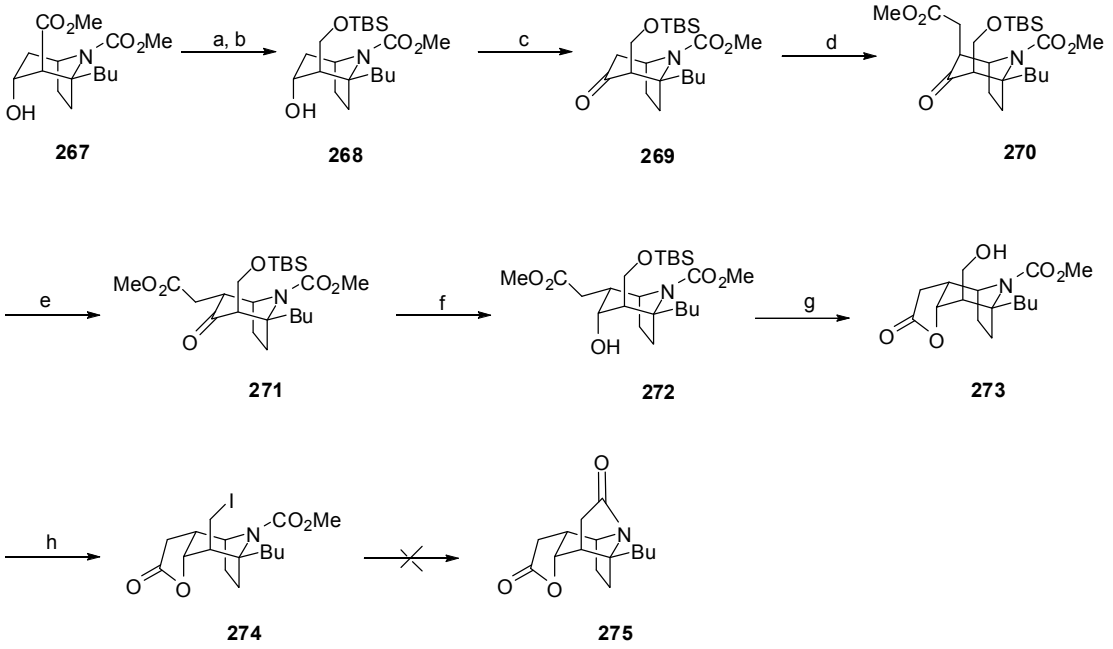


Scheme 66

Reagents and conditions: (a) KHMDS, allyl iodide, -78 °C, (**263:264** = 80:20), 56%; (b) *t*-BuOK, CH_2Cl_2, methanol, rt, 88%; (c) LDA, allyl bromide, -78 °C to rt, (**265:266** = 65:35), 39%.

Methyl ester **(267)** was reduced with DIBAL-H to give the primary alcohol followed by an immediate regioselective silyl ether protection to yield alcohol **(268)** which was directly oxidised to give ketone **(269)**. Alkylation of ketone **(269)** with bromoacetate and potassium hexamethyldisilazide produced the unfavourable axial methyl ester **(270)**, which was quickly corrected by epimerising the stereocentre in question to the desirable equatorial epimer **(271)** with potassium *tert*-butoxide. A chemo and stereoselective reduction of ketone **(271)** using zinc

borohydride provided the axially configurated alcohol **(272)**, and upon desilylation of the silyl ether with tetrabutylammonium fluoride provided the hydroxylactone **(273)**. Hydroxylactone **(273)** was converted to the primary iodide **(274)**, but unfortunately all attempts to promote a lithium-halogen exchange cyclisation to lactam **(275)** proved to be unsuccessful (scheme 67).



267 268 269 270 271 272 273 274 275

Scheme 67

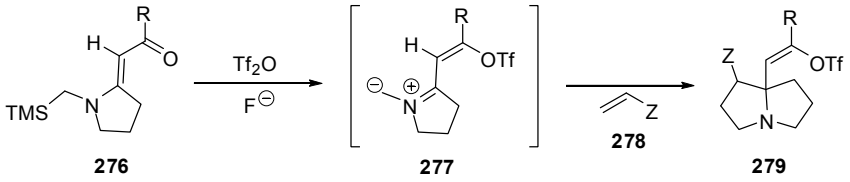
Reagents & conditions: (a) DIBAL-H, CH_2Cl_2, -78 °C, then $NaBH_4$, 63%; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 94%; (c) PDC, CH_2Cl_2, 98%; (d) KHMDS, $BrCH_2CO_2Me$, -78 °C to rt, 58%; (e) *t*-BuOK, CH_2Cl_2, methanol, 66%; (f) $ZnCl_2$, $NaCNBH_3$, 74%; (g) TBAF, THF, 84%; (h) I_2, PPh_3, imid, 80%.

In summary, Thomas and co-workers have successfully adopted a stereoselective cyclisation protocol as the key transformation *en route* to the tetracyclic core of the pyrrollizidine alkaloid *stemofoline*. Stereoselective cyclisation proceeded smoothly to deliver aza-bicyclic adducts in modest yields, and the third ring was installed by cyclisation of organolithium species onto the

carbonyl carbon of the carbamate *via* lithium-halogen exchange. Further elaboration of this tricyclic lactam to the tetracyclic ether was achieved *via* a regioselective remote oxidation using excess lead (IV) acetate. Alkylation of tricyclic intermediates proved to be less efficient, while the azabicyclic keto-ester **(267)** proved to be constructive in the assembly of lactone **(273)**. Unfortunately, their quest for lactam **(275)** proved unsuccessful as further chemical manipulation of primary iodide **(274)** only led to a complicated mixture of unidentified products. Finally there is the scope for an asymmetric synthesis *en route* to the advanced intermediates utilising the iminium ion cyclisation of more complex precursors analogous to the ketoester **(242)**.

Gin's approach towards *stemofoline.* [183]

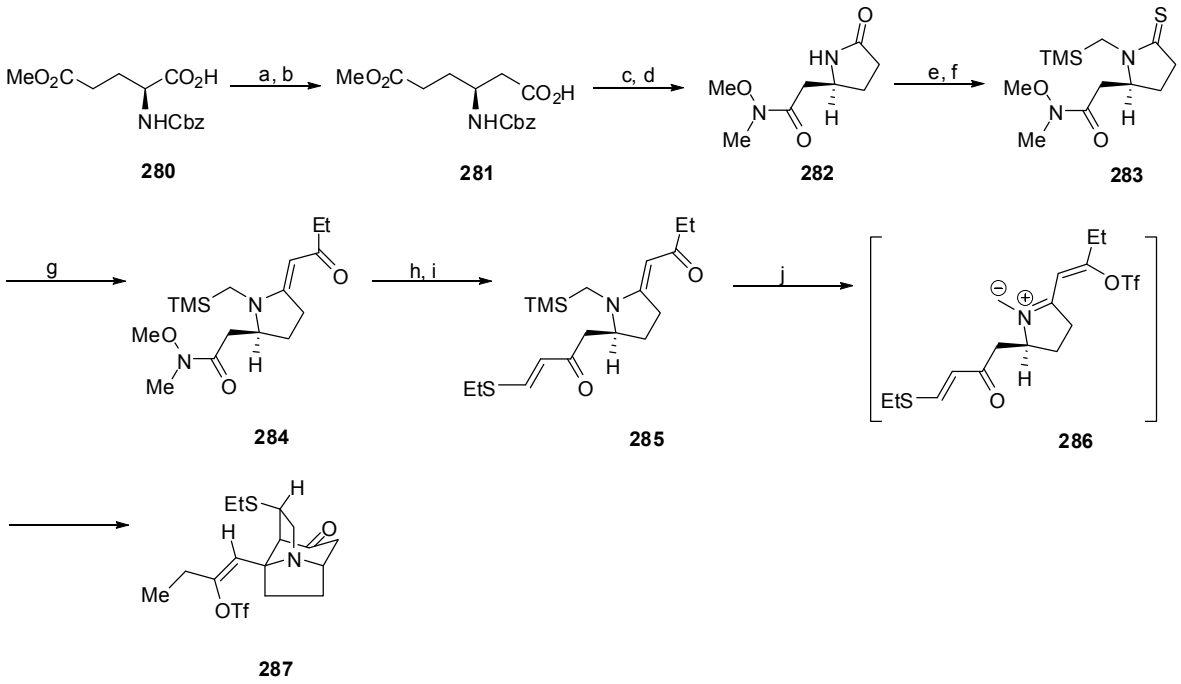
Gin and co-workers envisaged the synthesis of a bridged pyrrolizidine core structure **(279)** of *asparagamine* A, utilising a [1,3]-dipolar cycloaddition of azomethine ylides **(277)**. These ylides are derived from the sulfonylation of vinylogous amides **(276)** (scheme 68).



Scheme 68

To obtain the azatricyclodecane core of *asparagamine* A, an intramolecular [1,3]-dipolar cycloaddition strategy would have to be adopted *en route* to the synthesis of this bridged functionalised pyrrolizidine alkaloid. The synthesis commenced with methyl ester **(280)** (scheme 69)[195] and it was anticipated that the stereocentre of **(280)** would dictate the stereochemical outcome in the subsequent steps. An Arndt-Eistert reaction of **(280)** with ethyl chloroformate and triethylamine and subsequent treatment with silver acetate resulted in the homologous acid **(281)**.

Acid **(281)** was converted to lactam **(282)** *via* the formation of a Weinreb amide using *N,O*-dimethylamine hydrochloride followed by hydrogenolysis of benzyl carbamate, which led to a spontaneous lactamisation to afford **(282)**. *N*-Alkylation of lactam **(282)** with chloromethyltrimethylsilane was followed by chemoselective thionation with Lawessen's reagent to provide thiolactam **(283)**. Vinylogous amide **(284)** was obtained as a single stereoisomer *via* S-alkylation of thiolactam **(283)** with bromobutanone followed by an Eschenmoser sulphide contraction. Treatment of the Weinreb amide functionality of the vinylogous amide **(284)** with ethynylmagnesium chloride followed by hydrolysis and conjugate addition of ethanethiol furnished the [1,3]-dipolar cycloaddition precursor **(285)**, as a 6:1 mixture of (*E*) and (*Z*) geometric isomers. The next step of this synthetic sequence was to generate the azomethine ylide intermediate **(286)**, and this was successfully accomplished by treatment of **(285)** with triflic anhydride in chloroform followed by desilylation with tetrabutylammonium triphenyldifluorosilicate (TBAT).[196] The azomethine ylide intermediate **(286)** was heated at 65 °C for 24 h, to furnish the bridged pyrrolizidine motif **(287)** as a single regio and stereoisomer, whose structure was elucidated by X-Ray crystallography.



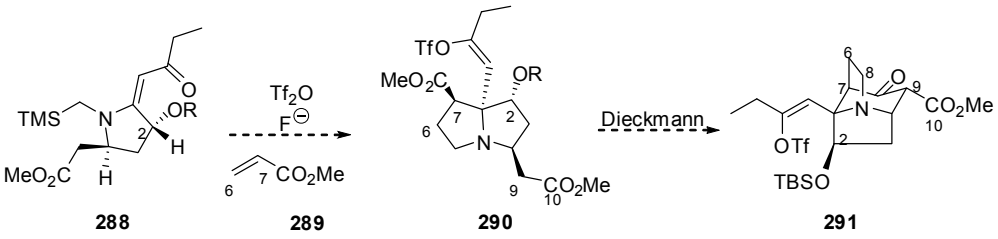
280 **281** **282** **283** **284** **285** **286** **287**

Scheme 69

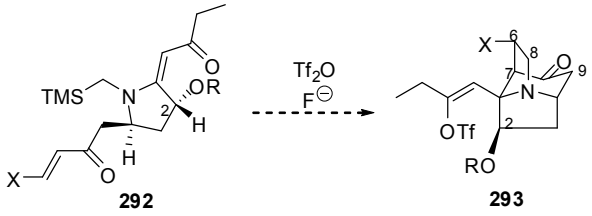
Reagents and conditions: (a) EtOCOCl, Et_3N, THF, 0 °C; CH_2N_2, Et_2O, 87%; (b) AgOAc, 1,4-dioxane, H_2O, rt °C, 86%; (c) EDCI, MeONHMe, Et_3N, $CHCl_3$, rt °C, 89%; (d) H_2, 10% Pd/C, MeOH, rt, 1 atm, 99%; (e) NaH, $TMSCH_2Cl$, DMF, rt, 49%; (f) Lawessons reagent (0.51 eq), toluene, rt, 88%; (g) $BrCH_2COEt$, then PPh_3, Et_3N, MeCN, rt, 92%; (h) HCCMgCl, THF, 0 °C; (i) EtSH, Et_3N, CH_2Cl_2, rt, 75%; (j) Tf_2O, $CHCl_3$, rt, TBAT, 65 °C, 24 h, 51%.

Having succeeded with an intramolecular cycloaddition route to the core structure of the stemona alkaloids, the group then turned their attention to an asymmetric synthesis of fully oxygenated tricyclic core using their already established azomethine ylide dipolar cycloaddition methodology.[179] Two possible synthetic avenues to the tricyclc core were considered. An intermolecular *endo* selective dipolar cycloaddition between methyl acrylate **(289)** and the azomethine ylid generated from vinylogous amide **(288)** would give the pyrrolizidine skeleton **(290)**, followed by a subsequent Dieckman condensation to furnish **(291)** (scheme 70a). Alternatively, an intramolecular approach using the functionalised vinylogous amide

incorporating the OR group (C2) and the dienophile (C6-C7) could be used as the azomethine ylide precursor **(292)** for the cycloaddition to provide the tricyclic core **(293)** of the stemona alkaloids (scheme 70b).



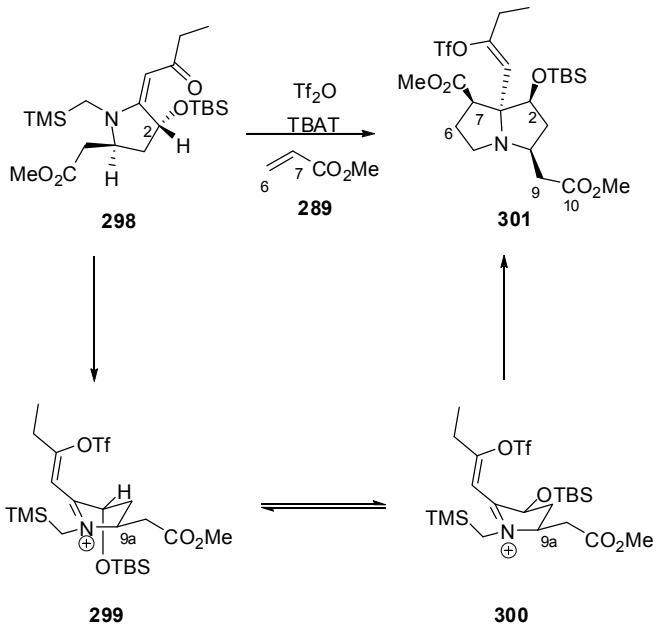
Scheme 70a



Scheme 70b

An intermolecular cycloaddition-Dieckmann approach was pursued and vinylogous amide **(298)** was synthesised using the chemistry described earlier. With the correctly functionalised vinylogous amide in hand, **(298)** was then treated sequentially with triflic anhydride in chloroform and TBAT in the presence of the dienophile methyl acrylate which underwent a [3+2] *endo*, regio-selective cycloaddition to furnish the unexpected pyrrolizidine **(301)** with the incorrect stereochemistry at C2. This unexpected stereochemical outcome was attributed to the epimerisation of the imminium triflate **(299)** at the C2 stereocentre to form the more thermodynamically stable *cis* stereoisomer **(300)**. In this conformer, the silicon protected alcohol (C2) and the methyl ester (C9a) substituents adopt a favourable pseudo-equatorial arrangement that underwent a face-selective cycloaddition to furnish the cycloadduct **(301)**. The structure of

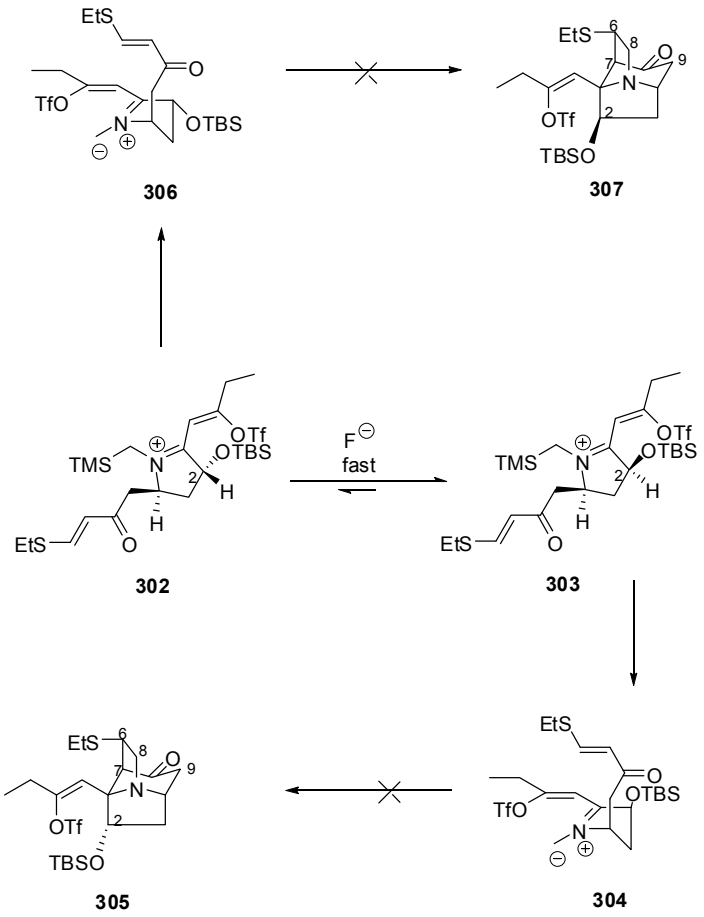
the cycloadduct **(301)** was confirmed by extensive nOe studies, in particular there were signals between the C2 and C9a protons. There was also strong evidence for the formation of the more thermodynamically stable imminium triflate ion **(300)** by in situ ^{1}H NMR spectroscopic studies that showed the emergence of a 4:1 mixture of *trans* and *cis* stereoisomers after an hour. Increasing reaction times led to undesirable 1:2 mixture of *trans* to *cis* imminium trfilates, indicating a strong thermodynamic preference for **(300)** (scheme 71). Unfortunately for the group, all attempts to prevent epimerisation at C2 of the imminium triflate **(300)** were unsuccessful, along with attempts to epimerise C2 and C9 stereocentres of the cycloadduct **(301),** which was essential for the intramolecular Dieckmann condensation.



Scheme 71

After the failure of the intermolecular cycloaddition-Dieckmann strategy, the group then turned their attention to the alternative intramolecular cycloaddition approach. The conversion of the requisite vinylogous amide **(306)**, to the azomethine ylide was achieved using similar chemical transformations as described earlier, setting the stage for the crucial transformation required for

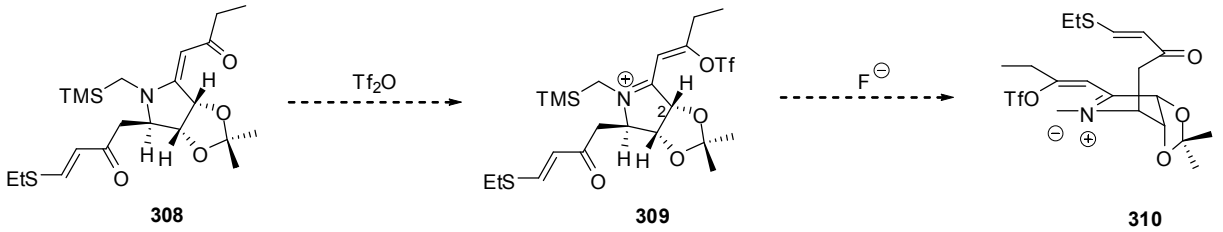
the synthesis of the fully oxygenated tricyclic core of stemofoline alkaloids. Treatment of the vinylogous amide with trifilic anhydride followed by the addition of TBAT resulted in the formation of imminium triflate **(302)**, which established a rapid equilibrium with its stereoisomer **(303)** at C2, presumably due to the fluoride ion acting as a base prior to desilylation. The reaction was dominated by the formation of imminium triflate **(304)** which suffered from severe 1,3 diaxial interactions that led to decomposition pathways over the desired cycloaddition reaction (scheme 72).



Scheme 72

With this problematic C2 epimerisation also occurring in the intramolecular approach, they needed a contingency plan in order to perform the key cycloaddition to obtain the fully

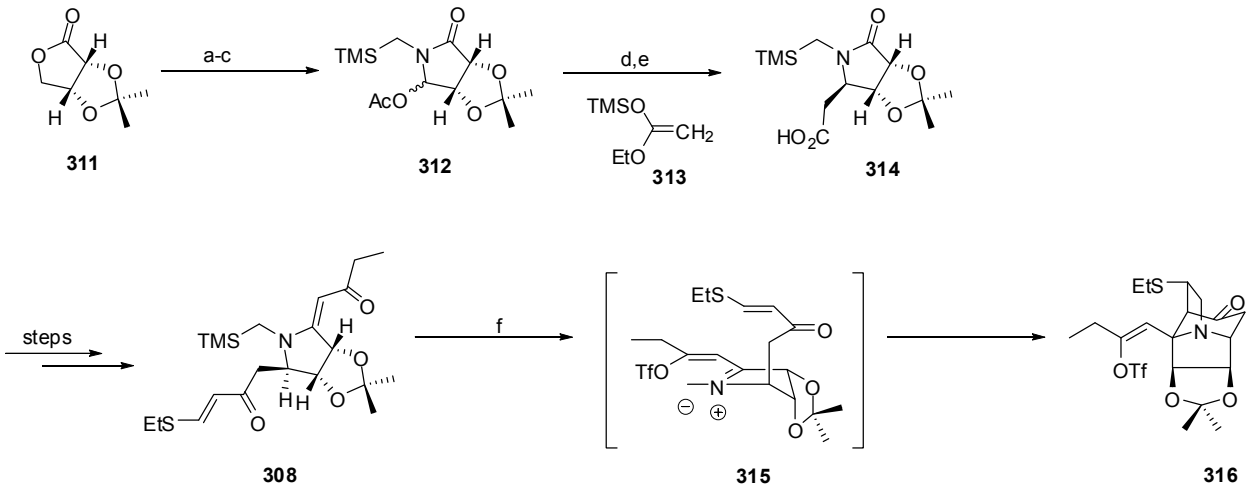
oxygenated tricyclic core of the stemona alkaloids. A solution to their predicament was to assemble an azomethine ylide cycloaddition precursor that was incapable of epimerisation. This ultimately led to the proposed synthesis of *cis* fused isopropylidene ketal **(308)** that could be converted to imminium trifilate **(309)** which would have a high energy barrier to inversion to a *trans* fused system (scheme 73).



308 309 310

Scheme 73

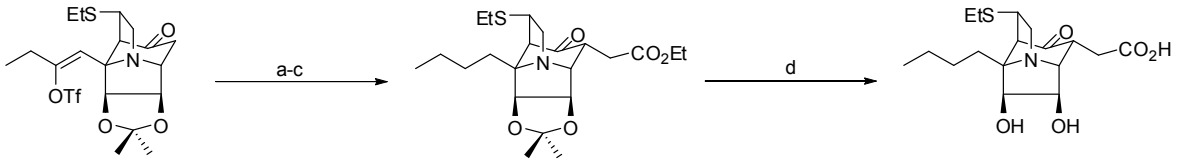
Synthesis of intermediate **(308)** began with treatment of the commercially available (-)-2,3-*O*-isopropylidine-D-erythronolactone **(311)** with (trimethylsilyl)methylamine to afford the primary alcohol, which was subsequently oxidised using Parikh-Doering protocol to afford a hemiaminal that was acetylated using acetic anhydride and pyridine to furnish aminal **(312)**. Aminal **(312)** was subjected to a Lewis acid-promoted Mannich reaction with **(313)**, which was followed by hydrolysis of the resulting ester to give carboxylic acid **(314)**. Cycloaddition substrate **(308)** was obtained from carboxylic acid **(314)** using the previously described chemistry. Cycloaddition of **(308)** proceeded smoothly under the standard conditions previously employed by the group to give the desired non-racemic fully oxygenated pyrrolizidine core **(316)** of the stemona alkaloid **(316)** (scheme 74).



Scheme 74

Reagents and conditions: (a) $TMSCH_2NH_3Cl$, Et_3N, THF, 70 °C, 97%; (b) SO_3, Py, Et_3N, DMSO, rt; (c) Ac_2O, Py, 69% (two steps); (d) TMSOTf, CH_2Cl_2, rt, 72%; (e) LiOH, THF, H_2O, rt, 96%; (f) Tf_2O, TBAT, $CHCl_3$, -45 °C to rt, 71%.

The cycloadduct **(316)** was further elaborated firstly by reduction of the enol triflate to provide the butyl side chain using H_2 in Pd/C. This was followed by enolate alkylation of the ketone with LDA and ethyl iodoacetate to furnish ester **(317)**, after epimerisation with DBU. The final transformation saw the deprotection of isopropylidene unit and hydrolysis of the ester using aqueous HCl to furnish the key intermediate **(318)** containing the stemofoline framework (scheme 75).



316 317 318

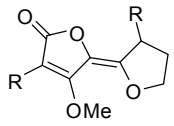
Scheme 75

Reagents and conditions: (a) H_2, 1 atm, 10% Pd/C, MeOH, rt, 89%; (b) LDA, ICH_2CO_2Et, THF, HMPA, 0 °C; (c) DBU, PhMe, 80 °C, 58% (two steps); (d) 2.5 M HCl, THF, 60 °C, 96%.

In summary, Gin and co-workers have successfully demonstrated the utility of the [1,3]-dipolar cycloaddition by applying this to an intramolecular cycloaddition methodology. [3+2] Cycloaddition of an azomethine ylide derived from the sulfonylation of vinylogous amides led to the enantiospecific, fully functionalised, bridged pyrrolizidine of the stemona alkaloid *stemofoline*. This represents an enantioselective synthesis of the oxygenated tricyclic core of *stemofoline* and is produced in 11 steps from a commercially available starting material. The scope of this methodology can be extended to other highly functionalised pyrrolidines, pyrrolizidines and indolizidines.

Olivio's synthesis of bicyclic γ-ylidenetetronates.[177]

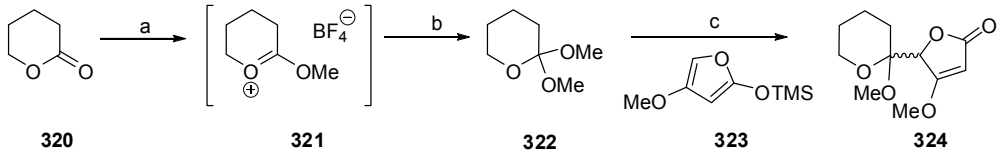
An efficient and concise synthesis of γ-ylidentetonates **(319)** will facilitate the syntheses of stemona alkaloids and other natural products containing this structural motif.



319

Olivio and co-workers developed an efficient methodology for the synthesis of bicyclic γ-ylidentetronates using methyltetronates and lactone derivatives as coupling partners. There was precedent for the nucleophilic lithium enolate addition to aldehydes and ketones.[197-199] However, Olivio's group found lactones to be unreactive towards such species derived from methyltetronates. Their investigation into the Lewis-acid promoted addition of 2-trimethylsiloxy-4-methoxyfuran **(323)** to lactones was also unsuccessful and thus, subsequently more reactive lactones were investigated.

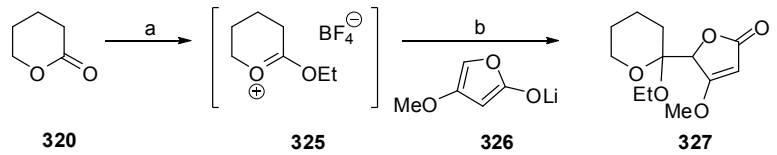
The group then focused their attention toward the masked acetal lactone **(322)** which was synthesised from valerolactone **(320)** *via* the intermediate oxonium ion **(321)** using Deslongchamps protocol in 80% yield.[200] Treatment of compound **(322)** with 2-trimethylsiloxy-4-methoxyfuran **(323)**, with $ZnCl_2$ afforded a mixture of desired ketals **(324)**, albeit in poor yields (< 45% scheme 76). A variety of Lewis acids such as $TiCl_4$ and $BF_3.OEt_2$ were also investigated without any success.



Scheme 76

Reagents & conditions: (a) Me_3OBF_4, rt, CH_2Cl_2; (b) NaOMe, MeOH, -78 °C to rt, 80%; (c) $ZnCl_2$, -10 °C to rt, 43%.

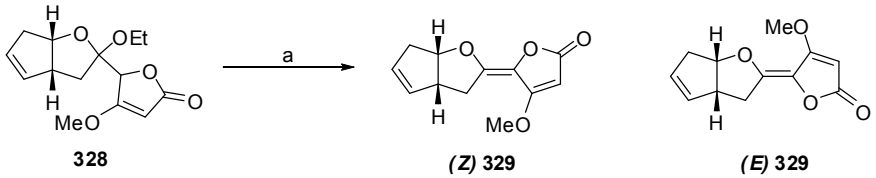
With this moderate level of success in mind the group envisioned that direct addition of **(323)** to oxonium species **(325)** could potentially improve the yields of ketals. After extensive studies the group found that mixed ethyl ketals **(327)** could be obtained in 70% yield by the use of excess triethyloxonium tetrafluoroborates with direct addition of the lithium enolate **(326)** (scheme 77).



Scheme 77

Reagents & conditions: (a) Et_3OBF_4 (6 equiv), rt, CH_2Cl_2; (b); **(325)** (1.3 equiv), THF, -78 °C, 70%

With the optimum conditions in hand the group utilised this methodology to synthesise a number of mixed ethyl ketals in very good yields (65-90%). The next challenge was to perform the dealkoxylation reaction of such mixed ethyl ketals to form the conjugated bicyclic γ-ylidentetronates present in the stemona alkaloids. Dealkoxylation reactions were initially attempted with literature procedures based on the formation of acyclic γ-ylidentetronates without any success.[201, 202] It was only when **(328)** was treated with $TiCl_4$ followed by the addition of Hünig's base resulted in a successful transformation to the desired γ-ylidentetronates **(329)** in moderate selectivity (scheme 78).



Scheme 78

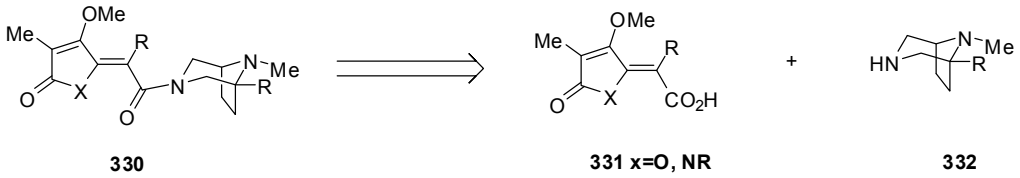
Reagents & conditions: a) $TiCl_4$, $(i\text{-Pr})_2NEt$, -30 °C, CH_2Cl_2, 89%, (6:1, *Z: E*)

In summary, Olivio and co-workers have developed a methodology for the construction of bicyclic γ-ylidentetronates that can be applied to the syntheses of stemona alkaloids. This was achieved from dealkoxylation of mixed ethyl ketals, which in turn were derived from

valerolactone and lithium enolate of methyl tetronate in very good yields. This methodology provides the foundation for the challenging assembly of such motifs present in the stemona alkaloids.

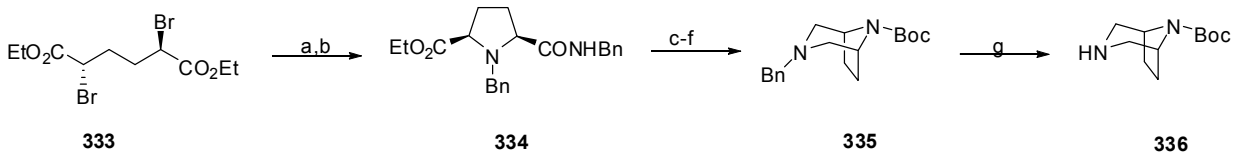
Smith's approach to the synthesis of 2 substituted pyrrolidines.[176]

Smith and co-workers devised a route to synthesise structurally simplified compounds based on *stemofoline* such as the fused piperazine analogues **(330)** that can be disconnected to tetronate **(331)**[203] (X=O) and tetramate **(331)**[204] (X=NR) (which are easily prepared according to literature procedures) and 2,8-diazabicyclo[3.2.1]octane **(332)** as the coupling partner (scheme 79). They envisaged doing this with three key objectives in mind: 1) maintain the structural rigidity of the natural product and 2) mimic the *n*-butyl side chains by incorporating alkyl substituents.



Scheme 79

Synthesis of azabicyclic compound **(336)** began with ring closure of the commercially available diethyl *meso*-2,5-dibromoadipate **(333)** using benzylamine to deliver the *cis* mono-amide **(334)** and its undesired *trans* diastereomer which was simply removed by column chromatography. Pyrrolidine **(334)** was converted to bicycle **(335)** in four steps: heating to remove the ethanol, deprotection of the benzyl group with H_2, reduction of the amide with lithium aluminium hydride and then Boc protection. A Pd/C hydrogenolysis of the benzyl group then furnished the desired diazabicyclic product **(336)** (scheme 80).



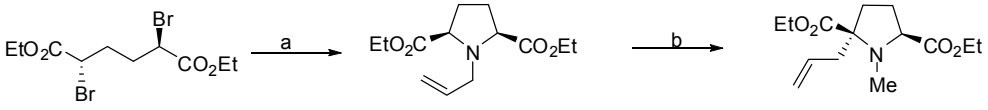
333 334 335 336

Scheme 80

Reagents and conditions: (a) benzylamine (3.1 equiv), toluene, 85 °C; (b) benzylamine, xylene, reflux, (71% over two steps); (c) 230 °C, distill off EtOH, 73%; (d) H_2, Pd/C, MeOH, HCl, 85%; (e) $LiAlH_4$, Et_2O, reflux; (f) $(Boc)_2O$, CH_2Cl_2, rt, 60% over two steps; (g) H_2, Pd/C, MeOH, 72%.

Having successfully constructed the diazabicyclic motif **336)** utilising the tandem cyclisation methodology, the next task was to incorporate an alkyl side chain that would mimic the *n*-butyl side chain of *stemofoline*, *via* a [2,3]-Stevens rearrangement strategy followed by tandem cyclisation**.**

[2,3]-Stevens rearrangement product **(338)**, a substituted pyrrolidine, was prepared starting from the *meso* compound **(333)**. Compound **(333)** was treated with excess allylamine to yield a 3:1 diastereomeric mixture of the Stevens rearrangement precursor pyrrolidine **(337)** that was separated by column chromatography. The desired *cis* pyrrolidine **(337)** was subjected to the standard Stevens rearrangement protocol[205] using excess iodomethane and potassium carbonate in DMF at 55 °C over two days, which resulted in a separable 4:1 mixture of allyl pyrrolidine **(338)** in a modest 42% yield (scheme 81).

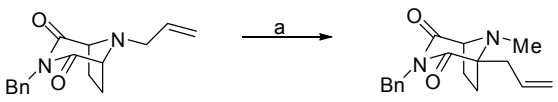


333 337 338

Scheme 81

Reagents & conditions: (a) allylamine (3.1 equiv), toluene, 85 °C, 80%; (b) MeI, K_2CO_3, DMF, 55 °C, 2 d, 42%.

The rationale for this modest yield was attributed to the allyl pyrrolidine **(338)** quaternising under the reaction conditions. The group also have noticed, perhaps unsurprisingly, that a [2,3]-Stevens rearrangement on the diazabicyclic compound **(339)** only yielded 2% of the desired product **(340)**. This observation can be rationalised presumably by the lack of anion formation at the bridgehead position of **(340)** (scheme 82).



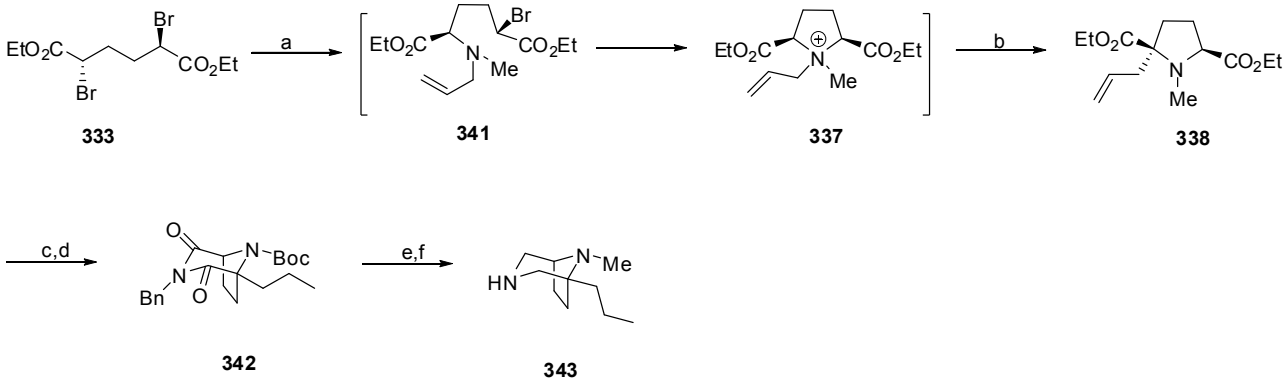
339 340

Scheme 82

Reagents & conditions: a) MeI, K_2CO_3, DMF, 55 °C, 2 d, 2%.

The inability to form an anion at the bridgehead position led to a slightly different approach towards diazabyclo ring systems. This slightly modified approach focused on a one-pot *N*-methylallylamine addition to *meso* dibromo ester **(333)** followed by standard Stevens conditions to furnish the desired product **(338)** as a 13:5 separable diastereomeric mixture by column chromatography in an overall yield of 58%.[206] This one-pot process occurred *via* an intramolecular cyclisation rather than intermolecular quaternisation. This was then followed by a Stevens rearrangement which occurred smoothly to provide **(341)**. The next step in this synthetic

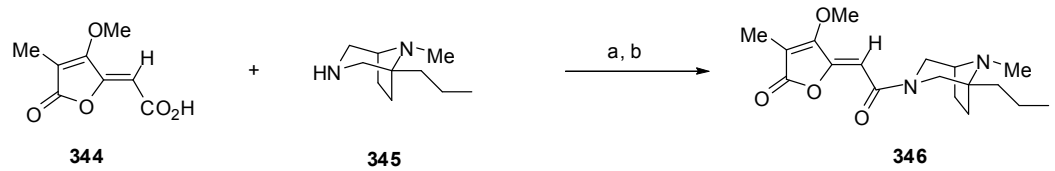
sequence was to perform an already established tandem cyclisation of **(341)**, and further chemical manipulations led to diazabicyclic product **(343)** using the conditions described above (scheme 83).



Scheme 83

Reagents & conditions: (a) *N*-methylallylamine, K_2CO_3, DMF, rt, (13:5) 58%; (b) benzylamine, xylene, reflux, 2 d, 55%; (c) H_2, Pd/C, EtOH, quant; (d) 230 °C, distil EtOH, 71%; (e) $LiAlH_4$, Et_2O, reflux, 79%; (f) H_2, Pd/C, EtOH, 3 h, 94%.

Having the diazabicyclo-species **(345)** in hand, the group successfully coupled **(345)** with a number of tetronic **(344)** and tetramic acid derivatives with oxalyl chloride, triethylamine and catalytic amounts of DMF, to give the *stemofoline* mimic **(346)** as shown in scheme 84.



Scheme 84

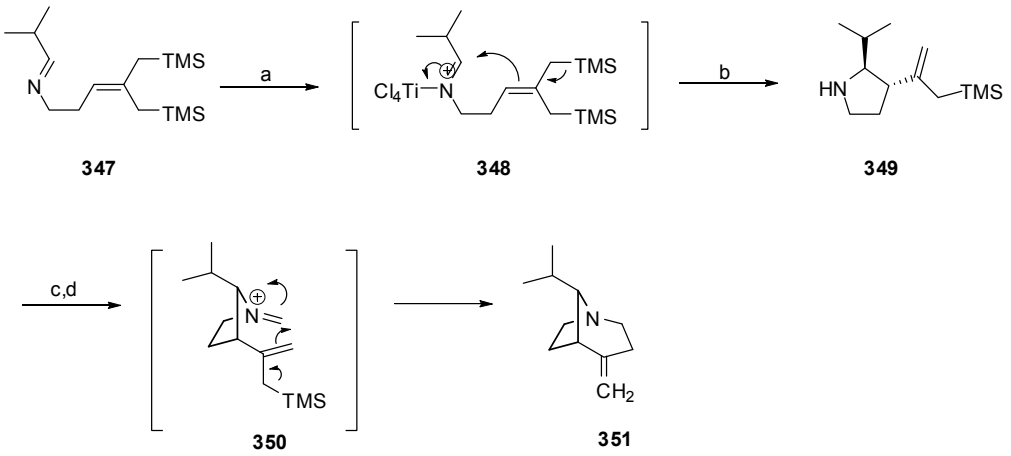
Reagents & conditions: (a) oxalyl chloride, THF, DMF (cat), rt, 1 h; (b), Et_3N, rt, 4 h, 57%.

In conclusion, the Smith group have successfully demonstrated the tandem cyclisation and Stevens rearrangement methodology, followed by further chemical transformations, in acquiring a diazabicyclo-ring system in good yield. This was then coupled to tetronic and tetramic acid derivatives to furnish *stemofoline* mimcs. This approach can also be applied for the synthesis of other substituted pyrrolidines and derivatives of other cyclic amines such as proline.

Livingstone's stereocontrolled synthesis of bridged pyrrolizidines.[173]

Livingstone and co-workers devised an intramolecular allylsilane addition to iminium species for the construction bridged pyrrolizidine core unit present in *stemofoline*. They commenced their investigation with the intention of achieving high levels of diastereoselectivity, of which their where a few examples in the literature.[205-210]

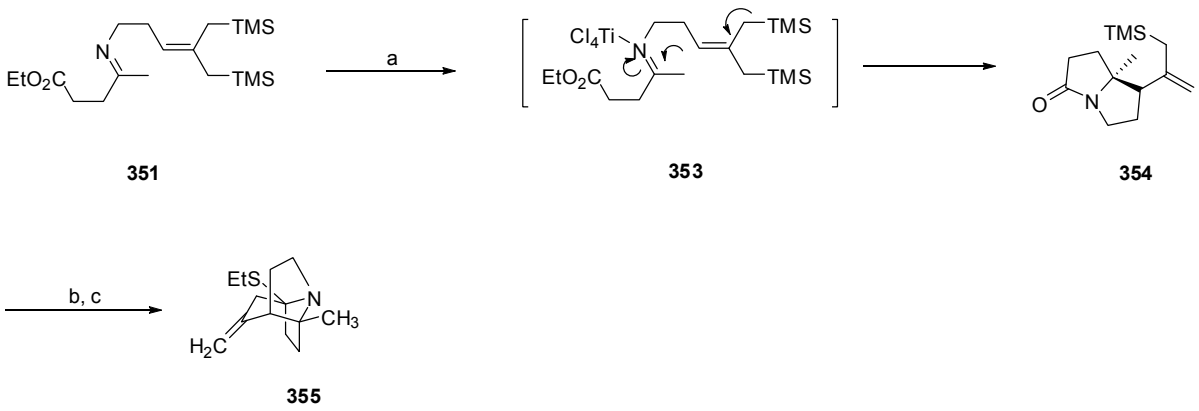
Monodesilylative cyclisation of imine **(347)** was attempted with successful activation with titanium tetrachloride, which was followed by treatment with potassium hydrogen carbonate to furnish the 1,2 disubstituted pyrrolidine **(349)** as a single isolated diastereomer in 98% yield (scheme 85). Sequential treatment of **(349)** with formaldehyde and trifluoroacetaic acid resulted in the second allylsilane cyclisation *via* intermediate **(350)** to provide the azabicyclic system **(351)**.



Scheme 85

Reagents & conditions: (a) $TiCl_4$, CH_2Cl_2, -78 °C to rt; (b) aqueous $KHCO_3$, 98 %; (c) CH_2O (2 equiv), H_2O-THF (3:1), (d) TFA (1.05 equiv), 0 °C to rt, 73%.

This methodology was further extended to assemble the core tricyclic pyrrolizidine structure of *stemofoline* by tandem intramolecular bis-silane iminium cyclisation. Imine **(351)** was pre-complexed with titanium chloride which initiated the stereoselective allylsilane-iminium cyclisation to provide pyrrolizidine **(354)** as a single isolated diastereomer (scheme 86). Functional group interconversion with Lawesson's reagent provided thiolactam which was *S*-alkylated followed by an additional intramolecular desilylative cyclisation delivered the tricyclic compound **(355)** in 90% isolated yield.



351 **353** **354** **355**

Scheme 86

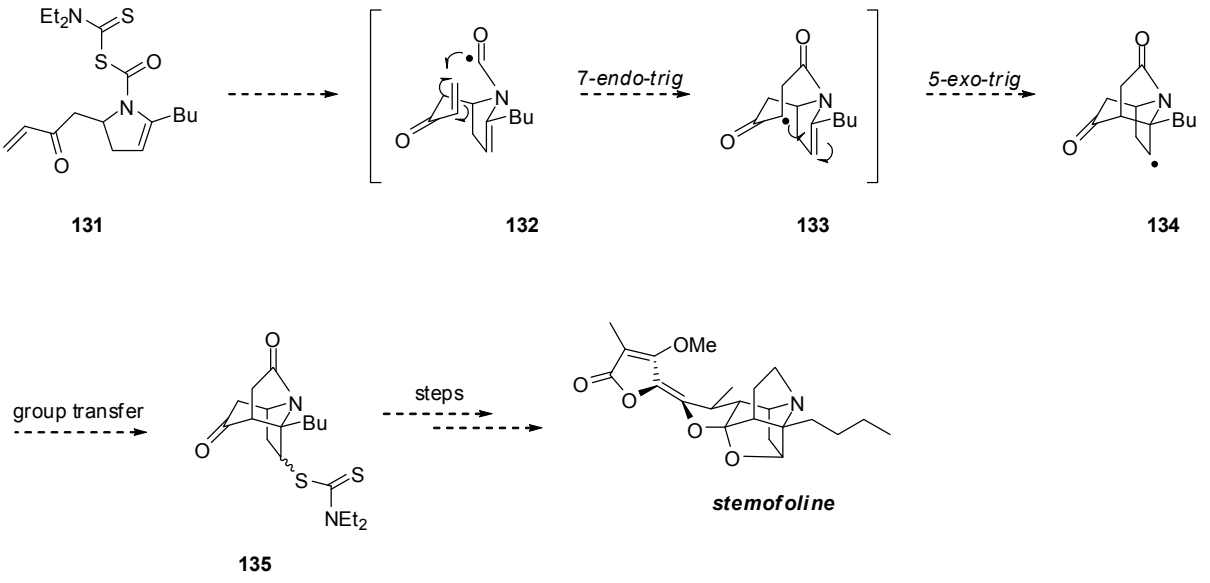
Reagents & conditions: (a) $TiCl_4$, CH_2Cl_2, -78 °C to rt, then aqueous $KHCO_3$, 80%; (b) Lawessons reagent (0.55 equiv), DIPEA (0.25 equiv), 97% (c) Et_3OBF_4, MeCN, 0 °C to rt, 90%.

In summary, Livingstone and co-workers have demonstrated the power of 2-propylidene-1,3-bis(silane) derivatives to act as bis-nucleophiles in forming the bridged polycyclic units in highly efficient and stereoselctive manner which are prevalent in alkaloid natural products. They have utilised this methodology for the construction of azabicyclic and tricyclic ring systems found in tropane, and the more challenging stemona alkaloid natural products.

5. SYNTHETIC EFFORTS TOWARD *STEMOFOLINE*

Proposed synthesis of *stemofoline*

As previously discussed, the key step in the proposed synthesis of *stemofoline* is a tandem radical cyclisation followed by group transfer of carbamoyl dithiocarbamate **(131)**. Formation of carbamoyl radical **(132)** can arise by irradiation with a 500 W halogen lamp or with a chemical initiator such as lauroyl peroxide. Two successive radical cyclisations in a *7-endo-trig* and *5-exo-trig* fashion should deliver the secondary radical **(134)**. Finally, a dithiocarbamate group transfer with carbamoyl dithiocarbamate **(131)** should furnish the desired product **(135)**, which can be further elaborated to deliver *stemofoline* (scheme 30). This strategy is quite unique from those previously discussed earlier in section 1. Therefore the primary aim of the project is the synthesis of cyclisation precursor **(131)**, initially in racemic form. If the tandem cyclisation-group transfer strategy proves successful, an asymmetric approach can be considered.

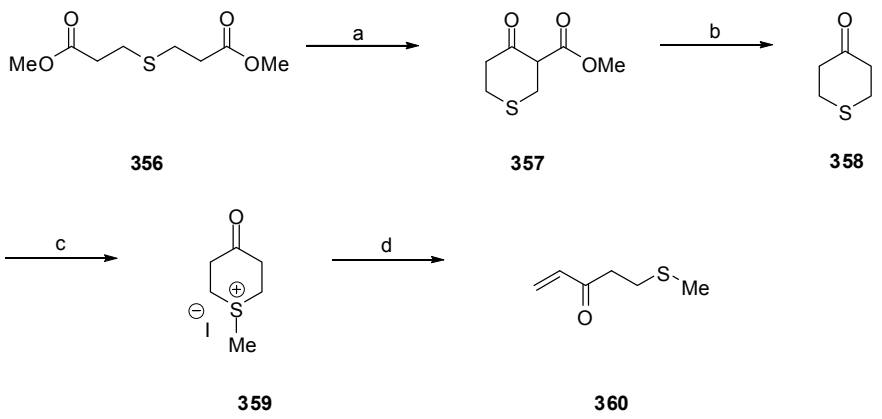


Scheme 30

Route to cyclisation precursor *via* carbamoyl chloride.

The synthesis began with a Dieckmann cyclisation from the commercially available dimethyl 3,3-thiodipropionate **(356)** with sodium methoxide in THF to furnish the dicarbonyl species **(357)** in

92% yield. A one pot ester hydrolysis of **(387)** followed by decarboxylation was achieved under acidic conditions by refluxing the reaction mixture in aqueous sulfuric acid to provide the desired tertrahydrothiopyranone **(358)** in 80% yield.[211] With this commercially expensive material in hand, tetrahydrothiopyranone **(358)** was activated with iodomethane in acetone to deliver the sulphonium salt **(359)** in 53% yield after two days at room temperature. Under solvent free conditions using excess iodomethane, an isolated yield of 93% was achieved after three days at room temperature. Treatment of sulphonium salt **(359)** with Hünig's base in a 9:1 mixture of acetonitrile and water afforded the conjugated enone motif **(360)** in 78% isolated yield after column chromatography (scheme 87).

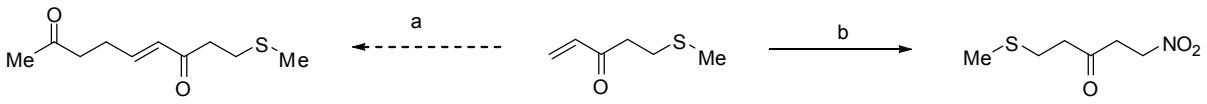


Scheme 87

Reagents & conditions: a) NaOMe (1.3 eq), THF, rt, 4 h, 92%; b) H_2SO_4 (10%), reflux, 1 h, 80%; c) MeI (20 eq), rt, 3 d, 93%; d) DIPEA (3 eq), MeCN/H_2O (9:1), rt, 2 d, 78%.

With this key intermediate in hand, a model cross metathesis reaction was attempted with 5-hexene-2-one, which if successful would provide a plausible pathway to our primary target **(131)**. Unfortunately the attempted metathesis of enone **(360)** with 5-hexen-2-one, employing Grubb's second generation catalyst, failed to deliver the desired compound **(361)**.[212] This lack of reactivity is presumably attributed to the lone pair of sulfur occupying a coordination site on ruthenium,

hence acting as a poison for the catalyst. Attention therefore quickly turned to an alternative strategy based on a 1,4-conjugate addition reaction. Enone **(360)** was first subjected to sodium nitrate and acetic acid in THF providing the β-nitro ketone **(362)**, albeit in a very low isolated yield of 30% after column chromatography. Increasing the stoichiometry of reagents to two equivalents of sodium nitrate and acetic acid had a positive result as the desired compound was isolated in 75% isolated yield based on recovered starting material (scheme 88).[213]

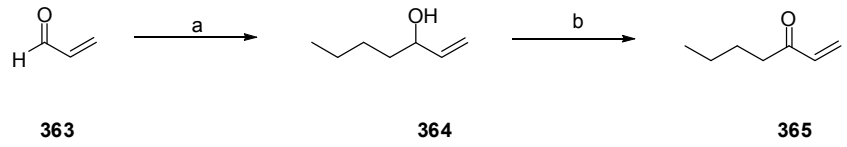


361 **360** **362**

Scheme 88

Reagents & conditions: a) 5-hexene-2-one. Grubbs 2nd generation catalyst (5-10 mol%), DCM, reflux; b) $NaNO_2$ (2 eq), AcOH (2 eq), THF, rt, 2 d, 75% BRSM.

Having β-nitro ketone available, attention focused on the synthesis of the coupling partner, butyl enone **(365)**. Treatment of commercially available acrolein **(363)** with *n*-butyllithium in THF proceeded smoothly through a 1,2 addition to yield the butyl allylic alcohol **(364)** in an excellent isolated yield of 92%.[214] Attempted oxidation of allylic alcohol **(364)** with a large excess of activated manganese dioxide[215] or under Swern[216] conditions proved ineffective, leaving the majority of the starting material unconsumed by TLC analysis. Eventually the allylic alcohol was oxidised with the hypervalent iodine oxidant IBX in DMSO to gratifyingly furnish the requisite butyl enone **(365)** in 88% isolated yield (scheme 89).[217]

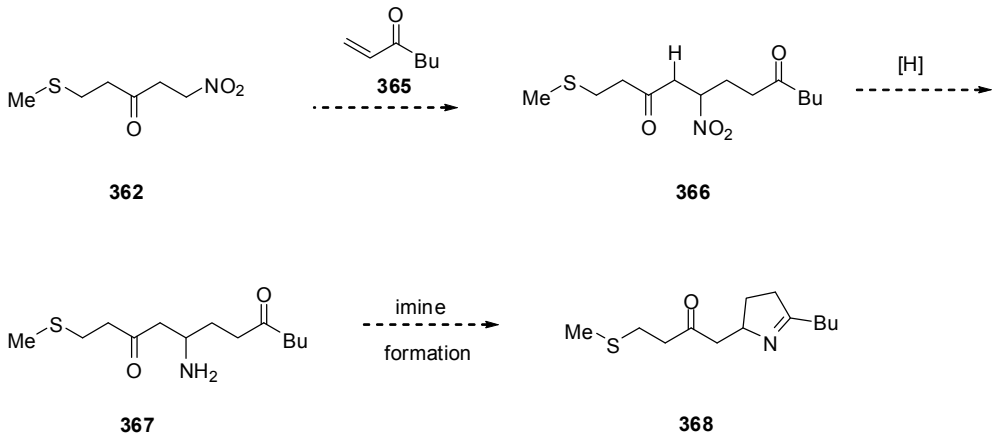


363 **364** **365**

Scheme 89

Reagents & conditions: a) *n*- BuLi, -78 °C, THF, rt, 16 h, 92%; b) IBX (2 eq), DMSO, rt, 3 h, 88%.

From the outset, the focus was on synthesising butyl imine species **(368)**, which can be derived from β-nitro ketone **(366)** and keto amine **(367)**. An initial conjugate addition of the nitronate anion of **(362)** onto butyl enone **(365)** should result in the functionalised β-nitro ketone **(366)**. A chemoselective nitro reduction of **(366)** should furnish keto amine **(367)**, which through intramolecular reductive amination would deliver the advanced cyclic imine intermediate **(368)** (scheme 90).



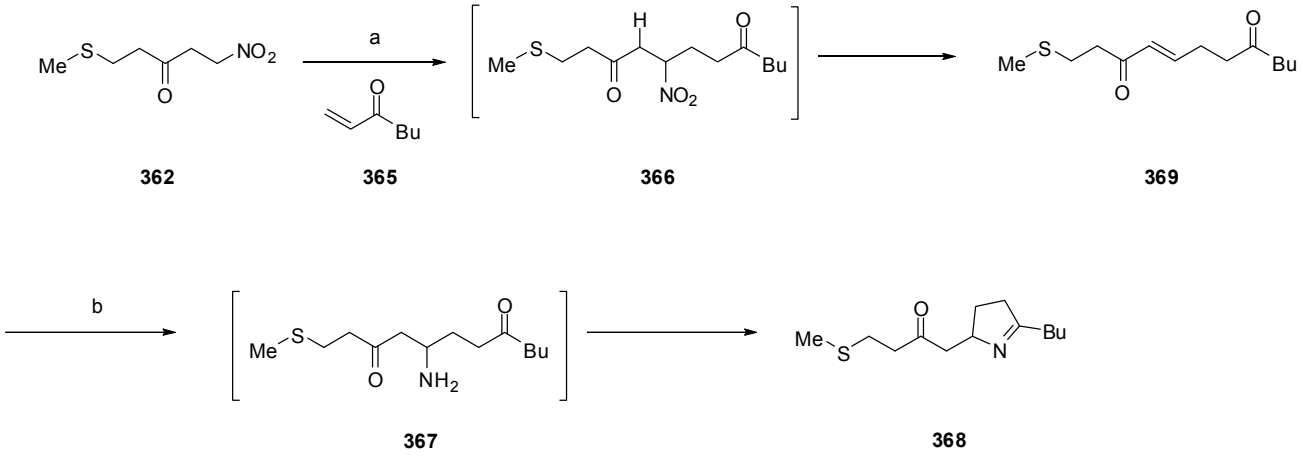
362 **366**

367 **368**

Scheme 90

Having established synthetic routes to the respective coupling partners **(362)** and **(365)**, 1,4-conjugate addition step was attempted, anticipating the formation of an isolable β-nitro ketone **(366)**. However, this intermediate was not observed by ^{1}H NMR spectroscopy or isolated upon

treatment with basic alumina in DCM. Instead the potentially useful enone species **(369)** was isolated, albeit in poor yield after column chromatography.[218, 219] The mechanism of this transformation is believed to occur initially by means of a 1,4-Michael addition of the nitronate anion of **(362)** onto the butyl enone **(365)** resulting in intermediate **(366)**, which was subsequently followed by a rapid elimination of HNO_2. Although this was not the desired outcome from the conjugate addition reaction, it was recognised that conjugate addition of ammonia to enone **(369)** should furnish keto amine **(367)**. Pleasingly, ammonia addition onto enone **(369)** directly provided the cyclic butylimine **(368)** in a one pot conversion (scheme 91).

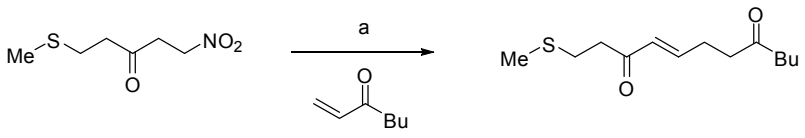


Scheme 91

Reagents & conditions: a) basic Al_2O_3 (40 eq), DCM, rt, 16 h, 15%; b) aq NH_3, MeOH, rt, 16 h, 88%.

In an attempt to optimise the preparation of enone **(369)**, various bases were screened.[220-230] The desired enone **(369)** was only isolated upon treatment with a large excess of basic alumina (20 equivalents), whereas anything less resulted in no reaction (table 1, entries 1-4). Increasing the stoichiometry of basic alumina to 40 equivalents furnished the required enone **(369)** in 15% isolated yield after column chromatography (table 1, entry 5). Using alternative bases such as DBU and sodium hydride resulted in complete decomposition of both substrates, whilst

employing sodium acetate in DMSO resulted in complete lack of reaction as both substrates were recovered (table 1, entries 6-8). The use of potassium carbonate, aqueous sodium hydroxide or Hünig's base also proved unsuccessful, leading to complete decomposition of both substrates (table 1, entries 8-11). Despite the low yield of **(369)**, it was decided to continue with the synthesis of carbamoyl dithiocarbamate **(131)**, in order to test the key tandem radical cyclisation and group transfer methodology.



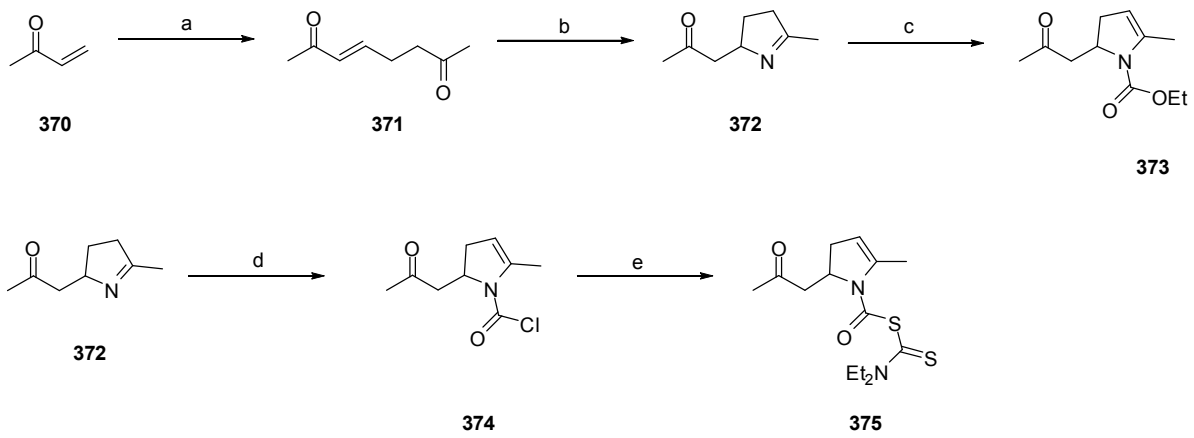
362 **365** **369**

Entry	Reagents	Temperature	Time (h)	Outcome
1	Enone **(365)** (1.5 eq), Al_2O_3 (2 eq) DCM	rt	16	No reaction
2	Enone **(365)** (1.5 eq), Al_2O_3 (4 eq) DCM	rt	16	No reaction
3	Enone **(365)** (1.5 eq), Al_2O_3 (12 eq) DCM	rt	16	No reaction
4	Enone **(365)** (1.0 eq), Al_2O_3 (20 eq) DCM	rt	16	< 10 %
5	Enone **(365)** (1.0 eq), Al_2O_3 (40 eq) DCM	rt	16	15 %
6	Enone **(365)** (1 eq), DBU (1 eq, MeCN	rt	2 h	decomposition
7	Enone **(365)** (1 eq), NaH (10 eq), THF	rt	16	decomposition
8	Enone **(365)** (1 eq), sodium acetate (1 eq), DMSO	rt	16	No reaction
9	Enone **(365)** (1 eq), K_2CO_3 (2 eq), H_2O	rt	16	decomposition
10	Enone **(365)** (1 eq), aq NaOH, TBAB	rt	16	decomposition
11	Enone **(365)** (1 eq), DIPEA (up to 2 eq), $CHCl_3$	rt	16	decomposition

Table 8: Attempted conjugate addition – elimination of **362** to **369**

Previous work within the Grainger group suggested that formation of carbamoyl chlorides from amines at most require 16 hours stirring at room temperature.[88] Displacement of carbamoyl chlorides with sodium diethyldithiocarbamate trihydrate salt at ambient temperature provides

carbamoyl dithiocarbamates. However, acylation of cyclic imines with triphosgene followed by sodium diethyldithiocarbamate displacement to form carbamoyl dithiocarbamates had never been previously attempted within the group. On that basis, a model study was pursued to establish the reactivity of imines towards acylating agents, in particular with triphosgene to form carbamoyl chlorides followed by subsequent displacement with sodium diethyldithiocarbamates to furnish carbamoyl dithiocarbamates. Dimerisation of methylvinyl ketone **(370)** with sub-stoichiometric amounts of sodium nitrite and acetic acid in DMSO resulted in 1,6-diketone **(371)** in 86% yield in a one pot transformation.[231] Conjugate addition with aqueous ammonia followed by dehydration provided the corresponding cyclic imine **(372)** in 71% yield.[232] At this point prior to acylation with triphosgene, cyclic imine **(372)** was reacted with ethyl chloroformate which proceeded to deliver ethyl carbamate **(373)**, in poor isolated yield of 28%.[233] Treatment of **(372)** with sub-stoichiometric amounts of triphosgene and a slight excess of pyridine in toluene at ambient temperatures provided carbamoyl chloride **(374)**, which was directly used in the subsequent step without further purification. Displacement of chloride with sodium diethyldithiocarbamate trihydrate in refluxing acetone provided the desired bright yellow carbamoyl dithiocarbamate **(375)** in 52% isolated yield over two steps (scheme 92). Gratifyingly, this particular model study set excellent precedent for the assembly of carbamoyl dithiocarbamates from imines for incorporation in the real system.

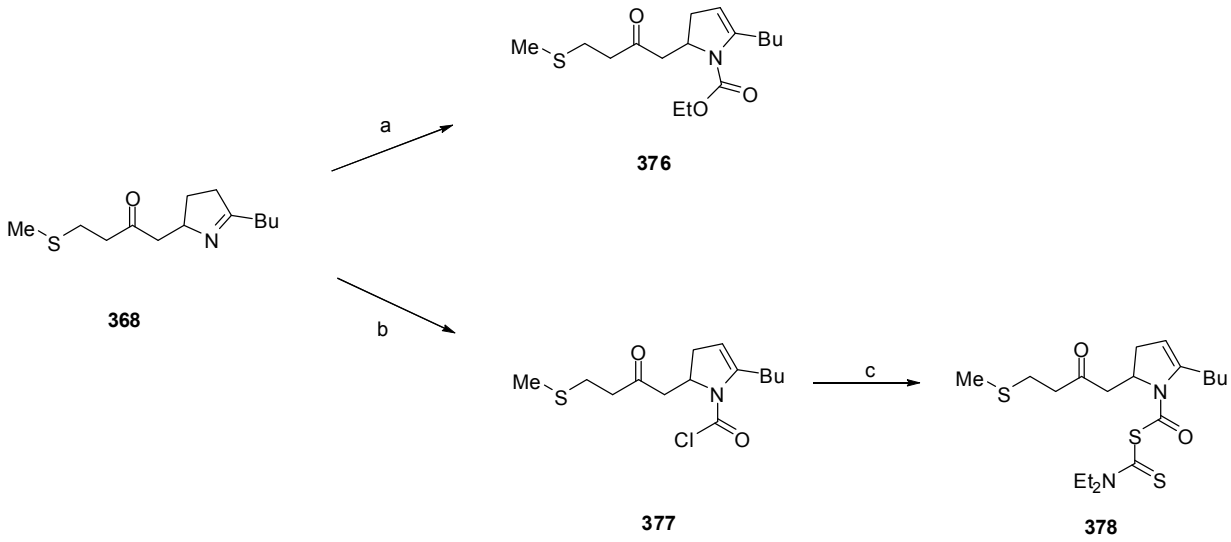


Scheme 92

Reagents & conditions: a) $NaNO_2$ (5 eq), AcOH (5 eq), DMSO, 86%; b) NH_3, MeOH, rt, 16 h, 71%; c) EtOCOCl (2 eq), Et_3N (2 eq), THF, -78 °C to rt, 16 h, 28%; d) triphosgene (0.33 eq), pyridine (1.5 eq), toluene, rt, 16 h; e) sodium diethyldithiocarbamate trihydrate (2 eq), acetone, reflux, 2 h, 52% over two steps.

As before, prior to acylating cyclic imine **(368)** with triphosgene, **(368)** was treated with ethyl chloroformate and triethylamine in THF to furnish carbamate **(376)** in a very good isolated yield after column chromatography.[233] This was encouraging precedent for imine acylation, and thus progressed towards the preliminary target **(131)** using the group's chemistry. Cyclic imine **(368)** was treated with sub-stoichiometric amounts of triphosgene and slight excess of pyridine in toluene to provide carbamoyl chloride **(377)**, which was used directly in the subsequent step. However, direct displacement with sodium diethyldithiocarbamate trihydrate salt in acetone at room temperature disappointingly failed to yield the desired carbamoyl dithiocarbamate **(378)**. Fortunately, it was possible to obtain carbamoyl dithiocarbamate **(378)** after refluxing compound **(377)** in acetone after 4 hours. Purification by column chromatography proved difficult as the desired species ran extremely close to unknown impurities and product degradation was observed

by TLC over time. Despite these problems, carbamoyl dithiocarbamate **(378)** was isolated in 44% yield over two steps from cyclic imine **(368)** (scheme 93).



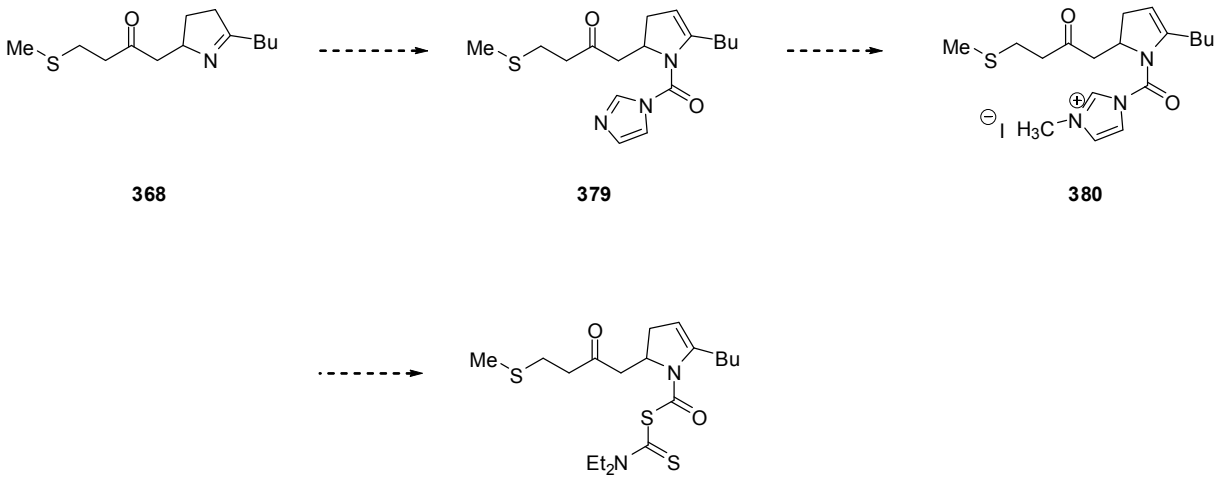
Scheme 93

Reagents & conditions: a) EtOCOCl (2 eq), Et_3N (2eq), THF, -78 °C to rt, 16 h, 80%; b) triphosgene (0.33 eq), pyridine (1.5 eq), toluene, rt, 16 h; c) sodium diethyldithiocarbamate trihydrate (4 eq), acetone, reflux, 4 h, 44% over two steps from **368**.

Proposed route to cyclisation precursor *via* imidazolide

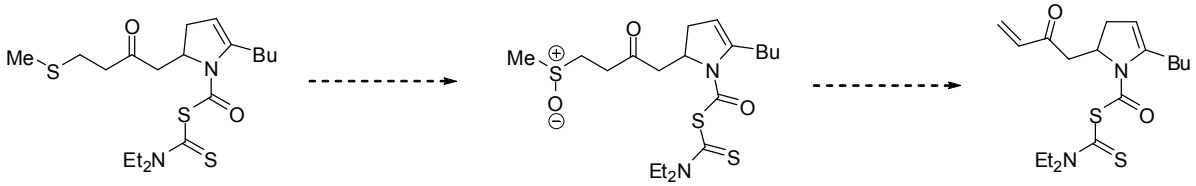
With a disappointing overall yield of carbamoyl dithiocarbamate **(378)**, an alternative approach utilising carbonyl diimidazolium chemistry was investigated.[103] Previous work on carbonyl diimidazolium chemistry in the group was established using secondary amines, but never with imines. It was anticipated that treatment of cyclic imine **(368)** with carbonyl diimidazole would furnish imidazolide **(379)**, which followed by activation with iodomethane to deliver imidazolium salt **(380)**. Subsequent displacement with sodium diethyldithiocarbamate trihydrate in refluxing acetone would provide carbamoyl dithiocarbamate **(378)** (scheme 94). Unfortunately, imine **(368)** proved to be completely unreactive to carbonyl diimidazole even at elevated

temperature using high boiling solvents (toluene, reflux), and thus, this approach was abandoned. Therefore, for the purpose of the synthesis of cyclisation precursor **(131)**, the previous strategy was adopted.



Scheme 94

At this stage of the synthesis, a sulfide oxidation to the sulfoxide followed by elimination was anticipated to provide the cyclisation precursor **(131)**. A chemoselective oxidation of methyl sulfide **(378)** with an electrophilic oxidant such as *m*CPBA should deliver sulfoxide **(381)**, although it was not clear which is the most nucleophilic sulfur. Bearing in mind the relative instability of carbamoyl dithiocarbamate **(378)**, it was immediately subjected to the subsequent oxidation step; initially with *m*CPBA.[234] Dropwise addition of a solution of *m*CPBA in DCM to a solution of **(378)** in DCM at 0 °C and subsequent warming to ambient temperature resulted in a complex mixture of products by TLC analysis. Unfortunately, the same outcome was observed with the oxidants $NaIO_4$ and DMDO (scheme 95).[235, 236] Regrettably at this stage of the synthesis, it was not possible to advance any further to acquire the cyclisation precursor **(131)**; therefore an alternative approach was devised.

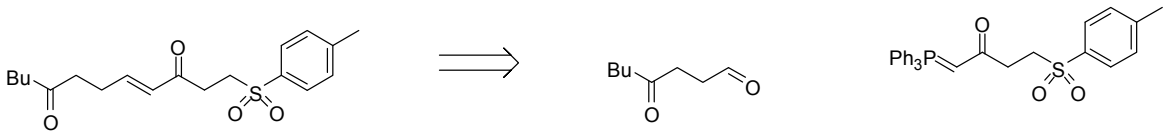


378 **381** **52**

Scheme 95

Proposed route to cyclisation precursor *via* Wittig olefination

A new strategy to synthesise carbamoyl dithiocarbamate **(131)** using a Wittig olefination as a key step to provide enone **(382)** was envisioned. This would arise from the coupling of 1,4-dicarbonyl **(383)** and triphenylphosphonium ylide **(384)**, respectively (scheme 100). The rationale for pursuing this enone intermediate species **382** is largely due to the instability of carbamoyl dithiocarbamates. In general they rapidly degrade in the presence of light and more specifically carbamoyl dithiocarbamate **(378)**, isolated in low yields, could not be effectively oxidised to the required sulfoxide **(381)**. With enone **(382)** there is the possibility of assembling the carbamoyl dithiocarbamate motif as the last synthetic step *en route* to cyclisation precursor **(131)**.

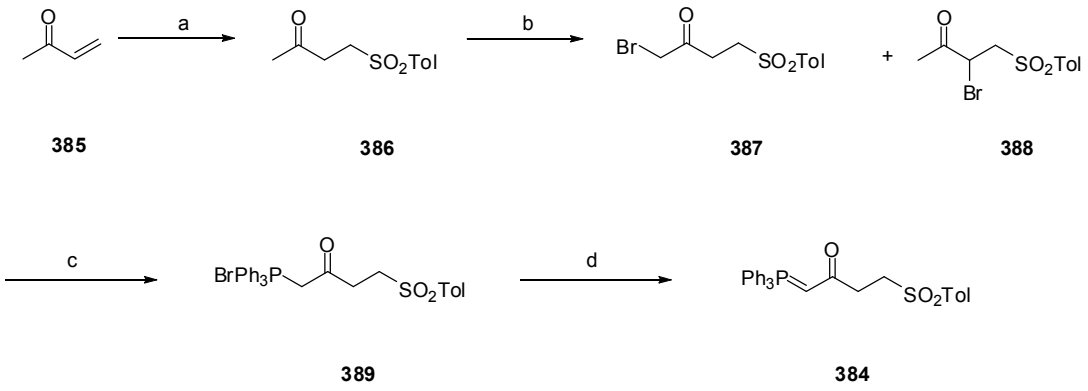


382 **383** **384**

Scheme 100

Synthesis of phosphonium ylid **(384)** was carried out as described in the literature.[237, 238] Conjugate addition of sodium tosylate hydrate with commercially available methylvinyl ketone **(385)** provided β-tosyl ketone **(386)**.[237] Kinetic bromination of **(386)** was best achieved with freshly prepared pyridinium perbromide[239] in acetic acid to deliver the desired brominated ketone **387)** in modest yield accompanied by its regioisomer **(388)**. Phosphorus ylide **(384)** was obtained

in excellent yield through the formation of phosphonium bromide salt **(389)**, followed by deprotonation using sodium hydroxide in methanol (scheme 101).[238]

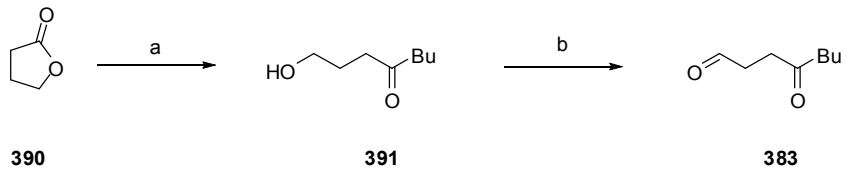


Scheme 101

Reagents & conditions: a) $NaSO_2Tol$, THF, rt, 16 h, 90%; b) $PyHBr_3$, AcOH, 70 °C, 16 h, **32**, 45%; c) PPh_3, toluene, 40 °C, 6 h, 87%; d) NaOH, MeOH, 0 °C, 30 min, 95%.

Synthesis of 1,4-dicarbonyl compound **(383)** commenced with treatment of commercially available *γ*-butyrolactone with *n*-butyllithium in diethyl ether at -78 °C followed by warming to ambient temperature to furnish alcohol **(391)** in 65% yield after column chromatography.[214] Oxidation of alcohol **(391)** to aldehyde **(383)** proved to be unexpectedly complicated, as various oxidants failed to deliver the desired compound in respectable yields. Oxidation using Jones reagent[240] only provided **(383)** in typically 15-20% isolable yield, whereas employing TPAP[236] with catalytic amounts of NMO only yielded 13% of **(383)** after purification. Changing oxidant to IBX in DMSO was particularly discouraging as it resulted in multiple spots by TLC.[217] Subjecting alcohol **(391)** to Swern conditions was most effective, delivering **(383)** in 40% yield (scheme 102).[216] After work up, the crude yield was in excess of 80% but a closer observation of TLC showed there was an impurity which ran extremely close to the desired product during chromatography. Thus, purification of **(383)** proved problematic despite attempted optimisation

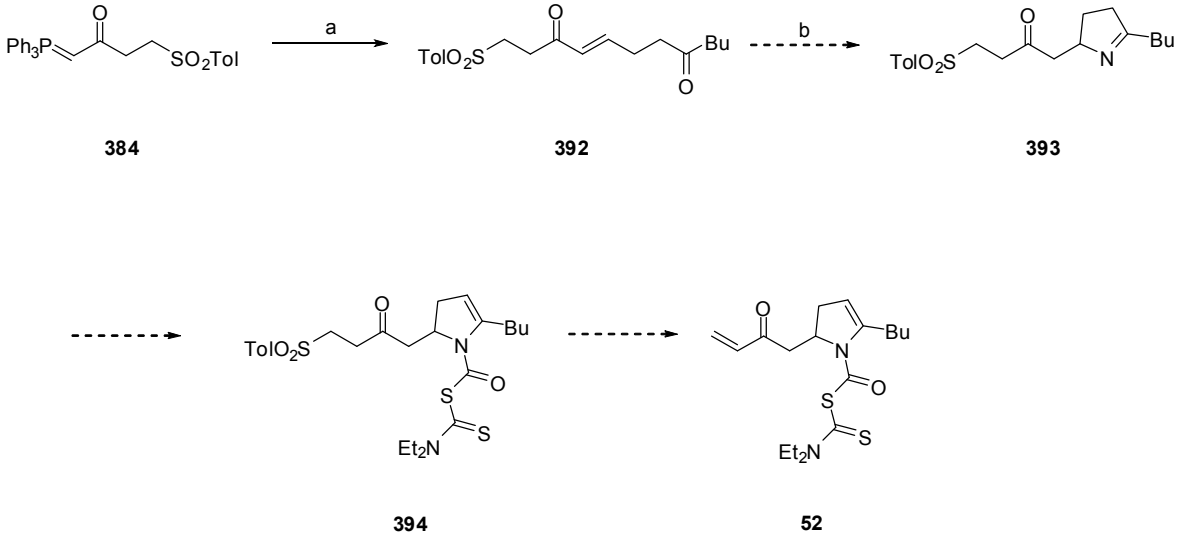
of the eluent system. Therefore, for the purposes of the synthesis only a small amount of pure material could be collected and carried forwards.



Scheme 102

Reagents & conditions: a) *n*-BuLi, Et_2O, -78 °C to rt, 16 h, 65%; b) DMSO (2 eq), $(COCl)_2$, Et_3N, DCM, -78 °C, 40%.

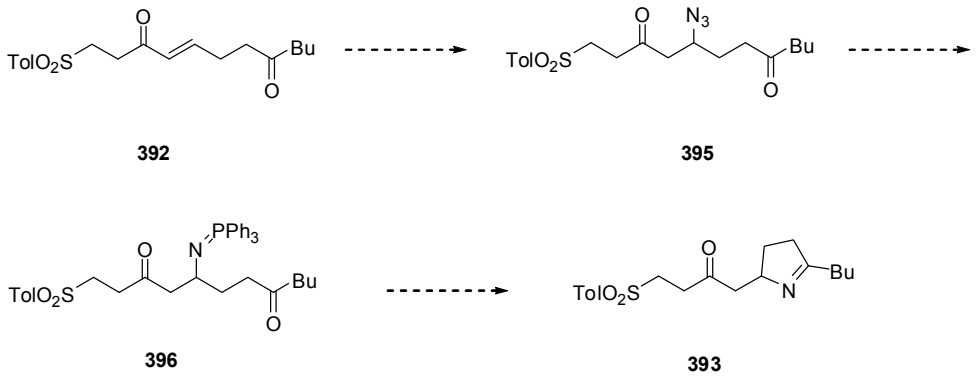
With the coupling partners **(383)** and **(384)** in hand, the Wittig olefination step was attempted, using toluene as solvent. At room temperature there was complete lack of reactivity, but slowly warming the reaction mixture up to 70 °C eventually led to the consumption of both starting materials. The optimised conditions for this olefination were heating the reaction mixture at 70 °C for four days, providing enone **(392)** in 67% isolated yield after purification. Unfortunately, the resultant enone **(392)** decomposed upon treatment with aqueous ammonia in methanol; hence butyl imine **(393)** was not obtained using this strategy. A possible factor contributing towards decomposition might be the ammonia promoted elimination of the tosylate group to provide an α,β-unsaturated system, which can also serve as a Michael acceptor site. Disappointingly, this failure to synthesise imine **(393)** prevented further study into the synthesis of cyclisation precursor **(131)** through the assembly of carbamoyl dithiocarbamate **(394)** and tosylate elimination (scheme 103).



Scheme 103

Reagents & conditions: a) **383**, toluene, 70 °C, 4 d, 67%; b) NH_3, MeOH, rt, decomposition.

An alternative strategy for the assembly of imine **(393)** was through an aza-Wittig reaction.[241-243] Conjugate addition of azide to enone **(392)** would deliver the azide species **(395)**, which would then be converted into ylide **(396)** by treatment with triphenylphosphine. Finally, an intramolecular aza-Wittig reaction driven by the formation of triphenylphosphine oxide should furnish the required imine **(393)** (scheme 104). However, this aza-Wittig approach failed at the very first as treatment of enone **(392)** with sodium azide proved ineffective.



Scheme 104

Conclusion and future work

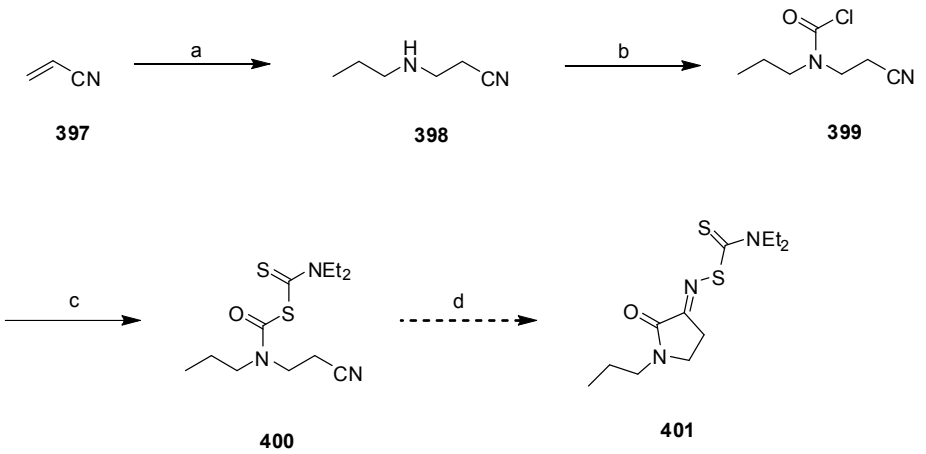
In summary, significant progress has been made towards the cyclisation precursor **(131)**, with the synthesis of the advanced intermediate, carbamoyl dithiocarmate species **(378)**. Regrettably, **(378)** could not be functionalised further to the desired sulfoxide which would have undergone a spontaneous elimination to give **(131)**. Alternatively, Wittig olefination and the aza-Wittig routes were investigated with minimal success.

However, a potential future route to **(131)** can arise from *S*-methylation and a base promoted elimination of **(378)**, as an alternative to sulfoxide elimination (an earlier adopted strategy to make enone **(360)** from tetrahydrothiopyranone **(356)**.

6. STUDY OF CARBAMOYL RADICAL CYCLISATIONS ONTO NITRILES AND ENONES

Attempted carbamoyl radical cyclisation onto nitriles

The study of carbamoyl radical cyclisation onto nitriles was initiated with a conjugate addition of propylamine onto acrylonitrile **(397)** to provide β-aminonitrile **(398)** in very good yield. Treatment of **(398)** with sub-stoichiometric amount of triphosgene and slight excess of pyridine in toluene resulted in carbamoyl chloride **(399)**, which was subsequently treated, without further purification, with excess sodium diethyldithiocarbamate trihydrate to give the carbamoyl dithiocarbamate **(400)** in excellent isolated yield after column chromatography.[88] Irradiation of **(400)** with a 500 W halogen lamp in cyclohexane resulted in full decomposition after 3.5 hours, and thus disappointingly, the desired cyclised product **(401)** was not obtained (scheme 105). Similarly, the use of a chemical initiator such as lauroyl peroxide resulted in a complicated mixtures by TLC analysis, and on that basis, this attempted carbamoyl radical cyclisation-dithiocarbamate group transfer was abandoned at this stage.

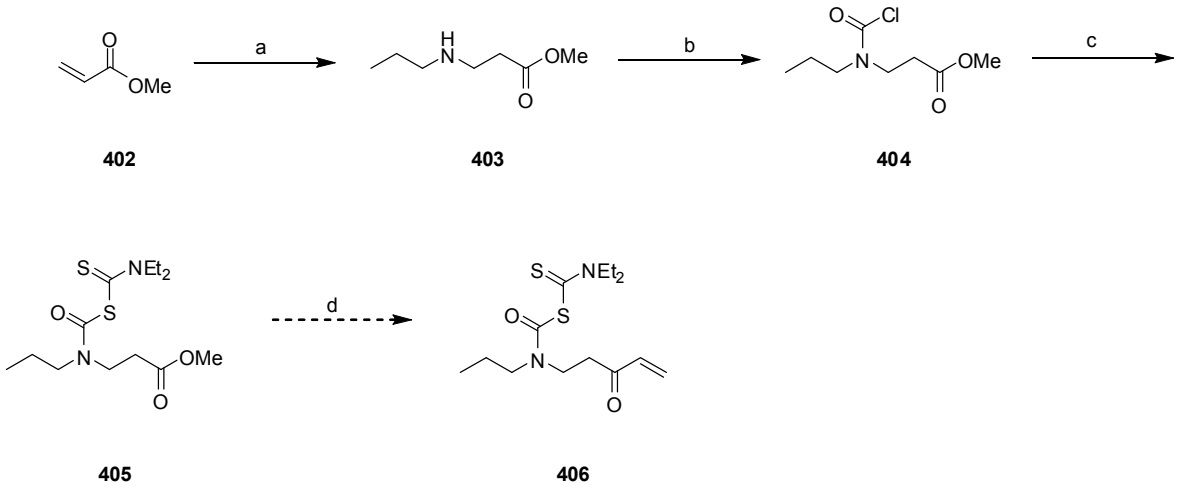


Scheme 105

Reagents & conditions: a) propylamine (1.1 eq), rt, 4 d, 82%; b) triphosgene (0.33 eq), pyridine (1.5 eq), toluene, rt, 1 h, 80%; c) sodium diethyldithiocarbamate trihydrate (4 eq), acetone, rt, 16 h, 91%; d) hν, cyclohexane, reflux, 3.5 h, decomposition.

Attempted carbamoyl radical cyclisation onto enones

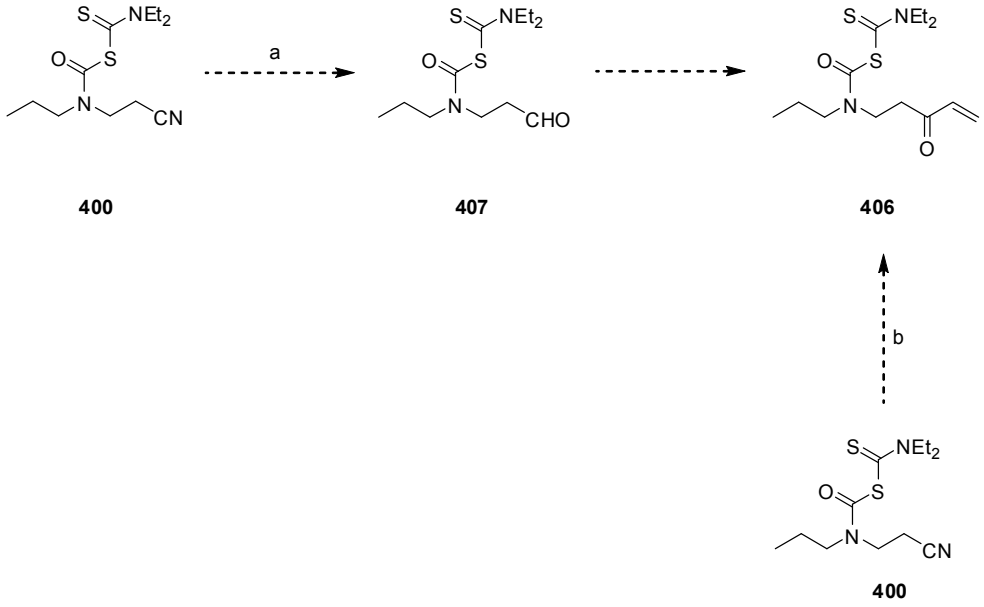
With the intention of studying carbamoyl radical cyclisation onto enones (a key step in the previously described approach to *stemofoline*), another model study was undertaken to test the feasibility of this methodology. Conjugate addition of propylamine onto methyl acrylate **(402)** resulted in amino ester **(403)** in moderate yield. Reaction of **(403)** with triphosgene and pyridine in toluene yielded carbamoyl chloride **(404)**, which was immediately treated with sodium diethyldithiocarbamate trihydrate to furnish carbamoyl dithiocarbamate **(405)** in 61% isolated yield after purification.[88] Transformation of ester **(405)** to the cyclisation precursor **(406)** was unsuccessful as treatment with vinylmagnesium bromide in THF resulted in decomposition (scheme 106).[244]



Scheme 106

Reagents & conditions: a) propylamine (1.1 eq), 0 °C to rt, 2 d, 54%; b) triphosgene (0.33 eq), pyridine (1.5 eq), toluene, rt, 1 h, quant; c) sodium diethyldithiocarbamate trihydrate (4 eq), acetone, rt, 16 h, 61%; d) vinyl magnesiumbromide, THF, rt, 3 d, decomposition.

Alternative approaches to the cyclisation precursor **(406)** were carried out which involved the chemoselective reduction of carbamoyl dithiocarbamate **(400)** with DIBAL-H to provide aldehyde **(407)**, which in turn would be treated with a vinyl Grignard reagent. However, chemoselective reduction of the nitrile failed to deliver aldehyde **(407)**.[245] Also, direct treatment of **(400)** with vinylmagnesium bromide led to a complicated mixture by TLC analysis, and thus, approaches towards cyclisation precursor **(406)** were abandoned at this stage.[244] As a consequence, the intramolecular carbamoyl radical cyclisation onto an enone could not be investigated further (scheme 107).



Scheme 107

Reagents & conditions: a) DIBAL-H (4.1 eq), DCM, -78 °C, 1 h, decomposition; b) vinyl magnesium bromide (2 eq), Et_2O, 0 °C to rt, multiple spots.

In summary, attempted radical cyclisation of carbamoyl radical onto nitriles failed to deliver the desired five-membered cyclised product *via* a *5-exo-dig* pathway as the reaction led to complicated mixtures by TLC analysis. Unfortunately, synthesis of cyclisation precursor **(406)**

proved ineffective and thus, intramolecular carbamoyl radical cyclisation of onto enone was not attempted.

7. EXPERIMENTAL SECTION

General experimental

^{1}H and ^{13}C NMR data were recorded on a Bruker AC300, Bruker AV300, Bruker AMX400 or a Brucker DRX500 spectrometer. Spectra were recorded in water or deuterochloroform referenced to residual $CHCl_3$ (^{1}H, 7.26 ppm; ^{13}C, 77.0) or D_6-DMSO referenced to residual D_5-DMSO (^{1}H, 2.50 ppm; ^{13}C, 39.43). Chemical shifts were measured in ppm (δ) and coupling constants (*J*) were measured in Hz. The following abbreviations are used; s-singlet, d-doublet, t-triplet, q-quartet, br-broad, ap. apparent. Mass spectra were obtained on a Jeol AX505W spectrometer using EI or CI or a Micromass LCT spectrometer utilising electrospray (ESI) ionisation (and a MeOH mobile phase), or on a VG ProSpec mass spectrometer utilising electron impact (EI) ionisation. Analytical HPLC was carried out on a DIONEX summit P580 quaternary low pressure gradient pump with built-in vacuum degasser using a Summit UVD 170s UV/VIS multi-channel detector with analytical flow cell and chromeleon software and HPLC grade solvents. Melting points were determined using open glass capillaries on a Gallenkamp melting point apparatus and are uncorrected. Analytical TLC was carried out on Merck 60 F_{245} aluminium backed silica gel plates. Short wave UV (245 nm), $KMnO_4$, anisaldehyde or vanillin were used to visualise components. Compounds were purified by column chromatography using Merck silica gel 60 (0.040 - 0.063 mm), or by fractional or bulb-to-bulb distillation.

Single crystal data for **168** and **174** was recorded at rt by Dr B. Kariuki, at the University of Birmingham, on a Bruker Smart 6000 diffractometer equipped with a CCD detector and a copper tube source. Structures were solved and refined using SHELXL (1). Non-hydrogen atoms were refined anisotropically and a riding model was used for C-H hydrogen atoms.

Single crystal data for ferrugine perchlorate salt were recorded by Dr. R. A. Stephenson at the University of Southampton on a Bruker instrument with an APEX CCD detector and a Bede Mo

Microsource. Structures were solved and refined using SHELXL (1). Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located from difference Fourier maps and their coordinates and isotropic atomic displacements were freely refined.

Solvents and reagents were purified as follows:

Solvents were degassed by bubbling nitrogen or argon through a needle immersed in the solvent for the stated length of time. *n*-BuLi was purchased as either 2.5 M or 1.6 M solutions in hexanes and the solutions were titrated with menthol in the presence of 1-(biphenyl-4-yl)-3-phenyl-2-azapropene or 1,10-phenanthroline. CuI was subjected to continuous extraction with THF overnight and dried under vacuum at 35 °C. $CuSO_4$ was dried by heating overnight in an oven set at 150 °C. Diisopropylamine was distilled from CaH_2 and stored over KOH pellets. Et_2O was distilled from sodium and benzophenone. NaH was freed of mineral oil by triturating three times with 60-80 °C pet. ether. *m*-CPBA was purified by washing with a pH 7 phosphate buffer (*vide infra*). Quinoline was distilled through a 30 cm *v*igreux column under reduced pressure. THF was distilled from sodium and benzophenone. TMEDA was distilled from CaH_2. Toluene was distilled from sodium. TMSCl was distilled from CaH_2. NEt_3 was distilled from, and stored over, 4 Å molecular sieves. All other reagents were purchased from Aldrich or Lancaster and were used as received. The following cooling baths were used; 0 °C (ice/water), – 48 °C (dry ice/MeCN), –78 °C (dry ice/acetone). All reactions in non-aqueous solvents were carried out under argon in oven-dried glassware.

***N, N*-Dimethyl-1-cyclopenten-1-amine (143).**

143

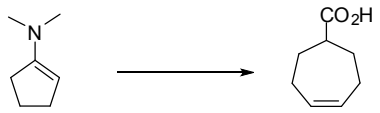
Prepared according to the literature procedure.[28]

Dimethylamine hydrochloride (40 g, 500 mmol) was dissolved in a minimum amount of water, and the resulting solution was added dropwise to sodium hydroxide (40 g, 1 mol) to produce dimethylamine as a gas which was passed through a drying tube containing sodium hydroxide and condensed in a flask submerged in a dry ice/acetone bath. After the addition of the solution was complete, the mixture was stirred for one hour and a slight vacuum was employed to transfer the remaining amine from the reaction flask to afford dimethylamine as a liquid (ca. 30 mL).

Liquid dimethylamine (30 mL) and cyclopentanone (10 mL, 113 mmol) were added to a suspension of calcium chloride in ether (200 mL) at -78 °C. The reaction mixture was allowed to warm to room temperature and stirred for 60 h. The solution was filtered, and the calcium chloride washed with ether (3 x 100 mL). Distillation under reduced pressure afforded enamine **(143)** (11.3 g, 90%) as a yellow oil, whose analytical data were in agreement with those reported in the literature.[28]

δ_H(300 MHz; $CDCl_3$) 1.73-1.83 (2 H, m), 1.97-2.02 (2 H, m), 2.19-2.23 (2 H, m), 2.48 (6 H, s, NCH_3 x 2), 4.07 (1H, s, CC*H*).

4-Cyclohepten-1-carboxylic acid (146).



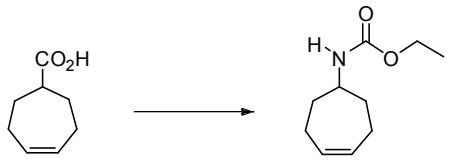
143 **146**

Prepared according to the literature procedure.[28]

Freshly distilled acrolein (5.11 mL, 68.9 mmol) was added dropwise over 1 h to enamine **(143)** (7.65 g, 68.9 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 3 h. Anhydrous acetonitrile (18 mL) was added, the solution was cooled to 0 °C, and iodomethane (4.18 mL, 103 mmol) was added dropwise over 5 min. The reaction mixture was allowed to warm to room temperature and stirred for a further 2 h. An aqueous solution of sodium hydroxide (20%, 75 mL) was added and the resultant mixture was heated at reflux for 16 h. The brown mixture was cooled, and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). Acidification (pH 1) of the aqueous layer with conc HCl (ca. 5 mL) afforded the acid **(146)** (2.25 g, 23%) as yellow precipitate, whose analytical data were in agreement with those reported in the literature.[28]

Mp 64-66 °C; δ_H(300 MHz; $CDCl_3$) 1.60-1.71 (2 H, m), 1.94-2.14 (4 H, m), 2.28-2.33 (2 H, m), 2.57-2.65 (1 H, m), 5.77 (2 H, s).

Cyclohept-4-enylcarbamic acid ethyl ester (154).



146 **154**

Method A:

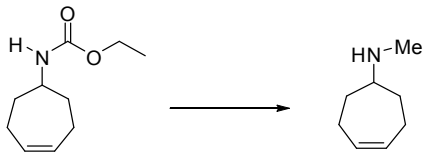
Prepared by modification of the literature procedure.[28]

To a solution of acid **(146)** (1.50 g, 10.71 mmol) in 1,2-dichloroethane (22.5 mL) was added *N,N*-diisopropylethylamine (1.95 mL, 21.42 mmol) and diphenyl phosphoryl azide (4.61 mL, 21.42 mmol). The reaction mixture was stirred at room temperature for 10 min and heated at reflux for 2 h. The mixture was allowed to cool to room temperature and concentrated under reduced pressure. Absolute ethanol (120 mL) was added to the reaction mixture and the resultant solution was heated at reflux for 3.5 d. The solvent was then removed under reduced pressure to give a brown oil which was purified by column chromatography (98:2 to 95:5, hexane/ethyl acetate) to afford the *title compound* **(154)** as a white solid (1.51 g, 77%). R_f 0.40 (4:1 hexane: ethyl acetate); mp 68-70 °C; ν_{max}(KBr disc)/cm^{-1} 3056 (N-H), 1755 (C=O), 1633 (C=C), 1602; δ_H(300 MHz; $CDCl_3$) 1.19 (3 H, t, *J* 7.1, OCH_2CH_3); 1.28-1.33 (2 H, m), 1.87-2.13 (6 H, m), 3.70-3.73 (1 H, m), 4.06 (2 H, q, *J* 7.1, OCH_2CH_3), 4.82 (1 H, br s, N*H*), 5.72-5.75 (2 H, m, *H*C=C*H*); δ_C(90 MHz; $CDCl_3$) 14.5 (CH_3), 24.2 (CH_2), 33.4 (CH_2), 53.5 (CH), 60.4 (CH_2), 131.7 (CH), 155.5 (C); *m/z* (HREI) 183.1266 (M^+. $C_{10}H_{17}NO_2$ requires 183.1259), (LREI) 183 (15%), 115 (82), 94 (100) and 79 (95).

Method B:

To a solution of acid **(146)** (5.0 g, 35.71 mmol) in 1,2-dichloroethane (7.5 mL) was added *N,N*-diisopropylethylamine (6.52 mL, 71.42 mmol) and diphenyl phosphoryl azide (15.4 mL, 71.42 mmol). The reaction mixture was stirred at room temperature for 10 min and heated at reflux for 2 h. The mixture was allowed to cool to room temperature and concentrated under reduced pressure. Absolute ethanol (300 mL) and copper (I) chloride (3.55 g, 35.70 mmol) was added to the reaction mixture and the resultant solution was strirred for 16 h at room temperature. Copper chloride was filtered off and concentrated under reduced pressure to leave a thick residue wihich was purified by column chromatography (98:2 to 95:5, hexane/ethyl acetate) to afford the *title compound* **(154)** as a white solid (2.89 g, 45%) whose analytical data were in agreement with method A.

5-Methylaminocycloheptene (155).

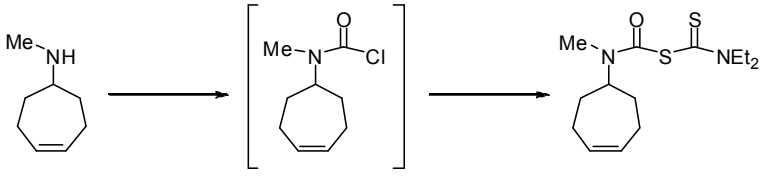


154 **155**

To a suspension of $LiAlH_4$ (1.94 g, 51.02 mmol) in dry diethyl ether (30 mL) was added dropwise a solution of carbamate **(154)** (1.0 g, 5.1 mmol) in diethyl ether (20 mL), and the resulting mixture was heated at reflux for 4 h. The solution was allowed to cool to room temperature and quenched with excess solution of saturated sodium potassium tartrate (50 mL) to leave two clear layers. The resulting solution was filtered and the residue was washed with diethyl ether (3 x 50

mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 x 25 mL). The combined organic layers were washed with brine (50 mL), dried over magnesium sulfate and concentrated under reduced pressure at 0 °C to afford the volatile *title compound* **(155)** as colourless oil (crude, 640 mg, 100%). R_f 0.10 (95:5 ethyl acetate: triethylamine); ν_{max}(neat)/cm^{-1} 2854, 2253, 1712, 1531, 1455; δ_H(300 MHz; $CDCl_3$) 1.29-1.34 (3 H, m), 1.82-1.91 (2 H, m), 1.96-2.05 (2 H, m), 2.17-2.21 (2 H, m), 2.43 (3 H, s, NC*H*$_3$), 2.55-2.61 (1 H, m, CH_2CHCH_2), 5.72-5.78 (2H, m, *H*C=C*H*); δ_C(75 MHz; $CDCl_3$) 24.6 (CH_2), 32.8 (CH_2), 34.0 (CH_3), 62.4 (CH), 131.8 (CH_2); *m/z* (HREI) 125.1201 (M^+. $C_8H_{15}N$ requires 125.1205), (LREI) and 125 (5%), 96 (15) and 57 (100),

***N*-Methyl-*N*-cyclohept-4-enylcarbamoylcarbodithioate (110).**

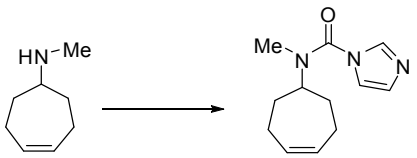


155 **156** **110**

To a solution of triphosgene (80 mg, 27 mmol) in dry THF (10 mL), was added pyridine (0.1 mL) dropwise and the resulting mixture was stirred at room temperature for 10 min. A solution of amine **(155)** (100 mg, 0.80 mmol) in dry THF (20 mL) was then added to the reaction mixture and heated at reflux for 16 h. The reaction was quenched with water (10 mL) and the aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with 0.033M HCl (20 mL), water (20 mL), brine (30 mL), dried over magnesium sulfate and concentrated under reduced pressure to afford the carbamoyl chloride **(156)** which was used directly in the next step without any purification (120 mg, 80%) as an orange oil. R_f 0.60 (4:1

ethyl acetate: hexane). A solution of *N*-methyl-*N*-cyclohept-4-enylcarbamoyl chloride **(156)** (120 mg, 0.64 mmol) in acetone (10 mL) was treated with sodium diethyldithiocarbamate trihydrate (0.56 g, 2.56 mmol). The reaction mixture was stirred overnight at room temperature and quenched with saturated aqueous solution of sodium hydrogen carbonate (5 mL). The aqueous layer was extracted with diethyl ether (3 x 30 mL) and the combined organic layers were washed with water (30 mL) and brine (30 mL). The organic phase was dried over magnesium sulfate and concentrated under reduced pressure and purified by column chromatography (9:1 hexane: ethyl acetate) to afford the *title compound* **(110)** as a yellow oil (150 mg, 79%, 63% over two steps). R_f 0.44 (4:1 ethyl acetate: hexane); ν_{max}(neat)/cm^{-1} 2927, 2853, 1668 (C=O), 1488; δ_H(300 MHz; $CDCl_3$) 1.13 (6 H, t, *J* 7.1, 2 x $NCH_2\mathit{CH_3}$); 1.21-1.34 (2 H, m), 1.41-1.53 (2 H, m), 1.75-1.81 (2 H, m), 2.04-2.29 (2 H, m), 2.68 (3 H, s, $N\mathit{CH_3}$), 3.14 (4 H, q, *J* 7.1, 2 x $N\mathit{CH_2}CH_3$), 3.65-3.73 (1 H, m, $CH_2C\mathit{H}CH_2$), 5.80-5.84 (2 H, m, *H*C=C*H*); δ_C(75 MHz; $CDCl_3$) mixture of rotamers, 11.0 (CH_3), 13.3 (CH_3), 25.1 (CH_2), 30.8 (CH_2), 31.0 (CH), 31.8 (CH_2), 42.1 (CH_2), 48.7 (CH_2), 49.8 (CH_2), 50.1 (CH_2), 60.2 (CH_3), 131.9 (CH), 161.4 (C), 185.1 (C); *m/z* (HRESI) 323.1236 (M^+. $C_{14}H_{24}N_2ONaS_2$ requires 323.1228) and (LRESI) 323.1 (100%).

5-Methylaminocycloheptene-imidazole-1-carboxamide (157).

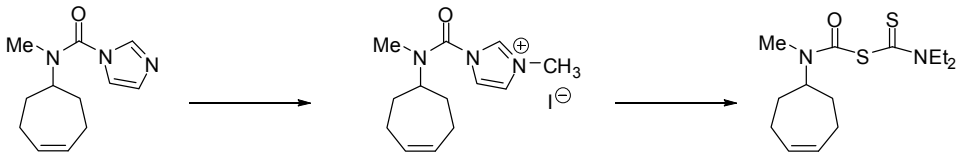


155 **157**

To a solution of 5-methylaminocycloheptene **(155)** (52 mg, 0.42 mmol) in THF (4 mL) was added in one portion carbonyldiimidazole (340 mg, 2.08 mmol) and K_2CO_3 (290 mg, 2.08 mmol).

The resulting mixture was heated at reflux for 16 h. The reaction mixture was allowed to cool to room temperature, water (10 mL) was added and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, concentrated under under reduced pressure and purified by column chromatography (EtOAc) to afford the *title compound* **(157)** as a white solid (73 mg, 80%); R_f 0.35 (ethyl acetate); mp 67-69 °C; ν_{max}(neat disc)/cm^{-1} 2932, 1686 (C=O), 1483, 1444, 1406; δ_H(300 MHz; $CDCl_3$) 1.49-1.61 (2 H, m), 1.81-1.86 (2 H, m), 1.95-2.06 (2 H, m), 2.18-2.27 (2 H, m), 2.89 (3 H, s, NCH_3), 4.01-4.09 (1 H, m), 5.76-5.81 (2 H, m), 7.03 (1 H, s,), 7.16 (1 H, s), 7.82 (1 H, s); δ_C(75 MHz; $CDCl_3$) 24.9 (CH_2), 30.9 (CH_2), 31.5 (CH_3), 61.7 (CH), 117.8 (CH), 129.3 (CH), 131.6 (CH), 136.7 (CH), 150.9 (C); *m/z* (HREI) 219.1378 (M^+. $C_{12}H_{17}N_3O$ requires 219.1372), LREI) and 219 (15%), 152 (70) and 95 (100).

_N_-Methyl-_N_-cyclohept-4-enylcarbamoylcarbodithioate (110).

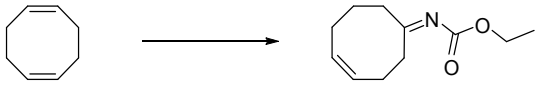


157 **158** **110**

To imidazolide **(157)** (66 mg, 0.28 mmol) was added MeI (2.0 g, 14.21 mmol) dropwise over 1 min and the resultant mixture was stirred at room temperature for 16 h. Excess solvent was removed under reduced pressure and the resultant white solid, imidazolium salt **(158)** (95 mg, 90%) was used in the next step without further purification. To a solution of imidazolium salt (32 mg, 0.09 mmol) in acetone (8 mL) was added sodium diethyldithiocarbamate (40 mg, 0.18 mmol) and the solution was heated to reflux for 5 h. The reaction mixture was cooled to room

temperature and water (5 mL) was added. The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic extracts were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (1:1 hexane: diethyl ether) to afford the *title compound* **(110)** (20 mg, 75%) as a yellow oil, whose analytical data were in agreement with the earlier procedure *via* carbamoyl chloride **(156).**

Ethyl-cyclooct-4-enyldiene-carbamate (409).



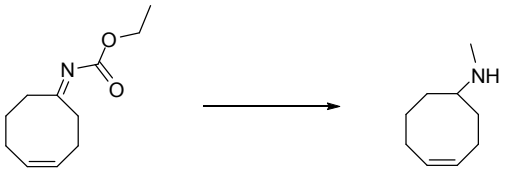
409

Prepared according to the literature procedure.[104]

A solution of ethyl azidoformate (5.70 g, 49.56 mmol) and cyclo-octadiene (20 mL) was heated at 100 °C for 16 h. The reaction mixture was cooled to room temperature, concentrated under reduced pressure and purified by reduced pressure distillation (0.02 mmHg, 142-146 °C) to afford carbamate **(409)** (6.55 g, 68%) as a colourless oil whose data were in agreement with those reported in the literature.[104]

ν_{max}(neat)/cm^{-1} 2936, 2864, 1718, 1663, 1539; δ_H(300 MHz; $CDCl_3$) 1.32 (3 H, t, *J* 7.1), 1.60-1.64 (5 H, m), 2.15-2.42 (5 H, m), 4.20-4.27 (2 H, q, *J* 6.2), 5.70-5.74 (2 H, m); *m/z* (LREI) 195 (60%), 194 (100) and 180 (25).

5-Methylaminocyclooctene (160).



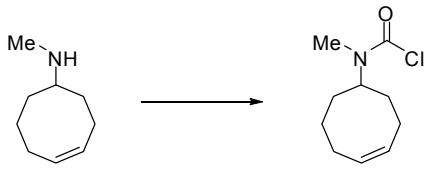
409 **160**

Prepared according to the literature procedure.[104]

To a suspension of $LiAlH_4$ (150 mg, 3.94 mmol) in dry diethyl ether (4 mL) was added dropwise a solution of **(409)** (512 mg, 2.63 mmol) in dry diethyl ether (5 mL), and the resulting mixture was heated at reflux for 4 h. The solution was allowed to cool to room temperature and quenched with excess solution of saturated sodium potassium tartrate (10 mL) to leave two clear layers. The resulting solution was filtered and the residue was washed with diethyl ether (3 x 20 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 x 25 mL). The combined organic layers were washed with brine (50 mL), dried over magnesium sulfate and concentrated under reduced pressure at 0 °C to afford the volatile amine **(160)** as colourless oil (320 mg, 87%) whose analytical data were in agreement with those reported in the literature.[104]

ν_{max}(neat)/cm^{-1} 2930, 2855, 1705, 1650, 1540, 1466, 1367; δ_H(300 MHz; $CDCl_3$) 1.18-1.42 (2 H, m), 1.52-1.84 (6 H, m), 2.02-2.20 (3 H, m), 2.36 (3 H, s, NCH_3), 2.44-2.48 (1 H, m), 5.56-5.70 (2 H, m); δ_C(75 MHz; $CDCl_3$) 23.6 (CH_2), 25.8 (CH_2), 26.6 (CH_2), 32.2 (CH_2), 33.9 (CH_3), 35.1 (CH_2), 60.0 (CH), 129.5 (CH), 130.0 (CH); *m/z* (LREI) 140.6 (100%).

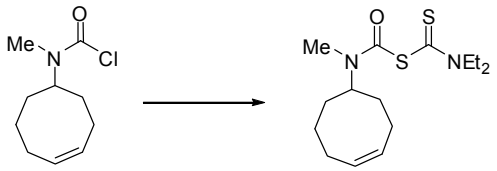
***N*-Methyl-*N*-cyclooctyl-4-enylcarbamoylchloride (161).**



160 **161**

To a solution of triphosgene (610 mg, 2.06 mmol) in dry toluene (38 mL), was added pyridine (0.92 mL) dropwise and the resulting mixture was stirred at room temperature for 10 min. A solution of amine **(160)** (860 mg, 6.19 mmol) in dry toluene (24 mL) was then added to the reaction mixture and stirred for 1 h at room temperature. The reaction was quenched with water (20 mL) and the aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over magnesium sulfate and concentrated under reduced pressure to afford the carbamoyl chloride **(161)** (510 mg, 65%) as an orange oil. R_f 0.5 (1:1 hexane: Et_2O); ν_{max}(neat)/cm^{-1} 2391, 2857, 1732 (CO), 1468, 1396, 1358; δ_H(300 MHz; $CDCl_3$) 1.58-1.77 (6 H, m), 2.13-2.35 (4 H, m), 2.88 & 2.96 (mixture of rotamers, 3 H, s, NCH_3), 4.18-4.40 (1 H, m), 5.65-5.72 (2 H, m); δ_C(75 MHz; $CDCl_3$) 23.0 (CH_2), 25.4 (CH_2), 26.3 (CH_2), 32.1 (CH_2), 32.6 (CH_2), 33.8 (CH_3), 59.1 (CH), 129.0 (CH), 130.3 (CH).

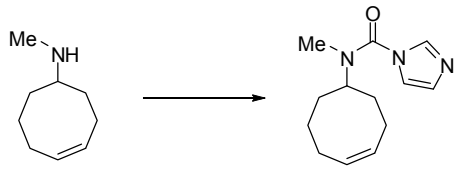
***N*-Methyl-*N*-cyclooctyl-4-enylcarbamoylcarbodithioate (159).**



161 **159**

A solution of *N*-methyl-*N*-cyclooct-4-enylcarbamoyl chloride **(161)** (2.10 g, 10.42 mmol) in acetone (100 mL) was treated with sodium dithiocarbamate trihydrate (4.40 g, 42.4 mmol). The reaction mixture was stirred overnight at room temperature and quenched with saturated aqueous solution of sodium hydrogen carbonate (20 mL). The aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic layers were washed with water (50 mL) and brine (50 mL). The organic phase was dried over magnesium sulfate and concentrated under reduced pressure and purified by column chromatography (2:1 hexane: diethyl ether) to afford the *title compound* **(159)** as a yellow oil. R_f 0.44 (4:1 ethyl acetate: hexane); ν_{max}(neat)/cm^{-1} 2932, 2857, 1667 (C=O), 1489, 1463, 1418; δ_H(300 MHz, $CDCl_3$); 1.30 (6 H, t, *J* 7.2), 1.69-1.72 (6 H, m), 2.14-2.29 (4 H, m), 2.87 (3 H, s, N*CH*$_3$), 3.76-4.01 (4 H, m), 4.37-4.43 (1 H, m), 5.63-5.69 (2 H, m); δ_C(75 MHz, $CDCl_3$) mixture of rotamers, 10.7 (CH_3), 12.9 (CH_3), 22.5 (CH_2), 22.8 (CH_2), 25.0 (CH_2), 25.4 (CH_2), 25.8 (CH_2), 26.0 (CH), 29.6 (CH_3), 31.1 (CH_3), 31.7 (CH_2), 31.9 (CH_2), 32.6 (CH_2), 32.8 (CH_2), 48.3 (CH_2), 49.5 (CH_2), 56.2 (CH), 58.4 (CH), 128.4 (CH), 128.8 (CH), 129.7 (CH), 130.1 (CH), 160.6 (C), 184.7 (C); *m/z* (HRESI) 337.1377 (M^+. $C_{15}H_{26}N_2ONaS_2$ requires 337.1384) and (LRESI) 337 (100%).

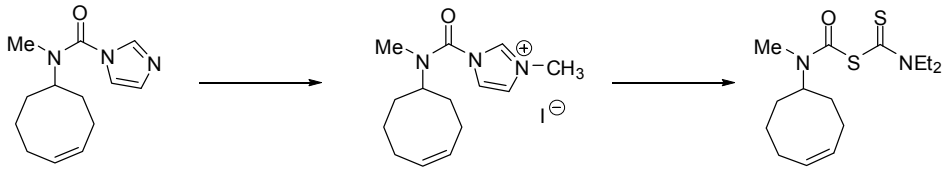
5-Methylaminocyclo-octene-imidazole-1-carboxamide (162).



160 **162**

To a solution of 5-methylaminocyclooctene **(160)** (70 mg, 0.50 mmol) in THF (10 mL) was added in one portion carbonyldiimidazole (580 mg, 2.5 mmol) and K_2CO_3 (500 mg, 2.5 mmol). The resulting mixture was heated at reflux for 16 h. The reaction mixture was allowed to cool to room temperature, H_2O (10 mL) was added and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, concentrated under under reduced pressure and purified by column chromatography (EtOAc) to afford the *title compound* **(162)** as a viscous oil (88 mg, 75%). R_f 0.35 (ethyl acetate); ν_{max}(neat disc)/cm^{-1} 2933, 2253, 1690 (C=O), 1468, 1444, 1407; δ_H(300 MHz; $CDCl_3$) 1.59-1.87 (5 H, m), 2.09-2.39 (5 H, m), 2.94 (3 H, s, NCH_3), 4.04-4.13 (1 H, m), 5.64-5.69 (2 H, m), 7.08 (1 H, s), 7.13 (1 H, s), 7.85 (1 H, s); δ_C(75 MHz; $CDCl_3$) 22.8 (CH_2), 25.3 (CH_2), 25.9 (CH_2), 31.9 (CH_3) 32.1 (CH_2), 32.6 (CH_2), 57.7 (CH), 117.7 (CH), 128.7 (CH), 129.9 (CH), 130.4 (CH), 136.6 (CH), 151.0 (C); *m/z* (HREI) 233.1535 (M^+. $C_{12}H_{19}N_3O$ requires 233.1528), (LREI) 233 (25%), 166 (70), 109 (60) and 67 (100).

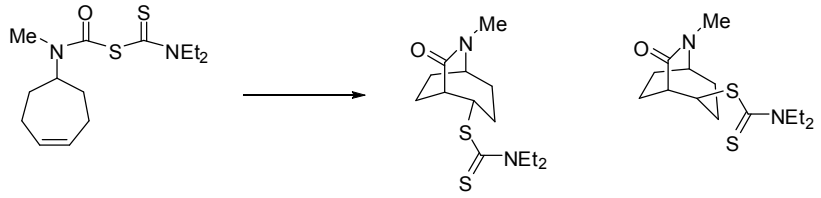
***N*-Methyl-*N*-cyclooctyl-4-enylcarbamoylcarbodithioate (159).**



162 **163** **159**

To imidazole-carboxamide **(162)** (85 mg, 0.36 mmol) was added MeI (2.5 g, 18.24 mmol) dropwise and the resultant mixture was stirred at room temperature for 16 h. Excess solvent was removed under reduced pressure and the resultant white solid, imidazolium salt **(163)** (131 mg, 97%) used in next step without purification. To a solution of imidazolium salt (61 mg, 0.16 mmol) in acetone (2 mL) was added sodium diethyldithiocarbamate (170 mg, 0.76 mmol) and the solution was heated at reflux for 16 h. The reaction mixture was cooled to room temperature and H_2O (5 mL) was added. The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic extracts were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (2:1 hexane : diethyl ether) to afford the *title compound* **(159)** (35 mg, 68%, 50% over three steps) as a yellow oil, whose analytical data were in agreement with those reported for the earlier procedure *via* carbamoyl choloride **(161)**.

***rac*-(1*R*, 2*S*, 5*R*)-6-Methyl-7-oxo-6-azabicyclo[3.2.2]nonan-2-yldiethylcarbamodithioate (164) and *rac*-(1*R*, 2*R*, 5*R*,)-6-Methyl-7-oxo-6-azabicyclo[3.2.2]nonan-2-yldiethylcarbamodithioate (165).**

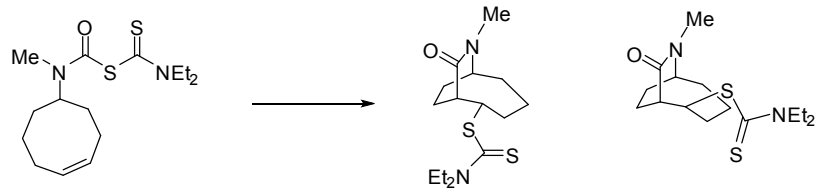


110 **164** **165**

Carbamoyl dithiocarbamate **(110)** (562 mg, 1.87 mmol) was dissolved in cyclohexane (17.5 mL) and irradiated with a 500 W halogen lamp that generated enough heat to bring the solvent to reflux. After 5 h the reaction mixture was allowed to cool to room temperature, concentrated under reduced pressure and purified by column chromatography (ethyl acetate) to afford first the *title compound* **(164)** (360 mg, 64%) as a yellow oil, followed by the *title compound* **(165)** (59 mg, 10%) as a yellow oil. **(164)** R_f 0.35 (ethyl acetate); ν_{max}(neat)/cm^{-1} 2934, 1649 (C=O), 1417; δ_H(300 MHz; $CDCl_3$) 1.24 (6 H, t, *J* 7.1, 2 x CH_2CH_3), 1.77-2.09 (7 H, m), 2.23-2.30 (1 H, m), 2.93-2.95 (1 H, d, *J* 4.9), 2.98 (3 H, s, NCH_3), 3.46-3.48 (1 H, m), 3.64-3.72 (2 H, m), 3.93-4.04 (2 H, m), 4.19-4.24 (1 H, dd, *J* 5.1 and 4.7); δ_C(75 MHz; $CDCl_3$) mixture of rotamers, 11.5 (CH_3), 12.4 (CH_3), 20.2 (CH_2), 24.0 (CH_2), 27.9 (CH_2), 31.2 (CH_2), 33.2 (CH_3), 46.5 (CH_2), 47.3 (CH), 49.0 (CH_2), 50.1 (CH), 55.5 (CH), 172.6 (C), 193.2 (C); *m/z* (HRESI) 323.1222 (M^+. $C_{14}H_{24}N_2ONaS_2$ requires 323.1228) and (LRESI) 325.1 (10%), 324.1 (15) and 323.1 (100). **(165)** R_f 0.28 (ethyl acetate); ν_{max}(neat)/cm^{-1} 2922, 2853, 1658 (C=O), 1462; δ_H(300 MHz; $CDCl_3$) 1.26 (6 H, t, *J* 7.2), 1.58-2.28 (8 H, m), 2.99 (3 H, s, NCH_3), 3.00-3.05 (1 H, m), 3.57-3.67 (2 H, m), 3.79-3.93 (2 H, m), 4.07-4.21 (2 H, m); δ_C(75 MHz; $CDCl_3$) mixture of rotamers, 11.5 (CH_3), 12.4 (CH_3), 20.2 (CH_2), 24.0 (CH_2), 28.0 (CH_2), 31.2 (CH_2), 33.3 (CH_3), 46.5 (CH_2), 47.3 (CH),

49.0 (CH_2), 50.1 (CH), 55.5 (CH), 172.6 (C), 193.2 (C); *m/z* (HRESI) 323.1223 (M^+. $C_{14}H_{24}N_2NaS_2$ requires 323.1228), (LRESI) 323.1 (100%) and 301.2 (40)

rac-(1*R*, 2*S*, 5*R*)-6-Methyl-7-oxo-6-azabicyclo[4.2.2]nonan-2-yldiethylcarbamodithioate (167) and _rac_-(1*R*, 2*R*, 5*R*,)-6-Methyl-7-oxo-6-azabicyclo[4.2.2]nonan-2-yldiethylcarbamodithioate (168).

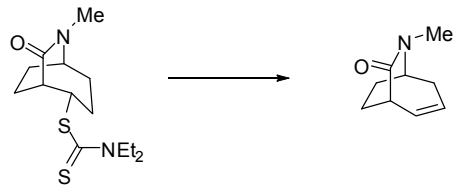


159 **167** **168**

Carbamoyl dithiocarbamate **(159)** (0.733 g, 2.33 mmol) was dissolved in cyclohexane (17.5 mL) and irradiated with a 500 W halogen lamp that generated enough heat to bring the solvent to reflux. After 5 h the reaction mixture was allowed to cool to room temperature, concentrated under reduced pressure and purified by column chromatography (ethyl acetate) to afford first the *title compound* **(167)** (352 mg, 48%) as a yellow oil, followed by the *title compound* **(168)** (142 mg, 20%) as a yellow oil. **(167)** R_f 0.40 (ethyl acetate); ν_{max}(neat)/cm^{-1} 2932, 2817, 1634 (C=O), 1486, 1442, 1417, 1356; δ_H(300 MHz; $CDCl_3$) 1.24 (6 H, t, *J* 6.9, 2 x NCH_2CH_3,), 1.50-1.54 (1 H, m), 1.73-1.80 (3 H, m), 1.96-2.27 (5 H, m), 2.93 (3 H, s, NCH_3), 3.12-3.17 (1 H, m), 3.65-3.74 (4 H, m), 3.96-4.03 (2 H, m), 4.45-4.51 (1 H, m); δ_C(75 MHz; $CDCl_3$) 11.5 (CH_3), 12.5 (CH_3), 20.4 (CH_2), 21.5 (CH_2), 25.6 (CH_2), 31.6 (CH_2), 34.0 (CH), 34.7 (CH_2), 44.4 (CH), 46.5 (CH_2), 49.1 (CH_2), 56.1 (CH), 173.0 (C), 193.4 (C); *m/z* (HRESI) 337.1375 (M^+. $C_{15}H_{26}N_2ONaS_2$ requires 337.1384) and (LRESI) 337.2 (100%). **(168)** R_f 0.20; ν_{max}(neat)/cm^{-1} 2932, 1633 (C=O),

1487, 1417, 1268; δ_H(300 MHz; $CDCl_3$) 1.26 (6 H, t, *J* 7.1, 2 x NCH_2CH_3), 1.76-1.79 (6 H, m), 2.07-2.32 (4 H, m), 3.01 (3 H, s, NCH_3), 3.14-3.18 (1 H, m), 3.85-3.96 (4 H, m), 4.04-4.13 (1 H, m), 4.31-4.36 (1 H, m); δ_C(75 MHz; $CDCl_3$) 11.5 (CH_3), 12.4 (CH_3), 23.0 (CH_2), 23.5 (CH_2), 26.0 (CH_2), 31.44 (CH_2), 33.0 (CH_2), 33.9 (CH), 44.8 (CH), 46.5 (CH_2), 49.2 (CH_2), 58.7 (CH_2), 171.5 (C), 195.2 (C) *m/z* (HRESI) 337.1376 (M^+. $C_{15}H_{26}N_2ONaS_2$ requires 337.1384) and (LRESI) 337.1 (100%).

***rac*-6-Methyl-7-oxo-6-azabicyclo[3.2.2]non-2-ene (173).**

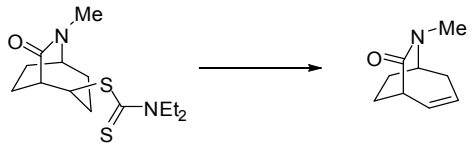


164 **173**

Method A: from **(164)**.

A solution of *rac*-(1*R*, 2*S*, 5*R*)-6-methyl-7-oxo-6-azabicyclo[3.2.2]nonan-2-yl diethylcarbamodithioate **(164)** (200 mg, 0.67 mmol) in diphenyl ether (6 mL) was heated at reflux for 2 h. The reaction mixture was allowed to cool to room temperature and purified by column chromatography (1:1 hexane: ethyl acetate) to afford the *title compound* **(173)** as a brown solid (90 mg, 89%). R_f 0.30 (ethyl acetate); mp 53-55 °C; ν_{max}(KBr disc)/cm^{-1} 2957, 1654 (C=O), 1488; δ_H(300 MHz; $CDCl_3$) 1.79-2.22 (5 H, m), 2.53-2.63 (1 H, m), 2.97 (3 H, s, NCH_3), 2.97-2.93 (1 H, m), 3.49-3.54 (1 H, m), 5.50-5.56 (1 H, m), 5.88-5.94 (1 H, m); δ_C(75 MHz; $CDCl_3$) 25.7 (CH_2), 28.8 (CH_2), 32.5 (CH_3), 34.7 (CH_2), 42.1 (CH), 55.0 (CH), 127.3 (CH), 127.9 (CH),

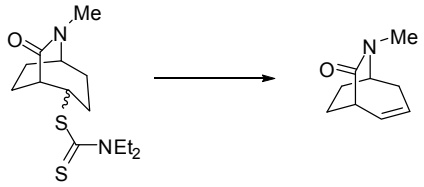
174.9 (C); *m/z* (HREI) 151.0994 (M^+. $C_9H_{13}NO$ requires 151.0997), (LREI) 151 (100%), 136 (15), 79 (87), 57 (75), 42 (47).



165 **173**

Method B: from **(165)**.

A solution of *rac*-(1*R*, 2*R*, 5*R*,)-6-methyl-7-oxo-6-azabicyclo[3.2.2]nonan-2-yl diethylcarbamodithioate **(165)** (62.5 mg, 0.21 mmol) in diphenyl ether (4 mL) was heated at reflux for 2 h. The reaction mixture was allowed to cool to room temperature and purified by column chromatography (1:1 hexane: ethyl acetate) afforded the *title compound* **(173)** as a brown solid (22.0 mg, 70%), whose analytical data were in agreement with method A.

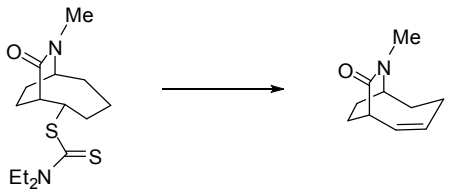


164+165 **173**

Method C: from a mixture of **(164)** and **(165)**.

A solution of **(164)** and **(165)** (8:1) (138.2 mg, 0.46 mmol) in diphenyl ether (5 mL) was heated at reflux for 2 h. The reaction was allowed to cool at room temperature and purified by column chromatography (1:1 hexane: ethyl acetate) to afford the *title compound* **(173)** as a brown solid (60 mg, 86%), whose analytical data were in agreement with method A.

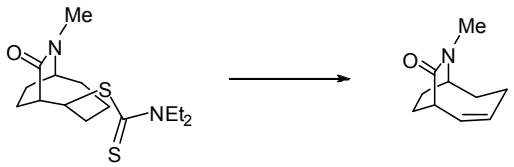
***rac*-6-Methyl-7-oxo-6-azabicyclo[4.2.2]non-2-ene (174).**



167 **174**

Method A: From **(167)** (major)

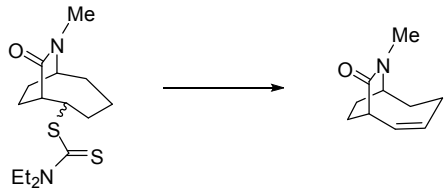
A solution of *rac*-(1*R*, 2*S*, 5*R*)-6-methyl-7-oxo-6-azabicyclo[4.2.2]nonan-2-yldiethylcarbamodithioate **(167)** (250 mg, 079 mmol) in diphenyl ether (8 mL) was heated at reflux for 2 h. The reaction mixture was allowed to cool to room temperature and purified by column chromatography (1:1 hexane: ethyl acetate) to afford the *title compound* **(174)** as a brown solid (90 mg, 80%). R_f 0.30 (ethyl acetate); ν_{max}(neat disc)/cm^{-1} 2930, 1640 (C=O), 1483; δ_H(300 MHz; $CDCl_3$) 1.72-1.86 (4 H, m), 1.92-1.98 (2 H, m), 2.12-2.26 (2 H, m), 2.90 (3 H, s, NCH_3), 3.21-3.23 (1 H, m), 3.66-3.72 (1 H, m), 5.46-5.52 (1 H, m), 5.75-5.84 (1 H, m); δ_C(75 MHz; $CDCl_3$) 20.4 (CH_2), 25.0 (CH_2), 25.1 (CH_2), 33.4 (CH), 36.0 (CH_2), 44.5 (CH), 55.0 (CH), 128.9 (CH), 129.2 (CH), 175.9 (C); *m/z* (HRESI) 188.1048 (M^+. $C_{10}H_{15}NO$ requires 188.1051) and (LRESI) 188.1 (100%).



168 **174**

Method B: From **(168)** (minor)

A solution of *rac*-(1*R*, 2*R*, 5*R*)-6-methyl-7-oxo-6-azabicyclo[3.2.2]nonan-2-yl diethylcarbamodithioate **(168)** (27 mg, 0.09 mmol) in diphenyl ether (1 mL) was heated at reflux for 2 h. The reaction mixture was allowed to cool to room temperature and purified by column chromatography (1:1 hexane: ethyl acetate) afforded the *title compound* **(174)** as a brown solid (12 mg, 81%), whose analytical data were in agreement with method A.

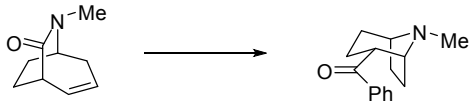


167+168 **174**

Method C: From a mixture of **(167)** and **(168)**.

A solution of **(167)** and **(168)** (2.5:1) (61 mg, 0.14 mmol) in diphenyl ether (2 mL) was heated at reflux for 2 h. The reaction was allowed to cool at room temperature and purified by column chromatography (1:1 hexane: ethyl acetate) to afford the *title compound* **(174)** as a brown solid (23 mg, 73%), whose analytical data were in agreement with method A.

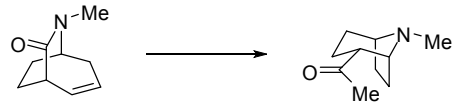
rac-Ferrugine.



173 ***ferrugine***

To a stirred solution of 6-methyl-7-oxo-6-azabicyclo[4.2.2]non-2-ene **(173)** (35 mg, 0.185 mmol) in THF (2.5 ml) at 0 °C was added dropwise phenyllithium (1.8 M in THF, 1.03 mL, 1.28 mmol) over 5 min and stirred for 1 h. The reaction was quenched with water (10 mL), basified (pH 12-14) with 5% sodium hydroxide solution, and stirred for 20 h at room temperature. THF was removed under reduced pressure, and the aqueous phase was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over magnesium sulfate, concentrated under reduced pressure and purified by column chromatography on neutral alumina (99:1 ethyl acetate: triethylamine) to afford *ferrugine* (35 mg, 66%) as a brown oil. R_f 0.65 (on neutral alumina, 99:1 ethyl acetate: triethylamine); ν_{max}(neat)/cm^{-1} 2959, 1675 (C=O), 1596, 1448, 1378; δ_H(300 MHz, $CDCl_3$) 1.42-1.60 (3 H, m), 1.75-2.07 (5 H, m), 2.36 (3 H, s, N*CH*$_3$), 3.18-3.20 (1 H, m), 3.35-3.37 (1 H, m), 3.78-3.81 (1 H, m), 7.43-7.53 (3 H, m, *Ar*), 7.94-7.96 (2 H, m, *Ar*); δ_C(75 MHz; $CDCl_3$) 18.5 (CH_2), 22.8 (CH_2), 26.1 (CH_2), 29.9 (CH_2), 40. 4 (CH_3), 47.7 (CH), 61.8 (CH), 63.7 (CH), 128.3 (CH), 128.7 (CH), 132.8 (CH), 136.4 (C), 201.6 (C); *m/z* (HRCI) 230.1535 (M^+. $C_{15}H_{20}NO$ requires 230.1545) and (LRCI) 230 (100%).

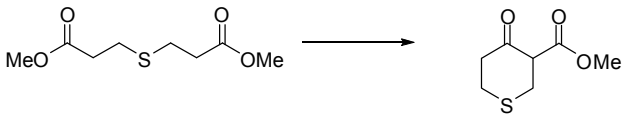
2-Ethanoyl-8-methyl-8-azabicyclo[3.2.1]octane (178).



173 **178**

To a solution of 6-methyl-7-oxo-6-azabicyclo[3.2.2]non-2-ene **(173)** (192.6 mg, 0.54 mmol) in THF (10 mL) at 0 °C was added dropwise methyllithium (1.6 M in diethyl ether, 0.81 mL, 1.08 mmol) over 5 min, and the resultant solution stirred for 1 h. The reaction was quenched with water (10 mL), basified (pH 12-14) with 5% sodium hydroxide solution, and stirred for 6 h at room temperature. THF was removed under reduced pressure, and the aqueous phase was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over magnesium sulfate, concentrated under reduced pressure and purified by column chromatography on basic alumina (99:1 ethyl acetate: triethylamine) to afford the *title compound* **(178)** (110 mg, 69%) as a brown oil. R_f 0.45 (on neutral alumina, 99:1 ethyl acetate: triethylamine); ν_{max}(neat)/cm^{-1} 2943, 2253, 1702 (C=O), 1475, 1450, 1351; δ_H(300 MHz, $CDCl_3$) 1.40-1.49 (3 H, m), 1.57-1.75 (2 H, m), 1.69-1.75 (1 H, m), 1.87-1.94 (2 H, m), 2.11 (3 H, s, NCH_3 or COCH_3), 2.31 (3 H, s, NCH_3 or COCH_3), 2.77-2.83 (1 H, m), 3.10-3.12 (1 H, m), 3.38-3.40 (1H, d, *J* 6.2); δ_C(75 MHz; $CDCl_3$) 18.0 (CH_2), 23.3 (CH_2), 25.8 (CH_2), 28.4 (CH_3), 29.7 (CH_2), 40.2 (CH_3), 53.2 (CH), 60.8 (CH), 62.4 (CH), 209.7 (C); *m/z* (HREI) 167.1305 (M^+. $C_{10}H_{17}N$ requires 167.1310), (LREI) 167 (25%), 96 (70), 82 (100), 57 (68%).

Methyl-4-oxotetrahydro-*2H*-thiopyran-3-carboxylate (357).



357

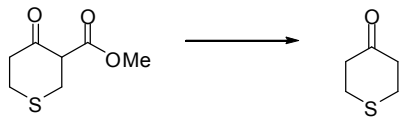
Prepared according to the literature procedure.[211]

Anhydrous MeOH (7.4 mL, 1.70 mmol) was added dropwise over 30 min to a stirred suspension of Na metal (4 g, 174 mmol) in THF (54 mL) at 0 °C. The ice bath was removed and the stirring continued at room temperature for 16 h, at which point most of the Na metal was consumed leaving a greyish white mixture of NaOMe in THF. The mixture was cooled in ice and the diester (27.67 g, 133.78 mmol) was added drop wise over 1 h. The ice bath was removed and the mixture was stirred at room temperature for 3 h. The mixture was then cooled at 0 °C and aqueous H_2SO_4 (0.475 mol) was added slowly with stirring maintaining the temperature below 20 °C; the final pH was 6-7. To the resulting creamy yellow mixture was added CH_2Cl_2 (100 mL) after which Na_2SO_4 hydrate precipitated as granules that readily settle, leaving a pale yellow solution; a small amount of water (10 mL) was added to achieve desired consistency. Na_2SO_4 (10 g) and $NaHCO_3$ (10 g) were added with stirring and after 30 min, the precipitate was filtered and the residue was washed with CH_2Cl_2 (100 mL). The combined organic layers were concentrated to afford **357** (21.31 g, 92%) as a pale yellow oil, which was used directly in the next step without further purification. Analytical data were in agreement with those reported in the literature.[211]

ν_{max}(neat)/cm^{-1} 2953, 1740, 1714, 1656, 1613, 1440, 1412; δ_H(300 MHz; $CDCl_3$) of keto-enol 2.60 (2 H, t, *J* 5.9), 2.78 (2 H, t, *J* 5.9), 3.35 (2 H, s), 3.76 (3 H, s, OC*H*$_3$), 12.51 (1 H, s, O*H*);

δ_C(75 MHz; $CDCl_3$) 23.4 (CH_2), 30.2 (CH_2), 43.4 (CH_2), 51.7 (CH_3), 58.5 (CH), 172.3 (C), 203.5 (C).

Dihydro-2H-thiopyran-4(3H)-one (358).



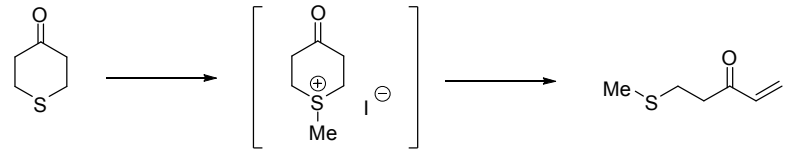
357 **358**

Prepared according to the literature procedure.[211]

To a solution of aqueous H_2SO_4 (10%, 100 mL) was added keto ester **(357)** (100 g, 0.57 mol) over 10 min at room temperature and the resultant mixture was refluxed for 1 h. the reaction mixture was allowed to cool to room temperature and the aqueous layer was decanted from a yellow oil that separated and settled. The yellow oil was washed with water (500 mL) and the combined aqueous phases were extracted with CH_2Cl_2 (3 x 200 mL) with each extract passed through a column of basic alumina. The column was finally eluted with CH_2Cl_2 (600 mL) and the combined eluents were concentrated under reduced pressure and then re-concentrated from hexane to give compound **(358)** (42.6 g, 64%) as a white free flowing crystalline solid whose analytical data were in agreement with those reported in the literature.[211]

ν_{max}(neat)/cm^{-1} 2945, 2910, 1708, 1421; δ_H(300 MHz; $CDCl_3$) 2.67-2.71 (4 H, m), 2.93-2.87 (4 H, m); δ_C(75 MHz; $CDCl_3$) 29.9 (CH_2), 39.9 (CH_2), 208.1 (C).

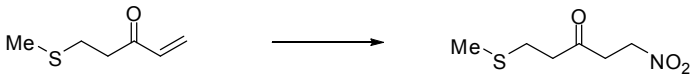
5-(methylthio)pent-1-en-3-one (360).



358 **359** **360**

To a solution of **(358)** (1.93 g, 16.64 mmol) in acetone (2 mL) was added MeI (10.3 mL, 166.4 mmol) portionwise and the reaction stirred at room temperature for 3 d in the dark. The resulting white precipitate was filtered off, washed with acetone (3 x 20 mL) and dried under vacuum to afford the sulfonium salt **(359)** (3.70 g, 92%) and was directly used in the next step. To a solution of sulfonium salt **(359)** (3.70 g, 14.33 mmol) in acetonitrile and water (9:1, 145 mL), was added DIPEA (7.5 mL, 43.04 mmol). The resulting mixture was stirred at room temperature for 2 d. The aqueous phase was extracted with EtOAc (3 x 30 mL), and the combined organic phases were washed with water (30 mL), brine (300 mL), dried over magnesium sulfate and concentrated under pressure and purified by column chromatography (4:1 hexane: EtOAc) to afford the *title compound* **(360)** (1.85 g, 86% over two steps). R_f 0.5 (1:1 hexane: Et_2O); ν_{max}(neat)/cm^{-1} 2919, 2253, 1679, 1617 1403, 1094; δ_H(300 MHz; $CDCl_3$) 2.13 (3 H, s, SC*H*$_3$), 2.75-2.82 (2 H, m), 2.89-2.92 (2 H, m), 5.86-5.90 (1 H, dd, *J* 1.4, 10.2), 6.22-6.28 (1 H, dd, *J* 1.4, 17.7), 6.33-6.42 (1 H, dd, *J* 10.2, 17.7); δ_C(75 MHz; $CDCl_3$) 15.64 (CH_3), 27.9 (CH_2), 39.2 (CH_2), 128.4 (CH_2), 136.1 (CH), 198.6 (C); *m/z* (LREI) 130 (15%), 82 (90%), 55 (100%).

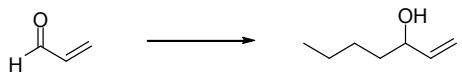
1-(Methylthio)-5-nitropentan-3-one (362).



360 **362**

To a solution of enone **(360)** (671 mg, 5.16 mmol) in THF (4 mL) was added $NaNO_2$ (710 mg, 10.3 mmol) and AcOH (0.59 mL, 10.3 mmol) at room temperature. The resultant mixture was stirred at this temperature for 16 h, diluted with water (10 mL), and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, concentrated under pressure and purified by column chromatography (4:1 hexane: EtOAc) to afford the *title compound* **(362)**. Further elution gave recovered starting materials (561 mg, 75% BRSM) as a yellow viscous oil. R_f (0.2 hexane: EtOAc); ν_{max}(neat)/cm^{-1} 2920, 1716 (CO), 1556, 1465; δ_H(300 MHz; $CDCl_3$) 2.13 (3 H, s, SCH_3), 2.74-2.84 (4 H, m), 3.08-3.12 (2 H, m), 4.67 (2 H, t, *J* 6.1); δ_C(75 MHz; $CDCl_3$) 15.4 (CH_3), 27.3 (CH_2), 38.2 (CH_2), 42.1 (CH_2), 68.7 (CH_2), 204.3 (C); *m/z* (HREI) 177.0452 (M^+. $C_6H_{11}NO_3S$ requires 177.0460), (LREI) and 177 (50%), 74 (75%), 61 (100%), 55 (95%).

Hept-1-en-3-ol 364.



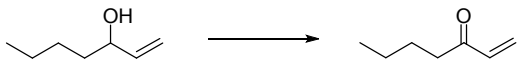
363 **364**

Prepared according to the literature procedure.[247]

To a solution of acrolein **(363)** (1.1 g, 19.84 mmol) in THF (10 mL) was added a solution of *n*-BuLi in THF (2.0 M, 23.81 mmol, 10.4 mL) at -78 °C and the resultant solution was slowly warmed to room temperature over 12 h. The reaction mixture was quenched with 1M $NaH_2P_2O_4$ (10 mL). The aqueous phase was extracted with Et_2O (3 x 20 mL), and the combined organic extracts were washed with water (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford the allylic alcohol as a colourless oil **(364)** (2.08 g, 92%), whose analytical data were in agreement with those reported in the literature.[248]

R_f 0.4 (1:1 hex: Et_2O) ν_{max}(neat)/cm^{-1} 3346, 2958, 2932, 1467; δ_H(300 MHz; $CDCl_3$) 0.90 (3 H, t, *J* 7.3), 1.23-1.59 (7 H, m), 4.06-4.10 (1 H, m), 5.08-5.12 (1 H, dd, *J* 1.5 & 9.2), 5.18-5.25 (1 H, dd, *J* 1.3 & 15.7), 5.81-5.92 (1 H, m); δ_C(75 MHz; $CDCl_3$) 13.8 (CH_3), 22.5 (CH_2), 27.4 (CH_2), 36.6 (CH_2), 114.1 (C), 141.3 (C); *m/z* (LREI) 114.1 (10%), 72.1 (20%) and 57.1 (100%),

Hept-1-en-3-one (365).



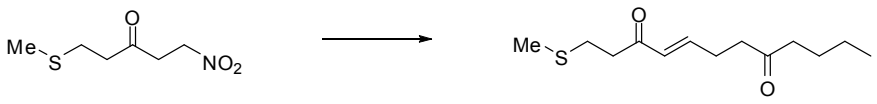
364 **365**

Prepared accoding to a general procedure.[217]

To a solution of IBX (62 mg, 2.24 mmol) in DMSO (6 mL) was added allylic alcohol **(364)** (130 mg, 1.12 mmol) at room temperature and the reaction was stirred at this temperature for 3 h. The reaction mixture was quenched with water (10 mL), the aqueous phase was extracted with Et_2O (3 x 20 mL) and the combined organic extracts were washed with water (20 mL), brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford the enone **(365)** as a

colourless oil (113 mg, 88%) used directly in the next step without further purification. R_f 0.5 hexane: EtOAc); ν_{max}(neat)/cm^{-1} 2959, 2934, 2874, 1700, 1683, 1615; δ_H(300 MHz; $CDCl_3$) 0.92 (3 H, t, *J* 7.3), 1.30-1.38 (2 H, m), 1.58-1.63 (2 H, m), 2.58 (2 H, t, *J* 7.6), 5.79-5.83 (1 H, dd, *J* 1.5 & 10.3), 6.18-6.24 (1 H, dd, *J* 1.4 & 17.7), 6.31-6.40 (1 H, dd, *J* 7.2 & 10.3); δ_C(75 MHz; $CDCl_3$) 13.6 (CH_3), 22.1 (CH_2), 25.9 (CH_2), 39.1 (CH_2), 127.6 (CH_2), 136.3 (CH), 200.8 (C); *m/z* (HRESI) 112.087 (M^+ $C_7H_{12}O$ requires 112.0888), (LRESI) 112.1 (10%), 70.0 (100), 55.0 (90) and 97.1 (50).

(*E*)-1-(Methylthio)dodec-4-ene-3,8-dione (369).

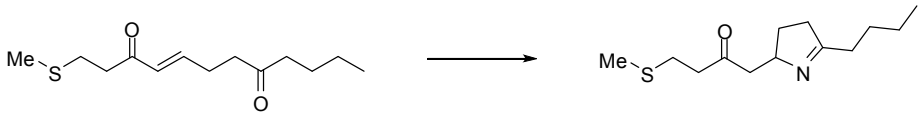


362 **369**

To a solution of enone **(365)** (2.06 g, 18.10 mmol) and β-nitro ketone **(362)** (3.20 g, 18.10 mmol) in DCM (100 mL) was added basic Al_2O_3 (72 g, 706 mmol) at room temperature. The resultant mixture was stirred at this temperature for 16 h, Al_2O_3 filtered off and washed with excess DCM (100 mL), concentrated under reduced pressure and purified by column chromatography (4:1 hexane: Et_2O) to afford the *title compound* **(369)** (466 mg, 11%) as a colourless oil. R_f 0.25 (1:1 hexane: Et_2O); ν_{max}(neat)/cm^{-1} 2361, 2874, 1712 (CO), 1670, 1630, 1540; δ_H(300 MHz; $CDCl_3$) 0.89 (3 H, t, *J* 7.3), 1.23-1.57 (4 H, m), 2.10 (3 H, s, SC*H*$_3$), 2.38-2.60 (6 H, m), 2.71-2.85 (4 H, m), 6.06-6.12 (1 H, m), 6.78-6.87 (1 H, m); δ_C(75 MHz; $CDCl_3$) 13.8 (CH_3), 15.8 (CH_3), 22.3 (CH_2), 25.9 (CH_2), 26.2 (CH_2), 28.2 (CH_2), 39.4 (CH_2), 40.5 (CH_2), 42.6 (CH_2), 130.5 (CH),

146.0 (CH), 198.3 (C), 209.1 (C); *m/z* (HRESI) 265.1242 (M+Na $C_{13}H_{22}O_2NaS$ requires 265.1238) and (LRESI) 265.1 (100%).

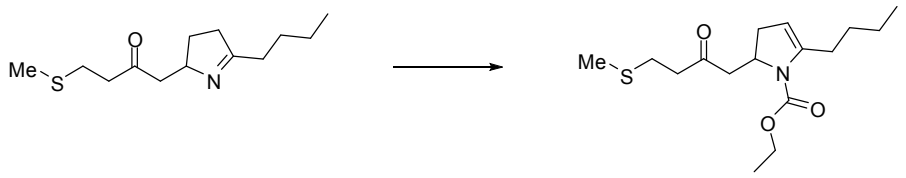
1-(5-Butyl-3,4-dihydro-2H-pyrrol-2-yl)-4-(methylthio)butan-2-one (368).



369 **368**

To a solution of enone **(369)** (466 mg, 1.93 mmol) in MeOH (20 mL) was added aqueous ammonia (35%, 5.5 mL) dropwise over 1 min at room temperature. The resultant mixture was stirred at this temperature for 16 h. MeOH was removed under reduced pressure and the aqueous phase was extracted with DCM (3 x 10 mL), and the combined organic extracts were washed with water (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford *title compound* as a brown oil **(368)** (411 mg, 88%) which was used in the next step without further purification. R_f 0.4 (Et_2O); ν_{max}(neat)/cm^{-1} 2929, 2871, 1712 (CO), 1442, 1457; δ_H(300 MHz; $CDCl_3$) 0.91 (3 H, t, *J* 7.3), 1.27-1.59 (6 H, m), 2.11 (3 H, s, SCH_3), 2.28-2.53 (5 H, m), 2.72-2.78 (4 H, m), 2.89-2.96 (1 H, m), 4.30-4.35 (1 H, m); δ_C(75 MHz; $CDCl_3$) 13.6 (CH_3), 15.5 (CH_3), 22.3 (CH_2), 27.7 (CH_2), 28.3 (CH_2), 28.7 (CH_2), 33.3 (CH_2), 37.0 (CH_2), 42.8 (CH_2), 49.4 (CH_2), 67.9 (CH), 178.3 (C), 207.5 (C); *m/z* (HRESI) 264.1393 (M+Na $C_{13}H_{23}NONaS$ requires 264.1398) and (LRESI) 264.2 (100%).

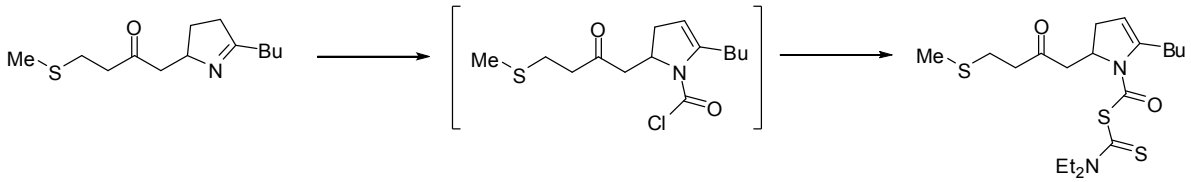
Ethyl-5-butyl-2-(4-(methylthio)-2-oxobutyl)-2,3-dihydro-*1H*-pyrrole-1-carboxylate (376).



368 **376**

To a solution of imine **(368)** (30 mg, 0.12 mmol) and triethylamine (30 mg, 0.25 mmol) in THF (4 mL) was added ethyl chloroformate (30 mg, 0.25 mmol) at -78 °C. The resultant mixture was stirred at this temperature for 1 h and slowly warmed to room temperature overnight. The reaction mixture was quenched with water (5 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (1:1 Pet-ether: Et_2O) to afford the *title compound* **(376)** as a brown oil (30 mg, 80%). R_f 0.35 (1:1 hexane: Et_2O); ν_{max}(neat)/cm^{-1} 2959, 2872, 1706, 1481, 1465; δ_H(300 MHz; $CDCl_3$) 0.90 (3 H, t, *J* 7.0), 1.23-1.43 (7 H, m), 1.92-2.12 (5H, m), 2.36-2.93 (3 H, s, SC*H*$_3$ & 6 H, m), 4.10-4.21 (2 H, m), 4.47-4.72 (1 H, m); δ_C(75 MHz; $CDCl_3$) 13.8 (CH_3), 14.6 (CH_3), 15.8 (CH_3), 23.23 (CH_2), 26.11 (CH_2), 27.1 (CH_2), 27.91 (CH_2), 31.1 (CH_2), 42.9 (CH_2), 46.7 (CH_2), 56.1 (CH), 61.2 (CH_2), 108.3 (CH), 136.8 (C), 207.2 (C), 207.3 (C); *m/z* (HRESI) 336.1611 (M+Na $C_{16}H_{27}NO_3NaS$ requires 336.1609), 354.1 (100%) and (LRESI) 336.1 (50%).

5-Butyl-2-(4-(methylthio)-2-oxobutyl)-2,3-dihydro-1*H*-pyrrole-1-carboxylic-diethylcarbamothioic-thioanhydride (378).

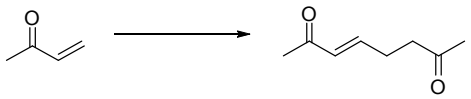


368 **377** **378**

To a solution of triphosgene (50 mg, 0.17 mmol) in toluene (6 mL) was added pyridine (0.062 mL, 0.77 mmol) dropwise at room temperature and stirred for 10 min, followed by the addition of a solution of imine **(368)** (123 mg, 0.51 mmol) in toluene (2 mL). The resultant mixture was stirred at room temperature for 16 h and quenched with water (2 mL). The aqueous phase was extracted with Et_2O (3 x 10 mL)), and the combined organic extracts were washed with water (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude carbamoyl chloride **(377)** as a brown oil (208 mg) which was used in the next step without further purification. To a solution of carbamoyl chloride **(377)** (208 mg, 0.68 mmol) in acetone (7 mL) was added sodium diethyldithiocarbamate trihydrate (610 mg, 2.71 mmol). The resultant mixture was refluxed for 4 h, cooled to room temperature and quenched with water (5 mL). The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic extracts were washed with water (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure and purified by column chromatography to afford the *title compound* **(378)** as a bright yellow oil (94 mg, 44% over two steps). R_f 0.35 (1:1 hexane:Et_2O); ν_{max}(neat)/cm^{-1} 2930, 1675, 1679, 1681, 1489, 1422; δ_H(300 MHz; $CDCl_3$) 0.90 (3 H, t, *J* 7.3), 1.20-1.57 (10 H, m), 1.97-2.11 (2 H, m), 2.10 (3 H, s, SC*H*$_3$), 2.40-3.15 (8 H, m), 3.70-4.11 (4 H, m), 4.51-4.68 (1 H, m), 4.97-4.98 (1 H, m); δ_C(75 MHz; $CDCl_3$) mixture or rotamers 11.1 (CH_3), 11.2 (CH_3), 13.4 (CH_3), 13.5

(CH_3), 13.81 (CH_3), 13.88 (CH_3), 15.7 (CH_3), 22.2 (CH_2), 22.8 (CH_2), 26.2 (CH_2), 27.5 (CH_2), 27.9 (CH_2), 29.0 (CH_2), 29.7 (CH_2), 30.9 (CH_2), 34.2 (CH_2), 42.8 (CH_2), 42.9 (CH_2), 46.9 (CH_2), 47.7 (CH_2), 48.9 (CH_2), 50.1 (CH_2), 50.3 (CH_2), 57.7 (CH), 109.5 (CH), 137.1 (C), 144.9 (C), 184.6 (C), 206.7 (C); *m/z* (HRESI) 439.1530 (M+Na $C_{19}H_{32}N_2O_2NaS_3$ requires 439.1524), and (LRESI) 439.1 (100%).

***(E)*-Oct-3-ene-2,7-dione (371).**



370 **371**

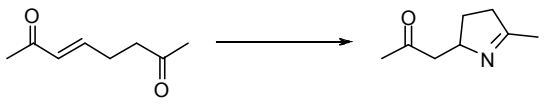
Prepared according to the literature procedure.[231]

To a solution of sodium nitrite (690 mg, 0.01 mmol) and 3-butene-2-one **(370)** (3.5 g, 46.1 mmol) in DMSO (10 mL) was added acetic acid (600 mg, 0.01 mmol) dropwise at room temperature and the resultant mixture was stirred at this temperature for 16 h. The reaction mixture was acidified with aqueous HCl (0.1 M, 10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography to afford enone **(371)** (2.02 g, 80%) as a brown oil whose analytical data were in agreement with those reported in the literature.[231]

R_f 0.4 Et_2O); ν_{max}(neat)/cm^{-1} 2921, 1718, 1672, 1628, 1556, 1424; δ_H(300 MHz; $CDCl_3$) 2.17 (3 H, s, COCH_3), 2.23 (3 H, s, COCH_3), 2.45-2.65 (4 H, m), 6.03-6.09 (1 H, m), 6.73-6.83 (1 H, m);

δ_C(75 MHz; $CDCl_3$) 25.9 (CH_2), 26.7 (CH_3), 30.0 (CH_3), 131.4 (CH), 146.2 (CH), 198.3 (C), 206.6 (C); *m/z* (LREI) 140.1 (20%) and 97.0 (100%)

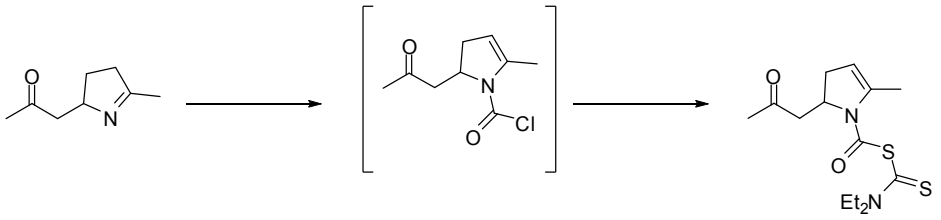
1-(5-Methyl-3,4-dihydro-2*H*-pyrrole-2-yl)-propan-2-one (372).



371 **372**

To a solution of of enone **(371)** (100 mg, 0.71 mmol) in MeOH (7 mL) was added a solution of aqueous ammonia (35%, 2 mL) at room temperature and the resultant mixture was stirred at this temperature for 16 h and diluted with water (10 mL). MeOH was removed under pressure and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic phases were washed with water (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford the *title compound* **(372)** (120 mg, 100%) which was carried forward to the next step without further purification. R_f 0.5 (Et_2O); ν_{max}(neat)/cm^{-1} 2955, 1712 (CO), 1650, 1431; δ_H(300 MHz; $CDCl_3$) 2.02 (3 H, s, NCC*H*$_3$), 2.15-2.17 (1H, m), 2.19 (3H, s, COC*H*$_3$), 2.44-2.54 (4 H, m), 2.87-2.95 (1 H, m), 4.29-4.35 (1 H, m); δ_C(75 MHz; $CDCl_3$) 19.7 (CH_3), 29.4 (CH_2), 30.5 (CH_3), 39.0 (CH_2), 50.4 (CH_2), 68.4 (CH), 175.0 (C), 207.5 (C); *m/z* (HRESI) 139.0452 (M^+ requires $C_8H_{13}NO$ 139.0455), (LRESI) 82 (100%), 96 (95%) and 139 (15%).

Diethylcarbamothioic-5-methyl-2-(2-oxopropyl)-2,3-dihydro-1*H*-pyrrole-1-carboxylic thioanhydride (375).

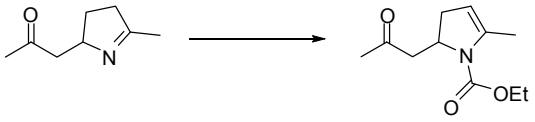


372 **374** **375**

To a solution of triphosgene (70 mg, 0.24 mmol) in toluene (6 mL) was added pyridine (0.11 mL, 1.08 mmol) at room temperature and the mixture was stirred at this temperature for 10 min. To this reaction mixture was added a solution of imine **(372)** (100 mg, 0.72 mmol) in toluene (4 mL) and the resultant mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with water (10 mL) and the aqueous phase was extracted with Et_2O (3 x 15 mL) and the combined organic phases were washed with water (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford the carbamoyl chloride **(374)** (138 mg) which was used directly in the next step without further purification. To a solution of carbamoyl chloride **(374)** (138 mg, 0.68 mmol) in acetone (7 mL) was added sodium diethyldithiocarbamate trihydrate (310 mg, 1.37 mmol) and the resultant mixture was refluxed for 2 h. The reaction mixture was allowed to cool to room temperature and quenched with saturated $NaHCO_3$ (10 mL) and the aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with water (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford the *title compound* **(375)** (110 mg, 50% over two steps) as a bright yellow oil. R_f 0.25 (1:1 hexane: Et_2O); ν_{max}(neat)/cm^{-1} 2980, 2253, 1712, 1678, 1651, 1492, 1456; δ_H(300 MHz; $CDCl_3$) 1.26-1.35 (6 H, m), 2.16 (3 H, s, NCCH_3), 2.17 (3 H, s, COCH_3), 2.55-3.19 (3 H, m), 3.68-4.17 (5 H, m), 4.57-4.63 (1 H, m), 4.91-4.92 (1 H, m); δ_C(75 MHz; $CDCl_3$) 11.0 (CH_3),

13.3 (CH_3), 15.9 (CH_3), 30.4 (CH_3), 34.1 (CH_2), 48.2 (CH_2), 48.8 (CH_2), 50.0 (CH_2), 57.2 (CH), 110.2 (CH), 139.8 (C), 157.5 (C), 184.0 (C), 206.1 (C); *m/z* (HRESI) 337.1027 (M^+Na. $C_{14}H_{22}N_2O_2S_2Na$ requires 337.1020) and (LRESI) 337.2 (100%).

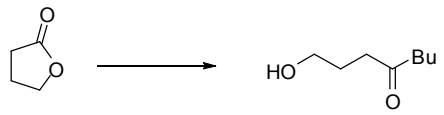
Ethyl-5-methyl-2-(2-oxopropyl)-2,3-dihydro-1*H*-pyrrole-1-carboxylate (373).



372 **373**

To a solution of imine **(372)** (120 mg, 0.86 mmol) in CH_2Cl_2 (10 mL) was added at -78 °C, ethyl chloroformate (136 mg, 1.29 mmol) and Et_3N (0.72 mL, 5.16 mmol) over 1 min and the resultant mixture as slowly warmed to room temperature and stirred at this temperature for 16 h. The reaction mixture was quenched with water (10 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated under *vacuo* and purified by column chromatography (1:1 hexane: ether) to afford the *title compound* **(373)** (50 mg, 28%) as a colourless oil. R_f 0.35 (1:1 hexane: Et_2O); ν_{max}(neat)/cm^{-1} 2983, 2253, 1713 (CO), 1510, 1446; δ_H(300 MHz; $CDCl_3$) 1.25 (3 H, t, *J* 7.1), 2.06 (3 H, s, NCCH_3), 2.14 (3 H, s, COCH_3), 2.59-2.96 (4 H, m), 4.09-4.16 (2 H, q, *J* 7.1), 4.54-4.67 (2 H, m); δ_C(75 MHz; $CDCl_3$) 14.5 (CH_3), 30.5 (CH_3), 33.8 (CH_2), 47.4 (CH_3), 48.4 (CH_2), 55.7 (CH_2), 61.0 (CH), 106.2 (CH), 139.0 (C), 207.0 (C), 208.2 (C); *m/z* (HREI) 211.1216 (M^+. $C_{11}H_{17}NO_3$ requires 211.1208), (LREI) 43 (100%), 116 (55%) and 172 (45%).

1-Hydroxyoctan-4-one (391).



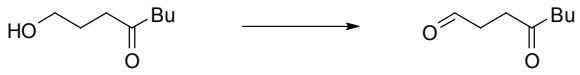
390 **391**

Prepared according to the literature procedure.[214]

To a solution of γ-butyralactone **(390)** (1 g, 11.6 mmol) in Et_2O (24 mL) was added *n*-BuLi (2.6 M in toluene, 5 mL, 12.5 mmol) over 10 min at -78 °C. The resultant mixture was stirred at this temperature for 2 h and slowly warmed to room temperature overnight. The reaction mixture was quenched with saturated NH_4Cl (10 mL). The aqueous phase was extracted with Et_2O (3 x 15 mL) and the the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under *vacuo* and purified by column chromatography (1:1 pet-ether: EtOAc) to afford the *title compound* **391** (1.05 g, 63%) as a colourless oil whose analytical data were in agreement with those reported in literature.[214]

ν_{max}(neat)/cm^{-1} 3390, 2856, 2874, 1711, 1467; δ_H(300 MHz; $CDCl_3$) 0.90 (3 H, t, *J* 7.3), 1.25-1.27 (2 H, m), 1.51-1.67 (2 H, m), 1.82-1.86 (2 H, m), 2.44 (2 H, t, *J* 7.3), 2.56 (2 H, t, *J* 6.1), 3.64-6.66 (2 H, m); δ_C(75 MHz; $CDCl_3$) 13.8 (CH_3), 22.3 (CH_2), 25.9 (CH_2), 26.5 (CH_2), 39.4 (CH_2), 42.6 (CH_2), 62.1 (CH_2), 212.0 (C).

4-Oxooctanal (383).



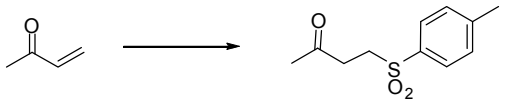
391 **383**

Prepared by modification of the literature procedure.[216]

DMSO (0.21 mL, 2.98 mmol) was added dropwise to oxalyl chloride (0.12 mL, 1.39 mmol) in CH_2Cl_2 (6 mL) at -78 °C and stirred for 10 min. Keto-alcohol **(391)** (100 mg, 0.69 mmol) was then added and stirred for 30 min followed by the addition of Et_3N (0.96 mL, 6.9 mmol). The reaction mixture was slowly warmed to room temperature and stirred for 1.5 h and quenched with water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under *vacuo* and purified by column chromatography (4:1 hexane: EtOAc) to afford the *title compound* **(383)** (38 mg, 38%) as a colourless oil whose analytical data were in agreement with those reported in the literature.[214]

R_f 0.35 (4:1 hexane**:** EtOAc); ν_{max}(neat)/cm^{-1} 2959, 2873, 1712, 1466, 1411; δ_H(300 MHz; $CDCl_3$) 0.90 (3 H, t, *J* 7.3), 1.20-1.35 (2 H, m), 1.52-1.60 (2 H, m), 2.47 (2 H, t, *J* 7.3), 2.73-2.75 (4 H, m), 9.81 (1 H, s); δ_C(75 MHz; $CDCl_3$) 13.7 (CH_3), 22.1 (CH_2), 25.8 (CH_2), 34.5 (CH_2), 37.3 (CH_2), 42.3 (CH_2), 200.4 (COH), 208.7 (C); *m/z* (LREI) and 140.1 (10%), 85 (40), and 57.1 (100).

4-Tosylbutan-2-one (386).



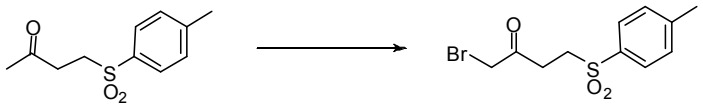
385 **386**

Prepared according to the literature procedure.[238]

To methyl vinyl ketone **(385)** (10 g, 142.86 mmol) was added a solution of sodium *p*-toluenesulfinate dihydrate (38.18 g, 214.29 mmol) in ethanol (95%, 150 mL) and glacial acetic acid (12.66 mL, 221.4 mmol) at room temperature. The solution was stirred at this temperature for 16 h then extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (100 mL), dried over $MgSO_4$ and concentrated under *vacuo* to give a viscous yellow residue which afforded crystalline sulfone **(386)** (27.22 g, 84%) after triturating with hexane. Analytical data were in agreement with those reported in literature. [238]

Mp 74-76 °C; δ_H(300 MHz; $CDCl_3$) 2.18 (3 H, s, ArC*H*$_3$), 2.46 (3 H, s, COC*H*$_3$), 2.90-2.95 (2 H, m), 3.33-3.38 (2 H, m), 7.36-7.40 (2 H, d, *J* 3.8), 7.77-7.82 (2 H, d, *J* 8.4); δ_C(75 MHz; $CDCl_3$) 21.6 (CH_3), 29.8 (CH_3), 35.9 (CH_2), 50.5 (CH_2), 127.9 (CH), 129.9 (CH), 135.9 (C), 144.9 (C), 203.7 (C).

1-Bromo-4-(4-methylphenyl)-sulfonyl-2-butanone (387).



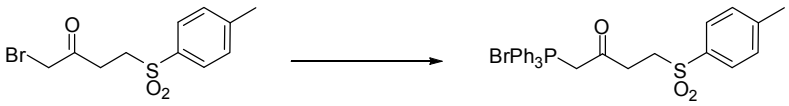
386 **387**

Prepared according to the literature procedure.[238]

To a solution of ketone **(386)** (10 g, 44.25 mmol) in glacial acetic acid (92 mL), was added pyridinium bromide perbromide (14.38 g, 44.25 mmol) and the resultant mixture was heated at 70 °C for 16 h. Acetic acid was removed under *vacuo* and the residue was purified by column chromatography (1:1 pet-ether: ether) to afford the bromoketone **(387)** (5.55 g, 42%) whose analytical data were in agreement with those reported in literature. [238]

Mp. 107-109°C; δ_H(300 MHz; $CDCl_3$) 2.45 (3 H, s, ArC*H*$_3$), 3.14 (2 H, t, *J* 7.2), 3.40 (2 H, t, *J* 7.2), 3.91 (2 H, s, BrC*H*$_2$), 7.36-7.39 (2 H, d, *J* 8.0), 7.76-7.79 (2 H, d, *J* 8.3); δ_C(75 MHz; $CDCl_3$) 21.6 (CH_3), 32.6 (CH_2), 33.6 (CH_2), 50.7 (CH_2), 127.9 (CH), 130.0 (CH), 135.6 (C), 145.1 (C), 198.0 (C); *m/z* (LRESI) 329.3 (100%)

4-(4-Methylphenyl)-sulfonyl)-2-oxobutyl-(triphenylphosphonium bromide) (389).



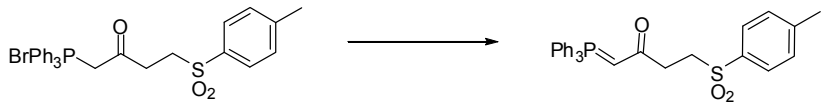
387 **389**

Prepared according to the literature procedure.[238]

A solution of bromoketone **(387)** (2.5 g, 8.20 mmol) and triphenylphosphine (2.15 g, 8.20mmol) in toluene (10 mL) was stirred at 40 °C for 6 h. The precipitated phosphonium salt **(389)** (4.02 g, 87%) salt was collected by filtration as a white solid whose analytical data were in agreement with those reported in literature. [238]

Mp 131-133 °C; ν_{max}(neat disc)/cm^{-1} 2788, 1070, 1596, 1438; δ_H(300 MHz; $CDCl_3$) 2.33 (3 H, s, ArC*H*$_3$), 3.41-3.42 (4 H, m), 5.93-5.97 (2 H, d, *J* 11.6), 7.55-7.88 (19 H, m, Ar); *m/z* (LRESI-Br) 487.5 (100%).

4-(4-Methylphenyl)-sulfonyl)-1-(triphenylphosphoranylidene)-2-butanone (384).



389 **384**

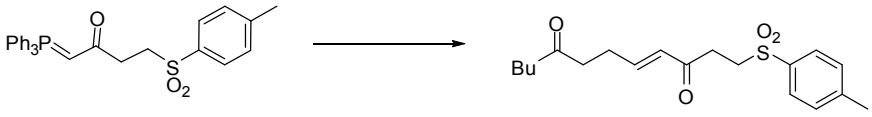
Prepared according to the literature procedure.[238]

To a solution of phosphonium salt **(389)** (3.57 g, 6.30 mmol) in methanol (20 mL) at 0 °C was added dropwise over 5 min an aqueous solution of sodium hydroxide (12.5 %) until pH 8-9 was reached. Water (100 mL) was added and the precipitated phosphorane **(384)** (2.89 g, 95%) was collected by filtration as a white solid whose analytical data were in agreement with those reported in literature.[238]

Mp 164-166 °C; ν_{max}(neat disc)/cm^{-1} 2990, 1711, 1634, 1596; δ_H(300 MHz; $CDCl_3$) 2.41 (3 H, s, ArC*H*$_3$), 2.70-2.76 (2 H, m), 3.43-3.48 (2 H, m), 7.29 (1 H, s), 7.32-7.79 (19 H, m, Ar); δ_C(75

MHz; $CDCl_3$) 21.4 (CH_3), 33.6 (CH_2), 53.6 (CH_2), 127.0 (C), 128.0 (CH), 128.7 (CH), 129.5 (CH), 132.0 (CH), 132.7 (CH), 136.3 (C), 144.1 (C), 187.1 (C); *m/z* (LRESI) 509.4 (100%).

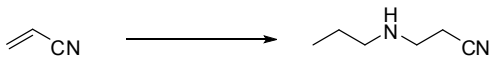
***(E)*-1-Tosyldodec-4-ene-3,8-dienone (392).**



384 **392**

To a a solution of keto-aldehyde **(383)** (175 mg, 1.23 mmol) in toluene (4 mL) was added phosphonium ylid **(384)** (720 mg, 1.48 mmol) in toluene (6 mL) at room temperature. Tthe reaction mixture was slowly warmed to 70 °C over 10 min and stirred at this temperature for 4 d. The reaction mixture was diluted with water (5 mL) and the aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, concentrated under *vacuo* and purified by column chromatography (1:1 pet-ether: ether) to afford the *title compound* **(392)** (198 mg, 67%) as a colourless oil. R_f 0.35 (1:1 pet-ether: ether); ν_{max}(neat)/cm^{-1} 2960, 1698, 1667, 1418; δ_H(300 MHz; $CDCl_3$); 091 (3 H, t, *J* 7.3), 1.18-1.37 (3 H, m), 1.51-1.61 (3 H, m), 2.46 (3 H, s, C*H*$_3$Tol), 2.39-1.61 (4 H, m), 3.0-3.05 (2 H, m), 3.36-3.41 (2 H, m), 6.05-6.11 (1 H, m), 6.80-6.89 (1 H, m), 7.35-7.38 (2 H, d, *J* 8.4), 7.77-7.80 (2 H, d, *J* 8.4); δ_C(75 MHz; $CDCl_3$) 13.8 (CH_3), 21.6 (CH_3), 22.3 (CH_2), 25.8 (CH_2), 26.2 (CH_2), 32.5 (CH_2), 40.3 (CH_2), 42.5 (CH_2), 50.7 (CH_2), 127.9 (CH), 129.8 (CH), 129.9 (CH), 136.0 (C), 144.9 (C), 147.2 (CH), 195.1 (C), 208.9 (C); *m/z* (HRESI) 373.1453 (M^+. $C_{19}H_{26}O_4NaS$ requires 373.1450) and (LRESI) 373.1 (100%).

3-(Propylamino)-propanenitrile (398).



398

Prepared according to the literature procedure.[246]

A mixture of acrylonitrile (12.41 mL, 188.5 mmol) and propylamine (16.55 mL, 207.3 mmol) was stirred at room temperature for 4 d and concentrated under reduced pressure. The reaction mixture was purified by reduced pressure distillation (2.0 mmHg, 40-42 °C) to obtain compound **(398)** (17 g, 82%) whose analytical data were in agreement with those reported in the literature.[246]

ν_{max}(neat)/cm^{-1} 2963, 2254, 1462, 1423, 1301, 1127; δ_H(300 MHz; $CDCl_3$) 0.92 (3 H, t, *J* 7.4, C*H*$_3$), 1.44-1.54 (2 H, m), 2.51 (2 H, t, *J* 6.6), 2.59 (2 H, t, *J* 7.1), 2.92 (2 H, t, *J* 6.6); δ_C(75 MHz; $CDCl_3$) 11.4 (CH_3), 18.5 (CH_2), 22.9 (CH_2), 44.8 (CH_2), 50.8 (CH_2), 118.6 (C); *m/z* (LREI) 112 (5), 83 (100), 72 (40), 54 (25) and 42 (55%).

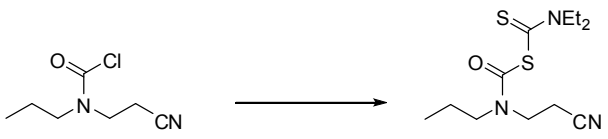
2-Cyanoethyl(propyl)carbamic chloride (399).

398 **399**

To a solution of triphosgene (0.88 g, 2.98 mmol) in dry toluene (30 mL), was added pyridine (1.1 mL) dropwise and the resulting mixture was stirred at room temperature for 10 min. A solution of amine **(398)** (1.0 g, 8.93 mmol) in dry toluene (20 mL) was then added to the reaction mixture

and stirred for 1 h at room temperature. The reaction was quenched with water (10 mL) and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried over magnesium sulfate and concentrated under reduced pressure to afford the *title compound* **(399)** (1.24 g, 80%) as an orange oil. R_f 0.5 (Et_2O); ν_{max}(neat)/cm^{-1} 2969, 1726 (CO), 1463, 1404, 1376, 1212; δ_H(300 MHz; $CDCl_3$) 0.91 (3 H, t, *J* 7.4), 1.58-1.69 (2 H, m), 2.66-2.72 (2 H, m), 3.35-3.49 (2 H, dt, *J* 7.7 & 15.5), 3.56-3.73 (2 H, dt, *J* 6.9 & 13.8; δ_C(75 MHz; $CDCl_3$) mixture of rotamers 10.6 (CH_3), 15.8 (CH_2), 17.1 (CH_2), 20.4 (CH_2), 21.4 (CH_2), 45.5 (CH_2), 46.3 (CH_2), 51.9 (CH_2), 53.6 (CH_2), 117.2 (C), 149.4 (C); *m/z* (HREI**)** 174.0552 (M^+. $C_7H_{11}N_2OCl$ requires 174.0560), (LREI) 43 (60%), 97 (50), 117 (35), 134 (55), 145 (100) and 174 (10).

2-Cyanoethyl-(propyl)-carbamodiethyldithiocarbamate (400).

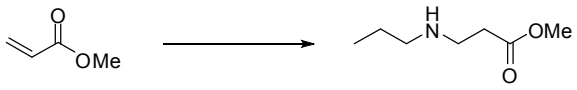


399 **400**

A solution of carbamoyl chloride **(399)** (1.01 g, 5.81 mmol) in acetone (60 mL) was treated with sodium diethyldithiocarbamate trihydrate (5.22 g, 23.24 mmol). The reaction mixture was stirred overnight at room temperature and quenched with a saturated aqueous solution of sodium hydrogen carbonate (20 mL). The aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic layers were washed with water (50 mL) and brine (50 mL). The organic phase was dried over magnesium sulfate and concentrated under reduced pressure and purified by column chromatography (diethyl ether) to afford the *title compound* **(400)** as a yellow oil (1.53 g,

91%). R_f 0.30 (Et_2O); ν_{max}(neat)/cm^{-1} 2970, 1667 (CO), 1493, 1460, 1422, 1330; δ_H(300 MHz; $CDCl_3$) 0.95 (3 H, t, *J* 7.3), 1.28-1.35 (6 H, m), 1.62-1.72 (2 H, m), 2.76 (2 H, t, *J* 6.9), 3.41 (2 H, t, *J* 7.6), 3.63-3.80 (4 H, m), 3.97-4.02 (2 H, q, *J* 7.1); δ_C(75 MHz; $CDCl_3$) 11.0 (CH_3), 13.2 (CH_3), 15.9 (CH_2), 22.0 (CH_2), 44.3 (CH_2), 48.8 (CH_2), 49.8 (CH_2), 52.2 (CH_2), 117.7 (C), 162.3 (C), 184.2 (C); *m/z* (HRESI) 310.1131 (M^+. $C_{12}H_{21}N_3ONaS_2$ requires 310.1126) and (LRESI) 310.1 (100%).

Methyl-3-(propylamino)-propanoate (403).

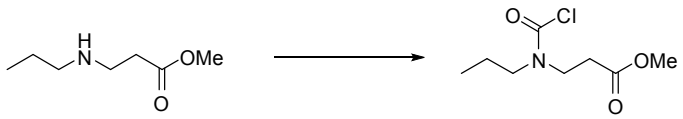


403

To methyl acrylate (5.23 mL, 58.14 mmol) was added dropwise propylamine (5.25 mL, 63.95 mmol) at 0 °C. The resulting mixture was stirred at this temperature for 10 min and warmed to room temperature and stirred at this temperature for 2 d. The reaction mixture was concentrated under reduced pressure and purified by reduced pressure distillation (kugelrohr) (2.0 mmHg, 39-42 °C) to obtain compound **(403)** (4.54 g, 54%) as a colourless oil whose analytical data were in agreement with those reported in the literature.[246]

ν_{max}(neat)/cm^{-1} 2969, 2255, 1726 (CO), 1463, 1404, 1212, 1114; δ_H(300 MHz; $CDCl_3$) 0.90 (3 H, t, *J* 7.4), 1.23 (1 H, s, N*H*), 1.44-1.52 (2 H, m), 2.51 (2 H, t, *J* 6.6), 2.57 (2 H, t, *J* 7.4), 2.86 (2 H, t, *J* 6.6), 3.67 (3 H, s, OCH_3); δ_C(75 MHz; $CDCl_3$) 11.2 (CH_3), 22.7 (CH_2), 34.1 (CH_2), 44.6 (CH_2), 51.0 (CH_2), 51.2 (CH_3), 172.7 (C); *m/z* (LREI) 145 (5), 116 (95), 84 (100), 72 (75) and 42 (90%).

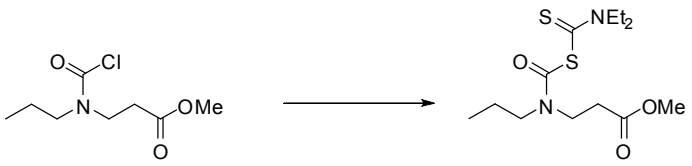
Methyl-3-(chlorocarbonyl-(propyl)-amino)-propanoate (404).



403 **404**

To a solution of triphosgene (0.68 g, 2.30 mmol) in dry toluene (40 mL), was added pyridine (1.02 mL) dropwise and the resulting mixture was stirred at room temperature for 10 min. A solution of amine **(403)** (1.0 g, 6.90 mmol) in dry toluene (30 mL) was then added to the reaction mixture and stirred for 1 h at room temperature. The reaction was quenched with water (20 mL) and the aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over magnesium sulfate and concentrated under reduced pressure to afford the *title compound* **(404)** (1.46 g, 100%) as an orange oil. R_f 0.5 (1:1 hexane: Et_2O); ν_{max}(neat)/cm^{-1} 2968, 1732 (CO), 1462, 1439, 1405, 1383, 1204, 1112; δ_H(300 MHz; $CDCl_3$) 0.89 (3 H, t, *J* 7.3), 1.57-1.63 (2 H, m), 2.60-2.67 (2 H, q, *J* 6.3), 3.27-3.60 (4 H, m), 3.64 (3 H, s, OCH_3); δ_C(75 MHz; $CDCl_3$) mixture of rotamers 10.8 (CH_3), 20.6 (CH_2), 21.6 (CH_2), 31.9 (CH_2), 33.1 (CH_2), 45.6 (CH_2), 46.5 (CH_2), 51.7 (CH_2), 53.4 (CH_2), 149.1 (C), 171.44 (C); *m/z* (HRESI) 230.0563 (M^+. $C_8H_{14}NO_3NaCl$ requires 230.0560) and (LRESI) 230 (100%).

Methyl-3-((diethylcarbamothioylthio)-carbonyl-(propyl)-amino)-propanoate (405).



404 **405**

A solution of carbamoyl chloride **(404)** (1.35 g, 6.51 mmol) in acetone (60 mL) was treated with sodium diethyldithiocarbamate trihydrate (5.81 g, 26.04 mmol). The reaction mixture was stirred overnight at room temperature and quenched with saturated aqueous solution of sodium hydrogen carbonate (20 mL). The aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic layers were washed with water (50 mL) and brine (50 mL). The organic phase was dried over magnesium sulfate and concentrated under reduced pressure and purified by column chromatography (1:1 hexane: diethyl ether) to afford the *title compound* **(405)** as a yellow oil (0.86 g, 42%); R_f 0.2 (1:1 hexane: Et_2O); ν_{max}(neat)/cm^{-1} 2874, 1738 (CO), 1668 (N*CO*S), 1491, 1421, 1380, 1356; δ_H(300 MHz; $CDCl_3$) 0.91 (3 H, t, *J* 7.3), 1.30 (6 H, t, *J* 7.2, 2 x NCH_2CH_3), 1.60-1.67 (2 H, m), 2.70 (2 H, t, *J* 6.7), 3.32 (2 H, t, *J* 7.0), 3.62-3.80 (4 H, m), 3.68 (3 H, s, OCH_3), 3.97-4.04 (2 H, q, *J* 7.0); δ_C(75 MHz; $CDCl_3$) 10.8 (CH_3), 13.0 (CH_3), 21.7 (CH_2), 31.8 (CH_2), 43.8 (CH_2), 48.5 (CH_2), 49.7 (CH_2), 51.4 (CH_3), 51.6 (CH_2), 161.5 (C), 171.7 (C), 184.5 (C); *m/z* (HRESI) 343.1131 ($[M+Na]^+$. $C_{13}H_{24}N_2O_3NaS_2$ requires 343.1126) and (LRESI) 343.1 (100%).

8. REFERENCES

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APPENDIX

X-ray crystal data for 168

Table 1. Crystal data and structure refinement for **168**

Identification code	sa301t	
Empirical formula	C15 H28 N2 O2 S2	
Formula weight	332.51	
Temperature	296(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	Pna21	
Unit cell dimensions	a = 34.451(9) Å	α= 90°.
	b = 19.752(5) Å	β= 90°.
	c = 7.442(2) Å	γ = 90°.
Volume	5064(2) $Å^3$	
Z	12	
Density (calculated)	1.308 Mg/m^3	
Absorption coefficient	2.905 mm^{-1}	
F(000)	2160	
Crystal size	0.10 x 0.08 x 0.06 mm^3	
Theta range for data collection	2.57 to 66.41°.	
Index ranges	-40<=h<=38, -23<=k<=23, -8<=l<=8	
Reflections collected	33173	
Independent reflections	8354 [R(int) = 0.0900]	
Completeness to theta = 66.41°	99.0 %	
Max. and min. transmission	0.8450 and 0.7599	

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8354 / 581 / 568
Goodness-of-fit on F^2	1.470
Final R indices [I>2sigma(I)]	R1 = 0.1629, wR2 = 0.3892
R indices (all data)	R1 = 0.2263, wR2 = 0.4484
Absolute structure parameter	0.45(6)
Largest diff. peak and hole	2.271 and -0.705 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for sa301t. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	978(2)	8656(4)	9019(15)	61(4)
C(2)	876(3)	8153(6)	10531(19)	112(9)
C(3)	1210(4)	7641(4)	10749(19)	158(13)
C(4)	1453(4)	7787(5)	12434(15)	96(6)
C(5)	1667(3)	8468(4)	12367(10)	89(6)
C(6)	1937(2)	8581(8)	10760(12)	96(7)
C(7)	1714(2)	8733(6)	9024(9)	64(4)
C(8)	1330(2)	9106(4)	9361(8)	32(3)
C(9)	1294(3)	9481(4)	11159(7)	42(4)
C(10)	1383(6)	9383(8)	14656(12)	133(10)
C(11)	279(2)	8735(3)	7078(9)	122(9)
C(12)	-373(4)	8794(9)	5539(15)	125(8)
C(13)	-660(5)	8283(10)	6330(30)	210(20)
C(14)	-229(5)	9704(5)	8077(17)	142(10)
C(15)	-371(5)	9341(9)	9770(18)	105(7)
N(1)	1390(3)	9052(4)	12808(8)	76(4)
N(2)	-125(2)	9047(6)	7099(14)	94(5)
O(1)	1092(2)	9963(4)	11323(12)	49(3)
S(1)	413(1)	8055(3)	5999(8)	90(2)

S(2)	564(1)	9199(2)	8624(6)	44(1)
C(16)	9308(2)	6334(4)	3458(13)	40(3)
C(17)	9203(3)	6835(6)	1922(19)	68(4)
C(18)	9530(4)	7338(5)	1470(20)	84(7)
C(19)	9756(4)	7156(6)	-210(20)	99(7)
C(20)	10013(3)	6528(5)	17(17)	83(6)
C(21)	10273(3)	6457(9)	1651(18)	110(9)
C(22)	10056(3)	6267(7)	3362(17)	85(6)
C(23)	9667(2)	5901(5)	3088(14)	54(4)
C(24)	9620(3)	5540(4)	1270(11)	37(4)
C(25)	9644(5)	5691(9)	-2079(15)	118(8)
C(26)	8609(2)	6271(5)	5370(16)	63(4)
C(27)	8100(3)	5390(6)	4626(17)	64(4)
C(28)	7904(5)	5625(10)	2910(20)	125(9)
C(29)	8003(4)	6116(7)	7554(18)	137(11)
C(30)	7748(6)	6630(9)	6560(30)	141(11)
N(3)	9785(3)	5885(5)	-256(13)	72(4)
N(4)	8231(3)	5961(6)	5791(18)	91(5)
O(2)	9435(2)	5032(4)	1115(12)	43(2)
S(3)	8745(1)	6964(3)	6331(9)	99(2)
S(4)	8886(1)	5794(2)	3861(8)	66(1)
C(31)	2351(2)	1342(4)	8727(12)	32(2)
C(32)	2445(3)	1883(5)	7292(17)	53(4)
C(33)	2105(3)	2350(5)	6831(18)	57(4)

C(34)	1879(4)	2145(6)	5162(18)	90(6)
C(35)	1635(3)	1502(5)	5348(15)	69(5)
C(36)	1385(3)	1406(8)	6998(16)	84(5)
C(37)	1610(3)	1212(6)	8692(15)	58(4)
C(38)	2002(2)	887(5)	8331(12)	42(3)
C(39)	2055(3)	536(5)	6521(11)	36(3)
C(40)	2020(4)	718(9)	3187(13)	90(6)
C(41)	3061(2)	1283(5)	10533(15)	55(4)
C(42)	3569(3)	413(6)	9642(15)	60(4)
C(43)	3746(5)	643(9)	7870(20)	112(8)
C(44)	3688(5)	1125(8)	12566(19)	151(12)
C(45)	3926(6)	1657(9)	11520(30)	174(15)
N(5)	1877(3)	880(4)	5025(10)	42(3)
N(6)	3444(3)	979(7)	10838(19)	98(6)
O(3)	2241(2)	32(4)	6322(12)	44(2)
S(5)	2920(1)	1955(3)	11611(8)	82(2)
S(6)	2782(1)	815(2)	9006(7)	61(1)
O(1A)	495(9)	9175(12)	13650(80)	370(20)
O(2A)	8895(3)	5827(6)	-1501(18)	85(4)
O(3A)	2770(3)	787(5)	3703(15)	71(3)

Table 3. Bond lengths [Å] and angles [°] for sa301t.

C(1)-C(8)	1.525(8)
C(1)-C(2)	1.541(2)
C(1)-S(2)	1.808(4)
C(2)-C(3)	1.539(2)
C(3)-C(4)	1.536(2)
C(4)-C(5)	1.535(2)
C(5)-C(6)	1.532(2)
C(5)-N(1)	1.533(2)
C(6)-C(7)	1.534(2)
C(7)-C(8)	1.533(2)
C(8)-C(9)	1.534(2)
C(9)-O(1)	1.186(8)
C(9)-N(1)	1.527(2)
C(10)-N(1)	1.524(2)
C(11)-N(2)	1.523(2)
C(11)-S(1)	1.632(4)
C(11)-S(2)	1.768(4)
C(12)-N(2)	1.526(2)
C(12)-C(13)	1.530(2)
C(14)-N(2)	1.530(2)
C(14)-C(15)	1.530(2)
C(16)-C(23)	1.528(9)

C(16)-C(17)	1.554(9)
C(16)-S(4)	1.829(7)
C(17)-C(18)	1.539(9)
C(18)-C(19)	1.517(10)
C(19)-C(20)	1.534(9)
C(20)-N(3)	1.508(9)
C(20)-C(21)	1.516(9)
C(21)-C(22)	1.524(9)
C(22)-C(23)	1.535(8)
C(23)-C(24)	1.538(8)
C(24)-O(2)	1.194(9)
C(24)-N(3)	1.440(8)
C(25)-N(3)	1.491(9)
C(26)-N(4)	1.474(8)
C(26)-S(3)	1.614(8)
C(26)-S(4)	1.749(8)
C(27)-N(4)	1.492(8)
C(27)-C(28)	1.520(10)
C(29)-C(30)	1.537(10)
C(29)-N(4)	1.559(10)
C(31)-C(38)	1.529(9)
C(31)-C(32)	1.546(8)
C(31)-S(6)	1.825(7)
C(32)-C(33)	1.531(9)

C(33)-C(34)	1.520(9)
C(34)-C(35)	1.530(9)
C(35)-N(5)	1.504(9)
C(35)-C(36)	1.512(9)
C(36)-C(37)	1.529(9)
C(37)-C(38)	1.519(8)
C(38)-C(39)	1.526(8)
C(39)-O(3)	1.194(8)
C(39)-N(5)	1.442(8)
C(40)-N(5)	1.489(9)
C(41)-N(6)	1.469(8)
C(41)-S(5)	1.626(8)
C(41)-S(6)	1.752(8)
C(42)-N(6)	1.491(8)
C(42)-C(43)	1.521(10)
C(44)-C(45)	1.542(10)
C(44)-N(6)	1.562(10)

C(8)-C(1)-C(2)	115.8(7)
C(8)-C(1)-S(2)	108.0(5)
C(2)-C(1)-S(2)	108.7(5)
C(3)-C(2)-C(1)	109.3(5)
C(4)-C(3)-C(2)	111.7(6)
C(5)-C(4)-C(3)	113.6(5)

C(6)-C(5)-N(1)	115.8(6)
C(6)-C(5)-C(4)	116.5(6)
N(1)-C(5)-C(4)	110.6(7)
C(5)-C(6)-C(7)	112.4(4)
C(8)-C(7)-C(6)	112.9(4)
C(1)-C(8)-C(7)	112.2(5)
C(1)-C(8)-C(9)	111.3(7)
C(7)-C(8)-C(9)	116.3(5)
O(1)-C(9)-N(1)	119.3(6)
O(1)-C(9)-C(8)	121.6(6)
N(1)-C(9)-C(8)	114.6(6)
N(2)-C(11)-S(1)	126.6(5)
N(2)-C(11)-S(2)	106.9(4)
S(1)-C(11)-S(2)	126.2(4)
N(2)-C(12)-C(13)	106.6(2)
N(2)-C(14)-C(15)	94.0(8)
C(10)-N(1)-C(9)	118.9(8)
C(10)-N(1)-C(5)	121.8(9)
C(9)-N(1)-C(5)	112.3(5)
C(11)-N(2)-C(12)	111.9(8)
C(11)-N(2)-C(14)	124.2(8)
C(12)-N(2)-C(14)	120.5(9)
C(11)-S(2)-C(1)	103.7(4)
C(23)-C(16)-C(17)	114.3(7)

C(23)-C(16)-S(4)	110.2(5)
C(17)-C(16)-S(4)	107.8(6)
C(18)-C(17)-C(16)	113.7(9)
C(19)-C(18)-C(17)	113.8(10)
C(18)-C(19)-C(20)	113.3(9)
N(3)-C(20)-C(21)	109.8(8)
N(3)-C(20)-C(19)	111.4(9)
C(21)-C(20)-C(19)	120.3(10)
C(20)-C(21)-C(22)	113.8(9)
C(21)-C(22)-C(23)	115.6(8)
C(16)-C(23)-C(22)	114.7(8)
C(16)-C(23)-C(24)	109.4(7)
C(22)-C(23)-C(24)	115.3(8)
O(2)-C(24)-N(3)	122.1(8)
O(2)-C(24)-C(23)	122.1(7)
N(3)-C(24)-C(23)	115.6(7)
N(4)-C(26)-S(3)	121.0(6)
N(4)-C(26)-S(4)	113.3(6)
S(3)-C(26)-S(4)	125.7(5)
N(4)-C(27)-C(28)	113.2(11)
C(30)-C(29)-N(4)	90.6(11)
C(24)-N(3)-C(25)	117.9(9)
C(24)-N(3)-C(20)	119.9(8)
C(25)-N(3)-C(20)	120.6(9)

C(26)-N(4)-C(27)	117.2(8)
C(26)-N(4)-C(29)	122.8(9)
C(27)-N(4)-C(29)	119.1(9)
C(26)-S(4)-C(16)	103.0(4)
C(38)-C(31)-C(32)	116.0(7)
C(38)-C(31)-S(6)	109.0(5)
C(32)-C(31)-S(6)	107.6(6)
C(33)-C(32)-C(31)	114.2(8)
C(34)-C(33)-C(32)	114.4(9)
C(33)-C(34)-C(35)	115.4(9)
N(5)-C(35)-C(36)	110.1(8)
N(5)-C(35)-C(34)	111.0(9)
C(36)-C(35)-C(34)	119.4(10)
C(35)-C(36)-C(37)	114.3(8)
C(38)-C(37)-C(36)	114.3(8)
C(37)-C(38)-C(39)	117.0(7)
C(37)-C(38)-C(31)	114.6(7)
C(39)-C(38)-C(31)	110.1(7)
O(3)-C(39)-N(5)	121.7(7)
O(3)-C(39)-C(38)	123.6(7)
N(5)-C(39)-C(38)	114.6(7)
N(6)-C(41)-S(5)	121.7(6)
N(6)-C(41)-S(6)	112.3(6)
S(5)-C(41)-S(6)	126.0(5)

N(6)-C(42)-C(43)	114.1(11)
C(45)-C(44)-N(6)	89.8(11)
C(39)-N(5)-C(40)	117.9(8)
C(39)-N(5)-C(35)	119.8(7)
C(40)-N(5)-C(35)	120.4(8)
C(41)-N(6)-C(42)	118.1(8)
C(41)-N(6)-C(44)	122.4(9)
C(42)-N(6)-C(44)	118.4(9)
C(41)-S(6)-C(31)	102.7(4)

Symmetry transformations used to generate equivalent atoms:

X-ray crystal data for 174

Table 1. Crystal data and structure refinement for **174**.

Identification code	sa300	
Empirical formula	C10 H15 N O	
Formula weight	165.23	
Temperature	296(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P212121	
Unit cell dimensions	a = 6.2729(13) Å	α= 90°.
	b = 11.291(2) Å	β= 90°.
	c = 12.464(3) Å	γ = 90°.

Volume	882.8(3) $Å^3$
Z	4
Density (calculated)	1.243 Mg/m^3
Absorption coefficient	0.628 mm^{-1}
F(000)	360
Crystal size	0.30 x 0.25 x 0.20 mm^3
Theta range for data collection	7.11 to 66.46°.
Index ranges	-7<=h<=7, -11<=k<=13, -13<=l<=14
Reflections collected	5489
Independent reflections	1460 [R(int) = 0.0671]
Completeness to theta = 66.46°	96.5 %
Absorption correction	Empirical
Max. and min. transmission	0.8847 and 0.8340
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1460 / 0 / 111
Goodness-of-fit on F^2	0.944
Final R indices [I>2sigma(I)]	R1 = 0.0356, wR2 = 0.0736
R indices (all data)	R1 = 0.0501, wR2 = 0.0793
Absolute structure parameter	0.3(4)
Extinction coefficient	0.0109(12)
Largest diff. peak and hole	0.121 and -0.131 $e.Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for sa300m. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	-36(2)	5851(1)	1519(1)	40(1)
O(1)	3405(2)	6439(1)	1379(1)	67(1)
C(5)	-1532(3)	4907(2)	1848(1)	41(1)
C(1)	2038(3)	5814(2)	1810(1)	43(1)
C(4)	-1282(3)	4583(2)	3035(1)	47(1)
C(2)	2562(3)	5011(2)	2743(1)	45(1)
C(3)	735(3)	5047(2)	3549(1)	49(1)
C(9)	-1371(3)	3852(2)	1081(2)	51(1)
C(7)	2345(3)	3120(2)	1637(2)	57(1)
C(6)	3088(3)	3756(2)	2445(2)	51(1)
C(8)	890(4)	3503(2)	756(2)	56(1)
C(10)	-662(3)	6565(2)	602(1)	55(1)

Table 3. Bond lengths [Å] and angles [°] for sa300m.

N(1)-C(1)	1.351(2)
N(1)-C(10)	1.453(2)
N(1)-C(5)	1.478(2)
O(1)-C(1)	1.234(2)
C(5)-C(9)	1.531(3)
C(5)-C(4)	1.532(3)
C(1)-C(2)	1.511(3)
C(4)-C(3)	1.512(3)
C(2)-C(6)	1.502(3)
C(2)-C(3)	1.525(2)
C(9)-C(8)	1.527(3)
C(7)-C(6)	1.322(3)
C(7)-C(8)	1.492(3)

C(1)-N(1)-C(10)	119.27(16)
C(1)-N(1)-C(5)	120.93(15)
C(10)-N(1)-C(5)	116.57(15)
N(1)-C(5)-C(9)	110.22(14)
N(1)-C(5)-C(4)	112.08(15)
C(9)-C(5)-C(4)	114.21(16)
O(1)-C(1)-N(1)	122.28(16)
O(1)-C(1)-C(2)	121.83(17)

N(1)-C(1)-C(2)	115.80(16)
C(3)-C(4)-C(5)	114.30(15)
C(6)-C(2)-C(1)	115.05(15)
C(6)-C(2)-C(3)	110.70(16)
C(1)-C(2)-C(3)	109.09(15)
C(4)-C(3)-C(2)	109.94(13)
C(8)-C(9)-C(5)	115.32(16)
C(6)-C(7)-C(8)	128.2(2)
C(7)-C(6)-C(2)	128.60(19)
C(7)-C(8)-C(9)	116.61(16)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3)for sa300m. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	37(1)	42(1)	40(1)	5(1)	-1(1)	-2(1)
O(1)	52(1)	65(1)	83(1)	17(1)	8(1)	-15(1)
C(5)	31(1)	50(1)	43(1)	0(1)	0(1)	-2(1)
C(1)	41(1)	40(1)	50(1)	-3(1)	5(1)	-5(1)
C(4)	39(1)	59(1)	43(1)	4(1)	5(1)	-1(1)
C(2)	34(1)	49(1)	51(1)	-1(1)	-8(1)	-3(1)
C(3)	51(1)	56(1)	40(1)	0(1)	-7(1)	1(1)
C(9)	53(1)	54(1)	47(1)	-3(1)	-3(1)	-12(1)
C(7)	53(1)	45(1)	72(1)	-1(1)	16(1)	6(1)
C(6)	36(1)	52(1)	66(1)	10(1)	2(1)	7(1)
C(8)	66(2)	47(1)	55(1)	-12(1)	11(1)	-2(1)
C(10)	66(2)	54(1)	45(1)	9(1)	-4(1)	0(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for sa300m.

	x	y	z	U(eq)
H(5)	-2971	5232	1765	49
H(4A)	-2498	4890	3427	56
H(4B)	-1302	3727	3102	56
H(2)	3820	5342	3100	54
H(3A)	1091	4568	4169	59
H(3B)	512	5855	3789	59
H(9A)	-2047	3174	1417	61
H(9B)	-2172	4037	437	61
H(7)	2785	2333	1615	68
H(6)	4066	3375	2887	62
H(8A)	795	2864	238	67
H(8B)	1539	4173	395	67
H(10A)	131	7292	603	82
H(10B)	-2158	6738	645	82
H(10C)	-373	6138	-48	82

X-ray data for ferrugine perchlorate salt

Table 1. Crystal data and structure refinement.

Identification code	**2008src0691**	
Empirical formula	$C_{15}H_{20}ClNO_5$	
Formula weight	329.77	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 9.9385(4) Å	α = 90°
	b = 10.4713(3) Å	β = 93.959(2)°
	c = 29.9752(11) Å	γ = 90°
Volume	3112.05(19) Å^3	
Z	8	
Density (calculated)	1.408 Mg / m^3	
Absorption coefficient	0.269 mm^{-1}	
F(000)	1392	
Crystal	Plate; colourless	
Crystal size	0.10 × 0.04 × 0.02 mm^3	
θ range for data collection	2.94 – 27.57°	
Index ranges	$-12 \le h \le 12$, $-12 \le k \le 13$, $-38 \le l \le 38$	
Reflections collected	35133	
Independent reflections	7131 [R_{int} = 0.1569]	

Completeness to θ = 27.57°	99.0 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9947 and 0.9736
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7131 / 0 / 400
Goodness-of-fit on F^2	0.958
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0818, *wR2* = 0.1800
R indices (all data)	*R1* = 0.1934, *wR2* = 0.2366
Extinction coefficient	0.0026(6)
Largest diff. peak and hole	0.416 and –0.512 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). S**tructure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). S**tructure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** *ORTEP3 for Windows* (L. J. Farrugia, J. Appl. Crystallogr. 1997, 30, 565).

Special details:

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	1249(4)	5335(4)	3366(1)	32(1)	1
C2	149(4)	6176(4)	3149(2)	36(1)	1
C3	−1126(5)	5322(4)	3104(2)	41(1)	1
C4	−699(4)	4056(4)	3316(2)	33(1)	1
C5	−779(5)	4029(4)	3822(2)	39(1)	1
C6	−40(4)	5149(4)	4054(2)	35(1)	1
C7	1359(4)	5354(4)	3877(1)	29(1)	1
C8	1059(5)	3681(4)	2762(1)	41(1)	1
C9	2005(4)	6599(4)	4038(2)	31(1)	1
C10	2312(4)	6831(4)	4524(1)	31(1)	1
C11	2645(4)	5847(4)	4827(2)	37(1)	1
C12	3002(5)	6128(5)	5270(2)	43(1)	1
C13	3000(5)	7367(5)	5416(2)	42(1)	1
C14	2652(5)	8349(4)	5119(2)	41(1)	1
C15	2315(4)	8087(4)	4677(2)	34(1)	1
C16	5345(4)	8205(4)	3327(2)	35(1)	1
C17	6176(5)	9145(4)	3071(2)	45(1)	1
C18	5325(5)	10368(4)	3016(2)	48(1)	1
C19	4029(5)	10072(4)	3238(2)	39(1)	1
C20	4108(5)	10349(4)	3733(2)	39(1)	1

C21	5369(5)	9749(4)	3972(2)	36(1)	1
C22	5516(4)	8348(4)	3835(1)	31(1)	1
C23	3442(5)	8196(4)	2731(2)	44(1)	1
C24	6867(5)	7820(4)	4017(2)	38(1)	1
C25	7189(4)	7849(4)	4504(2)	34(1)	1
C26	6236(5)	7652(4)	4815(2)	39(1)	1
C27	6594(5)	7699(4)	5268(2)	42(1)	1
C28	7902(5)	7970(4)	5422(2)	44(1)	1
C29	8864(5)	8176(5)	5115(2)	50(1)	1
C30	8526(5)	8098(5)	4664(2)	46(1)	1
O1	2270(3)	7422(3)	3770(1)	40(1)	1
O2	7685(3)	7433(3)	3763(1)	52(1)	1
O3	5134(4)	10166(3)	1155(1)	68(1)	1
O4	5409(3)	9977(3)	1929(1)	52(1)	1
O5	3994(3)	8544(3)	1521(1)	54(1)	1
O6	6325(3)	8440(3)	1471(1)	54(1)	1
O7	10447(6)	5126(5)	1219(2)	116(2)	1
O8	9245(4)	4399(3)	1810(1)	67(1)	1
O9	10881(3)	5974(3)	1931(1)	55(1)	1
O10	8857(3)	6436(3)	1516(1)	49(1)	1
N1	782(3)	4009(3)	3229(1)	34(1)	1
N2	3915(3)	8640(3)	3185(1)	31(1)	1
Cl1	5201(1)	9283(1)	1517(1)	37(1)	1
Cl2	9877(1)	5469(1)	1616(1)	46(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–N1	1.511(5)	C8–H8B	0.9800
C1–C2	1.516(6)	C8–H8C	0.9800
C1–C7	1.527(5)	C9–O1	1.221(5)
C1–H1	1.0000	C9–C10	1.487(6)
C2–C3	1.549(6)	C10–C15	1.392(6)
C2–H2A	0.9900	C10–C11	1.397(6)
C2–H2B	0.9900	C11–C12	1.382(6)
C3–C4	1.517(6)	C11–H11	0.9500
C3–H3A	0.9900	C12–C13	1.369(6)
C3–H3B	0.9900	C12–H12	0.9500
C4–N1	1.514(5)	C13–C14	1.389(6)
C4–C5	1.525(6)	C13–H13	0.9500
C4–H4	1.0000	C14–C15	1.374(6)
C5–C6	1.527(6)	C14–H14	0.9500
C5–H5A	0.9900	C15–H15	0.9500
C5–H5B	0.9900	C16–N2	1.525(5)
C6–C7	1.538(6)	C16–C22	1.526(6)
C6–H6A	0.9900	C16–C17	1.526(6)
C6–H6B	0.9900	C16–H16	1.0000
C7–C9	1.518(6)	C17–C18	1.538(6)
C7–H7	1.0000	C17–H17A	0.9900
C8–N1	1.485(5)	C17–H17B	0.9900
C8–H8A	0.9800	C18–C19	1.521(6)

C18–H18A	0.9900	C25–C30	1.406(6)
C18–H18B	0.9900	C26–C27	1.380(6)
C19–C20	1.508(6)	C26–H26	0.9500
C19–N2	1.512(5)	C27–C28	1.379(6)
C19–H19	1.0000	C27–H27	0.9500
C20–C21	1.535(6)	C28–C29	1.388(7)
C20–H20A	0.9900	C28–H28	0.9500
C20–H20B	0.9900	C29–C30	1.374(7)
C21–C22	1.533(6)	C29–H29	0.9500
C21–H21A	0.9900	C30–H30	0.9500
C21–H21B	0.9900	O3–Cl1	1.424(3)
C22–C24	1.518(6)	O4–Cl1	1.436(3)
C22–H22	1.0000	O5–Cl1	1.427(3)
C23–N2	1.484(5)	O6–Cl1	1.438(3)
C23–H23A	0.9800	O7–Cl2	1.399(4)
C23–H23B	0.9800	O8–Cl2	1.427(4)
C23–H23C	0.9800	O9–Cl2	1.429(3)
C24–O2	1.222(5)	O10–Cl2	1.450(3)
C24–C25	1.471(6)	N1–H1A	0.9300
C25–C26	1.391(6)	N2–H2	0.9300

N1–C1–C2	102.6(3)	C2–C1–H1	110.8
N1–C1–C7	106.5(3)	C7–C1–H1	110.8
C2–C1–C7	115.0(4)	C1–C2–C3	105.2(3)
N1–C1–H1	110.8	C1–C2–H2A	110.7

C3–C2–H2A	110.7	C7–C6–H6B	109.3
C1–C2–H2B	110.7	C5–C6–H6B	109.3
C3–C2–H2B	110.7	H6A–C6–H6B	108.0
H2A–C2–H2B	108.8	C9–C7–C1	109.3(3)
C4–C3–C2	105.4(3)	C9–C7–C6	112.4(3)
C4–C3–H3A	110.7	C1–C7–C6	110.0(3)
C2–C3–H3A	110.7	C9–C7–H7	108.3
C4–C3–H3B	110.7	C1–C7–H7	108.3
C2–C3–H3B	110.7	C6–C7–H7	108.3
H3A–C3–H3B	108.8	N1–C8–H8A	109.5
N1–C4–C3	101.7(3)	N1–C8–H8B	109.5
N1–C4–C5	106.8(3)	H8A–C8–H8B	109.5
C3–C4–C5	113.6(4)	N1–C8–H8C	109.5
N1–C4–H4	111.4	H8A–C8–H8C	109.5
C3–C4–H4	111.4	H8B–C8–H8C	109.5
C5–C4–H4	111.4	O1–C9–C10	119.5(4)
C4–C5–C6	112.6(4)	O1–C9–C7	120.1(4)
C4–C5–H5A	109.1	C10–C9–C7	120.5(4)
C6–C5–H5A	109.1	C15–C10–C11	119.3(4)
C4–C5–H5B	109.1	C15–C10–C9	118.1(4)
C6–C5–H5B	109.1	C11–C10–C9	122.6(4)
H5A–C5–H5B	107.8	C12–C11–C10	120.0(4)
C7–C6–C5	111.5(3)	C12–C11–H11	120.0
C7–C6–H6A	109.3	C10–C11–H11	120.0
C5–C6–H6A	109.3	C13–C12–C11	120.3(5)

C13–C12–H12	119.9	C17–C18–H18A	110.7
C11–C12–H12	119.9	C19–C18–H18B	110.7
C12–C13–C14	120.1(4)	C17–C18–H18B	110.7
C12–C13–H13	119.9	H18A–C18–H18B	108.8
C14–C13–H13	119.9	C20–C19–N2	107.0(3)
C15–C14–C13	120.3(4)	C20–C19–C18	113.7(4)
C15–C14–H14	119.9	N2–C19–C18	102.5(3)
C13–C14–H14	119.9	C20–C19–H19	111.1
C14–C15–C10	120.0(4)	N2–C19–H19	111.1
C14–C15–H15	120.0	C18–C19–H19	111.1
C10–C15–H15	120.0	C19–C20–C21	111.5(4)
N2–C16–C22	106.7(3)	C19–C20–H20A	109.3
N2–C16–C17	101.1(3)	C21–C20–H20A	109.3
C22–C16–C17	114.3(4)	C19–C20–H20B	109.3
N2–C16–H16	111.4	C21–C20–H20B	109.3
C22–C16–H16	111.4	H20A–C20–H20B	108.0
C17–C16–H16	111.4	C20–C21–C22	110.9(4)
C16–C17–C18	106.2(4)	C20–C21–H21A	109.5
C16–C17–H17A	110.5	C22–C21–H21A	109.5
C18–C17–H17A	110.5	C20–C21–H21B	109.5
C16–C17–H17B	110.5	C22–C21–H21B	109.5
C18–C17–H17B	110.5	H21A–C21–H21B	108.0
H17A–C17–H17B	108.7	C24–C22–C16	111.0(4)
C19–C18–C17	105.0(4)	C24–C22–C21	110.5(4)
C19–C18–H18A	110.7	C16–C22–C21	110.8(4)

C24–C22–H22	108.2	C30–C29–H29	119.6
C16–C22–H22	108.2	C28–C29–H29	119.6
C21–C22–H22	108.2	C29–C30–C25	120.6(5)
N2–C23–H23A	109.5	C29–C30–H30	119.7
N2–C23–H23B	109.5	C25–C30–H30	119.7
H23A–C23–H23B	109.5	C8–N1–C1	113.3(3)
N2–C23–H23C	109.5	C8–N1–C4	114.6(3)
H23A–C23–H23C	109.5	C1–N1–C4	102.0(3)
H23B–C23–H23C	109.5	C8–N1–H1A	108.9
O2–C24–C25	121.1(4)	C1–N1–H1A	108.9
O2–C24–C22	120.4(4)	C4–N1–H1A	108.9
C25–C24–C22	118.4(4)	C23–N2–C19	115.0(3)
C26–C25–C30	118.0(4)	C23–N2–C16	113.2(3)
C26–C25–C24	123.4(4)	C19–N2–C16	101.8(3)
C30–C25–C24	118.6(4)	C23–N2–H2	108.8
C27–C26–C25	120.9(4)	C19–N2–H2	108.8
C27–C26–H26	119.5	C16–N2–H2	108.8
C25–C26–H26	119.5	O3–Cl1–O5	111.3(2)
C26–C27–C28	120.7(5)	O3–Cl1–O4	108.9(2)
C26–C27–H27	119.7	O5–Cl1–O4	109.8(2)
C28–C27–H27	119.7	O3–Cl1–O6	108.8(2)
C27–C28–C29	119.1(5)	O5–Cl1–O6	109.11(19)
C27–C28–H28	120.5	O4–Cl1–O6	109.0(2)
C29–C28–H28	120.5	O7–Cl2–O8	111.1(3)
C30–C29–C28	120.7(5)	O7–Cl2–O9	110.6(3)

O8–Cl2–O9	109.1(2)
O7–Cl2–O10	108.8(3)
O8–Cl2–O10	108.1(2)
O9–Cl2–O10	108.92(19)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\ h\ k\ a^*\ b^*\ U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	37(3)	30(2)	28(2)	−1(2)	−1(2)	1(2)
C2	43(3)	32(2)	30(3)	6(2)	−9(2)	1(2)
C3	37(3)	43(3)	41(3)	−10(2)	−5(2)	5(2)
C4	30(2)	34(2)	36(3)	−5(2)	−1(2)	−1(2)
C5	36(3)	43(3)	38(3)	−2(2)	6(2)	−8(2)
C6	33(3)	38(3)	34(3)	−4(2)	0(2)	−2(2)
C7	29(2)	31(2)	26(2)	3(2)	−3(2)	−1(2)
C8	51(3)	45(3)	27(3)	−6(2)	5(2)	2(2)
C9	27(2)	30(2)	37(3)	0(2)	0(2)	2(2)
C10	27(2)	34(3)	31(3)	−2(2)	−1(2)	−2(2)
C11	42(3)	33(3)	36(3)	1(2)	−2(2)	−3(2)
C12	46(3)	48(3)	34(3)	1(2)	−6(2)	−5(2)
C13	42(3)	54(3)	30(3)	−7(2)	−4(2)	−11(2)
C14	44(3)	37(3)	43(3)	−8(2)	4(2)	−4(2)
C15	32(3)	34(3)	36(3)	3(2)	1(2)	0(2)
C16	36(3)	33(2)	36(3)	0(2)	1(2)	5(2)
C17	43(3)	55(3)	36(3)	−3(2)	13(2)	−7(3)
C18	66(4)	41(3)	38(3)	1(2)	11(3)	−12(3)
C19	55(3)	27(2)	33(3)	1(2)	4(2)	7(2)
C20	51(3)	31(2)	35(3)	−2(2)	−2(2)	7(2)
C21	41(3)	34(3)	34(3)	−7(2)	1(2)	−2(2)

C22	35(3)	31(2)	26(2)	0(2)	1(2)	1(2)
C23	56(3)	43(3)	31(3)	−5(2)	−4(2)	2(2)
C24	37(3)	31(2)	44(3)	−8(2)	−2(2)	2(2)
C25	31(3)	38(3)	31(3)	−4(2)	−4(2)	7(2)
C26	32(3)	43(3)	42(3)	−3(2)	−6(2)	4(2)
C27	38(3)	53(3)	35(3)	1(2)	−3(2)	5(2)
C28	54(3)	43(3)	33(3)	−1(2)	−5(2)	13(3)
C29	37(3)	59(3)	53(4)	−1(3)	−6(3)	4(2)
C30	35(3)	59(3)	44(3)	−6(3)	−2(2)	10(2)
O1	44(2)	36(2)	38(2)	7(2)	−3(2)	−8(2)
O2	42(2)	68(2)	44(2)	−13(2)	4(2)	18(2)
O3	98(3)	60(2)	44(2)	19(2)	−7(2)	−7(2)
O4	66(2)	57(2)	34(2)	−16(2)	5(2)	−4(2)
O5	26(2)	56(2)	79(3)	3(2)	−3(2)	−10(2)
O6	33(2)	37(2)	94(3)	−15(2)	9(2)	2(2)
O7	157(5)	140(4)	55(3)	−8(3)	38(3)	67(4)
O8	80(3)	38(2)	78(3)	18(2)	−26(2)	−14(2)
O9	45(2)	47(2)	71(3)	9(2)	−18(2)	−2(2)
O10	52(2)	33(2)	58(2)	7(2)	−11(2)	4(2)
N1	37(2)	33(2)	30(2)	1(2)	0(2)	3(2)
N2	36(2)	32(2)	25(2)	0(2)	−5(2)	1(2)
Cl1	39(1)	35(1)	37(1)	−1(1)	−1(1)	−1(1)
Cl2	57(1)	42(1)	40(1)	1(1)	1(1)	9(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1	2140	5532	3246	38	1
H2A	394	6471	2851	43	1
H2B	−4	6932	3337	43	1
H3A	−1866	5709	3263	49	1
H3B	−1435	5203	2786	49	1
H4	−1205	3327	3169	40	1
H5A	−384	3220	3941	47	1
H5B	−1738	4049	3892	47	1
H6A	−584	5935	4006	42	1
H6B	64	4984	4380	42	1
H7	1958	4635	3985	35	1
H8A	656	2850	2683	61	1
H8B	2036	3641	2736	61	1
H8C	669	4336	2558	61	1
H11	2625	4984	4728	45	1
H12	3251	5460	5473	52	1
H13	3236	7554	5722	51	1
H14	2646	9207	5223	49	1
H15	2084	8763	4474	41	1
H16	5504	7305	3233	42	1
H17A	6361	8791	2775	53	1
H17B	7046	9326	3240	53	1
H18A	5801	11100	3165	58	1

H18B	5131	10575	2696	58	1
H19	3240	10514	3081	46	1
H20A	3294	10009	3863	47	1
H20B	4128	11285	3780	47	1
H21A	5305	9802	4299	43	1
H21B	6179	10231	3896	43	1
H22	4787	7846	3968	37	1
H23A	3998	8584	2510	66	1
H23B	2498	8448	2667	66	1
H23C	3517	7264	2716	66	1
H26	5326	7482	4715	47	1
H27	5933	7544	5476	50	1
H28	8142	8016	5734	52	1
H29	9765	8373	5219	60	1
H30	9202	8213	4458	55	1
H1A	1211	3418	3421	40	1
H2	3332	8330	3389	38	1

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*D*H*A*)
N2–H2···O1	0.93	1.87	2.786(5)	169.8
N1–H1A···O6^{i}	0.93	2.45	3.012(5)	119.1
N1–H1A···O10^{i}	0.93	2.08	2.817(5)	134.6

Symmetry transformations used to generate equivalent atoms:

(i) –x+1,y–1/2,–z+1/2