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Gold-catalysed Cycloisomerisations of Ketoalkynes

by

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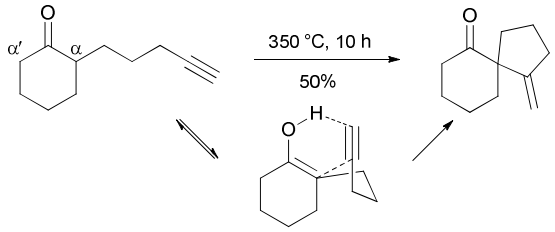
Abstract

The direct cyclisation between alkynes and ketones was described by Conia in 1964. Under high temperatures (150-650 °C), alkynyl and alkenyl ketones were converted into carbocycles, bis-fused carbocycles and spiro compounds by a pericyclic ene-type reaction. However, the use of elevated temperatures limits its applications to thermally robust molecules.

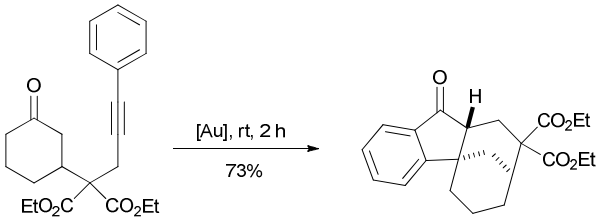


Scheme **1**. The thermal Conia cyclisation

Since the original report, a significant amount of effort has been made to develop alternative approaches under mild conditions. These methods employ activated methylenes, frozen enol equivalents or enamine intermediates as nucleophiles in the presence of a Lewis acid (Hg, W, Pt, Au) to activate the unsaturated moiety. Although, synthetically useful, these processes are limited by the necessity to use a preformed enol or a co-catalyst, which involves additional synthetic steps and reagents.

In this thesis, we will show how the direct Conia-type cyclisation of ketoalkynes can be achieved without recourse to preactivation of the ketone. The use of a π-Lewis acid catalyst enables synthetically efficient direct cyclisations to occur at room temperature. In our study we tested a range of Lewis acids and discovered that the use of gold complexes allows a variety of bis-fused [4.3.0], [3.3.0], [4.4.0] and spiro carbocycles to be obtained smoothly from readily assembled starting materials. Details of the mechanistic aspects will be discussed

as well as the scope and the limitations of this new process. Additionally, we will show an extension of this work into cascade polycyclisation reactions, which transform simple starting materials into complex carbocyclic structures in one synthetic manipulation.



Scheme **2**. Formation of tetracyclic framework

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LIST OF ABBREVIATIONS

2D	two dimensions
Å	Angstrom (10^{-10} metre)
app	apparent
Ar	aromatic
br	broad
^{n}Bu	linear butyl
^{t}Bu	tertiary butyl
c	Centi (10^{-2})
C	Celsius
COSY	correlation spectroscopy
d	day(s)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DEPT	distortionless enhancement by polarisation transfer
DMAP	4-(dimethylamino)pyridine
DMC	dimethyl carbonate
DMF	*N, N*-dimethylformamide
DME	1,2-dimethoxyethane
dppm	1,1-bis(diphenylphosphino)methane
EDG	electron-donating group
EI	electron impact ionisation
eq	equivalent(s)
ES	electrospray ionisation
eV	electron Volt
EWG	electron-withdrawing group
GC	gas chromatography
GOESY	gradient enhanced Overhauser

	spectroscopy (gradient-assisted 1D nOe experiment)
h	hour(s)
HMBC	heteronuclear multiple quantum correlation
HOMO	highest occupied molecular orbital
HSQC	heteronuclear single quantum correlation
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
L	ligand
LA	Lewis acid
LME	London Metal Exchange
LUMO	lowest unoccupied molecular orbital
μ	micro (10^{-6})
m	meta
m	metre
M	metal
M	molar
Me	methyl
MEK	methyl ethyl ketone
min	minute(s)
mol	mole
mp	melting point
MS	molecular sieves
MS	mass spectrometry
NMR	nuclear magnetic resonance spectroscopy
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
o	ortho
oz	ounce

p	para
Ph	phenyl
ppm	parts per million
^{i}Pr	*iso*-propyl
quant	quantitative
R_f	relative front
rt	room temperature
t	time
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TIPS	triisopropylsilyl
TLC	thin layer chromatography
THF	tetrahydrofuran
TMS	trimethylsilyl
TOF	time of flight
t_r	retention time
Ts	*para*-toluenesulfonyl
*p*TSA	*para*-toluenesulfonic acid

Chapter 1: Introduction

1.1 General considerations on homogeneous gold catalysis

Although gold has been employed for a long time in jewellery, ornamentation and monetisation; its utilisation in chemistry, notably in catalysis has been scarce until very recently. However, the first observations of its catalytic abilities were mentioned in 1823, following the decomposition of ammonia in its presence.[1] From this date until the 1970s, the catalytic properties of gold were reported in only a few scattered examples, as illustrated by the Lancaster-Rapson survey[2] and Bond's seminal work on olefin hydrogenation over supported gold catalysts.[3] Its *supposed* inertness and elevated price might have arrested subsequent and in-depth developments. Nevertheless, several years later, its ability to catalyse ethyne hydrochlorination[4] and carbon monoxide oxidation[5] helped to arouse the attention of the scientific community and furthered the development of heterogeneous gold catalysis. At about the same time, homogeneous gold catalysis was hardly investigated despite remarkable results obtained by Ito in asymmetric aldol condensations,[6] and by Utimoto in alkyne activation.[7] Gratifyingly, this situation was rapidly modified within a few years and homogeneous gold catalysis has gained more attention to its current state as a dynamic field in catalysis research.

The use of gold salts and complexes has been particularly rewarding, since novel chemical transformations have been found and complex structures have been produced in an atom-economic manner. In these reactions,[6-8] gold catalysts could behave either as oxophilic Lewis acids or as carbophilic acids. While the π-acidity of Au(I) and Au(III) is well known and this propensity moderately used,[8] the reactivity of gold complexes towards carbonyl functionality has been barely exploited.[9,10] The use of gold catalysts either as carbophilic Lewis acids or

oxophilic acids mainly lies on two factors: the intrinsic chemical properties of gold and its price. For a chemical transformation, at equal reactivities and efficiencies, the least expensive catalyst is obviously preferred and thus will be more employed. Besides, gold catalysts are generally more expensive than conventional oxophilic Lewis acids, but less expensive than Rh or Pt salts, which also activate multiple bond systems. For instance, in 2004, aluminium and gold prices were, respectively, 1717 $/tonne and 410 $/oz (equal to 14,462,324 $/tonne); whereas platinum was sold at 846 $/oz.[11] Recent prices are also aligned with the above trends. On the 27th October 2010, aluminium was sold at 2322 $/tonne (LME official), while gold was traded at 1324.5 $/oz (London fix) and platinum at 1860.5 $/oz (London fix but on 26th).[12]

In addition to the price dictate, gold's intrinsic properties mainly cause its preferential use as a π-acid (*i.e.* multiple bond activation) rather than a σ-acid (carbonyl activation).[13] Gold catalysts are well known to be soft Lewis acids, thus interacting preferentially with soft Lewis bases such as alkynyl or alkenyl units. This interaction leads to the activation of the unsaturated unit, by depletion of its electron density through coordination with the metal, thus enabling attack by a nucleophile. Relativistic effects can be employed to explain such behaviour, as the contraction of the 6s and 6p orbitals and the expansion of the 5d orbitals of Au, lead to greatly strengthened and shortened Au-ligand bonds and induce a relatively low-lying LUMO, responsible for its elevated π-acidity.[8,14] While, based on Pearson theory,[15] interaction with the carbonyl functionality should be disfavoured although possible. Au^{+} does not exclusively exhibit strong π-acidity; H^{+}, Pt^{2+} and the toxic Hg^{2+} also demonstrate such activation for example. However, as the contraction of the 6s orbital is more pronounced in the case of Au, it displays a superior π-acidity compared to neighboring elements such as Pt and Hg.[14] Furthermore, several drawbacks accompanied the use of H^{+} or Hg^{2+}. In the former

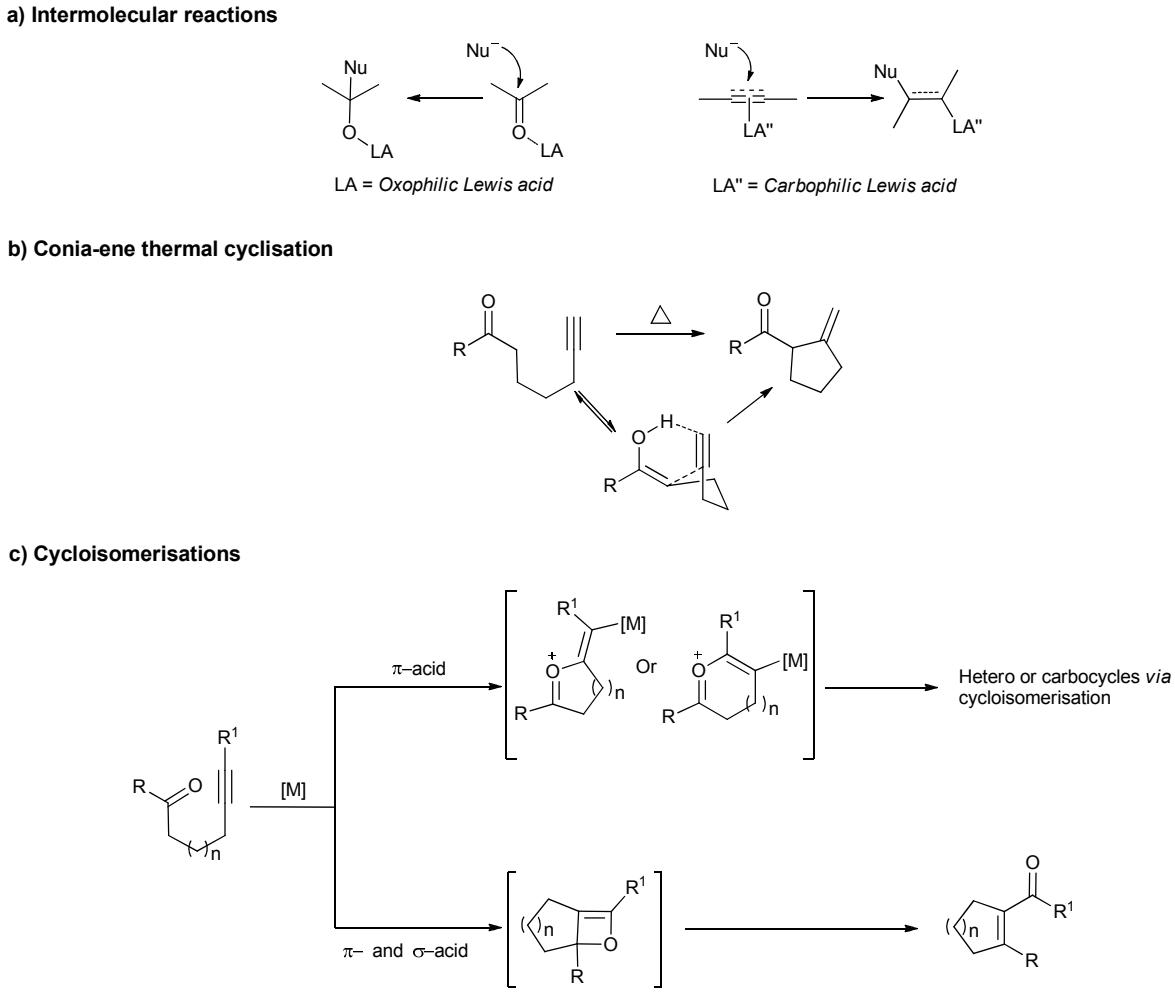
case, the reaction conditions can engender various side reactions; while in the second case, the Hg^{2+}-C bond is kinetically stable and necessitates an extra step for cleavage, in contrast to the Au^{+}-C bond which is kinetically labile.

The above characteristics render gold catalysts very suitable for chemoselective activation of alkynes or alkenes and less frequently of carbonyl functionalities. In systems containing carbonyl functionality and unsaturated bond units, gold catalysts have been used to obtain interesting building blocks, through intriguing mechanisms. The subsequent chapters will depict these transformations; but first the field of the study needs to be presented.

1.2 Alkynyl ketones and alkynyl aldehydes as starting materials: defining the scope of the study

Compounds containing both alkynyl and carbonyl functional groups are common among synthetic organic molecules since various further modifications can be done through interaction of these functionalities with external reactants. Under suitable conditions, external nucleophiles or electrophiles can be easily added, either on the carbonyl unit or on the alkyne (Scheme 1.a). Nevertheless, their use is not mandatory. Carbonyl and alkynyl units can react together, assisted by external reagents or not. Interesting and useful compounds have been obtained by employing this approach. One of the early examples was reported by Conia and co-workers, who observed that unsaturated carbonyl compounds cyclise through a pericyclic ene-type reaction to give carbocycles under elevated temperatures (Scheme 1.b). Since the original report, alternative methods, in which the *C*-nucleophilicity of the carbonyl functional unit is increased, have been developed to allow nucleophilic attack on an activated electrophilic alkynyl moiety (Chapters 1.3 and 1.4.1).

In the absence of substrate modification, the lone pair of the carbonyl oxygen atom can act as a nucleophile (Scheme 1.c, upper route). This second approach has generally been used to prepare oxygen-containing heterocycles (furans and related compounds) or complex carbocycles if a second alkynyl unit is present in the system (Chapters 1.4.2 and 1.4.3). Under gold catalysis, these two routes are favoured when the complexes display a carbophilic Lewis activity, so called π-acidity.[8] Alkynyl carbonyl substrates can also undergo a metathesis reaction (Scheme 1.c, lower route). In this case, the resulting products are generally enone derivatives, which can undergo subsequent transformations depending on the structure of the starting material (Chapter 1.4.4). The scope and the limitations of the aforementioned routes will be discussed in the next chapters along with their mechanistic aspects.

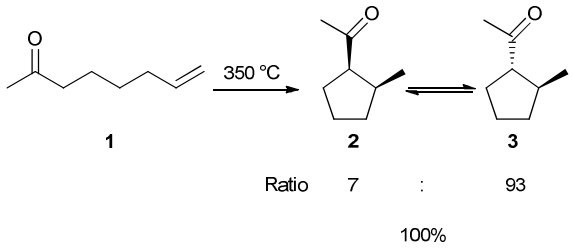


Scheme 1. Reactivity of unsaturated carbonyl compounds

1.3 Uncatalysed reactions of unsaturated carbonyl compounds: the Conia-ene thermal cyclisation

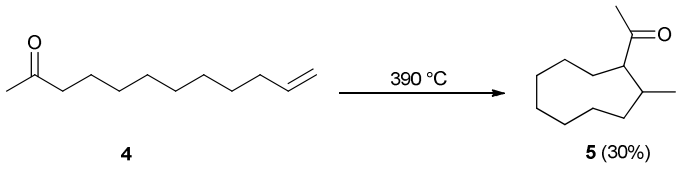
The thermal cyclisation of unsaturated carbonyl compounds is an intramolecular C-C bond-forming process, which was described by Conia in 1964.[16,17] The reaction requires high temperatures using different heating techniques (simple heating under nitrogen, in a sealed tube, static vapour, or gas flow process) depending on the type of carbonyl compounds and the scale. Both ene- and yne-ones may be employed and one of the first examples of the

thermal cyclisation is represented by the oct-7-en-2-one system **1**.[18] At around 350 °C, in a sealed tube or vapour phase, **1** was converted quantitatively into a mixture of *cis*- and *trans*-2-methylacetylcyclopentanes **2** and **3** in the ratio of 7:93 (Scheme 2).



Scheme 2. The thermal cyclisation of oct-7-en-2-one

Generally, the cyclisation to form 5- and 6-membered-ring systems proceeds smoothly; whereas larger ring compounds are obtained with difficulty in reduced yields. For instance, dodec-11-en-2-one **4** was converted into the cyclononane **5** with a yield of only 30% (Scheme 3). On the other hand, under thermal conditions, the formation of smaller rings is unviable as the process is reversible and ring-opening is favoured.[19]



Scheme 3. The thermal cyclisation of dodec-11-en-2-one

This method was used to synthesise various compounds including bicyclic and bridged compounds, as well as steroid derivatives. For instance, under elevated temperatures, ε-acetylenic ketones were converted into cycloalkyl ketones, ε-unsaturated aldehydes into formylcyclopentanes, and acylcycloalkanes substituted by an unsaturated side chain were transformed into polycyclic ketones (Table 1).[20]

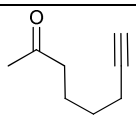
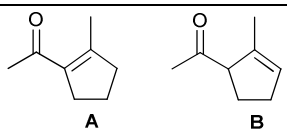
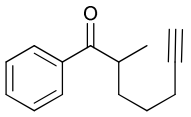
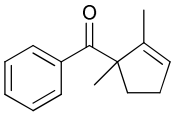
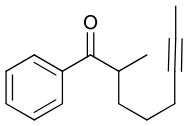
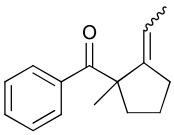
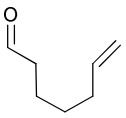
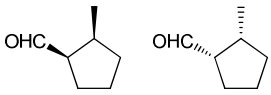
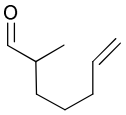
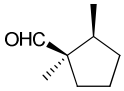
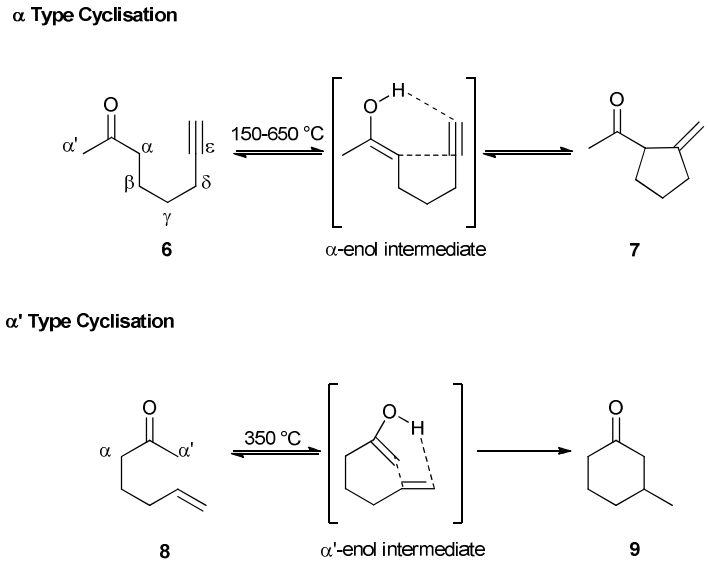
Entry	Substrate	Product	Conditions	Yield (%)
1		 **A** **B**	260 °C, 3 h	98 ratio: 85:15 (**A**:**B**)
2			350 °C, 1 h	80
3			300 °C, 2 h 30 min	90
4			320 °C, 1 h	< 25
5			320 °C, 1 h	80

Table 1. Thermal cyclisation of acetylenic ketones and ethylenic aldehydes

It was found to be necessary to alkylate at both the α-position of the ketone and the terminal extremity of the alkene or alkyne bond to avoid isomerisation of the double bond of the cyclised product (Table 1, entry 3 *vs* 1 and 2). The equivalent cyclisation of aldehyde substrates hardly occurred as the reactants and the products decomposed under high temperatures. 2-Methyl hept-6-enal (entry 5), is less sensitive to the thermal decomposition and represents an exception. In all cases, the mechanism involves two steps: the formation of an α-enol intermediate[a] generated by tautomerisation at high temperatures and a six-electron cyclic process: hydrogen shift from the enol group to the unsaturated termini with concomitant formation of the σ-bond (Scheme 4).

[a] The α-enol intermediate is described as the enol formed between the carbonyl moiety and the alkyne; while the α′-enol is the external isomer.



Scheme 4. Mechanism of the thermal cyclisation of alkynyl and alkenyl ketones

The formation of the σ-bond between the α- and ε-carbon atoms requires the generation of the α-enol intermediate. When the α-enol intermediate would lead to the formation of an unviable cycle, the cyclisation can occur *via* the formation of the α′-enol intermediate (Scheme 4).

The mechanism of the thermal cyclisation is a concerted cyclisation similar to the ene reaction. The process involves three steps: (1) a shift of one double bond due to interactions between the σ orbital of the O-H bond (or C-H bond in ene reaction) with the π* orbital of the C-C double bond; (2) an hydrogen transfer to the alkyne (or alkene) due to an overlap of the π orbital of the alkyne with the σ* of the O-H bond; and (3) a formation of a bond between the two unsaturated termini resulting from overlap between the π orbital of the C-C double bond and the alkyne π* molecular orbital (Figure 1).

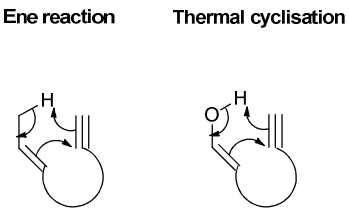


Figure 1. Mechanism of the thermal cyclisation *vs* the ene reaction

While this process has been extended to a wide range of substrates, such as ε-alkenic ketones, ε-unsaturated aldehydes, unsaturated β-ketoesters and even applied to the synthesis of a natural product,[21] the use of high temperatures is a limiting factor to this method's potential utility since some functional groups are unstable under thermal conditions. In an attempt to address these issues, Conia and colleagues developed alternative strategies that require less drastic conditions.[22]

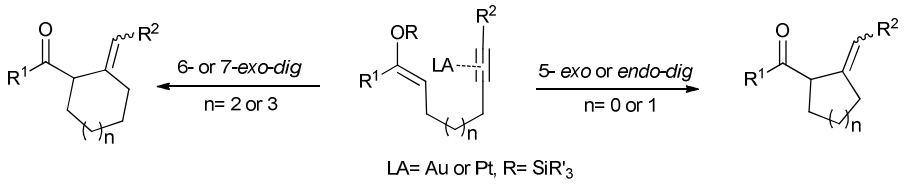
1.4 Cycloisomerisations of ketoalkynes and formyl alkynes under gold catalysis

1.4.1 Alternative approaches of the Conia-ene reaction:

The Conia-ene reaction has allowed the preparation of valuable carbocyclic frameworks from relatively simple starting materials. However, the use of elevated temperatures limits its utility to thermally stable substrates and cyclised products, as illustrated by the difficult cyclisation of formyl alkynes. Alternative approaches are characterised (1) by a modification of the starting material structure to increase the *C*-nucleophilicity of the carbonyl functionality either as an alkyl or a silyl enol ether or as a β-ketoester and (2) by an activation of the unsaturated moiety by means of Lewis acids.

4.1.1 Cyclisation of carbonyl compounds *via* their silyl enol ether derivatives

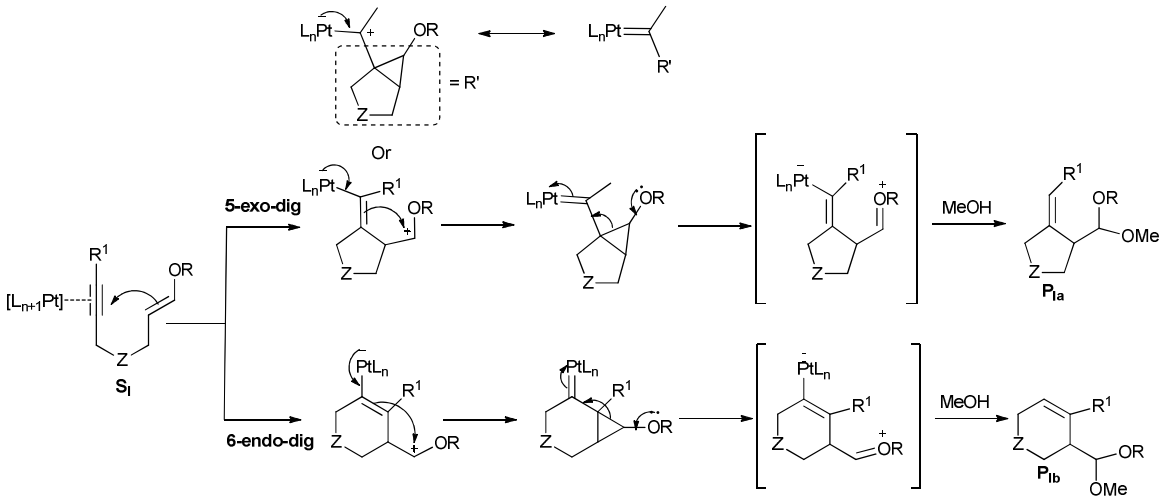
Various Lewis acids have been tested for the cyclisation of acetylenic silyl (or alkyl) enol ethers into carbocycles. Among them, a H^+/Hg^{2+} combined catalyst,[22] $EtAlCl_2$[23] and tungsten carbonyl catalysts ($W(CO)_5$.THF or $W(CO)_6$)[24] have proven their efficacy. However, severe drawbacks are associated with their use. Generally, stoichiometric amounts of catalyst are required with $EtAlCl_2$, $W(CO)_6$ and Hg^{2+} catalysts. With $W(CO)_5$.THF, although stoichiometric amounts of catalyst are not always necessary, the fact that the reaction evolves intermediate metal vinylidenes (also applicable to $W(CO)_6$) restricts its scope to terminal alkynes. The above constraints diminish somewhat the synthetic utility of these methodologies, rendering new approaches desirable. Thus, alternative catalysts have been researched and notably the investigations were orientated towards non-toxic late transition metals, known to be strong π-acids (Scheme 5). Early examples were run in the presence of platinum salts and will be presented here for comparative purposes.



Scheme 5. Cyclisation of silyl enol ethers with tethered alkynes

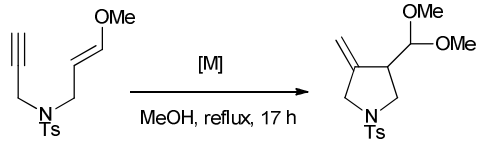
Inspired by their previous work on Pt-catalysed cyclisation of enynes, and the results reported by Iwasawa and by Dankwardt, in 2003 Echavarren *et al.* reported cyclisations of enol ethers and trialkylsilyl enol ethers with alkynes in the presence of platinum salts and other late transition metals.[25] They found that frozen nucleophiles $\mathbf{S_I}$ attack a triple bond activated by sub-stoichiometric amounts (5-10 mol%) of a late transition metal, mainly Pt(II) or Au(III) to give cyclised products $\mathbf{P_I}$ with very good yields. Indeed, they suggested that the cyclisation

takes place *via* an *exo*- or *endo-dig* mode to provide an intermediate carbocation, which after stabilisation by back-donation of the metallic centre proceeds to a transient cyclopropyl metal carbene. Subsequent rearrangement and acetalisation by means of methanol ultimately give **P_I** (Scheme 6). Although, some DFT calculations on cyclisation promoted by $PtCl_2$ and $AuCl_3$ support the formation of cyclopropyl metal carbenes, these mechanistic hypotheses must be taken with caution, especially in the case of gold wherein the nature of the Au-C bond in [L-Au(I)-CHR]$^+$ complexes causes controversy. It has been demonstrated that depending on the carbene substituents and the ancillary ligand, the mechanism evolves either a gold-stabilised carbocation or a gold carbene or something between these structural extremes.[8, 26]



Scheme 6. General mechanism for the Pt-catalysed cyclisation of enol ethers with alkynes

With Pd(II) and Cu(II), the cyclised products were obtained in relatively good yields, depending on the substrates. Nevertheless, Pt(II) and Au(III) were more efficacious and exhibited a wider applicability. For instance, enol ether **10** was uneventfully converted into methylene pyrrolidine **11** in the presence of the former transition metals; however with Au(III) and Pt(II), only 5% of catalyst loading were required to achieve the cyclisation in a better yield (Table 2).

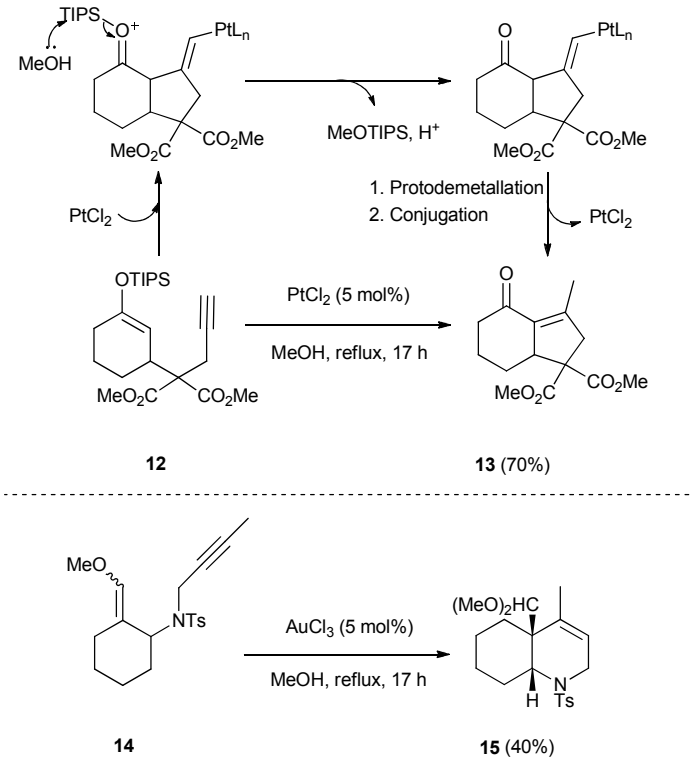


10 **11**

Entry	[M]	Yield (%)
1	$PtCl_2$ (5 mol %)	84
2	$PdCl_2$ (10 mol %)	81
3	$[Cu(MeCN)_4]PF_6$ (10 mol %)	77
4	$AuCl_3$ (5 mol %)	97

Table 2. Transition-metal catalysed cyclisation of enol ethers

Bis-fused cyclic compounds could also be obtained *via* this strategy in the presence of just 5 mol% of Pt(II) or Au(III) salts, contrary to mercuric salts methodologies requiring stoichiometric amounts of Hg^{2+}. For example, the transformation of **12** *via* a 5-*exo*-*dig* cyclisation provided bis-fused ketone **13** in good yield; whereas 6-*endo*-*dig* cyclisation of **14** afforded **15** in moderate yield (Scheme 7). The formation of bis-fused ketone **13** rather than bicyclic acetal was explained by the cleavage of the labile acetal (**P_{Ia}**), followed by the conjugation of the alkene. Nevertheless, an alternative route can be suggested. Indeed, after nucleophilic attack of the silyl enol ether on the activated alkynyl moiety, the O-Si bond is labile and methanol mediated desilylation might easily occur rather than acetalisation.



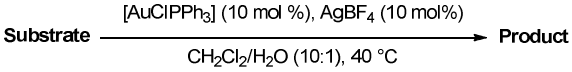
Scheme 7. Synthesis of bicyclic frameworks

The mechanism of the Au(III)-catalysed cyclisation was not depicted by the authors. However, with regards to the mechanism with platinum, the first step of the reaction involves the attack of the enol ether on the terminal or internal carbon of the activated alkyne (Scheme 6). The preferential formation of the 5- *vs* the 6-membered ring lies on the relative stability of their different transition states. Studies of the energy profiles of a [M]-6-octen-1-yne complex (M = platinum or gold) reveal that the cyclisation follows the *endo* pathway when there is a heteroatom in the hydrocarbon chain. This behaviour is explained by geometrical restrictions which are stronger in the *exo* transition state. Compound **15** illustrates this conduct.

More recently, Toste and co-workers reported similar cyclisation reactions.[27] They showed that in the presence of 10 mol% of [Ph_3PAuCl] and 10 mol% of AgX (X = OTf, SbF_6, ClO_4, BF_4), silyl enol ethers bearing terminal or internal alkynes are rapidly converted into bicyclic

ketones with moderate to good yields. The use of Ph_3PAuBF_4 salts (*i.e.* Au(I)), generated *in situ* after addition of the silver activator, $AgBF_4$, to gold halide, Ph_3PAuCl, led to cyclised products in high yields after *ca* 30 minutes at room temperature, whereas 17 hours and 65 °C were required under Au(III) or Pt(II) catalysis in Echavarren's cyclisations. Because Au(I) and Au(III) exhibit similar π-acidity, the differences between Echavarren and Toste's Au-catalysed cyclisations can only be explained qualitatively, *i.e.* structure of the substrate, concentration of the reaction mixture. For Au(I) *vs* Pt(II) salts, relativistic effects are responsible for the higher reactivity of Au(I) as discussed in Chapter 1.1.

The reactions were carried out in CH_2Cl_2/ROH or PhMe/ROH (ratio 10:1). The use of ROH (H_2O or MeOH) as a second solvent was required because it provides the proton source necessary for the protonolysis of the vinyl gold intermediate and the nucleophile for cleavage of the silicon bond. Furthermore, the α-type cyclisations were diastereoselective and took place in different modes: 5- or 6-*exo-dig*, 5-*endo-dig* or *–trig* depending on the number of carbons between the α-carbon and the tethered alkyne. The methodology was applied to a wide range of substrates, acyclic or cyclic, polysubstituted and/or highly functionalised silyl enol ethers with a terminal or internal tethered alkyne. Representative examples are indicated in Table 3.



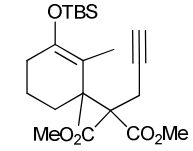
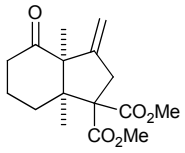
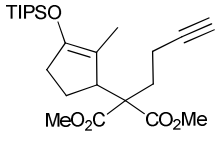
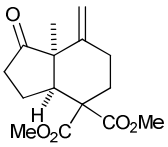
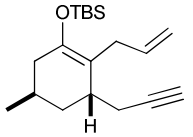
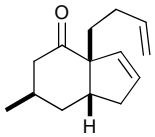
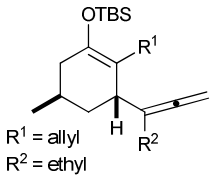
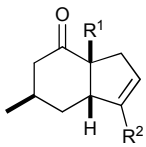
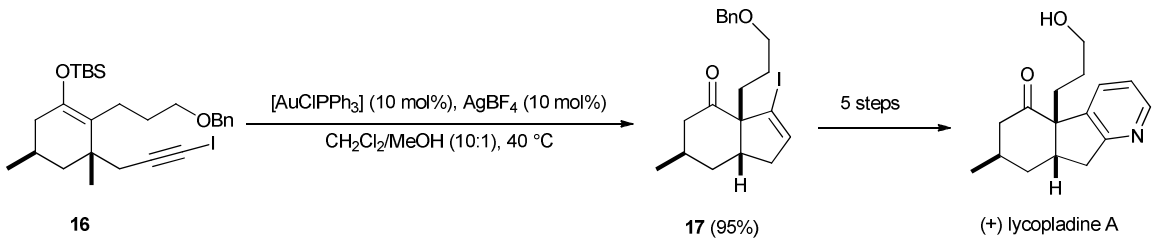
Entry	Substrate	Product	Yield (%)
1			90
2			94
3			77
4			72

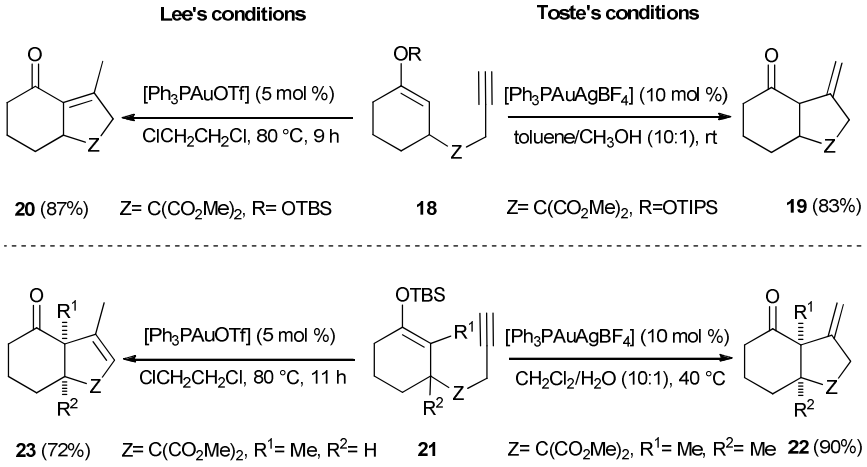
Table 3. Scope of Au(I)-catalysed carbocyclisations

The synthetic utility of this process was demonstrated by an efficient total synthesis of lycopladine A, wherein the Au-catalysed cyclisation of silyl enol ether **16** into bis-fused ketone **17** was the key step. The reaction tolerated the presence of halide and benzyl ether functionalities, allowing further modifications in the subsequent steps (Scheme 8). Total syntheses of fawcettimine[28] and platencin, a promising antibiotic,[29] have also employed a similar approach for the preparation of key intermediates.



Scheme 8. Synthesis of (+) lycopladine A

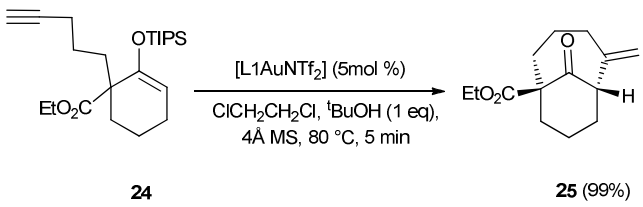
In line with the work of Toste, P. Lee and K. Lee reported the Au-catalysed 5- and 6-*exo-dig* cyclisations of alkynyl silyl enol ethers having a terminal or internal alkynyl group.[30] Intriguingly, although the structures of the described substrates were very similar to those depicted in Toste paper, harsher conditions were required. Effectively, 5 mol% of $Ph_3PAuOTf$ salts (which is a stronger π-acid than Ph_3PAuBF_4 salts due to weakened coordinated counterion ^{-}OTf[31]) and a temperature of 80 °C, along with prolonged reaction times (from 2 to 13 h) were needed to accomplish the transformations in similar yields. No proton source was added to achieve the transformation (ROH). Under these reaction conditions none of the *exo*-methylene products were produced (although postulated as intermediates by the authors); on the contrary, conjugated bicyclic enones were generally afforded, probably due to their stability and the absence of α-substituent (Scheme 9).



Scheme 9. Au(I)-catalysed 5-*exo*-dig cyclisation Lee *vs* Toste's conditions

Very recently, Sawamura and co-workers reported the first 7-*exo-dig* cyclisation of acetylenic silyl enol ethers catalysed by a Au(I) complex.[32] They showed that although the transformation was not possible with conventional gold complexes, *e.g.* $Ph_3PAuNTf_2$; the use

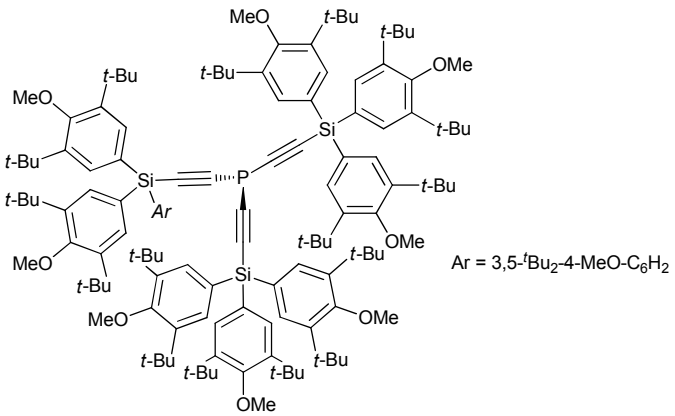
of triethynylphosphine **L1**-Au(I) complex allowed smooth access to methylene cycloheptane frameworks (Scheme 10).



24 **25** (99%)

Scheme 10. Au(I)-catalysed 7-*exo*-dig cyclisation of acetylenic silyl enol ether **24**

The reaction proceeded at variable temperatures, in chlorinated solvents, in the presence of molecular sieves, with 5 mol% of **L1**-$AuNTf_2$ and one equivalent *t*BuOH (proton source). Under these conditions, various cyclic and acyclic silyl enol ethers were converted into methylene cycloheptanes within 5 minutes in high to quantitative yields. The authors explained such reactivity by the fact that the cavity of the ligand **L1** forces the nucleophilic centre close to the gold-alkyne complex, resulting in an entropy-based rate enhancement (Figure 2).

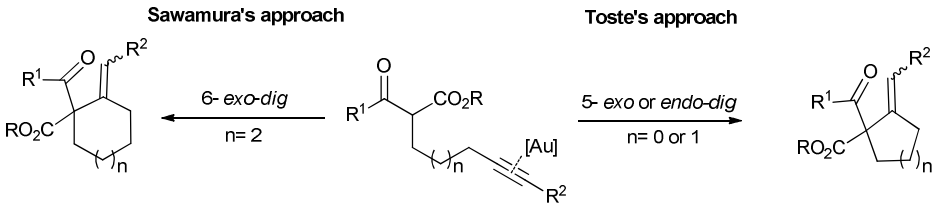


L1

Figure 2. Triethynylphosphine ligand **L1**

4.1.2 Conia-Ene reaction of β-ketoesters with alkynes

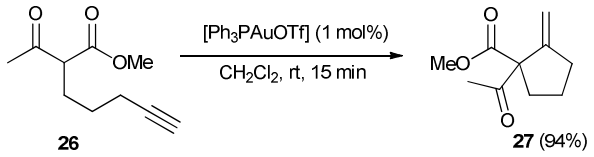
The Conia-ene reaction of β-ketoesters with alkynes is a C-C bond-forming process which provides access to vinylated ketones. Since early work under thermal conditions, many efforts have been made to find milder reaction conditions. In the 1980s, the first alternatives employed either stoichiometric or sub-stoichiometric amounts of mercuric salts. A few years later, some early and late transition metals (*e.g.* Mo and Pd) were also found to be efficacious. It is only since the 2000s that the reaction regained attention and various reagents employed such as Ni(II)[33], In(III)[34], I_2[35], Cu(I)[36] or (II), Zn(II)[37] and Pd (II)[38] probably due to Toste's seminal work on the Au-catalysed Conia-ene cyclisation of β-ketoesters.[39]



Scheme 11. Cyclisation of β-ketoesters with alkynes

In 2004, Toste *et al*. found an elegant alternative to the thermal cyclisation of unsaturated β-ketoesters, which proceeded under mild conditions.[39] They showed that ε-alkynyl ketoester **26** could cyclise in the presence of $Ph_3PAuOTf$, at room temperature, after 15 minutes to provide cyclic product **27** (Scheme 12). Only 1 mol% of catalyst loading was required and the process was not moisture-sensitive (*i.e.* it took place under "open-flask" conditions). Other catalysts were also tested. With $AgOTf/PPh_3$, Ph_3PAuCl, $[(CyNC)_2Au]PF_6$ and $[(Ph_3PAu)_3O]BF_4$, no cyclisation occurred. While, $AuCl_3$ and AgOTf gave respectively 30 and 50% of conversion, probably due to the degradation of products or/and substrates caused by the strong acidity of the former, whereas a weak reactivity can explain the second result. $[(Ph_3PAu)_3O]BF_4$/HOTf

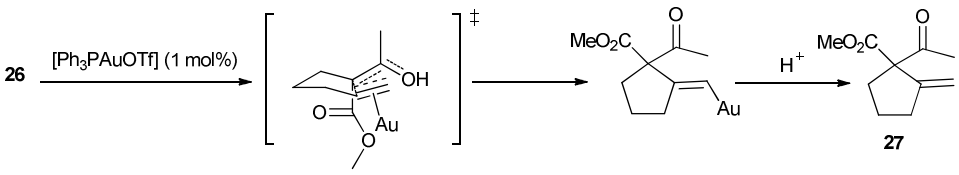
gave similar results to $Ph_3PAuCl/AgOTf$. From the above results, the authors deduced that cationic triphenylphosphinegold (I) ($Ph_3PAu(I)^+$) was the catalytically active species.



Scheme 12. Gold-catalysed Conia-Ene reaction

Under these conditions, a wide range of ketoester substrates with a terminal alkynyl tether were smoothly converted into monocyclic or bicyclic ketones in good yields (between 79 and 96%).

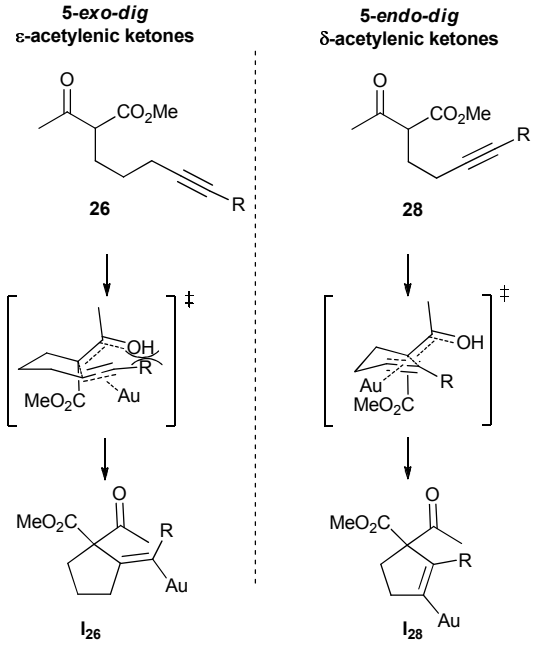
Mechanistic studies on the reaction clearly demonstrated that the process consists of nucleophilic attack on a Au(I)-alkyne complex by the enol form of the ketoester, leading to a vinyl-Au intermediate, which after protodemetallation gives the cyclised ketone (Scheme 13).



Scheme 13. Mechanism of Gold-Catalysed Conia-Ene Reaction

The reaction could not be extended to ketoesters tethered to an internal alkyne since less than 10% of conversion occurred with these substrates. The authors explained this poor reactivity by the fact that severe 1,3-allylic strain is developed in the transition state. Thus, to overcome this limitation, they examined δ-internal alkynyl ketoester substrates and based on the above described mechanism, they formulated that interactions between the alkynyl substituent and the catalyst should be minor in the transition state, due to the 5-*endo-dig* mode of cyclisation

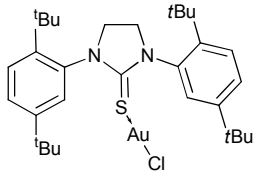
(Scheme 14).[40] To confirm this hypothesis different δ-internal alkynyl ketoesters were subjected to cationic gold salts. Indeed, in the presence of 1 mol% of $Ph_3PAuOTf$, various ketoesters bearing internal alkynyl tethers with diverse substituents such as aryl, alkyl, alkenyl groups and even halide were smoothly converted into cyclopentenes (74-99% yield).



Scheme 14. Proposed transition states for the Au(I)-catalysed 5-*exo*-dig- *vs* 5-*endo-dig*-carbocyclisation

More recently, Yang and Sawamura revisited the Au-catalysed Conia-ene cyclisation of acetylenic 1,3-dicarbonyl compounds by furthering the scope of the neutral ligand used to coordinate the metallic centre. Yang and co-workers demonstrated that PPh_3 ligand was not vital for the transformation and they showed that gold catalyst **29** with a N,N'-disubstituted bulky cyclic thiourea ligand successfully catalyses 5-*exo-dig* cyclisations at room temperature in air.[41] Sawamura *et al.* found that 6-*exo-dig* cyclisations of β-ketoesters with terminal alkynes could proceed smoothly in the presence of triethynylphosphine gold complex **L1**-$AuNTf_2$ (described on page 17), while with conventional triphenylphosphine gold complexes,

the cyclisation was either sluggish or impossible. They also demonstrated that this catalytic system was effective for the cyclisation of ketoesters with internal alkynes.[42,43]



29

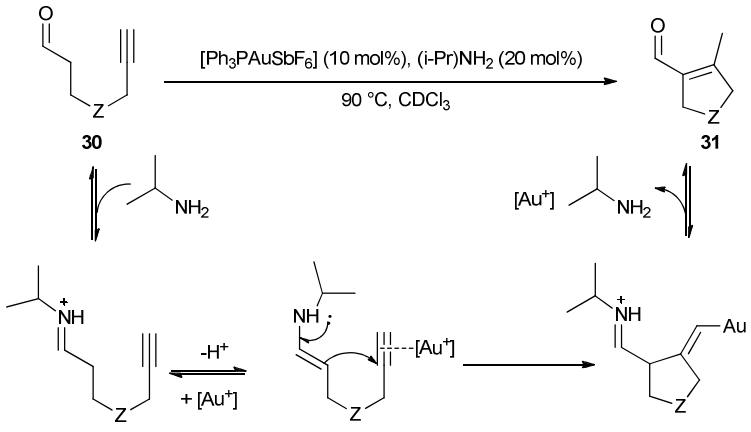
Figure 3. N,N'-disubstituted bulky cyclic thiourea gold catalyst **29**

4.1.3 Combined gold catalysis and aminocatalysis

Gold-catalysed carbophilic activation has proven a highly successful strategy for the cyclisation of unsaturated carbonyl compounds in which the *C*-nucleophilicity of the carbonyl functionality is pre-enhanced. Nucleophilic attack of activated methylene compounds or silyl enol ethers to adjacent reactive electrophiles has allowed rapid and efficient intramolecular C-C bond-forming processes to occur. Nonetheless, the synthetic utility of this transformation is somewhat diminished due to the additional synthetic step that requires the synthesis of enol equivalents. To overcome this limitation, *in situ* activation of the carbonyl unit, probably *via* the formation of an enamine intermediate, combined with a transition metal-catalysed alkyne or alkene electrophilic activation strategy has been examined and successful results obtained in the presence of $Pd(PPh_3)_4$[44], $Cu(OTf)_2$[45] and cationic gold complexes.[46]

Various cationic gold complexes as well as Ag(I) and Pt(II) salts were screened by Kirsch and co-workers for the carbocyclisation of formyl alkynes and ketoalkynes.[46] Among them, $Ph_3PAuSbF_6$ and $[(Ph_3PAu)_3O]BF_4$ displayed a higher reactivity and allowed efficient conversion of terminal alkynyl aldehydes in $CDCl_3$ at 70 °C in the presence of an amine co-catalyst. Although H_2N(i-Pr), HN(i-Pr)$_2$ and HN(i-Pr)(c-Hex) were effective for this

transformation, other amine bases such as pyrrolidine could also catalyse the reaction to afford the cyclised products in similar yields. The cyclopentene rings could be obtained in moderate to high yields (55-97%) within 1 and 4 hours; however for α-branched aldehydes, γ-aromatic-substituted aldehydes and ketoalkynes bearing an ester group, longer reaction times were required along with elevated temperatures (for the latter case) to achieve successful 5-*exo-dig* cyclisation and subsequent isomerisation (Scheme 15).



Z	Time, h	Yield, %
$C(CH_2OCH_3)_2$	2	81
$C(C(O)CH_3)_2$	4	71
$NCC(CO_2Et)$	4	97

Scheme 15. Proposed mechanism of the combined gold catalysis and aminocatalysis

1.4.2 Furan synthesis and related rings

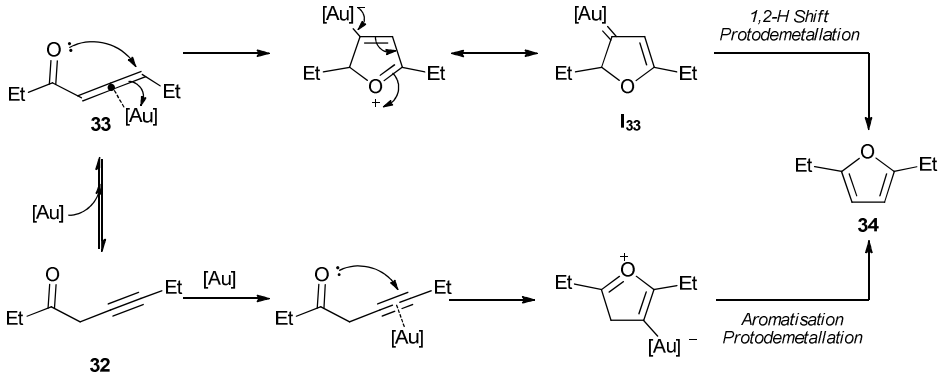
As described above, ketoalkynes smoothly undergo cycloisomerisation under gold catalysis to furnish fused and spiro carbocycles in good to high yields. The reaction proceeds *via* electrophilic activation of an alkynyl moiety, followed by intramolecular ring closure initiated by an altered carbonyl unit. The modification of the carbonyl functional group consists of increasing its *C*-nucleophilicity under the guise of enol tautomer equivalents or enamine intermediates. In the absence of such modifications, intramolecular reactions between a carbonyl functionality and an alkyne could be allowed by nucleophilic attack of the lone pair

of the carbonyl oxygen atom on the activated alkyne. This approach has been investigated for the preparation of furans and related rings.

Substituted furans are useful building blocks present in many natural products and synthetic compounds. Various well established methodologies have allowed furan synthesis either from the introduction of substituents to furan rings or from the intra- or intermolecular reactions of appropriate functionalities. Among the diverse intramolecular approaches, the transition metal-catalysed cyclisation of unsaturated compounds containing an oxygen atom has recently been paid more attention, as highly substituted furan molecules can be built under mild reaction conditions from readily accessible starting materials. Various transition metal catalysts have been employed for these transformations; *e.g.* Pd(II), Cu(I), Ag(I) and Au catalysts.[47] In the case of gold catalysts, the starting materials used for these cyclisations are generally allenyl ketones, ketoalkynes, alkynyl enones (with the assistance of an external nucleophile), α-alkenyl β-diketones and alkynyl cyclopropyl ketones to only mention those containing a carbonyl group.[47, 48]

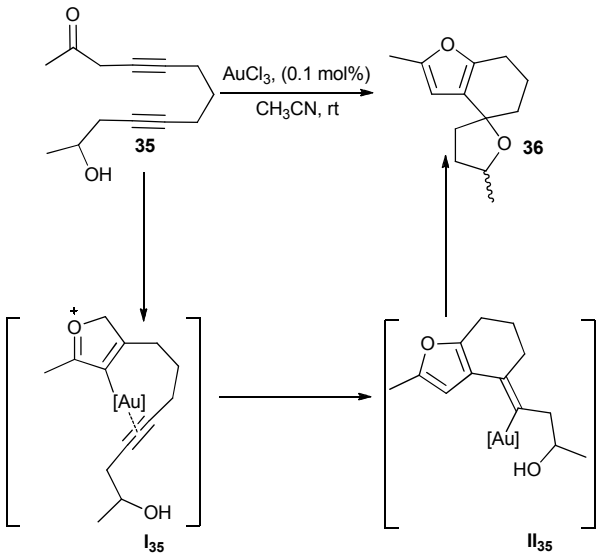
Furan preparation *via* the gold-catalysed intramolecular cyclisation of ketoalkynes (not assisted with an external nucleophile) has been scarcely described in the literature, although allowing the synthesis of interesting motifs. Pioneering work in this field has been done by Hashmi *et al*.[49] Based on the Ag^{I}-catalysed Marshal reaction[50], they reported the cyclisation of propargyl ketone **32** in the presence of 0.1 mol% of $AuCl_3$. The reaction took place at room temperature and acetonitrile was used as solvent. The 2,5-diethyl furan **34** was obtained in quantitative yield after a few minutes. With a Ag(I) catalyst the reaction failed, and a temperature of 100 °C was required with a palladium catalyst. The authors did not discuss the mechanistic aspects of the reaction. However, as allenyl ketone **33** also provided furan **34**,

two pathways could explain the reaction outcomes. Either the gold catalyses isomerisation of **32** into **33**, then subsequent ring closure affords the Au-carbene intermediate $\mathbf{I_{33}}$, which can undergo a 1,2-H shift, or the gold catalyst activates the alkynyl moiety, enhancing its electrophilicity by depletion of the electronic density through coordination. *5-Endo-dig* ring closure initiated by nucleophilic attack of the carbonyl oxygen atom can thus occur, followed by aromatisation and protodemetallation to furnish the furan ring.



Scheme 16. Proposed mechanistic pathways for the preparation of furan rings

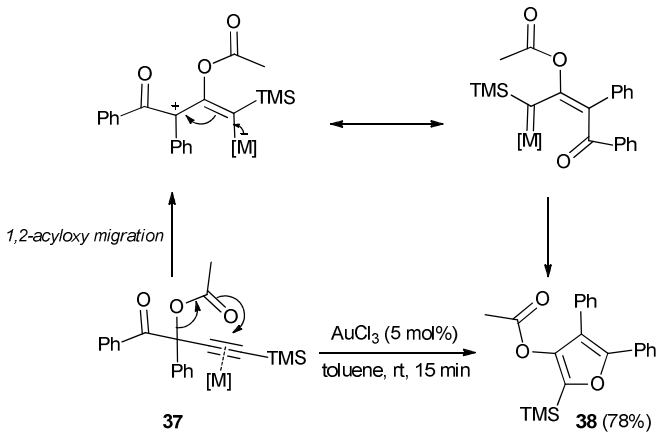
An interesting cascade cyclisation of diynyl ketone **35** was reported in the same paper and proceeded under the same reaction conditions to afford the oxaspiro compound **36** in 61%. The presence of the second alkynyl unit might have induced a second cyclisation with probably the furyl gold species $\mathbf{I_{35}}$ to provide the intermediate $\mathbf{II_{35}}$ described by the authors. $\mathbf{II_{35}}$ then suffers additional nondiastereoselective C-O bond formation to give **36**.



Scheme 17. Key intermediates in $AuCl_3$-catalysed cascade cyclisation of **35** into **36**

Gevorgyan *et al.* have also investigated the preparation of furan rings starting from unsaturated carbonyl compounds. They developed diverse methods to synthesise di-, tri- and tetra-substituted furans from allenyl or alkynyl ketones.[51,52] Various transition metals and conventional Lewis acids were tested for these transformations and in the majority of the cases Cu(I) appeared to be the most effective. However, for some substrates, a gold catalyst was preferred, notably with allenyl ketones. Preparations employing alkynyl ketones were few and limited to specific structures. For instance, they reported that acyloxy alkynyl ketones underwent smooth cycloisomerisations to produce trisubstituted acyloxy furans in good to quantitative yields under $AgBF_4$ or $Cu(OTf)_2$ catalysis.[51] For one of the substrates with a TMS-substituted alkyne (substrate **37**), silver salts were abandoned in favour of $AuCl_3$ due to TMS group incompatibility with the former catalyst. They elegantly demonstrated by means of labelled starting materials that the reaction proceeds *via* 1,2-acyloxy migration to form a metal carbenoid (or carbene), which can be trapped by the carbonyl oxygen of the ketone to afford the corresponding furan (Rautenstrauch type reaction). 2 and 3-selenofurans could also be obtained from propargyl selenoalkynones under $AuCl_3$; however its effectiveness was

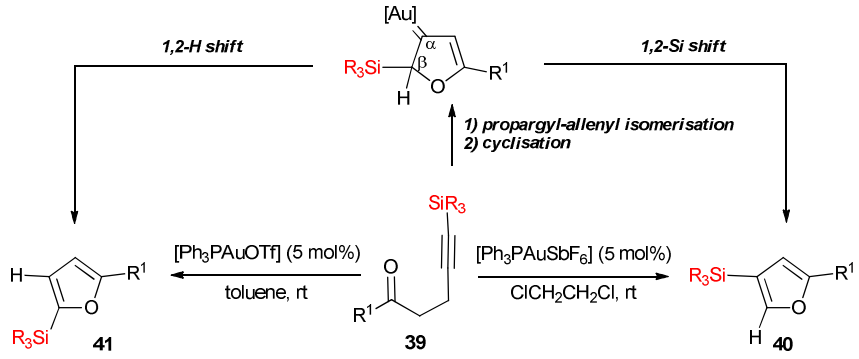
lower compared to counterparts such as CuCl or $PtCl_2$, which provided products with better yields and selectivity.



Scheme 18. $AuCl_3$-catalysed tetrasubstituted furan synthesis from α-acyloxy ketone bearing silyl alkynyl tether

More recently, they further investigated the scope of the reactions employing silyl alkynyl ketones as substrates in order to prepare diverse silyl furans, wherein the silyl group could react with various reagents and allow further modifications.[53] Indeed, they found that homopropargylic ketones with an alkynyl moiety capped with diverse silyl groups (TMS, TES and PhMeSi) and without an acyloxy substituent at the α-position underwent cycloisomerisation in the presence of 5 mol% of cationic Au(I) complexes to provide uneventfully 2- or 3-silyl furans in good to high yields. The cyclisation proceeded smoothly with ketones bearing an electron-rich or electron-poor aryl unit or an alkyl chain. In the absence of the acyloxy substituent, experimental results, as well as DFT calculations, demonstrated that the cycloisomerisation might involve a propargyl-allenyl isomerisation, followed by cyclisation to give a β-Si-substituted Au-carbene. Subsequent 1,2-Si migration in this intermediate provides the 3-silyl furan. This pathway was favoured when $Ph_3PAuSbF_6$ was employed, regardless the solvent (DCE or toluene) used. In the case of $Ph_3PAuOTf$, in a

nonpolar solvent, 1,2-H migration was preferred and 2-silyl furan was obtained, while in polar media, 1,2-Si migration occurred preferentially.

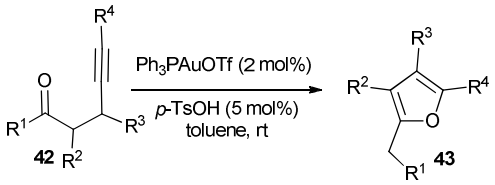


R/R[1]	Catalyst	Solvent	**40**:**41** Ratio[a]
CH_3/C_6H_6	$Ph_3PAuSbF_6$	$ClCH_2CH_2Cl$	100:0
	$Ph_3PAuOTf$	$ClCH_2CH_2Cl$	66:34
	$Ph_3PAuOTf$	toluene	7:93
$CH_3/n\text{-}C_8H_{17}$	$Ph_3PAuSbF_6$	$ClCH_2CH_2Cl$	100:0

Scheme 19. 1,2-Si migration *vs* 1,2-H shift in Au(I)-catalysed cycloisomerisations of silyl alkynones. [a] ^{1}H NMR ratio of products for reactions performed on 0.5 mmol scale.

Although interesting, the above examples are limited to the preparation of silyl furans. Prior to the Gevorgyan and Li publication[53], a general study to gain access to diverse substituted furans was conducted by Krause and Belting.[54] Alk-4-yn-1-ones **42** were converted to fused and tetrasubstituted furans in the presence of 2 mol% of $Ph_3PAuOTf$ at room temperature in toluene. Generally, the cyclisation proceeded smoothly under gold catalysis; however optimisation of the reaction conditions showed that the addition of 5 mol% of *p*-TsOH.H_2O slightly increases the reaction rate and the yield. Under these optimum conditions (in the presence or the absence of the Brønsted acid *p*-TsOH depending on the substrate) both terminal and internal ketoalkynes could be converted to substituted furans in 57-87% yields. The presence of sterically demanding groups, of electron-rich or electron-deficient aryl groups on the alkyne, of an ester group, and even of a second alkynyl unit was tolerated.

Examples with alkynones bearing silyl or halogen substituents were not reported. Like in the previous descriptions, the mechanism is characterised by the nucleophilic attack of an internal nucleophile on to the activated alkynyl moiety. The authors suggested that the internal nucleophile is an enol tautomer of alkynone **42** generated under Brønsted acid catalysis.

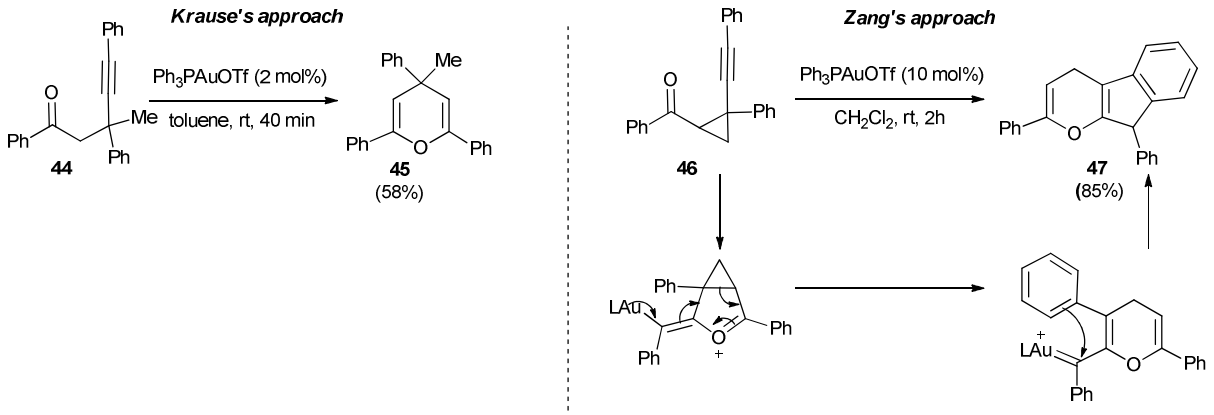


R^1	R^2	R^3	R^4	Time/min	**43** Yield/%[a]
i-Pr	CH_3	C_6H_6	C_6H_6	90	75
C_6H_6	H	H	H	20 (30)	87 (82)
C_6H_6	H	H	4-BrC_6H_6	60	84
CH_3CH_2	CH_3	C_6H_6	4-MeOC_6H_6	60	71

Table 4. Au(I)-catalysed cycloisomerisations of alkynones into 2- and 3-substituted furans. [a] Reaction time and yield given in parenthesis refer to cyclisation performed in the absence of *p*-TsOH . H_2O.

In contrast to the Hashmi furan synthesis in which *5-endo-dig* cyclisation was the only viable route for propargylic ketones, with homopropargylic ketones, *exo-dig* or *endo-dig* cyclisation mode can occur. In fact, with alkynones bearing two substituents at the β position (*e.g.* **44**), the *5-exo-dig* cyclisation was diverted (due to the absence of a labile proton) and only the *6-endo-dig* reaction could occur, affording stable products. *4H*-Pyrans were obtained *via* this pathway after protonolysis and protodemetallation of an oxonium intermediate. Zang and Tu developed a similar approach by attaching a cyclopropyl ring between α and β position.[55] In this latter case, the *5-exo-dig* cyclisation still took place, nonetheless the cyclopropyl ring triggered the formation of a Au-carbene pyranyl intermediate, which, after subsequent Friedel-Crafts reaction and protodemetallation, yielded pyran-fused indene. The pyranyl derivatives were obtained in very good yields, although 10 mol% catalyst loading was

required to achieve the transformation at room temperature in dichloromethane. The reaction was also limited to ketoalkynes bearing an aryl substituent at the β position. These results suggested that the reaction pathway is controlled either by the stability of the cationic gold species intermediate or by the stability of the cyclised product (*e.g.* in the Hashmi synthesis, no 4-*exo-dig* cyclisation was observed). These observations also explain why alkynyl (oxo)benzenes undergo *6-endo-dig* cyclisation through a benzopyrylium cation intermediate rather than *5-exo-dig* mode.



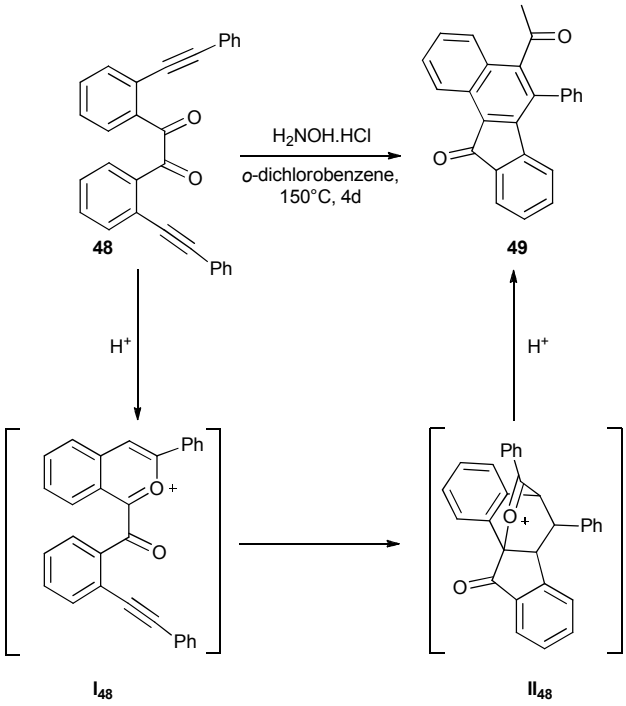
Scheme 20. Synthesis of *4H*-pyrans

1.4.3 Cycloaddition reactions through a benzo[c]pyrylium cation intermediate

Methods for the preparation of benzopyrylium cation intermediates are nowadays well established. In the literature, numerous examples can be found since these motifs are key building blocks for further complex molecular transformations. Recently, the synthesis of these useful cationic species has gained a revival, notably under gold catalysis in the effective synthesis of valuable aromatic compounds with applications in natural product synthesis. Generally, these reactions involve the intermolecular cycloaddition reaction of the benzopyrylium cation with a nucleophile as reaction partner[56] or an appropriate dienophile, *e.g.* carbonyl compounds,[57,58] benzenediazonium 2-carboxylate (as a precursor of

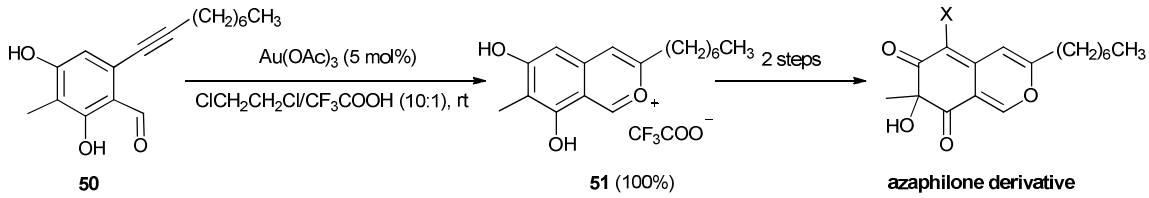
benzyne)[59,60] and alkynes.[61,62,63,64] Intramolecular cycloadditions of benzopyrylium intermediates with alkynyl units have also been developed and usually employ ynals and ynones bearing a pendant alkynyl moiety as starting materials. The structures of the obtained products often depend on the nature of the gold catalyst employed and on the reaction conditions.

One of the first examples of an intramolecular ketoalkyne cyclisation which implicates a benzopyrylium intermediate was reported by Dyker *et al.*[65] They found that bisalkynylbenzyl compound **48** did not afford oxime in the presence of hydroxylamine hydrochloride, but cyclised *via* a domino process. Benzopyrylium formation (**I_{48}**), followed by an intramolecular Diels-Alder reaction of the incipient diene and the alkynyl partner, gave benzo[a]fluorenone **49** after an intramolecular rearrangement of intermediate **II_{48}**. Although the product was obtained in quantitative yield, harsh reaction conditions were required (150 °C and 4 d); thus, alternatives approaches were desirable.[65]



Scheme 21. Synthesis of benzo[a]fluorenone

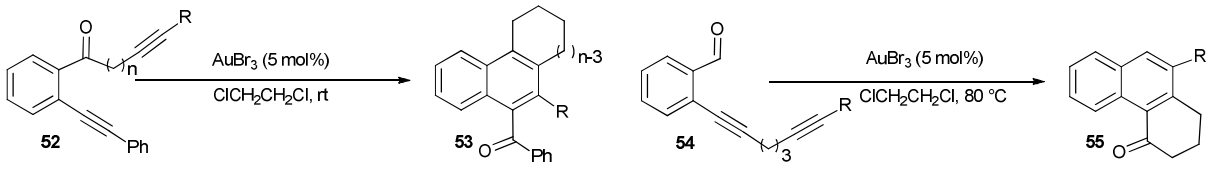
Porco and co-workers developed a milder alternative under gold catalysis where the benzopyrylium species **51** was the key intermediate to gain access to various azaphilones and related compounds possessing potential biological activity.[66] Among the gold catalysts tested, $Au(OAc)_3$ proved to be the most efficient, beyond $AuCl_3$ and $AuBr_3$, in the presence of a 10:1 mixture of DCE:TFA. Because the reaction also occurred in the absence of the Lewis acid in TFA as solvent, the authors proposed two possible reaction pathways. While, in the presence of Lewis acid, coordination of the triple bond followed by nucleophilic attack generates an ate complex susceptible to afford a stabilised benzopyrylium salt through strong ionic interactions with the anionic counterion CF_3COO^-; under Brønsted catalysis, the salt may be obtained directly from activation of the multiple bond by TFA (Scheme 22).



50 **51** (100%) **azaphilone derivative**

Scheme 22. Synthesis of azaphilones

More recently, Yamamoto *et al.* made a significant contribution to this area by further investigating the reported domino process (see page 30-31).[67] For this purpose, *o*-alkynyl(oxo)benzenes **52**, bearing an unsaturated chain were prepared and their behaviour studied under gold catalysis. Based on their successful results in the $AuCl_3$-catalysed intermolecular [4+2] benzannulation of *o*-alkynylbenzaldehydes with alkynes[61], this catalyst was *ab initio* tested for the cyclisation of *o*-alkynyl(oxo)benzenes, bearing a carbon chain attached to the carbonyl group. In DCE, the reaction proceeded smoothly at room temperature to afford naphthalene analogues **53**. However, switching to $AuBr_3$ led to an increased yield. Under these optimum conditions, various *o*-alkynyl(oxo)benzenes were converted to naphthyl ketones in high yields for substrates bearing an alkynyl pendant with aryl substituents. Lower yields (40-57%) were obtained with butyl and silyl substituents as well as for terminal alkynes (Scheme 23, inset). These electron-deficient groups (in comparison with aryl unit) might disfavour the [4+2] Diels-Alder step. The same reaction conditions were also successful for the benzannulation of diverse *o*-diynylbenzaldehydes **54** bearing terminal alkynes or internal alkynes with aromatic, alkyl or silyl substituents. However, in these cases, elevated temperatures were required (80 °C). The utility of this methodology was demonstrated in efficient syntheses of several natural products such as heliophenanthrone[68], (+)-ochromycinone and (+)-rubiginone B_2.[69]



n= 3 or 4

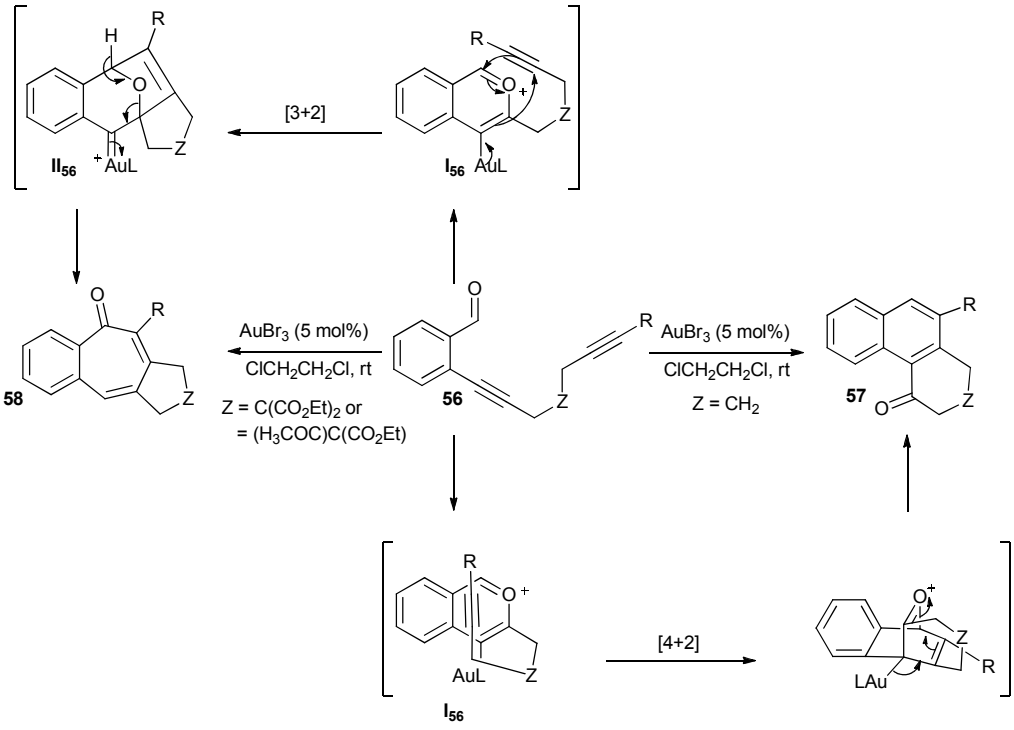
R	n	Time (h)	Yield (%)
Ph	3	3	92
Bu	3	5	57
H	3	4.5	41
TMS	3	36	40

R	Time (h)	Yield (%)
Ph	4	66
Bu	2	89
H	1.5	91
TIPS	3	88

Scheme 23. $AuBr_3$-catalysed intramolecular cyclisation

Intriguingly, Oh and co-workers reported different results for the intramolecular cyclisation of diynebenzaldehydes under identical conditions.[70] They found that alkynyl benzaldehydes **56**, bearing a pendant terminal or internal alkyne led to synthetically valuable [6.7.5]-tricyclic compounds **58** under Lewis acid catalysis (Scheme 24). Among the various acids tested, $AuBr_3$ was found to be the best catalyst at room temperature for the chemoselective synthesis of compounds **58** *vs* compounds **57**. However, when the temperature was raised up to 80 °C, the two isomeric products were obtained in roughly 1:1 ratio for diynals with an internal alkyne, while with a diynal possessing a terminal alkyne, compound **57** was the major isomer. The authors explained the formation of these two tricyclic frameworks by the existence of two possible pathways. They proposed that the reaction might proceed at first, through the formation of the benzopyrylium-type intermediate $\mathbf{I_{56}}$, described by Dyker and Yamamoto. Then, depending on the temperature, this zwitterion might react with the pendant alkynyl moiety through an intramolecular [3+2] or [4+2] cycloaddition. They suggested that at low temperature, the Huisgen-type [3+2] cycloaddition was favoured and after a sequential fragmentation of the incipient Au-carbene species $\mathbf{II_{56}}$ gives the [6.7.5] motif; at higher temperatures, it is the [4+2] cycloaddition which is preferred. Surprisingly, they also demonstrated that the presence of the gem-diester was key for the preparation of [6.7.5]

tricycle **58** *viz* [3+2] cycloaddition, presumably due to a Thorpe-Ingold effect; without the diester, only [6.6.6] isomer **57** was obtained at room temperature. The above conditions were also applied to alkynyl benzaldehydes with pendant terminal alkenes. Dyker employed a similar approach in which benzopyrylium intermediate was a key intermediate and a intramolecular [3+2] cycloaddition a key step, for the preparation of steroid frameworks.[71]



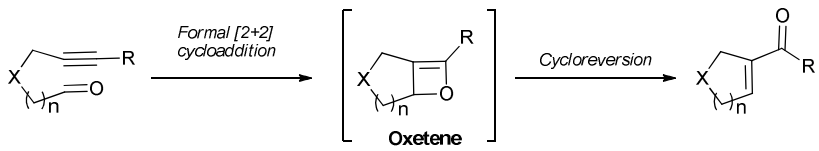
Scheme 24. Intramolecular cyclisation of formyl alkynes: [3+2] *vs* [4+2] cycloaddition

1.4.4 Alkyne-carbonyl metathesis

Coupling reactions of alkynes and carbonyl compounds are scarcely described in the literature although the reaction has been known for some time[72] and the obtained enone products are useful building blocks with numerous applications. With aldehydes, inter- and intramolecular versions of this transformation have been developed and various Lewis and Brønsted acids tested. Early examples of intermolecular alkyne-aldehyde metathesis employed stoichiometric amounts of $GaCl_3$ (80 mol %)[73] or SbF_5,[74] to give enone compounds, in moderate to very

good yields. Catalytic approaches were however desirable and $Yb(OTf)_3$[75], SbF_5[76] and SbF_6, $BF_3(OEt_2)$ and HBF_4[77] were found to be effective in these cases. Krische[77] and Saá[78] independently reported interesting examples of intramolecular alkyne-aldehyde coupling catalysed by $AgSbF_6$ and TFA, respectively. The two catalysts displayed a wide applicability allowing the preparation of valuable enones from terminal or internal alkynyl aldehydes.

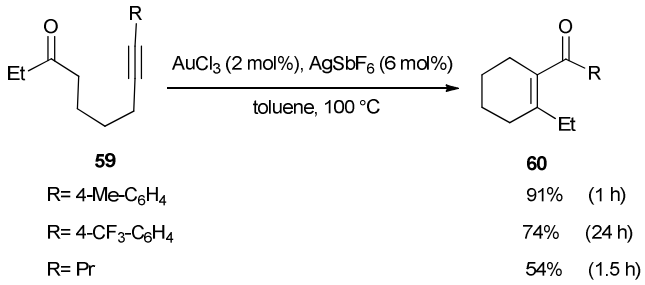
With ketones, intermolecular coupling reactions are hitherto unknown, although intramolecular versions have been examined for several years. The first examples were reported by Harding, who observed that, in the presence of $BF_3(OEt_2)$, cyclic ketoalkynes rearranged to furnish bis-fused conjugated enones *via* a cycloreversion of an intermediate oxetene (Scheme 25).[79] Although useful, severe limitations were encountered on the structures of the substrates and stoichiometric quantities of catalyst were required.



Scheme 25. Mechanism of the alkyne-carbonyl metathesis

Recently, Yamamoto and Jin re-examined this transformation by employing acyclic ketoalkynes as starting materials (Scheme 26). They found that under Brønsted[80] and Lewis acid[81, 82] conditions these substrates cyclise to provide tetrasubstituted enones in high yields. Among the Lewis acids tested by Yamamoto and Jin, $AgSbF_6$, AgOTf, $Cu(OTf)_2$, $CuCl_2/AgSbF_6$ and $AuCl_3/AgSbF_6$ afforded the cyclised products in good to high yields. However, the combination of $AuCl_3/AgSbF_6$, respectively 2 and 6 mol%, in toluene exhibited wide applicability. Aryl alkynyl ketones such as **59** and α-aryl alkynyl cyclic ketones underwent the [2+2] cycloaddition/cycloreversion uneventfully to afford tetra-substituted α,β-

unsaturated enones **60** in generally high yields (74-95%), except for alkynyl moieties bearing aliphatic chains (*e.g.* propyl group) wherein the products were obtained in moderate yields.



59

R= 4-Me-C_6H_4

R= 4-CF_3-C_6H_4

R= Pr

60

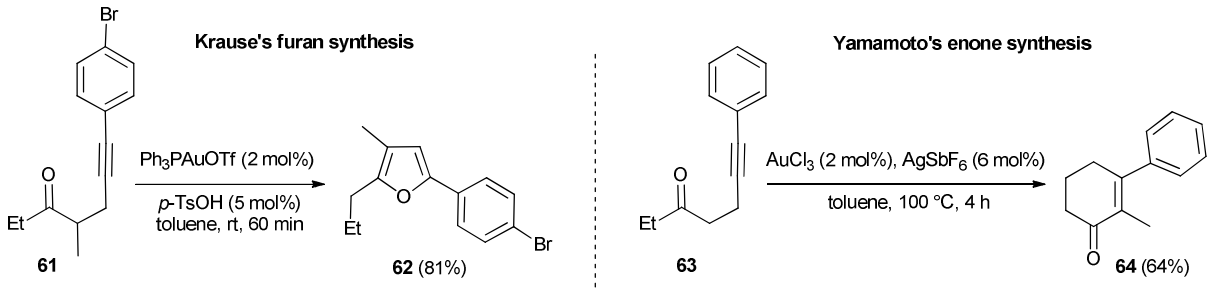
91% (1 h)

74% (24 h)

54% (1.5 h)

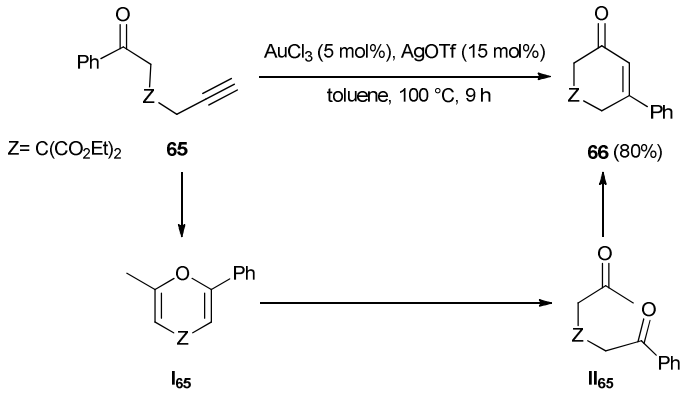
Scheme 26. $AuCl_3/AgSbF_6$-catalysed carbocyclisation of internal alkynyl ketones

When internal homopropargylic ketones, such as **63**, were employed, the alkyne-ketone metathesis (which should provide 4-membered carbocycle) did not occur but instead 6-*endo-dig* cyclisation took precedence through the nucleophilic attack of a α'-enol tautomer on an activated unsaturated bond to afford cyclohexenone **64** in moderate yield (Scheme 27). Intriguingly, these results were in sharp contrast with Krause's observations, in which homopropargylic ketone **61** is converted into furan compound **62** in the presence of a cationic gold complex. This difference can be explained by the fact that the $AuCl_3/AgSbF_6$ combined catalyst exhibits a higher π-acidity than $Ph_3PAuOTf$ and in its presence and at elevated temperatures the 6-*endo-dig* cyclisation preferentially occurs. Nevertheless, because the yield of **64** is moderate, it is possible that furan formation also occurs, followed by degradation caused by the elevated reaction temperatures.



Scheme 27. Cycloisomerisation of homopropargyl ketones

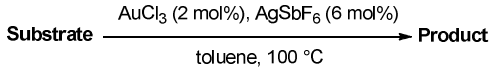
With terminal alkynyl ketones, for example substrate **65**, like for homopropargylic substrates, the alkyne-ketone metathesis did not take place. The enone products were obtained *via* $AuCl_3$/AgOTf catalysed pyran $\mathbf{I_{65}}$ synthesis and subsequent rearrangement to yield diketone intermediate $\mathbf{II_{65}}$, which undergoes an aldol condensation to produce the desired compounds. This mechanism was elegantly demonstrated by monitored reactions and the conversion of the aforementioned intermediates under the reaction conditions.



Scheme 28. $AuCl_3$/AgOTf-catalysed carbocyclisation of terminal alkynyl ketones

The oxophilic and carbophilic properties of the $AuCl_3/AgSbF_6$ combined catalyst were elegantly used in the cyclisation of acyclic 1,3-enynyl ketones (Table 5). Under the described conditions, these substrates diastereoselectively cyclised to afford in very good yields polycyclic enones through hetero-enyne metathesis and subsequent Nazarov type reaction-

catalysed by Au(III), which in the latter step exclusively displays an oxophilic activation. Representative examples are presented in Table 5.



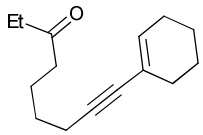
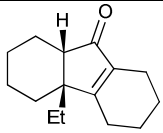
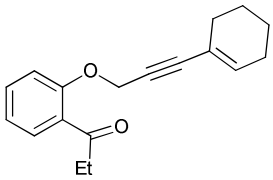
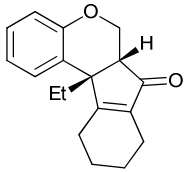
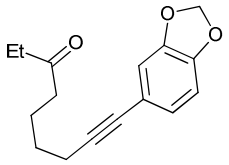
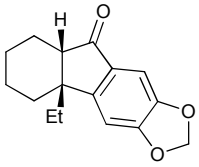
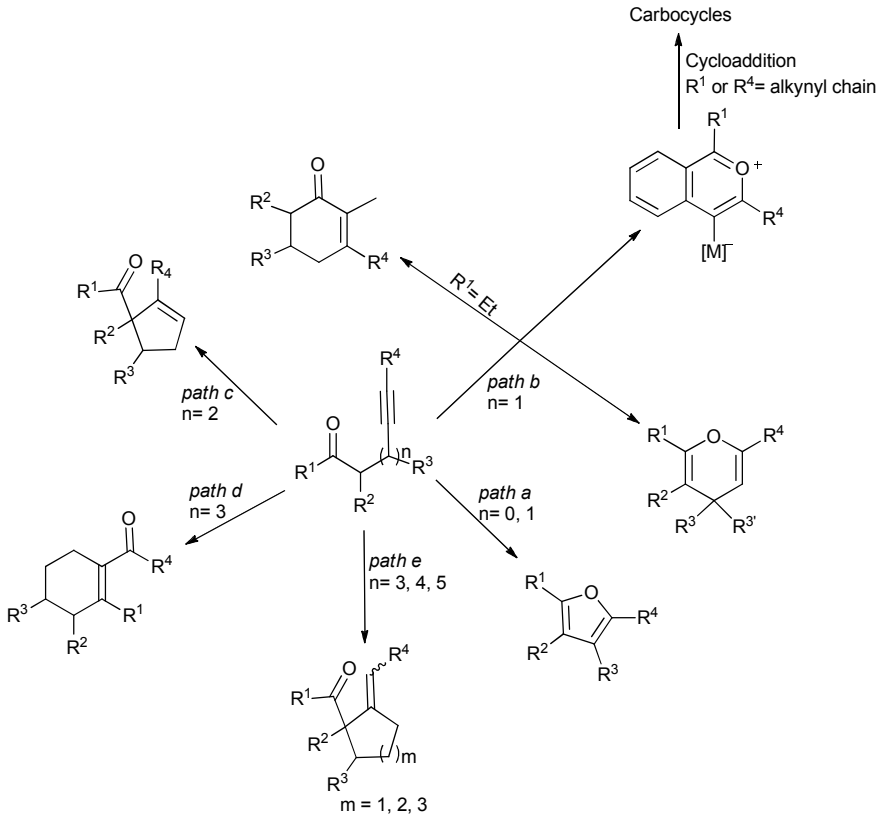
Entry	Substrate	Time (h)	Product	Yield (%)
1		1		80[a]
2		2		40
3		4		66

Table 5. Au-catalysed tandem heteroenyne metathesis and Nazarov reaction. [a] at 50 °C.

1.5 Summary and aims

Gold-catalysed cycloisomerisations of ketoalkynes (or formylalkynes) have been fairly well investigated over the last years as depicted in the previous pages. Under homogeneous gold catalysis, intramolecular ring closure of β-alkynyl ketones exclusively provided furan compounds (Scheme 29, path a, n = 0); whereas γ-alkynyl ketones depending on the reaction conditions cyclised either into heterocycles (furanyl or pyranyl derivatives) or carbocycles (Scheme 29, path b and path a, n = 1). Altered δ-alkynyl ketones (*i.e.* in the guise of silyl enol ethers or β-ketoesters) were converted into cyclopentene rings *via* 5-*endo*-*dig* cyclisation

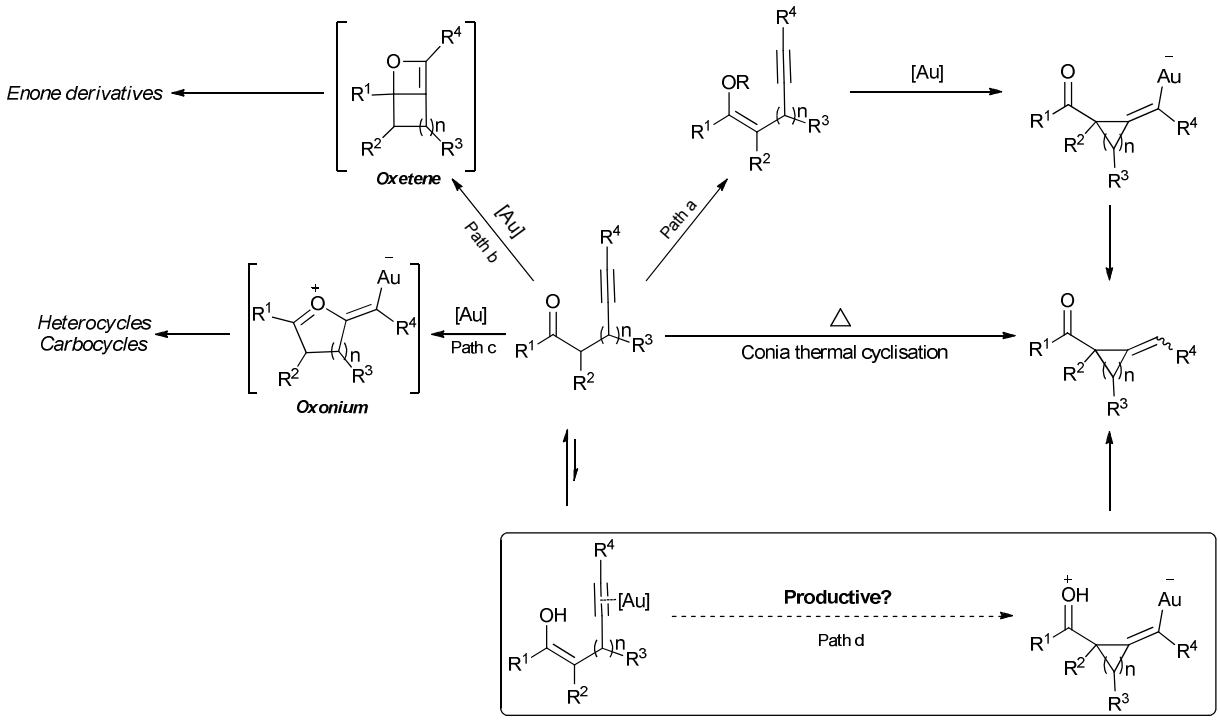
(Scheme 29, path c); while counterparts with longer tethers (*i.e.* altered ε-, ζ- and η-alkynyl ketones) yielded 5-, 6- and 7-membered rings, through a *exo-dig* mode (Scheme 29, path e). ε-Ketoalkynes could also cyclise *via* alkyne-ketone metathesis to afford carbocyclic enone derivatives (Scheme 29, path d).



Scheme 29. Cycloisomerisations of ketoalkynes under homogeneous gold catalysis

In all of these transformations, the conversion of ketoalkynes into heterocycles or carbocycles was controlled by the properties of the gold catalyst (*i.e.* π-acid or σ-acid) and the reaction conditions. Three main mechanisms are involved. Generally, the cyclic motifs are obtained *via* gold-catalysed triple bond activation, followed by the attack of a neighbouring nucleophile (Scheme 30). This nucleophile could either be the carbonyl oxygen atom or the carbon α to the carbonyl functionality. The attack of the oxygen atom lone pair to the electrophilic alkyne-metal complex can allow the formation of furanyl, pyranyl and carbocyclic compounds

through the formation of an oxonium intermediate (Scheme 30, path c). While, if an oxetene intermediate is generated from the alkynyl ketone precursor, the reaction leads to carbocyclic enone derivatives (Scheme 30, path b). Ketoalkynes can also cyclise *via* a pericyclic process at elevated temperatures: the Conia-ene reaction. Under thermal conditions, a new C-C bond is formed by α-modification of an enolisable carbonyl group with an alkyne. Although this transformation has allowed the preparation of diverse and interesting structures, applications are limited by the high temperatures required. Elegant variations of the Conia-ene cyclisation combine Lewis acid-catalysed alkyne activation with structural alterations of the carbonyl function such as silyl enol ethers or β-ketoesters to enhance the *C*-nucleophilicity (Scheme 30, path a, R = $OSiR'_3$ or R = H and R^2=CO_2R''). In this context, we questioned whether the high reaction temperatures and/or enhancement of the *C*-nucleophilicity were always necessary to achieve this powerful transformation. Would π-acid activation of an alkyne be sufficient for direct C–C bond formation with the *C*-nucleophilic enol tautomer of an unactivated enolisable carbonyl unit? If such activation were productive, even when the nucleophile is in low effective concentration, a direct 'Conia-like' *exo*-mode carbocyclisation of ketoalkynes might be achievable under mild reaction conditions (Scheme 30, path d). This would avoid the synthetic impact associated with separately (pre)activating the carbonyl compound. Our aim was therefore to develop a new methodology similar to the Conia thermal cyclisation, allowing the cyclisation of ketones with alkynes through the formation of a new C-C bond between the two functionalities under mild π-acid conditions. Ketones bearing terminal or internal alkynes will be studied.



Scheme 30. Possible pathways for ketoalkyne cyclisation

Chapter 2: Preliminary studies

2.1 Introduction

Intramolecular cyclisations of carbonyl units with terminal or internal alkynes under homogeneous gold catalysis have allowed the preparation of valuable building blocks as depicted in Chapter 1. In these cyclisations, despite the complexity of the products, the cyclisation precursors are generally uncomplicated frameworks, which are obtained after a small number of synthetic steps with an overall good yield. Under the Conia thermal conditions, the starting materials employed are usually composed of a carbonyl group attached to the alkynyl partner by means of a saturated chain. Under mild catalysis reaction conditions, the Conia-like processes mainly occurred with cyclic or acyclic enol ether equivalents or β-ketoesters with tethered terminal or internal alkynes. These substrates generally display a good reactivity in the presence of Lewis acids, notably gold catalysts. To explore the gold-catalysed cyclisation of alkynes tethered to enolisable, unactivated ketones, substrates such as **75** and **80a** were prepared to allow a comparison with those employed in the thermal process and related catalysed reactions (Figure 4).

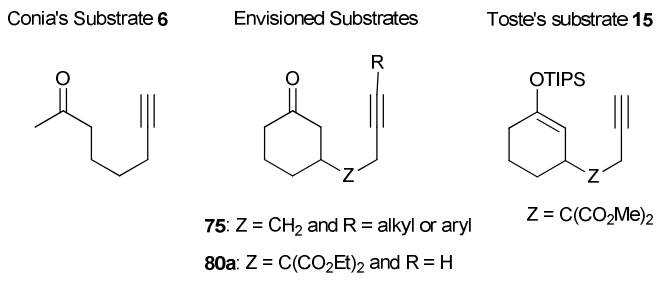


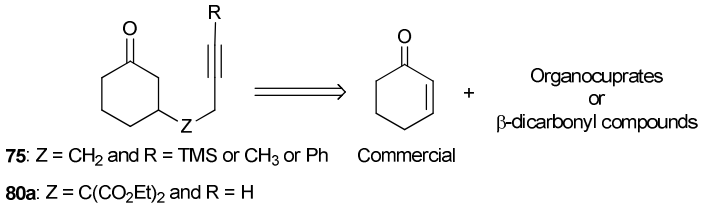
Figure 4. Envisioned substrates *vs* literature substrates

As the preparation of ketoalkynes **75** and **80a** is achieved by a conjugate addition of an appropriate nucleophile bearing an alkynyl group to a cyclic enone, diversity can be easily

introduced in the system by increasing or decreasing either the size of the enone ring or the length of the alkynyl chain. Acyclic ketoalkynes can also be prepared *via* the same approach.

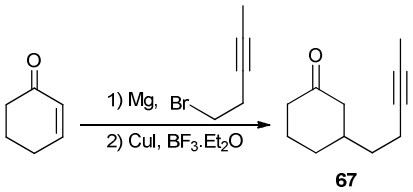
2.2 Synthesis of the cyclisation precursors

Nucleophilic addition to α,β-unsaturated carbonyl compounds can occur on two reactive sites: the carbonyl carbon or the β-carbon of the enone. When hard nucleophiles, e.g Grignard reagents are used, the nucleophilic attack preferentially occurs on the carbonyl carbon as electrostatic interactions between the latter and the negatively charged nucleophile are favoured. On the contrary, when soft nucleophiles are utilised, their more diffuse orbitals (HOMO) better interact with large orbitals (LUMO) such as the orbitals of the carbons of the multiple bond provoking 1,4-addition rather than 1,2-addition. Organocuprates and β-dicarbonyl compounds generally display such reactivity. Thus, owing to their propensity to undergo conjugate addition to α,β-unsaturated ketones, the addition of organo cuprates to commercially available 2-cyclohexen-1-one was considered (**Scheme 31**).



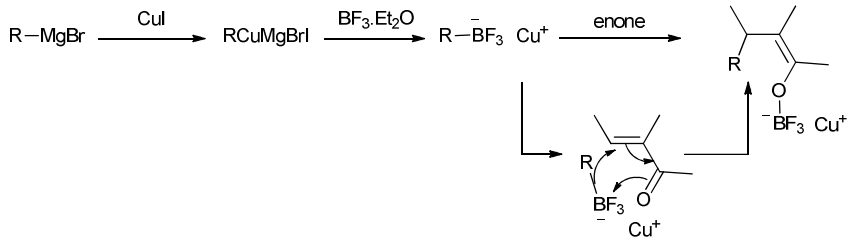
Scheme 31. Retrosynthetic analysis for substrates **75** and **80a**

In the first instance, the procedure described by Snider and Kirk for the preparation of compound **67** was followed for the synthesis of substrates **75**, based on their structural analogies (**Scheme 32**).[83]



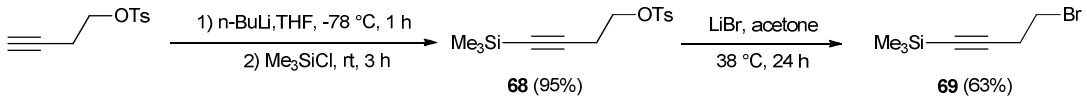
Scheme 32. Synthesis of ketoalkyne **67**

In Kirk's example, the organo cuprate was generated *in situ* from a Grignard reagent and CuI and then, 1,4-addition to 2-cyclohexen-1-one took place in the presence of $BF_3.Et_2O$. This Lewis acid could either enhance the electrophilicity at the β-carbon *via* coordination with the carbonyl oxygen or could generate the very reactive $RCu.BF_3$ species, which could add to the starting enone through a concerted cycloaddition, outlined in Scheme 33.[84]



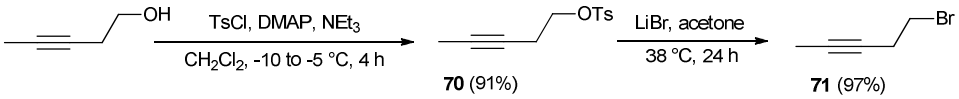
Scheme 33. Mechanism of $RCu.BF_3$ addition to enone

To test these conditions, several homopropargyl bromides were prepared from homopropargyl alcohol in two steps: alcohol activation and nucleophilic substitution.[85] Although longer than a direct alcohol substitution by bromine (Br_2) in the presence of PPh_3, this two-step route afforded the desired homopropargylic bromides, under mild reaction conditions, in an overall good yield. Bromide **69** was synthesised from commercially available 3-butynyl-p-toluenesulfonate, using this approach. The terminal alkyne was capped by a Me_3Si group before Grignard or/and cuprate formation to avoid any undesirable polymerisation reactions. Then, nucleophilic substitution by the halide afforded **69** in two steps with an overall good yield of 60% (**Scheme 34**).



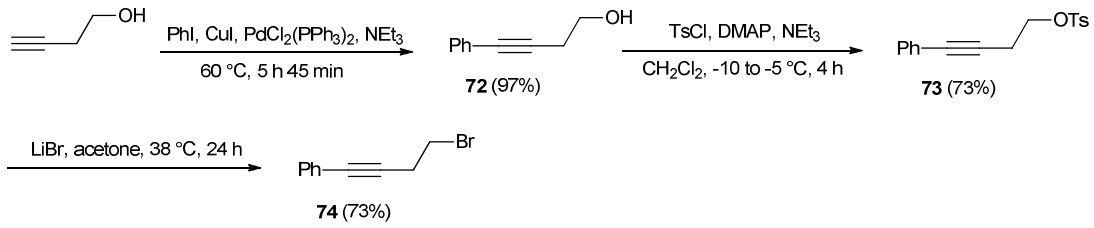
Scheme 34. Preparation of bromobutyne **69**

Internal alkyne **71** was prepared in a similar way. At first, tosylate **70** was synthesised in 91% yield from pent-3-yn-1-ol using TsCl, DMAP and NEt_3. Once the alcohol was activated, nucleophilic substitution with bromide afforded **71** in nearly quantitative yield (Scheme 35).



Scheme 35. Preparation of bromopentyne **71**

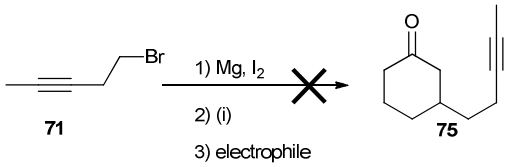
The same method was applied to the synthesis of 1-bromo-4-phenyl-3-butyne **74**, but starting from 4-phenyl-3-butyn-1-ol, which was obtained in 97% yield by Sonogashira coupling between 3-butyn-1-ol and iodobenzene in the presence of CuI and $PdCl_2(PPh_3)_2$ as catalysts (Scheme 36).[86]



Scheme 36. Preparation of 1-bromo-4-phenyl-3-butyne **74**

With these compounds in hand, the 1,4-addition on to cyclohexenone was examined. Starting with substrate **71**, the corresponding Grignard reagent was prepared by adding bromide **71** to magnesium turnings, in the presence of I_2 to facilitate the Grignard formation. The conjugate addition was tried following the procedure described by Snider and Kirk (Table 6, entry 1).

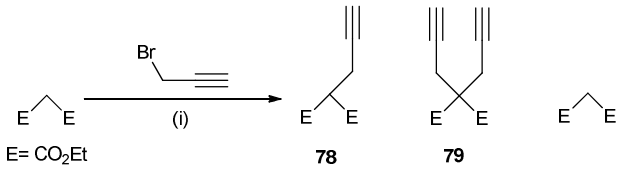
Despite two trials, the desired product was not obtained. Instead, 2-cyclohexen-1-one was incompletely recovered, along with unknown by-products. The recovery of the starting enone could be caused by the presence of traces of water, which could react with the incipient nucleophiles (Grignard or/and cuprate reagents) and inhibit the reaction or/and by an incomplete formation of Grignard (or/and cuprate) reagent or/and by a poor activation of the carbonyl unit. Whereas, by-product formation could be due to unknown side reactions, probably initiated by the reagents (CuI or/and $BF_3.Et_2O$) or some impurities present in the reaction mixture. To establish whether the source of copper or the Lewis acid were responsible for these issues, two control experiments were run. First, the conjugate addition was tried following the Kirk procedure but without $BF_3.Et_2O$. Second, CuI was replaced by combined catalyst CuBr/LiCl (known to be more effective for conjugate addition, due to the coordination of carbonyl oxygen with Li^+) and TMS-Cl was added to accelerate the conjugate addition by trapping the intermediate enolate as described by Lipshutz *et al.* (Table 6, entry 3).[87] Again, unknown by-products and unreacted cyclohexenone were obtained in the former case, while the latter proved unsuccessful and led to unknown by-products. Considering the above results, the formation of the Grignard reagent was suggested to be the problematic step. Thus, to determine whether this reagent was obtained, a preparation of this nucleophile was performed and the mixture directly added to benzaldehyde. A complex mixture of compounds was obtained. Therefore due to these results, alternative approaches which avoid the formation of Grignard reagents and cuprates were explored.



Entry	Reagent (i)	Electrophile and additives	Results
1	CuI/ $BF_3.Et_2O$	cyclohexenone	unreacted cyclohexenone, unknown by-products
2	CuI	cyclohexenone	unreacted cyclohexenone, unknown by-products
3	CuBr.Me_2S/LiCl	cyclohexenone, TMS-Cl	unknown by-products
4		benzaldehyde	complex mixture

Table 6. Attempted preparation of substrate **75**

A procedure employing β-dicarbonyl compounds such as propargylmalonates was next examined. Diethyl propargyl malonate was initially prepared by a one-step addition reaction of propargyl bromide to diethyl malonate in the presence of sodium ethoxide or sodium hydride. A mixture of mono- and bis-adducts was obtained (Scheme 37). Column chromatography always afforded the desired product contaminated with diethyl dipropargylmalonate **79** and diethyl malonate. Diethyl malonate can react in the next step and decrease the reaction yield. The use of dimethyl malonate gave similar results.

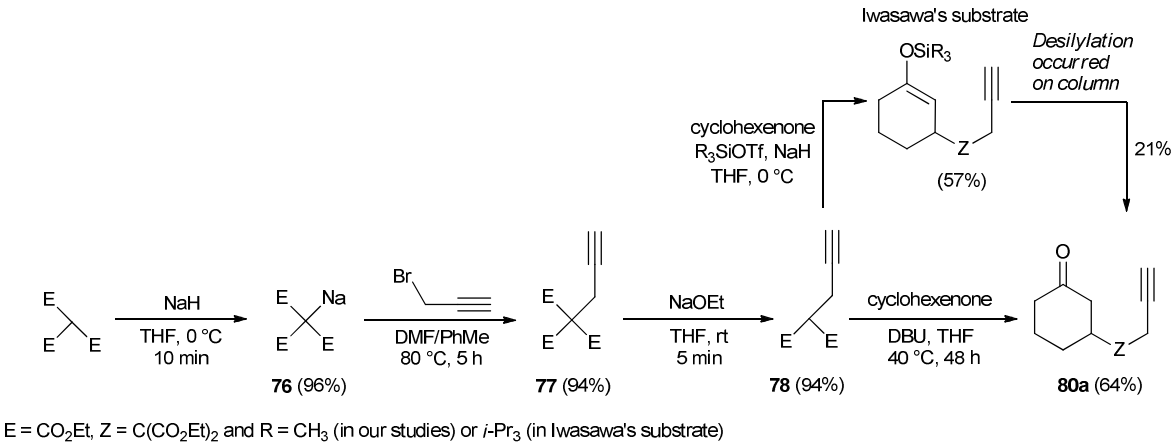


Reagent (i)	Ratio **78**:**79**:**SM**[a]	Yield (%)
NaOEt	50:25:25	100
NaH	50:25:25	100

Scheme 37. Preparation of diethylpropargyl malonate **78**. [a] Ratio determined by NMR analysis of the crude mixture.

To avoid this problem, propargyl bromide was added to triethyl sodiomethanetricarboxylate **76** in DMF/toluene at 80 °C, which was obtained quantitatively from deprotonation of triethyl

methanetricarboxylate in THF (Scheme 38). The resulting propargyl triester **77** was then converted in 5 minutes into diethyl propargyl malonate **78** with a yield of 94% by decarbethoxylation with sodium ethoxide. This three-step strategy afforded **78** in 85% overall yield, with no need for further purification.[88] In the first instance, **78** was added to cyclohexenone following a procedure reported by Iwasawa *et al.* based on the structural analogy between Iwasawa's substrate and **80a**.[24b] This protocol consisted of treating cyclohexenone with the Na salt of diethyl propargylmalonate in the presence of TBSOTf at 0 °C for 1 h. However, in our case, to obtain the desired ketone **80a**, an additional step of deprotection of the silyl group would be necessary (Scheme 38). Diethyl propargyl malonate **78**, cyclohexenone and TMSOTf were added at 0 °C to a solution of NaH in THF following the above procedure. After one night at room temperature, column chromatography afforded silyl enol ether in 57% yield along with ketoalkyne **80a** in 21% yield. Ultimately, this procedure was abandoned, as it was found that the Michael addition could occur in THF, in the presence of DBU at room temperature.[89] Under these conditions, β-alkylation of cyclohexenone proceeded smoothly to give **80a** with a yield of 64%. This strategy was very convenient and the starting materials were generally prepared *via* this method as it avoided the requirement for TMSOTf (accelerated the 1,4-addition by trapping the intermediate enolate) and the hydrolysis of the TMS enol ether.

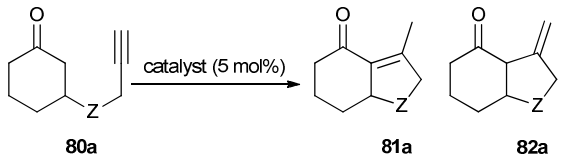


Scheme 38. Synthesis of ketoalkyne **80a** from diethyl propargyl malonate **78**

Since an efficient method for the preparation of substrate **80a** was established, its behaviour under π-acid catalysis was studied.

2.3 Development of the reaction conditions

An initial screening was performed with different strong π-acids, following a standard procedure (Table 7). A solution of ketoalkyne **80a** in the required solvent (0.1 M) was added to the catalyst under an argon atmosphere. The mixture was stirred either at room temperature or at 70 °C. To our delight, catalyst screening appeared promising. The use of simple gold and platinum salts did yield the cyclised product **81a** and its isomer **82a**, albeit in low conversion even at elevated temperatures (Table 7, entries 2 and 3) or prolonged reaction times (Table 7, entry 1).



80a **81a** **82a**

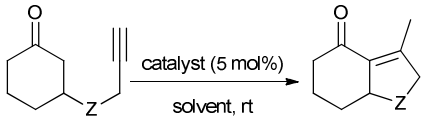
Entry	Conditions	Time, h	Ratio **80a**:**81a**:**82a**
1	$PtCl_2$, distilled toluene [a]	5 d	92:8:0
2	$PtCl_2$, distilled toluene, 70 °C	48	98:2:0
3	AuCl, distilled toluene, 70 °C	48	78:22:0
4	AuCl, undistilled toluene, 70 °C	48	78:0:0
5	AuCl, distilled DCM	48	98.6:0:0
6	AuCl, undistilled DCM, rt	48	98.6:1.4:0
7	AuCl, distilled THF, 70 °C	24	100:0:0

Table 7. Initial screening of the reaction conditions

[a] The reaction temperature was progressively increased: 3 d at rt, 1 d at 45 °C, 1 d at 70 °C. The ratios were determined by ^{1}H NMR analysis of the crude mixture.

In light of these results, optimisation focused on the use of gold (I) salts, notably cationic gold species, which are known to be very effective in Conia-like *exo*-mode carbocyclisations.[27-30] The use of the cationic gold species PPh_3AuNTf_2[90] afforded the conjugated enone cycloisomerisation product **81a** at room temperature with reasonable conversion and yield (Table 8, entry 1); exomethylene isomer **82a** was not observed in more than trace amounts. Variations on these reaction conditions were explored, including choice of solvent (Table 8, entries 1-5), counterion (Table 8, entries 6-10) and gold source (Table 8, entries 11 and 12). From these experiments, it was found that the use of PPh_3AuOTf in chlorinated solvents enabled direct cyclisation to occur (Table 8, entry 8). Control reactions showed the gold to be a necessary part of this reaction system (Table 8, entries 13-16). In the absence of PPh_3AuCl, AgOTf afforded only very low conversion. The use of triflic and *p*-toluenesulfonic Brønsted acids gave rapid decomposition and no reaction respectively. A 10:1 dichloromethane/water solvent mixture previously employed in the gold-catalysed cyclisation of silyl enol ethers[27]

gave no conversion in this reaction (Table 5, entry 5). Ultimately, substrate **80a** was converted cleanly into bicyclic enone **81a** with reasonable catalyst loading (6 mol%) at room temperature by 5-*exo* cyclisation in CH_2Cl_2 (0.1 M), in the presence of $PPh_3AuCl/AgOTf$. As the yield from the gold-catalysed room-temperature cyclisation of **80a** was comparable to the reactions of analogous substrates containing preformed enol equivalents, a range of ketones with tethered terminal alkynes (Chapter 3) and ketones with tethered internal alkynes (Chapter 4) was prepared to study the process.



80a **81a**

Entry	Catalyst[b]	Solvent	Time (h)	Yield (%) **81a** (**80a**)[c]
1	PPh_3AuNTf_2	CH_2Cl_2	19	59(3)
2	PPh_3AuNTf_2	toluene	19	16(27)
3	PPh_3AuNTf_2	THF	19	22(60)
4	PPh_3AuNTf_2	$Cl_2CH_2CH_2Cl_2$	19	66(20)
5	PPh_3AuNTf_2	CH_2Cl_2/H_2O[d]	19	0(79)
6	PPh_3AuBF_4	CH_2Cl_2	24	26(18)
7	PPh_3AuNTf_2	CH_2Cl_2	3.5	43(44)
8	PPh_3AuOTf	CH_2Cl_2	3.5	77(12)
9	PPh_3AuSbF_6	CH_2Cl_2	3.5	46(3)
10	PPh_3AuPF_6	CH_2Cl_2	3.5	0(92)
11	$(PPh_3Au)_3OBF_4$	CH_2Cl_2	2.5	0(100)
12	$dppm(AuCl)_2/AgOTf$[e]	CH_2Cl_2	19	9(84)
13	AgOTf	CH_2Cl_2	3.5	<5(59)
14	HOTf	CH_2Cl_2	0.25	0(0)[f]
15	HOTf[g]	CH_2Cl_2	1	0(0)[f]
16	*p*TSA	CH_2Cl_2	2.5	0(95)

Table 8. Optimisation of the reaction conditions[a]

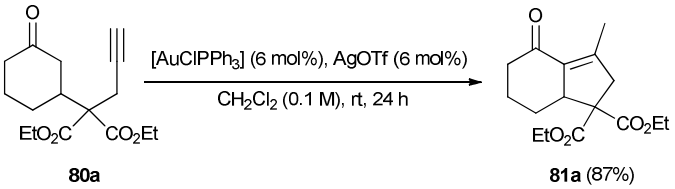
[a] A solution of **80a** (0.2 mmol) in solvent (0.1 M) was added to a mixture of the (pre)catalyst. [b] With the exception of commercially available PPh_3AuNTf_2, PPh_3AuX catalysts were prepared *in situ* by mixing equimolar

quantities of PPh_3AuCl and the required Ag(I) salts. [c] Yields determined by ^1H NMR against a known quantity of 1,2,4,5-tetramethylbenzene. [d] In a 10:1 ratio. [e] 10 mol% AgOTf employed. [f] Complete degradation was observed. [g] 0.5 mol% loading.

Chapter 3: Gold-catalysed cyclisation of ketones with tethered terminal alkynes

3.1 Introduction

Preliminary studies had shown that ketoalkyne **80a** was smoothly converted into bis-fused [4.3.0] carbocycle **81a**, at room temperature, in CH_2Cl_2, in the presence of 6 mol% of PPh_3AuOTf, generated *in situ* from an equimolar combination of PPh_3AuCl and AgOTf (Scheme 39).



Scheme 39. Gold-catalysed cycloisomerisation of ketoalkyne **80a**

Under the above conditions and starting from a cyclic unactivated enolisable ketone, an efficient C-C bond-forming process could occur, although literature conditions generally required the enhancement of *C*-nucleophilicity of the carbonyl unit. The substrate scope was investigated to establish whether the above approach displayed a wide applicability compared to existing cycloisomerisation methods. A range of ketones with tethered terminal alkynes was prepared. The choice of substrates was made to study the behaviour of: (1) cyclic enolisable ketones with tethered terminal alkynes to gain access to bis-fused [*n*.3.0], [*m*.4.0] carbocycles and spiro compounds; (2) acyclic enolisable ketones with tethered terminal alkynes to determine the influence of substrate conformational flexibility on the reaction rate; and (3) substrates for challenging α'-cycloisomerisations.

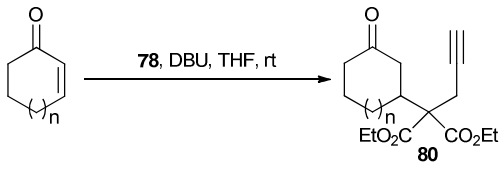
3.2 5- and 6-*exo*-*dig* cyclisation: cyclic series

Intramolecular cyclisations *via* 5- and 6-*exo*-*dig* modes are particularly appealing, as they yield carbocyclic frameworks, frequent motifs of many natural and synthetic molecules. Access to bis-fused [*n*.3.0], [*m*.4.0], [*l*.5.0] carbocycles and spiro compounds from simple accessible precursors is of great interest, especially if the process is atom-economic and allows the presence of other functionalities. The proposed methodology can potentially provide such cyclic structures with respect of the above features.

3.2.1 Construction of bicyclic [*n*.3.0] frameworks

To gain access to bicyclic [*n*.3.0] frameworks under the described gold catalysis, cyclic ketones of different ring sizes with tethered terminal alkynes were assembled by conjugate addition of the appropriate nucleophile to the cyclic enone.

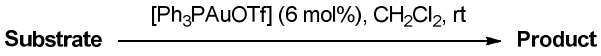
Cyclisation precursors **80b**, **80c** and **80d** were obtained from diethyl propargyl malonate addition to cyclopentenone, cycloheptenone and cyclooctenone respectively (Table 9). The conjugate addition proceeded smoothly at room temperature to afford the cyclic ketones tethered with terminal alkynes in moderate to good yields. For the larger membered rings, prolonged reaction times were required and even after 48 hours unreacted enone and propargyl malonate **78** were still present in the reaction mixture (Table 9, entries 2 and 3).



Entry	n	Time, h	**80** (yield, %)
1	0	24	**80b** (88)
2	2	>48	**80c** (56)
3	3	>48	**80d** (42)

Table 9. Synthesis of cyclisation precursors **80b-d**

These substrates were then subjected to the [PPh_3AuOTf]-catalysis. Analogously to substrate **80a**, they underwent cycloisomerisation and were transformed into bicyclic fused [3.3.0], [5.3.0] and [6.3.0] motifs. The size of the existing ring in the starting material did play an important role in the cyclisation. Substrates containing 5-, 6- and 7-membered rings afforded the desired products in good yields (Table 10, entries 1-3) and in most cases the conjugated alkene was formed as the sole or major isomer. Cyclisation of substrate **80b** led to a mixture of alkene isomers **81b** in 3.7:2:1 ratio, with the α,β-unsaturated enone as the major product. 8-Membered ring substrate **80d** only cyclised slowly to give exomethylene product **82d** as the major isomer, albeit in low yield alongside unreacted starting material (16%) and unidentified products (Table 10, entry 4). **82d** was a literature compound. Its data were in agreement with those reported in the literature and based on reported results the stereochemistry of the ring junction was assigned *trans*.



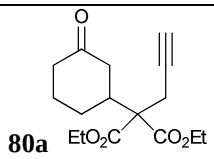
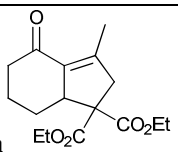
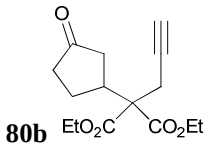
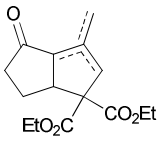
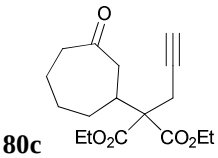
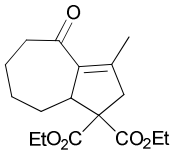
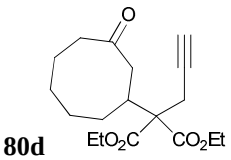
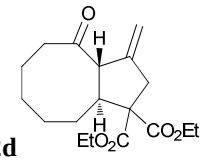
Entry	Substrate	Product	Time (h)	Yield (%)
1	 **80a**	 **81a**	24	87
2	 **80b**	 **81b**	24	98[a]
3	 **80c**	 **81c**	24	64
4	 **80d**	 **82d**	48	26[b]

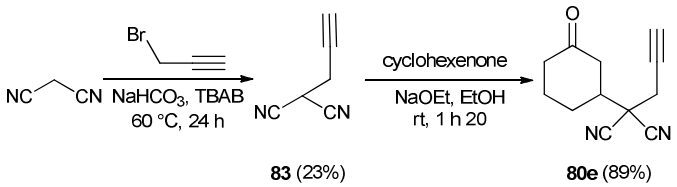
Table 10. Gold-catalysed cycloisomerisation of ketoalkynes **80a-d**

[a] Three enone isomers in a ratio of 3.7:2:1 (α,β-unsaturated : exomethylene β,γ-unsaturated : β,γ-unsaturated). [b] Small amounts of unidentified products were also recovered alongside 16% of **80d**.

To study the influence of substituents on the tether in the cycloisomerisation process, cyclisation precursors **80e** and **80f** were explored, bearing cyano and carbonyl unit substituents respectively. Conjugate addition of propargyl malononitrile **83** or propargyl β-ketoester **84** to cyclohexenone could afford the desired adducts **80e** and **80f**.

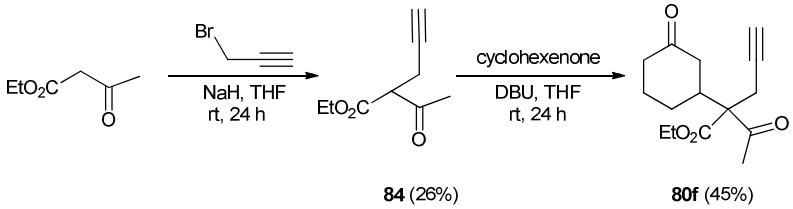
Propargyl malononitrile **83** was synthesised by addition of propargyl bromide to malononitrile, following a procedure reported by Diez-Barra *et al.* under phase transfer conditions.[91] Mono- and dialkylation occurred during the process. However, in contrast to mono- and dialkylated diethyl malonate which co-eluted (*q.v.* preliminary studies), flash

column chromatography allowed efficient separation of the products. Propargyl malononitrile **83** was obtained in 23%, along with dialkylated malononitrile (19%) and unreacted malononitrile. Conjugate addition of **83** to cyclohexenone was then attempted using a method described by Parham and Czuba, in the presence of sodium ethoxide rather than DBU.[92] The comparison of pK_a values could explain this choice. In water, pK_a values of malononitrile and DBU are 13 and 12, respectively; while sodium ethoxide has a pK_a around 15. Thus, to ensure complete deprotonation of the monoalkylated malononitrile, NaOEt was employed. Gratifyingly, ketone **80e** possessing two cyano substituents on the tether was produced at room temperature in 89% (Scheme 40).



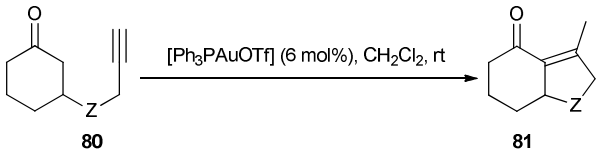
Scheme 40. Synthesis of ketoalkyne **80e**

Substrate **80f**, which bears two enolisable carbonyl groups and hence the potential for several alternative routes was synthesised from propargyl ethyl acetoacetate **84** using the standard procedure previously described on page 53. Non-optimised reaction conditions afforded a 1.1:1 mixture of diastereoisomers **80f** in 45% after 24 hours, along with unreacted starting materials. Reactant **84** was produced from the reaction of propargyl bromide with ethyl acetoacetate, albeit in low yield (26%) due to the competitive dialkylation process (Scheme 41).[93]



Scheme 41. Synthesis of ketoalkyne **80f**

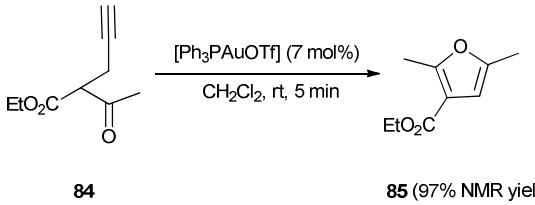
Under gold catalysis, at room temperature, cyclisation precursors **80e** and **80f** were successfully converted into bis-fused carbocycles *via exo*-mode cyclisation. Although substrate **80e** afforded the cyclised product in similar yield than **80a**, a longer reaction time was required (Table 11, entry 1 *vs* entry 2).



Entry	Z	Time, h	**81** (yield, %)
1	$C(CO_2Et)_2$	24	**81a** (87)
2	$C(CN)_2$	34	**81e** (81)
3	$C(COCH_3)CO_2Et$	15	**81f** (44)

Table 11. Cycloisomerisation of ketoalkynes bearing different substituents on the tether

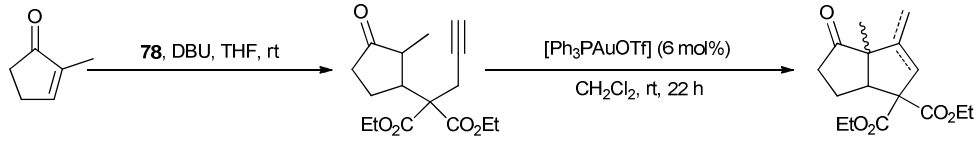
In contrast, in a relatively short time, substrate **80f** afforded products **81f** in a 1:1.2 ratio of diastereoisomers, albeit in a moderate yield. Side reactions might have occurred initiated by the keto substituent, which could attack the electrophilic Au-multiple bond complex *via* the lone pair of the carbonyl oxygen. On the TLC plate, an intense blue spot was visible under UV light, but attempts to isolate it by flash column chromatography failed. Cycloisomerisation of compound **84** under gold catalysis supports the above hypothesis (Scheme 42).[47]



84 **85** (97% NMR yield)

Scheme 42. Furan synthesis from ethyl 2-acetylpent-4-ynoate **84**

The effects of steric hindrance on the cycloisomerisation process were also examined. To this end, cyclisation precursor **80g** which possesses an α-methyl substituent was prepared from commercially available 2-methyl-2-cyclopenten-1-one, according to the general procedure. On this enone, conjugate addition was sluggish and even after several days, major diastereoisomer **80g** was only obtained in 19% along with unreacted propargyl malonate **78** (51%) and 2-methyl-2-cyclopenten-1-one. Under [$Ph_3PAuOTf$]-catalysis, **80g** was smoothly converted into a mixture of alkene isomers **81g** and **82g** in 58% after 22 hours (Scheme 43). Unknown by-products were also obtained, probably due to side reactions or degradation. α-Substituted ketones have more stable enol tautomers compared to non-substituted ketones; thus they possess a higher enol content, which might have favoured the cyclisation rate alongside degradation or/and side reactions.



80g (19%) **81g** and **82g** (58%)

Scheme 43. Gold-catalysed cycloisomerisation of sterically hindered substrate **80g**

Complete structural determination of alkenes diastereoisomers **81g** and **82g** was not possible. These isomers were inseparable by flash column chromatography, and HPLC separation was also unsuccessful. GC/EI of the mixture revealed the presence of three isomers. NMR

spectroscopy (^{1}H and COSY) showed that two of these alkenes were exomethylene compounds (one multiplet at 5.03 ppm integrating for two protons, one doublet at 4.86 and one doublet of doublet at 4.84 ppm both integrating for one proton) and the third one, a β, γ-enone (one multiplet at 5.48 ppm integrating for one proton). Comparison of the ^{1}H NMR spectrum of **81g** and **82g** with ^{1}H NMR spectra of literature analogues **L81g** and **L82g** allowed us to establish the stereochemistry of their ring junction (Figure 5).[27,30] Based on this comparison, cyclised product **81g** had a *cis* junction, as well as one of the two alkene **82g**. The the ring junction of the second alkene **82g** was assigned *trans*, by elimination.

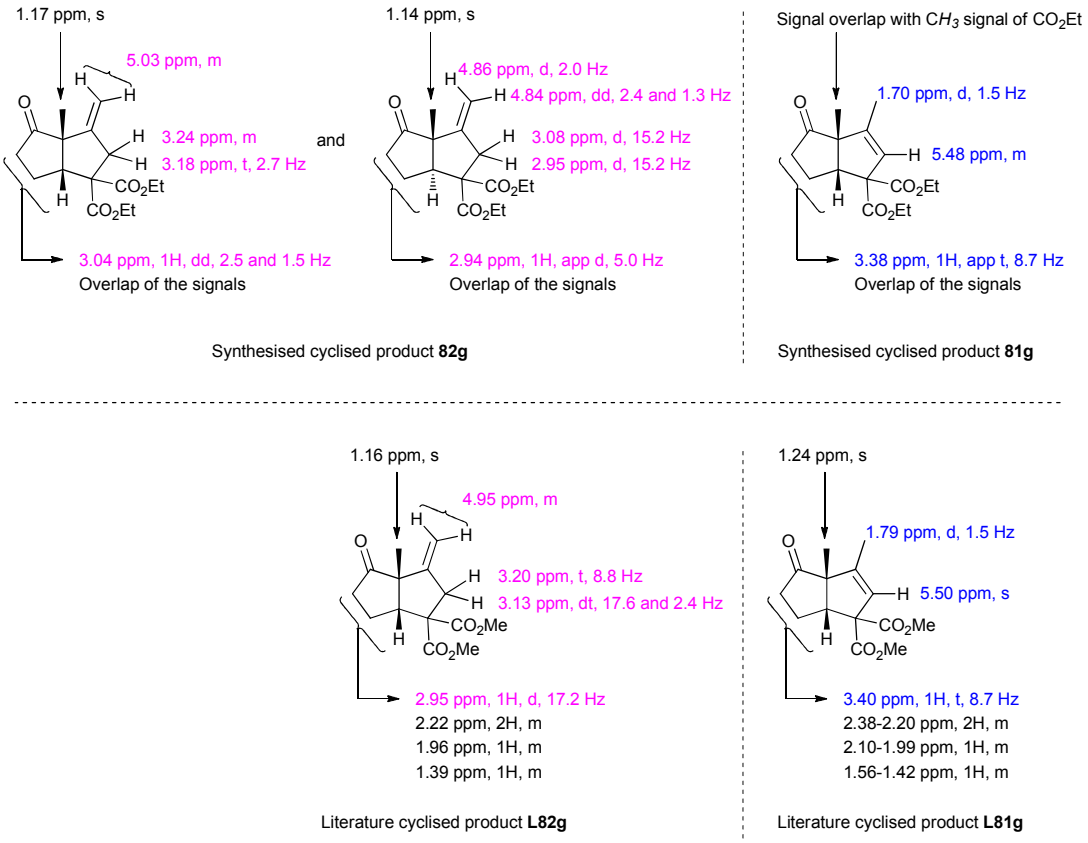
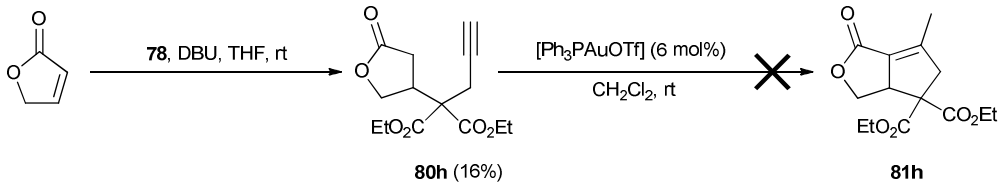


Figure 5. Comparison of **L82g** and **L81g** NMR signals *vs* **82g** and **81g** NMR signals

Alkynyl lactone **80h**, which was obtained from propargyl malonate addition to commercially available 2(5*H*)-furanone, was also subjected to the gold catalysis to study the influence of

enol content on the cycloisomerisation. Unsurprisingly, no cyclised product was produced after prolonged reaction time (Scheme 44). Effectively, for esters the carbonyl form is resonance stabilised and K_{enol} is 10^{-20}, while for ketones the enol content is higher with K_{enol} around 10^{-8}.[94]

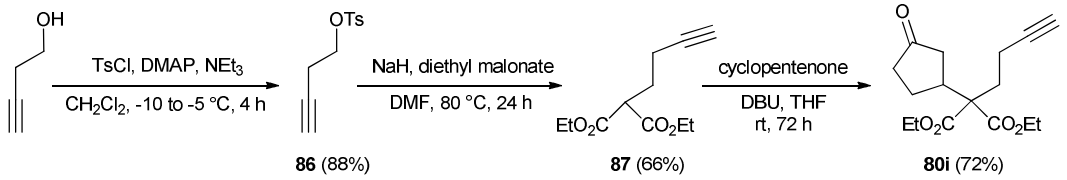


Scheme 44. Unsuccessful cycloisomerisation of lactone cyclisation precursor

3.2.2 Construction of bicyclic [*n*.4.0] and [*m*.5.0] frameworks

Access to bicyclic fused [*n*.4.0] and [*m*.5.0] frameworks could take place under our optimised gold catalysis conditions, *via* 6- and 7-*exo-dig* cyclisation of cyclic ketones with terminal alkynes. The cyclisation precursors could be synthesised in a similar way to previously used substrates.

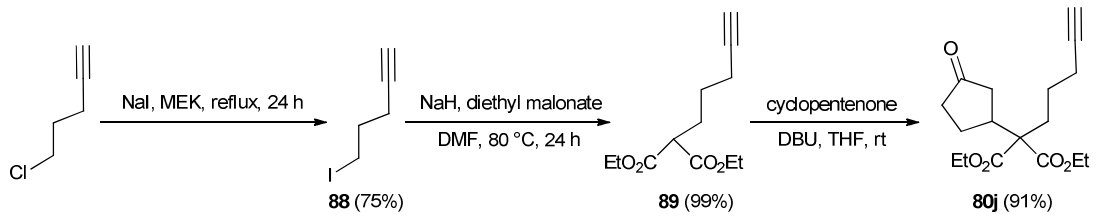
Prior to the conjugate addition to cyclic enones, homopropargylic nucleophile **87** was synthesised from 3-butyn-1-ol in two steps which consisted of alcohol activation and subsequent tosylate displacement by diethyl malonate. The reaction took place using NaH as base in place of NaOEt, by a modification of a literature method.[95] Interestingly, homopropargylic malonate **87** was obtained as the sole alkylated product in an overall yield of 58%. The conjugate addition to cyclopentenone was tried and adduct **80i** was afforded in 72% afer 72 hours (Scheme 45).



86 (88%) **87** (66%) **80i** (72%)

Scheme 45. Synthesis of cyclisation precursor **80i**

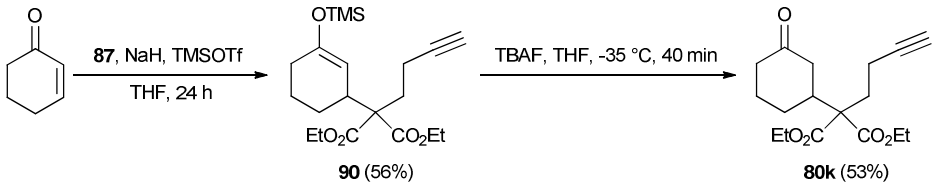
Likewise, cyclisation precursor **80j** was synthesised in very good yield following the same approach, starting from commercially available 5-chloropent-1-yne which was efficiently converted into 5-iodopent-1-yne **88** after 24 hours, by using of an excess of sodium iodide (4 eq) to drive the reaction to completion.[96] Nucleophilic substitution of diethyl malonate to halide **88** afforded reactant **89** in quantitative yield, which was then employed in the conjugate addition (Scheme 46).



88 (75%) **89** (99%) **80j** (91%)

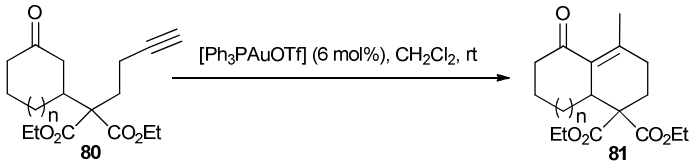
Scheme 46. Synthesis of cyclisation precursor **80j**

Attempts to synthesise substrate **80k**, *via* the conjugate addition of homopropargyl malonate **87** to cyclohexenone in the presence of DBU failed. To circumvent this difficulty, silyl enol ether **90** was prepared from the addition of homopropargyl malonate **87** to cyclohexenone in the presence of NaH and TMSOTf to trap the intermediate enolate. After purification by flash column chromatography, silyl enol ether **90** was isolated in 56% along with 7% of desilylated substrate **80k**. Cyclisation precursor **80k** was ultimately produced in moderate yield after cleavage of the O-Si bond of compound **90** by TBAF (Scheme 47).



Scheme 47. Synthesis of cyclisation precursor **80k**

With these substrates in hand, [$Ph_3PAuOTf$]-catalysed 6- and 7-*exo-dig* cyclisation was examined. The results are shown in Table 12. 5- and 6-membered ring precursors **80i** and **80k** smoothly afforded bis-fused [3.4.0] and [4.4.0] carbocycles **81i** and **81k** at room temperature. **81i** and **81k** cyclised products were obtained as the major isomers respectively in 79 and 61% alongside 2% of isomeric products for the former and 7% of isomeric products for the latter. Unfortunately, substrate **80j** which could undergo a 7-*exo-dig* ring closure did not cyclise. After prolonged reaction time, unreacted starting material was completely recovered. The more remote location of the nucleophilic centre and the alkyne moiety might have disfavoured the cyclisation. In fact, with silyl enol ethers tethered with terminal alkynes, such cyclisation did not take place with conventional cationic gold complexes. It is only very recently that Sawamura *et al.* reported the first example of gold-catalysed 7-*exo-dig* cyclisation of acetylenic silyl enol ethers, by employing triethynylphosphine-gold complex **L1**-$Au(NTf)_2$.[32]

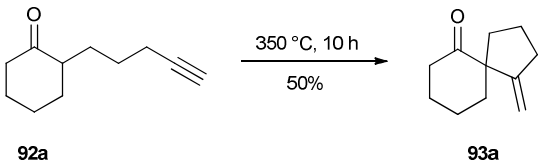


n	Time, h	**81** (yield, %)
0	17	**81i** (79)
1	22	**81k** (61)

Table 12. Gold-catalysed 6-*exo-dig* cyclisation

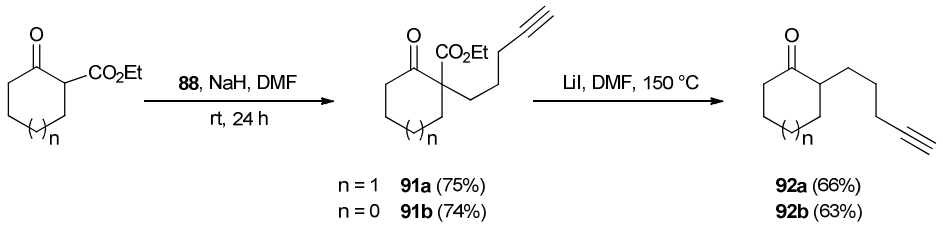
3.2.3 Synthesis of spiro compounds

Spiro cyclic frameworks are present in many natural and synthetic compounds of particular interest. Various methods for their preparation already exist; but they usually encountered several difficulties associated with substituent incompatibility under the reaction conditions. For instance, Conia *et al.* reported that conversion of precursor **92a** into spiro[4.5]dec-3-en-6-one **93a** took place at 350 °C, after 10 hours (Scheme 48). Many functional groups would be degraded under such drastic conditions. Alternative methods are thus appealing and our proposed methodology can be applied to this end. Substrates **92a-d** were readily assembled *via* α-alkylation of cyclic ketones and then subjected to the gold catalysis.



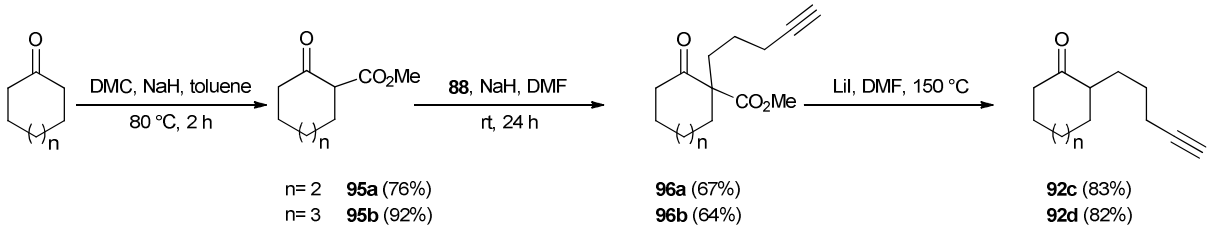
Scheme 48. Conia-thermal cyclisation of precursor **92a**

Although the introduction of alkynyl substituents at the α-carbon of ketones can take place *via* the direct deprotonation of ketones with strong and non nucleophilic bases, the two-step approach which involves α-alkylation of activated esters followed by decarboxylation was chosen.[89] The dialkylated intermediates generated in the first step can also be used as cyclisation precursors (see Chapter 3.5). α-Alkylation of cyclic β-ketoesters took place at room temperature in the presence of NaH to afford dialkylated ketones **91a** and **91b** in good yields. Subsequent decarbethoxylation at 150 °C, in the presence of a large excess of LiI afforded the desired substrates **92a** and **92b** in good yields (Scheme 49).



Scheme 49. Synthesis of cyclisation precursors **92a-b**

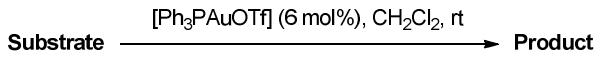
An identical procedure was employed for the preparation of substrates **92c-d** starting from cyclic β-ketoesters **95a-b**, which were obtained in very good yields and short reaction times following the addition of dimethylcarbonate to cycloheptanone or cyclooctanone in the presence of sodium hydride (Scheme 50).[97]



Scheme 50. Synthesis of cyclisation precursors **92c-d**

α-Alkylated cyclisation precursors were then reacted in the presence of 6 mol% of [$Ph_3PAuOTf$], at room temperature. To our delight, the cyclisation took place smoothly with complete consumption of the starting ketones. Spirocyclic compounds **94a** and **94d** were afforded in relatively short times, in 61 and 58% respectively (Table 13, entries 1 and 4). α-Substitution of the carbonyl functionality occurred uneventfully; even though the carbonyl oxygen could act as a nucleophile to the activated alkyne. Furthermore, the room-temperature cyclisation of substrate **92a** serves as a useful comparison to the thermal Conia-cyclisation. Under gold catalysis at room-temperature, internal alkene product **94a** was isolated in 61% yield (Table 13, entry 1), whereas under thermal conditions, a temperature of 350 ºC led to the exomethylene cyclisation product **93a** in 50% yield (Scheme 48). Strangely, with 5- and 7-

membered rings, side reactions or/and degradation occurred. In the presence of 6 mol% of catalyst loading, in CH_2Cl_2 (0.1 M), substrate **92b** was smoothly converted into [4.4]-spirocyclic framework **94b**, in good yield, after stirring for 19 hours. After flash column chromatography, the cyclised product was isolated as a mixture of the desired product **94b** and an unknown isomer as indicated by GC/EI analysis. Increasing the concentration up to 0.2 M afforded **94b** in 72% yield, in a 2.8:1 mixture of spiro ketone **94b** and this unknown isomer which possesses similar spectroscopic data to compound **94b**. With substrate **92c**, although the cycloisomerisation took place as usual, purification afforded cyclised product **94c** with an inseparable unknown impurity, in a lower yield. The presence of this by-product prevented full interpretation of the NMR spectrum.



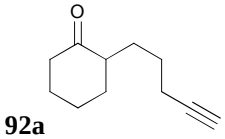
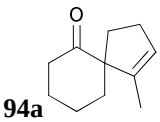
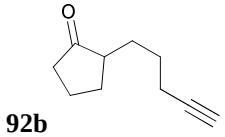
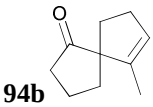
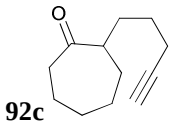
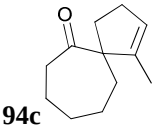
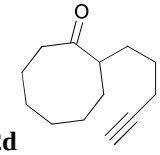
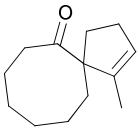
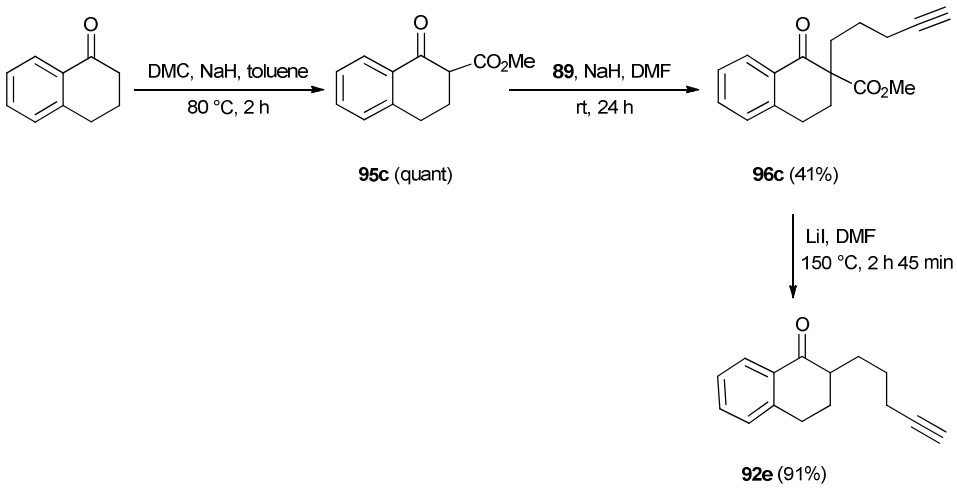
Entry	Substrate	Product	Time/h	Yield/%
1	 **92a**	 **94a**	18	61
2	 **92b**	 **94b**	24	72
3	 **92c**	 **94c**	38 (19)	-
4	 **92d**	 **94d**	16	58

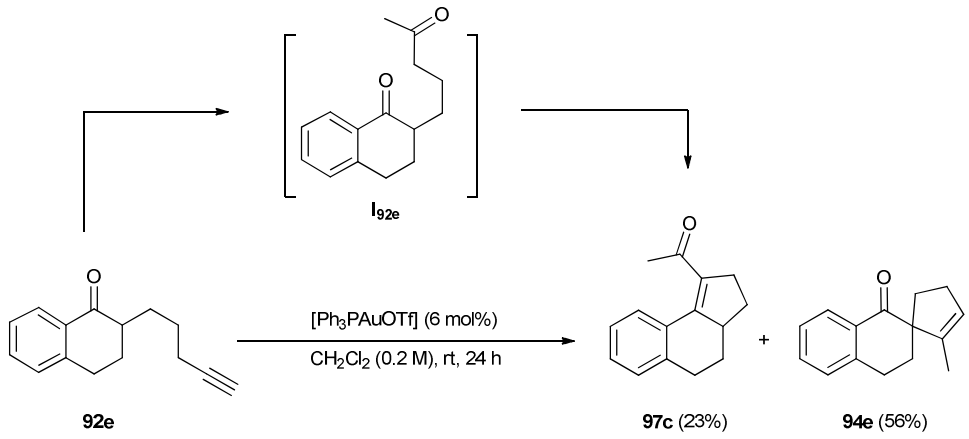
Table 13. Gold-catalysed synthesis of spirocyclic frameworks **94a-d**.

Preparation of tricyclic frameworks was also investigated under the proposed methodology. Cyclisation precursor **92e** was synthesised to this end, following the standard two-step procedure previously employed, starting from **95c**, which was quantitatively obtained after addition of dimethyl carbonate to tetralone (Scheme 51).



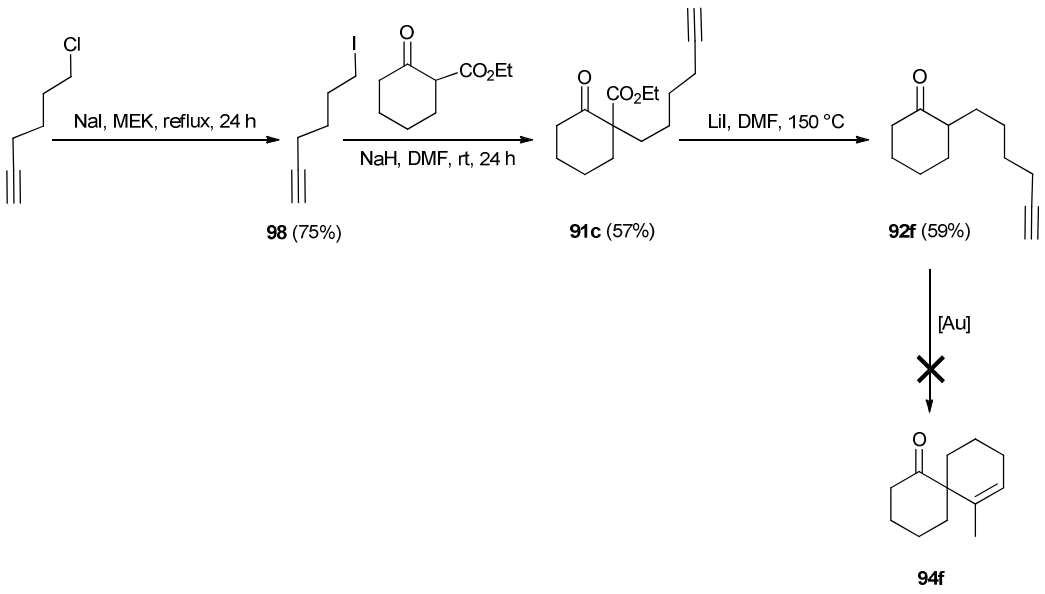
Scheme 51. Synthesis of cyclisation precursor **92e**

Intriguingly, under gold catalysis, substrate **92e** was converted into spirocyclic framework **94e** and tricyclic enone **97c**, after 24 hours, in 56% and 23% yields, respectively. A 0.2 M concentration was necessary to ensure total conversion. The formation of tricyclic framework **97c** was somewhat surprising, but could be explained *via* intramolecular aldol dehydration process of intermediate $\mathbf{I_{92e}}$, which was generated *in situ* following alkyne hydration promoted by the gold catalyst in the presence of adventitious water (Scheme 52).



Scheme 52. Cycloisomerisation of α-alkylated tetralone **92e** catalysed by [$Ph_3PAuOTf$] catalyst

An attempt to synthesise [5.5] spirocyclic motifs was examined starting from α-hexynyl ketoalkyne **92f**. Unfortunately, only traces of cyclised product **94f** were furnished along with unreacted starting material even after a prolonged reaction time (Scheme 53). The remote location of the nucleophilic centre and the activated alkyne unit might have arrested the cycloisomerisation.



Scheme 53. Attempt to synthesise [5.5] spirocyclic framework **94f**

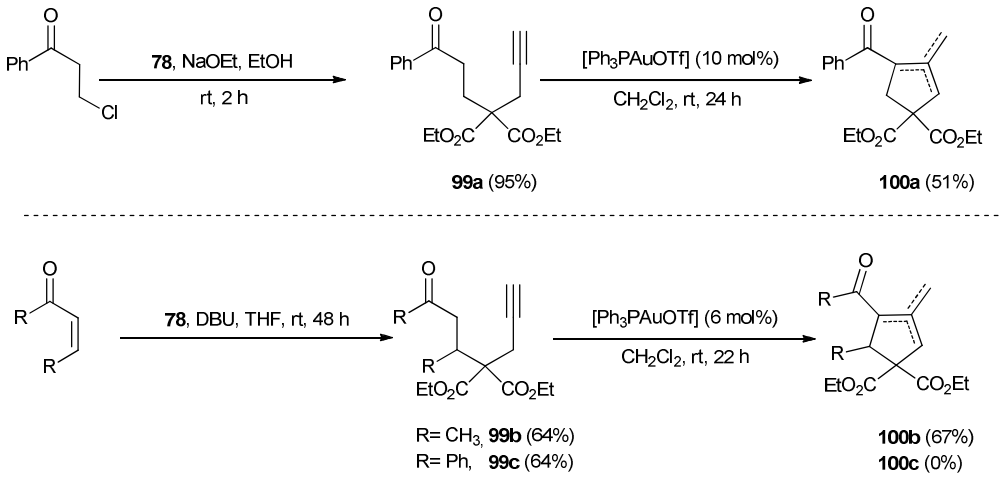
3.3 5- and 6-*exo-dig* cyclisation: acyclic series

In light of the results obtained with cyclic substrates, the cycloisomerisation of acyclic starting materials was also examined under gold catalysis. Ketones tethered with propargyl and homopropargyl terminal alkynes were synthesised with a view to comparing the reactivity of cyclic *vs* acyclic systems.

3.3.1 5-*exo-dig* cyclisation

Analogously to cyclic ketoalkynes, acyclic ketoalkynes can potentially cyclise under mild conditions, in the presence of [$Ph_3PAuOTf$] catalyst. Cyclisation precursors **99a-c** were readily assembled by nucleophilic substitution[24a] or conjugate addition of homopropargyl malonate **78** to the corresponding enone.

Cycloisomerisation of acyclic precursors **99a** and **99b** by 5-*exo-dig* mode was viable under the gold catalysis. In the presence of 10 mol% catalyst loading, **99a** cyclised to provide product **100a** in 51% yield, isolated as a mixture of three isomers in a 10:3:1 ratio with the major being α,ß-unsaturated enone. Unknown by-products were also isolated, indicating that side reactions took place and competed with the principal pathway. Similar results were obtained with branched ketoalkyne **99b**. Nonetheless, only 6 mol% of catalyst was required and cyclised product **100b** was isolated as 6.3:1.3:1 mixture of isomers in a better yield (Scheme 54).

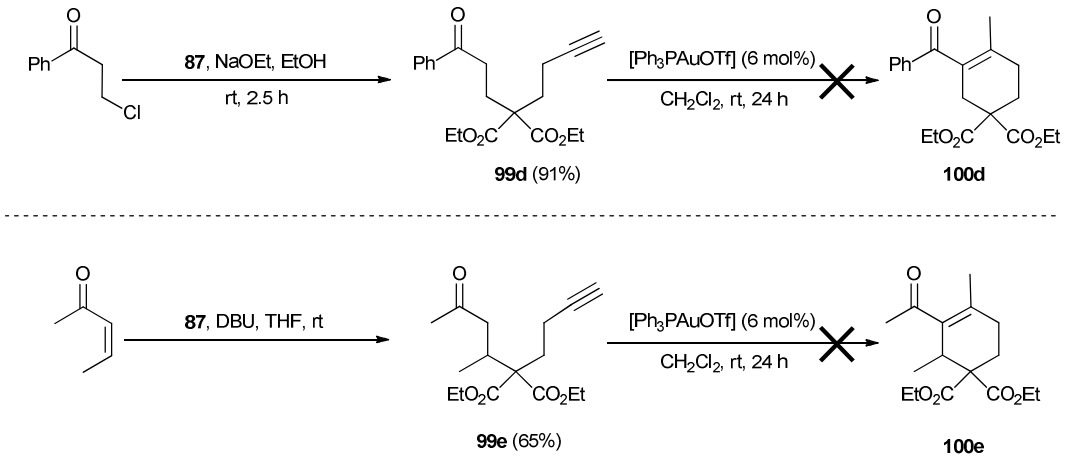


Scheme 54. Gold-catalysed cycloisomerisation of acyclic ketoalkynes

Sterically hindered acyclic ketoalkynes, such as compound **99c** did not undergo cycloisomerisation (Scheme 54). Steric interactions between the two phenyl units may prevent a favourable reactive conformation from being adopted.

3.3.2 6-*exo-dig* cyclisation

To gain access to cyclohexene derivative frameworks, acyclic ketoalkynes **99d** and **99e**, bearing a homopropargyl moiety were subjected to our gold catalysis conditions. These cyclisation precursors were readily obtained in good to excellent yields, starting from homopropargyl malonate, using an identical procedure to substrates **99a-c**. Contrary to cyclic ketoalkynes in which a 6-*exo-dig* cyclisation was viable, the acyclic ketoalkynes did not undergo cycloisomerisation and unreacted starting material was recovered (Scheme 55).



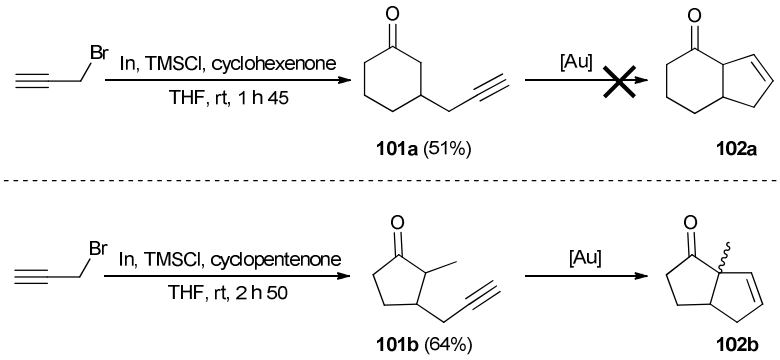
Scheme 55. Attempts to synthesise cyclohexene derivatives

In summary, in the presence of [$Ph_3PAuOTf$], at room temperature, the cycloisomerisation of acyclic ketoalkynes was generally either sluggish or non-existent. In all the cases, cyclised products suffered isomerisation although α,β-unsaturated enone was obtained as the major isomer. The weak reactivity exhibited by acyclic ketoalkynes mainly lies on the fact that bond rotation is more facile and somewhat diminishes favourable interactions between the two reactive centres. In contrast, cyclic ketoalkyne precursors, such as cyclohexanone with a tethered terminal alkynyl unit, have a more restricted number of conformers and are therefore more disposed to react. To force the cycloisomerisation of acyclic ketoalkynes, one of the solutions would be to employ a semihollow-shaped ligand with the gold catalyst, based on Sawamura model[32], to shorten the distance between the reactive centres.

3.4 5-*endo-dig* cyclisation

The gold-catalysed 5-*endo-dig* cyclisation of altered ketones (under the guise of silyl enol ethers or β-ketoesters) with tethered terminal alkynes has recently been studied by Toste and co-workers.[40] They have elegantly demonstrated that in the presence of cationic gold

complexes, these substrates were uneventfully converted into bicyclic compounds (see Chapter 1). To examine whether a similar outcome could be obtained for unactivated enolisable ketoalkynes, cyclisation precursors **101a-b** were prepared according to the procedure reported by Lee *et al*.[98] Addition of an organoindium reagent, generated *in situ* from propargyl bromide addition to indium powder, allowed conjugate addition to enone in the presence of TMSCl. Adducts **101a** and **101b** were produced in 51% and 64% yields, from 2-cyclohexen-1-one and 2-methyl-2-cyclopenten-1-one, respectively. Next [$Ph_3PAuOTf$] catalysis was applied to them (Scheme 56).

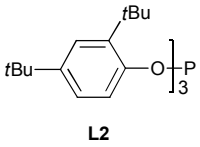


Scheme 56. Attempts to perform 5-*endo-dig* cyclisations

Treatment of cyclisation precursors **101a-b** with a CH_2Cl_2 solution containing 6 mol% of $Ph_3PAuOTf$ resulted in complete recovery of the starting ketoalkynes. When $AgSbF_6$ was used and Ph_3P ligand replaced with bulky triarylphosphite ligand **L2** which renders the gold more electrophilic, only very little conversion took place. With substrate **101a**, ^1H NMR spectroscopy showed that cyclopentene derivative product **102a** was obtained in more than trace amounts, while under these optimised conditions, cyclisation of substrate **101b** afforded bicyclic isomer **102b** and unreacted starting material in 32%, after a prolonged reaction time of 53 hours. These low yields can be due to degradation of the product or/and starting ketoalkyne, which might have occurred during such a long period of time. It should be noted

that purification by flash chromatography furnished the cyclised product, contaminated with an unknown impurity, rendering its characterisation uncertain.

Entry	Substrate	Catalyst	Time, h	Yield, % **100** (**102**)
1	**101a**	PPh_3AuOTf	24	100 (0)
2	**101a**	L2AuOTf	24	98 (2)
3	**101b**	PPh_3AuOTf	24	100 (0)
4	**101b**	$L2AuSbF_6$	53	32 (29)

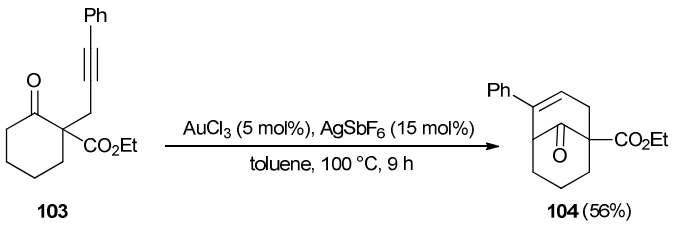


L2

Table 14. Study of the gold-catalysed 5-*endo-dig* cyclisation

3.5 α′ cyclisation

Gold-catalysed α′-cyclisation of cyclic ketoalkynes has been barely investigated. In 2007, Yamamoto and co-workers reported two examples of α′-carbonyl substitution through 6-*endo-dig* cyclisation on to aryl-capped alkynes at elevated temperatures, in the presence of a Au(III) catalyst (Scheme 57).[81]



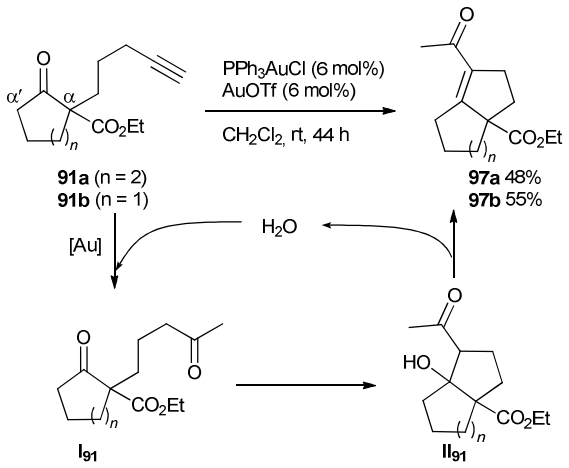
103 **104** (56%)

Scheme 57. $AuCl_3$-catalysed α′-cycloisomerisation of ketone with tethered internal alkyne

Very recently, Sawamura *et al.* demonstrated that α′-carbonyl substitution could also proceed with terminal alkynes, albeit with silyl enol ethers as nucleophilic partners. In the presence of their cationic gold complex **L1**$AuNTf_2$, cyclic acetylenic silyl enol ethers were smoothly

converted to bicyclo [4.*n*.1] and [*m*.4.1] methylene frameworks *via* 7-*exo-dig* cyclisation (see Chapter 1).[32]

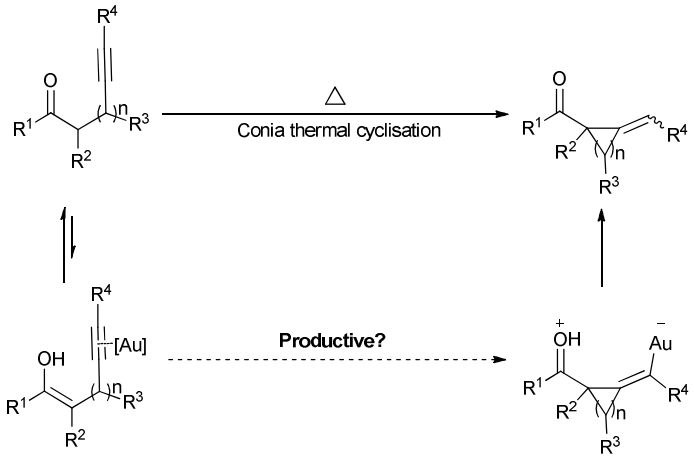
To further extend the scope of the gold-catalysed α′-cycloisomerisation of ketoalkynes and develop a milder alternative method, the cyclisation of previously prepared precursors **91a-b**, (see Chapter 3.2.3) was explored under the standard gold conditions. Unfortunately, the reaction of ketoalkynes **91a-b** was very sluggish at room temperature in the presence of 6 mol% of $Ph_3PAuOTf$. In contrast to Sawamura's result, no bicyclo [4.*n*.1] frameworks were furnished; instead bicyclic enones **97a-b** were formed in moderate yields (Scheme 58). These products were inconsistent with either reaction of the alkyne at the enolisable α'-position or direct enone formation through oxetenium intermediates.[77,81] Formation of **97** could be explained *via* the gold-promoted hydration of the alkyne in the presence of adventitious water to afford diketones $\mathbf{I_{91}}$. Using **91a** a small quantity of $\mathbf{I_{91a}}$ was isolated from the reaction mixture. Subsequently, intramolecular aldol dehydration with preferential formation of a five-membered ring would afford the observed product and regenerate water. The latter step may be promoted by the gold catalyst or traces of Brønsted acid generated *in situ* from it.[99]



Scheme 58. Formation of bicyclic enones

3.6 Mechanistic studies

Initially, it was formulated that cycloisomerisation of unactivated enolisable ketones with alkynes could take place in the presence of cationic gold complexes at room temperature through nucleophilic attack of an incipient enol tautomer to an activated alkynyl moiety (Scheme 59).



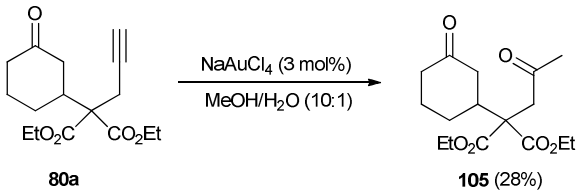
Scheme 59. Initial hypothesis

The overall transformation was possible and could be applied to various cyclic and acyclic ketoalkynes. Nonetheless, for some substrates, notably **92e** and **91a-b**, alternative pathways took precedence. In place of the direct C-C bond-forming process, gold-promoted alkyne hydration was followed by an aldol-dehydration process. Thus, further experiments were performed with **80a** to ascertain whether a similar hydration-aldol dehydration pathway could account for all the cyclisations rather than direct carbon-carbon bond-formation.

In the first place, we found that thermal cyclisation of **80a**, at 168 °C, for 7 h, also led to conjugated enone isomer **81a** in 55% yield alongside unreacted starting material (15%). Some degradation of material was also observed. Subjecting keto-alkyne **80a** to the hydrative

conditions developed by Liu [$PtCl_2$, CO (1 atm), dioxane/H_2O, 100 ºC, 2.5 h] afforded complete conversion with the cyclic enone **81a** formed in 66% NMR yield alongside several byproducts at 6 mol% catalyst loading.[100] As previously seen in our study, larger quantities of water shut down the gold-catalysed reaction completely (Chapter 2, Table 8, entry 5). Similarly, when 1 equivalent of water was added to the reaction mixture, the reaction progress was significantly retarded, and a lower overall combined yield of product and recovered starting material was obtained (Scheme 61). However, the use of undistilled CH_2Cl_2 gave the same yield of **81a** as did using distilled CH_2Cl_2.[101] When using dry solvent the hygroscopic silver salts employed in these reactions are a potential source of adventitious water. No product was observed when the reaction was run in the presence of activated molecular sieves to counter this issue. These results confirm that a small amount of water is necesary for the cyclisation of **80a**. However, larger amounts of water have a negative effect, apparently due to catalyst deactivation and increasing levels of either product or starting material degradation.

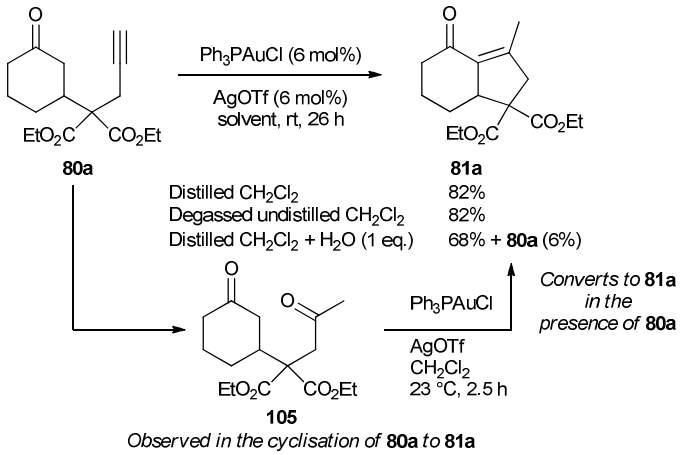
To further explore the role of water, the immediate product of alkyne hydration, diketone **105**, was independently prepared. Unoptimised $NaAuCl_4$-promoted hydration gave **105** in moderate yields alongside a mixture of **80a** and **81a** in 48% yield (Scheme 60).



Scheme 60. Preparation of diketone **105**

No reaction was observed when **105** was subjected to the standard gold-catalysed cyclisation conditions. However, when a small amount of **80a** was added to a solution of $Ph_3PAuOTf$ and **105** in CH_2Cl_2, after 2 hours, a reaction was initiated and product **81a** was formed. On near

complete consumption of **105**, analysis of the product mixture confirms that both ketoalkyne **80a** and diketone **105** are converted into enone **81a** under the reaction conditions (see appendices). The formation of a small amount of **105** was observed when the gold-catalysed cyclisation of **80a** was performed in an NMR tube and monitored regularly by ^{1}H NMR spectroscopy (see appendices). Addition of independently synthesised **105** to this reaction confirmed this observation. On depletion of ketoalkyne, remaining diketone was consumed. These results prove that, despite the low level of water, intermolecular alkyne hydration occurs under the reaction conditions. Furthermore, a species generated in the reaction of **80a** is capable of mediating aldol dehydration of **105**. While the direct carbon-carbon bond-forming process (Scheme 59) cannot be eliminated as a possibility, as water would also aid the required keto-enol tautomerisation, the alkyne hydration adol-dehydration pathway is shown to be at least competitive with this intramolecular cyclisation.



Scheme 61. Study of the possible hydration-aldol-dehydration process. Yields determined by ^{1}H NMR spectroscopy against a known quantity of 1,2,4,5-tetramethylbenzene.

3.7 Conclusion

In summary, we have demonstrated the overall cycloisomerisation of unactivated ketones with alkynes at room temperature under gold catalysis. This straightforward process has been used to assemble a range of fused and spiro carbocyclic structures from simple precursors under mild conditions, in the presence of [$Ph_3PAuOTf$]. However, under these conditions, 5-*endo-dig* cyclisations was either unviable or sluggish. With linear acetylenic ketones, similar results were obtained. Furthermore, α′-cycloisomerisations did not take place under these mild conditions and in lieu an alkyne hydration-aldol condensation was favoured assisted by the presence of adventitious water. Mechanistic studies have shown that water is finely poised between being an integral component of the reaction system and contributing to catalyst and substrate degradation.

Chapter 4: Gold-catalysed cyclisation of ketones with tethered internal alkynes

4.1 Introduction

In Chapter 3, it has been demonstrated that the overall cycloisomerisation of unactivated enolisable ketones with terminal alkynes could take place at room temperature, in the presence of 6 mol% of [$Ph_3PAuOTf$]. The standard procedure generally involved the addition of a 0.1 M solution of cyclisation precursor to the cationic gold complex in CH_2Cl_2, which was generated *in situ* by mixing equimolar quantities of Ph_3PAuCl and AgOTf. A range of bicyclic and spirocyclic frameworks have been constructed *via* this straightforward process, from simple precursors, by overall 5-*exo* and 6-*exo* C-C bond-forming cyclisations. To further expand the scope of the reaction, the cyclisation of enolisable ketones with tethered internal alkynes was considered.

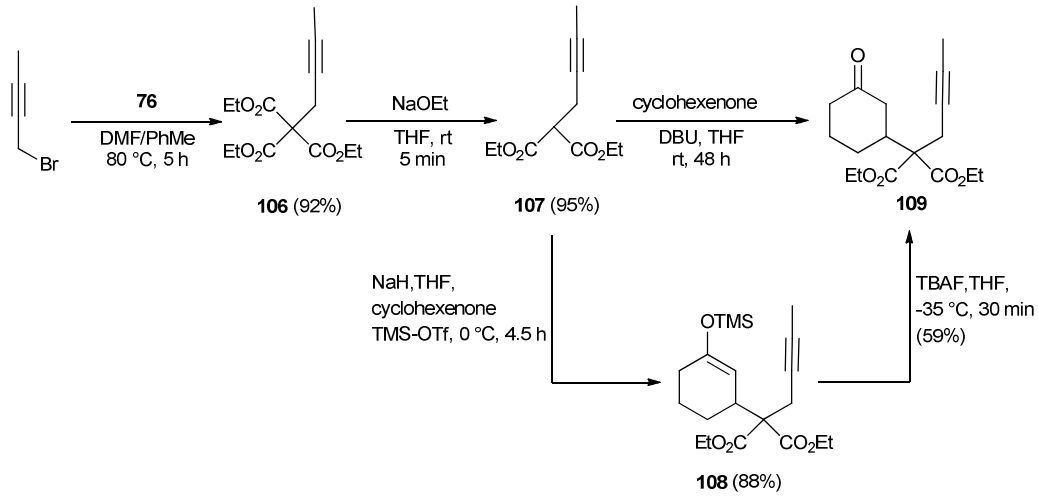
4.2 Screening of the cyclisation precursors

Exo- or *endo*-*dig* cyclisations to access substituted bicyclic [*n*.3.0] and [*m*.4.0] structures generally proceed using either silyl enol ethers with internal alkynes or β-ketoesters with internal alkynes[27-30, 39-43], as cyclisation precursors under gold catalysis (see Chapter 1). α-Modification of unactivated enolisable ketones with internal alkynes, through *exo*- or *endo*-*dig* cyclisation has been hardly investigated under mild conditions. Yamamoto *et al.* have shown a few examples where the reaction took place with aryl-capped alkynes, albeit at elevated temperatures through an *endo*-dig mode.[81] No example of cycloisomerisation of unactivated enolisable ketones with tethered internal alkynes has yet been reported under gold catalysis *via* the *exo*-mode. Our study focused on the use of cyclic ketones with ε-internal

alkynes bearing either an alkyl group or an aryl unit to access substituted [*m*.4.0] or [*n*.3.0] bicyclic frameworks *via* either *exo*- or *endo*-dig cyclisations.

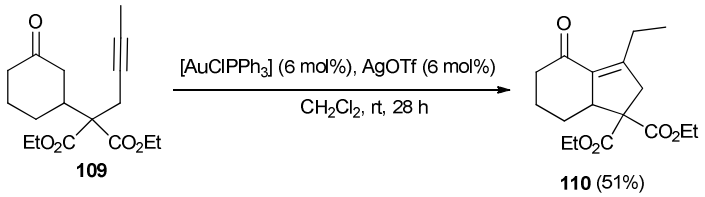
4.2.1 *Exo-dig* cyclisation of cyclic ketones with tethered alkyl alkynes

To construct substituted [*n*.3.0] bicyclic structures, *via* the gold-catalysed 5-*exo-dig* cyclisation of enolisable ketones with tethered internal alkynes, the preparation of cyclisation precursor **109** was examined. In the first place, on account of results obtained with DBU-promoted conjugate addition of propargyl malonate **78** to cyclohexenone, the addition of butynyl malonate **107** to cyclohexenone was considered in the presence of this amidino base. To prevent the formation of dialkylated malonate, butynyl malonate **107** was synthesised following the standard two-step procedure (Chapter 2), which involves addition of 1-bromo-2-butyne to sodium triester **76**, followed by NaOEt-catalysed decarbethoxylation. Compound **107** was obtained in an overall good yield of 87%, without chromatography purification (Scheme 62). Treatment of butynyl malonate **107** with DBU and cyclohexenone did afford adduct **109**, albeit in low yield and isolated with an unknown by-product which co-eluted. Addition of an excess of butynyl malonate and DBU improved the yield, but only up to 19%. This procedure was finally abandoned and adduct **109** was produced with a better yield (52% overall yield) *via* the preparation of silyl enol ether **108**, followed by O-Si bond cleavage by TBAF. Note that although effective, to take advantage of our proposed methodology, the preparation of silyl enol ether derivatives to access ketones with tethered internal alkynes was avoided whenever possible as they are also employed in Conia-like processes as substrates.



Scheme 62. Synthesis of cyclisation precursor **109**

Cyclisation precursor **109** was then subjected to 6 mol% of PPh_3AuOTf, in CH_2Cl_2, at room temperature. Under these mild reaction conditions, ketoalkyne **109** underwent cycloisomerisation to afford bicyclic compound **110** in 51% yield after 28 hours, alongside unreacted cyclisation precursor (5% yield) and unknown by-products. As for cyclic ketones with terminal alkynes, the conjugated enone product was obtained as the sole isomer.



Scheme 63. Gold-catalysed cycloisomerisation of cyclic ketone with internal alkyne

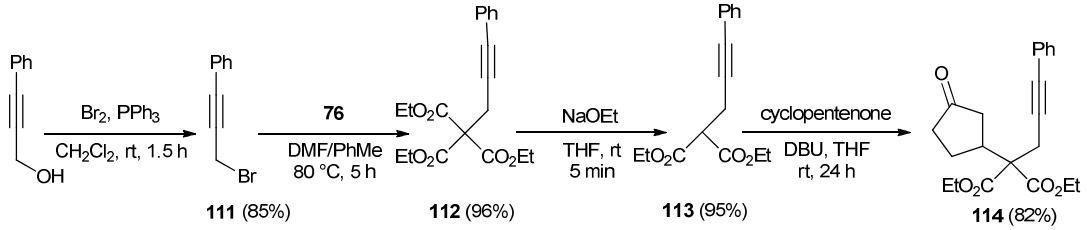
Although the yield of product **110** was moderate under the above unoptimised reaction conditions, this result was encouraging. Further investigations were oriented towards the cycloisomerisation of cyclic ketones with tethered aryl alkynes.

4.2.2 *Exo* and *endo-dig* cyclisation of cyclic ketones with tethered aryl alkynes

To examine whether cyclic ketones with tethered aryl alkynes could undergo α-modification *via* a similar 5-*exo-dig* cyclisation as depicted above or a 6-*endo-dig* process, cyclic precursors were prepared by addition of phenyl propargyl malonate to 2-cyclopenten-1-one or 2-cyclohexen-1-one, following the standard procedure previously described.

2.1. Cyclopentanone with tethered phenyl-substituted alkyne as substrate

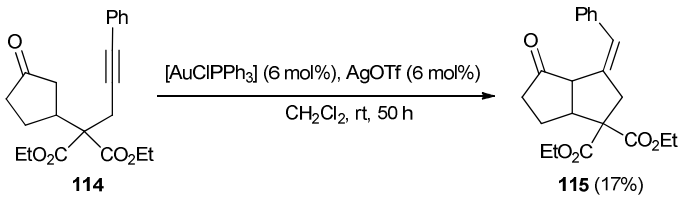
As described above, addition of phenyl propargyl malonate **113** to 2-cyclopenten-1-one provided cyclopentanone with tethered phenyl-substituted alkyne **114** in 82% yield. Prior to this addition, monoalkylated malonate **113** was produced in nearly quantitative yield, by treatment of triethyl sodiomethanetricarboxylate **76** with 1-phenyl-3-bromoprop-1-yne **111**, followed by decarbethoxylation. Nucleophilic substitution of phenyl-2-propyn-1-ol hydroxyl group by bromide provided halide **111** in a very good yield within 1.5 hours.[102] Owing to the low reactivity of alcohol to undergo direct S_N reaction, PPh_3 was required to promote the substitution (Scheme 64).



Scheme 64. Preparation of cyclisation precursor **114**

With compound **114** in hand, gold-catalysed cycloisomerisation of ketones with aryl alkynes was tried. Analogously to substrate **109**, in the presence of 6 mol% of [$Ph_3PAuOTf$],

ketoalkyne **114** slowly underwent cycloisomerisation and after 50 hours only little conversion to carbocyclic product was observed. Under these conditions, bicyclic[3.3.0] exomethylene compound **115** was produced as a white solid in 17% yield, alongside 58% of unreacted starting material and unknown by-products (Scheme 65). In contrast to the cyclisation of methyl-substituted alkyne **109** to conjugated enone **110**, the alkene remains conjugated to the aromatic unit from the cyclisation of **114**.



Scheme 65. Gold-catalysed 5-*exo-dig* cyclisation of cyclopentanone with phenyl-substituted alkyne

Crystallisation of **115** from CH_2Cl_2/pentanes afforded good-quality crystals, which allowed structure determination by X-ray crystallography, and assignment of the *Z*-stereochemistry at the alkene.

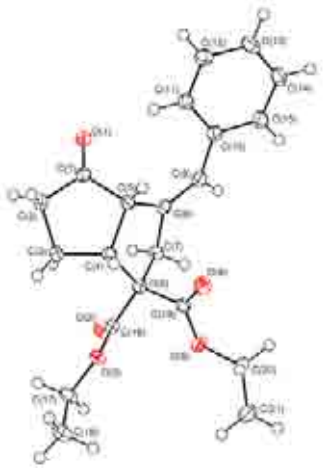
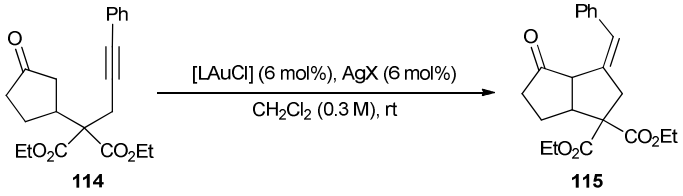


Figure 6. X-ray crystallography of **115**

To increase the yield of *Z*-alkene **115**, additional experiments were run (Table 15). First, the concentration of the solution was increased to 0.3 M and the silver source and the neutral ligand were modified. With [$Ph_3PAuSbF_6$] catalyst which is more reactive than [$Ph_3PAuOTf$] catalyst, although starting ketone **114** was recovered in 21% yield, **115** was obtained only in 14% yield alongside unknown by-products. Replacement of PPh_3 with ligand L2 (Table 15, entry 3), which has a weaker σ-donor potential, rendering the gold more electrophilic, allowed complete conversion after 72 hours, with cyclisation product **115** afforded in 29% yield alongside unknown by products.



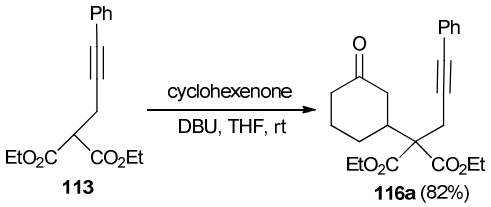
Entry	Ligand	AgX	Time, h	**115** (**114**) Yield, %
1	Ph_3P	AgOTf	50	17 (58)[a]
2	Ph_3P	$AgSbF_6$	72	14 (21)
3	[2,4-(*t*Bu)$C_6H_3O]_3P$	AgOTf	72	29 (0)

Table 15. Study of the gold-catalysed cycloisomerisation of ketoalkyne **114**.[a] CH_2Cl_2 (0.1 M).

Although different conditions were tested to improve the yield, notably by enhancing the electrophilicity of the cationic gold complex, alkene **115** was obtained in poor yield in each case. Degradation of the product might have occurred at this high concentration and prolonged reaction time (Table 15, entries 2 and 3). Furthermore, aryl-substituted alkyne **114** underwent 5-*exo*-*dig* cyclisation like ketoalkyne **109**, albeit without suffering isomerisation.

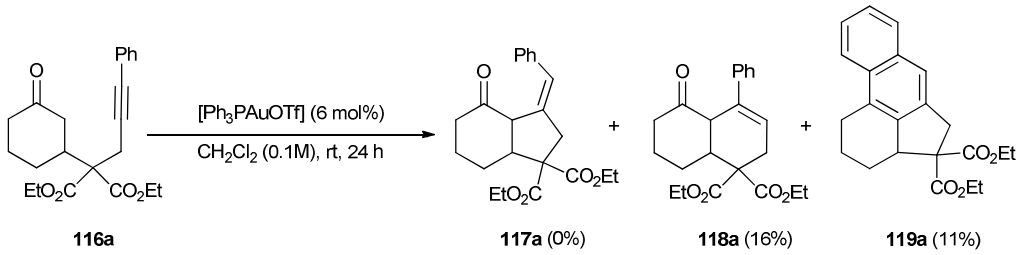
2.2. Cyclohexanone with tethered phenyl-substituted alkyne as substrate

For initial studies, cyclohexanone with tethered phenyl-substituted alkyne **116a** was synthesised in 82% by conjugate addition of phenyl propargyl malonate **113** to 2-cyclohexen-1-one, according to the standard method (Scheme 66).



Scheme 66. Preparation of cyclohexanone with tethered phenyl-substituted alkyne **116a**

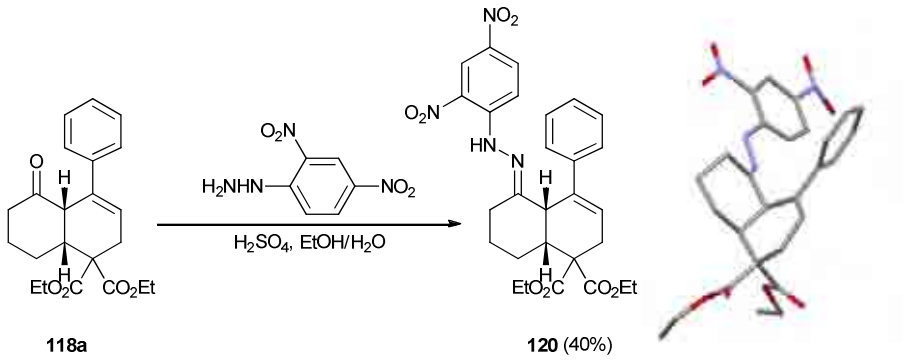
Interestingly, treatment of a 0.1 M solution of cyclisation precursor **116a** in CH_2Cl_2, with 6 mol% of $Ph_3PAuOTf$ did not afford 5-*exo*-*dig* cyclisation product **117a** as had been previously observed with the above internal alkynes. Instead, alternative pathways took precedence to yield [4.3.0] bicyclic compound **118a** and acephenanthrylene derivative **119a**, which were obtained in 16% and 11% yield respectively (Scheme 67). Unknown by-products were also produced. Acephenanthrylene derivative **119a** was furnished as a crystalline solid. Its structure was determined by conventional spectroscopic methods and confirmed by X-ray crystallography. The formation of this polycyclic compound was surprising and of interest as such structures generally require multistep synthesis from aromatic precursors in the few strategies described. No preparation, involving a single step has been yet reported from alicyclic substrates.[103]



116a **117a** (0%) **118a** (16%) **119a** (11%)

Scheme 67. Cycloisomerisation of cyclohexanone with phenyl-substituted alkyne

In a similar way, the structure of bicyclic framework **118a** was established by means of NMR spectroscopic analysis. Strong 4-bond coupling of vinyl to allylic hydrogens across the phenyl ring was observable with a coupling constant equal to 2.6 Hz. As the signal of the β hydrogen (from the carbonyl functionality) overlaps with other ring signals, nOe experiments were ineffective to ascribe the relative stereochemistry of the ring junction. Thus, attempts to crystallise **118a** were made. The conversion of ketoalkyne **118a** into dinitrophenyl hydrazone **120** provided crystals, which were of sufficient quality to establish that decalin **118a** had a *cis* junction (Scheme 68).

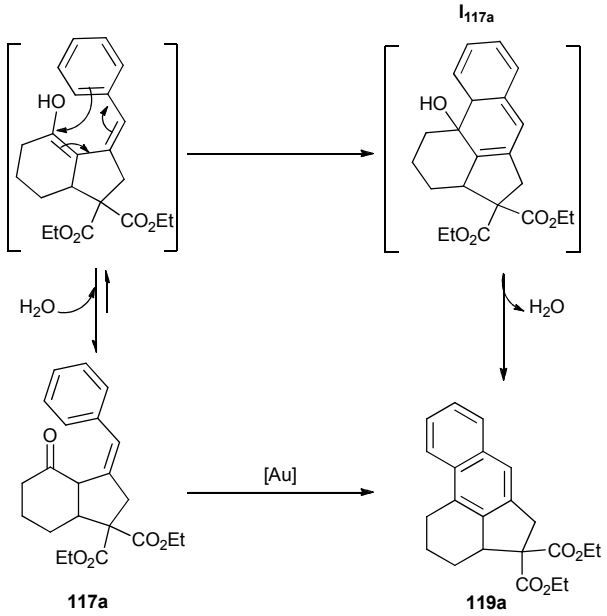


118a **120** (40%)

Scheme 68. Preparation of dinitrophenyl hydrazone **120**

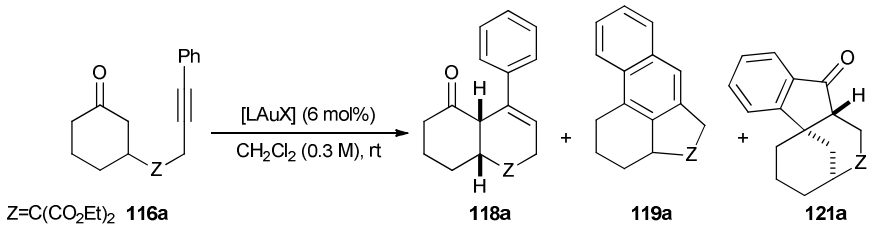
Furthermore, bicyclic compound **118a** might have resulted from gold-promoted 6-*endo-dig* cyclisation of cyclohexanone with phenyl-substituted alkyne. Although the *exo*-product **117a** was not isolated, its formation during the reaction cannot be excluded. The presence of

acephenanthrylene derivative **119a** could be explained by a gold-catalysed 5-*exo-dig* ring closure to yield *exo*-product **117a**; which *via* its enol tautomer can undergo a pericyclic rearrangement, reminiscent of a [4+2] cycloaddition to afford intermediate $\mathbf{I_{117a}}$. Under gold catalysis, $\mathbf{I_{117a}}$ evolves into acephenanthrylene derivative after aromatisation by proton and hydroxyl elimination to release water. Water might have also assisted the desired keto-enol tautomerisation as in the cycloisomerisation of ketones with terminal alkynes (Chapter 3). Furthermore, steric interactions between the OH group in the enol tautomer and the aromatic ring might have contributed to the formation of intermediate $\mathbf{I_{117a}}$ (Scheme 69)



Scheme 69. Possible pathway for the formation of acephenanthrylene derivative **119a**

Further investigations were conducted to improve the yields of the above cyclisation products (Table 16). During this study it was seen that through modifications of the spectator ligand or the choice of counterion, small improvements could be achieved but alongside this, a new isomer, tetracyclic compound **121a**, could be prepared in good yield.



Entry	Catalyst/additive	Time, h	Product (yield, %)
1	$Ph_3PAuOTf$[a]	24	**118a** (16), **119a** (11)
2	$Ph_3PAuOTf$	46	**118a** (19)
3	[2,4-(*t*Bu)$C_6H_3O]_3PAuOTf$	55	**118a** (47)
4	$Ph_3PAuSbF_6$	2	**121a** (70)
5	[2,4-(*t*Bu)$C_6H_3O]_3PAuSbF_6$	2	**121a** (60)
6	[2,4-(*t*Bu)$C_6H_3O]_3PAuSbF_6$	6	**121a** (57)
7	$Ph_3PAuSbF_6$/MeOH (1.6 eq)	26	**118a** (43), **119a** (24)
8	[2,4-(*t*Bu)$C_6H_3O]_3PAuSbF_6$/MeOH (2.5 eq)	18	**118a** (31), **119a** (16)

Table 16. Study of the gold-catalysed cycloisomerisation of cyclohexanone with aryl alkyne. [a] CH_2Cl_2 (0.1 M)

Initial observations showed that, cyclohexanone with aryl alkyne **116a** slowly reacted in the presence of 6 mol% of [$Ph_3PAuOTf$], in CH_2Cl_2 (0.1 M) to afford cyclisation products **117a** and **118a** in poor yields. Increasing the concentration up to 0.3 M allowed a small improvement and bicyclic compound **118a** was afforded as the sole isomer, albeit in low yield. Degradation of product or/and starting material might have occurred (Table 16, entry 2). Replacement of PPh_3 with a weaker donor ligand such as [2,4-(*t*Bu)$C_6H_3O]_3P$ furnished *endo*-product **118a** as the major isomer in 47%, after 55 hours (Table 16, entry 3). Unexpectedly, employing SbF_6^- as counterion led to tetracyclic isomer **121a** as a single diastereoisomer in moderate to high yield, irrespective of the neutral ligand used. [$Ph_3PAuSbF_6$] was the most effective catalyst for this transformation (Table 16, entries 4-6 *vs* entries1-3). Intriguingly, addition of methanol to this catalytic system bypassed this route and compounds **118a** and **119a** were obtained *via endo*- and *exo*- *dig* cyclisation, in moderate to low yield alongside unknown by-products (Table 16, entries 7 and 8).

The stereochemistry of compound **121a** was ascribed by interpretation of 2D GOESY spectra, shown in Figure 7. A strong nOe was observed from α-H to CH_2Z and from α-H to β-C-CH_2CH, allowing a *trans* relationship between the α-hydrogen and β-C-CH_2CH bond of the bis-fused [3.3.1] carbocycle to be assigned (Figure 7).

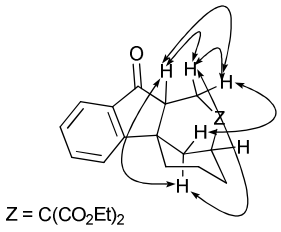


Figure 7. Selected GOESY data for **121a**

X-ray crystallography also supported the opposite orientations of these substituents (Figure 8).

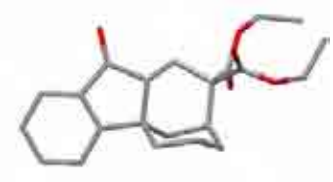
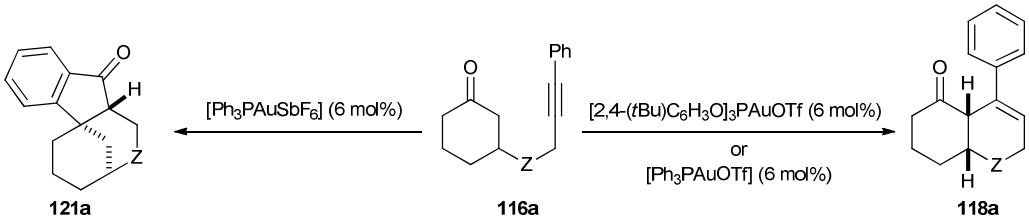


Figure 8. X-ray crystal structure of **121a**

4.3 Cycloisomerisation of cyclohexanone with tethered aryl alkynes

Contrary to ketones with internal alkynes **109** and **114**, which cyclised *via* an *exo-dig* mode, ketone with aryl alkyne **116a** was smoothly converted, depending on the reaction conditions, either into bicyclic compound **118a** and acephenanthrylene derivative **119a** or into polycyclic skeleton **121a**. Interestingly, a counterion effect was observed, allowing diverse carbocyclic structures to be obtained from the same cyclisation precursor. In the presence of SbF_6^-

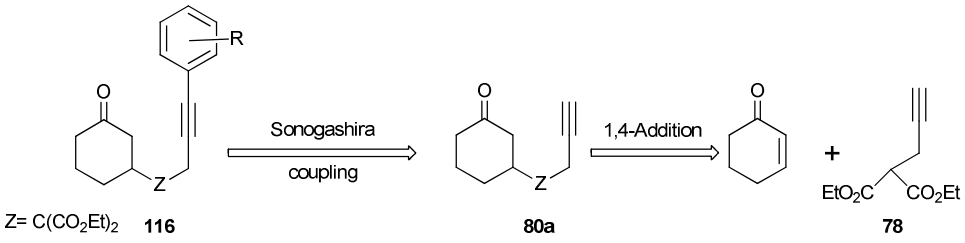
counterion, tetracyclic framework **121a** was afforded, while with OTf^-, bis-fused [4.4.0] skeleton **118a** could be furnished as the sole isomer (Scheme 70). To study the scope of this process different cyclohexanones with substituted aryl alkynes were synthesised.



Scheme 70. Divergent pathways for the cycloisomerisation of cyclohexanone with aryl alkyne

4.3.1 Synthesis of the cyclisation precursors

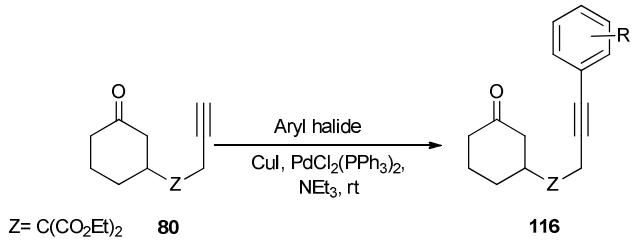
Cyclohexanones with tethered internal alkynes bearing either an electron-rich or electron-poor aromatic ring were readily assembled *via* Sonogashira coupling of acetylenic cyclohexanone **80a** with an appropriate aryl halide.[104] Acetylenic cyclohexanone **80a** had been previously synthesised by conjugate addition of propargyl malonate **78** into 2-cyclohexen-1-one (see Chapter 2).



Scheme 71. Retrosynthetic analysis for the preparation of ketoalkynes **116**

Diverse cyclisation precursors **116a-l** were afforded in good to quantitative yields following this route, regardless of the nature of the aromatic substituent, albeit with the exception of

precursor **116n**, which was obtained in moderate yield, probably due to side reactions provoked by the presence of the unprotected amino group (Table 17).



Entry	RC_6H_4	Ketoalkyne **116** (yield, %)
1	C_6H_5	**a** (95)
2	*o*-MeC_6H_4	**b** (79)
3	*m*-MeC_6H_4	**c** (90)
4	*p*-MeC_6H_4	**d** (88)
5	*o*-$^{i}PrC_6H_4$	**e** (81)
6	*m*-$MeOC_6H_4$	**f** (91)
7	*p*-$MeOC_6H_4$	**g** (73)
8	*p*-$CF_3C_6H_4$	**h** (99)
9	*p*-FC_6H_4	**i** (84)
10	*p*-BrC_6H_4	**j** (87)
11	*3,5-difluoro*C_6H_4	**k** (91)
12	2-naphthyl	**l** (89)
13	C_6H_5 and Z = $C(CO)CO_2Et$	**m** (73)
14	*p*-$NH_2C_6H_4$	**n** (47)

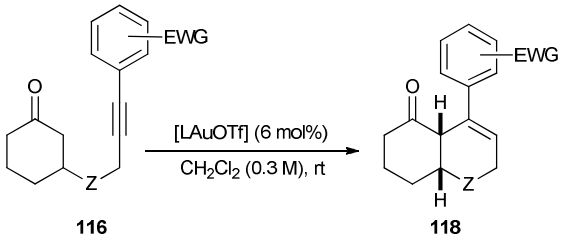
Table 17. Synthesis of cyclisation precursors **116a-n**

4.3.2 Study of Au-catalysed cycloisomerisation of cyclohexanone with tethered aryl alkynes

Our investigations started with the study of the behaviour of alkynes bearing either electron-poor or electron-rich aromatic rings.

To gain access to bicyclic structures **118** and tetracyclic skeletons **121**, bearing an electron-withdrawing substituent on the aromatic ring, cyclic ketones with internal alkyne **116h-j** were

reacted under the optimal conditions developed, either with $Ph_3PAuSbF_6$ or with LAuOTf. Intriguingly, unlike the substrate with an unsubstituted phenyl ring **116a**, the counterion effect was not observed with the electron-deficient system. The cyclisations produced *endo*-products regardless of the nature of the silver source or the phosphine ligand. The cyclisation products were generally afforded, after prolonged reaction times, in poor yield alongside unreacted starting materials (Table 18). With cyclisation precursor **116h**, *endo*-product **118h** was isolated with an unknown isomer, preventing full interpretation of the NMR spectrum.

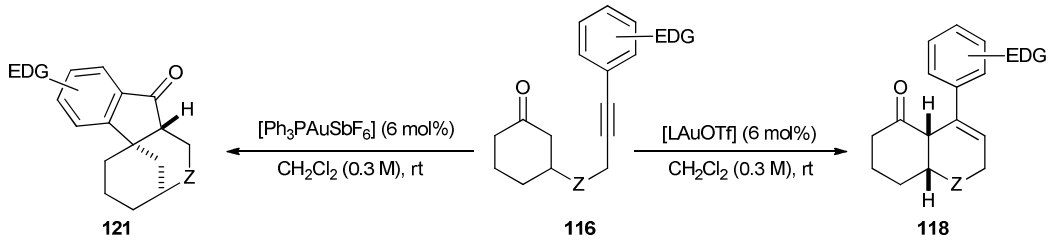


116 **118**

Entry	RC_6H_4	Catalyst	Time, h	Product (yield, %)
1	*p*-$CF_3C_6H_4$	$Ph_3PAuOTf$	54[a]	**118h** (12), **116h** (55)
2	*p*-$CF_3C_6H_4$	$Ph_3PAuSbF_6$	54[a]	**118h** (17), **116h** (42)
3	*p*-FC_6H_4	[2,4-(*t*Bu)C_6H_3O]$_3$PAuOTf	48	**118i** (17), **116i** (42)
4	*p*-FC_6H_4	$Ph_3PAuSbF_6$	48	**118i** (21), **116i** (37)
5	*p*-BrC_6H_4	$Ph_3PAuSbF_6$	45	**118j** (27), **116j** (49)
6	*p*-BrC_6H_4	[2,4-(*t*Bu)C_6H_3O]$_3$PAuOTf	>48	**118j** (31), **116j** (31)

Table 18. Cycloisomerisation of ketones with alkynes substituted with electron-deficient aromatic ring. [a] With an unknown isomer.

Cyclic ketones with alkynes substituted with electron-rich aromatic rings behaved in a similar way to electron-deficient ketoalkynes, except that in this latter case, tetracyclic structures **121c** and **121g** were furnished as the sole or major isomer, after a shorter reaction time. However, although the cyclisation precursors were completely consumed, the products were delivered in poor yields which indicated that degradation might have also taken place (Table 19).



Entry	RC_6H_4	Catalyst	Time, h	Product (yield, %))
1	*m*-MeC_6H_4	$Ph_3PAuOTf$	24	**121c:118c** (95:5, 36)
2	*m*-MeC_6H_4	$Ph_3PAuSbF_6$	24	**121c:118c** (98:2, 26)
3	*p*-$MeOC_6H_4$	$Ph_3PAuOTf$	24	**121g** (37), **118g** (6)
4	*p*-$MeOC_6H_4$	$Ph_3PAuSbF_6$	24	**121g** (33)

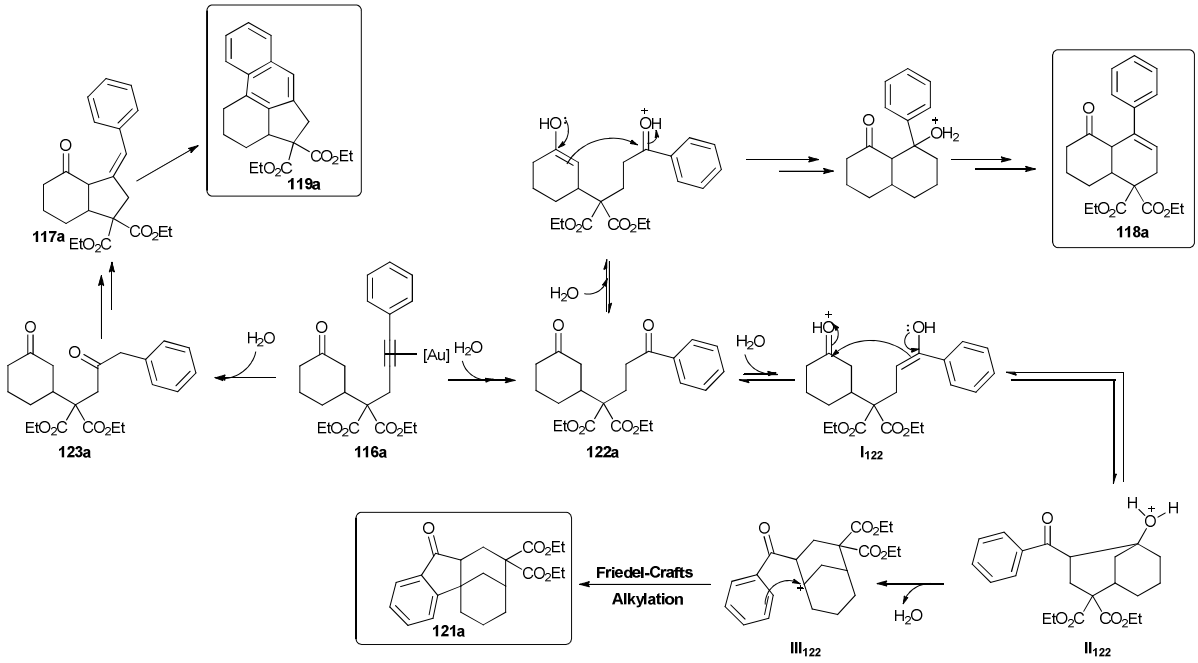
Table 19. Cycloisomerisation of ketones with alkynes substituted with electron-rich aromatic ring

Further studies were thus conducted to understand the mechanisms which controlled the formation of the different isomers and acephenanthrylene derivative, in a view to selectively access either the tetracyclic framework or the *endo*-product by modulation of the catalytic system.

4.3.3 Mechanistic studies of gold-catalysed cycloisomerisation of ketones with aryl alkynes

Initially, we hypothesised that the formation of *endo*-product **118a** and acephenanthrylene compound **119a** might have been promoted by a gold-catalysed 6-*endo-dig* cycloisomerisation in the former case, and 5-*exo-dig* cyclisation-cycloaddition in the latter. However, the formation of these products could also be explained *via* the alkyne hydration process, previously observed in the cycloisomerisation of ketones with terminal alkynes (see Chapter 3). Indeed, in the presence of cationic gold complexes, alkyne hydration of ketoalkyne **116** can potentially furnish two diketones: Markovnikov ketone **122a** and anti-Markovnikov product **123a** (Scheme 72). Diketone **122a** can then undergo aldol condensation

by means of either the enol tautomer of cyclohexanone or the enol tautomer adjacent to the phenyl ring. Aldol condensation initiated by the enol tautomer of cyclohexanone would afford *endo*-product **118a**, whereas the attack of the enol tautomer adjacent to the phenyl ring into cyclohexanone would lead to intermediate $\mathbf{I_{122}}$, which on release of water evolves into carbocyclic cation $\mathbf{III_{122}}$. The sp^2 hybridised cation would possess the planar geometry to undergo Friedel-Crafts alkylation of the aromatic ring and evolves into polycyclic indanone **121a**. The anti-Markovnikov diketone **123a** can undergo aldol condensation like diketone **122a**, to furnish *exo*-product **117a**, which after further transformations would afford acephenanthrylene derivative **119a** (see Scheme 69).

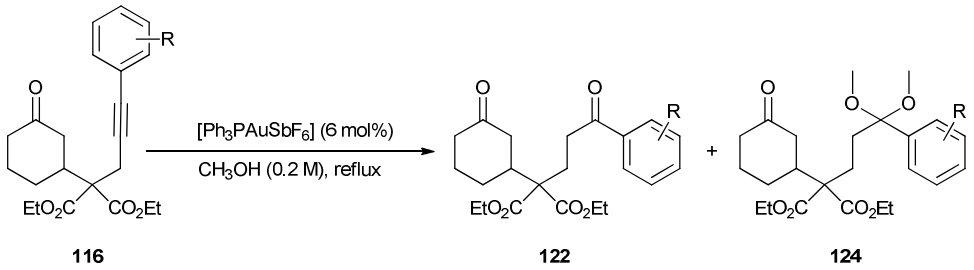


Scheme 72. Mechanistic hypotheses for the synthesis of compound **118a**, **119a** and **121a**

For initial studies, ketoalkyne **116a** was subjected to thermal conditions in a view to examine if a pericyclic rearrangement was involved in the formation of acephenanthrylene derivative **119a**. Generally, pericyclic processes often require high temperature to proceed. Besides, the conversion of ketoalkyne **80a** into conjugated enone **81a** had been previously observed under

these conditions (see Chapter 3). Intriguingly and in contrast to ketone with terminal alkyne **80a**, cyclic ketone with aryl alkyne **116a** was reluctant to undergo cycloisomerisation under thermal conditions. Despite the high temperatures used, no cyclised product was observed after 8 hours at 140 °C, then 4 hours at 160 °C, and finally degradation occurred at 200 °C.

As in the cycloisomerisation of ketones with terminal alkynes water played a critical role, its influence on the cyclisation of cyclohexanone with a tethered aryl alkyne was therefore investigated. Under the hydrative conditions developed by Liu [$PtCl_2$, CO (1 atm), dioxane-H_2O, 100 °C) no cycloisomerisation occurred.[100] Although, these conditions were ineffective for the cyclisation of ketoalkyne **116a**; the participation of diketone **122a** in the cyclisation process could not be eliminated. Effectively, the lack of reactivity of ketoalkyne **116a** in the presence of platinum salts can lie on the fact that Pt(II) is a weaker π-acid than Au(I). Thus, to examine whether diketone **122a** was a viable intermediate for the formation of either *endo*-product **118a** or tetracyclic framework **121a**, its synthesis was considered in order to perform control experiments. Different literature procedures, allowing alkyne hydration, were tested to prepare diketone **122a** from cyclisation precursor **116a** in the presence of a π-acid and water. Despite several trials with either $NaAuCl_4$ or $(MeCN)_2PdCl_2$, no diketone product **122a** was obtained.[105,106] Ultimately, it was found that diketone **122a** could be smoothly furnished when ketoalkyne **116a** was treated with $Ph_3PAuSbF_6$, in methanol at reflux. This method allowed a range of ketones with aryl alkynes to be converted into diketones, as highlighted in Table 20. However, when applied to ketones with terminal alkynes, the diketone could not be isolated under these harsh conditions and aldol condensation of the transient ketone took precedence. Note that for ketones with substituted aryl alkynes, under longer reaction times, irrespective of the substituent nature, diketone **122** were converted into acetals **124** (Table 20, entries 3 and 4).



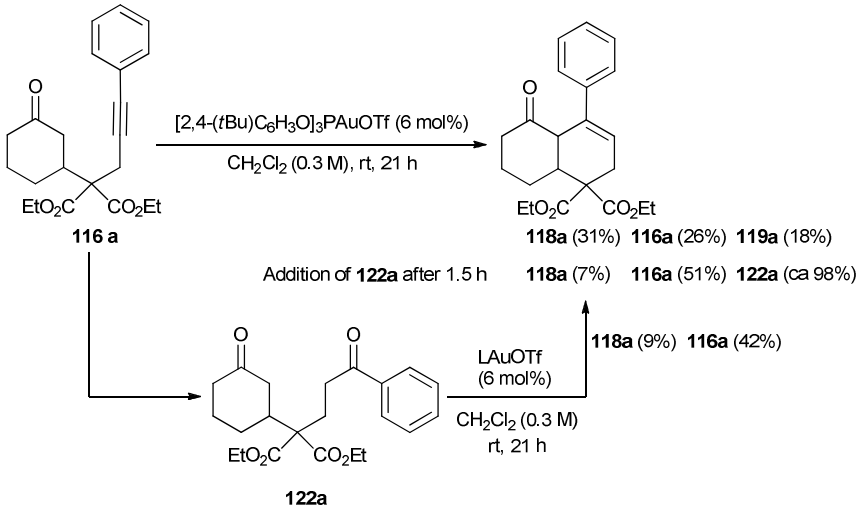
116 122 124

Entry	RC_6H_4	Time, h	Product (yield, %))
1	-	20.5	**81a** (74)
2	C_6H_4	2.5	**122a** (65)
		23	**122a** (87)
3	*p*-FC_6H_4	2.5	**122i** (56)
		7	**122i** (28), **124i** (49)
4	*p*-$MeOC_6H_4$	7	**122g** (0), **124g** (64)

Table 20. Hydration of cyclisation precursors **80a**, **116a**, **116i**, **116g**

With diketone **122a** in hand, control experiments were run. First, diketone **122a** was treated under the optimum conditions which afforded *endo* product **118a** as the major isomer from **116a**. In the presence of 6 mol% of [2,4-(*t*Bu)C_6H_3O]$_3$PAuOTf, diketone was slowly converted into *endo* product **118a** in 9% yield and unreacted diketone **122a** was recovered in 42% yield alongside unknown by-products. In the presence of 6 mol% of [2,4-(*t*Bu)C_6H_3O]$_3$PAuOTf, ketoalkyne precursor **116a** was converted into bicyclic compound **118a** in a better yield of 31%, alongside acephenanthrylene derivative **119a** (18%) and unreacted **116a** (26% yield). The lower yield of *endo* product obtained with diketone **122a** as cyclisation precursor can be explained by the fact that at elevated content of **122a**, the catalyst's activity is reduced by stable coordinations with the oxygen atoms of the ketones. Besides, it has been observed that on addition of diketone **122a** to a solution containing substrate **116a** and catalyst [2,4-(*t*Bu)C_6H_3O]$_3$PAuOTf, which had already reacted together for 1.5 hour, the yield of *endo*-product was decreased to 22% (Scheme 73). Although the catalyst's activity is reduced in the presence of diketone **122a**, this feature cannot exclude

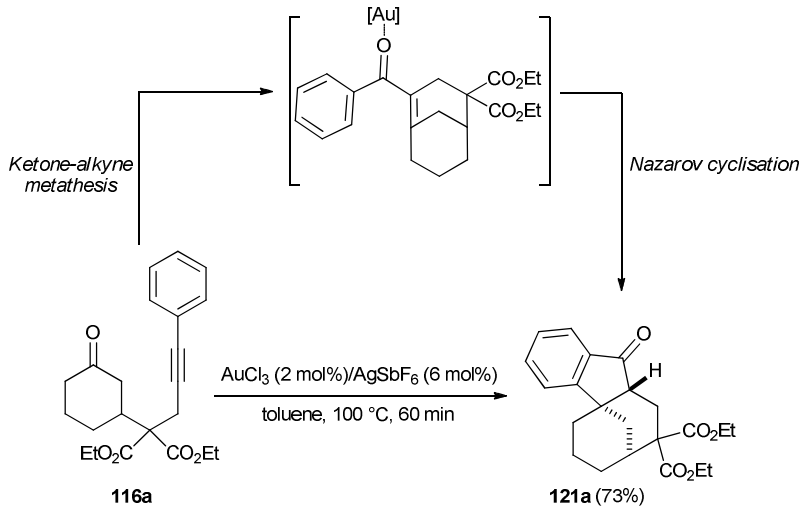
diketone **122a** as a viable intermediate in the formation of *endo* product **118a**. The above results support at least that the formation of *endo*-product **118a** might involve either an aldol-dehydration mechanism (as previously seen in Chapter 3 with ketones bearing terminal alkynes) or the direct 6-*endo-dig* cyclisation *via* the attack of an enol tautomer on the electrophilic alkyne-metal complex.



Scheme 73. Study of the cycloisomerisation of diketone **122a**

Under gold catalysis, ketoalkynes are converted into carbocycles or heterocycles *via* three main routes. Either an enol tautomer equivalent attacks the electrophilic alkyne-metal complex or the carbonyl oxygen lone pair does. It has also been demonstrated that in the presence of a Lewis acid, ketones with tethered alkynes can cyclise *via* a [2+2] cycloaddition-cycloreversion (see Chapter 1). In our case, control experiments have revealed that the *endo* product **118a** was generated either from the attack of the enol tautomer of cyclohexanone to the activated alkyne-metal complex or *via* the formation of $\mathbf{I_{122}}$. Furthermore, as under the conditions which strictly afforded tetracyclic **121a**, diketone **122a** exclusively cyclised into *endo* product **118a**, diketone **122a** is an unviable intermediate for the synthesis of tetracyclic compound **121a**. Thus, considering previous literature examples and the results of our control

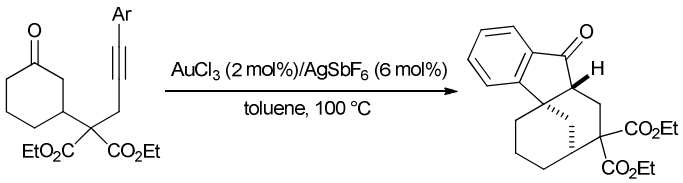
experiments, the formation of indanone derivative **121a** could occur *via* an alkyne-ketone metathesis-cycloreversion process, followed by a gold-promoted Nazarov cyclisation. However, the [2+2] cycloaddition-cycloreversion of cyclic ketone **116a** would evolve into the anti-Bredt intermediate $\mathbf{I_{116a}}$ (Scheme 74).[79] Nonetheless, to examine whether a similar reaction could take place with cyclic ketone bearing aryl alkyne **116a**, literature conditions developed by Yamamoto for the cyclisation of linear ketoalkynes were tested for our substrate.[82] To our delight, in the presence of $AuCl_3$ and $AgSbF_6$ (2 and 6 mol% respectively), substrate **116a** smoothly underwent cycloisomerisation to deliver indanone derivative **121a** in 73% within an hour. As this yield was comparable to the one obtained when the reaction was performed with 6 mol% of [$Ph_3PAuSbF_6$] (see Chapter 4.2.2.2), the scope of the gold-catalysed cycloisomerisation of cyclohexanone with aryl alkyne was re-examined with Au(III).



Scheme 74. Cycloisomerisation of ketoalkyne **116a** *via* gold-promoted ketone-alkyne metathesis/Nazarov cyclisation

4.4 Scope of Au-catalysed tandem [2+2] cycloaddition/Nazarov reaction

Treatment of cyclisation precursors **116**, with $AuCl_3$ and $AgSbF_6$, respectively 2 and 6 mol%, resulted in a smooth conversion to substituted indanone derivatives **121**. Table 21 presents our results obtained with Au(III)-catalysed-cycloisomerisation of cyclic ketones with tethered aryl alkynes *en route* to substituted indanone derivatives.



116 **121**

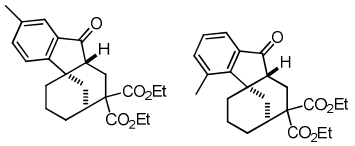
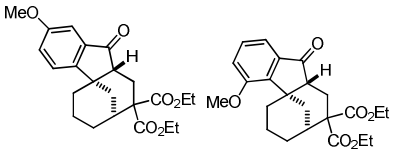
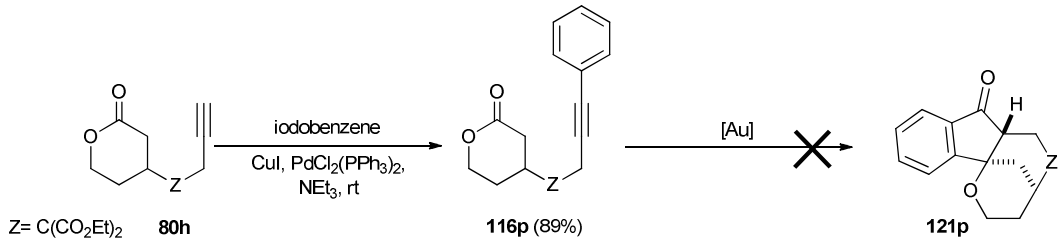
Entry	**116**, Ar =	Time, min	Yield, %
1	**116a**, H	120	73
2	**116b**, *o*-MeC_6H_4	20	98
3	**116c**, *m*-MeC_6H_4	50	75 (Ratio: 10:12)
			
4	**116d**, *p*-MeC_6H_4	20	80
5	**116e**, *o*-$^{i}PrC_6H_4$	33	82
6	**116f**, *m*-$MeOC_6H_4$	15	72 (Ratio: 76:10)
			
7	**116g**, *p*-$MeOC_6H_4$	50	65
8	**116h**, *p*-$CF_3C_6H_4$	120	52
9	**116i**, *p*-FC_6H_4	50	63
10	**116j**, *3,5-difluoro*C_6H_4	120	43
11	**116k**, 2-naphthyl	20	88
12	**116l**, *p*-BrC_6H_4	22	66
13	**116m**, H , Z = $C(CO)CO_2Et$	10	57
14	**116n**, *p*-$NH_2C_6H_4$		-

Table 21. Au(III)-catalysed cycloisomerisation of cyclohexanone with tethered aryl alkyne

The cyclisation of ketones with substituted aryl alkynes proceeded very rapidly, being completed within minutes to furnish in good yields indanone derivatives. With tethered phenyl alkyne **116a** and more electron-deficient aryl alkynes **116h** and **116j**, the reaction was slower and 2 hours were required to allow complete conversion. With electron-deficient aryl alkynes, indanone derivatives **121h** and **121j** were obtained in moderate yields, respectively

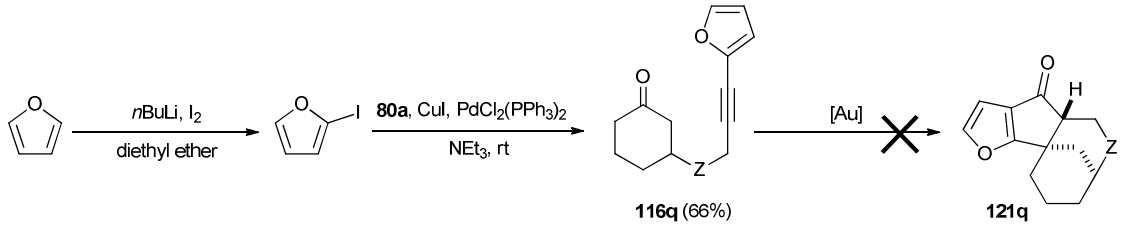
52% and 43% yield, and in the latter case, unreacted starting material was recovered (11%) alongside unknown by-products. Cyclisation precursor **116n**, which bears an unprotected amino group did not undergo cycloisomerisation, probably due to catalyst deactivation by the amine. The reaction was not affected by the position of the substituent on the ring. *Ortho*-, *meta*- and *para*- substituted aryl alkynes reacted uneventfully to afford cyclised products in similar yields (Table 21, entries 4 to 6 for example). Whilst *o*- and *p*-substituted aryl alkynes can only afford one viable regioisomer, ketones with *m*-substituted aromatic rings yielded two regioisomers (Table 21, entries 3 and 7). The replacement of malonate substituent with a β-ketoester resulted again in the formation of indanone derivative **121m** obtained as a 1.2:1 mixture of diastereoisomers, albeit in moderate yield. Side reactions might have occurred due to the presence of the free ketone (see Chapter 3 for previous discussion on the effect of the free ketone).

The preparation of polycyclic indanone derivatives bearing a heteroatom on the bis-fused ring was also examined. To this end, cyclisation precursor **116p** was prepared in very good yield by Sonogashira coupling, starting from compound **80h** which was readily available from previous synthesis. When subjected to the gold catalysis, no cyclisation occurred and the starting material was totally recovered. The lack of reactivity of cyclic ester to undergo [2+2] cycloaddition with an alkynyl partner can explain this result.



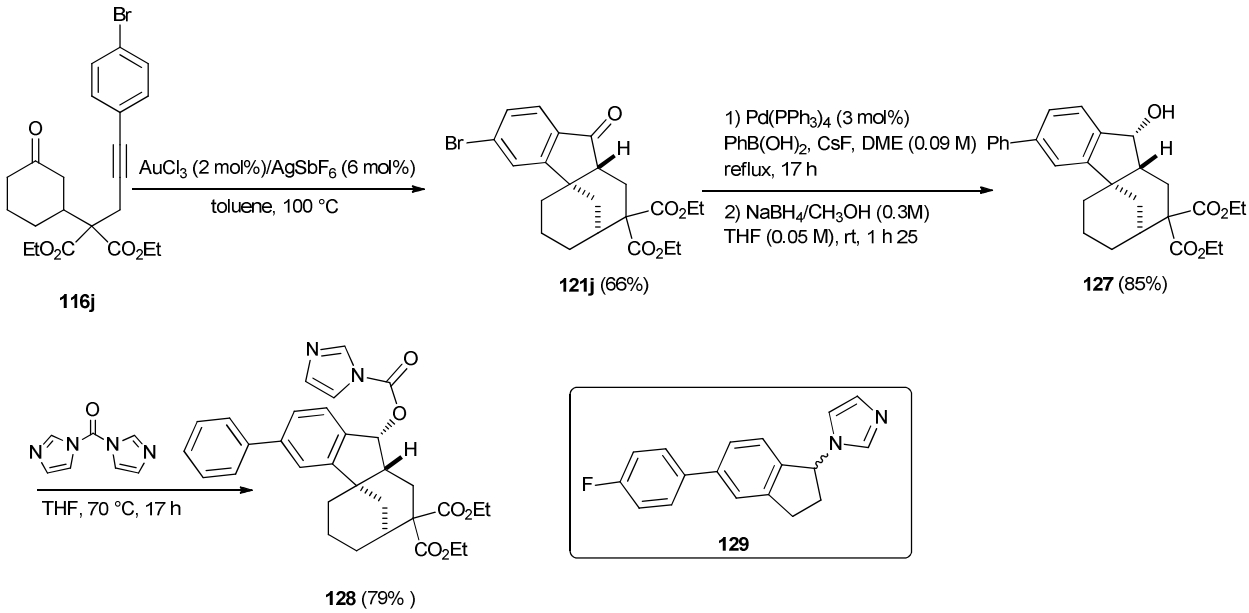
Scheme 75. Attempts to synthesise polycyclic indanone derivative containing a heteroatom

Next, the cyclisation of ketone with furanyl alkyne en route to tetracyclic heteroaromatic compound was considered. Thus, ketoalkyne **116q** was synthesised by coupling of **80a** with 2-iodofuran, according to the standard procedure. Treatment of precursor **116q** with $AuCl_3$ and $AgSbF_6$, respectively 2 and 6 mol%, did not afford cyclisation product; unreacted substrate was incompletely recovered (Scheme 76).



Scheme 76. Attempts to synthesise tetracyclic heteroaromatic compound **121q**

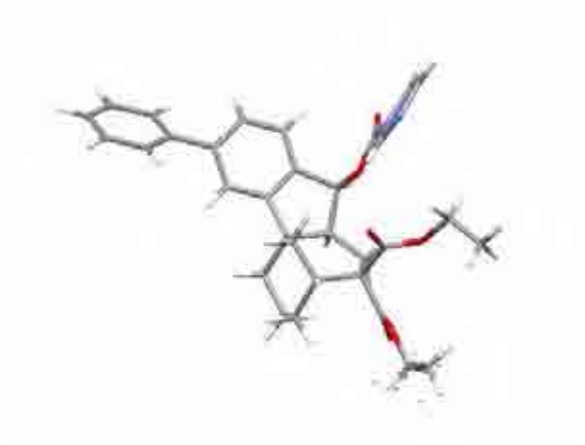
This methodology was next applied to the synthesis of indanone derivative **128**, in which the core structure is reminiscent of compound **129**, a potential P450 17 inhibitor.[107a] Starting from cyclisation precursor **116j**, in the presence of $AuCl_3/AgSbF_6$ combined catalyst, indanone derivative **116j** was diastereoselectively produced in good yield after 22 minutes, in a single synthetic manipulation. Then Pd-catalysed Suzuki-Miyaura cross coupling, followed by ketone reduction in the presence of a large excess of $NaBH_4$ provided alcohol **127** in an overall good yield of 85% (Scheme 77). X-ray crystallography of compound **128** allowed to assign a *trans* relation between the hydroxyl centre and the α-hydrogen of alcohol **127**. Unfortunately, alcohol replacement by imidazole did not take place in the presence of *N*,*N*′-carbonyldiimidazole as reported by Njar and Hartmann for similar substrates.[107a-b] Instead, *O*-alkylation took precedence and product **128** was delivered in 79% yield. We found later that the procedure described by Njar is erroneous.[107c]



Scheme 77. Attempted synthesis of an analogue of **129**

Furthermore, indanone derivative **128** was a crystalline solid and its stereochemistry was elucidated by X-ray crystallography.

Figure 9. X-ray crystallography of compound **128**



4.5 Conclusion

The cycloisomerisation of unactivated ketones with internal alkynes under gold catalysis was generally sluggish at room temperature. Ketones with tethered internal alkynes could hardly

cyclise into bis-fused frameworks, in the presence of 6 mol% of [$Ph_3PAuOTf$]. The cyclisation products were generally obtained in poor yield, through the 5-*exo-dig* mode. Intriguingly, cyclohexanone with a tethered aryl alkyne did not undergo 5-*exo-dig* cyclisation. In lieu, the formation of an unexpected tetracyclic took precedence when [$Ph_3PAuSbF_6$] was employed, while with [$Ph_3PAuOTf$] a 6-*endo-dig* ring closure took place to lead to a bicyclic compound in poor yield. With cyclohexanones bearing aryl alkynes with diverse substituents on the aromatic ring, this counterion effect (SbF_6^- *vs* OTf^-) did not occur and electron-rich aryl alkynes led exclusively to tetracyclic compounds, whereas with electron-deficient aryl alkynes *endo* products were afforded alongside unreacted starting ketoalkynes. However, in both cases the cyclised products were afforded in poor to moderate yields under optimised conditions. Ultimately, the use of $AuCl_3$ in toluene provided tetracyclic compounds in good to high yields, irrespective of the aromatic substituents.

4.6 Future work

In this thesis, we demonstrated that the direct Conia-type cyclisation of ketoalkynes can be achieved without recourse to preactivation of ketone. The use of [$Ph_3PAuOTf$], in CH_2Cl_2, at room-temperature, allowed the preparation of diverse bicyclic compounds from various ketones with tethered terminal alkynes. Generally, the cyclisation proceeded smoothly. However, the type of the ketone (cyclic or acyclic), the length of the tether linking the two functionalities and the presence of substituents at the α- or β-position could all dramatically reduce the yield of the reaction. Mechanistic studies demonstrated that the ring closure could proceed either *via* the direct attack of an incipient enol tautomer of the ketone into an electrophilic gold-alkyne complex, or through a gold-promoted alkyne hydration process and

a subsequent aldol condensation-dehydration reaction. Although the gold-catalysed alkyne hydration process was evidenced by the the presence of the diketone intermediate under the reaction conditions, the aldol condensation of this intermediate initiated by the gold catalyst could not be proven. Indeed, it was found that a "species" generated *in situ*, under the reaction conditions, was responsible for this step. This species could be TfOH, generated from [$Ph_3PAuOTf$] and traces of water. To test this hypothesis, it would be worthwhile subjecting cyclisation precursor **80a** to the gold catalyst in the presence of an acid scavenger. Monitoring of the reaction by ^1H NMR spectroscopy would establish whether or not the diketone intermediate is consumed during the reaction.

Ketones with tethered internal alkynes reacted similarly to ketones with tethered terminal alkynes and underwent 5-*exo* cyclisations, albeit in low to moderate yield. In the case of cyclohexanones with tethered electron-deficient aryl alkynes, a 6-*endo* cyclisation was observed in the presence of [$L_3PAuOTf$]. Switching to $AuCl_3$ provided substituted tetracyclic compounds, irrespective of the nature of the substituents on the aromatic ring. Further work would focus on modifying the size of the ketone ring, increasing the length of tether, and introducing an heteroatom into the tether.

Chapter 5: Experimental

5.1 Instruments

Melting points were recorded on a Kofler hot stage using open capillaries.

Elemental analysis was accomplished with a Carlo Erba EA1110 simultaneous CHNS analyser which is based on a dynamic flash combustion and G.C. separation system.

Infra red spectra were recorded on a Perkin–Elmer Paragon 1600 FTIR spectrometer. Only selected absorbencies (υ_{max}) are reported in cm^{-1}.

NMR spectra were recorded on Bruker AC300 (^{1}H = 300 MHz, ^{13}C = 75.5 MHz), Bruker AV300 (^{1}H = 300 MHz, ^{13}C = 75.5 MHz), Bruker AVIII300 (^{1}H = 300 MHz, ^{13}C = 75.5 MHz), Bruker AV400 (^{1}H = 400 MHz, ^{13}C = 101 MHz) and Bruker AVIII400 (^{1}H = 400 MHz, ^{13}C = 101 MHz) in the solvents indicated. Chemical shifts (δ) are given in ppm relative to TMS. The solvent signals were used as references and the chemical shifts converted to the TMS scale (residual $CHCl_3$ in $CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.0 ppm; residual CH_2Cl_2 in CD_2Cl_2: δ_H = 5.32 ppm, δ_C = 53.8 ppm). Coupling constants (*J*) are reported in Hz. Multiplicity is denoted in ^{1}H NMR by: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), quint (quintet, quintuplet), sex (sextet, sextuplet), sept (septet, septuplet), m (multiplet). Multiplicity is denoted in ^{13}C NMR as s, d, t, q for C, CH, CH_2, CH_3 respectively. 1D and 2D spectra were recorded using the following pulse sequences from the Bruker standard pulse program library: PENDANT, DEPT 45, DEPT 135; Gradient COSY 90; Gradient HSQC for ^{1}J(C,H) = 145 Hz; Gradient HMBC for correlations *via* ^{n}J(C,H). When given NMR signal assignments are based on COSY and HSQC and/or HMBC. The

numbering schemes are arbitrary and are shown in the inserts. GOESY experiments were used to elucidate relative stereochemistry.

EI mass spectra were recorded on either a VG ProSpec or VG Zabspec instrument at 70 eV. High resolution EI spectra were measured using perfluorokerosene (PFK) as an internal calibrant. ES spectra were performed on a Micromass LCT spectrometer using a methanol mobile phase. High resolution mass spectrometry (HRMS) was obtained using a lock-mass to adjust the calibrated mass scale. Mass spectral data are reported as *m/z* (relative intensity).

GC-MS were performed using a HP 5890 Series II apparatus.

Analytical HPLC was performed on a Dionex Summit instrument. Pump: Summit UVD 170s UV/VIS multi-channel detector with analytical flow cell; column: 5 μ Luna silica (2); 250 mm × 4.6 mm. Semi-preparative HPLC was performed on a reverse phase fitted with a Dionex P580 pump and a Dionex UVD170S detector (used at 230 nm) using a helium degassed HPLC grade acetonitrile/water isocratic, without acidic additives. Elution was monitored and spectra were recorded on Dionex Chromeleon 6.11 software.

5.2 Chemicals and reagents

Commercially available compounds were purchased from Aldrich, Fluka, Acros, Strem, Alfa Aesar and used without further purification; except for 2-cyclohexen-1-one which was purified by Kugelrohr distillation (oven temperature 90 °C, pressure 50 mBar).

Dry THF was obtained by distilling commercial solvent from sodium benzophenone ketyl, CH_2Cl_2 from calcium hydride, toluene from sodium and EtOH from magnesium turnings. Anhydrous DMF and DCE were purchased from Aldrich. TMSCl was distilled under argon

from calcium hydride. Triethylamine was distilled from NaOH pellets and stored over 4 Å molecular sieves. 2-Cyclohepten-1-one and 2-cycloocten-1-one were synthesised following a known procedure.[108] 2-Iodofuran was prepared according to a known procedure.[109] Ph_3PAuCl and $[2,4\text{-}(t\text{Bu})C_6H_3O]_3PAuCl$ were prepared according to a known procedure.[110,111] All the solutions are aqueous and saturated unless specified otherwise.

5.3 Reactions

Air-sensitive reactions were carried out in heat-gun dried glassware, under an anhydrous argon atmosphere with magnetic stirring. Freshly distilled or dried solvent was used unless specified otherwise. Evaporation and concentration under reduced pressure was performed at 10 – 600 mbar at 40 °C unless specified otherwise. Residual solvent was removed under high vacuum (< 1 mbar). Reactions were monitored by thin layer chromatography (TLC), performed on Macherey Nagel silica gel $60F_{254}$ analytical plates (plastic support) which were developed using standard visualing agents: UV fluorescence (254 and 366 nm), phosphomolybdic acid /Δ, and potassium permanganate /Δ. Flash chromatography (FC) was conducted on silica gel 60 (0.043-0.063 mm, supplied by Fluorochem). Asynt DrySin heating blocks or oil baths on stirrer hotplates were employed for reactions with temperature controlled *via* external probe.

5.4 Procedures and characterisation

General procedures (GP)

GP1: Tosylation of alcohols,[85] synthesis of **70**, **73**

Alkynyl alcohol (1.0 eq) was added to a solution of TsCl (1.0 eq), DMAP (0.25 eq) and NEt_3 (1.2 eq) in CH_2Cl_2 (0.4 M) at –10 °C. The reaction mixture was stirred between –10 °C and –5 °C over 4 h, during which time a white precipitate appeared. The mixture was filtered and the filtrate treated with NH_4Cl solution (1 × solvent volume). The layers were separated and the organic layer was washed with NH_4Cl solution (2 × volume of organic phase), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure.

GP2: Tosyl displacement by bromide,[85] synthesis of alkynyl halides **69**, **71**, **74**

LiBr (8.0 eq) was added to a solution of alkynyl tosylate (1.0 eq) in acetone (0.1 M) and the mixture was stirred at 38 °C for 24 h. Deionised water (1 × solvent volume) and pentane (1 × solvent volume) were added to the mixture. The two layers were separated and the aqueous layer was extracted with pentane (2 × volume of aqueous phase). The combined organic layers were dried over $MgSO_4$, filtered and the solvent carefully removed under reduced pressure, owing to the volatility of the synthesised alkynyl halide.

GP3: Alkylation of triethyl sodiomethanetricarboxylate,[88] synthesis of triesters **77**, **106**, **112**

Triethyl sodiomethanetricarboxylate **76** (1.0 eq) was dissolved in DMF/toluene (0.45 M, 1/1). The alkynyl halide (1.0 eq) was then added and the mixture was stirred at 80 °C for 5 h. The reaction mixture was allowed to cool to rt, before deionised water (1 × solvent volume) and toluene (1 × solvent volume) were added and the two layers separated. The organic layer was washed with deionised water (2 × volume of the organic phase), dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure to afford the alkynyl triester.

GP4: Decarbethoxylation of substituted triesters,[88] synthesis of diesters **78**, **107**, **113**

Sodium (1.2 eq) was dissolved in EtOH (1.2 eq) and the mixture was stirred at rt until consumption of the alkali metal. THF (0.55 M) was then added to this mixture and the solution was stirred for 5 min at rt before alkynyl triester (1.0 eq) was added. After 5 min (consumption of the starting material was monitored by TLC) the reaction was quenched with NH_4Cl solution (2 × solvent volume). Toluene (2 × solvent volume) was added and the two layers were separated. The organic layer was washed twice with deionised water (2 × volume of the organic phase), dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure to afford the diester.

GP5: Michael addition using a diethyl malonate reagent,[89] synthesis of ketoalkynes **80a-k**

Enone reagent (1.0 eq) and DBU (1.0 eq) were added to a solution of diethyl malonate reagent (1.0 eq) in THF (0.44 – 1.17 M). The mixture was stirred at rt for 24 h to 6 d (until completion of the reaction) before NH_4Cl solution (2 × solvent volume) was added, followed by EtOAc (2 × solvent volume). The two layers were separated. The organic layer was

washed with brine (1 × volume of the organic phase), dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. The residue was purified by flash chromatography.

GP6: Michael addition using a propargyl indium reagent,[98] synthesis of ketoalkynes **101a-b**

Propargyl bromide (3.0 eq, 80% in toluene) was added to a solution of indium powder (2.0 eq) in THF (0.33 M) at rt under an argon atmosphere. After stirring for 30 min, Me_3SiCl (5.0 eq) and enone reagent (1.0 eq) were successively added dropwise over 3 min to the reaction mixture. The reaction was then stirred for 2 h before pre-cooled deionised water (1 × solvent volume, 0 ºC) was added to quench the reaction. The aqueous layer was extracted with Et_2O (2 × volume of aqueous phase) and the combined organic layers were washed with deionised water (1 × volume of the organic phase) then with brine (1 × volume of the organic phase), before being dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography.

GP7: α-Alkylation of β-ketoesters,[89] synthesis of **91a-c**, **96a-c**

β-Ketoester (1.0 eq) was added dropwise over 2 min to a suspension of sodium hydride (1.2 eq) in DMF (0.96 M) at 0 °C. The reaction mixture was stirred at rt for 55 min before 5-iodo or 6-iodo-alkyne (1.0 eq) was added dropwise over 1 min. After the addition, the mixture was stirred at rt for 24 h before a 1 M solution of HCl (10 × solvent volume) was added followed by toluene (10 × solvent volume). The two layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. The residue was purified by flash column chromatography.

GP8: Decarbethoxylation of alkylated β-ketoesters,[89] synthesis of ketoalkynes **92a-f**

LiI (5.0 eq) was added to a solution of alkylated β-ketoester (1.0 eq) in DMF (0.76 M). The reaction mixture was stirred at 150 °C. After completion, the reaction mixture was allowed to cool to rt and quenched with a 1 M solution of HCl (10 × solvent volume). Et_2O was added (10 × solvent volume) and the two layers were separated. The aqueous layer was extracted twice with Et_2O and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and the solvent removed carefully under reduced pressure. The residue was purified by flash column chromatography.

GP9: Sonogashira coupling,[104] synthesis of ketoalkynes **116a-q**

CuI (2.5 mol%) and $PdCl_2(PPh_3)_2$ (5 mol%) were added to a solution of the ketone with the tethered terminal alkyne (1.0 eq) in NEt_3 (0.1 M reaction concentration) at rt. The reaction mixture was stirred at rt for 5 min before the aryl halide (1.2 eq) was added. The suspension was then stirred until the reaction was complete (consumption of the starting material was monitored by TLC). NH_4Cl solution (1 × solvent volume) and EtOAc (1 × solvent volume) were added and the two layers were separated. The aqueous phase was extracted with EtOAc (2 × solvent volume) and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography.

GP10: Cyclisation of ketones tethered with terminal alkynes

AgOTf (0.06 eq) was added into a dried Schlenk (or carousel tube) under an argon atmosphere, followed by the addition of the PPh_3AuCl (0.06 eq). Immediately after this addition, a 0.1 M solution of the substrate in the desired solvent was added *via* a pipette, and

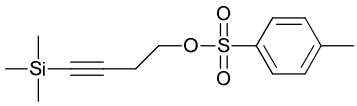
the mixture stirred at rt for the required length of time. On completion of the reaction, the solution was either loaded directly on to a silica gel column followed by elution with the appropriate eluent, or filtered through a short pad of silica gel (CH_2Cl_2, diethyl ether or hexane/ethyl acetate: 8/2), the solvent removed under reduced pressure and the residue was purified by flash column chromatography. When required the ratio of isomers was determined by NMR analysis of the crude reaction mixture.

GP11: Cyclisation of ketones tethered with internal alkynes

$AuCl_3$ (0.02 eq) was added into a dried Schlenk under an argon atmosphere, followed by the addition of the $AgSbF_6$ (0.06 eq). Immediately after this addition, a 0.2 M solution of the substrate in toluene was added *via* a syringe, and the mixture stirred at 100 °C for the desired length of time. On completion of the reaction, the solution was either loaded directly on silica gel column followed by elution with the appropriate eluent or filtered through a short pad of silica gel (CH_2Cl_2, Et_2O or hexane/EtOAc: 8/2), the solvent removed under reduced pressure, and if required, the residue was purified by flash column chromatography. The ratio of isomers was determined by NMR analysis of the crude reaction mixture.

Characterisation

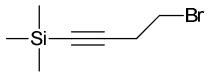
4-(Trimethylsilyl)but-3-yn-1-yl-4-methylbenzenesulfonate 68



n-BuLi (2.7 mL, 6.70 mmol, 2.50 M in hexanes) was added dropwise over 5 min to a solution of 3-butynyl-*p*-toluenesulfonate (1.0 mL, 4.51 mmol) in THF (30 mL) at –78 °C. The solution was stirred for 1 h at –78 °C before Me_3SiCl (0.86 mL, 6.70 mmol) was added. The cooling bath was removed and the solution was allowed to warm to rt. After stirring for 3 h at rt, NH_4Cl solution (5 mL) was added, followed by deionised water (15 mL). The mixture was extracted with Et_2O (3 × 15 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to afford the alkynyl silane **68** as a yellow oil (1.26 g, 95%); R_f 0.48 (hexane/EtOAc: 8/2); δ_H(300 MHz; $CDCl_3$) 0.12 (9 H, s, 3 × SiCH_3), 2.44 (3 H, s, Ar-CH_3), 2.59 (2 H, t, *J* 7.3, OCH_2CH_2), 4.07 (2 H, t, *J* 7.3, OCH_2CH_2), 7.35 (2 H, d, *J* 8.1, 2 × Ar-*H*), 7.80 (2 H, d, *J* 8.1, 2 × Ar-*H*); *m/z* (TOF ES+) 319.1 ($[M+Na]^+$, 100%).

Data were in agreement with those reported in the literature.[85]

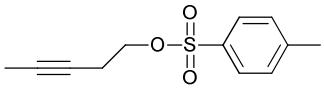
(4-Bromobut-1-yn-1-yl)trimethylsilane 69



Bromobutynyl silane **69** was prepared from LiBr (1.41 g, 16.19 mmol) and 4-trimethylsilyl butynyl tosylate **68** (0.60 g, 2.02 mmol) according to general procedure GP2. After 24 h, work-up afforded alkynyl halide **69** as yellow oil (0.26 g, 63%); R_f 0.86 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2960, 2778; δ_H(300 MHz; $CDCl_3$) 0.15 (9 H, s, 3 × SiCH_3), 2.77 (2 H, t, *J* 7.3, $BrCH_2CH_2$), 3.42 (2 H, t, *J* 7.3, $BrCH_2CH_2$); *m/z* (EI+) 191 ([M(^{81}Br)$^+$-CH_3], 100%), 189 (99), 163 (66), 161 (67), 139 (42), 137 (41), 109 (18).

Data were in agreement with those reported in the literature.[85]

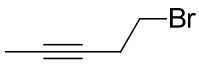
Pent-3-yn-1-yl-4-methylbenzene sulfonate 70



Tosylate **70** was synthesised from TsCl (2.45 g, 11.90 mmol) and 3-pentyn-1-ol (1.10 mL, 11.90 mmol) according to general procedure GP1. After 4 h, work-up afforded alkynyl tosylate **70** as a white solid without further purification (2.57 g, 91%); R_f 0.42 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2923, 1596 (C=C); δ_H(300 MHz; $CDCl_3$) 1.70 (3 H, t, *J* 2.2, C≡CCH_3), 2.44 (3 H, s, Ar-CH_3), 2.50-2.46 (2 H, m, OCH_2CH_2), 4.03 (2 H, t, *J* 7.3, OCH_2CH_2), 7.34 (2 H, d, *J* 8.5, 2 × Ar-*H*), 7.79 (2 H, d, *J* 8.5, 2 × Ar-*H*); δ_C(75.5 MHz; $CDCl_3$) 3.4 (q, H_3CC≡C), 19.7 (t, C≡CCH_2), 21.6 (q, Ar-CH_3), 68.2 (t, CH_2OTs), 73.1 (s, H_3CC≡C), 78.2 (s, C≡CCH_2), 127.9 (2 d, Ar-*C*H), 129.8 (2 d, Ar-*C*H), 133.0 (s, Ar-*C*), 144.8 (s, Ar-*C*); *m/z* (TOF ES+) 261.0 ([M+Na]$^+$, 100%).

Data were in agreement with those reported in the literature.[112]

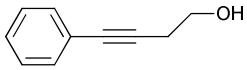
5-Bromopent-2-yne 71



5-Bromopent-2-yne **71** was synthesised from LiBr (6.70 g, 77.21 mmol) and tosylate **70** (2.30 g, 9.65 mmol) according to general procedure GP2. After 24 h, work-up and evaporation of the solvent under reduced pressure (P = 500 mBar, T= 40 °C) afforded alkynyl halide **71** as a yellow oil (1.37 g, 97%); R_f 0.58 (hexane/EtOAc: 7/3); δ_H(300 MHz; $CDCl_3$) 1.79 (3 H, t, *J* 2.6, C≡CC*H*$_3$), 2.66-2.72 (2 H, m, BrCH$_2$C*H*$_2$), 3.40 (2 H, t, *J* 7.3, BrC*H*$_2$CH$_2$); δ_C(75.5 MHz; $CDCl_3$) 3.3 (q, H$_3$*C*C≡C), 23.2 (t, C≡C*C*H$_2$), 30.1 (t, *C*H$_2$Br), 75.9 (s, H$_3$C*C*≡C), 77.7 (s, C≡*C*CH$_2$); *m/z* (EI+) 148 ([M(^{81}Br)]$^+$, 26%), 146 (29), 67 (100), 53 (20).

Data were in agreement with those reported in the literature.[113]

4-Phenylbut-3-yn-1-ol 72

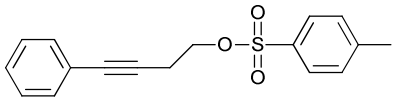


Phenyl iodide (2.2 mL, 19.81 mmol), CuI (25 mg, 0.13 mmol), $PdCl_2(PPh_3)_2$ (185 mg, 0.26 mmol) and NEt_3 (8 mL) were added to a two-neck round bottom flask. After stirring for 5 min, 3-butyn-1-ol (1.0 mL, 13.21 mmol) was added and the reaction mixture stirred at 60 °C for 5 h 45 min. The reaction mixture was then allowed to cool to rt. Et_2O (20 mL) was added, the mixture filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc: 2/1) to afford 4-phenylbut-3-yn-1-ol **72** as a brown oil (1.59 g, 82%); R_f 0.28 (hexane/EtOAc: 2/1); υ_{max}(film)/cm^{-1} 3345 (OH), 2884, 1598 (C=C), 1490 (C=C); δ_H(300 MHz; $CDCl_3$) 1.86 (1 H, t, *J* 5.1, O*H*), 2.70 (2 H, t, *J*

5.9, CH_2CH$_2$OH), 3.82 (2 H, dt, *J* 5.9 and 5.1, CH_2OH), 7.27-7.33 (3 H, m, 3 × Ar-*H*), 7.36-7.46 (2 H, m, 2 × Ar-*H*); *m/z* (EI+) 146 (M^+, 47%), 128 (10), 115 (100), 105 (6), 89 (8).

Data were in agreement with those reported in the literature.[86]

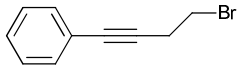
4-Phenylbut-3-yn-1-yl-4-methylbenzene sulfonate 73



Tosylate **73** was prepared from TsCl (1.55 g, 8.15 mmol) and 4-phenylbut-3-yn-1-ol **72** (1.0 mL, 8.15 mmol) according to GP1. After 4 h, work-up afforded internal alkynyl tosylate **73** as a brown oil, which was taken through into the next step without further purification (1.78 g, 73%); R_f 0.46 (hexane/EtOAc: 7/3); υ_{max}(film)/cm^{-1} 2923, 1722, 1651 (C=C), 1598 (C=C), 1572 (C=C), 1491 (C=C), 1359 (S=O), 1175 (S=O); δ_H(300 MHz; $CDCl_3$) 2.41 (3 H, s, CH_3), 2.78 (2 H, t, *J* 7.0, CH_2CH$_2$OTs), 4.18 (2 H, t, *J* 7.0, CH_2OTs), 7.27-7.34 (7 H, m, Ar-*H*), 7.82 (2 H, d, *J* 8.3, Ar-*H*); *m/z* (TOF ES+) 323.1 ([M+Na]$^+$, 100%).

Data were in agreement with those reported in the literature.[114]

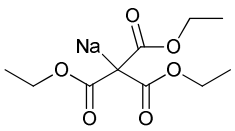
1-Phenyl-4-bromobut-1-yne 74



1-Phenyl-4-bromobut-1-yne **74** was prepared from LiBr (2.86 g, 33.02 mmol) and tosylate **73** (1.0 mL, 4.12 mmol) according to GP2. After 24 h, work-up afforded internal alkynyl halide **74** as yellow oil (0.75 g, 73%); R_f 0.78 (hexane/EtOAc: 7/3); υ_{max}(film)/cm^{-1} 2971, 1739, 1598 (C=C), 1571 (C=C), 1490 (C=C); δ_H(300 MHz; $CDCl_3$) 2.98 (2 H, t, *J* 7.3, C*H*$_2$CH$_2$Br), 3.53 (2 H, t, *J* 7.3, CH$_2$Br), 7.28-7.32 (3 H, m, Ar-*H*), 7.40-7.43 (2 H, m, Ar-*H*); *m/z* (EI+) 210 (M$^+$, 54%), 208 (55), 129 (44), 128 (73), 127 (30), 115 (100), 104 (7).

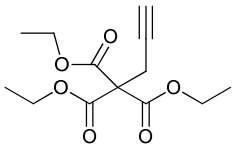
Data were in agreement with those reported in the literature.[85]

Triethyl sodiomethanetricarboxylate 76



Triethyl methanetricarboxylate (11.50 mL, 52.22 mmol) was added dropwise over 5 min to a suspension of NaH (2.38 g, 59.64 mmol, 60% dispersion in mineral oil) in THF (90 mL) at 0 °C, according to a literature procedure.[88] The reaction mixture was stirred at this temperature for 15 min, while a white precipitate appeared. This precipitate was then collected by filtration, washed with anhydrous THF and dried under reduced pressure to give the title salt **76** as a non-hygroscopic white powder (13.26 g, 96%); mp 199 °C; υ_{max}(film)/cm^{-1} 2981, 2934, 1709 (C=O), 1659 (C=O), 1635 (C=O); *m/z* (TOF ES+) 255.0 ([M+Na]$^+$, 100%).

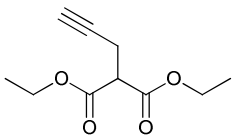
Triethyl but-3-yne-1,1,1-tricarboxylate 77



Alkynyl triester **77** was prepared from triethyl sodiomethanetricarboxylate **76** (6.00 g, 23.60 mmol) and propargyl bromide (2.5 mL, 23.60 mmol, 80% in toluene) according to GP3. After 5 h, work-up afforded **77** as an orange liquid (6.01 g, 94%); R_f 0.37 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 3284 (C≡CH), 2984, 1733 (C=O); δ_H(300 MHz; $CDCl_3$) 1.30 (9 H, t, *J* 7.1, 3 × OCH_2CH_3), 2.05 (1 H, t, *J* 2.6, C≡C*H*), 3.02 (2 H, d, *J* 2.6, $CH_2C{\equiv}CH$), 4.29 (6 H, q, *J* 7.1, 3 × OCH_2CH_3); δ_C(75.5 MHz; $CDCl_3$) 13.9 (3 q, OCH_2CH_3), 23.3 (t, $CH_2C{\equiv}CH$), 62.5 (3 t, OCH_2CH_3), 64.5 (s, $C(CO_2Et)_3$), 70.7 (d, $CH_2C{\equiv}CH$), 78.7 (s, $CH_2C{\equiv}CH$), 165.7 (3 s, CO_2Et); *m/z* (TOF ES+) 293.1 ($[M+Na]^+$, 100%).

Data were in agreement with those reported in the literature.[115]

Diethyl 2-(prop-2-yn-1-yl)malonate 78

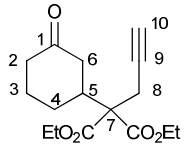


Diethyl propargylmalonate **78** was synthesised from alkynyl triester **77** (5.99 g, 22.16 mmol) according to GP4. After 5 min, work-up afforded diester **78** as an orange liquid (4.14 g, 94%). R_f 0.50 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 3287 (C≡CH), 2984, 1732 (C=O); δ_H(300 MHz; $CDCl_3$) 1.27 (6 H, t, *J* 7.1, 2 × OCH_2CH_3), 2.01 (1 H, t, *J* 2.6, C≡C*H*), 2.77 (2 H, dd, *J* 7.7 and 2.6, $CHCH_2C{\equiv}CH$), 3.55 (1 H, t, *J* 7.7, $CHCH_2C{\equiv}CH$), 4.22 (4 H, q, *J* 7.1, 2 × OCH_2CH_3); δ_C(75.5 MHz; $CDCl_3$) 14.0 (2 q, OCH_2CH_3), 18.4 (t, $CH_2C{\equiv}CH$), 51.2 (d, $CH(CO_2Et)_2$), 61.8

(2 t, O*C*H_2CH$_3$), 70.3 (d, $CH_2C{\equiv}CH$), 80.0 (s, $CH_2C{\equiv}CH$), 167.8 (2 s, *C*O_2Et); *m/z* (TOF ES+) 221.1 ([M+Na]$^+$, 100%).

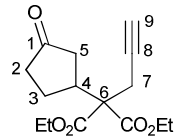
Data were in agreement with those reported in the literature.[115]

Diethyl 2-(3-oxocyclohexyl)-2-(prop-2-yn-1-yl)malonate 80a



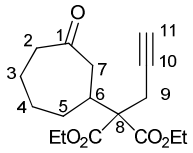
Ketoalkyne **80a** was prepared from 2-cyclohexen-1-one (1.46 mL, 15.13 mmol) and diethyl propargylmalonate **78** (3.00 g, 15.13 mmol) according to GP5. After 48 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded *alkynyl cyclohexanone* **80a** as a light yellow oil (3.43 g, 77%); R_f 0.20 (hexane/EtOAc: 8/2); (Found: C, 65.43; H, 7.81. $C_{16}H_{22}O_5$ requires C, 65.29; H, 7.53%); υ_{max} (film)/cm^{-1} 3278 (C≡CH), 2981, 2940, 2870, 1727 (C=O); δ_H(300 MHz; $CDCl_3$) 1.27 (6 H, t, *J* 7.1, 2 × CH_2CH_3), 1.36-1.52 (1 H, m, 4-H), 1.59-1.76 (1 H, m, 3-H), 2.03 (1 H, t, *J* 2.6, 10-H), 2.05-2.16 (2 H, m, 4-H and 3-H), 2.16-2.27 (1 H, m, 2-H), 2.30 (1 H, d, *J* 13.4, 6-H), 2.37-2.48 (1 H, m, 2-H), 2.53-2.63 (1 H, m, 6-H), 2.63-2.74 (1 H, m, 5-H), 2.86 (2 H, d, *J* 2.6, 8-H), 4.23 (4 H, q, *J* 7.1, 2 × C*H*$_2$CH$_3$); δ_C(75.5 MHz; $CDCl_3$) 13.9 (2 q, CH_2CH_3), 22.6 (t, 8-C), 24.5 (t, 3-C), 26.9 (t, 4-C), 40.6 (d, 5-C), 40.9 (t, 2-C), 43.4 (t, 6-C), 59.5 (s, 7-C), 61.5 (2 t, *C*H_2CH$_3$), 71.7 (d, 10-C), 78.6 (s, 9-C), 168.9 (s, 2 × *C*O_2Et), 209.8 (s, 1-C); *m/z* (TOF ES+) 317.1 ([M+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 317.1369 ([M+Na]$^+$. $C_{16}H_{22}O_5$Na requires 317.1365).

Diethyl 2-(3-oxocyclopentyl)-2-(prop-2-yn-1-yl)malonate 80b



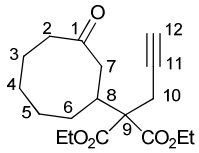
Ketoalkyne **80b** was prepared from 2-cyclopenten-1-one (0.21 mL, 2.52 mmol) and diethyl propargylmalonate **78** (0.50 g, 2.52 mmol) according to GP5. After 24 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded *alkynyl cyclopentanone* **80b** as a colourless liquid (623 mg, 88%); R_f 0.28 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 3279 (C≡CH), 2982, 2937, 2907, 1729 (C=O); δ_H(300 MHz; $CDCl_3$) 1.27 (6 H, t, *J* 7.1, 2 × CH_2CH_3), 1.62-1.80 (1 H, m, 3-H), 2.04 (1 H, t, *J* 2.4, 9-H), 2.14-2.43 (4 H, m, 2 × 2-H, 3-H and 5-H), 2.60 (1 H, dd, *J* 18.4 and 7.4, 5-H), 2.85 (1 H, dd, J_{AB} 17.4 and 2.4, 7-H), 2.93 (1 H, dd, J_{AB}, 17.4 and 2.4, 7-H), 3.00-3.15 (1 H, m, 4-H), 4.18-4.28 (4 H, m, 2 × CH_2CH_3); δ_C(75.5 MHz; $CDCl_3$) 14.0 (2 q, CH_2CH_3), 23.7 (t, 7-C), 24.9 (t, 3-C), 38.5 (t, 2-C), 39.4 (d, 4-C), 41.1 (t, 5-C), 58.8 (s, 6-C), 61.8 (2 t, CH_2CH_3), 71.8 (d, 9-C), 78.6 (s, 8-C), 169.2 (s, CO_2Et), 169.3 (s, CO_2Et), 217.3 (s, 1-C); *m/z* (TOF ES+) 303.1 ([M+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 303.1199 ([M+Na]$^+$. $C_{15}H_{20}O_5Na$: 303.1208).

Diethyl 2-(3-oxocycloheptyl)-2-(prop-2-yn-1-yl)malonate 80c



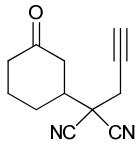
Ketoalkyne **80c** was prepared from 2-cyclohepten-1-one (266 mg, 2.42 mmol) and diethyl propargylmalonate **78** (480 mg, 2.42 mmol) according to GP5. After 10 d, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded *alkynyl cycloheptanone* **80c** as a yellow oil (418 mg, 56%); R_f 0.28 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 3277 (C≡CH), 2935, 1725 (C=O, ester), 1701 (C=O, ketone); δ_H(300 MHz; $CDCl_3$) 1.13-1.24 (1 H, m, 5-H), 1.26 (3 H, t, *J* 7.1, CH_2CH_3), 1.28 (3 H, t, *J* 7.1, CH_2CH_3), 1.45-1.60 (2 H, m, 3-H and 4-H), 1.91-2.09 (3 H, m, 3-H, 4-H, 5-H), 2.05 (1 H, t, *J* 2.7, 11-H), 2.43-2.52 (2 H, m, 2-H, 7-H), 2.60-2.76 (3 H, m, 2-H, 7-H, 6-H), 2.82 (1 H, dd, J_{AB} 17.5 and 2.7, 9-H), 2.89 (1 H, dd, J_{AB} 17.5 and 2.7, 9-H), 4.18-4.28 (4 H, m, 2 × CH_2CH_3); δ_C(75.5 MHz; $CDCl_3$) 14.0 (2 q, CH_2CH_3), 23.0 (t, 9-C), 25.1 (t, 3-C), 29.4 (t, 4-C), 32.3 (t, 5-C), 38.4 (d, 6-C), 43.1 (t, 2-C), 46.0 (t, 7-C), 60.5 (s, 8-C), 61.7 (2 t, CH_2CH_3), 71.8 (d, 11-C), 78.9 (s, 10-C), 169.2 (s, CO_2Et), 169.4 (s, CO_2Et), 212.8 (s, 1-C); *m/z* (TOF ES+) 331.1 ([M+Na]$^+$, 100%); HRMS *m/z*(TOF ES+): 331.1517 ([M+Na]$^+$. $C_{17}H_{24}O_5Na$ requires 331.1521).

Diethyl 2-(3-oxo-cyclooctyl)-2-(prop-2-yn-1-yl)malonate 80d



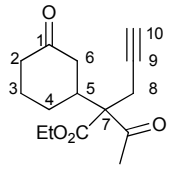
Ketoalkyne **80d** was prepared from 2-cycloocten-1-one (200 mg, 1.61 mmol) and diethyl propargylmalonate **78** (319 mg, 1.61 mmol) according to GP5. After 8 d, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded *alkynyl cyclooctanone* **80d** as a light yellow oil (218 mg, 42%); R_f 0.29 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 3277 (C≡CH), 2937, 2861, 1729 (C=O, ester), 1699 (C=O, ketone); δ_H(300 MHz; $CDCl_3$) 1.05-1.23 (1 H, m, 5-H), 1.27 (3 H, t, *J* 7.1, CH_2CH_3), 1.28 (3 H, t, *J* 7.1, CH_2CH_3), 1.32-1.49 (2 H, m, 6-H, 4-H), 1.59-1.96 (5 H, m, 6-H, 5-H, 4-H, 2 × 3-H), 2.08 (1 H, t, *J* 2.8, 12-H), 2.26-2.37 (2 H, m, 2-H, 8-H), 2.66-2.74 (1 H, m, 8-H), 2.82 (1 H, dd, J_{AB} 17.5 and 2.7, 10-H), 2.80-2.89 (1 H, m, 2-H), 2.97 (1 H, dd, J_{AB} 17.5 and 2.7, 10-H), 3.18 (1 H, tt, *J* 12.6, and 3.4, 7-H), 4.14-4.31 (4 H, m, 2 × CH_2CH_3); δ_C(75.5 MHz; $CDCl_3$) 14.0 (2 q, CH_2CH_3), 23.0 (t, 10-C), 23.8 (t, 5-C), 25.8 (t, 3-C), 28.0 (t, 4-C), 29.5 (t, 6-C), 36.5 (d, 7-C), 40.6 (t, 2-C), 46.1 (t, 8-C), 60.0 (s, 9-C), 61.7 (2 t, CH_2CH_3), 71.8 (d, 12-C), 79.0 (s, 11-C), 169.4 (s, CO_2Et), 169.8 (s, CO_2Et), 215.9 (s, 1-C); *m/z* (TOF ES+) 345.2 ([M+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 345.1690 ([M+Na]$^+$. $C_{18}H_{26}O_5Na$ requires 345.1678).

2-(3-Oxo-cyclohexyl)-2-(prop-2-yn-1-yl)malononitrile 80e



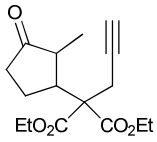
2-Cyclohexen-1-one (93 μL, 0.96 mmol) and propargyl malononitrile **83** (200 mg, 1.92 mmol) were added to a solution of NaOEt, prepared from Na (8.6 mg, 0.37 mmol) and absolute EtOH (1.2 mL). The red solution was allowed to stir for 1 h 20 min at rt, before brine (20 mL) and Et_2O (20 mL) were added. The two phases were separated and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc 7:3) to afford *ketoalkyne* **80e** as a light yellow solid (170 mg, 89%); R_f 0.23 (hexane/EtOAc: 7/3); mp 96-98 ºC; υ_{max}(film)/cm^{-1} 3246 (C≡CH), 2985, 2930, 2878, 1714(C=O); δ_H(300 MHz; $CDCl_3$), 1.63-1.84 (2 H, m), 2.19-2.39 (4 H, m), 2.40 (1 H, t, *J* 2.7), 2.45-2.60 (2 H, m), 2.63-2.74 (1 H, m), 2.92 (1 H, dd, J_{AB} 17.0 and 2.7), 3.02 (1 H, dd, J_{AB} 17.0 and 2.7); δ_C(75.5 MHz; $CDCl_3$) 23.5 (t), 26.0 (t), 26.8 (t), 40.3 (t), 41.4 (s), 42.4 (t), 42.4 (d), 73.7 (s), 75.8 (d), 113.0 (s), 113.4 (s), 206.1 (s); *m/z* (TOF ES+) 223.1 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 223.0842 ($[M+Na]^+$. $C_{12}H_{12}N_2ONa$ requires 223.0847).

Ethyl 2-acetyl-2-(3-oxo-cyclohexyl)pent-4-ynoate 80f



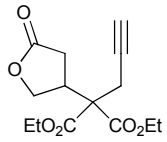
Ketoalkyne **80f** was synthesised from 2-cyclohexen-1-one (0.29 mL, 2.98 mmol) and ethyl 2-acetylpent-4-ynoate **84** (0.50 g, 2.98 mmol) according to GP5. After 24 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded *alkynyl ketone* **80f** as a colourless oil in a 1.1:1 mixture of diastereoisomers (357 mg, 45%); R_f 0.23 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 3278 (C≡CH), 2940, 1705 (C=O); δ_H(300 MHz; $CDCl_3$) 1.30 (3 H, t, *J* 7.1, CH_2CH_3 of isomer a or b), 1.31 (3 H, t, *J* 7.2, CH_2CH_3 of isomer b or a), 1.40 (1 H, dt, *J* 12.8 and 3.3, 4-H of isomer a or b), 1.43 (1 H, dt, *J* 12.8 and 3.4, 4-H of isomer b or a), 1.57-1.75 (2 H, m, 3-H, both isomers), 1.92-2.01 (2 H, m, 4-H, both isomers), 2.03 (1 H, t, *J* 2.7, 10-H of isomer a), 2.04 (1 H, t, *J* 2.7, 10-H of isomer b), 2.05-2.19 (4 H, m, 3-H, 2-H, both isomers), 2.22 (3 H, s, CH_3 of isomer a), 2.22 (3 H, s, CH_3 of isomer b), 2.27 (2 H, dd, *J* 16.8 and 11.5, 6-H, both isomers), 2.33-2.51 (4 H, m, 2-H and 6-H, both isomers), 2.62-2.77 (2 H, m, 5-H, both isomers), 2.79 (2 H, dd, *J* 4.6 and 2.7, 8-H, isomer a), 2.82 (2 H, d, *J* 2.7, 8-H, isomer b), 4.20-4.33 (4 H, m, CH_2CH_3, both isomers); δ_C(75.5 MHz; $CDCl_3$) 13.8 (2 q, CH_2CH_3), 20.9 (t, 8-C), 21.1 (t, 8-C), 24.6 (2 t, 3-C), 26.5 (t, 4-C), 27.3 (t, 4-C), 27.5 (q, CH_3), 27.8 (q, CH_3), 40.1 (d, 5-C), 40.5 (d, 5-C), 40.7 (t, 2-C), 40.9 (t, 2-C), 42.9 (t, 6-C), 43.4 (t, 6-C), 61.6 (t, CH_2CH_3), 61.7 (t, CH_2CH_3), 64.7 (s, 7-C), 64.9 (s, 7-C), 71.9 (d, 10-C), 72.0 (d, 10-C), 78.6 (s, 9-C), 79.0 (s, 9-C), 169.7 (2 s, CO_2Et), 202.0 (s, 1-C), 202.1 (s, 1-C), 209.5 (2 s, *C*OMe); *m/z* (TOF ES+) 287.1 ([M+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 287.1251 ([M+Na]$^+$. $C_{15}H_{20}O_4Na$ requires 287.1259).

Diethyl 2-(2-methyl-3-oxocyclopentyl)-2-(prop-2-yn-1-yl)malonate 80g



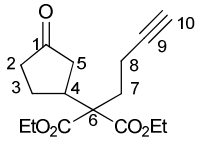
Ketoalkyne **80g** was prepared from 2-methyl-2-cyclopenten-1-one (148 µL, 1.51 mmol) and diethyl propargylmalonate **78** (0.30 g, 1.51 mmol) according to GP5. After 6 d, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded *alkynyl ketone* **80g**, as the major diastereoisomer, as a colourless oil (85.3 mg, 19%); R_f 0.27 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 3279 (C≡CH), 2980, 2936, 1737 (C=O); δ_H(300 MHz; $CDCl_3$) 1.18 (3 H, d, *J* 7.1), 1.27 (3 H, t, *J* 7.1), 1.28 (3 H, t, *J* 7.1), 1.71-1.88 (1 H, m), 2.06 (1 H, t, *J* 2.7), 2.11-2.41 (4 H, m), 2.78 (1 H, dt, *J* 9.6 and 6.3), 2.87 (1 H, dd, J_{AB} 18.7 and 2.7), 2.94 (1 H, dd, J_{AB}, 18.7 and 2.7), 4.10-4.35 (4 H, m); δ_C(75.5 MHz; $CDCl_3$) 13.9 (q), 14.0 (q), 15.7 (q), 22.8 (t), 23.8 (t), 36.4 (t), 46.2 (d), 46.5 (d), 59.2 (s), 61.7 (2 t), 71.9 (d), 79.1 (s), 169.3 (2 s), 219.6 (s); *m/z* (TOF ES+) 317.1 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 317.1368 ($[M+Na]^+$. $C_{16}H_{22}O_5Na$ requires 317.1365).

Diethyl 2-(5-oxotetrahydrofuran-3-yl)-2-(prop-2-yn-1-yl)malonate 80h



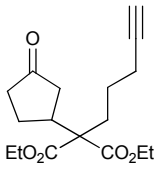
Alkynyl lactone **80h** was prepared from 2(5*H*)-furanone (173 µL, 2.44 mmol) and diethyl propargylmalonate **78** (484 mg, 2.44 mmol) according to GP5. After 7 d, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded **80h** as a colourless liquid (117 mg, 16%); R_f 0.19 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 3274 (C≡CH), 2983, 1779 (C=O, lactone), 1726 (C=O, ester); δ_H(300 MHz; $CDCl_3$) 1.27 (3 H, t, *J* 7.1, CH_2CH_3), 1.27 (3 H, t, *J* 7.1, CH_2CH_3), 2.08 (1 H, t, *J* 2.7, C≡C*H*), 2.60 (1 H, dd, J_{AB} 18.1 and 8.3, C(O)CH_2), 2.74 (1 H, dd, J_{AB} 18.1 and 9.5, C(O)CH_2), 2.81 (1 H, dd, J_{AB} 17.4 and 2.7, CH_2C≡CH), 2.90 (1 H, dd, J_{AB}, 17.4 and 2.7, CH_2C≡CH), 3.47 (1 H, dddd, *J* 9.5, 8.3, 8.3 and 7.1, C*H*), 4.18-4.31 (4 H, m, 2 × C$H_2$$CH_3$), 4.35 (1 H, dd, J_{AB} 9.8 and 7.1, OCH_2), 4.59 (1 H, dd, J_{AB} 9.8 and 8.3, OCH_2); δ_C(75.5 MHz; $CDCl_3$) 13.8 (2 q, CH_2CH_3), 23.8 (t, CH_2C≡CH), 30.3 (t, C(O)CH_2), 37.5 (d, *C*H), 57.8 (s, *C*$(CO_2Et)_2$), 62.2 (t, CH_2CH_3), 62.3 (t, CH_2CH_3), 69.3 (t, OCH_2), 72.5 (d, C≡*C*H), 77.5 (s, *C*≡CH), 168.3 (s, *C*O_2Et), 168.4 (s, *C*O_2Et), 175.6 (s, *C*O); *m/z* (TOF ES+) 305.0 ([M+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 305.1007 ([M+Na]$^+$. $C_{14}H_{18}O_6Na$ requires 305.1001).

Diethyl 2-(but-3-yn-1-yl)-2-(3-oxo-cyclopentyl)malonate 80i



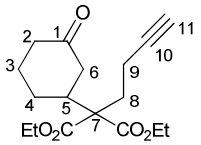
Ketoalkyne **80i** was prepared from 2-cyclopenten-1-one (0.16 mL, 1.89 mmol) and diethyl 2-(but-3-ynyl)malonate **87** (400 mg, 1.89 mmol) according to GP5. After 72 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded *alkynyl ketone* **80i** as a colourless liquid (400 mg, 72%); R_f 0.33 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 3283 (C≡CH), 2981, 2938, 1725 (C=O); δ_H(300 MHz; $CDCl_3$) 1.27 (6 H, t, *J* 7.1, 2 × CH_2CH_3), 1.62-1.79 (1 H, m, 3-H), 1.97 (1 H, t, *J* 2.4, 10-H), 2.10-2.40 (8 H, m, 2 × 7-H, 2 × 8-H, 2 × 2-H, 5-H, 3-H), 2.50 (1 H, dd, *J* 18.7 and 7.9, 5-H), 2.74-2.88 (1 H, m, 4-H), 4.21 (4 H, q, *J* 7.1, 2 × CH_2CH_3); δ_C(75.5 MHz; $CDCl_3$) 14.0 (2 q, CH_2CH_3), 14.4 (t, 7-C), 24.8 (t, 3-C), 32.7 (t, 8-C), 38.4 (t, 2-C), 40.3 (d, 4-C), 41.1 (t, 5-C), 59.3 (s, 6-C), 61.5 (2 t, CH_2CH_3), 68.9 (d, 10-C), 83.0 (s, 9-C), 169.8 (s, CO_2Et), 170.0 (s, CO_2Et), 217.2 (s, 1-C); *m/z* (TOF ES+) 317.1 ([M+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 317.1359 ([M+Na]$^+$. $C_{16}H_{22}O_5Na$ requires 317.1365).

Diethyl 2-(3-oxocyclopentyl)-2-(pent-4-yn-1-yl)malonate 80j



Ketoalkyne **80j** was synthesised from 2-cyclopenten-1-one (92.5 µL, 1.10 mmol) and diethyl 2-(pent-4-ynyl)malonate **89** (500 mg, 2.20 mmol) according to GP5. After 5 d, work-up and purification by flash column chromatography (hexane/EtOAc: 7/3) afforded *alkynyl ketone* **80j** as a colourless oil (311 mg, 91%); R_f 0.35 (hexane/EtOAc: 7/3); υ_{max}(film)/cm^{-1} 3283 (C≡CH), 2979, 1722 (C=O); δ_H(300 MHz; $CDCl_3$) 1.26 (6 H, t, *J* 7.1), 1.39-1.56 (2 H, m), 1.63-1.79 (1 H, m), 1.97 (1 H, t, *J* 2.6), 2.00-2.58 (9 H, m), 2.71-2.91 (1 H, m), 4.08-4.33 (4 H, m); δ_C(75.5 MHz; $CDCl_3$) 13.7 (2 q), 18.2 (t), 23.2 (t), 24.5 (t), 32.5 (t), 38.0 (t), 39.5 (d), 40.7 (t), 59.2 (s), 60.9 (2 t), 68.7 (d), 83.0 (s), 169.9 (s), 170.1 (s), 216.9 (s); *m/z* (TOF ES+) 331.2 ([M+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 331.1521 ([M+Na]$^+$. $C_{17}H_{24}O_5Na$ requires 331.1516).

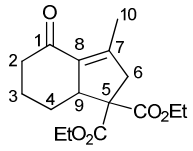
Diethyl 2-(but-3-yn-1-yl)-2-(3-oxo-cyclohexyl)malonate 80k



TBAF (1.0 mL, 1.00 mmol, 1 M in THF) was added to a solution of silyl enol ether **90**[b] (300 mg, 0.79 mmol) in THF (8.5 mL) at – 35 °C. The mixture was stirred for 40 min at this temperature, before NH_4Cl solution (25 mL) was added to quench the reaction. The aqueous phase was extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc: 8/2) to afford *ketoalkyne* **80k** as a yellow liquid (129 mg, 53%). R_f 0.21 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 3281 (C≡CH), 2937, 2870, 1715 (C=O); δ_H(300 MHz; $CDCl_3$) 1.27 (6 H, t, *J* 7.1, 2 × CH_2CH_3), 1.33-1.69 (2 H, m, 4-H), 1.96 (1 H, t, *J* 2.2, 11-H), 1.98-2.52 (11 H, m, 2 × 8-H, 2 × 9-H, 2 × 3-H, 2 × 2-H, 2 × 6-H and 5-H), 4.21 (2 H, q, *J* 7.1, CH_2CH_3), 4.22 (2 H, q, *J* 7.1, CH_2CH_3); δ_C(75.5 MHz; $CDCl_3$) 14.1 (2 q, CH_2CH_3),14.5 (t, 8-C), 24.7 (t, 3-C), 27.0 (t, 4-C), 32.5 (t, 9-C), 41.1 (t, 2-C), 42.2 (d, 5-C), 43.6 (t, 6-C), 60.2 (s, 7-C), 61.4 (2 t, CH_2CH_3), 68.8 (d, 11-C), 83.1 (s, 10-C), 169.6 (s, CO_2Et), 169.8 (s, CO_2Et), 210.0 (s, 1-C); *m/z* (TOF ES+) 331.1 ([M+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 331.1526 ([M+Na]$^+$. $C_{17}H_{24}O_5Na$ requires 331.1521).

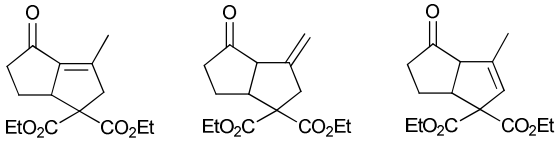
[b] see charaterisation on page 141.

Diethyl 3-methyl-4-oxo2,4,5,6,7,7a-hexahydroindene-1,1-dicarboxylate 81a



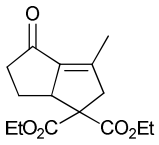
Ketoalkyne **80a** (117 mg, 0.40 mmol) was reacted with with Ph_3PAuCl/AgOTf (11.9 mg/6.2 mg, 0.024 mmol) in CH_2Cl_2 according to GP10. After 24 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) provided *enone* **81a** as a yellow oil (102 mg, 87%); R_f 0.33 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2981, 2942, 2871, 1731 (C=O, ester), 1682 (C=O, enone), 1626 (C=C); δ_H(300 MHz; $CDCl_3$) 1.07-1.14 (1 H, m, 4-H), 1.20 (6 H, t, *J* 7.1, 2 × CH_2CH_3), 1.61-1.81 (1 H, m, 3-H), 1.91-2.00 (1 H, m, 3-H), 2.03 (3 H, s, 10-H), 2.05-2.19 (2 H, m, 4-H, 2-H), 2.31-2.44 (1 H, m, 2-H), 2.70 (1 H, br d, J_{AB} 18.3, 6-H), 3.04 (1 H, br d, J_{AB} 18.3, 6-H), 3.59-3.73 (1 H, m, 9-H), 4.02-4.28 (4 H, m, 2 × CH_2CH_3); δ_C(75.5 MHz; $CDCl_3$) 13.9 (q, CH_2CH_3), 14.0 (q, CH_2CH_3), 15.5 (q, 10-C), 23.4 (t, 3-C), 27.4 (t, 4-C), 40.5 (t, 2-C), 46.0 (t, 6-C), 51.6 (d, 9-C), 61.2 (t, CH_2CH_3), 61.3 (t, CH_2CH_3), 61.8 (s, 5-C), 131.9 (s, 7-C), 149.3 (s, 8-C), 170.1 (s, CO_2Et), 171.0 (s, CO_2Et), 199.1 (s, 1-C); *m/z* (TOF ES+) 317.1 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 317.1362 ($[M+Na]^+$. $C_{16}H_{22}O_5Na$ requires 317.1365).

Diethyl 3-methyl-4-oxo-4,5,6,6a-tetrahydropentalene-1,1 (*2H*)-dicarboxylate, diethyl 3-methylene-4-oxohexahydropentalene-1,1(*2H*)-dicarboxylate and diethyl 3-methyl-4-oxo-4,5,6,6a-tetrahydropentalene-1,1(3a*H*)-dicarboxylate 81b



Ketoalkyne **80b** (112 mg, 0.40 mmol) was reacted with Ph_3PAuCl/AgOTf (11.9 mg/6.2 mg, 0.024 mmol) in CH_2Cl_2 according to GP10. After 24 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) provided isomers **81ba**, **81bb** and **81bc** in a 3.8:2.1:1 ratio as a light yellow oil (111 mg, 99%); R_f 0.36 (hexane/EtOAc: 8/2); HRMS *m/z* (TOF ES+) 303.1202 ($[M+Na]^+$. $C_{15}H_{20}O_5Na$ requires 303.1208). These isomers were inseparable by flash column chromatography. Analytically pure samples of each isomer were obtained by preparative HPLC (t = 0 → 40 min, MeCN/H_2O 40:60).

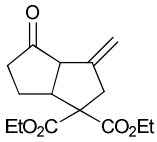
Diethyl 3-methyl-4-oxo-4,5,6,6a-tetrahydropentalene-1,1 (*2H*)-dicarboxylate 81ba



Isomer **81ba**: HPLC: t_R = 25.7 min; υ_{max}(film)/cm^{-1} 2931, 1728 (C=O, ester), 1713 (C=O, ketone), 1665 (C=C); δ_H(300 MHz; $CDCl_3$) 1.25 (3 H, t, *J* 7.1, CH_2CH_3), 1.26 (3 H, t, *J* 7.1, CH_2CH_3), 1.23-1.46 (2 H, m, CH_2), 2.04 (3 H, s, CH_3), 2.13-2.27 (1 H, m, C*H*), 2.39-2.54 (2 H, m, CH_2), 3.07 (1 H, br d, J_{AB} 18.3, H_2CC=C), 3.41 (1 H, br d, J_{AB} 18.3, H_2CC=C), 4.08-4.34 (4 H, m, CH_2CH_3); δ_C(75.5 MHz; $CDCl_3$) 14.1 (q, CH_2CH_3), 14.2 (q, CH_2CH_3), 14.6 (q, CH_3), 26.1 (t, CH_2), 43.8 (t, CH_2), 50.7 (t, H_2CC=C), 53.8 (d, *C*H), 61.5 (t, CH_2CH_3), 61.7 (t,

CH_2CH_3), 62.6 (s, *C*($CO_2Et)_2$), 137.3 (s, C=*C*CH_3), 146.1 (s, *C*=CCH_3), 169.8 (s, CO_2Et), 171.0 (s, CO_2Et), 201.0 (s, *C*O); *m/z* (TOF ES+) 303.0 ($[M+Na]^+$, 100%).

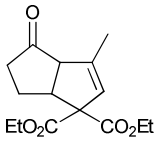
Diethyl 3- methylene-4-oxohexahydropentalene-1,1(*2H*)-dicarboxylate 81bb



Isomer **81bb**: HPLC: t_R = 28.5 min; υ_{max}(film)/cm^{-1} 2981, 1726 (C=O); δ_H(300 MHz; $CDCl_3$) 1.19-1.28 (6 H, m), 1.37-1.67 (2 H, m), 2.12-2.39 (2 H, m), 2.79 (1 H, d, *J* 17.6), 3.20 (1 H, ddd, *J* 17.6, 5.5, 2.7), 3.26-3.35 (2 H, m), 4.03-4.28 (4 H, m), 5.06 (1 H, br d, *J* 1.6), 5.17 (1 H, td, *J* 2.7, 1.6); δ_C(75.5 MHz; $CDCl_3$) 13.9 (q), 14.1 (q), 23.1 (t), 38.2 (t), 38.3 (t), 46.9 (d), 56.6 (d), 61.5 (t), 61.6 (t), 62.5 (s), 111.3 (t), 142.9 (s), 169.2 (s), 171.2 (s), 215.2 (s); *m/z* (TOF ES+) 303.0 ($[M+Na]^+$, 100%).

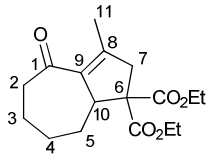
Data were in agreement with those reported in the literature.[24b]

Diethyl 3-methyl-4-oxo-4,5,6,6a-tetrahydropentalene-1,1(3a*H*)-dicarboxylate 81bc



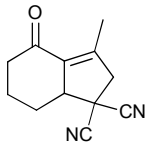
Isomer **81bc**: HPLC: t_R = 28.5 min; υ_{max}(film)/cm^{-1} 2981, 1726 (C=O); δ_H(300 MHz; $CDCl_3$) 1.19-1.28 (6 H, m), 1.79 (3 H, s), 1.96-2.10 (2 H, m), 2.12-2.39 (2 H, m), 3.39 (1 H, dt, *J* 10.1, 7.7), 3.62 (1 H, dt, *J* 10.1, 7.7), 4.03-4.28 (4 H, m), 5.51 (1 H, m); δ_C(75.5 MHz; $CDCl_3$) 13.9 (q), 14.1 (q), 14.6 (q), 23.8 (t), 38.4 (t), 44.7 (d), 61.2 (s), 61.3 (d), 61.5 (t), 61.6 (t), 124.3 (d), 142.0 (s), 169.5 (s), 170.0 (s), 215.2 (s); *m/z* (TOF ES+) 303.0 ($[M+Na]^+$, 100%).

Diethyl 3-methyl-4-oxo-4,5,6,7,8,8a-hexahydroazulene-1,1(2*H*)-dicarboxylate 81c



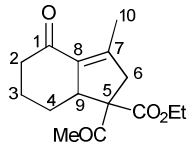
Ketoalkyne **80c** (134 mg, 0.40 mmol) was reacted with Ph_3PAuCl/AgOTf (11.9 mg/6.2 mg, 0.024 mmol) in CH_2Cl_2 according to GP10. After 24 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) provided *enone* **81c** as a yellow oil (86 mg, 64%); R_f 0.39 (hexane/EtOAc: 8/2); υ_{max} (film)/cm^{-1} 2929, 1729 (C=O, ester), 1675 (C=O, ketone), 1618 (C=C); δ_H(300 MHz; $CDCl_3$) 1.24 (3 H, t, *J* 7.1, CH_2CH_3), 1.25 (3 H, t, *J* 7.1, CH_2CH_3), 1.28-1.47 (2 H, m, 5-H, 3-H), 1.46-1.67 (1 H, m, 4-H), 1.76-2.01 (3 H, m, 5-H, 4-H, 3-H), 2.03-2.08 (3 H, m, 11-H), 2.44-2.62 (2 H, m, 2-H), 2.79 (1 H, dq, J_{AB} 18.7 and 1.4, 7-H), 3.32 (1 H, dq, J_{AB} 18.7 and 1.4, 7-H), 3.72 (1 H, br d, *J* 11.9, 10-H), 4.08-4.29 (4 H, m, 2 × CH_2CH_3); δ_C(75.5 MHz; $CDCl_3$) 13.9 (q, CH_2CH_3), 14.0 (q, CH_2CH_3), 16.2 (q, 11-C), 24.6 (t, 3-C), 30.4 (t, 4-C), 31.6 (t, 5-C), 45.3 (2 t, 2-C and 7-C), 51.4 (d, 10-C), 61.4 (t, CH_2CH_3), 61.6 (t, CH_2CH_3), 62.7 (s, 6-C), 137.2 (s, 8-C), 150.8 (s, 9-C), 169.7 (s, CO_2Et), 171.2 (s, CO_2Et), 201.5 (s, 1-C); *m/z* (TOF ES+) 331.1 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 331.1042 ($[M+Na]^+$. $C_{17}H_{24}O_5Na$ requires 331.1029).

3-methyl-4-oxo-5,6,7,7a-tetrahyhydro-1*H*-indene-1,1 (2*H*,4*H*)-dicarbonitrile 81e



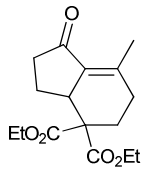
Ketoalkyne **80e** (80 mg, 0.40 mmol) was reacted with with $Ph_3PAuCl/AgOTf$ (11.9 mg/6.2 mg, 0.024 mmol) in CH_2Cl_2 according to GP10. After 34 h, work-up and purification by flash column chromatography (hexane/Et_2O: 7/3) provided enone **81e** as a white solid (65 mg, 81%); R_f 0.12 (hexane/Et_2O: 7/3); mp 80-82 ºC; υ_{max}(film)/cm^{-1} 2964, 2872, 2254 (C≡N), 1681 (C=O), 1623 (C=C); δ_H(300 MHz; $CDCl_3$) 1.71-1.94 (2 H, m), 2.14-2.21 (3 H, m), 2.21-2.39 (3 H, m), 2.50-2.62 (1 H, m), 3.12 (1 H, br d, *J* 17.4), 3.24 (1 H, br d, *J* 17.4), 3.43-3.53 (1 H, m); δ_C(75.5 MHz; $CDCl_3$) 15.8 (q), 22.1 (t), 26.8 (t), 38.2 (s), 40.2 (t), 48.5 (t), 54.7 (d), 114.4 (s), 115.0 (s), 130.8 (s), 148.3 (s), 196.8 (s); *m/z* (EI+) 200.1 (92%), 185.1 (28), 171.1(38), 157.1 (51), 145.1 (100), 130.1 (20), 104.1 (18); HRMS *m/z* (EI+) 200.0954 (M^+. $C_{12}H_{12}N_2O$: requires 200.0949).

Ethyl 1-acetyl-3-methyl-4-oxo-2,4,5,6,7,7a-hexahydro-1*H*-indene-1-carboxylate 81f



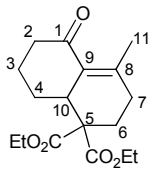
Ketoalkyne **80f** (106 mg, 0.40 mmol) was reacted with Ph_3PAuCl/AgOTf (11.9 mg/6.2 mg, 0.024 mmol) in CH_2Cl_2 according to GP10. After 15 h, work-up and purification by flash column chromatography (hexane/Et_2O: 6/4) afforded *diastereoisomers* **81fa** and **81fb** in 1.9:1 ratio as a pale yellow oil (47 mg, 44%); data for the mixture unless specified otherwise: R_f 0.18 (hexane/Et_2O: 6/4); υ_{max}(film)/cm^{-1} 2941, 1709 (C=O, ester), 1682 (C=O, ketone), 1623 (C=C); δ_H(300 MHz; $CDCl_3$) minor diastereoisomer 1.09-1.25 (1 H, m, 4-H), 1.28 (3 H, t, *J* 7.1, CH_2CH_3), 1.67-1.87 (1 H, m, 3-H), 1.95-2.28 (6 H, m, 3-H, 4-H, 2-H, $COCH_3$), 2.18 (3 H, s, 10-H), 2.40-2.51 (1 H, m, 2-H), 2.60 (1 H, br d, J_{AB} 18.3, 6-H), 3.12 (1 H, br d, J_{AB} 18.3, 6-H), 3.66-3.83 (1 H, m, 9-H), 4.14-4.31 (2 H, m, CH_2CH_3); δ_H(300 MHz; $CDCl_3$) major diastereoisomer 1.09-1.25 (1 H, m, 4-H), 1.29 (3 H, t, *J* 7.1, CH_2CH_3), 1.67-1.87 (1 H, m, 3-H), 1.95-2.28 (6 H, m, 3-H, 4-H, 2-H, $COCH_3$), 2.17 (3 H, s, 10-H), 2.40-2.51 (1 H, m, 2-H), 2.73 (1 H, br d, J_{AB} 18.4, 6-H), 3.0.2 (1 H, br d, J_{AB} 18.4, 6-H), 3.66-3.83 (1 H, m, 9-H), 4.14-4.31 (2 H, m, CH_2CH_3); δ_C(75.5 MHz; $CDCl_3$) minor diastereoisomer: 14.1 (q, CH_2CH_3), 15.7 (q, $COCH_3$), 23.5 (t, 3-C), 27.2 (q, 10-C), 27.6 (t, 4-C), 40.6 (t, 2-C), 45.1 (t, 6-C), 49.6 (d, 9-C), 61.4 (t, CH_2CH_3), 68.4 (s, 5-C), 132.4 (s, 7-C), 147.8 (s, 8-C), 170.8 (s, CO_2Et), 199.3 (s, 1-C), 202.0 (s, *C*OMe); major diastereoisomer: 14.0 (q, CH_2CH_3), 15.7 (q, $COCH_3$), 23.7 (t, 3-C), 27.1 (t, 4-C), 28.6 (q, 10-C), 40.5 (t, 2-C), 45.3 (t, 6-C), 51.8 (d, 9-C), 61.6 (t, CH_2CH_3), 67.5 (s, 5-C), 131.7 (s, 7-C), 149.9 (s, 8-C), 172.5 (s, CO_2Et), 199.0 (s, 1-C), 203.0 (s, *C*OMe); *m/z* (TOF ES+) 287.1 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 287.1246 ($[M+Na]^+$. $C_{15}H_{20}O_4Na$ requires 287.1259).

Diethyl 7-methyl-1-oxo-3,3a,5,6-tetrahydro-1*H*-indene-4,4(2*H*)-dicarboxylate 81i



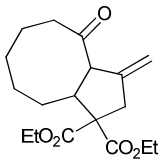
Ketoalkyne **80i** (117 mg, 0.40 mmol) was reacted with Ph_3PAuCl/AgOTf (11.9 mg/6.2 mg, 0.024 mmol) in CH_2Cl_2 according to GP10. After 17 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded *enone* **81i** as a light yellow liquid (93 mg, 79%); R_f 0.33 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2981, 1726 (C=O, ester), 1710 (C=O, ketone), 1643 (C=C); δ_H(300 MHz; $CDCl_3$) 1.22 (3 H, t, *J* 7.1), 1.28 (3 H, t, *J* 7.1), 1.86-2.10 (2 H, m), 2.10-2.17 (3 H, m), 2.17-2.50 (6 H, m), 3.01-3.13 (1 H, m), 4.15 (2 H, q, *J* 7.1), 4.24 (2 H, qd, *J* 7.1 and 1.7); δ_C(75.5 MHz; $CDCl_3$) 13.9 (q), 14.0 (q), 18.2 (q), 22.8 (t), 29.4 (t), 31.3 (t), 38.5 (t), 43.8 (d), 55.2 (s), 60.7 (t), 61.3 (t), 129.2 (s), 146.5 (s), 169.1 (s), 171.3 (s), 205.9 (s); *m/z* (TOF ES+) 294.1 ($[M+Na]^+$, 100%); HRMS *m/z* (EI+) 294.1461 (M^+. $C_{16}H_{22}O_5$ requires 294.1467).

Diethyl 4-methyl-5-oxo-2,3,6,7,8,8a-hexahydronaphthalene-1,1(5*H*)-dicarboxylate 81k



Ketoalkyne **80k** (115 mg, 0.37 mmol) was reacted with Ph_3PAuCl/AgOTf (11.9 mg/6.2 mg, 0.024 mmol) in CH_2Cl_2 according to GP10. After 22 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded *enone* **81k** as a light yellow oil (70 mg, 61%); R_f 0.25 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2940, 2872, 1732 (C=O, ester), 1694 (C=O, ketone), 1632 (C=C); δ_H(300 MHz; $CDCl_3$) 1.19-1.29 (6 H, m, 2 × CH_2CH_3), 1.59-1.73 (2 H, m, 4-H), 1.73-1.94 (1 H, m, 3-H), 1.87-1.92 (3 H, m, 11-H), 1.92-2.20 (5 H, m, 3-H, 2 × 6-H, 2 × 7-H), 2.32 (1 H, ddd, *J* 15.8, 9.8, and 6.1, 2-H), 2.53 (1 H, dt, *J* 15.8 and 5.4, 2-H), 3.02-3.12 (1 H, m, 10-H), 4.07-4.29 (4 H, m, 2 × CH_2CH_3); δ_C(75.5 MHz; $CDCl_3$) 13.9 (2 q, CH_2CH_3), 20.7 (q, 11-C), 22.0 (t, 3-C), 24.9 (t, 6 or 7-C), 26.8 (t, 4-C), 30.2 (t, 6 or 7-C), 40.3 (d, 10-C), 41.2 (s, 5-C), 56.6 (t, 2-C), 61.0 (t, CH_2CH_3), 61.3 (t, CH_2CH_3), 132.0 (s, 8-C), 140.3 (s, 9-C), 170.0 (s, CO_2Et), 170.4 (s, CO_2Et), 203.1 (s, 1-C); *m/z* (TOF ES+) 331.2 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 331.1518 ($[M+Na]^+$. $C_{17}H_{24}O_5Na$ requires 331.1521).

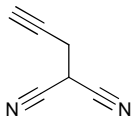
Diethyl 2-oxo-11-methylene-bicyclo[6.3.0]undecane-9,9-dicarboxylate 82d



Ketoalkyne **80d** (77 mg, 0.24 mmol) was reacted with Ph_3PAuCl/AgOTf (7.1 mg/3.7 mg, 0.014 mmol) in CH_2Cl_2 according to GP10. After 48 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded exomethylene compound **82d** as the major constituent (20 mg, 26%). A number of mixture fractions were collected including recovered starting material (13 mg, 17%); R_f 0.41 (hexane/EtOAc: 8/2); δ_H(300 MHz; $CDCl_3$) 1.12-1.21 (1 H, m), 1.26 (3 H, t, *J* 7.1), 1.27 (3 H, t, *J* 7.1), 1.31-1.54 (2 H, m), 1.62-2.08 (5 H, m), 2.22-2.37 (1 H, m), 2.58-2.70 (1 H, m), 2.73-2.85 (1 H, m), 3.06 (1 H, dt, *J* 12.6 and 3.3), 3.21 (1 H, br d, *J* 17.4), 3.36 (1 H, dd, *J* 12.9 and 1.9), 4.06-4.32 (4 H, m), 4.76 (1 H, dd, J_{AB} 5.0, 2.4), 5.00 (1 H, dd, J_{AB} 4.8, 2.4); *m/z* (TOF ES+) 345.2 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 345.1676 ($[M+Na]^+$. $C_{18}H_{26}O_5Na$ requires 345.1678).

Data were in agreement with those reported in the literature.[24b]

2-Prop-2-yn-1-yl)malononitrile 83

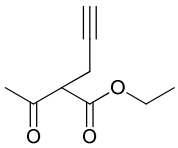


Malononitrile (2.00 g, 30.27 mmol), $NaHCO_3$ (2.54 g, 30.27 mmol) and TBAB (195 mg, 0.60 mmol) were stirred at 60 °C for 30 min, before propargyl bromide (1.7 mL, 15.14 mmol, 80% in toluene) was added. The reaction mixture was then stirred at this temperature overnight. NH_4Cl solution (20 mL) and CH_2Cl_2 (20 mL) were added and the layers separated. The

aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine (40 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (hexane/Et_2O: 6/4) afforded **83** as a yellow liquid (355 mg, 23%); R_f 0.31 (hexane/Et_2O: 6/4); υ_{max}(film)/cm^{-1} 3300 (C≡CH), 2983, 2924, 2263 (C≡N); δ_H(300 MHz; $CDCl_3$) 2.39 (1 H, t, *J* 2.6, C≡C*H*), 2.94 (2 H, dd, *J* 6.6 and 2.6, CH_2C≡CH), 3.96 (1 H, t, *J* 6.6, C*H*$(CN)_2$); δ_C(75.5 MHz; $CDCl_3$) 21.7 (t, *C*H_2C≡CH), 22.9 (d, *C*H$(CN)_2$), 74.8 (d, C≡*C*H), 75.0 (s, *C*≡CH), 111.5 (2 s, *C*N); *m/z* (EI+) 104 (M^+, 100%), 76 (43%), 65 (7), 50 (53).

Data were in agreement with those reported in the literature.[91]

Ethyl 2-acetylpent-4-ynoate 84

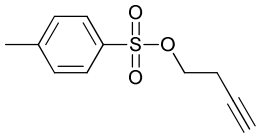


Ethyl acetoacetate (4.9 mL, 38.4 mmol) was added dropwise over 15 min to a suspension of NaH (1.53 g, 38.4 mmol, 60% dispersion in mineral oil) in THF (70 mL) at 0 °C. After the addition was completed, the mixture was allowed to warm to rt for 30 min. Propargyl bromide (4.3 mL, 38.4 mmol, 80 % in toluene) was then added dropwise over 4 h. The solution was stirred at rt overnight. H_2O (50 mL) and EtOAc (50 mL) were added and the layers separated. The aqueous phase was extracted with EtOAc (2 × 50 mL) and the combined organic extracts were washed with NH_4Cl solution (50 mL), brine (50 mL), dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. Reduced pressure distillation (kugelrohr, 1 mbar, 50-60 °C) afforded compound **84** as a colourless liquid (1.82 g, 26%, 94% pure as ^{1}H NMR shows the presence of 6% of dialkylated product); R_f 0.47 (hexane/EtOAc: 8/2);

υ_{max}(film)/cm^{-1} 3287 (C≡CH), 3003, 2945, 1737 (C=O, ester), 1722 (C=O, ketone); δ_H(300 MHz; $CDCl_3$) 1.26 (3 H, t, *J* 7.1, OCH_2CH_3), 1.98 (1 H, t, *J* 2.7, C≡C*H*), 2.28 (3 H, s, CH_3), 2.64-2.72 (2 H, m, $CHCH_2C{\equiv}CH$), 3.67 (1 H, t, *J* 7.5, $CHCH_2C{\equiv}CH$), 4.20 (2 H, q, *J* 7.1, OCH_2CH_3); δ_C(75.5 MHz; $CDCl_3$) 14.0 (q, OCH_2CH_3), 17.3 (t, $CH_2C{\equiv}CH$), 29.4 (q, CH_3), 58.1 (d, $CH(CO_2Et)$), 61.7 (t, OCH_2CH_3), 70.2 (d, C≡*C*H), 80.3 (s, *C*≡CH), 168.0 (s, CO_2Et), 201.0 (CO); *m/z* (EI+) 168 (M^+, 10%), 139 (11), 126 (100), 97 (35), 79 (12), 70 (27).

Data were in agreement with those reported in the literature.[93]

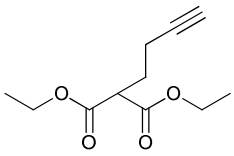
But-3-yn-1-yl 4-methylbenzenesulfonate 86



But-3-ynyl 4-methylbenzenesulfonate **86** was prepared from TsCl (2.72 g, 14.26 mmol) and 3-butyn-1-ol (1.0 mL, 14.26 mmol) according to GP1. After 4 h, work-up afforded compound **86** as a light yellow liquid, which was taken through into the next step with no further purification (2.83 g, 88%); R_f 0.33 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 3291 (C≡CH), 2962, 2924, 1598 (C=C), 1360 (S=O), 1190 (S=O); δ_H(300 MHz; $CDCl_3$) 1.97 (1 H, t, *J* 2.7, $CH_2C{\equiv}CH$), 2.45 (3 H, br s, CH_3), 2.56 (2 H, td, *J* 7.1 and 2.7, $CH_2C{\equiv}CH$), 4.10 (2 H, t, *J* 7.1, $CH_2CH_2C{\equiv}CH$), 7.36 (2 H, d, *J* 8.1, Ar-*H*), 7.81 (2 H, d, *J* 8.1, Ar-*H*); δ_C(75.5 MHz; $CDCl_3$) 19.4 (t, $CH_2C{\equiv}CH$), 21.6 (q, CH_3), 67.4 (t, $CH_2CH_2C{\equiv}CH$), 70.7 (d, $CH_2C{\equiv}CH$), 78.3 (s, $CH_2C{\equiv}CH$), 127.9 (2 d, Ar-*C*H), 129.9 (2 d, Ar-*C*H), 132.8 (s, Ar-*C*), 145.0 (s, Ar-*C*); *m/z* (TOF ES+) 247.1 ($[M+Na]^+$, 100%).

Data were in agreement with those reported in the literature.[95]

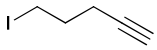
Diethyl 2-(but-3-yn-1-yl)malonate 87



Diethyl malonate (0.88 mL, 5.80 mmol) was added to a suspension of NaH (107 mg, 4.46 mmol, 60% dispersion in mineral oil) in DMF (5 mL) at 0 °C. After the evolution of H_2 was complete, but-3-ynyl 4-methylbenzenesulfonate (1.00 g, 4.46 mmol) was added and the reaction mixture stirred for 24 h at 80 °C. The solution was allowed to cool to rt, before NH_4Cl solution (15 mL) was added followed by the addition of EtOAc (15 mL). The two layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. Flash column chromatography (hexane/Et_2O 8/2) afforded compound **87** as a colourless liquid (624 mg, 66%); R_f 0.31 (hexane/ Et_2O: 8/2); υ_{max}(film)/cm^{-1} 3448, 3289 (C≡CH), 2983, 2940, 1731 (C=O); δ_H(300 MHz; $CDCl_3$) 1.27 (6 H, t, *J* 7.1, 2 × OCH_2CH_3), 2.00 (1 H, t, *J* 2.6, C≡C*H*), 2.08-2.19 (2 H, m, $CH_2CH_2C{\equiv}CH$), 2.30 (2 H, td, *J* 6.7 and 2.6, $CH_2C{\equiv}CH$), 3.57 (1 H, t, *J* 7.4, $CHCH_2CH_2C{\equiv}CH$), 4.20 (2 H, q, *J* 7.1, OCH_2CH_3), 4.21 (2 H, q, *J* 7.1, OCH_2CH_3); δ_C(75.5 MHz; $CDCl_3$) 14.0 (2 q, OCH_2CH_3), 16.3 (t), 27.3 (t), 50.5 (d, $CHCH_2CH_2C{\equiv}CH$), 61.4 (2 t, OCH_2CH_3), 69.6 (d, C≡CH), 82.4 (s, C≡CH), 168.9 (2 s, CO_2Et); *m/z* (TOF ES+) 235.1 ($[M+Na]^+$, 100%).

Data were in agreement with those reported in the literature.[116]

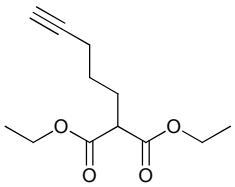
5-Iodopent-1-yne 88



5-Chloropent-1-yne (2.0 mL, 18.87 mmol) was added to a suspension of NaI (11.57 g, 77.19 mmol) in methyl ethyl ketone (65 mL) at rt. The reaction mixture was then stirred for 24 h at reflux. The solution was allowed to cool to rt before H_2O (60 mL) and Et_2O (60 mL) were added. The two layers were separated and the aqueous phase was extracted with Et_2O (60 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and the solvent carefully removed under reduced pressure to afford 5-iodopent-1-yne as a strongly odoured light orange liquid (2.76 g, 75%); R_f 0.92 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 3298 (C≡CH), 2923, 2853; δ_H(300 MHz; $CDCl_3$) 1.99 (1 H, t, *J* 2.7, C≡C*H*), 2.01 (2 H, quint, *J* 6.8, CH_2CH_2C≡CH), 2.35 (2 H, dt, *J* 6.8 and 2.7, CH_2C≡CH), 3.32 (2 H, t, *J* 6.8, ICH_2CH_2); δ_C(75.5 MHz; $CDCl_3$) 5.1 (t, I*C*H_2), 19.4 (t, ICH$_2$*C*H$_2$), 31.8 (t, ICH$_2$CH$_2$*C*H$_2$), 69.4 (d, C≡*C*H), 82.2 (s, *C*≡CH); *m/z* (EI+) 194 (M^+, 41%), 155 (7), 127 (5), 67 (100), 51 (4).

Data were in agreement with those reported in the literature.[96]

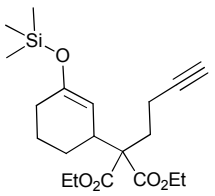
Diethyl 2-(pent-4-yn-1-yl) malonate 89



Diethyl malonate (0.78 mL, 5.16 mmol) was added to a suspension of NaH (222 mg, 5.55 mmol, 60% dispersion in mineral oil) in DMF (4 mL) at 0 °C. After the evolution of H_2 was complete, 5-iodopent-1-yne (1.16 g, 5.98 mmol) was added and the reaction mixture stirred for 24 h at 80 °C. The solution was allowed to cool to rt, before NH_4Cl solution (20 mL) was added followed by the addition of EtOAc (20 mL). The two layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to afford **90** as a light yellow liquid (1.16 g, 99%); which was taken through into the next step with no further purification; R_f 0.39 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 3288 (C≡CH), 2937, 2872, 1737 (C=O); δ_H(300 MHz; $CDCl_3$) 1.27 (3 H, t, *J* 7.1, OCH_2CH_3), 1.28 (3 H, t, *J* 7.1, OCH_2CH_3), 1.51-1.63 (2 H, m), 1.96 (1 H, t, *J* 2.6, C≡C*H*), 1.94-2.06 (2 H, m), 2.23 (2 H, td, *J* 7.0 and 2.6, CH_2C≡CH), 3.31-3.38 (1 H, m, $CHCH_2$), 4.20 (2 H, q, *J* 7.1, OCH_2CH_3), 4.21 (2 H, q, *J* 7.1, OCH_2CH_3); δ_C(75.5 MHz; $CDCl_3$) 13.6 (2 q), 17.6 (t), 25.6 (t), 27.3 (t), 51.0 (d), 60.8 (2 t), 68.6 (d), 82.8 (s), 168.6 (2 s); *m/z* (TOF ES+) 249.1 ($[M+Na]^+$, 100%).

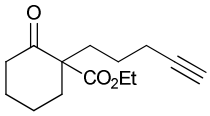
Data were in agreement with those reported in the literature.[116]

Diethyl 2-(but-3-yn-1-yl)-2-(3-((trimethylsilanyl)oxy)-cyclohex-2-en-1-yl)malonate 90



Diethyl 2-(but-3-ynyl)malonate **87** (379 mg, 1.79 mmol) was added dropwise over 5 min to a suspension of NaH (120 mg, 3.00 mmol, 60% dispersion in mineral oil) in THF (2.9 mL) at 0 °C. After the evolution of H_2, 2-cyclohexen-1-one (141 µL, 1.45 mmol) was added to the reaction mixture, followed by the addition of TMSOTf (288 µL, 1.59 mmol) at 0 °C. The mixture was stirred at 0 °C for 4 h before NH_4Cl solution (25 mL) was added, followed by EtOAc (25 mL). The two layers were separated. The organic layer was washed with brine (40 mL), dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc: 8/2) to afford the silyl enol ether **90** as a colourless liquid (0.311 g, 56%). R_f 0.70 (hexane/EtOAc: 8/2); δ_H(300 MHz; $CDCl_3$) 0.18 (9 H, s), 1.25 (3 H, t, *J* 7.1), 1.26 (3 H, t, *J* 7.1), 1.46-1.64 (2 H, m), 1.68-1.90 (3 H, m), 1.95 (1 H, t, *J* 2.6), 1.97-2.08 (1 H, m), 2.08-2.31 (4 H, m), 2.91-3.01 (1 H, m), 4.18 (2 H, q, *J* 7.1), 4.19 (2 H, q, *J* 7.1), 4.85-4.88 (1 H, m); δ_C(75.5 MHz; $CDCl_3$) 0.3 (3 q), 14.1 (2 q), 14.7 (t), 22.4 (t), 24.2 (t), 29.7 (t), 31.7 (t), 39.9 (d), 60.6 (s), 61.0 (2 t), 68.4 (d), 83.9 (s), 104.7 (d), 152.1 (s), 170.3 (s), 170.4 (s); *m/z* (TOF ES+) 403.2 ($[M+Na]^+$, 100%).

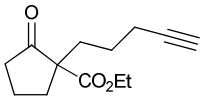
Ethyl 2-oxo-1-(pent-4-yn-1-yl)cyclohexane carboxylate 91a



Ethyl 2-oxo-1-(pent-4-ynyl)cyclohexane carboxylate **91a** was prepared from ethyl 2-oxocyclohexane carboxylate (0.41 mL, 2.58 mmol) and 5-iodopent-1-yne **88** (500 mg, 2.58 mmol) according to GP7. After 24 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded β-ketoester **91a** as a colourless liquid (454 mg, 75%); R_f 0.45 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 3285 (C≡CH), 2940, 2867, 1712 (C=O); δ_H(300 MHz; $CDCl_3$) 1.26 (3 H, t, *J* 7.1), 1.35-1.56 (3 H, m), 1.57-1.81 (4 H, m), 1.89-2.06 (2 H, m), 1.94 (1 H, t, *J* 2.6), 2.15-2.23 (2 H, m), 2.38-2.56 (3 H, m), 4.21 (2 H, q, *J* 7.1); δ_C(75.5 MHz; $CDCl_3$) 14.1 (q), 18.7 (t), 22.5 (t), 23.4 (t), 27.5 (t), 33.8 (t), 36.0 (t), 41.0 (t), 60.5 (s), 61.2 (t), 68.5 (d), 83.8 (s), 171.8 (s), 207.7 (s); *m/z* (TOF ES+) 259.2 ([M+Na]$^+$, 100%).

Data were in agreement with those reported in the literature.[89]

Ethyl 2-oxo-1-(pent-4-yn-1-yl)cyclopentane carboxylate 91b

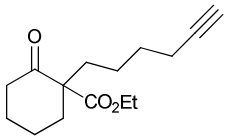


Ethyl 2-oxo-1-(pent-4-ynyl)cyclopentane carboxylate **91b** was prepared from ethyl 2-oxocyclopentane carboxylate (0.38 mL, 2.58 mmol) and 5-iodopent-1-yne **88** (500 mg, 2.58 mmol) according to GP7. Work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded β-ketoester **91b** as a colourless liquid (426 mg, 74%); R_f 0.41 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 3282 (C≡CH), 2964, 1749 (C=O, ester), 1722 (C=O, ketone); δ_H(300 MHz; $CDCl_3$) 1.25 (3 H, t, *J* 7.1), 1.37-1.55 (1 H, m), 1.57-1.73 (2 H, m),

1.83-2.10 (5 H, m), 2.16-2.33 (3 H, m), 2.36-2.59 (2 H, m), 4.16 (2 H, q, *J* 7.1); δ_C(75.5 MHz; $CDCl_3$) 13.6 (q), 18.2 (t), 19.1 (t), 23.4 (t), 32.4 (2 t), 37.3 (t), 59.5 (s), 60.8 (t), 68.4 (d), 83.1 (s), 170.3 (s), 213.8 (s); *m/z* (TOF ES+) 245.1 ($[M+Na]^+$, 100%).

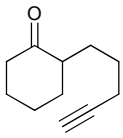
Data were in agreement with those reported in the literature.[89]

Ethyl 1-(hex-5-yn-1-yl)-2-oxocyclohexanecarboxylate 91c



Ethyl 1-(hex-5-ynyl)-2-oxocyclohexanecarboxylate **91c** was prepared from ethyl 2-oxocyclohexane carboxylate (0.77 mL, 4.81 mmol) and 6-iodohex-1-yne **98** (1.00 g, 4.81 mmol) according to GP7. After 24 h, work-up and purification by flash column chromatography (hexane/EtOAc: 9/1) afforded β-ketoester **91c** as a colourless liquid (689 mg, 57%); R_f 0.41 (hexane/EtOAc: 9/1); υ_{max}(film)/cm^{-1} 3286 (C≡CH), 2938, 2864, 1709 (C=O); δ_H(300 MHz; $CDCl_3$) 1.25 (3 H, t, *J* 7.1), 1.30-1.79 (9 H, m), 1.80-1.89 (1 H, m), 1.91 (1 H, t, *J* 2.6), 1.94-2.05 (1 H, m), 2.17 (2 H, dt, *J* 7.1 and 2.6), 2.37-2.57 (3 H, m), 4.19 (2 H, q, *J* 7.1); δ_C(75.5 MHz; $CDCl_3$) 14.1 (q), 18.1 (t), 22.6 (2 t), 23.3 (t), 27.6 (t), 28.7 (t), 34.1 (t), 41.1 (t), 60.7 (s), 61.1 (t), 68.3 (d), 84.2 (s), 171.9 (s), 207.9 (s); *m/z* (TOF ES+) 273.2 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 273.1470 ($[M+Na]^+$. $C_{15}H_{22}O_3Na$ requires 273.1467).

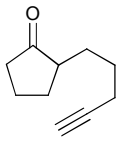
2-(Pent-4-yn-1-yl)cyclohexanone 92a



2-(Pent-4-ynyl)cyclohexanone **92a** was prepared from ethyl 2-oxo-1-(pentynyl)cyclohexane carboxylate **91a** (300 mg, 1.83 mmol) according to GP8. After 2 h and 40 min at 150 °C, work-up and purification (hexane/Et_2O: 9/1) afforded **92a** as a colourless liquid (140 mg, 66%); R_f 0.27 (hexane/Et_2O: 9/1); υ_{max}(film)/cm^{-1} 3291 (C≡CH), 2934, 2861, 1709 (C=O); δ_H(300 MHz; $CDCl_3$) 1.24-1.57 (4 H, m), 1.59-1.76 (2 H, m), 1.80-1.93 (2 H, m), 1.94 (1 H, t, *J* 2.6), 1.98-2.15 (2 H, m), 2.15-2.23 (2 H, m), 2.23-2.44 (3 H, m); δ_C(75.5 MHz; $CDCl_3$) 16.9 (t), 23.2 (t), 24.5 (t), 26.3 (t), 27.0 (t), 32.3 (t), 40.4 (t), 48.6 (d), 66.7 (d), 82.7 (s), 211.3 (s); *m/z* (EI+) 164 (M^+, 5%), 149 (21), 146 (5), 135 (34), 133 (4), 131 (16), 125 (11), 123 (35), 121 (100).

Data were in agreement with those reported in the literature.[89]

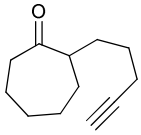
2-(Pent-4-yn-1-yl)cyclopentanone 92b



2-(Pent-4-ynyl)cyclopentanone **92b** was prepared from ethyl 2-oxo-1-(pentynyl)cyclopentane carboxylate **91b** (0.3 g, 1.35 mmol) according to GP8. After 4 h at 150 °C, work-up and purification by flash column chromatography (hexane/Et_2O: 9/1) afforded **92b** as a strongly odoured colourless liquid (128 mg, 63%); R_f 0.18 (hexane/Et_2O: 9/1); υ_{max}(film)/cm^{-1} 3289 (C≡CH), 2938, 2864, 1735 (C=O); δ_H(300 MHz; $CDCl_3$) 1.24-1.45 (2 H, m), 1.45-1.65 (3 H, m), 1.69-1.92 (2 H, m), 1.95 (1 H, t, *J* 2.7), 1.97-2.37 (6 H, m); δ_C(75.5 MHz; $CDCl_3$) 18.4 (t), 20.7 (t), 26.5 (t), 28.9 (t), 29.6 (t), 38.0 (t), 48.7 (d), 68.5 (d), 84.0 (s), 220.9 (s); *m/z* (EI+) 150 (M^+, 3%) 121 (6), 107 (8), 94 (12), 84 (100), 79 (34), 67 (13), 55 (26).

Data were in agreement with those reported in the literature.[89]

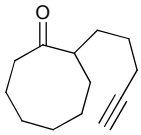
2-(Pent-4-yn-1-yl)cycloheptanone 92c



2-(Pent-4-ynyl)cycloheptanone **92c** was prepared from methyl 2-oxo-1-(pentynyl)cycloheptane carboxylate **96a** (632 mg, 2.68 mmol) according to GP8. After 3 h at 150 °C, work-up and purification by flash column chromatography (hexane/Et_2O: 8/2) afforded **92c** as a colourless liquid (398 mg, 83%); R_f 0.42 (hexane/Et_2O: 8/2), υ_{max}(film)/cm^{-1} 3291 (C≡CH), 2927, 2855, 1698 (C=O); δ_H(300 MHz; $CDCl_3$) 1.22-1.63 (7 H, m), 1.64-1.92 (5 H, m), 1.94 (1 H, t, *J* 2.7), 2.14-2.22 (2 H, m), 2.37-2.56 (3 H, m); δ_C(75.5 MHz; $CDCl_3$)

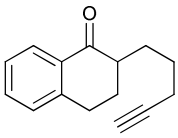
18.5 (t), 24.5 (t), 26.1 (t), 28.5 (t), 29.5 (t), 31.4 (2 t), 42.7 (t), 51.8 (d), 68.4 (d), 84.2 (s), 216.0 (s); *m/z* (EI+) 178 (M^+, 5%), 163 (10), 149 (20), 145 (9), 139 (13), 137 (41), 135 (100), 131 (15); HRMS *m/z* (TOF ES+) 178.1355 ($[M+Na]^+$. $C_{12}H_{18}ONa$ requires 178.1358).

2-(Pent-4-yn-1-yl)cyclooctanone 92d



2-(Pent-4-ynyl)cyclooctanone **92d** was prepared from methyl 2-oxo-1-(pentynyl)cyclooctane carboxylate **96b** (622 mg, 2.49 mmol) according to GP8. After 3 h at 150 °C, work-up and purification by flash column chromatography (hexane/Et_2O: 8/2) afforded **92d** as a light yellow liquid (392 mg, 82%); R_f 0.45 (hexane/Et_2O: 8/2), υ_{max}(film)/cm^{-1} 3292 (C≡CH), 2927, 2856, 1696 (C=O); δ_H(300 MHz; $CDCl_3$) 1.17-1.31 (1 H, m), 1.34-1.53 (6 H, m), 1.54-1.75 (4 H, m), 1.75-1.88 (2 H, m), 1.90-2.06 (1 H, m), 1.94 (1 H, t, *J* 2.7), 2.13-2.21 (2 H, m), 2.26-2.35 (1 H, m), 2.38-2.49 (1 H, m), 2.53-2.63 (1 H, m); δ_C(75.5 MHz; $CDCl_3$) 18.4 (t), 24.7 (t), 25.5 (t), 25.7 (t), 26.3 (t), 27.3 (t), 31.6 (t), 32.7 (t), 42.0 (t), 50.2 (d), 68.5 (d), 84.1 (s), 219.9 (s); *m/z* (EI+) 192 (M^+, 5%) 177 (12), 164 (16), 159 (11), 153 (11), 151 (45), 149 (79), 147 (11), 145 (21), 139 (9), 137 (17), 135 (100); HRMS *m/z* (TOF ES+) 215.1412 ($[M+Na]^+$. $C_{13}H_{20}ONa$ requires 215.1406).

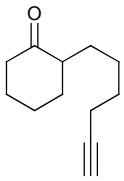
2-(Pent-4-yn-1-yl)-3,4-dihydronaphthalen-1(*2H*)-one 92e



2-(Pent-4-ynyl)-3,4-dihydronaphthalenone **92e** was prepared from methyl 1-oxo-2-(pentynyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate **96c** (296 mg, 1.09 mmol) according to GP8. After 2 h and 45 min at 150 °C, work-up and purification by flash column chromatography (hexane/Et_2O: 7/3) afforded **92e** as a light yellow liquid (212 mg, 91%); R_f 0.59 (hexane/Et_2O: 7/3), υ_{max}(film)/cm^{-1} 3294 (C≡CH), 2932, 2863, 1678 (C=O), 1601 (C=C); δ_H(300 MHz; $CDCl_3$) 1.58-1.73 (3 H, m), 1.84-1.94 (1 H, m), 1.96 (1 H, t, *J* 2.6), 1.97-2.10 (1 H, m), 2.19-2.30 (3 H, m), 2.45-2.56 (1 H, m), 2.97-3.04 (2 H, m), 7.23 (1 H, d, *J* 7.6), 7.30 (1 H, t, *J* 7.6), 7.46 (1 H, dt, *J* 7.6 and 1.4), 8.02 (1 H, dd, *J* 7.6 and 1.4); δ_C(75.5 MHz; $CDCl_3$) 18.6 (t), 26.0 (t), 28.4 (2 t), 28.8 (t), 47.1 (d), 68.5 (d), 84.2 (s), 126.6 (d), 127.4 (d), 128.6 (d), 132.5 (s), 133.1 (d), 143.8 (s), 199.9 (s); *m/z* (TOF ES+) 235.1 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 235.1092 ($[M+Na]^+$. $C_{15}H_{16}ONa$ requires 235.1099).

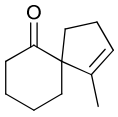
Data were in agreement with those reported in the literature.[117]

2-(Hex-5-yn-1-yl)cyclohexanone 92f



2-(Hex-5-ynyl)cyclohexanone **92f** was prepared from ethyl 1-(hexynyl)-2-oxocyclohexane carboxylate **91c** (400 mg, 1.60 mmol) according to GP8. After 10 h at 150 °C, work-up and purification (hexane/Et_2O: 8/2) afforded **92f** as a colourless liquid (169 mg, 59%); R_f 0.47 (hexane/Et_2O: 8/2); υ_{max}(film)/cm^{-1} 3292 (C≡CH), 2933, 2861, 1706 (C=O); δ_H(300 MHz; $CDCl_3$) 1.12-1.28 (1 H, m), 1.29-1.46 (3 H, m), 1.46-1.60 (2 H, m), 1.60-1.90 (4 H, m), 1.92 (1 H, t, *J* 2.6), 1.97-2.14 (2 H, m), 2.18 (2 H, dt, *J* 7.0 and 2.6), 2.22-2.44 (3 H, m); δ_C(75.5 MHz; $CDCl_3$) 18.3 (t), 24.9 (t), 26.3 (t), 26.3 (t), 28.0 (t), 28.5 (t), 33.9 (t), 42.0 (t), 50.6 (d), 68.2 (d), 84.5 (s), 213.2 (s); *m/z* (EI+) 178 (M^+, 8%), 163 (5), 149 (29), 145 (3), 139 (9), 137 (14), 135 (100), 123 (14), 121 (26).

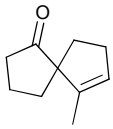
4-methylspiro[4.5]dec-3-ene-6-one 94a



Ketoalkyne **92a** (66 mg, 0.40 mmol) was reacted with Ph_3PAuCl/AgOTf (11.9 mg/6.2 mg, 0.024 mmol) in CH_2Cl_2 (0.1 M) according to GP10. After 18 h, work-up and purification by flash column chromatography (hexane/Et_2O: 8/2) afforded *spiro ketone* **94a** as a light yellow liquid (40 mg, 61%); R_f 0.48 (hexane/Et_2O: 8/2); υ_{max}(film)/cm^{-1} 2928, 2853, 1704 (C=O); δ_H(300 MHz; $CDCl_3$) 1.64-1.72 (5 H, m), 1.74-1.92 (3 H, m), 1.97-2.02 (2 H, m), 2.03-2.09 (1 H, m), 2.19-2.27 (2 H, m), 2.31-2.53 (2 H, m), 5.48-5.53 (1 H, m); δ_C(75.5 MHz; $CDCl_3$) 13.7

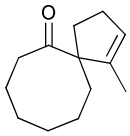
(q), 22.1 (t), 26.4 (t), 29.5 (t), 35.7 (t), 36.0 (t), 39.8 (t), 64.3 (s), 126.9 (d), 141.8 (s), 213.7 (s); *m/z* (EI+) 164 (42%), 149 (15), 136 (11), 120 (37), 107 (100), 93 (97), 79 (78); HRMS *m/z* (EI+) 164.1203 (M^+. $C_{11}H_{16}O$ requires 164.1201).

6-methylspiro[4.4]non-6-ene-1-one 94b



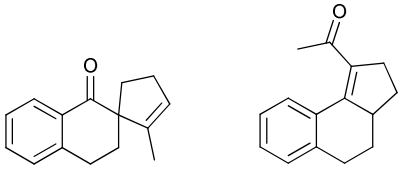
Ketoalkyne **92b** (60 mg, 0.40 mmol) was reacted with Ph_3PAuCl/AgOTf (11.9 mg/6.2 mg, 0.024 mmol) in CH_2Cl_2 (0.2 M) according to GP10. After 24 h, work-up and purification by flash column chromatography (hexane/Et_2O: 8/2) afforded *spiro ketone* **94b** and an unknown isomer in 2.8:1 ratio as a light yellow liquid (43 mg, 72%); data for the mixture unless specified otherwise; R_f 0.38 (hexane/Et_2O: 8/2); υ_{max}(film)/cm^{-1} 2935, 2851, 1732 (C=O, ketone), 1711 (C=O, ketone), major isomer **94b**: δ_H(300 MHz; $CDCl_3$) 1.25 (3 H, s), 1.43-1.73 (2 H, m), 1.99-2.40 (6 H, m), 2.46-2.50 (1 H, m), 2.56-2.68 (1 H, m), 5.32 (1 H, m); δ_C(75.5 MHz; $CDCl_3$) 23.7 (q), 25.1 (t), 25.8 (t), 28.5 (t), 29.7 (s), 32.2 (t), 38.1 (t), 122.7 (d), 146.6 (s), 214.4 (s); *m/z* (EI+) 150 (72%), 135 (8), 122 (6), 107 (100), 93 (34), 79 (98), 65 (8), 51 (10); HRMS *m/z* (EI+) 150.1049 (M^+. $C_{10}H_{14}O$ requires 150.1050).

1-Methyl-spiro[4.7]dodec-1-en-6-one 94d



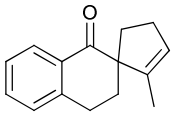
Ketoalkyne **92d** (77 mg, 0.40 mmol) was reacted with $Ph_3PAuCl/AgOTf$ (11.9 mg/6.2 mg, 0.024 mmol) in CH_2Cl_2 (0.2 M) according to GP10. After 16 h, work-up and purification by flash column chromatography (hexane/Et_2O: 8/2) afforded *spiro ketone* **94d** as a brown liquid (45 mg, 58%); R_f 0.64 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2924, 2854, 1693 (C=O); δ_H(300 MHz; $CDCl_3$) 0.93-1.11 (1 H, m), 1.28-1.43 (1 H, m), 1.43-1.74 (7 H, m), 1.76 (3 H, m), 1.81-1.94 (1 H, m), 2.13-2.28 (2 H, m), 2.32-2.59 (3 H, m), 2.78 (1 H, dt, *J* 11.4, 3.5), 5.41-5.46 (1 H, m); δ_C(75.5 MHz; $CDCl_3$) 14.3 (q), 24.6 (t), 25.8 (t), 26.3 (t), 30.2 (t), 30.5 (t), 32.6 (t), 32.6 (t), 39.2 (t), 66.0 (s), 128.6 (d), 141.3 (s), 218.4 (s); *m/z* (EI+) 192.3 (40%), 121.2 (6), 107.1 (100), 94.1 (93), 79.1 (49), 55.1 (10); HRMS *m/z* (EI+) 192.1508 (M^+. $C_{13}H_{20}O$ requires 192.1514).

2-Methyl-3', 4'-dihydro-1'*H*-spiro[cyclopent[2]ene-1,2'-naphthalen]-1'-one and 1-(3,3a,4,5-tetrahydro-2*H*-cyclopenta[a]naphthalen-1-yl)ethanone



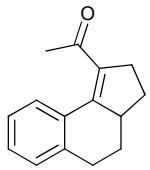
Ketoalkyne **92e** (85 mg, 0.40 mmol) was reacted with Ph_3PAuCl/AgOTf (11.9 mg/6.2 mg, 0.024 mmol) in CH_2Cl_2 (0.2 M) according to GP10. After 24 h, work-up and purification by flash column chromatography (hexane/Et_2O: 7/3) afforded *spiro ketone* **94e** and *tricyclic compound* **97c** in 2.4:1 ratio as a pale yellow liquid (67 mg, 79%).

2-Methyl-3', 4'-dihydro-1'*H*-spiro[cyclopent[2]ene-1,2'-naphthalen]-1'-one 94e



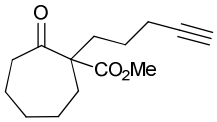
Spiro ketone **94e**: R_f 0.64 (hexane/Et_2O: 7/3); υ_{max}(film)/cm^{-1} 2925, 2852, 1677 (C=O), 1599 (C=C, C=C Ar); δ_H(300 MHz; $CDCl_3$) 1.66 (3 H, dt, *J* 2.1, 1.6), 1.86 (1 H, ddd, *J* 13.3, 4.6, 2.9), 1.98-2.14 (2 H, m), 2.26-2.36 (2 H, m), 2.40 (1 H, dd, *J* 13.1, 4.6), 2.93 (1 H, ddd, *J* 17.0, 4.6, 2.9), 3.16 (1 H, ddd, *J* 17.0, 13.1, 4.6), 5.62-5.65 (1 H, m), 7.24 (1 H, d, *J* 7.6), 7.30 (1 H, dd, *J* 7.6, 7.6), 7.46 (1 H, ddd, *J* 7.6, 7.6, 1.4), 8.06 (1 H, dd, *J* 7.6, 1.4); δ_C(75.5 MHz; $CDCl_3$) 13.4 (q), 26.3 (t), 29.6 (t), 32.0 (t), 33.6 (t), 61.1 (s), 126.6 (d), 127.9 (d), 127.9 (d), 128.5 (d), 131.9 (s), 133.1 (d), 142.1 (s), 143.7 (s), 200.4 (s); *m/z* (TOF ES+) 235.1 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF MS EI+) 212.1198 (M^+. $C_{15}H_{16}O$ requires 212.1201).

1-(3,3a,4,5-tetrahydro-2*H*-cyclopenta[a]naphthalen-1-yl)ethanone 97c



Tricyclic compound **97c**: R_f 0.45 (hexane/Et_2O: 7/3); υ_{max}(film)/cm^{-1} 2918, 2849, 1702 (C=O), 1600 (C=C, C=C Ar); δ_H(300 MHz; $CDCl_3$) 1.97-2.13 (1 H, m), 2.05 (3 H, s), 2.25-2.45 (3 H, m), 2.49-2.78 (2 H, m), 2.82-3.04 (2 H, m), 3.83-3.93 (1 H, m), 6.88-6.95 (1 H, m), 7.06-7.19 (3 H, m); δ_C(75.5 MHz; $CDCl_3$) 22.9 (t), 24.2 (q), 25.5 (t), 26.8 (t), 33.9 (t), 57.0 (d), 120.7 (d), 124.9 (d), 124.9 (d), 125.8 (d), 131.0 (s), 131.4 (s), 133.4 (s), 142.8 (s), 210.2 (s); *m/z* (TOF ES+) 235.1 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 235.1094 ($[M+Na]^+$. $C_{15}H_{16}ONa$ requires 235.1099).

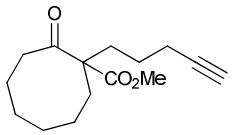
Methyl 2-oxo-1-(pent-4-yn-1-yl)-cycloheptane carboxylate 96a



Dimethylcarbonate (6.8 mL, 80.7 mmol) was added dropwise over 10 min to a suspension of NaH (2.14 g, 53.4 mmol, 60% dispersion in mineral oil) in toluene (30 mL) at rt and the reaction mixture was heated at 80 °C. Cycloheptanone (3.10 mL, 26.7 mmol) was then added dropwise over 1 h to this solution and the mixture was stirred for an additional hour at 80 °C. After 2 h, a yellowish-white precipitate appeared. The reaction was then cooled to rt and glacial acetic acid (25 mL) was added dropwise to quench the reaction mixture, followed by the addition of H_2O (25 mL). The two layers were separated and the organic phase was washed with H_2O (25 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The

residue, methyl 2-oxocycloheptane carboxylate **95a** (3.45 g, 76%) was taken through into the next step with no further purification. Methyl 2-oxocycloheptane carboxylate (880 mg, 5.17 mmol) was then reacted with 5-iodopent-1-yne **88** (1.0 g, 5.16 mmol) according to GP7. After 24 h, work-up and purification by flash column chromatography (hexane/Et_2O: 8/2) afforded **96a** as a colourless liquid (811 mg, 67%); R_f 0.30 (hexane/Et_2O: 8/2); υ_{max}(film)/cm^{-1} 3285 (C≡CH), 2934, 2862, 1735 (C=O, ester), 1702 (C=O, ketone); δ_H(300 MHz; $CDCl_3$) 1.38-1.82 (10 H, m), 1.94 (1 H, t, *J* 2.7), 1.98-2.30 (4 H, m), 2.43-2.53 (1 H, m), 2.57-2.68 (1 H, m), 2.66 (3 H, s); δ_C(75.5 MHz; $CDCl_3$) 18.3 (t), 23.3 (t), 24.4 (t), 25.1 (t), 29.4 (t), 32.4 (t), 34.1 (t), 41.4 (t), 51.6 (q), 62.1 (s), 68.4 (d), 83.2 (s), 172.2 (s), 208.5 (s); *m/z* (TOF ES+) 259.1 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 259.1320 ($[M+Na]^+$. $C_{14}H_{20}O_3Na$ requires 259.1310).

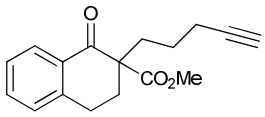
Methyl 2-oxo-1-(pent-4-yn-1-yl)-cyclooctane carboxylate 96b



Dimethylcarbonate (6.00 mL, 71.3 mmol) was added dropwise over 10 min to a suspension of NaH (1.90 g, 47.5 mmol, 60% dispersion in mineral oil) in toluene (30 mL) at rt and the reaction mixture was heated at 80 °C. Cyclooctanone (3.00 g, 23.7 mmol) was then added dropwise over 1 h to this solution and the mixture was stirred for additional 2 h at 80 °C. The reaction mixture was cooled to rt and glacial acetic acid (25 mL) was added dropwise to quench the reaction, followed by the addition of H_2O (25 mL). The two layers were separated and the organic phase was washed with H_2O (25 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue, methyl 2-oxocyclooctane carboxylate **95b** (4.00 g, 92%) was taken through into the next step with no further purification. Methyl 2-oxocyclooctane

carboxylate (955 mg, 5.18 mmol) was then reacted with 5-iodopent-1-yne **88** (1.0 g, 5.16 mmol) according to GP7. After 24 h, work-up and purification by flash column chromatography (hexane/Et_2O: 8/2) afforded **96b** as a colourless liquid (832 mg, 64%); R_f 0.36 (hexane/Et_2O: 8/2); υ_{max}(film)/cm^{-1} 3286 (C≡CH), 2930, 2859, 1736 (C=O, ester), 1705 (C=O, ketone); δ_H(300 MHz; $CDCl_3$) 0.87-1.03 (1 H, m), 1.21-1.89 (10 H, m), 1.93 (1 H, t, *J* 2.7), 1.96-2.30 (5 H, m), 2.47 (1 H, ddd, *J* 15.7, 11.6, 4.4), 2.69 (1 H, dt, *J* 11.9 and 3.8), 3.68 (3 H, s); δ_C(75.5 MHz; $CDCl_3$) 18.8 (t), 23.1 (t), 23.9 (t), 24.2 (t), 25.5 (t), 28.4 (t), 29.3 (t), 30.2 (t), 38.5 (t), 52.3 (q), 62.0 (s), 68.5 (d), 83.9 (s), 172.2 (s), 212.2 (s); *m/z* (TOF ES+) 273.2 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 273.1457 ($[M+Na]^+$. $C_{15}H_{22}O_3Na$ requires 273.1467).

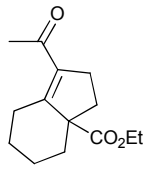
Methyl 1-oxo-2-(pent-4-yn-1-yl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate 96c



Dimethylcarbonate (5.2 mL, 61.6 mmol) was added dropwise over 10 min to a suspension of NaH (1.64 g, 41.0 mmol, 60% dispersion in mineral oil) in toluene (30 mL) at rt and the reaction mixture was heated at 80 °C. Tetralone (2.7 mL, 20.5 mmol) was then added dropwise over 1 h to this solution and the mixture was stirred for additional 2 h at 80 °C. The reaction mixture was cooled to rt and H_2O (50 mL) was added to quench the reaction, followed by the addition of CH_2Cl_2 (50 mL). The two layers were separated and the organic phase was washed with H_2O (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue, methyl 1-oxotetrahydronaphthalene-2-carboxylate (4.18 g, quant) was taken through into the next step with no further purification. Methyl 1-oxotetrahydronaphthalene-2-carboxylate **95c** (1.05 g, 5.15 mmol) was then reacted with 5-

iodopent-1-yne **88** (740 mg, 3.82 mmol) according to GP7. After 24 h, work-up and purification by flash column chromatography (hexane/EtO_2: 8/2) afforded **96c** as a pale yellow oil (421 mg, 41%); R_f 0.25 (hexane/Et_2O: 8/2); υ_{max}(film)/cm^{-1} 3290 (C≡CH), 2951, 1729 (C=O, ester), 1683 (C=O, ketone), 1601 (C=C); δ_H(300 MHz; $CDCl_3$) 1.48-1.75 (2 H, m), 1.95 (1 H, t, *J* 2.6), 1.98-2.28 (5 H, m), 2.58 (1 H, td, *J* 13.7 and 5.0), 2.93 (1 H, td, *J* 17.5 and 5.2), 3.07 (1 H, ddd, *J* 17.5, 9.7 and 4.6), 3.68 (3 H, s), 7.22 (1 H, d, *J* 7.6), 7.31 (1 H, app t, *J* 7.6), 7.48 (1 H, dt, *J* 7.6 and 1.3), 8.05 (1 H, dd, *J* 7.6 and 1.3); δ_C(75.5 MHz; $CDCl_3$) 18.8 (t), 23.8 (t), 25.8 (t), 30.5 (t), 33.1 (t), 52.4 (q), 57.3 (s), 68.7 (d), 83.7 (s), 126.7 (d), 128.0 (d), 128.7 (d), 131.8 (s), 133.4 (d), 143.0 (s), 172.2 (s), 195.1 (s); *m/z* (TOF ES+) 293.1 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 293.1157 ($[M+Na]^+$. $C_{17}H_{18}O_3Na$ requires 293.1154).

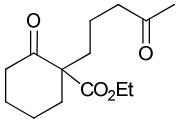
Ethyl 3-acetyl-2,4,5,6,7,7a-hexahydro-1*H*-indene-7a-carboxylate 97a



Ketoalkyne **91a** (55.0 mg, 0.23 mmol) was reacted with Ph_3PAuCl/AgOTf (6.9 mg/3.6 mg, 0.013 mmol) in CH_2Cl_2 according to GP10. After 44 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded bicyclic compound **97a** as a light yellow liquid (26.6 mg, 48%); R_f 0.40 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2935, 2857, 1725 (C=O, ester), 1682 (C=O, ketone), 1657, 1621 (C=C); δ_H(300 MHz; $CDCl_3$) 1.22 (3 H, t, *J* 7.1), 1.28-1.50 (3 H, m), 1.59-1.76 (2 H, m), 1.77-1.89 (1 H, m), 1.94-2.10 (1 H, m), 2.12-2.22 (1 H, m), 2.25 (3 H, s), 2.44-2.54 (1 H, m), 2.54-2.76 (2 H, m), 3.32-3.44 (1 H, m), 4.13 (2 H, q, *J* 7.1); δ_C(75.5 MHz; $CDCl_3$) 14.2 (q), 23.4 (t), 26.7 (t), 26.8 (t), 30.6 (d), 32.1 (t), 35.5 (2 t), 60.3 (s), 60.7 (t), 135.6 (s), 155.0 (s), 175.0 (s), 198.8 (s); *m/z* (TOF ES+) 259.1

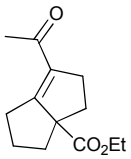
([M+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 259.1306 ([M+Na]$^+$. $C_{14}H_{20}O_3Na$ requires 259.1310).

Ethyl 2-oxo-1-(4-oxopentyl)cyclohexanecarboxylate I_{91a}



Product **I_{91a}** was obtained in small quantities as a side-product in the cyclisation of **91a** to **97a**; υ_{max}(film)/cm^{-1} 2962, 2940, 2864, 1739 (C=O, ester), 1706 (C=O, ketones); δ_H(300 MHz; $CDCl_3$) 1.24 (3 H, t, *J* 7.1), 1.36-1.83 (8 H, m), 1.91-2.04 (1 H, m), 2.10 (3 H, s), 2.32-2.54 (5 H, m), 4.18 (2 H, q, *J* 7.1); δ_C(75.5 MHz; $CDCl_3$) 14.1 (q), 18.6 (t), 22.5 (2 t), 27.5 (t), 29.8 (q), 33.9 (t), 41.0 (t), 43.7 (t), 60.7 (s), 61.2 (t), 171.8 (s), 207.9 (s), 208.3 (s); *m/z* (TOF ES+) 277.1 ([M+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 277.1411 ([M+Na]$^+$. $C_{14}H_{22}O_4Na$: requires 277.1416).

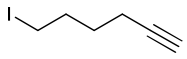
Ethyl 6-acetyl-1,2,3,3a,4,5-hexahydropentalene-3a-carboxylate 97b



Ketoalkyne **91b** (59.1 mg, 0.26 mmol) was reacted with Ph_3PAuCl/AgOTf (7.9 mg/4 mg, 0.016 mmol) in CH_2Cl_2 according to GP10. After 44 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded bicyclic compound **97b** as a light yellow liquid (29.8 mg, 50%); R_f 0.38 (hexane/EtOAc: 8/2); υ_{max}(film) /cm^{-1} 2929, 2857, 1723 (C=O), 1684, 1662 (C=C); δ_H(300 MHz; $CDCl_3$) 1.23 (3 H, t, *J* 7.1), 1.39-1.53 (1 H, m), 1.68-1.81 (1 H, m), 2.04-2.25 (2 H, m), 2.29 (3 H, s), 2.31-2.45 (2 H, m), 2.48-2.74 (2 H, m),

2.73-2.90 (1 H, m), 2.90-3.05 (1 H, m), 4.13 (2 H, q, *J* 7.1); δ_C(75.5 MHz; $CDCl_3$) 14.1 (q), 26.3 (t), 27.8 (t), 29.5 (q), 35.6 (2 t), 36.7 (t), 60.9 (t), 69.1 (s), 135.2 (s), 164.9 (s), 174.6 (2 s); *m/z* (TOF ES+) 245.1 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 245.1156 ($[M+Na]^+$. $C_{13}H_{18}O_3Na$ requires 245.1154).

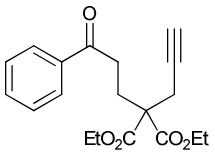
6-Iodohex-1-yne 98



6-Chlorohex-1-yne (1.55 mL, 12.86 mmol) was added to a suspension of NaI (9.6 g, 64.26 mmol) in methyl ethyl ketone (60 mL) at rt. The reaction mixture was then stirred at reflux for 24 h. The solution was allowed to cool to rt before H_2O (60 mL) and Et_2O (60 mL) were added. The two layers were separated and the aqueous phase was extracted with Et_2O (60 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and the solvent carefully removed under reduced pressure to afford 6-iodohex-1-yne **98** as a strongly odoured yellow liquid (2.68 g, 100%); R_f 0.73 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 3295 (C≡CH), 2940; δ_H(300 MHz; $CDCl_3$) 1.54-1.71 (2 H, m, CH_2), 1.89-2.02 (2 H, m, CH_2), 1.96 (1 H, t, *J* 2.7, C≡C*H*), 2.23 (2 H, td, *J* 6.9 and 2.7, CH_2CH_2C≡CH), 3.21 (2 H, t, *J* 6.9, ICH_2CH_2); δ_C(75.5 MHz; $CDCl_3$) 6.0 (t, ICH_2), 17.3 (t, ICH_2CH_2), 29.0 (t, $ICH_2CH_2CH_2$), 32.1 (t, $ICH_2CH_2CH_2CH_2$), 68.9 (d, C≡*C*H), 83.5 (s, *C*≡CH); *m/z* (EI+) 208 (M^+, 6%), 81 (100), 65 (6), 53 (39).

Data were in agreement with those reported in the literature.[118]

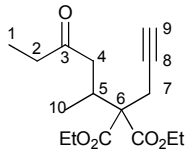
Diethyl 2-(3-oxo-3-phenylpropyl)-2-(prop-2-yn-1-yl)malonate 99a



Na (58 mg, 2.52 mmol) was carefully dissolved in absolute EtOH (7 mL). Diethyl propargylmalonate **78** (500 mg, 2.52 mmol) was added dropwise over 15 min, followed by the addition of 3-chloropropiophenone (302 mg, 1.79 mmol). The reaction mixture was then stirred at rt for 2 h; before H_2O (30 mL) was added to quench the reaction. The aqueous phase was extracted with Et_2OAc (2 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc: 8/2) to afford ketoalkyne **99a** as a white solid (562 mg, 95%); R_f 0.37 (hexane/EtOAc: 8/2); mp 38-39 °C; υ_{max}(film)/cm^{-1} 3294, 3251 (C≡CH), 2985, 1727 (C=O, ester), 1686 (C=O, ketone), 1669 (C=C), 1599 (C=C), 1582 (C=C); δ_H(300 MHz; $CDCl_3$) 1.25 (6 H, t, *J* 7.1), 2.01-2.05 (1 H, m), 2.45-2.54 (2 H, m), 2.89 (2 H, d, *J* 2.7), 2.99-3.09 (2 H, m), 4.08-4.30 (4 H, m), 7.42-7.49 (2 H, m), 7.53-7.60 (1 H, m), 7.94-7.99 (2 H, m); δ_C(75.5 MHz; $CDCl_3$) 14.0 (2 q), 23.8 (t), 27.0 (t), 33.7 (t), 56.1 (s), 61.8 (2 t), 71.8 (d), 78.7 (s), 128.1 (2 d), 128.6 (2 d), 133.1 (d), 154.1 (s), 170.0 (2 s), 198.6 (s); *m/z* (TOF ES+) 353.2 ([M+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 353.1375 ([M+Na]$^+$. $C_{19}H_{22}O_5Na$ requires 353.1365).

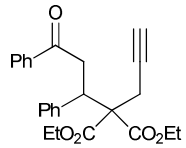
Data were in agreement with those reported in the literature.[24a]

Diethyl 2-(4-oxohexan-2-yl)-2-(prop-2-yn-1-yl)malonate 99b



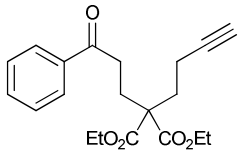
Ketoalkyne **99b** was prepared from 4-hexen-3-one (115 μL, 1.0 mmol) and diethyl propargylmalonate **78** (200 mg, 1.0 mmol) according to GP5. After 48 h, work-up and purification (hexane/EtOAc: 8/2) afforded **99b** as a clear yellow liquid (189 mg, 64%); R_f 0.29 (hexane/EtOAc: 8/2); υ_{max} /cm^{-1} (film) 3280 (C≡CH), 2980, 2939, 1729 (C=O); δ_H(300 MHz; $CDCl_3$) 0.94 (3 H, dd, *J* 6.9 and 0.6, 10-H), 1.06 (3 H, t, *J* 7.6, 1-H), 1.26 (3 H, t, *J* 7.1, CH_2CH_3), 1.27 (3 H, t, *J* 7.1, CH_2CH_3), 2.03 (1 H, t, *J* 2.7, 9-H), 2.26 (1 H, dd, *J* 16.6 and 10.6, 4-H), 2.42 (1 H, dq, J_{AB} 17.5 and 7.6, 2-H), 2.47 (1 H, dq, J_{AB} 17.5 and 7.6, 2-H), 2.80 (1 H, dd, J_{AB} 17.3 and 2.7, 7-H), 2.89 (1 H, dd, J_{AB} 17.3 and 2.7, 7-H), 2.88-2.95 (1 H, m, 4-H), 2.95-3.07 (1 H, m, 5-H), 4.16-4.28 (4 H, m, 2 × CH_2CH_3); δ_C(75.5 MHz; $CDCl_3$) 7.7 (q, 1-C), 13.8 (q, CH_2CH_3), 13.9 (q, CH_2CH_3), 15.4 (q, 10-C), 22.6 (t, 7-C), 31.5 (d, 5-C), 35.9 (t, 2-C), 45.8 (t, 4-C), 59.8 (s, 6-C), 61.3 (t, CH_2CH_3), 61.4 (t, CH_2CH_3), 71.4 (d, 9-C), 79.0 (s, 8-C), 169.2 (s, CO_2Et), 169.6 (s, CO_2Et), 209.7 (s, 3-C); *m/z* (TOF ES+) 319.1 ([M+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 319.1518 ([M+Na]$^+$ $C_{16}H_{24}O_5Na$ requires 319.1521).

Diethyl 2-(3-oxo-1,3-diphenylpropyl)-2-(pro-2-yn-1-yl)malonate 99c



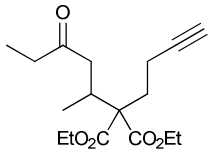
Ketoalkyne **99c** was prepared from chalcone (525 mg, 2.52 mmol) and diethyl propargylmalonate **78** (500 mg, 2.52 mmol) according to GP5. After 24 h, work-up and purification by flash column chromatography (hexane/Et_2O: 7/3) afforded **99c** as a light yellow oil (617 mg, 60%); R_f 0.26 (hexane/Et_2O: 7/3); υ_{max}(film)/cm^{-1} 3283 (C≡CH), 3087, 3062, 3031 (CH Ar), 2982, 2937, 1731 (C=O), 1692 (C=C), 1597 (C=C); δ_H(300 MHz; $CDCl_3$) 1.26 (3 H, t, *J* 7.1, CH_2CH_3), 1.33 (3 H, t, *J* 7.1, CH_2CH_3), 2.16 (1 H, t, *J* 2.7, C≡C*H*), 2.48 (1 H, dd, J_{AB} 17.2 and 2.7, CH_2C≡CH), 2.76 (1 H, dd, J_{AB} 17.2 and 2.7, CH_2C≡CH); 3.75 (1 H, dd, J_{AB} 17.5 and 10.8, CH_2CO), 3.89 (1 H, dd, J_{AB} 17.5 and 2.8, CH_2CO), 4.19 (1 H, qd, *J* 7.1 and 3.5, CH_2CH_3), 4.23 (1 H, qd, *J* 7.1 and 3.5, CH_2CH_3), 4.30 (1 H, app q, *J* 7.1, CH_2CH_3), 4.32 (1 H, app q, *J* 7.1, CH_2CH_3), 4.43 (1 H, dd, *J* 10.8 and 2.8, C*H*), 7.16-7.25 (5 H, m, Ar-H), 7.38-7.45 (2 H, m, Ar-H), 7.48-7.55 (1 H, m, Ar-H), 7.90-7.95 (2 H, m, Ar-*H*); δ_C(75.5 MHz; $CDCl_3$) 14.0 (2 q, CH_2CH_3), 24.1 (t, CH_2C≡CH), 41.6 (t, CH_2CO), 43.2 (d, CH), 60.6 (s, $C(CO_2Et)_2$), 61.7 (t, CH_2CH_3), 61.8 (t, CH_2CH_3), 72.3 (d, C≡CH), 79.4 (s, C≡CH), 127.4 (d, Ar-CH), 128.0 (2 d, Ar-CH), 128.2 (3 d, Ar-CH), 128.4 (d, Ar-CH), 129.0 (2 d, Ar-CH), 132.8 (d, Ar-CH), 137.0 (s, Ar-C), 138.6 (s, Ar-C), 169.4 (2 s, CO_2Et), 197.7 (s, CO); *m/z* (TOF ES+) 429.2 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 429.1676 ($[M+Na]^+$. $C_{25}H_{26}O_5Na$ requires 429.1678).

Diethyl 2-(but-3-yn-1-yl)-2-(3-oxo-3-phenylpropyl)malonate 99d



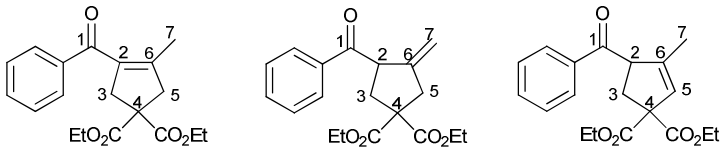
Na (58 mg, 2.52 mmol) was carefully dissolved in absolute EtOH (7 mL). Diethyl 2-(but-3-ynyl)malonate **87** (216 mg, 1.02 mmol) was added dropwise over 15 min, followed by the addition of 3-chloropropiophenone (121 mg, 0.72 mmol). The reaction mixture was then stirred at rt for 2 h 45 min before H_2O (30 mL) was added to quench the reaction. The aqueous phase was extracted with Et_2OAc (2 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc: 8/2) to afford *ketoalkyne* **99d** as a white solid (226 mg, 91%); R_f 0.39 (hexane/EtOAc: 8/2); mp 30-31 °C; υ_{max}(film)/cm^{-1} 3432 (C≡CH), 3294, 2980, 2938, 1727 (C=O), 1687 (C=C), 1598 (C=C); δ_H(300 MHz; $CDCl_3$) 1.25 (6 H, t, *J* 7.1), 1.94-1.97 (1 H, m), 2.20-2.24 (4 H, m), 2.30-2.38 (2 H, m), 2.96-3.04 (2 H, m), 4.20 (4 H, q, *J* 7.1), 7.42-7.50 (2 H, m), 7.53-7.60 (1 H, m), 7.92-7.98 (2 H, m); δ_C(75.5 MHz; $CDCl_3$) 14.0 (2 q), 27.1 (t), 32.5 (2 t), 33.6 (t), 56.4 (s), 61.4 (2 t), 68.8 (d), 83.1 (s), 127.9 (2 d), 128.5 (2 d), 133.1 (d), 136.6 (s), 170.7 (2 s), 198.5 (s); *m/z* (TOF ES+) 367.2 ([M+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 367.1526 ([M+Na]$^+$. $C_{20}H_{24}O_5Na$ requires 367.1521).

Diethyl 2-(but-3-yn-1-yl)-2-(4-oxohexan-2-yl)malonate 99e



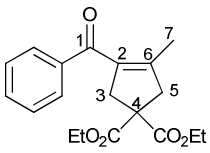
Ketoalkyne **99e** was prepared from 4-hexen-3-one (107 μL, 0.94 mmol) and diethyl 2-(but-3-ynyl)malonate **87** (200 mg, 0.94 mmol) according to GP5. After 4 d, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded **99e** as a colourless liquid (192 mg, 65%); R_f 0.47 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 3283 (C≡CH), 2979, 2939, 1724 (C=O); δ_H(300 MHz; $CDCl_3$) 0.91 (3 H, d, *J* 7.4), 1.05 (3 H, t, *J* 7.3), 1.26 (3 H, t, *J* 7.1), 1.28 (3 H, t, *J* 7.1), 1.96 (1 H, t, *J* 2.5), 2.08-2.54 (7 H, m), 2.66-2.81 (2 H, m), 4.19 (2 H, q, *J* 7.1), 4.21 (2 H, q, *J* 7.1); δ_C(75.5 MHz; $CDCl_3$) 7.6 (q), 13.8 (q), 13.9 (q), 14.3 (t), 15.6 (q), 32.3 (d), 32.4 (t), 36.1 (t), 45.9 (t), 60.3 (s), 61.0 (t), 61.0 (t), 68.5 (d), 83.2 (s), 169.9 (s), 170.3 (s), 209.5 (s); *m/z* (TOF ES+) 333.2 ([M+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 333.1676 ([M+Na]$^+$. $C_{17}H_{26}O_5Na$ requires 333.1678).

Diethyl 3-benzoyl-4-methylcyclopent-3-ene-1,1-dicarboxylate, diethyl 3-benzoyl-4-methylenecyclopentane-1,1-dicarboxylate and diethyl 4-benzoyl-3-methyl-cyclopent-2-ene-1,1-dicarboxylate 100a



Ketoalkyne **99a** (215 mg, 0.65 mmol) was reacted with Ph_3PAuCl/AgOTf (33 mg/17 mg, 0.066 mmol) in CH_2Cl_2 according to GP10. After 24 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded the title compounds **100a** as a light yellow oil (109 mg, 51%), in 9.7:3.1:1 mixture of three isomers (**100aa**:**100ab**:**100ac**); R_f 0.41 (hexane/EtOAc: 8/2). These isomers were inseparable by flash column chromatography. Analytically pure samples of each isomer were obtained by preparative HPLC (t = 0 → 65 min CH_3OH/H_2O 60:40).

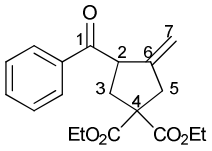
Diethyl 3-benzoyl-4-methylcyclopent-3-ene-1,1-dicarboxylate 100aa



Isomer **100aa**: HPLC: t_R = 53.2 min; υ_{max} (film)/cm^{-1} 2982, 1728 (C=O), 1641 (C=C), 1597 (C=C Ar), 1579 (C=C Ar); δ_H(300 MHz; $CDCl_3$) 1.26 (6 H, t, *J* 7.1, 2 × CH_2CH_3), 1.66 (3 H, s, 7-H), 3.16-3.21 (2 H, m, CH_2), 3.36-3.43 (2 H, m, CH_2), 4.22 (4 H, q, *J* 7.1, 2 × CH_2CH_3), 7.40-7.48 (2 H, m, Ar-H), 7.50-7.57 (1 H, m, Ar-H), 7.72-7.78 (2 H, m, Ar-H); δ_C(75.5 MHz; $CDCl_3$) 14.0 (2 q, CH_2CH_3), 16.3 (q, 7-C), 42.9 (t, 3 or 5-C), 47.1 (t, 3 or 5-C), 57.3 (s, 4-C), 61.8 (2 t, CH_2CH_3), 128.5 (2 d, Ar-C), 128.9 (2 d, Ar-C), 132.6 (d, Ar-C), 133.1 (s, 6-C),

138.6 (s, 2-C), 146.0 (s, Ar-C), 171.5 (2 s, *C*O_2Et), 195.3 (s, 1-C); *m/z* (TOF ES+) 353.1 ($[M+Na]^+$, 100%).

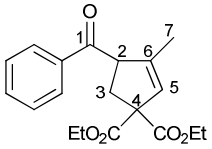
Diethyl 3-benzoyl-4-methylenecyclopentane-1,1-dicarboxylate 100ab



Isomer **100ab**: HPLC: t_R = 60.3 min; υ_{max}(film)/cm^{-1} 2983, 1728 (C=O), 1683 (C=C), 1597 (C=C Ar), 1580 (C=C Ar); δ_H(300 MHz; $CDCl_3$) 1.27 (3 H, t, *J* 7.1, CH_2CH_3), 1.27 (3 H, t, *J* 7.1, CH_2CH_3), 2.71 (2 H, d, *J* 8.7, 3-H), 2.96 (1 H, d, *J* 16.5, 5-H), 3.16 (1 H, ddt, *J* 16.5, 2.5, 2.5, 5-H), 4.17-4.29 (4 H, m, 2 × CH_2CH_3), 4.54-4.63 (1 H, m, 2-H), 4.73 (1 H, dd, *J* 4.0, 2.5, 7-H), 5.05 (1 H, dd, *J* 4.0, 2.5, 7-H), 7.41-7.54 (2 H, m, Ar-H), 7.56-7.62 (1 H, m, Ar-H), 7.97-8.03 (2 H, m, Ar-H); δ_C(75.5 MHz; $CDCl_3$) 14.0 (2 q, CH_2CH_3), 36.5 (t, 3-C), 41.3 (t, 5-C), 49.4 (d, 2-C), 58.9 (s, 4-C), 61.6 (t, CH_2CH_3), 61.7 (t, CH_2CH_3), 110.5 (t, 7-C), 128.7 (2 d, Ar-C), 129.1 (2 d, Ar-C), 133.2 (d, Ar-C), 136.9 (s, 6-C), 147.3 (s, Ar-C), 170.7 (s, CO_2Et), 171.7 (s, CO_2Et), 198.7 (s, 1-C); *m/z* (TOF ES+) 353.1 ($[M+Na]^+$, 100%).

Data were identical to those previously reported.[24a]

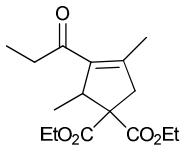
Diethyl 4-benzoyl-3-methyl-cyclopent-2-ene-1,1-dicarboxylate 100ac



Isomer **100ac**: HPLC: t_R = 43.4 min; υ_{max}(film)/cm^{-1} 2921, 1730 (C=O), 1682 (C=C), 1597 (C=C Ar); δ_H(300 MHz; $CDCl_3$) 1.20-1.30 (6 H, m, 2 × CH_2CH_3), 1.75-1.78 (3 H, m, 7-C),

2.63 (1 H, dd, J_{AB} 13.6, 6.2, 3-H), 2.94 (1 H, dd, J_{AB} 13.6, 9.1, 3-H), 4.12-4.29 (4 H, m, 2 × C*H*$_2$CH$_3$), 4.50-4.59 (1 H, m, 2-H), 5.71-5.75 (1 H, m, 5-H), 7.45-7.52 (2 H, m, Ar-H), 7.55-7.62 (1 H, m, Ar-H), 7.95-8.02 (2 H, m, Ar-H); δ_C(75.5 MHz; $CDCl_3$) 14.0 (2 q, CH$_2$*C*H$_3$), 16.0 (q, 7-C), 36.7 (t, 3-C), 54.9 (d, 2-C), 61.5 (t, *C*H$_2$CH$_3$), 61.7 (t, *C*H$_2$CH$_3$), 65.7 (s, 4-C), 126.5 (d, 5-C), 128.6 (2 d, Ar-C), 128.7 (2 d, Ar-C), 133.3 (d, Ar-C), 136.6 (s, 6-C), 144.1 (s, Ar-C), 170.5 (s, *C*O$_2$Et), 171.2 (s, *C*O$_2$Et), 199.8 (s, 1-C); *m/z* (TOF ES+) 353.1 ([M+Na]$^+$, 100%).

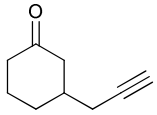
Diethyl 2,4-dimethyl-3-propionylcyclopent-3-ene-1,1-dicarboxylate 100ba



Ketoalkyne **99b** (59 mg, 0.20 mmol) was reacted with Ph$_3$PAuCl/AgOTf (5.9 mg/3 mg, 0.012 mmol) in CH_2Cl_2 according to GP10. After 24 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded **100b** as a clear yellow oil (40 mg, 67%) in a 6.3:1.3:1 mixture of isomers; R_f 0.41 (hexane/EtOAc: 8/2). These isomers were inseparable by flash column chromatography. Analytically pure sample of **100ba**, the *major isomer* was obtained by preparative HPLC (t = 0 → 40 min, H_2O/CH_3CN 55:45), t_R = 36.2 min; υ_{max}(film) /cm^{-1} 2978, 2935, 1730 (C=O), 1681, 1659 (C=C); δ_H(300 MHz; $CDCl_3$) 1.00 (3 H, d, *J* 7.0, C*H*$_3$CH), 1.09 (3 H, t, *J* 7.2, C*H*$_3$CH$_2$), 1.23 (3 H, t, *J* 7.0, CO$_2$CH$_2$C*H*$_3$), 1.26 (3 H, t, *J* 7.0, CO$_2$CH$_2$C*H*$_3$), 2.03 (3 H, s, C*H*$_3$C=C), 2.55 (1 H, dq, J_{AB} 17.4, 7.2, CH$_3$C*H*$_2$), 2.64 (1 H, qd, J_{AB} 17.4, 7.2, CH$_3$C*H*$_2$), 2.74 (1 H, d, J_{AB} 18.6, C*H*$_2$C=C), 3.50 (1 H, d, J_{AB} 18.6, C*H*$_2$C=C), 3.89 (1 H, q, *J* 7.0, CH$_3$C*H*), 4.10-4.28 (4 H, m, CO$_2$C*H*$_2$CH$_3$); δ_C(75.5 MHz; $CDCl_3$) 7.8 (q, *C*H$_3$CH$_2$), 14.0 (q, CO$_2$CH$_2$*C*H$_3$), 14.1 (q, CO$_2$CH$_2$*C*H$_3$), 15.4 (q, *C*H$_3$CH),

16.6 (q, *C*H_3C=C), 35.2 (t, CH_3CH_2), 45.2 (t, *C*H_2C=C), 45.3 (d, CH_3CH), 61.5 (t, $CO_2CH_2CH_3$), 61.6 (t, $CO_2CH_2CH_3$), 62.7 (s, *C*$(CO_2Et)_2$), 139.1 (s, CH_3C=C), 147.3 (s, CH_3C=*C*), 169.6 (s, *C*O_2Et), 171.6 (s, *C*O_2Et), 200.0 (s, *C*O); *m/z* (EI+) 296 (M^+, 18%), 267 (2), 251 (10), 222 (53), 207 (2), 193 (66), 177 (62), 165 (41), 149 (46), 137 (24), 121 (32), 111 (3), 105 (7), 99 (1), 93 (27), 77 (16), 65 (6), 57 (100), 43 (7); HRMS *m/z* (EI+) 296.1630 (M^+. $C_{16}H_{24}O_5$ requires 296.1624).

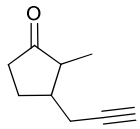
3-(prop-2-yn-1-yl)cyclohexanone 101a



Ketoalkyne **101a** was synthesised from 2-cyclohexen-1-one (96 μL, 0.99 mmol) and propargyl bromide (0.33 mL, 2.99 mmol, 80% in toluene) according to GP6. After 1 h and 45 min, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded **101a** as a yellow liquid (69 mg, 51%); R_f 0.35 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 3290 (C≡CH), 2934, 2868, 1710 (C=O); δ_H(300 MHz; $CDCl_3$) 1.46-1.57 (1 H, m), 1.60-1.72 (1 H, m), 1.92-2.10 (3 H, m), 2.03 (1 H, t, *J* 2.6), 2.16-2.29 (4 H, m), 2.33-2.39 (1 H, m), 2.44-2.49 (1 H, m); δ_C(75.5 MHz; $CDCl_3$) 24.8 (t), 25.4 (t), 30.2 (t), 37.7 (d), 41.0 (t), 47.0 (t), 70.4 (d), 81.3 (s), 211.0 (s); *m/z* (EI+) 136.2 (M^+, 21%) 121.2 (7), 108.2 (13), 97.1 (100), 93.1 (19), 79.1 (13); HRMS *m/z* (EI+) 136.0891 (M^+. $C_9H_{12}O$ requires 136.0888).

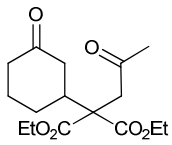
Data were in agreement with those reported in the literature.[98]

2-Methyl-3-(prop-2-yn-1-yl)cyclopentanone 101b



Ketoalkyne **101b** was synthesised from 2-methyl 2-cyclopenten-1-one (0.20 mL, 2.04 mmol) and propargyl bromide (0.54 mL, 6.11 mmol, 80% in toluene) according to GP6. After 3 h and 20 min, work-up and purification by flash column chromatography (hexane/Et_2O: 8/2) afforded **101b** as a light brown liquid (101 mg, 36%) in a 1:1 mixture of *diastereoisomers*; R_f 0.27 (hexane/Et_2O: 8/2); υ_{max}(film)/cm^{-1} 3288 (C≡CH), 2966, 2933, 2877, 1736 (C=O); δ_H(300 MHz; $CDCl_3$) 1.04 (3 H, d, *J* 7.3), 1.09 (3 H, d, *J* 6.7), 1.97 (1 H, t, *J* 2.7), 2.02 (1 H, t, *J* 2.7), 1.58-2.57 (16 H, m); δ_C(75.5 MHz; $CDCl_3$) 9.4 (q), 12.1 (q), 19.1 (t), 22.0 (t), 25.3 (t), 25.9 (t), 35.6 (t), 37.0 (t), 38.9 (d), 42.8 (d), 46.6 (d), 48.5 (d), 69.7 (d), 70.5 (d), 81.0 (s), 82.3 (s), 219.8 (s), 220.3 (s); *m/z* (EI+) 136 (M^+, 71%), 121 (51), 107 (18), 93 (42), 79 (100), 69 (74), 55 (52); HRMS *m/z* (EI+) 136.0884 (M^+. $C_9H_{12}O$ requires 136.0888).

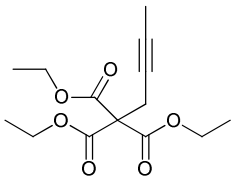
Diethyl 2-(3-oxocyclohexyl)-2-(2-oxopropyl)malonate 105



A mixture of 2-(3-oxocyclohexyl)-2-prop-2-ynylmalonic acid diethyl ester **80a** (100 mg, 0.34 mmol), $NaAuCl_4.2H_2O$ (4 mg, 0.01 mmol) in 1.36 mL of MeOH-H_2O (10:1) was irradiated by ultrasound at rt for 5 h. Saturated NH_4Cl(aq) (20 mL) was then added, followed by diethylether (20 mL). The two layers were separated. The organic layer was washed with saturated aqueous NaCl (20 mL), dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate:

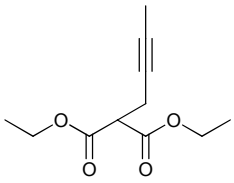
8/2) to afford **105** as a light yellow oil (30 mg, 28%); δ_H(300 MHz; $CDCl_3$) 1.25 (6 H, t, *J* 7.1), 1.32-1.50 (2 H, m), 1.50-1.72 (1 H, m), 1.89-2.53 (6 H, m), 2.17 (3 H, s), 3.04 (1 H, d, *J* 17.8), 3.11 (1 H, d, *J* 17.8), 4.20 (4 H, q, *J* 7.1); δ_C(75.5 MHz; $CDCl_3$) 13.9 (2q), 24.6 (t), 27.3 (t), 30.0 (q), 41.0 (t), 42.7 (d), 43.8 (t), 46.0 (t),58.4 (s), 61.6 (2t), 169.6 (s), 169.7 (s), 204.4 (s), 209.5 (s); HRMS *m/z* (TOF ES+) 335.1483 ($[M+Na]^+$. $C_{16}H_{24}O_6Na$ requires 335.1471).

Triethyl pent-3-yne-1,1,1-tricarboxylate 106



Triethyl pent-3-yne tricarboxylate **106** was prepared from triethyl sodiomethanetricarboxylate **76** (2.12 g, 8.32 mmol) and 1-bromo-2-butyne (0.73 mL, 8.32 mmol)) according to GP3. After 24 h, work-up afforded alkynyl triester **106** as an orange liquid, used in the subsequent step with no further purification (2.18 g, 92%); R_f 0.53 (hexane/EtOAc: 7/3); δ_H(300 MHz; $CDCl_3$) 1.28 (9 H, t, *J* 7.1, 3 × OCH_2CH_3), 1.75 (3 H, t, *J* 2.3, $CCH_2C{\equiv}CH_3$), 2.96 (2 H, q, *J* 2.3, $CCH_2C{\equiv}CH_3$), 4.27 (3 H, q, *J* 7.1, 3 × OCH_2CH_3), 4.28 (3 H, q, *J* 7.1, 3 × OCH_2CH_3); δ_C(75.5 MHz; $CDCl_3$) 3.6 (q, CH_3), 13.9 (3 q, OCH_2CH_3), 23.7 (t, $CH_2C{\equiv}CCH_3$), 62.3 (3 t, OCH_2CH_3), 64.9 (s, $C(CO_2Et)_3$), 73.4 (s, $CH_2C{\equiv}CCH_3$), 78.1 (s, $CH_2C{\equiv}CCH_3$), 166.0 (3 s, CO_2Et); m/z (TOF ES+) 307.1 ($[M+Na]^+$, 100%).

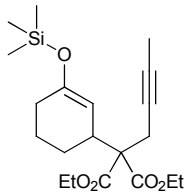
Diethyl 2-(but-2-yn-1-yl)malonate 107



Diethyl 2-(but-2-yn-1-yl)malonate **107** was synthesised from alkynyl triester **106** (2.17g, 7.65 mmol) according to GP4. After 5 min, work-up afforded diester **107** as an orange liquid (1.55 g, 95%); R_f 0.66 (hexane/EtOAc: 7/3); υ_{max}(film)/cm^{-1} 2983, 1731 (C=O); δ_H(300 MHz; $CDCl_3$) 1.27 (6 H, t, *J* 7.1, 2 × OCH_2CH_3), 1.74 (3 H, t, *J* 2.5, $CCH_2C{\equiv}CH_3$), 2.71 (2 H, dq, *J* 7.7 and 2.5, $CCH_2C{\equiv}CH_3$), 3.50 (1 H, t, *J* 7.7, $CHCH_2C{\equiv}CH_3$), 4.21 (4 H, q, *J* 7.1, 2 × OCH_2CH_3); δ_C(75.5 MHz; $CDCl_3$) 3.4 (q, CH_3), 14.0 (2 q, OCH_2CH_3), 18.8 (t, $CH_2C{\equiv}CCH_3$), 51.7 ($CH(CO_2Et)_2$), 61.6 (2 t, OCH_2CH_3), 74.7 (s, $CH_2C{\equiv}CCH_3$), 77.8 (s, $CH_2C{\equiv}CCH_3$), 168.2 (2 s, CO_2Et); *m/z* (TOF ES+) 235.0 ($[M+Na]^+$, 100%).

Data were in agreement with those reported in the literature.[119]

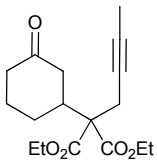
Diethyl 2-(but-2-yn-1-yl)-2-(3-((trimethylsilyl)oxy)cyclohex-2-en-1-yl)malonate 108



Diethyl 2-(but-2-ynyl)malonate **107** (1.00 g, 4.71 mmol) was added dropwise over 5 min to a suspension of NaH (280 mg, 7.00 mmol, 60% dispersion in mineral oil) in THF (7 mL) at 0°C. After the evolution of H_2, 2-cyclohexen-1-one (0.35 mL, 3.60 mmol) was added to the reaction mixture, followed by the addition of TMSOTf (0.72 mL, 3.98 mmol) at 0°C. The mixture was stirred at 0°C for 4 h and 30 min before NH_4Cl solution (40 mL) was added,

followed by EtOAc (40 mL). The two layers were separated. The organic layer was washed with brine (40 mL), dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc: 8/2) to afford the *silyl enol ether* **108** as a colourless oil (1.21 g, 88%). R_f 0.67 (hexane/EtOAc: 8/2); υ_{max} (film)/cm^{-1} 2926, 1727 (C=O), 1664 (C=C); δ_H(300 MHz; $CDCl_3$) 0.18 (9 H, s), 1.19-1.29 (6 H, m), 1.46-1.65 (2 H, m), 1.73 (3 H, t, *J* 2.5), 1.76-1.89 (2 H, m), 1.89-2.07 (2 H, m), 2.76 (2 H, q, *J* 2.5), 3.10-3.20 (1 H, m), 4.11-4.26 (4 H, m), 4.93 (1 H, br s); δ_C(75.5 MHz; $CDCl_3$) 0.3 (3 q), 3.5 (q), 14.1 (2 q), 22.3 (t), 22.9 (t), 24.0 (t), 29.7 (t), 38.4 (d), 60.6 (s), 61.0 (2 t), 74.2 (s), 78.3 (s), 104.9 (d), 152.0 (s), 170.3 (2 s); *m/z* (TOF ES+) 403.2 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 403.1934 ($[M+Na]^+$. $C_{20}H_{32}O_5SiNa$ requires 403.1917).

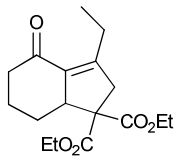
Diethyl 2-(but-2-yn-1yl)-2-(3-oxocyclohexyl)malonate 109



TBAF (2.2 mL, 2.20 mmol, 1 M in THF) was added to a solution of silyl enol ether **108** (700 mg, 1.83 mmol) in THF (15 mL) at – 35 °C. The mixture was stirred for 30 min at this temperature, before NH_4Cl solution (40 mL) was added to quench the reaction. The aqueous phase was extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc: 8/2) to afford *ketoalkyne* **109** as a yellow oil (335 mg, 59%); R_f 0.28 (hexane/EtOAc: 8/2); υ_{max} (film)/cm^{-1} 2979, 2938, 2868, 1727 (C=O); δ_H(300 MHz; $CDCl_3$) 1.26 (6 H, t, *J* 7.1), 1.31-1.47 (1 H, m), 1.61-1.70 (1 H, m), 1.73 (3 H, t, *J* 2.6), 2.02-2.17 (2 H, m), 2.24 (2 H, td, *J* 14.3 and 7.7),

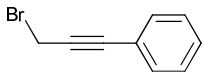
2.36-2.46 (1 H, m), 2.54-2.71 (2 H, m), 2.78 (1 H, dq, J_{AB} 17.1 and 2.6), 2.79 (1 H, dq, J_{AB} 17.1 and 2.6), 4.13-4.30 (4 H, m); δ_C(75.5 MHz; $CDCl_3$) 3.4 (q), 14.0 (2 q), 23.0 (t), 24.7 (t), 27.9 (t), 40.5 (d), 41.0 (t), 43.5 (t), 59.9 (s), 61.4 (2 t), 73.2 (s), 79.0 (s), 169.3 (s), 169.4 (s), 210.3 (s); *m/z* (TOF ES+) 331.1 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 331.1526 ($[M+Na]^+$. $C_{17}H_{24}O_5Na$ requires 331.1521).

diethyl 3-ethyl-4-oxo-5,6,7,7a-tetrahydro-1H-indene-1,1(2H,4H)-dicarboxylate 110



Ketoalkyne **109** (201 mg, 0.65 mmol) was reacted with with Ph_3PAuCl/AgOTf (19.3 mg/10.5 mg, 0.039 mmol) in CH_2Cl_2 according to GP10. After 28 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) provided enone **110** as a yellow oil (103 mg, 51%); δ_H(300 MHz; $CDCl_3$) 1.06 (2 H, t, *J* 7.6), 1.13-1.22 (1 H, m), 1.25 (3 H, t, *J* 7.1), 1.26 (3 H, t, *J* 7.1), 1.48-1.52 (1 H, m), 1.64-1.86 (1 H, m), 1.86-2.37 (3 H, m), 2.39-2.70 (3 H, m), 2.75 (1 H, br d, J_{AB} 18.2), 3.17 (1 H, br d, J_{AB} 18.2), 3.65-3.76 (1 H, m), 4.09-4.33 (4 H, m); δ_C(75.5 MHz; $CDCl_3$) 10.3 (q), 12.3 (q), 12.4 (q), 20.9 (t), 21.7 (t), 25.8 (t), 39.1 (t), 41.6 (t), 50.0 (d), 59.6 (t), 59.7 (t), 59.9 (s), 129.5 (s), 153.5 (s), 168.6 (s), 169.5 (s), 197.3 (s); *m/z* (TOF ES+) 331 ($[M+Na]^+$, 100%).

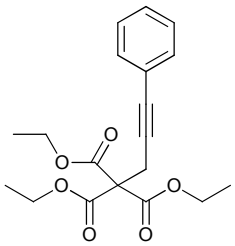
1-Phenyl-3-bromoprop-1-yne 111



Bromine (1.6 mL, 30.26 mmol) was added dropwise over 5 min at 0 °C to a solution of triphenyl phosphine (7.94 g, 30.26 mmol) in CH_2Cl_2 (80 mL). The reaction mixture was stirred for 30 min, before phenyl-2-propyn-1-ol (3.2 mL, 26.10 mmol) was added. The solution was left to stir at 0 °C for 1 h. $Na_2S_2O_3$ solution (100 mL) was added and the aqueous layer was extracted with hexane (2 × 100 mL). The combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure until the appearance of a white precipitate. The suspension was then passed through a short silica pad eluting with hexane. Concentration under reduced pressure afforded phenyl halide **111** as a light yellow liquid (4.34 g, 85%); R_f 0.90 (hexane/EtOAc: 7/3); υ_{max}(film)/cm^{-1} 3057, 2219 (C≡C), 1597 (C=C), 1490 (C=C); δ_H(300 MHz; $CDCl_3$) 4.17 (2 H, s, CH_2Br), 7.31-7.34 (3 H, m, Ar-H), 7.43-7.46 (2 H, m, Ar-H); δ_C(75.5 MHz; $CDCl_3$) 15.3 (t, *C*H_2C≡C), 84.2 (s, CH_2C≡*C*), 86.6 (s, CH_2*C*≡C), 122.0 (s, Ar-C), 128.2 (2 d, Ar-*C*H), 128.7 (d, Ar-*C*H), 131.7 (2 d, Ar-*C*H); *m/z* (EI+) 196 ([M(^{81}Br)]$^+$, 21%), 194 (24), 115 (100), 89 (18), 74 (8).

Data were in agreement with those reported in the literature.[119]

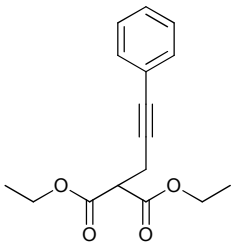
Triethyl 4-phenylbut-3-yne-1,1,1-tricarboxylate 112



Triethyl 4-phenylbut-3-yne tricarboxylate **112** was prepared from triethyl sodiomethanetricarboxylate **76** (4.00 g, 15.73 mmol) and 1-phenyl-3-bromopropyne **111** (3.00 g, 15.73 mmol) according to GP3. After 24 h, work-up afforded **112** as a brown liquid (5.21 g, 96%); R_f 0.81 (hexane/EtOAc: 7/3); δ_H(300 MHz; $CDCl_3$) 1.31 (9 H, t, *J* 7.1, 3 × OCH_2CH_3), 3.24 (2 H, s, $CCH_2C{\equiv}C$), 4.31 (6 H, q, *J* 7.1, 3 × OCH_2CH_3), 7.23-7.31 (3 H, m, Ar-H), 7.34-7.40 (2 H, m, Ar-H); δ_C(75.5 MHz; $CDCl_3$) 14.0 (3 q, OCH_2CH_3), 24.2 (t, $CH_2C{\equiv}C$), 62.5 (3 t, OCH_2CH_3), 65.1 (s, $C(CO_2Et)_3$), 82.7 (s, $CH_2C{\equiv}C$), 84.4 (s, $CH_2C{\equiv}C$), 123.4 (s, Ar-C), 127.9 (d, Ar-CH), 128.1 (2 d, Ar-CH), 131.6 (2 d, Ar-CH), 165.9 (3 s, CO_2Et); *m/z* (TOF ES+) 369.3 ($[M+Na]^+$, 100%).

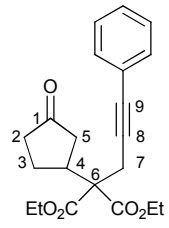
Data were in agreement with those reported in the literature.[119]

Diethyl 2-(3-phenylprop-2-yn-1-yl)malonate 113



Diethyl 2-(3-phenylprop-2-yn-1-yl)malonate **113** was synthesised from alkynyl triester **112** (5.21 g, 15.04 mmol) according to GP4. After 15 min, work-up afforded diester **113** as a brown oil (3.94 g, 95%); R_f 0.70 (hexane/EtOAc: 7/3); υ_{max}(film)/cm^{-1} 3057, 2982, 2936, 2872, 1738 (C=O), 1598 (C=C), 1491 (C=C); δ_H(300 MHz; $CDCl_3$) 1.29 (6 H, t, *J* 7.1, 2 × OCH_2CH_3), 3.00 (2 H, d, *J* 7.7, $CCH_2C{\equiv}C$), 3.64 (1 H, t, *J* 7.7, $CHCH_2C{\equiv}C$), 4.24 (4 H, q, *J* 7.1, 2 × OCH_2CH_3), 7.22-7.31 (3 H, m, Ar-H), 7.32-7.40 (2 H, m, Ar-H); δ_C(75.5 MHz; $CDCl_3$) 14.0 (2 q, OCH_2CH_3), 19.4 (t, $CH_2C{\equiv}C$), 51.5 (d, $HCCH_2C{\equiv}CPh$), 61.7 (2 t, OCH_2CH_3), 82.4 (s, $CH_2C{\equiv}C$), 85.4 (s, $CH_2C{\equiv}C$), 123.2 (s, Ar-C), 127.9 (d, Ar-CH), 128.1 (2 d, Ar-CH), 131.6 (2 d, Ar-CH), 168.0 (2 s, CO_2Et); *m/z* (TOF ES+) 297.2 ($[M+Na]^+$, 100%).

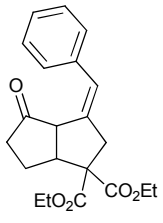
Diethyl 2-(3-oxo-cyclopentyl)-2-(3-phenyl-prop-2-yn-1-yl)malonate 114



Ketoalkyne **114** was prepared from 2-cyclopenten-1-one (0.15 mL, 1.82 mmol) and diethyl 2-(3-phenylpropargyl)malonate **113** (500 mg, 1.82 mmol) according to GP5. After 24 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded **114** as a pale yellow oil (532 mg, 82%); R_f 0.25 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 3467, 3056,

2981, 2937, 2906, 1731 (C=O), 1598 (C=C); δ_H(300 MHz; $CDCl_3$) 1.28 (6 H, t, *J* 7.1, 2 × CH_2CH_3), 1.79 (1 H, m, 3-H), 2.14-2.42 (4 H, m, 3-*H*, 2 × 2-H, 5-H), 2.63 (1 H, dd, *J* 18.9 and 7.6, 5-H), 3.01-3.21 (1 H, m, 4-H), 3.06 (1 H, d, J_{AB} 17.3, 7-H), 3.14 (1 H, d, J_{AB} 17.3, 7-*H*), 4.16-4.34 (4 H, m, 2 × CH_2CH_3), 7.27-7.31 (3 H, m, Ar-H), 7.31-7.37 (2 H, m, Ar-H); δ_C(75.5 MHz; $CDCl_3$) 14.1 (2 q, CH_2CH_3), 24.4 (t, 7-C), 25.0 (t, 3-C), 38.5 (t, 2-C), 39.7 (d, 4-C), 41.2 (t, 5-C), 59.3 (s, 6-C), 61.7 (2 t, CH_2CH_3), 83.7 (s, 8-C), 84.1 (s, 9-C), 122.9 (s, Ar-C), 128.1 (2 d, Ar-CH), 128.2 (d, Ar-CH), 131.5 (2 d, Ar-CH), 169.4 (s, CO_2Et), 169.4 (s, CO_2Et), 217.4 (s, 1-C); *m/z* (TOF ES+) 379.1 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 379.1528 ($[M+Na]^+$. $C_{21}H_{24}O_5Na$ requires 379.1521).

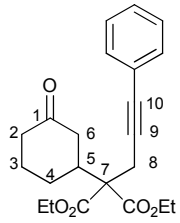
(*Z*)-diethyl 3-benzylidene-4-oxohexahydropentalene-1,1(2*H*)-dicarboxylate 115



Ketoalkyne **114** (71 mg, 0.20 mmol) was reacted with [2,4-(*t*Bu)C_6H_3O]$_3$PAuCl/AgOTf (10.6 mg/3.1 mg, 0.012 mmol) in CH_2Cl_2 (0.3 M) according to GP10. After 72 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded *keto-alkene* **(*Z*)-115** as a crystalline solid (21 mg, 29%); R_f 0.34 (hexane/EtOAc: 8/2); mp 84-85 ºC; υ_{max}(film)/cm^{-1} 2984, 1728 (C=O); δ_H(300 MHz; $CDCl_3$) 1.21 (3 H, t, *J* 7.2), 1.29 (3 H, t, *J* 7.2), 1.49-1.67 (1 H, m), 2.00-2.19 (2 H, m), 2.31-2.53 (1 H, m), 2.82 (1 H, br d, J_{AB} 15.4), 3.16 (1 H, br d, J_{AB} 15.4), 3.65-3.82 (2 H, m), 4.06-4.33 (4 H, m), 6.53 (1 H, br s), 7.19-7.36 (3 H, m), 7.56-7.63 (2 H, m); δ_C(75.5 MHz; $CDCl_3$) 14.0 (q), 14.1 (q), 22.8 (t), 39.4 (t), 42.1 (t), 45.4 (d), 52.9 (d), 61.6 (t), 61.7 (t), 62.0 (s), 127.3 (d), 127.8 (2 d), 127.8 (d), 128.2 (2 d), 135.5 (s), 136.2 (s), 169.4 (s), 170.7 (s), 215.6 (s); *m/z* (TOF ES+) 379.0 ($[M+Na]^+$, 100%);

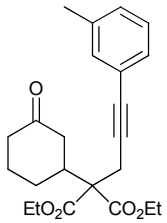
HRMS *m/z* (TOF ES+) 379.1515 ($[M+Na]^+$. $C_{21}H_{24}O_5Na$ requires 379.1521). The structure of **115** was also confirmed by X-ray crystallography.

Diethyl 2-(3-oxo-cyclohexyl)-2-(3-phenyl-prop-2-yn-1-yl)malonate 116a



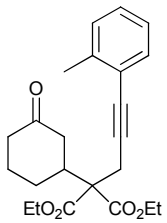
Ketoalkyne **116** was prepared from alkyne **80a** (364 mg, 1.23 mmol) and iodobenzene (160 μL, 1.48 mmol) according to GP9. After 24 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded **116** as an orange solid (436 mg, 95%); R_f 0.28 (hexane/EtOAc: 8/2); mp 53-55 °C; υ_{max}(film in nujol)/cm^{-1} 2724 (C≡CPh), 1748 (C=O, ester), 1715 (C=O, ketone); δ_H(300 MHz; $CDCl_3$) 1.28 (6 H, t, *J* 7.1, 2 × CH_2CH_3), 1.40-1.54 (1 H, m, 4-H), 1.59-1.77 (1 H, m, 3-H), 2.02-2.48 (5 H, m, 3-H, 4-H, 2 × 2-H, 6-H), 2.57-2.81 (2 H, m, 6-H, 5-H), 3.08 (2 H, s, 8-H), 4.14-4.32 (4 H, m, 2 × CH_2CH_3), 7.26-7.31 (3 H, m, Ar-H), 7.31-7.38 (2 H, m, Ar-H); δ_C(75.5 MHz; $CDCl_3$) 14.1 (2 q, CH_2CH_3), 23.5 (t, 8-C), 24.8 (t, 3-C), 27.1 (t, 4-C), 41.0 (d, 5-C), 41.1 (t, 2-C), 43.6 (t, 6-C), 60.1 (s, 7-C), 61.7 (2 t, CH_2CH_3), 83.7 (s, 9-C), 84.3 (s, 10-C), 123.0 (s, Ar-C), 128.0 (2 d, Ar-CH), 128.2 (d, Ar-CH), 131.5 (2 d, Ar-CH), 169.3 (2 s, CO_2Et), 210.1 (s, 1-C); *m/z* (TOF ES+) 393.2 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 393.1674 ($[M+Na]^+$. $C_{22}H_{26}O_5Na$ requires 393.1678).

Diethyl 2-(3-oxocyclohexyl)-2-(3-(m-tolyl)prop-2-yn-1-yl)malonate 116b



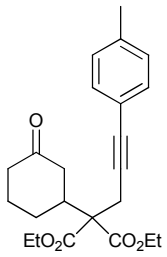
Ketoalkyne **116b** was prepared from alkyne **80a** (150 mg, 0.51 mmol) and 3-iodotoluene (78 μL, 0.61 mmol) according to GP9. After 22 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded **116b** as an orange oil (176 mg, 90%); R_f 0.34 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2980, 2935, 1714 (C=O), 1602 (C=C), 1581 (C=C); δ_H(300 MHz; $CDCl_3$) 1.28 (6 H, t, *J* 7.1), 1.40-1.53 (1 H, m), 1.59-1.76 (1 H, m), 2.04-2.29 (3 H, m), 2.31 (3 H, s), 2.32-2.47 (2 H, m), 2.59-2.80 (2 H, m), 3.07 (2 H, s), 4.19-4.31 (4 H, m), 7.05-7.20 (4 H, m); δ_C(75.5 MHz; $CDCl_3$) 14.0 (2 q), 21.0 (q), 23.4 (t), 24.7 (t), 27.0 (t), 40.8 (d), 41.0 (t), 43.5 (t), 60.0 (s), 61.5 (2 t), 83.8 (s), 83.8 (s), 122.7 (s), 128.0 (d), 128.5 (d), 128.8 (d), 132.0 (d), 137.8 (s), 169.2 (2 s), 210.0 (s); *m/z* (TOF ES+) 407.2 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 407.1829 ($[M+Na]^+$. $C_{23}H_{28}O_5Na$ requires 407.1834).

Diethyl 2-(3-oxocyclohexyl)-2-(3-(o-tolyl)prop-2-yn-1-yl)malonate 116c



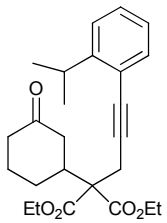
Ketoalkyne **116c** was prepared from alkyne **80a** (200 mg, 0.68 mmol) and 2-iodotoluene (104 μL, 0.81 mmol) according to GP9. After 22 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded **116c** as an orange oil (207 mg, 79%); R_f 0.37 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2971, 1716 (C=O); δ_H(300 MHz; $CDCl_3$) 1.28 (6 H, t, *J* 7.1), 1.41-1.54 (1 H, m), 1.58-1.75 (1 H, m), 2.04-2.33 (4 H, m), 2.36 (3 H, s), 2.39-2.47 (1 H, m), 2.60-2.82 (2 H, m), 3.13 (2 H, s), 4.24 (2 H, q, *J* 7.1), 4.25 (2 H, q, *J* 7.1), 7.05-7.22 (3 H, m), 7.28-7.34 (1 H, app d, *J* 7.3); δ_C(75.5 MHz; $CDCl_3$) 13.9 (2 q), 20.5 (q), 23.7 (t), 24.6 (t), 27.0 (t), 40.7 (d), 40.9 (t), 43.5 (t), 59.9 (s), 61.4 (2 t), 82.4 (s), 87.9 (s), 122.7 (s), 125.3 (d), 127.9 (d), 129.2 (d), 131.8 (d), 139.8 (s), 169.1 (s), 169.2 (s), 209.7 (s); *m/z* (TOF ES+) 407.1 ([M+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 407.1837 ([M+Na]$^+$. $C_{23}H_{28}O_5Na$ requires 407.1834).

Diethyl 2-(3-oxocyclohexyl)-2-(3-(p-tolyl)prop-2-yn-1-yl)malonate 116d



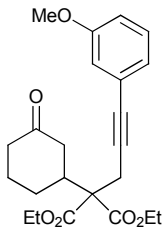
Ketoalkyne **116d** was prepared from alkyne **80a** (263 mg, 0.89 mmol) and 4-iodotoluene (234 mg, 1.07 mmol) according to GP9. After 22 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded **116d** as an orange oil (303 mg, 88%); R_f 0.32 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2948, 1737 (C=O, ester), 1726 (C=O, ketone); δ_H(300 MHz; $CDCl_3$) 1.28 (6 H, t, *J* 7.1), 1.41-1.52 (1 H, m), 1.58-1.77 (1 H, m), 2.04-2.48 (5 H, m), 2.33 (3 H, s), 2.57-2.80 (2 H, m), 3.06 (2 H, s), 4.18-4.31 (4 H, m), 7.07 (2 H, d, *J* 7.9), 7.22 (2 H, d, *J* 8.1); δ_C(75.5 MHz; $CDCl_3$) 14.0 (2 q), 21.3 (q), 23.4 (t), 24.7 (t), 27.0 (t), 40.9 (d, *C*H), 41.0 (t), 43.6 (t), 60.0 (s), 61.5 (2 t), 83.5 (s), 83.7 (s), 119.9 (s), 128.9 (2 d), 131.3 (2 d), 138.0 (s), 169.2 (s), 169.3 (s), 210.0 (s); *m/z* (TOF ES+) 407.1 ([M+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 407.1825 ([M+Na]$^+$. $C_{23}H_{28}O_5Na$ requires 407.1834).

Diethyl 2-(3-(2-isopropylphenyl)prop-2-yn-1-yl)-2-(3-oxocyclohexyl)malonate 116e



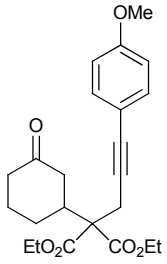
Ketoalkyne **116e** was prepared from alkyne **80a** (252 mg, 0.85 mmol) and 1-iodo-2-isopropylbenzene (163 μL, 1.02 mmol) according to GP9. After 22 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded **116e** as a pale orange oil (286 mg, 81%); R_f 0.32 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2961, 2869, 1718 (C=O); δ_H(300 MHz; $CDCl_3$) 1.21 (3 H, d, *J* 6.9), 1.22 (3 H, d, *J* 6.9), 1.28 (6 H, t, *J* 7.1), 1.40-1.53 (1 H, m), 1.58-1.74 (1 H, m), 2.03-2.48 (5 H, m), 2.60-2.82 (2 H, m), 3.13 (2 H, s), 3.35 (1 H, sept, *J* 6.9), 4.24 (2 H, q, *J* 7.1), 4.25 (2 H, q, *J* 7.1), 7.09 (1 H, ddd, *J* 8.7, 6.9 and 2.3), 7.22-7.23 (1 H, m), 7.23-7.25 (1 H, m), 7.32 (1 H, app d, *J* 6.9); δ_C(75.5 MHz; $CDCl_3$) 13.9 (2 q), 23.0 (2 q), 23.7 (t), 24.6 (t), 27.0 (t), 31.2 (d), 40.7 (d), 40.9 (t), 43.4 (t), 59.9 (s), 61.4 (2 t), 82.2 (s), 87.4 (s), 121.6 (s), 124.6 (d), 125.3 (d), 128.2 (d), 132.3 (d), 150.2 (s), 169.1 (s), 169.2 (s), 209.7 (s); *m/z* (TOF ES+) 435.3 ([M+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 435.2150 ([M+Na]$^+$. $C_{25}H_{32}O_5Na$ requires 435.2147).

Diethyl 2-(3-(3-methoxyphenyl)prop-2-yn-1-yl)-2-(3-oxocyclohexyl)malonate 116f



Ketoalkyne **116f** was prepared from alkyne **80a** (257 mg, 0.87 mmol) and 3-iodoanisole (125 μL, 1.05 mmol) according to GP9. After 5 h 30, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded **116f** as a light yellow oil (318 mg, 91%); R_f 0.32 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2939, 1715 (C=O), 1597 (C=C), 1575 (C=C); δ_H(300 MHz; $CDCl_3$) 1.28 (6 H, t, *J* 7.1), 1.45-1.76 (2 H), 2.04-2.47 (5 H), 2.56-2.79 (2 H, m), 3.07 (2 H, s), 3.78 (3 H, s), 4.15-4.31 (4 H, m), 6.80-6.87 (2 H, m), 6.90-6.98 (1 H, m), 7.14-7.21 (1 H, m); δ_C(75.5 MHz; $CDCl_3$) 14.1 (2 q), 23.5 (t), 24.8 (t), 27.1 (t), 41.0 (d), 41.1 (t), 43.6 (t), 55.2 (q), 60.1 (s), 61.6 (2 t), 83.6 (s), 84.2 (s), 114.5 (d), 116.5 (d), 124.0 (s), 124.1 (d), 129.3 (d), 159.2 (s), 169.2 (s), 169.3 (s), 210.0 (s); *m/z* (TOF ES+) 423.2 ([M+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 423.1789 ([M+Na]$^+$. $C_{23}H_{28}O_6Na$ requires 423.1784).

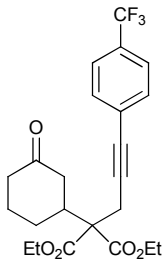
Diethyl 2-(3-(4-methoxyphenyl)prop-2-yn-1-yl)-2-(3-oxocyclohexyl)malonate 116g



Ketoalkyne **116g** was prepared from alkyne **80a** (150 mg, 0.51 mmol) and 4-iodoanisole (172 mg, 0.73 mmol) according to GP12. After 5 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded **116g** as a yellow oil (148 mg, 73%); R_f 0.23 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2945, 1717 (C=O), 1607 (C=C), 1569 (C=C); δ_H(300 MHz; $CDCl_3$) 1.27 (6 H, t, *J* 7.1), 1.45-1.77 (2 H, m), 2.03-2.30 (3 H, m), 2.30-2.47 (2 H, m), 2.58-2.79 (2 H, m), 3.05 (2 H, s), 3.79 (3 H, s), 4.15-4.32 (4 H, m), 6.79 (2 H, d, *J* 8.9), 7.27 (2 H, d, *J* 8.9); δ_C(75.5 MHz; $CDCl_3$) 13.9 (2 q), 23.4 (t), 24.7 (t), 27.0 (t), 40.8 (d), 41.0 (t), 43.5 (t), 55.1 (q), 60.0 (s), 61.5 (2 t), 82.6 (s), 83.4 (s), 113.7 (2 d), 115.0 (s), 132.7 (2 d), 159.3 (s), 169.2 (s), 169.2 (s), 209.9 (s); *m/z* (TOF ES+) 423.2 ([M+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 423.1775 ([M+Na]$^+$. $C_{23}H_{28}O_6Na$ requires 423.1784).

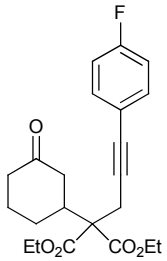
Diethyl 2-(3-oxocyclohexyl)-2-(3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-yl)malonate

116h



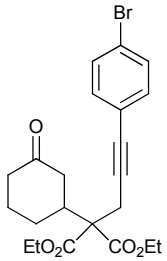
Ketoalkyne **116h** was prepared from alkyne **80a** (150 mg, 0.51 mmol) and 4-iodobenzotrifluoride (88 μL, 1.88 mmol) according to GP9. After 4 h 30, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded **116h** as a yellow oil (220 mg, 99%); R_f 0.37 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2982, 2962, 1715 (C=O); δ_H(300 MHz; $CDCl_3$) 1.29 (6 H, t, *J* 7.1), 1.40-1.55 (1 H, m), 1.59-1.77 (1 H, m), 2.03-2.48 (5 H, m), 2.56-2.78 (2 H, m), 3.08 (2 H, s), 4.20-4.31 (4 H, m), 7.37-7.44 (1 H, m), 7.47-7.59 (3 H, m); δ_C(75.5 MHz; $CDCl_3$) 13.9 (2 q), 23.4 (t), 24.6 (t), 27.0 (t), 40.9 (d), 40.9 (t), 43.5 (t), 59.9 (s), 61.6 (2 t), 82.1 (s), 86.2 (s), 123.6 (s, q $_{C-F}$, $^1J_{C-F}$ 272.3), 123.8 (s), 124.5 (d, app d $_{C-F}$, $^3J_{C-F}$ 2.6), 128.0 (d, app d $_{C-F}$, $^3J_{C-F}$ 3.1), 128.7 (d), 130.7 (s, q_{C-F}, $^2J_{C-F}$ 32.5), 134.6 (d), 169.0 (s), 169.0 (s), 209.7 (s); *m/z* (TOF ES+) 461.2 ([M+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 461.1547 ([M+Na]$^+$. $C_{23}H_{25}F_3O_5Na$ requires 461.1552).

Diethyl 2-(3-(4-fluorophenyl)prop-2-yn-1-yl)-2-(3-oxocyclohexyl)malonate 116i



Ketoalkyne **116i** was prepared from alkyne **80a** (203 mg, 0.69 mmol) and 4-fluoro-4-iodobenzene (94 μL, 0.82 mmol) according to GP9. After 22 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded **116i** as a pale orange oil (224 mg, 84%); R_f 0.30 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2980, 2936, 1714 (C=O), 1601 (C=C); δ_H(300 MHz; $CDCl_3$) 1.28 (6 H, t, *J* 7.1), 1.40-1.53 (1 H, m), 1.59-1.76 (1 H, m), 2.03-2.49 (5 H, m), 2.57-2.79 (2 H, m), 3.06 (2 H, s), 4.16-4.33 (4 H, m), 6.97 (2 H, app tt, *J* 8.8 and 2.3), 7.29 (1 H, app d, *J* 5.4), 7.31 (1 H, app d, *J* 5.4); δ_C(75.5 MHz; $CDCl_3$) 13.9 (2 q), 23.4 (t), 24.7 (t), 27.0 (t), 40.9 (d), 41.0 (t), 43.5 (t), 59.9 (s), 61.5 (2 t), 82.5 (s), 83.9 (s), 115.3 (2 d, d_{C-F}, $^2J_{C-F}$ 22.1), 119.0 (s), 133.2 (2 d, d_{C-F}, $^3J_{C-F}$ 8.2), 162.1 (s, d_{C-F}, $^1J_{C-F}$ 249), 169.1 (s), 169.2 (s), 209.9 (s); *m/z* (TOF ES+) 411.1 ([M+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 411.1578 ([M+Na]$^+$. $C_{22}H_{25}FO_5Na$ requires 411.1584).

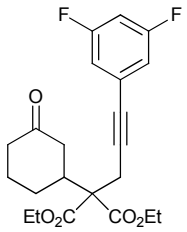
Diethyl 2-(3-(4-bromophenyl)prop-2-yn-1-yl)-2-(3-oxocyclohexyl)malonate 116j



Ketoalkyne **116j** was prepared from alkyne **80a** (228 mg, 0.77 mmol) and 1-bromo-4-iodobenzene (295 mg, 1.04 mmol) according to GP9. After 22 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded **116j** as a yellow oil (300 mg, 87%); R_f 0.35 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2980, 2936, 1714 (C=O); δ_H(300 MHz; $CDCl_3$) 1.28 (6 H, t, *J* 7.1), 1.40-1.55 (1 H, m), 1.58-1.76 (1 H, m), 2.03-2.48 (5 H, m), 2.56-2.77 (2 H, m), 3.05 (2 H, s), 4.17-4.33 (4 H, m), 7.19 (2 H, app d, *J* 8.5), 7.40 (2 H, app d, *J* 8.6); δ_C(75.5 MHz; $CDCl_3$) 13.9 (2 q), 23.4 (t), 24.6 (t), 26.9 (t), 40.9 (d), 40.9 (t), 43.4 (t), 59.9 (s), 61.5 (2 t), 82.5 (s), 85.6 (s), 121.8 (s), 122.1 (s), 131.3 (2 d), 132.8 (2 d), 169.0 (s), 169.0 (s), 209.6 (s); *m/z* (TOF ES+) 471.0 ([M(^{79}Br)+Na]$^+$, 88%), 473.0 ([M(^{81}Br)+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 471.0792 ([M(^{79}Br)+Na]$^+$. $C_{22}H_{25}O_5BrNa$ requires 471.0783).

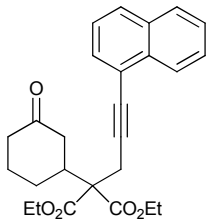
Diethyl diethyl 2-(3-(3,5-difluorophenyl)prop-2-yn-1-yl)-2-(3-oxocyclohexyl)malonate

116k



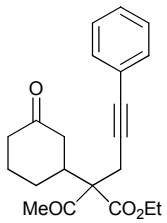
Ketoalkyne **116k** was prepared from alkyne **80a** (209 mg, 0.71 mmol) and difluoroiodobenzene (208 mg, 0.82 mmol) according to GP9. After 24 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded **116k** as a light orange oil (264 mg, 91%); R_f 0.39 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 3082, 2981, 2936, 1715 (C=O), 1617, 1585 (C=C); δ_H(300 MHz; $CDCl_3$) 1.28 (6 H, t, *J* 7.1), 1.39-1.55 (1 H, m), 1.59-1.80 (1 H, m), 2.03-2.49 (5 H, m), 2.54-2.76 (2 H, m), 3.06 (2 H, s), 4.17-4.33 (4 H, m), 6.76 (1 H, app tt, $^3J_{H-F}$ 11.1 and $^4J_{H-H}$ 2.1), 6.80-6.89 (2 H, m); δ_C(75.5 MHz; $CDCl_3$) 13.9 (2 q), 23.3 (t), 24.6 (t), 26.9 (t), 40.9 (t), 40.9 (d), 43.4 (t), 59.8 (s), 61.6 (2 t), 81.4 (s), 86.8 (s), 104.1 (d, t_{C-F}, $^2J_{C-F}$ 25.3), 114.2 (d, app d_{C-F}, $^2J_{C-F}$ 19.2), 114.4 (d, app d_{C-F}, $^2J_{C-F}$ 19.3), 125.5 (s, t_{C-F}, $^3J_{C-F}$ 11.7), 162.4 (s, d_{C-F}, $^1J_{C-F}$ 248.8), 162.5 (s, d_{C-F}, $^1J_{C-F}$ 248.8), 168.9 (s), 168.9 (s), 209.5 (s); *m/z* (TOF ES+) 429.2 ([M+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 429.1475 ([M+Na]$^+$. $C_{22}H_{24}F_2O_5Na$ requires 429.1490).

Diethyl 2-(3-(naphthalen-1-yl)prop-2-yn-1-yl)-2-(3-oxocyclohexyl)malonate 116l



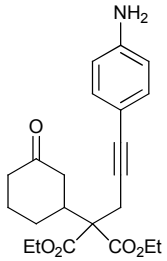
Ketoalkyne **116l** was prepared from alkyne **80a** (203 mg, 0.69 mmol) and 1-iodonaphthalene (119 μL, 0.81 mmol) according to GP9. After 24 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded **116l** as a pale orange oil (258 mg, 89%); R_f 0.31 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2979, 2942, 2873, 1713 (C=O), 1586 (C=C); δ_H(300 MHz; $CDCl_3$) 1.29 (6 H, t, *J* 7.1), 1.47-1.54 (1 H, m), 1.60-1.77 (1 H, m), 2.06-2.49 (5 H, m), 2.65-2.90 (2 H, m), 3.24 (2 H, s), 4.27 (4 H, q, *J* 7.1), 7.39 (1 H, dd, *J* 8.2 and 8.2), 7.46-7.61 (3 H, m), 7.79 (1 H, d, *J* 9.3), 7.83 (1 H, d, *J* 7.3), 8.23 (1 H, d, *J* 8.2); δ_C(75.5 MHz; $CDCl_3$) 13.9 (2 q), 23.8 (t), 24.6 (t), 27.0 (t), 40.9 (t), 41.0 (d), 43.5 (t), 60.0 (s), 61.5 (2 t), 81.6 (s), 89.1 (s), 120.5 (s), 124.9 (d), 125.8 (d), 126.1 (d), 126.5 (d), 128.0 (d), 128.3 (d), 130.2 (d), 132.9 (s), 133.2 (s), 169.1 (s), 169.2 (s), 209.6 (s); *m/z* (TOF ES+) 443.2 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 443.1844 ($[M+Na]^+$. $C_{26}H_{28}O_5Na$ requires 443.1834).

Ethyl 2-acetyl-2-(3-oxocyclohexyl)-5-phenylpent-4-ynoate 116m



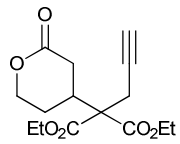
Ketoalkyne **116m** was prepared from alkyne **80f** (100 mg, 0.38 mmol) and iodobenzene (51 μL, 0.45 mmol) according to GP9. After 4 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded **116m** as a yellow oil (95 mg, 73%), in 1.1:1 mixture of diastereoisomers; R_f 0.33 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2935, 1707 (C=O), 1598 (C=C); δ_H(300 MHz; $CDCl_3$) 1.30 (3 H, t, *J* 7.1, isomer a), 1.31 (3 H, t, *J* 7.1, isomer b), 1.41-1.55 (2 H, m, both isomers), 1.58-1.77 (2 H, m, both isomers), 1.97-2.17 (4 H, m, both isomers), 2.17-2.24 (1 H, m, isomer a or b), 2.26 (6 H, br s, both isomers), 2.27-2.36 (2 H, m, both isomers), 2.36-2.57 (5 H, m, both isomers), 2.67-2.82 (2 H, m, both isomers), 2.98 (1 H, d, J_{AB} 17.8, isomer a), 3.04 (2 H, s, isomer b), 3.04 (1 H, d, J_{AB} 17.8, isomer a), 4.19-4.37 (4 H, m, both isomers), 7.27-7.36 (10 H, m, both isomers); δ_C(75. 5 MHz; $CDCl_3$) 14.0 (q), 14.0 (q), 21.9 (t), 22.0 (t), 24.8 (2 t), 26.7 (t), 27.4 (t), 27.6 (q), 27.8 (q), 40.5 (d), 40.8 (d), 41.0 (t), 41.1 (t), 43.2 (t), 43.7 (t), 61.7 (t), 61.8 (t), 65.3 (s), 65.4 (s), 83.9 (s), 84.0 (s), 84.2 (s), 84.6 (s), 122.8 (2 s), 128.1 (2 d), 128.2 (4 d), 131.4 (2 d), 131.4 (2 d), 170.0 (2 s), 202.3 (s), 202.4 (s), 209.8 (2 s); *m/z* (TOF ES+) 363.2 ([M+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 363.1580 ([M+Na]$^+$. $C_{21}H_{24}O_4Na$ requires 363.1572).

Diethyl 2-(3-(4-aminophenyl)prop-2-yn-1-yl)-2-(3-oxocyclohexyl)malonate 116n



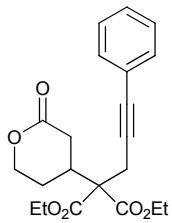
Ketoalkyne **116n** was prepared from alkyne **80a** (200 mg, 0.68 mmol) and 4-iodoaniline (179 mg, 0.82 mmol) according to GP9. After 24 h, work-up and purification by flash column chromatography (hexane/EtOAc: 6/4) afforded **116n** as a brown oil (122 mg, 47%); R_f 0.26 (hexane/EtOAc: 6/4); υ_{max}(film)/cm^{-1} 3470, 3376, 2948, 1737 (C=O, ester), 1726 (C=O, ketone), 1596 (C=C); δ_H(300 MHz; $CDCl_3$) 1.23-1.33 (6 H, m), 1.38-1.51 (1 H, m), 1.62-1.75 (1 H, m), 1.99-2.84 (8 H, m), 2.87-2.99 (1 H, m), 3.00-3.13 (1 H, m), 4.04-4.17 (1 H, m), 4.16-4.33 (4 H, m), 6.53-6.67 (1 H, m), 6.56 (1 H, d, *J* 8.6), 7.10-7.24 (1 H, m), 7.14 (1 H, d, *J* 8.6); δ_C(75.5 MHz; $CDCl_3$) 14.0 (2 q), 23.5 (t), 24.7 (t), 27.0 (t), 40.8 (d), 41.0 (t), 43.6 (t), 60.1 (s), 61.5 (2 t), 81.6 (s), 84.1 (s), 112.3 (s), 114.5 (2 d), 132.7 (2 d), 146.5 (s), 169.3 (2 s), 210.2 (s); *m/z* (TOF ES+) 408.1 ([M+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 408.1783 ([M+Na]$^+$. $C_{22}H_{27}NO_5Na$ requires 408.1787).

Diethyl 2-(2-oxotetrahydro-2H-pyran-4-yl)-2-(prop-2-yn-1-yl)malonate 80l



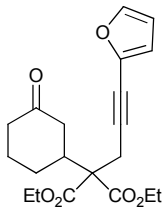
Diethyl 2(oxotetrahydro-pyranyl)-2-(propynyl) malonate **80l** was prepared from 5,6-dihydro-2H-pyran-2-one (280 µL, 3.25 mmol) and diethyl propargylmalonate **78** (767 mg, 3.87 mmol) according to GP5. After 13 d, work-up and purification by flash column chromatography (hexane/EtOAc: 6/4) afforded *lactone* **80l** as a light yellow oil (254 mg, 26%) in 1.1:1 mixture of conformers; R_f 0.51 (hexane/EtOAc: 6/4); υ_{max}(film)/cm^{-1} 3274 (C≡CH), 2984, 1725 (C=O); δ_H(300 MHz; $CDCl_3$) 1.18 (6 H, t, *J* 7.1), 1.20 (6 H, t, *J* 7.1), 1.83-2.22 (5 H, m), 2.07 (1 H, t, *J* 2.7), 2.09 (1 H, t, *J* 2.7), 2.27-2.97 (7 H, m), 2.97-3.16 (2 H, m), 4.00-4.21 (8 H, m), 4.21-4.50 (4 H, m); δ_C(75.5 MHz; $CDCl_3$) 13.6 (q), 13.8 (q), 13.9 (2 q), 22.6 (t), 24.0 (t), 25.3 (t), 25.8 (t), 34.6 (2 d), 35.1 (t), 35.1 (t), 56.1 (s), 57.5 (s), 60.7 (t), 60.7 (t), 62.1 (t), 62.3 (t), 67.9 (t), 68.9 (t), 72.2 (d), 72.9 (d), 78.5 (s), 78.8 (s), 168.1 (s), 168.4 (s), 168.5 (s), 169.2 (s), 170.8 (s), 171.0 (s); *m/z* (TOF ES+) 319.2 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 319.1172($[M+Na]^+$. $C_{15}H_{20}O_6Na$ requires 319.1158).

Diethyl 2-(2-oxotetrahydro-2H-pyran-4-yl)-2-(3-phenylprop-2-yn-1-yl)malonate 116o



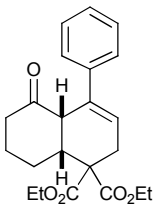
Alkynyl lactone **116o** was prepared from alkyne **80l** (157 mg, 0.53 mmol) and iodobenzene (71 µL, 0.64 mmol) according to GP9. After 24 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded **116o** as a light brown oil (176 mg, 89%) in 1.1:1 mixture of conformers; R_f 0.18 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2981, 2931, 1730 (C=O); δ_H(300 MHz; $CDCl_3$) 1.23-1.35 (6 H, m), 1.94-2.18 (2 H, m), 2.18-2.36 (1 H, m), 2.43-2.72 (1 H, m), 2.89-3.41 (3 H, m), 4.11-4.31 (4 H, m), 4.32-4.44 (1 H, m), 4.44-4.56 (1 H, m), 7.27-7.34 (3 H, m), 7.36-7.44 (2 H, m); δ_C(75.5 MHz; $CDCl_3$) 13.8 (q), 13.9 (q), 14.0 (2 q), 23.7 (t), 25.2 (t), 25.6 (t), 26.0 (t), 34.9 (d), 35.1 (d), 35.3 (2 t), 56.6 (s), 58.0 (s), 60.8 (2 t), 62.2 (t), 62.4 (t), 68.0 (t), 69.1 (t), 84.0 (s), 84.1 (s), 84.2 (s), 84.7 (s), 122.6 (s), 122.7 (s), 128.1 (6 d), 131.4 (2 d), 131.5 (2 d), 168.4 (s), 168.7 (s), 168.8 (s), 169.5 (s), 171.0 (s), 171.2 (s); *m/z* (TOF ES+) 395.0 ([M+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 395.1461 ([M+Na]$^+$. $C_{21}H_{24}O_6Na$ requires 395.1471).

Diethyl 2-(3-(furan-2-yl)prop-2-yn-1-yl)-2-(3-oxocyclohexyl)malonate 116p



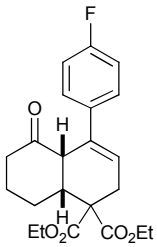
Ketoalkyne **116p** was prepared from alkyne **80a** (140 mg, 0.47 mmol) and 2-iodofuran (362 mg, 1.87 mmol) according to GP9. After 4 h 25 min, work-up and purification by flash column chromatography (hexane/EtOAc: 6/4) afforded **116p** as a yellow oil (113 mg, 66%); R_f 0.45 (hexane/EtOAc: 6/4); υ_{max}(film)/cm^{-1} 2942, 1737 (C=O, ester), 1729 (C=O, ketone); δ_H(300 MHz; $CDCl_3$) 1.25 (6 H, t, *J* 7.1), 1.36-1.73 (2 H, m), 1.97-2.45 (5 H, m), 2.45-2.74 (2 H, m), 3.07 (2 H, br s), 4.12-4.31 (4 H, m), 6.30 (1 H, dd, *J* 3.4 and 1.9), 6.43 (1 H, dd, *J* 3.4 and 0.6), 7.29 (1 H, dd, *J* 1.9 and 0.6); δ_C(75.5 MHz; $CDCl_3$) 13.9 (2 q), 23.5 (t), 24.6 (t), 26.9 (t), 40.9 (t), 41.0 (d), 43.5 (t), 59.9 (s), 61.7 (2 t), 73.9 (s), 88.9 (s), 110.6 (d), 114.6 (d), 136.7 (s), 143.1 (d), 169.0 (2 s), 209.7 (s); *m/z* (TOF ES+) 383.2 ([M+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 383.1477 ([M+Na]$^+$. $C_{20}H_{24}O_6Na$ requires 383.1471).

Diethyl 5-oxo-4-phenyl-4a,5,6,7,8,8a-hexahydronaphthalene-1,1(2*H*)-dicarboxylate 118a



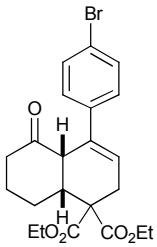
Ketoalkyne **116a** (148 mg, 0.40 mmol) was reacted with Ph_3PAuCl/AgOTf (11.9 mg/6.2 mg, 0.024 mmol) in 1,2-DCE according to GP10. After 24 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded *endo bicyclic ketone* **118a** as a light yellow oil (24 mg, 16%); R_f 0.29 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2980, 2940, 1732 (C=O, ester), 1714 (C=O, ketone); δ_H(300 MHz; $CDCl_3$) 1.25 (3 H, t, *J* 7.1), 1.26 (3 H, t, *J* 7.1), 1.57-1.76 (3 H, m), 1.93-2.11 (3 H, m), 2.82 (1 H, ddd, *J* 19.4, 4.2, 2.5), 2.96-3.12 (2 H, m), 3.94 (1 H, br s), 4.10-4.29 (4 H, m), 5.95 (1 H, td, *J* 5.3, 2.6), 7.15-7.29 (5 H, m); δ_C(75.5 MHz; $CDCl_3$) 14.0 (2 q), 23.5 (t), 25.9 (t), 27.4 (t), 39.8 (t), 40.8 (d), 52.8 (d), 56.1 (s), 61.8 (t), 61.8 (t), 124.5 (d), 127.0 (2 d), 127.3 (d), 128.1 (2 d), 134.3 (s), 139.9 (s), 169.6 (s), 169.8 (s), 211.6 (s); *m/z* (TOF ES+) 393.2 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 393.1683 ($[M+Na]^+$. $C_{22}H_{26}O_5Na$ requires 393.1678). The structure of **118a** was also confirmed by X-ray crystallography. The crystals were obtained after reaction with 2,4-DNPH.

Diethyl 4-(4-fluorophenyl)-5-oxo-4a,5,6,7,8,8a-hexahydronaphthalene-1,1(2*H*)-dicarboxylate 118i



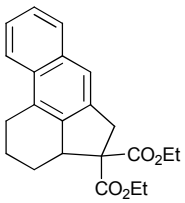
Ketoalkyne **116i** (92.0 mg, 0.24 mmol) was reacted with $Ph_3PAuCl/AgSbF_6$ (6.9 mg/4.8 mg, 0.014 mmol) in CH_2Cl_2 according to GP10. After 48 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded *endo bicyclic ketone* **118i** as a colourless oil (19.6 mg, 21%); R_f 0.39 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2971, 2941, 1729 (C=O, ester), 1729 (C=O, ketone), 1600 (C=C), 1509 (C=C); δ_H(300 MHz; $CDCl_3$) 1.25 (3 H, t, *J* 7.1), 1.26 (3 H, t, *J* 7.1), 1.52-1.75 (3 H, m), 1.93-2.12 (3 H, m), 2.74-3.11 (3 H, m), 3.91 (1 H, br s), 4.11-4.31 (2 H, m), 4.21 (2 H, q, *J* 7.1), 5.91 (1 H, td, *J* 5.3, 2.6), 6.93 (2 H, app t, *J* 8.8), 7.18 (2 H, dd, *J* 8.8 and 5.4); δ_C(75.5 MHz; $CDCl_3$) 14.0 (2 q), 23.5 (t), 25.8 (t), 27.3 (t), 39.8 (t), 40.6 (d), 52.8 (d), 56.0 (s), 61.8 (t), 61.9 (t), 115.1 (2 d, d_{C-F}, $^2J_{C-F}$ 21.4), 124.6 (d), 128.5 (2 d, d_{C-F}, $^3J_{C-F}$ 7.1), 133.3 (s), 135.8 (s), 162.1 (s, d_{C-F}, $^1J_{C-F}$ 246.2), 169.5 (s), 169.8 (s), 211.4 (s); *m/z* (TOF ES+) 411.1 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 411.1573 ($[M+Na]^+$. $C_{22}H_{25}O_5FNa$ requires 411.1584).

Diethyl 4-(4-bromophenyl)-5-oxo-4a,5,6,7,8,8a-hexahydronaphthalene-1,1(2*H*)-dicarboxylate 118j



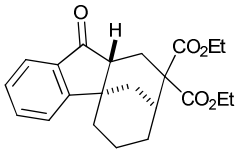
Ketoalkyne **116j** (89.6 mg, 0.2 mmol) was reacted with [2,4-(*t*Bu)C_6H_3O]$_3$PAuCl/AgOTf (10.5 mg/3.1 mg, 0.012 mmol) in CH_2Cl_2 according to GP10. After 48 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded *endo bicyclic ketone* **118j** as a light yellow oil (28 mg, 31%); R_f 0.48 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2936, 1728 (C=O, ester), 1713 (C=O, ketone), 1631 (C=C), 1587 (C=C); δ_H(300 MHz; $CDCl_3$) 1.24-1.29 (6 H, m), 1.57-1.72 (3 H, m), 1.93-2.08 (3 H, m), 2.81 (1 H, ddd, *J* 19.4, 4.2, 2.5), 2.96-3.12 (2 H, m), 3.90 (1 H, br s), 4.15-4.30 (4 H, m), 5.95 (1 H, td, *J* 5.3, 2.5), 7.08 (2 H, d, *J* 8.6), 7.36 (2 H, d, *J* 8.6); δ_C(75.5 MHz; $CDCl_3$) 14.0 (q), 14.1 (q), 23.4 (t), 25.8 (t), 27.4 (t), 39.8 (t), 40.6 (d), 52.6 (d), 56.0 (s), 61.8 (t), 61.9 (t), 121.4 (s), 125.2 (d), 128.6 (2 d), 131.3 (2 d), 133.3 (s), 138.7 (s), 169.5 (s), 169.7 (s), 211.2 (s); *m/z* (TOF ES+) 471.0 ([M(^{79}Br)+Na]$^+$, 100%), 473.0 ([M(^{81}Br)+Na]$^+$, 93%), 487.0 ([M(^{79}Br)+K]$^+$, 20%); HRMS *m/z* (TOF ES+) 471.0777 ([M(^{79}Br) +Na]$^+$. $C_{22}H_{25}O_5BrNa$ requires 471.0783).

Diethyl 1,2,3,3a-tetrahydroacephenanthrylene-4,4(5*H*)-dicarboxylate 119a



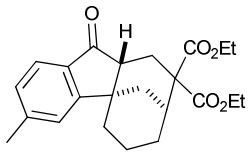
Ketoalkyne **116a** (74 mg, 0.20 mmol) was reacted with $Ph_3PAuCl/AgSbF_6$ (5.9 mg/4.1 mg, 0.012 mmol) in CH_2Cl_2, in the presence of CH_3OH (0.3 mmol, 13 μL), according to GP10. After 26 h, purification by flash column chromatography (hexane/EtOAc: 8/2) afforded acephenanthrylene derivative **119a** as a white solid (17 mg, 24%); R_f 0.54 (hexane/EtOAc: 8/2); mp 125-127 ºC; υ_{max}(film)/cm^{-1} 3052, 2942, 2894, 2830, 1752, 1722 (C=O), 1635 (C=C), 1607 (C=C); δ_H(300 MHz; $CDCl_3$) 1.16 (3 H, t, *J* 7.1), 1.33 (3 H, t, *J* 7.1), 1.22-1.46 (1 H, m), 1.86-2.06 (1 H, m), 2.24-2.44 (2 H, m), 2.77-2.96 (1 H, m), 3.19 (1 H, dd, *J* 17.5, 6.3), 3.36 (1 H, d, *J* 16.1), 3.64 (1 H, d, *J* 16.1), 3.81-3.93 (1 H, m), 3.97-4.17 (2 H, m), 4.21-4.40 (2 H, m), 7.35-7.47 (2 H, m), 7.52 (1 H, s), 7.72-7.89 (2 H, m); δ_C(75.5 MHz; $CDCl_3$) 14.1 (q), 14.1 (q), 23.7 (t), 23.8 (t), 25.8 (t), 40.0 (t), 47.8 (d), 61.0 (t), 61.4 (t), 65.3 (s), 120.0 (d), 122.7 (d), 124.8 (d), 125.0 (d), 128.5 (d), 129.3 (s), 131.3 (s), 133.9 (s), 138.2 (s), 138.5 (s), 170.2 (s), 171.4 (s); *m/z* (TOF ES+) 375.1 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 375.1575 ($[M+Na]^+$. $C_{22}H_{24}O_4Na$ requires 375.1572). The structure of **119a** was also confirmed by X-ray crystallography.

Diethyl 11-oxo-5,6,7,8,10a,11-hexahydro-4b,8-methanocycloocta[a]indene-9,9(10*H*)-dicarboxylate 121a



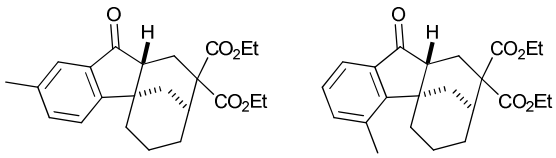
Ketoalkyne **116a** (74 mg, 0.20 mmol) was reacted with $Ph_3PAuCl/AgSbF_6$ (5.9 mg/4.1 mg, 0.012 mmol) in CH_2Cl_2 according to GP10. After 2 h, purification by flash column chromatography (hexane/EtOAc: 8/2) afforded *tetracyclic compound* **121a** as a crystalline solid (52 mg, 70%); R_f 0.33 (hexane/EtOAc: 8/2); mp 65-67 ºC; υ_{max}(film)/cm^{-1} 2941, 2856, 1718 (C=O, ester), 1703 (C=O, ketone), 1601 (C=C); δ_H(300 MHz; $CDCl_3$) 1.21 (3 H, t, *J* 7.1), 1.25 (3 H, t, *J* 7.1), 1.53-1.80 (7 H, m), 1.92-2.04 (1 H, m), 2.29 (1 H, dd, *J* 15.0 and 6.6), 2.68-2.76 (1 H, m), 2.81-2.96 (2 H, m), 4.11 (2 H, q, *J* 7.1), 4.19 (1 H, dq, *J* 10.8 and 7.1), 4.26 (1 H, dq, *J* 10.8 and 7.1), 7.35 (1 H, ddd, *J* 7.9, 7.4 and 0.9), 7.44 (1 H, td, *J* 7.6 and 0.9), 7.58 (1 H, ddd, *J* 7.6, 7.4 and 1.2), 7.72 (1 H, ddd, *J* 7.9, 1.2 and 0.9); δ_C(75.5 MHz; $CDCl_3$) 13.9 (q), 14.1 (q), 20.6 (t), 27.2 (2 t), 33.4 (d), 36.2 (t), 37.7 (t), 41.2 (s), 51.2 (d), 55.7 (s), 61.3 (t), 61.5 (t), 123.2 (d), 124.0 (d), 127.5 (d), 134.4 (s), 134.7 (d), 161.7 (s), 171.2 (s), 171.9 (s), 205.8 (s); *m/z* (TOF ES+) 393.2 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 393.1682 ($[M+Na]^+$. $C_{22}H_{26}O_5Na$ requires 393.1678). The structure of **121a** was also confirmed by X-ray crystallography.

Diethyl 3-methyl-11-oxo-5,6,7,8,10a,11-hexahydro-4b,8-methanocycloocta[a]indene-9,9(10*H*)-dicarboxylate 121b



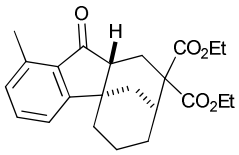
Ketoalkyne **116b** (45 mg, 0.12 mmol) was reacted with $AuCl_3/AgSbF_6$ (0.7 mg/2.4 mg, 0.002/0.007 mmol) according to GP11. After 20 min, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded *tetracyclic compound* **121b** as a light yellow solid (35.5 mg, 80%); R_f 0.46 (hexane/EtOAc: 8/2); mp 92-97 ºC; υ_{max}(film)/cm^{-1} 2927, 2876, 1727 (C=O, ester), 1705 (C=O, ketone), 1608 (C=C); δ_H(300 MHz; $CDCl_3$) 1.21 (3 H, t, *J* 7.1), 1.26 (3 H, t, *J* 7.1), 1.52-1.82 (7 H, m), 1.88-2.06 (1 H, m), 2.21 (1 H, dd, *J* 14.9, 7.0), 2.43 (3 H, s), 2.67-2.77 (1 H, m), 2.80-2.97 (2 H, m), 4.11 (2 H, q, *J* 7.1), 4.19 (1 H, dq, *J* 10.8 and 7.1), 4.26 (1 H, dq, *J* 10.8 and 7.1), 7.16 (1 H, d, *J* 7.8), 7.22 (1 H, s), 7.61 (1 H, d, *J* 7.8); δ_C(75.5 MHz; $CDCl_3$) 13.9 (q), 14.1 (q), 20.6 (t), 22.2 (q), 27.3 (t), 27.4 (t), 33.4 (d), 36.3 (t), 37.5 (t), 41.0 (s), 51.2 (d), 55.8 (s), 61.2 (t), 61.5 (t), 123.6 (d), 123.9 (d), 128.8 (d), 132.2 (s), 145.8 (s), 162.3 (s), 171.3 (s), 172.0 (s), 205.4 (s); *m/z* (TOF ES+) 407.2 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 407.1818 ($[M+Na]^+$. $C_{23}H_{28}O_5Na$ requires 407.1834).

Diethyl 2-methyl-11-oxo-5,6,7,8,10a,11-hexahydro-4b,8-methanocycloocta[a]indene-9,9(10*H*)-dicarboxylate and diethyl 4-methyl-11-oxo-5,6,7,8,10a,11-hexahydro-4b,8-methanocycloocta[a]indene-9,9(10*H*)-dicarboxylate 121c



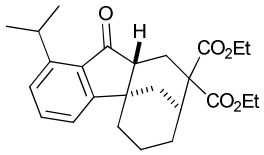
Ketoalkyne **116c** (96 mg, 0.25 mmol) was reacted with $AuCl_3/AgSbF_6$ (1.5 mg/5.3 mg, 0.005/0.015 mmol) according to GP11. After 50 min, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded *tetracyclic compound* **121c** as a light yellow oil in 1:1.2 mixture of isomers (72 mg, 75%); R_f 0.44 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2936, 1724 (C=O), 1618 (C=C), 1603 (C=C); δ_H(300 MHz; $CDCl_3$) 1.23 (3 H, t, *J* 7.1), 1.25 (3 H, t, *J* 7.1), 1.30 (3 H, t, *J* 7.1), 1.31 (3 H, t, *J* 7.1), 1.54-1.86 (13 H, m), 1.93-2.12 (2 H, m), 2.13-2.38 (3 H, m), 2.42 (3 H, s), 2.58 (3 H, s), 2.70-3.08 (6 H, m), 4.15 (4 H, q, *J* 7.1), 4.08-4.38 (4 H, m), 7.30 (1 H, d, *J* 7.4), 7.33-7.39 (2 H, m), 7.43-7.46 (1 H, m), 7.56 (1 H, br s), 7.64 (1 H, d, *J* 7.4); δ_C(75.5 MHz; $CDCl_3$) 13.9 (2 q), 14.0 (2 q), 20.1 (q), 20.5 (t), 20.6 (t), 21.0 (q), 27.2 (t), 27.3 (t), 28.2 (t), 33.0 (d), 33.4 (d), 33.6 (t), 35.0 (t), 35.0 (t), 36.3 (t), 37.6 (t), 40.8 (s), 43.1 (s), 50.5 (d), 51.3 (d), 55.6 (s), 55.7 (s), 61.2 (t), 61.2 (t), 61.4 (2 t), 121.9 (d), 122.9 (d), 123.9 (d), 127.6 (d), 134.6 (s), 135.4 (2 s), 135.8 (d), 137.4 (s), 137.9 (d), 158.4 (s), 159.3 (s), 171.2 (2 s), 171.9 (s), 172.0 (s), 205.9 (s), 206.7 (s); *m/z* (TOF ES+) 407.1 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 407.1826 ($[M+Na]^+$. $C_{23}H_{28}O_5Na$ requires 407.1834).

Diethyl 1-methyl-11-oxo-5,6,7,8,10a,11-hexahydro-4b,8-methanocycloocta[a]indene-9,9(10*H*)-dicarboxylate 121d



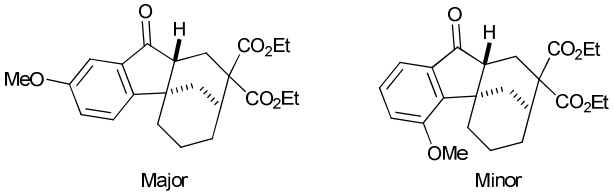
Ketoalkyne **116d** (38 mg, 0.10 mmol) was reacted with $AuCl_3/AgSbF_6$ (0.6 mg/2.1 mg, 0.002/0.006 mmol) according to GP11. After 20 min, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded *tetracyclic compound* **121d** as a light yellow solid (37 mg, 97%); R_f 0.59 (hexane/EtOAc: 8/2); mp 147-154 ºC; υ_{max}(film)/cm^{-1} 2982, 2924, 2879, 1723 (C=O, ester), 1708 (C=O, ketone), 1595 (C=C); δ_H(300 MHz; $CDCl_3$) 1.22 (3 H, t, *J* 7.1), 1.26 (3 H, t, *J* 7.1), 1.53-1.81 (7 H, m), 1.91-2.05 (1 H, m), 2.33 (1 H, dd, *J* 15.1, 6.3), 2.61 (3 H, s), 2.64-2.73 (1 H, m), 2.80-2.95 (2 H, m), 4.12 (2 H, q, *J* 7.1), 4.19 (1 H, dq, *J* 10.8 and 7.1), 4.26 (1 H, dq, *J* 10.8 and 7.1), 7.08 (1 H, d, *J* 7.4), 7.25 (1 H, d, *J* 7.4), 7.42 (1 H, t, *J* 7.4); δ_C(75.5 MHz; $CDCl_3$) 13.9 (q), 14.1 (q), 18.4 (q), 20.6 (t), 27.0 (t), 27.3 (t), 33.4 (d), 36.2 (t), 37.9 (t), 40.5 (s), 51.6 (d), 55.7 (s), 61.3 (t), 61.4 (t), 120.4 (d), 129.3 (d), 131.9 (s), 133.8 (d), 138.9 (s), 162.4 (s), 171.3 (s), 172.0 (s), 206.5 (s); *m/z* (TOF ES+) 407.2 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 407.1827 ($[M+Na]^+$. $C_{23}H_{28}O_5Na$ requires 407.1834).

Diethyl 1-isopropyl-11-oxo-5,6,7,8,10a,11-hexahydro-4b,8-methanocycloocta[a]indene-9,9(10*H*)-dicarboxylate 121e



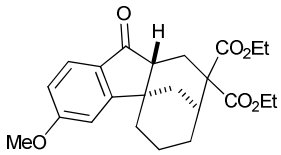
Ketoalkyne **116e** (55 mg, 0.13 mmol) was reacted with $AuCl_3/AgSbF_6$ (0.8 mg/2.8 mg, 0.003/0.008 mmol) according to GP11. After 33 min, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded *tetracyclic compound* **121e** as a colourless oil (45 mg, 82%); R_f 0.52 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2972, 2930, 2867, 1753, 1727 (C=O, ester), 1704 (C=O, ketone), 1592 (C=C); δ_H(300 MHz; $CDCl_3$) 1.08-1.24 (12 H, m), 1.47-1.81 (7 H, m), 1.86-2.02 (1 H, m), 2.33 (1 H, dd, *J* 15.2 and 5.9), 2.60 (1 H, dd, *J* 8.3 and 6.2), 2.74-2.87 (2 H, m), 3.98-4.27 (5 H, m), 7.19 (1 H, dd, *J* 6.6 and 0.9), 7.21 (1 H, d, *J* 6.6), 7.43 (1 H, t, *J* 6.6); δ_C(75.5 MHz; $CDCl_3$) 13.9 (q), 14.1 (q), 20.6 (t), 23.0 (q), 23.2 (q), 26.8 (t), 27.3 (t), 27.4 (d), 33.5 (d), 36.1 (t), 38.1 (t), 40.2 (s), 51.9 (d), 55.7 (s), 61.3 (t), 61.4 (t), 120.3 (d), 124.0 (d), 130.5 (s), 134.2 (d), 150.3 (s), 162.6 (s), 171.4 (s), 172.0 (s), 206.1 (s); *m/z* (TOF ES+) 435.1 ($[M+Na]^+$, 100%), 451.1 ($[M+K]^+$, 24%); HRMS *m/z* (TOF ES+) 435.2140 ($[M+Na]^+$. $C_{25}H_{32}O_5Na$ requires 435.2147).

Diethyl 2-methoxy-11-oxo-5,6,7,8,10a,11-hexahydro-4b,8-methanocycloocta[a]indene-9,9(10*H*)-dicarboxylate and diethyl 4-methoxy-11-oxo-5,6,7,8,10a,11-hexahydro-4b,8-methanocycloocta[a]indene-9,9(10*H*)-dicarboxylate 121f



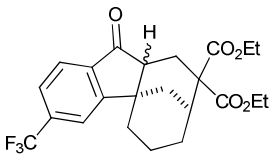
Ketoalkyne **116f** (40 mg, 0.10 mmol) was reacted with $AuCl_3/AgSbF_6$ (0.6 mg/2.1 mg, 0.002/0.006 mmol) according to GP11. After 15 min, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded *tetracyclic compound* **121f** as a yellow solid in a 7.6:1 mixture of isomers (29 mg, 72%); R_f 0.38 (hexane/EtOAc: 8/2); mp 104-108 ºC; υ_{max}(film)/cm^{-1} 2980, 2941, 2863, 1714 (C=O), 1612 (C=C); major isomer: δ_H(300 MHz; $CDCl_3$) 1.21 (3 H, t, *J* 7.1), 1.26 (3 H, t, *J* 7.1), 1.40-1.81 (7 H, m), 1.82-2.01 (1 H, m), 2.21 (1 H, dd, *J* 14.8, 7.1), 2.69-2.80 (1 H, m), 2.80-2.97 (2 H, m), 3.82 (3 H, s), 4.12 (2 H, q, *J* 7.1), 4.19 (1 H, dq, *J* 10.8 and 7.1), 4.26 (1 H, dq, *J* 10.8 and 7.1), 7.16 (1 H, s), 7.17 (1 H, dd, *J* 7.6 and 2.6), 7.32-7.38 (1 H, m); δ_C(75.5 MHz; $CDCl_3$) 13.9 (q), 14.1 (q), 20.7 (t), 27.2 (t), 27.5 (t), 33.5 (d), 36.6 (t), 37.7 (t), 40.6 (s), 51.5 (d), 55.6 (q), 55.8 (s), 61.3 (t), 61.5 (t), 105.3 (d), 123.8 (d), 124.1 (d), 135.7 (s), 154.9 (s), 159.5 (s), 171.3 (s), 172.0 (s), 205.9 (s); *m/z* (TOF ES+) 423.2 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 423.1788 ($[M+Na]^+$. $C_{23}H_{28}O_6Na$ requires 423.1784).

Diethyl 3-methoxy-11-oxo-5,6,7,8,10a,11-hexahydro-4b,8-methanocycloocta[a]indene-9,9(10*H*)-dicarboxylate 121g



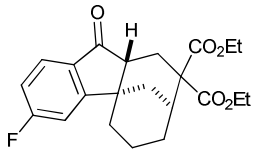
Ketoalkyne **116g** (40 mg, 0.10 mmol) was reacted with $AuCl_3/AgSbF_6$ (0.6 mg/2.1 mg, 0.002/0.006 mmol) according to GP11. After 50 min, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded *tetracyclic compound* **121g** as a yellow solid (26 mg, 65%); R_f 0.27 (hexane/EtOAc: 8/2); mp 129-131 ºC; υ_{max}(film)/cm^{-1} 2976, 2938, 2855, 1726 (C=O, ester), 1691 (C=O, ketone), 1609 (C=C), 1597 (C=C), 1585 (C=C); δ_H(300 MHz; $CDCl_3$) 1.21 (3 H, t, *J* 7.1), 1.26 (3 H, t, *J* 7.1), 1.52-1.79 (7 H, m), 1.85-2.05 (1 H, m), 2.14 (1 H, dd, *J* 14.8, 7.5), 2.73 (1 H, t, *J* 7.9), 2.86 (1 H, dd, *J* 14.8, 8.3), 2.95-2.99 (1 H, m), 3.88 (3 H, s), 4.11 (1 H, app q, *J* 7.1), 4.11 (1 H, app q, *J* 7.1), 4.19 (1 H, dq, *J* 10.8 and 7.1), 4.26 (1 H, dq, *J* 10.8 and 7.1), 6.85 (1 H, d, *J* 2.1), 6.88 (1 H, dd, *J* 8.4 and 2.1), 7.67 (1 H, d, *J* 8.4); δ_C(75.5 MHz; $CDCl_3$) 13.9 (q), 14.1 (q), 20.5 (t), 27.3 (t), 27.6 (t), 33.3 (d), 36.4 (t), 37.3 (t), 41.1 (s), 51.0 (d), 55.6 (q), 55.9 (s), 61.2 (t), 61.5 (t), 107.1 (d), 114.9 (d), 125.8 (d), 127.7 (s), 164.7 (s), 165.4 (s), 171.3 (s), 172.1 (s), 204.2 (s); *m/z* (TOF ES+) 423.2 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 423.1792 ($[M+Na]^+$. $C_{23}H_{28}O_6Na$ requires 423.1784).

Diethyl 11-oxo-3-(trifluoromethyl)-5,6,7,8,10a,11-hexahydro-4b,8-methanocycloocta[a]indene-9,9(10*H*)-dicarboxylate 121h



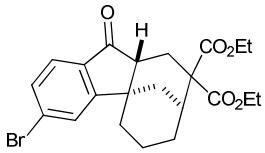
Ketoalkyne **116h** (44 mg, 0.10 mmol) was reacted with $AuCl_3/AgSbF_6$ (0.6 mg/2.1 mg, 0.002/0.006 mmol) according to GP11. After 2 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded *tetracyclic compound* **121h** as a colourless oil, in a 10:4.1 mixture of diastereoisomers (23 mg, 52%); R_f 0.38 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2942, 1727 (C=O), 1624 (C=C), 1581 (C=C); δ_H(300 MHz; $CDCl_3$) 1.21 (3 H, t, *J* 7.1), 1.26 (3 H, t, *J* 7.1), 1.53-1.84 (7 H, m), 1.85-2.05 (1 H, m), 2.31 (1 H, dd, *J* 15.0 and 6.3), 2.66-2.76 (1 H, m), 2.85 (1 H, dd, *J* 15.0 and 8.7), 2.89-2.96 (1 H, m), 4.11 (2 H, q, *J* 7.1), 4.16-4.33 (2 H, m), 7.49 (1 H, dd, *J* 8.2 and 1.5), 7.58 (1 H, d, *J* 8.2), 7.59 (1 H, br s); δ_C(75.5 MHz; $CDCl_3$) 13.9 (2 q), 14.1 (2 q), 20.9 (t), 26.8 (4 t), 27.0 (t), 33.4 (2 d), 34.2 (t), 35.8 (t), 35.9 (t), 37.7 (t), 41.6 (s), 44.6 (s), 52.6 (2 d), 55.4 (s), 55.6 (s), 61.4 (2 t), 61.5 (t), 61.6 (t), 121.4 (d, app d_{C-F}, $^3J_{C-F}$ 3.3), 122.6 (s), 124.0 (d), 125.3 (s), 127.5 (s), 127.9 (d), 128.1 (d), 131.2 (d), 132.8 (d, q_{C-F}, $^3J_{C-F}$ 5.9), 135.0 (s), 137.3 (2 s), 157.8 (s), 164.7 (s), 171.1 (s), 171.1 (s), 171.7 (s), 171.7 (s), 204.0 (s) 204.0 (s); *m/z* (TOF ES+) 461.1 ([M+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 461.1563 ([M+Na]$^+$. $C_{23}H_{25}F_3O_5Na$ requires 461.1552).

Diethyl 3-fluoro-11-oxo-5,6,7,8,10a,11-hexahydro-4b,8-methanocycloocta[a]indene-9,9(10*H*)-dicarboxylate 121i



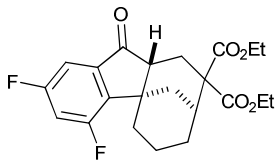
Ketoalkyne **116i** (58 mg, 0.15 mmol) was reacted with $AuCl_3/AgSbF_6$ (0.9 mg/3.0 mg, 0.003/0.009 mmol) according to GP11. After 50 min, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded *tetracyclic compound* **121i** as a light yellow solid (37 mg, 64%); R_f 0.48 (hexane/EtOAc: 8/2); mp 91-95 ºC; υ_{max}(film)/cm^{-1} 2986, 2930, 1718 (C=O), 1613 (C=C), 1591 (C=C); δ_H(300 MHz; $CDCl_3$) 1.21 (3 H, t, *J* 7.1), 1.26 (3 H, t, *J* 7.1), 1.53-1.81 (7 H, m), 1.84-2.13 (1 H, m), 2.27 (1 H, dd, *J* 14.8 and 6.5), 2.69-2.79 (1 H, m), 2.86 (1 H, dd, *J* 14.8 and 8.6), 2.90-2.97 (1 H, m), 4.11 (2 H, q, *J* 7.1), 4.19 (1 H, dq, *J* 10.8 and 7.1), 4.26 (1 H, dq, *J* 10.8 and 7.1), 7.03 (1 H, dd, *J* 8.5 and 2.1), 7.08 (1 H, dd, *J* 8.5 and 2.1), 7.72 (1 H, dd, *J* 8.3 and 5.3); δ_C(75.5 MHz; $CDCl_3$) 13.9 (q), 14.1 (q), 20.4 (t), 27.1 (t), 27.1 (t), 33.2 (d), 36.1 (t), 37.5 (t), 41.2 (s), 51.4 (d), 55.7 (s), 61.3 (t), 61.5 (t), 110.2 (d, d_{C-F}, $^2J_{C-F}$ 22.3), 115.7 (d, d_{C-F}, $^2J_{C-F}$ 23.7), 126.4 (d, d_{C-F}, $^3J_{C-F}$ 10.4), 130.8 (s), 164.7 (s, d_{C-F}, $^3J_{C-F}$ 8.9), 167.2 (s, d_{C-F}, $^1J_{C-F}$ 256.3), 171.1 (s), 171.9 (s), 203.9 (s); *m/z* (TOF ES+) 411.2 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 411.1588 ($[M+Na]^+$. $C_{22}H_{25}O_5FNa$ requires 411.1584).

Diethyl 3-bromo-11-oxo-5,6,7,8,10a,11-hexahydro-4b,8-methanocycloocta[a]indene-9,9(10*H*)-dicarboxylate 121j



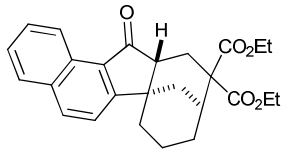
Ketoalkyne **116j** (45 mg, 0.10 mmol) was reacted with $AuCl_3/AgSbF_6$ (0.6 mg/2.1 mg, 0.002/0.006 mmol) according to GP11. After 18 min, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded *tetracyclic compound* **121j** as a light yellow solid (30 mg, 67%); R_f 0.49 (hexane/EtOAc: 8/2); mp 114-118 ºC; υ_{max}(film)/cm^{-1} 2991, 2930, 2867, 1715 (C=O), 1597 (C=C), 1573 (C=C); δ_H(300 MHz; $CDCl_3$) 1.21 (3 H, t, *J* 7.1), 1.26 (3 H, t, *J* 7.1), 1.53-1.81 (7 H, m), 1.85-2.05 (1 H, m), 2.31 (1 H, dd, *J* 15.0 and 6.3), 2.66-2.76 (1 H, m), 2.78-2.97 (2 H, m), 4.11 (2 H, q, *J* 7.1), 4.19 (1 H, dq, *J* 10.8 and 7.1), 4.26 (1 H, dq, *J* 10.8 and 7.1), 7.49 (1 H, dd, *J* 8.2 and 1.5), 7.58 (1 H, d, *J* 8.2), 7.59 (1 H, s); δ_C(75.5 MHz; $CDCl_3$) 13.9 (q), 14.1 (q), 20.5 (t), 27.0 (t), 27.1 (t), 33.3 (d), 36.0 (t), 37.7 (t), 41.3 (s), 51.4 (d), 55.6 (s), 61.4 (t), 61.6 (t), 125.4 (d), 126.8 (d), 129.9 (s), 131.1 (d), 133.3 (s), 163.3 (s), 171.1 (s), 171.8 (s), 204.4 (s); *m/z* (TOF ES+) 471.1 ($[M(^{79}Br)+Na]^+$, 100%), 474.1 (14%), 489.1 ($[M(^{81}Br)+K]^+$, 6%); HRMS *m/z* (TOF ES+) 471.0787 ($[M(^{79}Br)+Na]^+$. $C_{22}H_{25}O_5BrNa$ requires 471.0783).

Diethyl 2,4-difluoro-11-oxo-5,6,7,8,10a,11-hexahydro-4b,8-methanocycloocta[a]indene-9,9(10*H*)-dicarboxylate 121k



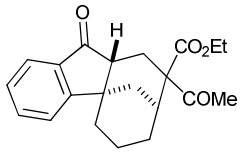
Ketoalkyne **116k** (41 mg, 0.10 mmol) was reacted with $AuCl_3/AgSbF_6$ (0.6 mg/2.1 mg, 0.002/0.006 mmol) according to GP11. After 2 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded *tetracyclic compound* **121k** as a light yellow oil (17.5 mg, 43%); R_f 0.48 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2938, 1728 (C=O), 1623 (C=C), 1595 (C=C); δ_H(300 MHz; $CDCl_3$) 1.21 (3 H, t, *J* 7.1), 1.27 (3 H, t, *J* 7.1), 1.44-1.91 (6 H, m), 2.02-2.37 (3 H, m), 2.77-2.94 (2 H, m), 2.94-3.03 (1 H, m), 4.11 (1 H, app q, *J* 7.1), 4.12 (1 H, app q, *J* 7.1), 4.19 (1 H, dq, *J* 10.8 and 7.1), 4.26 (1 H, dq, *J* 10.8 and 7.1), 7.02 (1 H, dt, *J* 9.5 and 2.2), 7.23 (1 H, dd, *J* 6.8 and 2.2); δ_C(75.5 MHz; $CDCl_3$) 13.9 (q), 14.1 (q), 20.4 (t), 27.0 (t), 27.8 (t), 33.0 (d), 35.0 (t), 35.4 (t), 41.2 (s), 51.3 (d), 55.6 (s), 61.3 (t), 61.6 (t), 106.3 (d, dd_{C-F}, $^2J_{C-F}$ 22.0 and $^4J_{C-F}$ 3.0), 110.4 (d, t_{C-F}, $^2J_{C-F}$ 26.0), 138.6 (s, app d_{C-F}, $^2J_{C-F}$ 15.5), 142.5 (s, d_{C-F}, $^3J_{C-F}$ 7.6), 160.7 (s, dd_{C-F}, $^1J_{C-F}$ 249.4 and $^3J_{C-F}$ 11.1), 162.5 (s, dd_{C-F}, $^1J_{C-F}$ 251.4 and $^3J_{C-F}$ 9.2), 171.1 (s), 171.9 (s), 204.1 (s); *m/z* (TOF ES+) 429.1 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 429.1485 ($[M+Na]^+$. $C_{22}H_{24}F_2O_5Na$ requires 429.1490).

Diethyl 13-oxo-7,8,9,10,12a,13-hexahydro-6b,10-methanocycloocta[3,4]cyclopenta[1,2-a]naphthalene-11,11(12*H*)-dicarboxylate 121l



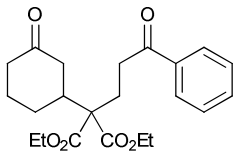
Ketoalkyne **116l** (49 mg, 0.116 mmol) was reacted with $AuCl_3/AgSbF_6$ (0.7 mg/2.4 mg, 0.002/0.007 mmol) according to GP11. After 20 min, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded *pentacyclic compound* **121l** as a white solid (43 mg, 88%); R_f 0.50 (hexane/EtOAc: 8/2); mp 130-135 ºC; υ_{max}(film)/cm^{-1} 2981, 2929, 2869, 1753, 1723 (C=O, ester), 1703 (C=O, ketone), 1626 (C=C), 1588 (C=C); δ_H(300 MHz; $CDCl_3$) 1.21 (3 H, t, *J* 7.1), 1.29 (3 H, t, *J* 7.1), 1.57-1.92 (7 H, m), 1.94-2.08 (1 H, m), 2.13 (1 H, dd, *J* 14.0, 7.5), 2.83-3.10 (3 H, m), 4.11 (1 H, app q, *J* 7.1), 4.12 (1 H, app q, *J* 7.1), 4.19 (1 H, dq, *J* 10.8 and 7.1), 4.26 (1 H, dq, *J* 10.8 and 7.1), 7.49-7.59 (2 H, m), 7.61-7.71 (1 H, m), 7.88 (1 H, d, *J* 8.1), 8.07 (1 H, d, *J* 8.4), 9.12 (1 H, d, *J* 8.9); δ_C(75.5 MHz; $CDCl_3$) 13.9 (q), 14.1 (q), 20.5 (t), 27.3 (t), 28.1 (t), 33.4 (d), 36.5 (t), 36.9 (t), 41.1 (s), 51.0 (d), 55.9 (s), 61.2 (t), 61.5 (t), 120.6 (d), 124.4 (d), 126.5 (d), 128.1 (d), 128.2 (s), 128.9 (d), 129.4 (s), 132.7 (s), 135.9 (d), 164.4 (s), 171.3 (s), 172.1 (s), 206.7 (s); *m/z* (TOF ES+) 443.2 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 443.1826 ($[M+Na]^+$. $C_{26}H_{28}O_5Na$ requires 443.1834).

Ethyl 9-acetyl-11-oxo-5,6,7,8,9,10,10a,11-octahydro-4b,8-methanocycloocta[a]indene-9-carboxylate 121m



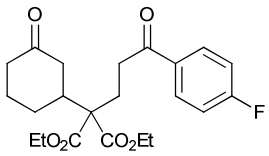
Ketoalkyne **116m** (34 mg, 0.1 mmol) was reacted with $AuCl_3/AgSbF_6$ (0.6 mg/2.1 mg, 0.002/0.006 mmol) according to GP11. After 10 min, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded *tetracyclic compound* **121m** as a light yellow oil in 1.2:1 mixture of diastereoisomers (19.4 mg, 57%); R_f 0.38 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2936, 2857, 1737, 1705 (C=O), 1604 (C=C); δ_H(300 MHz; $CDCl_3$) 1.24 (3 H, t, *J* 7.1), 1.28 (3 H, t, *J* 7.1), 1.50-1.85 (14 H, m), 1.89-2.11 (3 H, m), 2.15 (3 H, s), 2.17 (3 H, s), 2.50 (1 H, dd, *J* 15.4 and 4.4), 2.60-2.72 (1 H, m), 2.74-3.02 (5 H, m), 4.04-4.33 (2 H, q, *J* 7.1), 4.04-4.33 (2 H, q, *J* 7.1), 7.31-7.40 (2 H, m), 7.41-7.49 (2 H, m), 7.54-7.65 (2 H, m), 7.68-7.77 (2 H, m); δ_C(75.5 MHz; $CDCl_3$) 13.9 (q), 14.0 (q), 20.4 (t), 20.6 (t), 24.7 (t), 26.0 (q), 26.3 (t), 26.6 (t), 27.5 (t), 30.3 (q), 31.8 (d), 33.1 (d), 35.4 (t), 36.3 (t), 37.6 (t), 38.8 (t), 41.2 (2 s), 51.1 (d), 52.3 (d), 61.5 (t), 61.7 (t), 61.8 (s), 61.9 (s), 122.9 (d), 123.3 (d), 124.0 (2 d), 127.5 (d), 127.6 (d), 134.3 (2 s), 134.5 (d), 134.9 (d), 161.4 (s), 162.1 (s), 171.9 (s), 172.7 (s), 203.0 (s), 203.4 (s), 205.2 (s), 206.3 (s); *m/z* (TOF ES+) 363.1 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 363.1559 ($[M+Na]^+$. $C_{21}H_{24}O_4Na$ requires 363.1572).

Diethyl 2-(3-oxo-3-phenylpropyl)-2-(3-oxocyclohexyl)malonate 122a



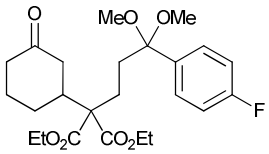
Ketoalkyne **116a** (35 mg, 0.09 mmol) was reacted with $Ph_3PAuCl/AgSbF_6$ (3.5 mg/2.5 mg, 0.007 mmol) in MeOH (0.2 M) at reflux according to GP10. After 23 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded *diketone* **122a** as a light yellow oil (32 mg, 87%); R_f 0.21 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2938, 1715 (C=O), 1686 (C=C), 1598 (C=C), 1581 (C=C); δ_H(300 MHz; $CDCl_3$) 1.26 (3 H, t, *J* 7.1), 1.27 (3 H, t, *J* 7.1), 1.39-1.73 (2 H, m), 1.99-2.58 (9 H, m), 2.97 (1 H, ddd, J_{AB} 17.4, 9.8, 5.6), 3.11 (1 H, ddd, J_{AB} 17.4, 10.0, 5.6), 4.15-4.31 (4 H, m), 7.45 (2 H, t, *J* 7.4), 7.56 (1 H, t, *J* 7.4), 7.89-7.8 (2 H, m); δ_C(75.5 MHz; $CDCl_3$) 14.1 (2 q), 24.7 (t), 26.9 (t), 27.3 (t), 34.2 (t), 41.1 (t), 43.0 (d), 43.8 (t), 60.2 (s), 61.4 (2 t), 128.0 (2 d), 128.6 (2 d), 133.1 (d), 136.6 (s), 170.1 (2 s), 198.7 (s), 210.0 (s); *m/z* (TOF ES+) 411.0 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 411.1775 ($[M+Na]^+$. $C_{22}H_{28}O_6Na$ requires 411.1784).

Diethyl 2-(3-(4-fluorophenyl)-3-oxopropyl)-2-(3-oxocyclohexyl)malonate 122i



Ketoalkyne **116i** (39 mg, 0.10 mmol) was reacted with $Ph_3PAuCl/AgSbF_6$ (3.0 mg/2.1 mg, 0.006 mmol) in MeOH (0.2 M) at reflux according to GP10. After 2 h 35, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded *diketone* **122i** as a light yellow oil (23 mg, 56%); R_f 0.23 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2940, 1714 (C=O), 1686 (C=C), 1598 (C=C); δ_H(300 MHz; $CDCl_3$) 1.26 (3 H, t, *J* 7.1), 1.27 (3 H, t, *J* 7.1), 1.45-1.72 (2 H, m), 1.93-2.57 (9 H, m), 2.93 (1 H, ddd, J_{AB} 17.4, 9.8, 5.7), 3.08 (1 H, ddd, J_{AB} 17.4, 10.0, 5.8), 4.06-4.31 (4 H, m), 7.12 (2 H, app t, *J* 8.8), 7.97 (2 H, dd, *J* 8.8 and 5.4); δ_C(75.5 MHz; $CDCl_3$) 14.1 (2 q), 24.7 (t), 26.9 (t), 27.3 (t), 34.2 (t), 41.1 (t), 43.1 (d), 43.8 (t), 60.2 (s), 61.4 (2 t), 115.7 (2 d, $^2J_{C\text{-}F}$ 21.7), 130.7 (2 d, $^3J_{C\text{-}F}$ 9.3), 133.0 (s), 165.7 (s, $^1J_{C\text{-}F}$ 254.7), 170.1 (2 s), 197.1 (s), 210.0 (s); *m/z* (TOF ES+) 429.0 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 429.1693 ($[M+Na]^+$. $C_{22}H_{27}FO_6Na$ requires 429.1689).

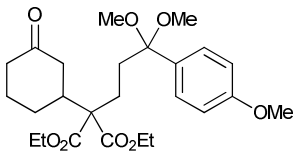
Diethyl 2-(3-(4-fluorophenyl)-3,3-dimethoxypropyl)-2-(3-oxocyclohexyl)malonate 124i



Ketoalkyne **116i** (39 mg, 0.10 mmol) was reacted with $Ph_3PAuCl/AgSbF_6$ (3.0 mg/2.1 mg, 0.006 mmol) in MeOH (0.2 M) at reflux according to GP10. After 7 h and 25 min, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded *acetal* **124i** as a colourless oil (22 mg, 49%); R_f 0.27 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2946, 2830, 1722 (C=O), 1687 (C=C), 1598 (C=C), 1507; δ_H(300 MHz; $CDCl_3$) 0.98-1.23 (3 H, m), 1.26 (3 H, t, *J* 7.1), 1.26 (3 H, t, *J* 7.1), 1.34-1.87 (3 H, m), 1.91-2.41 (5 H, m), 2.87-3.08 (2 H, m), 3.19 (6 H, br s), 4.06-4.29 (4 H, m), 7.12 (2 H, app t, *J* 8.8), 7.99 (2 H, dd, *J* 8.8 and 5.5); δ_C(75.5 MHz; $CDCl_3$) 14.1 (2 q), 22.3 (t), 27.4 (t), 27.7 (t), 32.7 (t), 34.4 (t), 34.8 (t), 39.4 (d), 47.5 (2 q), 60.4 (s), 61.1 (t), 61.1 (t), 100.4 (s), 115.7 (2 d, d_{C-F}, $^2J_{C-F}$ 21.8), 130.7 (2 d, d_{C-F}, $^3J_{C-F}$ 9.2), 133.2 (s), 165.7 (s, d_{C-F}, $^1J_{C-F}$ 254.4), 170.6 (s), 170.7 (s), 197.5 (s); *m/z* (TOF ES+) 475.1 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 475.2109 ($[M+Na]^+$. $C_{24}H_{33}FO_7Na$ requires 475.2108).

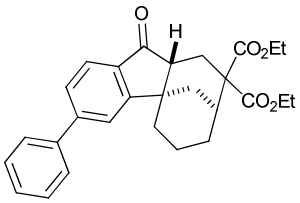
Diethyl 2-(3,3-dimethoxy-3-(4-methoxyphenyl)propyl)-2-(3-oxocyclohexyl)malonate

124g



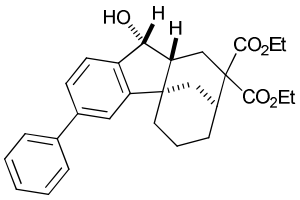
Ketoalkyne **116g** (51 mg, 0.13 mmol) was reacted with $Ph_3PAuCl/AgSbF_6$ (3.8 mg/2.7 mg, 0.008 mmol) in MeOH (0.2 M) at reflux according to GP10. After 7 h, work-up and purification by flash column chromatography (hexane/EtOAc: 8/2) afforded *acetal* **124g** as a colourless oil (38 mg, 64%); R_f 0.23 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2941, 1721 (C=O), 1677 (C=C), 1600, 1571; δ_H(300 MHz; $CDCl_3$) 0.96-1.21 (3 H, m), 1.25 (3 H, t, *J* 7.1), 1.25 (3 H, t, *J* 7.1), 1.31-1.53 (1 H, m), 1.60-1.83 (2 H, m), 1.94-2.08 (1 H, m), 2.10-2.41 (4 H, m), 2.82-3.06 (2 H, m), 3.18 (3 H, br s), 3.19 (3 H, br s), 3.85 (3 H, s), 4.07-4.29 (4 H, m), 6.91 (2 H, d, *J* 8.9), 7.93 (2 H, d, *J* 8.9); δ_C(75.5 MHz; $CDCl_3$) 14.1 (2 q), 22.3 (t), 27.3 (t), 27.9 (t), 32.7 (t), 34.0 (t), 34.8 (t), 39.2 (d), 47.5 (2 q), 55.4 (q), 60.4 (s), 61.0 (t), 61.0 (t), 100.4 (s), 113.7 (2 d), 129.8 (s), 130.3 (2 d), 163.4 (s), 170.6 (s), 170.8 (s), 197.7 (s); *m/z* (TOF ES+) 487.2 ($[M+Na]^+$, 100%); HRMS *m/z* (TOF ES+) 487.2297 ($[M+Na]^+$. $C_{25}H_{36}O_8Na$ requires 487.2308).

Diethyl 11-oxo-3-phenyl-5,6,7,8,10a,11-hexahydro-4b,8-methanocycloocta[a]indene-9,9(10*H*)-dicarboxylate 121ja



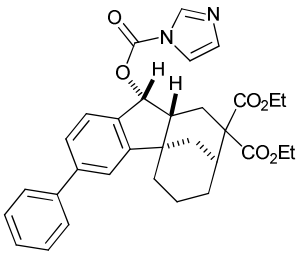
$PdCl_2(PPh_3)_2$ (2.4 mg, 0.002 mmol), CsF (21 mg, 0.14 mmol) and benzene boronic acid (8.6 mg, 0.07 mmol) were added to a solution of aryl halide **121j** (27 mg, 0.06 mmol) in DME (0.7 mL) at rt. The reaction mixture was stirred at rt under a flow of argon for 2 min, then heated at reflux for 17h. On completion of the reaction, the solution was loaded directly on silica gel column followed by elution with (hexane/EtOAc: 8/2) to afford *adduct* **121ja** as a colourless viscous oil (23 mg, 87%); R_f 0.42 (hexane/EtOAc: 8/2); υ_{max}(film)/cm^{-1} 2980, 2934, 2871, 1708 (C=O), 1604 (C=C), 1573; δ_H(300 MHz; $CDCl_3$) 1.25 (3 H, t, *J* 7.1), 1.30 (3 H, t, *J* 7.1), 1.63-1.90 (6 H, m), 2.02-2.15 (2 H, m), 2.35 (1 H, dd, J_{AB} 15.0 and 6.7), 2.78-2.86 (1 H, m), 2.93 (1 H, dd, J_{AB} 15.0 and 6.4), 2.96-3.02 (1 H, m), 4.15 (1 H, app q, *J* 7.1), 4.16 (1 H, app q, *J* 7.1), 4.23 (1 H, dq, *J* 10.7 and 7.1), 4.30 (1 H, dq, *J* 10.7 and 7.1), 6.84-6.96 (1 H, m), 7.22-7.29 (1 H, m), 7.40-7.47 (1 H, m), 7.48-7.54 (1 H, m), 7.59-7.70 (3 H, m), 7.82 (1 H, d, *J* 8.0); δ_C(75.5 MHz; $CDCl_3$) 13.9 (q), 14.1 (q), 20.6 (t), 27.3 (2 t), 33.4 (d), 36.3 (t), 37.7 (t), 41.3 (s), 51.5 (d), 55.8 (s), 61.3 (t), 61.5 (t), 115.3 (d), 121.8 (d), 124.4 (d), 127.0 (d), 127.5 (d), 128.3 (d), 128.9 (d), 129.6 (d), 133.3 (s), 140.4 (s), 147.9 (s), 162.5 (s), 171.3 (s), 172.0 (s), 205.5 (s); *m/z* (TOF ES+) 469.1 ([M+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 469.1996 ([M+Na]$^+$. $C_{28}H_{30}O_5Na$ requires 469.1991).

Diethyl 11-hydroxy-3-phenyl-5,6,7,8,10a,11-hexahydro-4b,8-methanocycloocta[a]indene-9,9(10*H*)-dicarboxylate 127



A solution of $NaBH_4$ (9.8 mg, 0.26 mmol) in MeOH (0.86 mL) was added to a solution of adduct **121ja** (19 mg, 0.04 mmol) in THF (0.81 mL). The reaction mixture was stirred at rt for 1 h 25 min before the addition of H_2O (10 mL) and CH_2Cl_2 (10 mL). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. Flash column chromatography (hexane/EtOAc: 8/2) afforded *alcohol* **127** as a white solid (19 mg, 98%); R_f 0.23 (hexane/EtOAc: 8/2); mp 170-178 °C; υ_{max}(film)/cm^{-1} 3528 (O-H), 3072, 2918, 2866, 1717 (C=O), 1601 (C=C); δ_H(300 MHz; $CDCl_3$) 1.24 (3 H, t, *J* 7.1), 1.25 (3 H, t, *J* 7.1), 1.41-1.79 (6 H, m), 1.79-2.18 (3 H, m), 2.29-2.40 (1 H, m), 2.62 (1 H, d, J_{AB} 16.2), 2.79 (1 H, br s), 3.07 (1 H, dd, J_{AB} 16.2 and 10.1), 4.03-4.31 (4 H, m), 4.93 (1 H, br s), 7.31-7.38 (2 H, m), 7.41-7.52 (4 H, m), 7.54-7.63 (2 H, m); δ_C(75.5 MHz; $CDCl_3$) 14.0 (q), 14.1 (q), 21.1 (t), 27.1 (t), 27.6 (t), 33.2 (d), 36.5 (t), 38.6 (t), 43.8 (s), 47.6 (d), 56.8 (s), 61.2 (t), 61.4 (t), 76.8 (d), 121.4 (d), 125.7 (d), 126.2 (d), 127.3 (3 d), 128.7 (2 d), 141.5 (s), 141.7 (s), 142.3 (s), 153.8 (s), 171.9 (s), 172.7 (s); *m/z* (TOF ES+) 471.2 ([M+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 471.2143 ([M+Na]$^+$. $C_{28}H_{32}O_5Na$ requires 471.2147).

Diethyl 11-(1H-imidazol-1-yl)-3-phenyl-5,6,7,8,10a,11-hexahydro-4b,8-methanocycloocta[a]indene-9,9(10*H*)-dicarboxylate 128

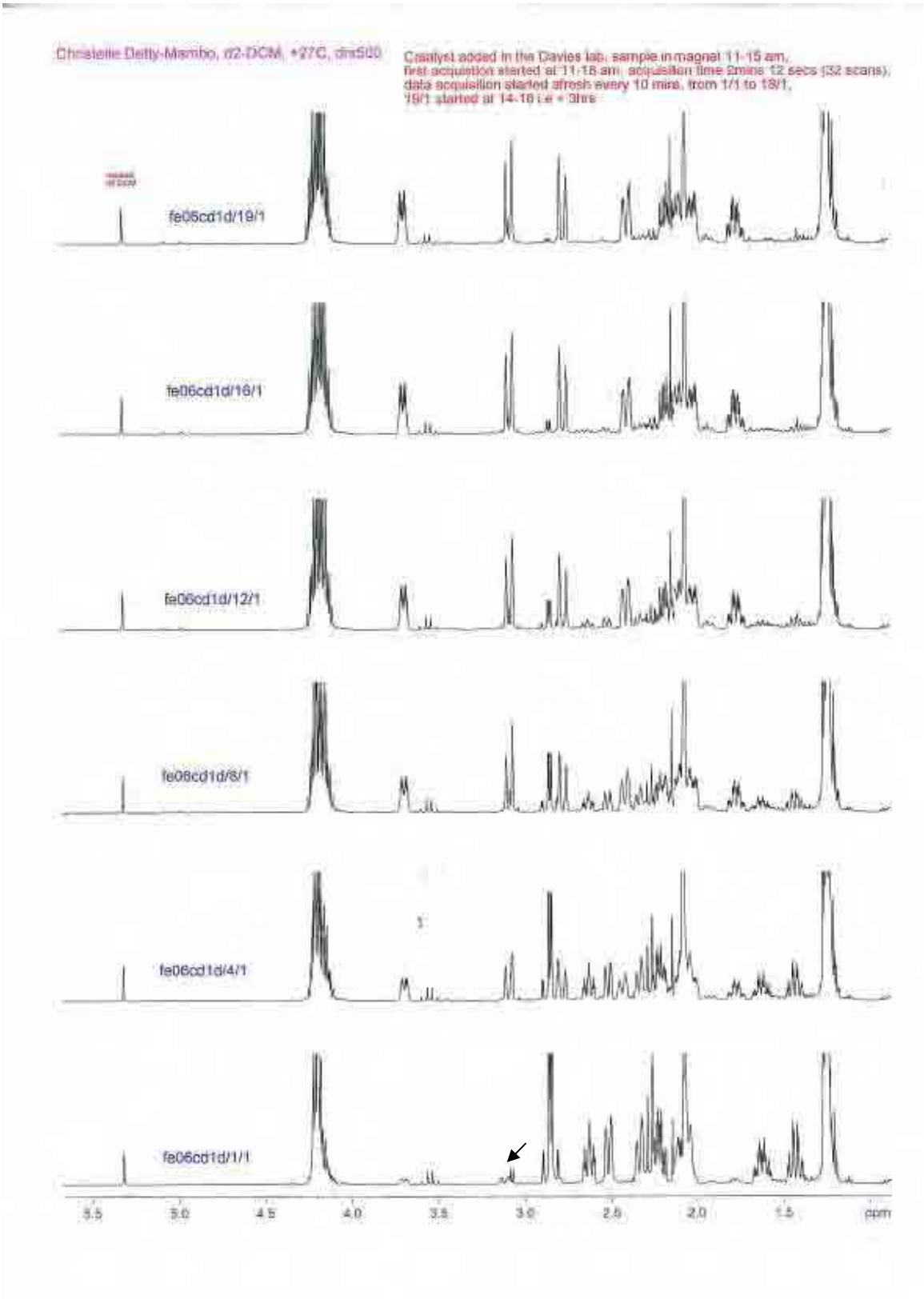


A solution of alcohol **127** (11 mg, 0.02 mmol) in THF (0.53 mL) was added to 1,1-carbonyldiimidazole (11 mg, 0.05 mmol) and the reaction mixture was stirred at 70 °C for 17 h. H_2O (10 mL) and CH_2Cl_2 (10 mL) were then added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. Flash column chromatography (hexane/EtOAc: 8/2) afforded *imidazolyl compound* **128** as a white crystalline solid (10 mg, 79%); mp 155-156 °C; υ_{max}(film)/cm^{-1} 3144, 2918, 2869, 2853, 1746 (C=O), 1720 (C=O), 1612 (C=C); δ_H(300 MHz; $CDCl_3$) 0.98 (3 H, t, *J* 7.0), 1.23 (3 H, t, *J* 7.0), 1.48-1.91 (7 H, m), 1.99-2.15 (2 H, m), 2.45 (1 H, dd, J_{AB} 16.6 and 1.5), 2.66-2.77 (1 H, m), 2.90 (1 H, br s), 3.22 (1 H, dd, J_{AB} 16.6 and 10.7), 3.33 (1 H, dq, *J* 10.8 and 7.0), 3.80 (1 H, dq, *J* 10.8 and 7.0), 4.10-4.28 (2 H, m), 6.48 (1 H, d, *J* 6.7), 7.03 (1 H, br s), 7.33-7.52 (6 H, m), 7.54-7.61 (2 H, m), 8.07 (1 H, s); δ_C(75.5 MHz; $CDCl_3$) 13.8 (q), 14.1 (q), 20.8 (t), 25.9 (t), 28.0 (t), 30.3 (d), 33.0 (d), 36.9 (t), 37.0 (t), 44.1 (s), 45.6 (d), 56.1 (s), 60.8 (t), 61.7 (t), 83.5 (d), 117.6 (d), 121.7 (d), 125.5 (d), 126.3 (d), 126.7 (d), 127.3 (d), 127.6 (d), 128.8 (d), 130.4 (d), 136.7 (s), 137.5 (d), 141.0 (s), 143.7 (s), 149.3 (s), 154.2 (s), 171. 8 (s), 171. 3 (s); *m/z* (TOF ES+) 521.2 ([M+Na]$^+$, 100%); HRMS *m/z* (TOF ES+) 521.2419 ([(M-CO_2) +Na]$^+$. $C_{31}H_{34}O_4N_2Na$ requires 521.2416).

Appendices

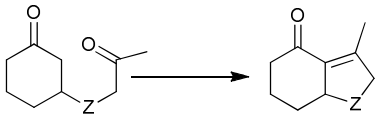
6.1 Kinetic studies

1) Experiment 1: monitored ^{1}H NMR of **80a** in the presence of $Ph_3PAuOTf$: trace amounts of diketone **105** at the early stage of the reaction.


Christelle Detty-Mambo, d2-DCM, +27C, dms500
Catalyst added in the Davies lab, sample in magnet 11-15 am,
first acquisition started at 11-18 am, acquisition time 2mins 12 secs (32 scans),
data acquisition started afresh every 10 mins, from 1/1 to 18/1,
19/1 started at 14-18 i.e = 3hrs
fe06cd1d/19/1
fe06cd1d/16/1
fe06cd1d/12/1
fe06cd1d/8/1
fe06cd1d/4/1
fe06cd1d/1/1
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

2) Experiment 2

The species generated during the course of the reaction in the presence of the ketoalkyne allows the aldol condensation



AgOTf (2.6 mg, 0.012 mmol), PPh_3AuCl (5.9 mg, 0.012 mmol) were added into a dried Schlenk under an argon atmosphere followed by the addition of CH_2Cl_2 (2 mL). The reaction mixture was stirred for 1 min, before a solution of diketone (4.3 mg, 0.014 mmol) in CH_2Cl_2 (14 µL) was added. After 2 h, no consumption of diketone was observed. Therefore, the keto alkyne was added to the reaction mixture (2.7 mg, 0.009 mmol) and after 1 min the formation of cyclised product could be observed. The reaction mixture was stirred for 24 h and then the solution was filtered through a short pad of silica gel (hexane/EtOAc: 6/4). The solvent was removed under reduced pressure. $Mass_{crude}$ = 7.9 mg, $Mass_{Internal\ Standard\ (1,2,4,5\text{-}tetramethylbenzene)}$ = 2.8 mg.

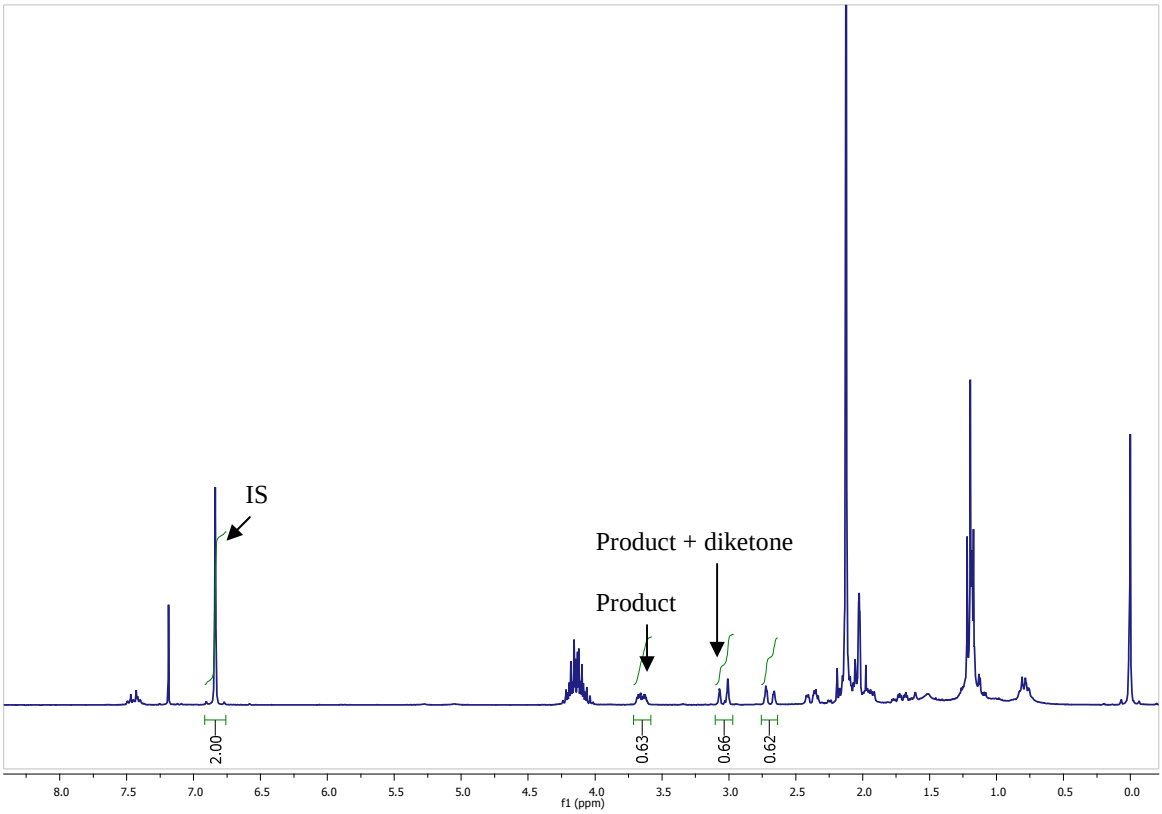
^{1}H NMR spectroscopy of experiment 2 after 24 h:

IS (0.020 mmol)

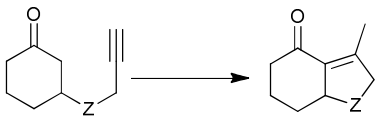
cyclised product (0.0131 mmol),

diketone (0.00031 mmol),

keto alkyne (0 mmol).



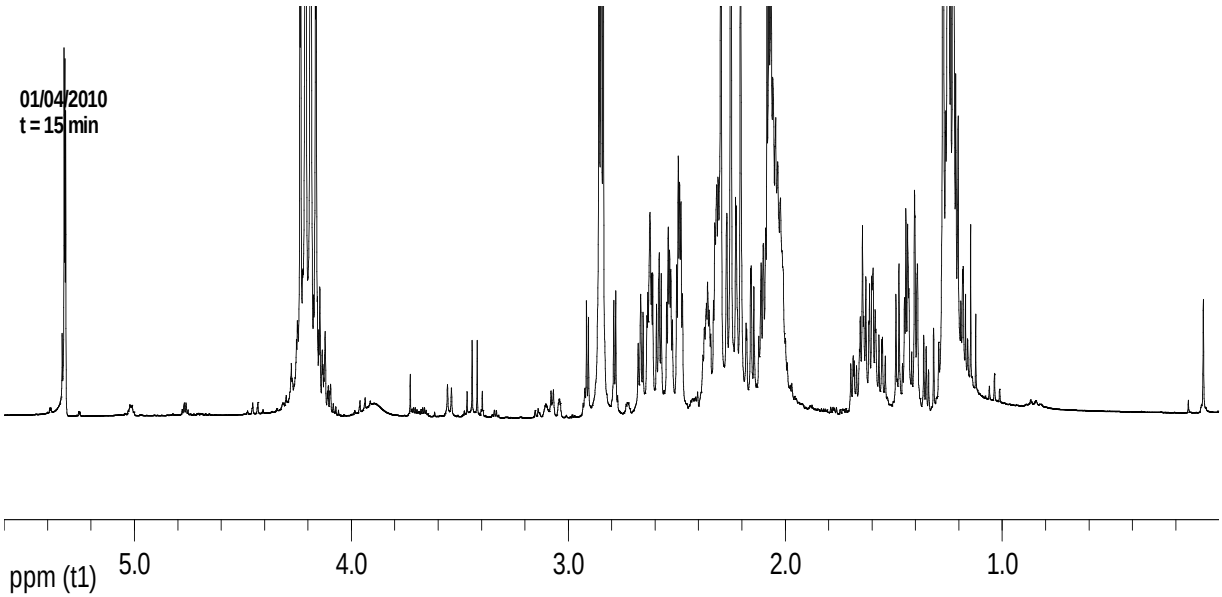
3) Experiment 3

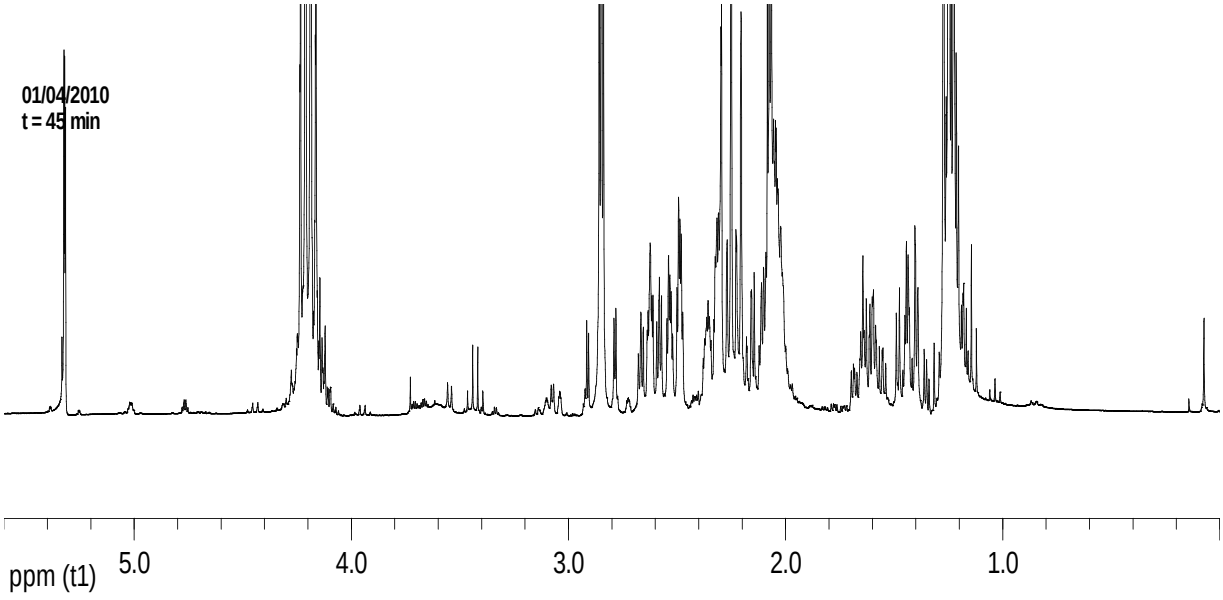


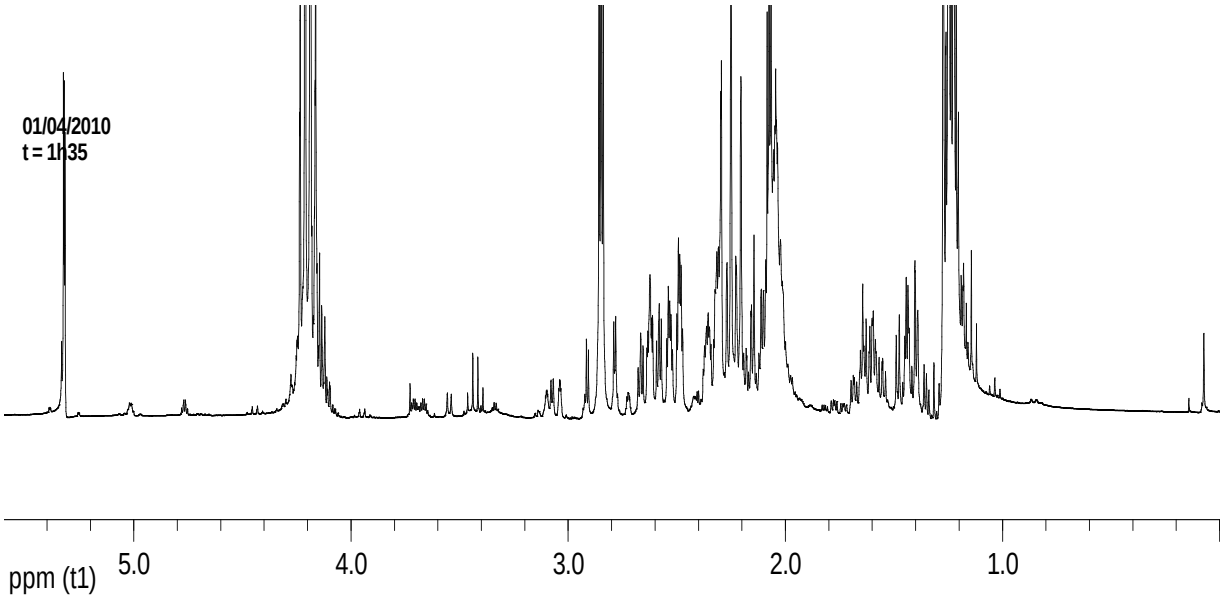
AgOTf (2.6 mg, 0.012 mmol) was added into a dried Schlenk under an argon atmosphere followed by the addition of PPh_3AuCl (5.9 mg, 0.012 mmol). Immediately after this addition, a solution of the substrate **80a** (58.7 mg, 0.2 mmol) in CD_2Cl_2 (0.8 mL) was added *via* a syringe into this system. The mixture was stirred at rt for 2 min and then was added *via* a pipette into the NMR tube under argon, after filtration through a plug of cotton wool. The Schlenk and the cotton

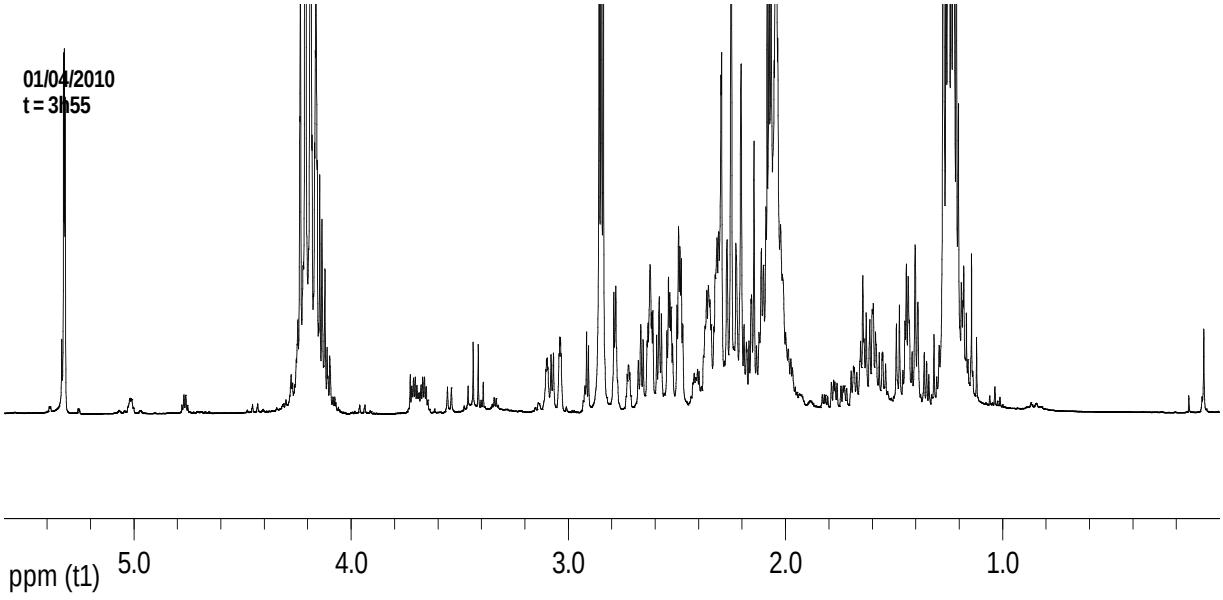
wool were washed with CD_2Cl_2 (0.2 mL). The NMR tube was shaken and the first NMR acquisition was made 15 min after the beginning of the reaction. The reaction was monitored by NMR spectroscopy. After 4.5 h, 0.1 mL of a solution of diketone in CD_2Cl_2 (0.1 M) was added into the NMR tube and the reaction mixture monitored by NMR spectroscopy. After 18.5 h, 50 µL of a solution of diketone in CD_2Cl_2 (0.2 M) was added and the monitoring of the reaction was continued until completion of the reaction (consumption of the substrate and the diketone).

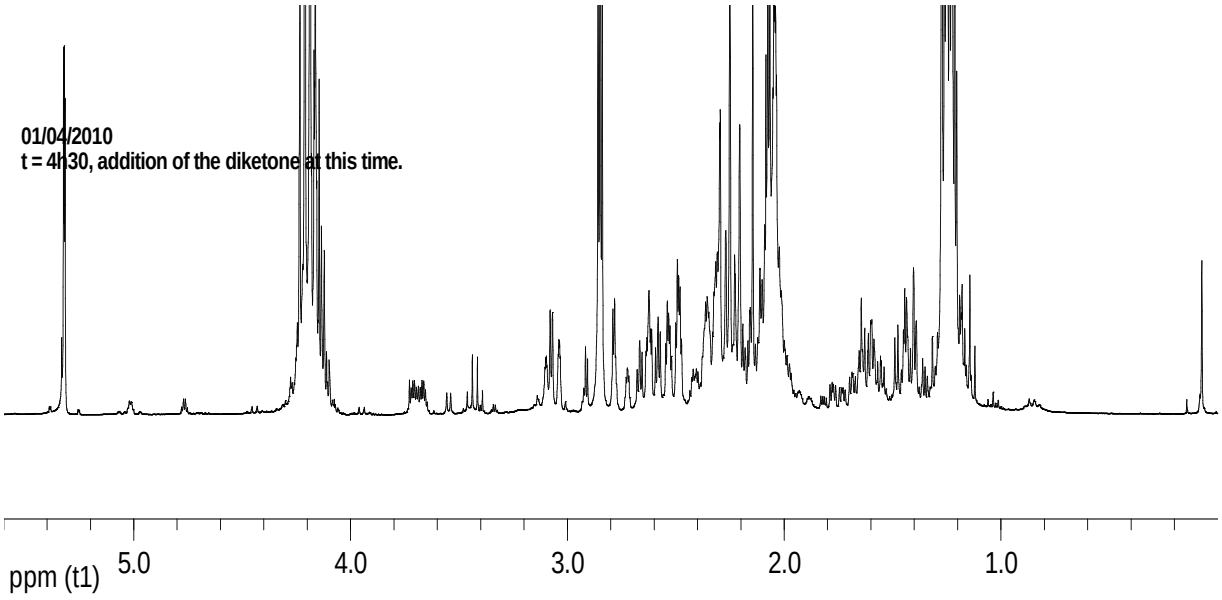
Monitored ^{1}H NMR spectroscopy of experiment 3:

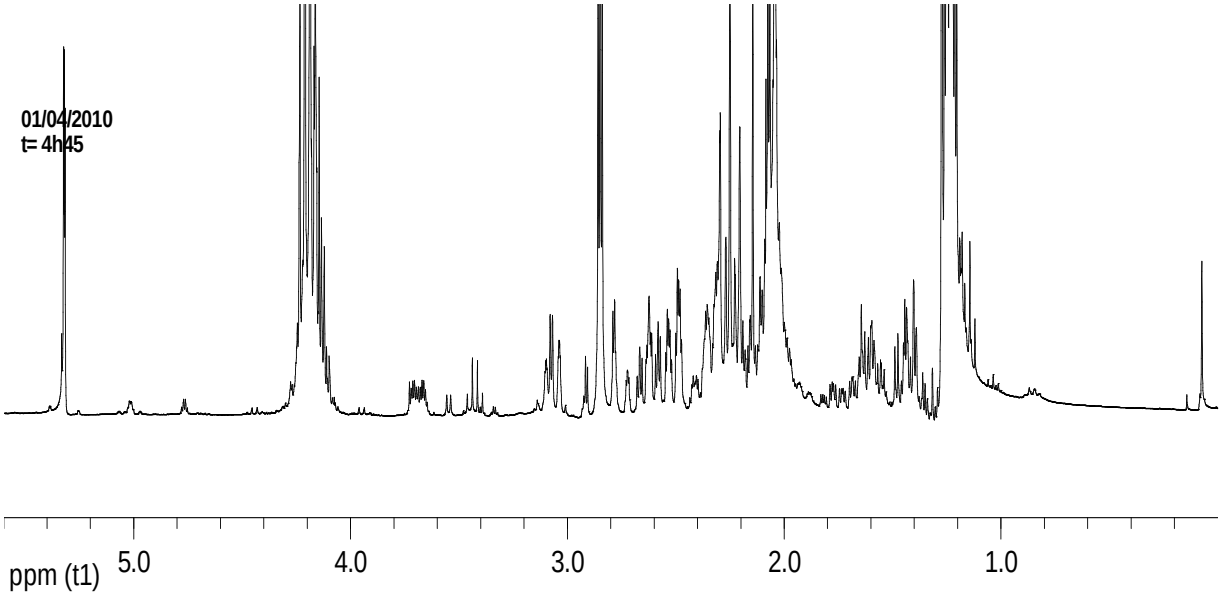


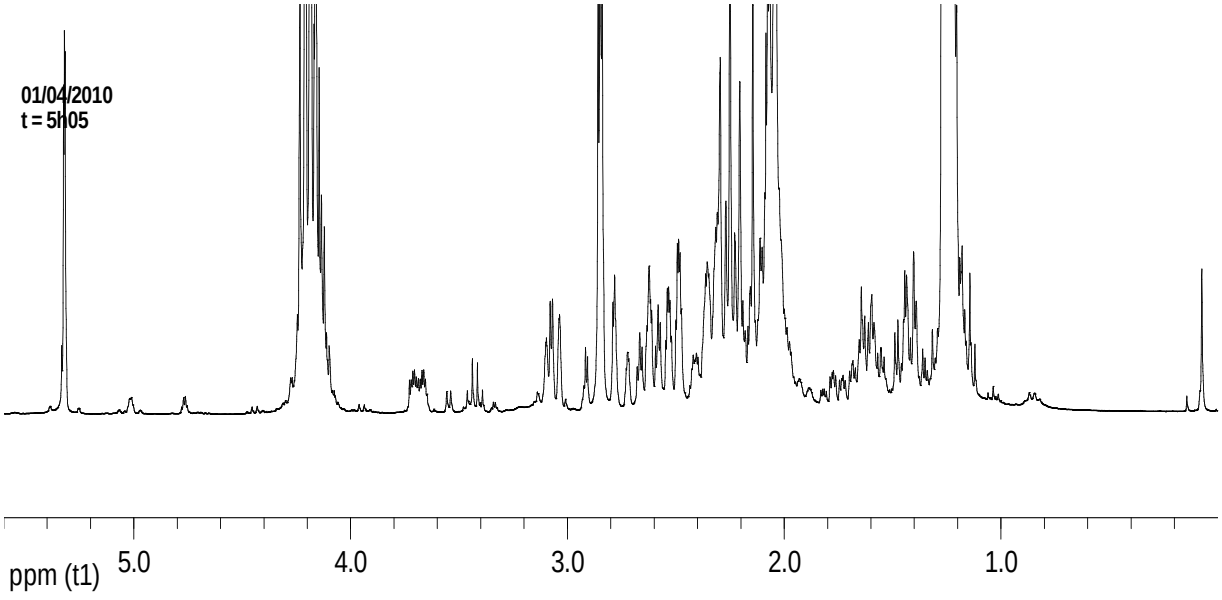

01/04/2010
t = 45 min
ppm (t1)
5.0
4.0
3.0
2.0
1.0

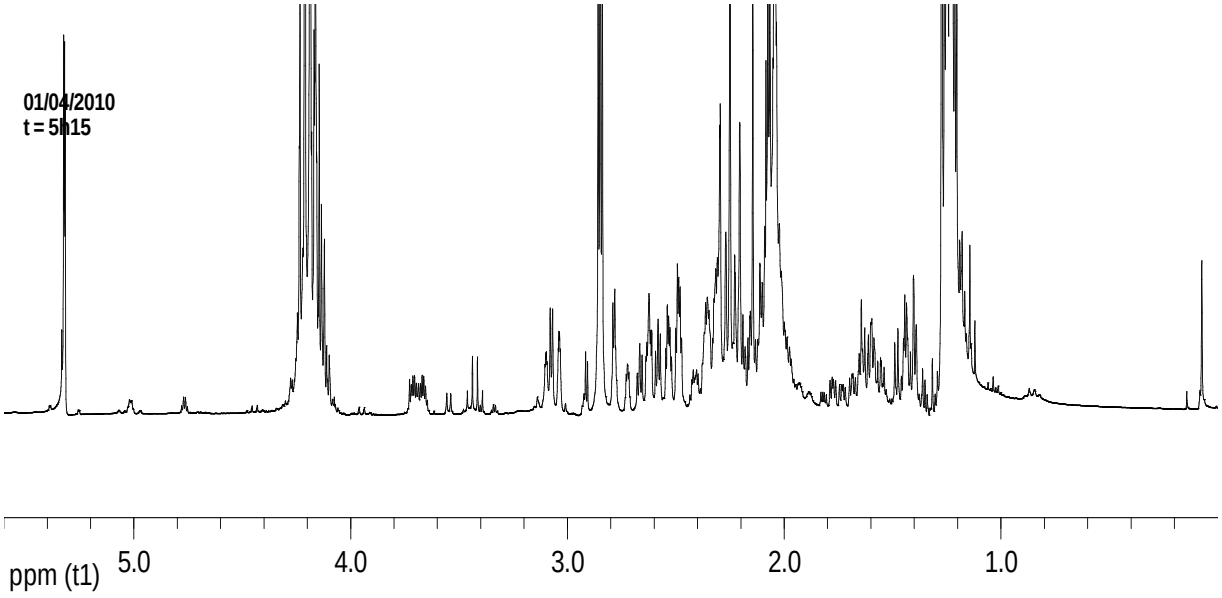

01/04/2010
t = 1h35
ppm (t1)
5.0
4.0
3.0
2.0
1.0

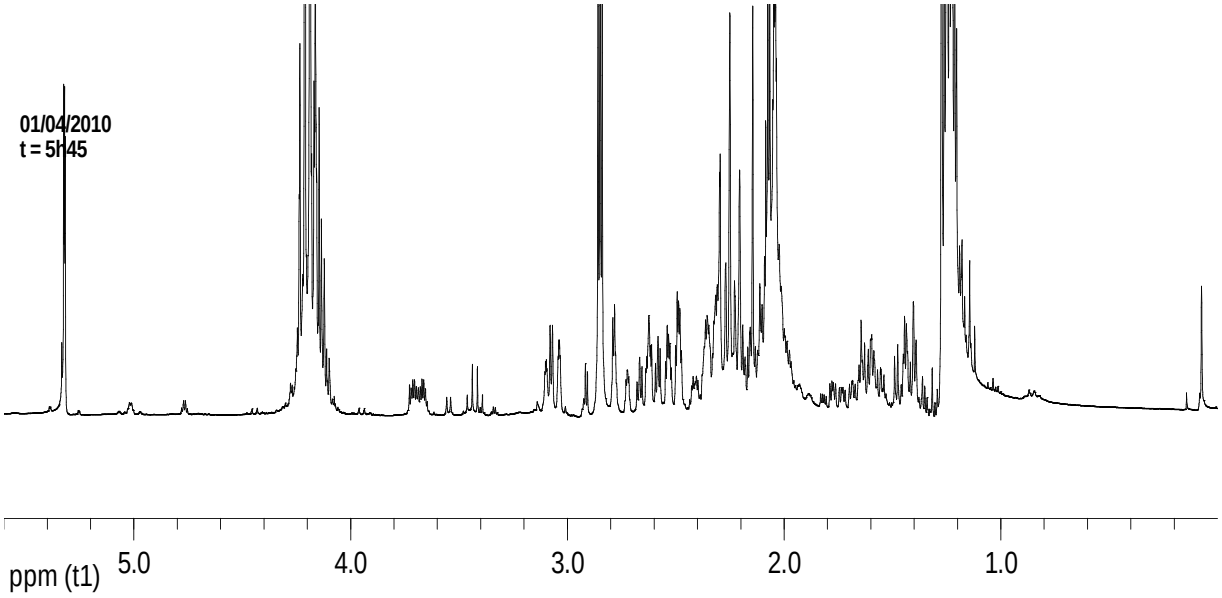

01/04/2010
t = 3h55
ppm (t1)
5.0
4.0
3.0
2.0
1.0

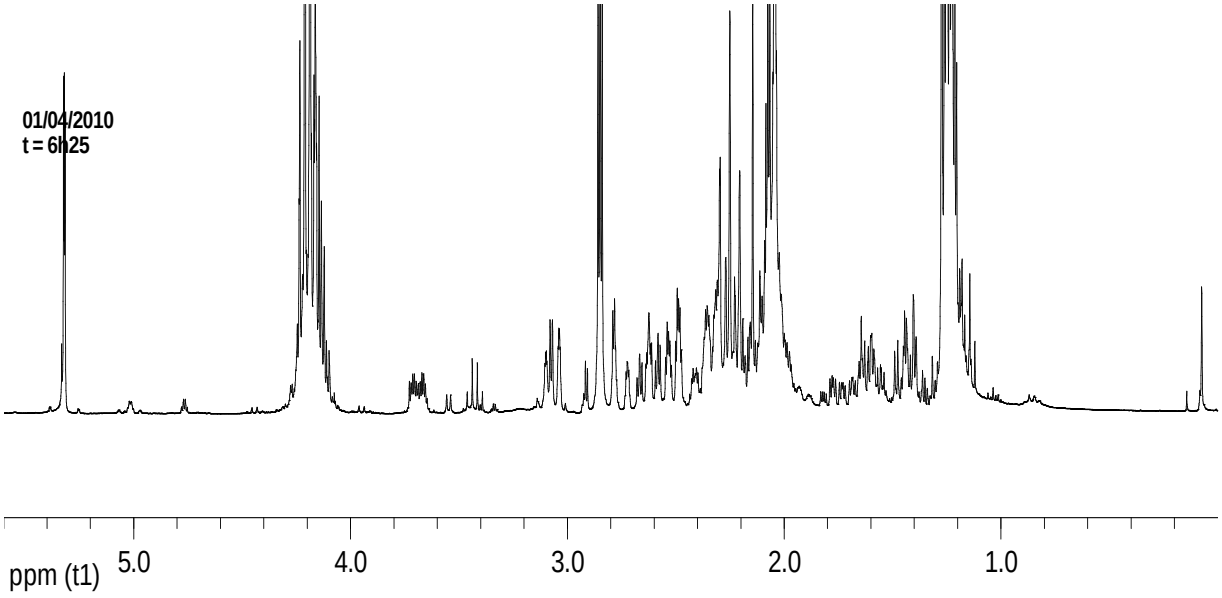

01/04/2010
t = 4h30, addition of the diketone at this time.
ppm (t1)
5.0
4.0
3.0
2.0
1.0

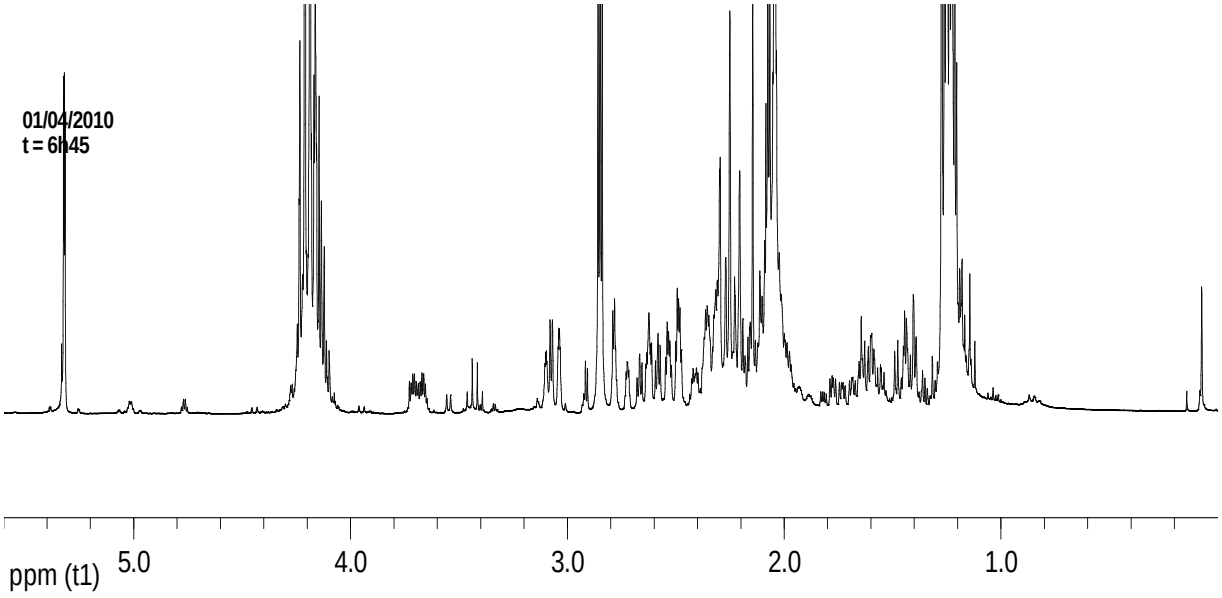

01/04/2010
t= 4h45
ppm (t1)
5.0
4.0
3.0
2.0
1.0

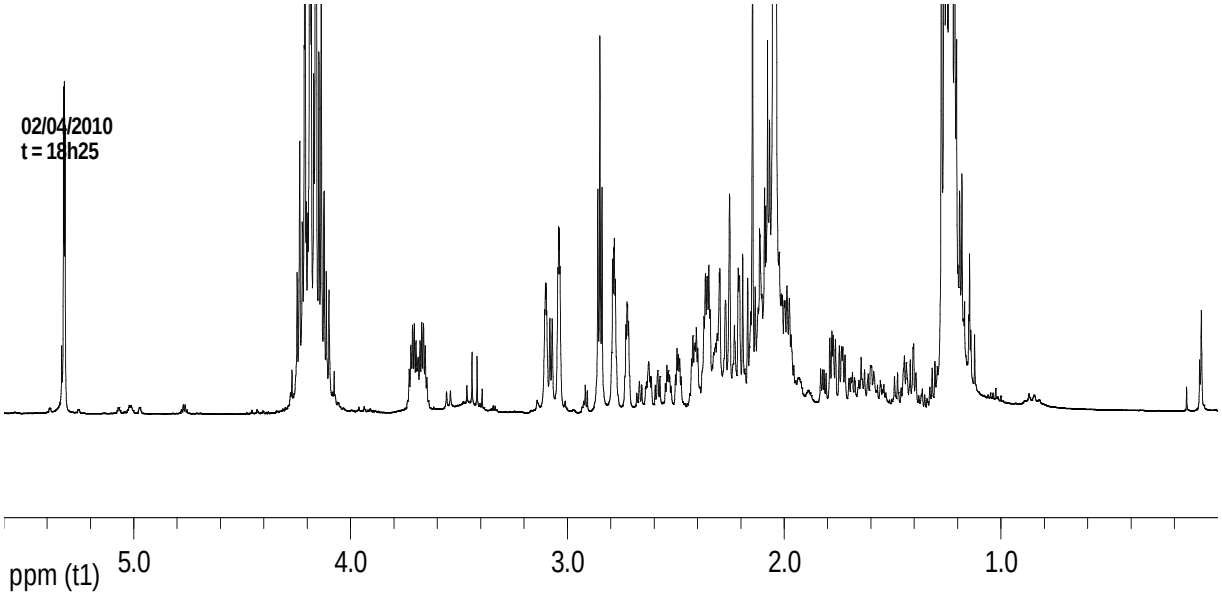

01/04/2010
t = 5h05
ppm (t1)
5.0
4.0
3.0
2.0
1.0

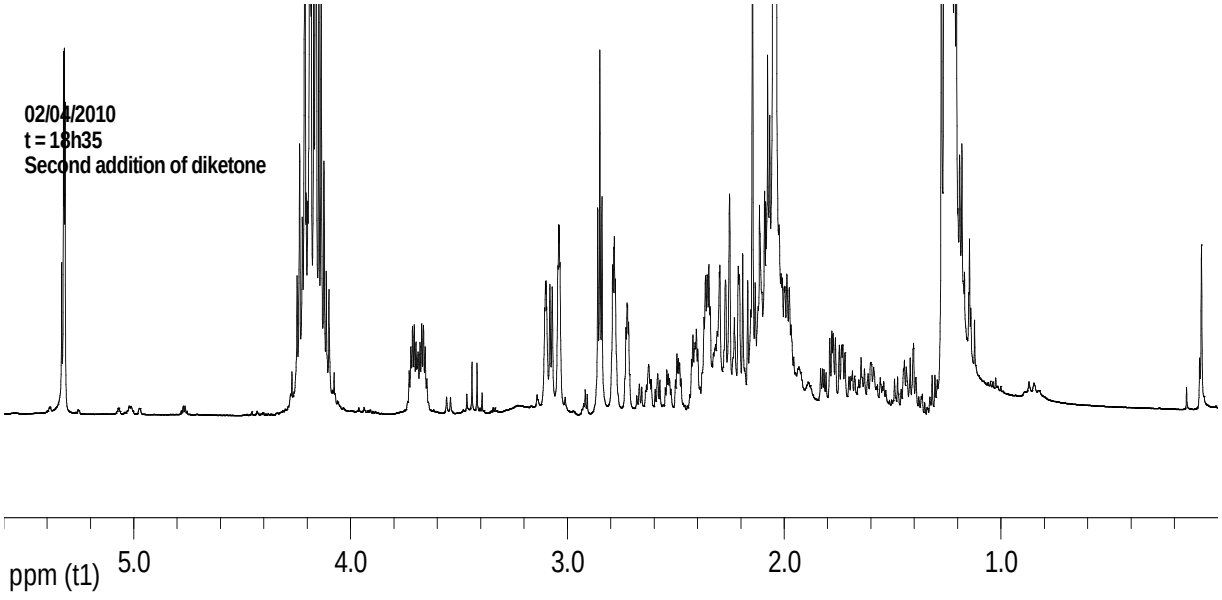

01/04/2010
t = 5h15
ppm (t1)
5.0
4.0
3.0
2.0
1.0

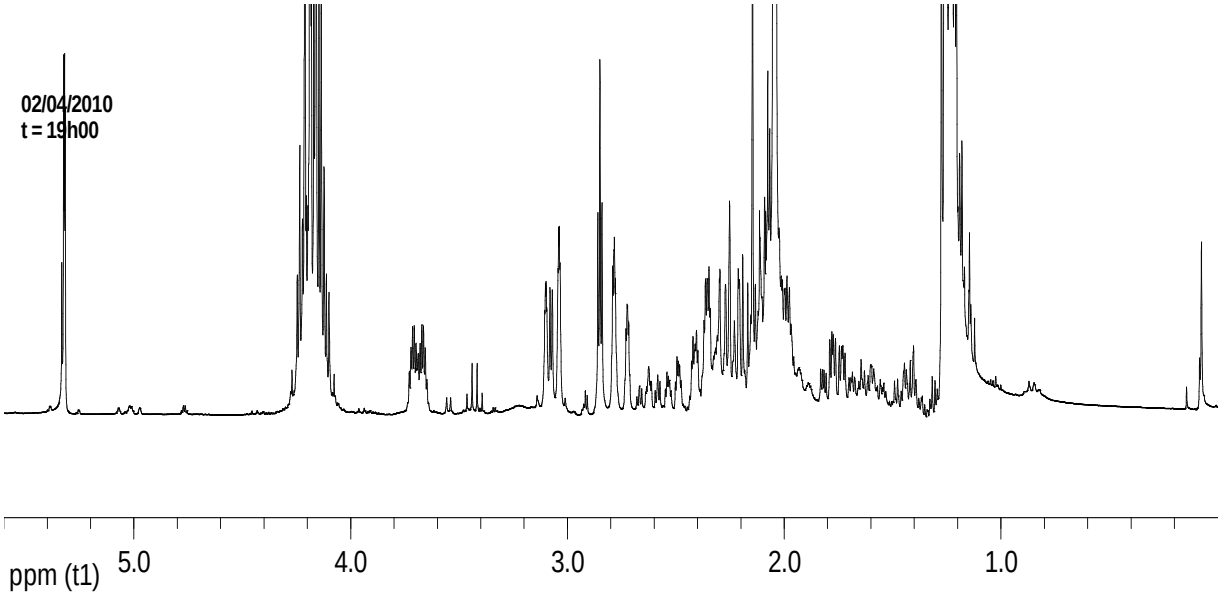

01/04/2010
t = 5h45
ppm (t1)
5.0
4.0
3.0
2.0
1.0

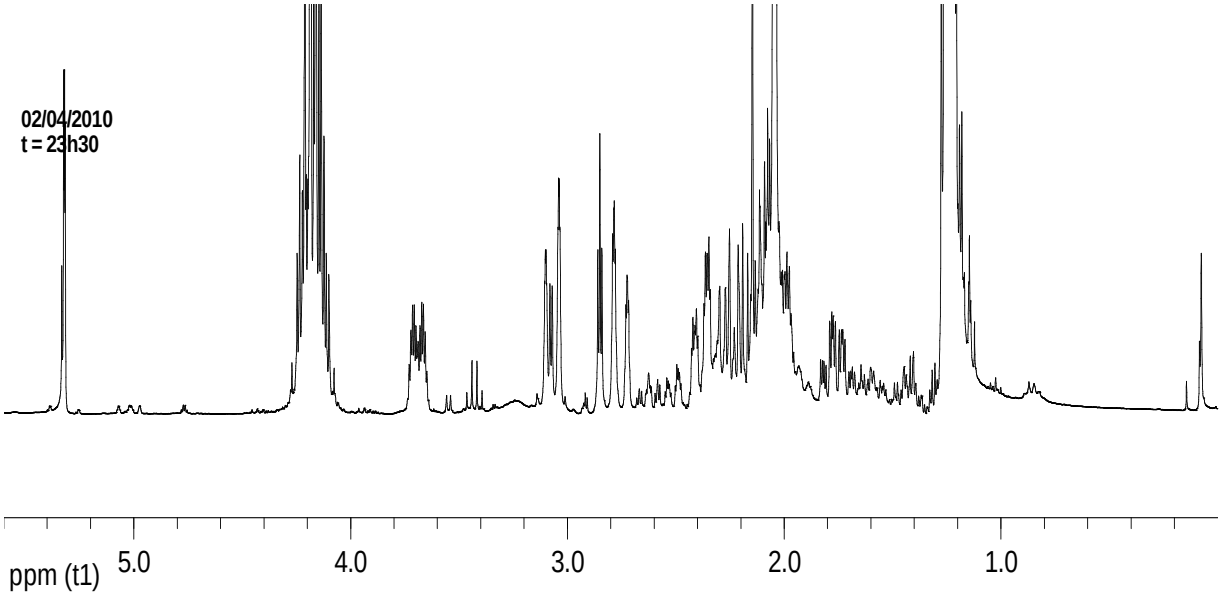

01/04/2010
t = 6h25
ppm (t1)
5.0
4.0
3.0
2.0
1.0

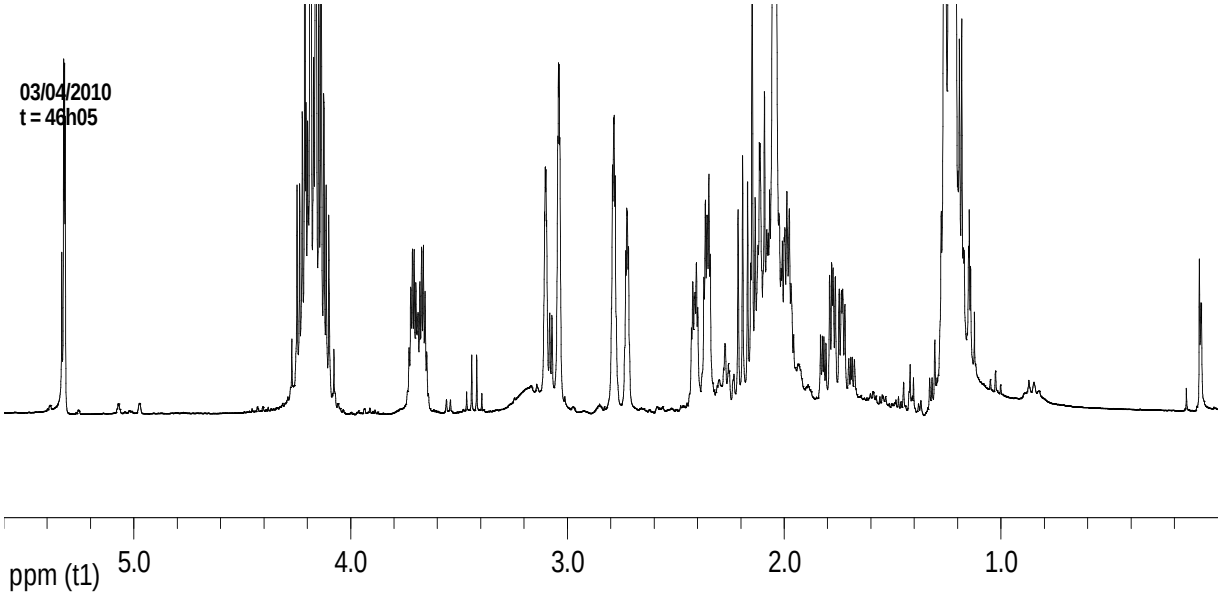

01/04/2010
t = 6h45
ppm (t1)
5.0
4.0
3.0
2.0
1.0

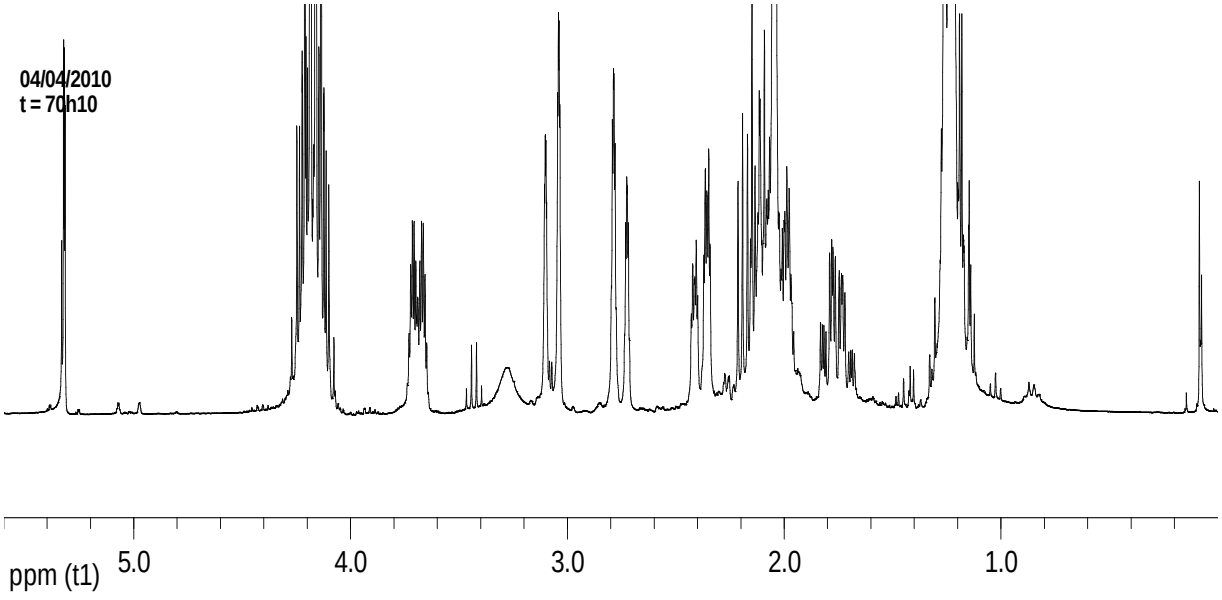

02/04/2010
t = 18h25
ppm (t1)
5.0
4.0
3.0
2.0
1.0

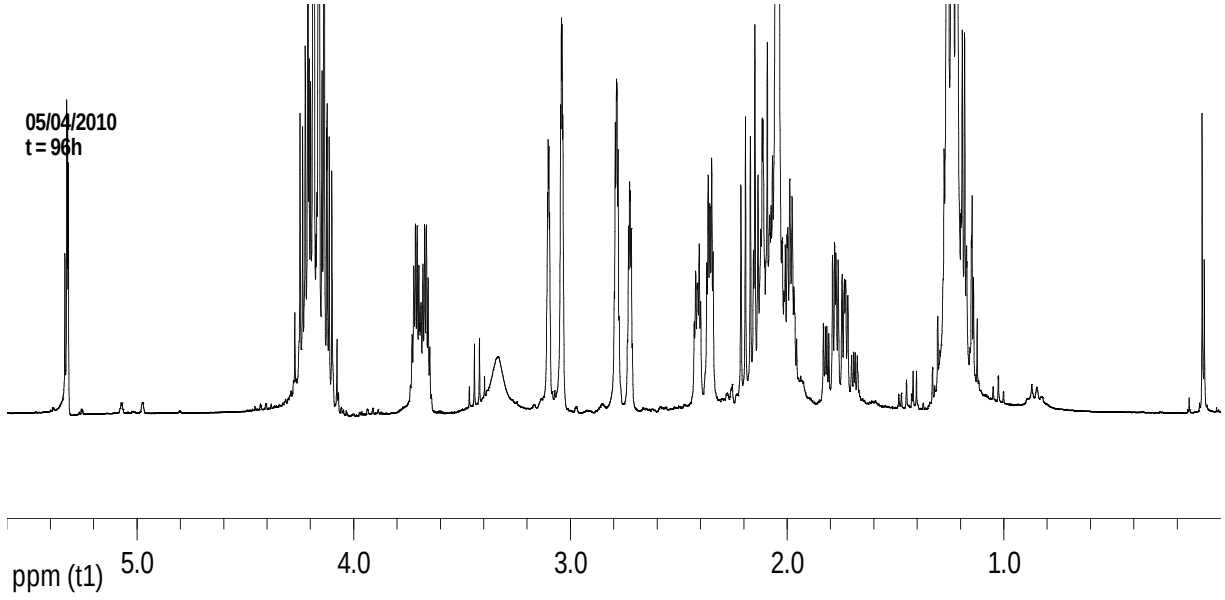

02/04/2010
t = 18h35
Second addition of diketone
ppm (t1)
5.0
4.0
3.0
2.0
1.0


02/04/2010
t = 19h00
ppm (t1)
5.0
4.0
3.0
2.0
1.0


02/04/2010
t = 23h30
ppm (t1)
5.0
4.0
3.0
2.0
1.0


03/04/2010
t = 46h05
ppm (t1)
5.0
4.0
3.0
2.0
1.0


04/04/2010
t = 70h10
ppm (t1)
5.0
4.0
3.0
2.0
1.0


05/04/2010
t = 96h
ppm (t1)
5.0
4.0
3.0
2.0
1.0

6.2 X-ray Crystal Structure Data for 115

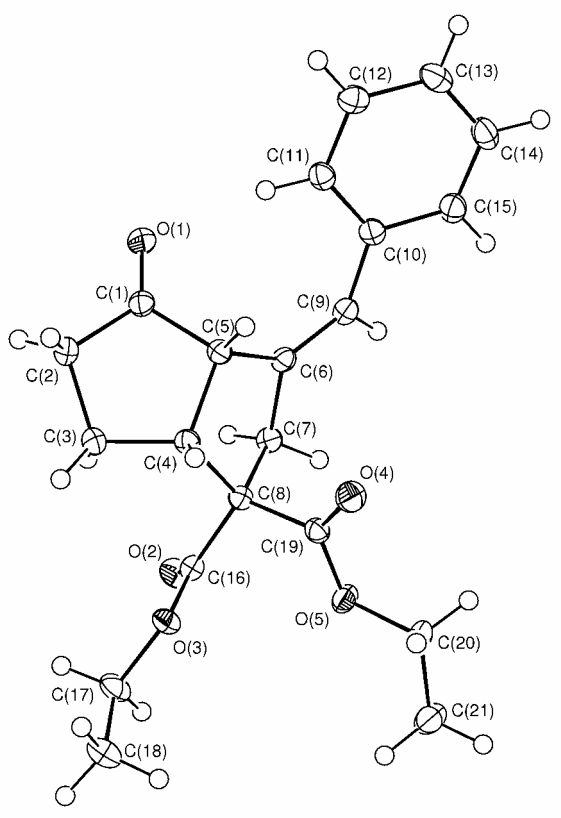


Table 1. Crystal data and structure refinement for 2008PD3.

Identification code	2008PD3, B-45
Empirical formula	C_{21} H_{24} O_5
Formula weight	356.40
Temperature	120(2) K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	P 2(1)/c

Unit cell dimensions	a = 6.9233(1) Å	α= 90°.
	b = 20.2621(4) Å	β= 92.7730(10)°.
	c = 12.9404(2) Å	γ = 90°.
Volume	1813.16(5) $Å^3$	
Z	4	
Density (calculated)	1.306 Mg/m^3	
Absorption coefficient	0.755 mm^{-1}	
F(000)	760	
Crystal size	0.22 x 0.16 x 0.16 mm^3	
Theta range for data collection	6.40 to 70.07°.	
Index ranges	-8<=h<=7, -24<=k<=24, -15<=l<=15	
Reflections collected	18475	
Independent reflections	3410 [R(int) = 0.0267]	
Completeness to theta = 70.07°	98.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8887 and 0.8514	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3410 / 0 / 237	
Goodness-of-fit on F^2	1.072	
Final R indices [I>2sigma(I)]	R1 = 0.0343, wR2 = 0.0859	
R indices (all data)	R1 = 0.0376, wR2 = 0.0891	
Largest diff. peak and hole	0.303 and -0.184 $e.Å^{-3}$	

Notes:

The hydrogen atoms were fixed as riding models.

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)

for 2008PD3. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	7957(2)	7438(1)	1762(1)	18(1)
C(2)	7948(2)	7821(1)	2760(1)	20(1)
C(3)	6448(2)	7459(1)	3372(1)	20(1)
C(4)	6712(2)	6720(1)	3093(1)	17(1)
C(5)	7594(2)	6707(1)	2007(1)	17(1)
C(6)	6140(2)	6361(1)	1285(1)	17(1)
C(7)	4230(2)	6386(1)	1794(1)	18(1)
C(8)	4778(2)	6331(1)	2963(1)	17(1)
C(9)	6398(2)	6034(1)	404(1)	19(1)
C(10)	8144(2)	5930(1)	-179(1)	19(1)
C(11)	9794(2)	6328(1)	-101(1)	20(1)
C(12)	11384(2)	6188(1)	-679(1)	23(1)
C(13)	11370(2)	5649(1)	-1344(1)	25(1)
C(14)	9732(2)	5256(1)	-1442(1)	26(1)

C(15)	8138(2)	5400(1)	-877(1)	23(1)
C(16)	3210(2)	6620(1)	3610(1)	18(1)
C(17)	2304(2)	6867(1)	5297(1)	25(1)
C(18)	2846(2)	6650(1)	6382(1)	28(1)
C(19)	5098(2)	5604(1)	3227(1)	18(1)
C(20)	3567(2)	4618(1)	3738(1)	24(1)
C(21)	1710(2)	4427(1)	4212(1)	31(1)
O(1)	8159(1)	7662(1)	909(1)	25(1)
O(2)	1767(1)	6887(1)	3258(1)	26(1)
O(3)	3673(1)	6567(1)	4620(1)	20(1)
O(4)	6615(1)	5320(1)	3172(1)	26(1)
O(5)	3450(1)	5319(1)	3488(1)	22(1)

Table 3. Bond lengths [Å] and angles [°] for 2008PD3.

C(1)-O(1)	1.2072(14)	C(10)-C(11)	1.3976(17)
C(1)-C(2)	1.5076(15)	C(10)-C(15)	1.4033(16)
C(1)-C(5)	1.5391(15)	C(11)-C(12)	1.3897(16)
C(2)-C(3)	1.5246(15)	C(11)-H(11)	0.9500
C(2)-H(2A)	0.9900	C(12)-C(13)	1.3896(18)
C(2)-H(2B)	0.9900	C(12)-H(12)	0.9500
C(3)-C(4)	1.5530(15)	C(13)-C(14)	1.3859(19)
C(3)-H(3A)	0.9900	C(13)-H(13)	0.9500
C(3)-H(3B)	0.9900	C(14)-C(15)	1.3841(18)
C(4)-C(8)	1.5559(15)	C(14)-H(14)	0.9500
C(4)-C(5)	1.5594(15)	C(15)-H(15)	0.9500
C(4)-H(4)	1.0000	C(16)-O(2)	1.2048(14)
C(5)-C(6)	1.5118(15)	C(16)-O(3)	1.3352(14)
C(5)-H(5)	1.0000	C(17)-O(3)	1.4557(13)
C(6)-C(9)	1.3380(16)	C(17)-C(18)	1.5018(17)
C(6)-C(7)	1.5063(15)	C(17)-H(17A)	0.9900
C(7)-C(8)	1.5458(15)	C(17)-H(17B)	0.9900
C(7)-H(7A)	0.9900	C(18)-H(18A)	0.9800
C(7)-H(7B)	0.9900	C(18)-H(18B)	0.9800
C(8)-C(16)	1.5196(15)	C(18)-H(18C)	0.9800
C(8)-C(19)	1.5271(15)	C(19)-O(4)	1.2025(14)
C(9)-C(10)	1.4707(16)	C(19)-O(5)	1.3359(14)
C(9)-H(9)	0.9500	C(20)-O(5)	1.4579(13)

C(20)-C(21)	1.5018(18)
C(20)-H(20A)	0.9900
C(20)-H(20B)	0.9900
C(21)-H(21A)	0.9800
C(21)-H(21B)	0.9800
C(21)-H(21C)	0.9800

O(1)-C(1)-C(2)	126.51(10)	C(1)-C(5)-C(4)	104.15(8)
O(1)-C(1)-C(5)	125.30(10)	C(6)-C(5)-H(5)	110.1
C(2)-C(1)-C(5)	108.16(9)	C(1)-C(5)-H(5)	110.1
C(1)-C(2)-C(3)	103.18(9)	C(4)-C(5)-H(5)	110.1
C(1)-C(2)-H(2A)	111.1	C(9)-C(6)-C(7)	123.04(10)
C(3)-C(2)-H(2A)	111.1	C(9)-C(6)-C(5)	130.05(10)
C(1)-C(2)-H(2B)	111.1	C(7)-C(6)-C(5)	106.67(9)
C(3)-C(2)-H(2B)	111.1	C(6)-C(7)-C(8)	104.25(9)
H(2A)-C(2)-H(2B)	109.1	C(6)-C(7)-H(7A)	110.9
C(2)-C(3)-C(4)	104.66(9)	C(8)-C(7)-H(7A)	110.9
C(2)-C(3)-H(3A)	110.8	C(6)-C(7)-H(7B)	110.9
C(4)-C(3)-H(3A)	110.8	C(8)-C(7)-H(7B)	110.9
C(2)-C(3)-H(3B)	110.8	H(7A)-C(7)-H(7B)	108.9
C(4)-C(3)-H(3B)	110.8	C(16)-C(8)-C(19)	110.42(9)
H(3A)-C(3)-H(3B)	108.9	C(16)-C(8)-C(7)	111.30(9)
C(3)-C(4)-C(8)	113.74(9)	C(19)-C(8)-C(7)	108.31(9)
C(3)-C(4)-C(5)	106.34(8)	C(16)-C(8)-C(4)	112.29(9)
C(8)-C(4)-C(5)	105.44(8)	C(19)-C(8)-C(4)	110.47(9)
C(3)-C(4)-H(4)	110.4	C(7)-C(8)-C(4)	103.82(8)
C(8)-C(4)-H(4)	110.4	C(6)-C(9)-C(10)	130.95(10)
C(5)-C(4)-H(4)	110.4	C(6)-C(9)-H(9)	114.5
C(6)-C(5)-C(1)	115.42(9)	C(10)-C(9)-H(9)	114.5
C(6)-C(5)-C(4)	106.67(9)	C(11)-C(10)-C(15)	117.70(11)

C(11)-C(10)-C(9)	124.72(10)	O(3)-C(17)-H(17B)	110.2
C(15)-C(10)-C(9)	117.58(10)	C(18)-C(17)-H(17B)	110.2
C(12)-C(11)-C(10)	120.64(11)	H(17A)-C(17)-H(17B)	108.5
C(12)-C(11)-H(11)	119.7	C(17)-C(18)-H(18A)	109.5
C(10)-C(11)-H(11)	119.7	C(17)-C(18)-H(18B)	109.5
C(11)-C(12)-C(13)	120.74(11)	H(18A)-C(18)-H(18B)	109.5
C(11)-C(12)-H(12)	119.6	C(17)-C(18)-H(18C)	109.5
C(13)-C(12)-H(12)	119.6	H(18A)-C(18)-H(18C)	109.5
C(14)-C(13)-C(12)	119.30(11)	H(18B)-C(18)-H(18C)	109.5
C(14)-C(13)-H(13)	120.4	O(4)-C(19)-O(5)	124.60(10)
C(12)-C(13)-H(13)	120.4	O(4)-C(19)-C(8)	124.48(10)
C(15)-C(14)-C(13)	120.03(11)	O(5)-C(19)-C(8)	110.88(9)
C(15)-C(14)-H(14)	120.0	O(5)-C(20)-C(21)	107.60(10)
C(13)-C(14)-H(14)	120.0	O(5)-C(20)-H(20A)	110.2
C(14)-C(15)-C(10)	121.55(11)	C(21)-C(20)-H(20A)	110.2
C(14)-C(15)-H(15)	119.2	O(5)-C(20)-H(20B)	110.2
C(10)-C(15)-H(15)	119.2	C(21)-C(20)-H(20B)	110.2
O(2)-C(16)-O(3)	124.12(10)	H(20A)-C(20)-H(20B)	108.5
O(2)-C(16)-C(8)	124.50(10)	C(20)-C(21)-H(21A)	109.5
O(3)-C(16)-C(8)	111.33(9)	C(20)-C(21)-H(21B)	109.5
O(3)-C(17)-C(18)	107.45(9)	H(21A)-C(21)-H(21B)	109.5
O(3)-C(17)-H(17A)	110.2	C(20)-C(21)-H(21C)	109.5
C(18)-C(17)-H(17A)	110.2	H(21A)-C(21)-H(21C)	109.5

H(21B)-C(21)-H(21C)	109.5
C(16)-O(3)-C(17)	115.03(9)
C(19)-O(5)-C(20)	115.94(9)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for 2008PD3. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	15(1)	19(1)	21(1)	-1(1)	1(1)	-1(1)
C(2)	22(1)	17(1)	22(1)	-2(1)	1(1)	-2(1)
C(3)	23(1)	19(1)	18(1)	-3(1)	1(1)	-1(1)
C(4)	17(1)	18(1)	15(1)	0(1)	0(1)	0(1)
C(5)	16(1)	17(1)	16(1)	-1(1)	1(1)	0(1)
C(6)	18(1)	16(1)	17(1)	2(1)	0(1)	-1(1)
C(7)	18(1)	20(1)	17(1)	0(1)	-1(1)	-1(1)
C(8)	17(1)	17(1)	16(1)	0(1)	1(1)	0(1)
C(9)	21(1)	18(1)	18(1)	1(1)	-2(1)	-2(1)
C(10)	24(1)	19(1)	14(1)	2(1)	-1(1)	2(1)
C(11)	23(1)	19(1)	17(1)	0(1)	0(1)	2(1)
C(12)	23(1)	25(1)	21(1)	4(1)	2(1)	2(1)
C(13)	29(1)	28(1)	19(1)	4(1)	5(1)	10(1)
C(14)	39(1)	22(1)	18(1)	-2(1)	3(1)	6(1)
C(15)	31(1)	21(1)	17(1)	0(1)	0(1)	-1(1)
C(16)	18(1)	16(1)	19(1)	0(1)	1(1)	-2(1)
C(17)	26(1)	27(1)	23(1)	-2(1)	8(1)	8(1)

C(18)	27(1)	35(1)	22(1)	-3(1)	6(1)	5(1)
C(19)	20(1)	18(1)	15(1)	-1(1)	1(1)	0(1)
C(20)	32(1)	14(1)	28(1)	1(1)	3(1)	-1(1)
C(21)	36(1)	25(1)	31(1)	5(1)	4(1)	-7(1)
O(1)	32(1)	22(1)	21(1)	1(1)	6(1)	-4(1)
O(2)	21(1)	31(1)	25(1)	1(1)	1(1)	8(1)
O(3)	19(1)	22(1)	17(1)	-1(1)	4(1)	4(1)
O(4)	24(1)	21(1)	34(1)	2(1)	6(1)	5(1)
O(5)	21(1)	15(1)	30(1)	2(1)	4(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 2008PD3.

	x	y	z	U(eq)
H(2A)	7565	8286	2634	24
H(2B)	9235	7811	3128	24
H(3A)	5125	7611	3167	24
H(3B)	6682	7531	4124	24
H(4)	7604	6500	3618	20
H(5)	8844	6459	2042	20
H(7A)	3389	6014	1560	22
H(7B)	3550	6806	1635	22
H(9)	5262	5835	105	23
H(11)	9830	6697	352	24
H(12)	12494	6463	-619	27
H(13)	12471	5551	-1726	30
H(14)	9703	4889	-1898	31
H(15)	7013	5133	-963	28

H(17A)	971	6724	5097	30
H(17B)	2364	7355	5246	30
H(18A)	2655	6173	6441	42
H(18B)	2030	6879	6866	42
H(18C)	4206	6757	6548	42
H(20A)	4677	4534	4232	29
H(20B)	3748	4357	3104	29
H(21A)	1596	4664	4867	46
H(21B)	1706	3951	4341	46
H(21C)	617	4543	3737	46

6.3 X-ray Crystal Structure Data for 119a

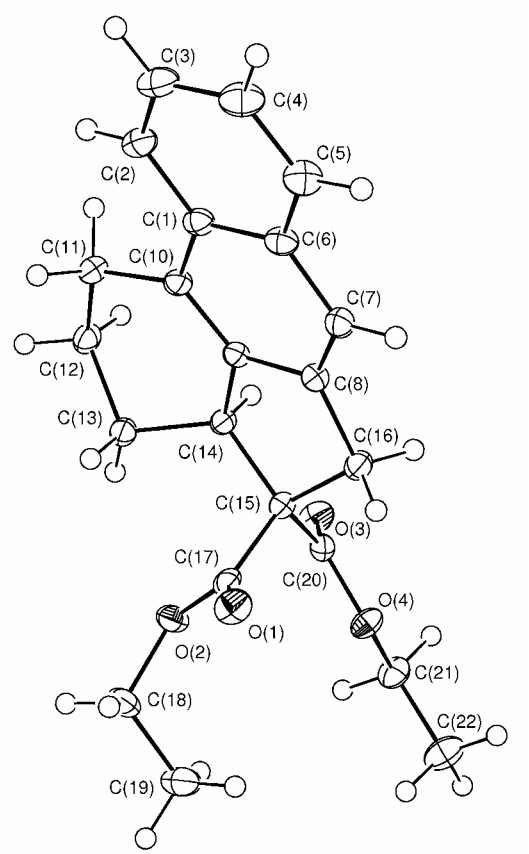


Table 1. Crystal data and structure refinement for DMC-B-364-F_1.

Identification code	DMC-B-364-F_1
Empirical formula	C_{22} H_{24} O_4
Formula weight	352.41
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P -1

Unit cell dimensions	a = 7.0360(2) Å	α= 74.630(2)°.
	b = 11.0030(3) Å	β= 73.6320(10)°.
	c = 12.4583(4) Å	γ = 84.988(2)°.
Volume	892.22(5) $Å^3$	
Z	2	
Density (calculated)	1.312 Mg/m^3	
Absorption coefficient	0.089 mm^{-1}	
F(000)	376	
Crystal size	0.20 x 0.12 x 0.05 mm^3	
Theta range for data collection	2.91 to 27.48°.	
Index ranges	-9<=h<=9, -13<=k<=14, -16<=l<=16	
Reflections collected	15812	
Independent reflections	4060 [R(int) = 0.0356]	
Completeness to theta = 27.48°	99.2 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9956 and 0.9824	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4060 / 0 / 237	
Goodness-of-fit on F^2	1.042	
Final R indices [I>2sigma(I)]	R1 = 0.0458, wR2 = 0.1035	
R indices (all data)	R1 = 0.0539, wR2 = 0.1098	
Largest diff. peak and hole	0.354 and -0.228 $e.Å^{-3}$	

Notes:

The hydrogen atoms were located at calculated positions and refined using a riding model.

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)

for 2009src0660. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	678(2)	-1538(1)	9171(1)	18(1)
C(2)	-409(2)	-2482(1)	10107(1)	22(1)
C(3)	456(2)	-3608(1)	10526(1)	26(1)
C(4)	2478(2)	-3838(1)	10038(1)	28(1)
C(5)	3581(2)	-2939(1)	9145(1)	25(1)
C(6)	2729(2)	-1775(1)	8674(1)	19(1)
C(7)	3854(2)	-877(1)	7698(1)	19(1)
C(8)	2955(2)	219(1)	7261(1)	18(1)
C(9)	941(2)	457(1)	7781(1)	16(1)
C(10)	-227(2)	-380(1)	8693(1)	17(1)
C(11)	-2418(2)	-111(1)	9122(1)	20(1)
C(12)	-3078(2)	1186(1)	8490(1)	21(1)
C(13)	-1947(2)	1584(1)	7208(1)	19(1)
C(14)	232(2)	1695(1)	7149(1)	16(1)

C(15)	1835(2)	2014(1)	5965(1)	17(1)
C(16)	3740(2)	1300(1)	6221(1)	20(1)
C(17)	1256(2)	1605(1)	5018(1)	19(1)
C(18)	-825(2)	2263(2)	3729(1)	27(1)
C(19)	334(3)	3197(2)	2689(1)	30(1)
C(20)	2156(2)	3436(1)	5527(1)	18(1)
C(21)	3590(2)	5068(1)	3893(1)	23(1)
C(22)	5078(2)	5205(2)	2740(1)	32(1)
O(1)	2030(2)	770(1)	4580(1)	26(1)
O(2)	-236(2)	2348(1)	4738(1)	22(1)
O(3)	1409(2)	4207(1)	6055(1)	26(1)
O(4)	3413(1)	3724(1)	4464(1)	22(1)

Table 3. Bond lengths [Å] and angles [°] for 2009src0660.

C(1)-C(2)	1.4203(19)	C(11)-H(11B)	0.9900
C(1)-C(6)	1.4319(19)	C(12)-C(13)	1.5329(19)
C(1)-C(10)	1.4328(19)	C(12)-H(12A)	0.9900
C(2)-C(3)	1.372(2)	C(12)-H(12B)	0.9900
C(2)-H(2)	0.9500	C(13)-C(14)	1.5275(17)
C(3)-C(4)	1.410(2)	C(13)-H(13A)	0.9900
C(3)-H(3)	0.9500	C(13)-H(13B)	0.9900
C(4)-C(5)	1.372(2)	C(14)-C(15)	1.5578(17)
C(4)-H(4)	0.9500	C(14)-H(14)	1.0000
C(5)-C(6)	1.4178(19)	C(15)-C(20)	1.5284(18)
C(5)-H(5)	0.9500	C(15)-C(17)	1.5319(18)
C(6)-C(7)	1.4279(19)	C(15)-C(16)	1.5617(18)
C(7)-C(8)	1.3651(19)	C(16)-H(16A)	0.9900
C(7)-H(7)	0.9500	C(16)-H(16B)	0.9900
C(8)-C(9)	1.4156(18)	C(17)-O(1)	1.2035(17)
C(8)-C(16)	1.5139(18)	C(17)-O(2)	1.3407(17)
C(9)-C(10)	1.3662(18)	C(18)-O(2)	1.4570(16)
C(9)-C(14)	1.5032(18)	C(18)-C(19)	1.498(2)
C(10)-C(11)	1.5125(18)	C(18)-H(18A)	0.9900
C(11)-C(12)	1.5390(19)	C(18)-H(18B)	0.9900
C(11)-H(11A)	0.9900	C(19)-H(19A)	0.9800

C(19)-H(19B)	0.9800	C(21)-H(21A)	0.9900
C(19)-H(19C)	0.9800	C(21)-H(21B)	0.9900
C(20)-O(3)	1.2042(17)	C(22)-H(22A)	0.9800
C(20)-O(4)	1.3428(16)	C(22)-H(22B)	0.9800
C(21)-O(4)	1.4599(16)	C(22)-H(22C)	0.9800
C(21)-C(22)	1.499(2)		

C(2)-C(1)-C(6)	118.48(12)	C(5)-C(6)-C(1)	118.37(13)
C(2)-C(1)-C(10)	122.10(12)	C(7)-C(6)-C(1)	120.34(12)
C(6)-C(1)-C(10)	119.39(12)	C(8)-C(7)-C(6)	119.06(12)
C(3)-C(2)-C(1)	121.53(14)	C(8)-C(7)-H(7)	120.5
C(3)-C(2)-H(2)	119.2	C(6)-C(7)-H(7)	120.5
C(1)-C(2)-H(2)	119.2	C(7)-C(8)-C(9)	119.99(12)
C(2)-C(3)-C(4)	119.89(14)	C(7)-C(8)-C(16)	130.54(12)
C(2)-C(3)-H(3)	120.1	C(9)-C(8)-C(16)	109.43(11)
C(4)-C(3)-H(3)	120.1	C(10)-C(9)-C(8)	123.68(12)
C(5)-C(4)-C(3)	120.16(14)	C(10)-C(9)-C(14)	124.80(12)
C(5)-C(4)-H(4)	119.9	C(8)-C(9)-C(14)	111.38(11)
C(3)-C(4)-H(4)	119.9	C(9)-C(10)-C(1)	117.48(12)
C(4)-C(5)-C(6)	121.55(14)	C(9)-C(10)-C(11)	120.40(12)
C(4)-C(5)-H(5)	119.2	C(1)-C(10)-C(11)	122.01(12)
C(6)-C(5)-H(5)	119.2	C(10)-C(11)-C(12)	113.44(11)
C(5)-C(6)-C(7)	121.25(13)	C(10)-C(11)-H(11A)	108.9

C(12)-C(11)-H(11A)	108.9	C(20)-C(15)-C(14)	110.70(10)
C(10)-C(11)-H(11B)	108.9	C(17)-C(15)-C(14)	112.80(10)
C(12)-C(11)-H(11B)	108.9	C(20)-C(15)-C(16)	111.47(10)
H(11A)-C(11)-H(11B)	107.7	C(17)-C(15)-C(16)	111.25(11)
C(13)-C(12)-C(11)	113.24(11)	C(14)-C(15)-C(16)	104.55(10)
C(13)-C(12)-H(12A)	108.9	C(8)-C(16)-C(15)	104.09(10)
C(11)-C(12)-H(12A)	108.9	C(8)-C(16)-H(16A)	110.9
C(13)-C(12)-H(12B)	108.9	C(15)-C(16)-H(16A)	110.9
C(11)-C(12)-H(12B)	108.9	C(8)-C(16)-H(16B)	110.9
H(12A)-C(12)-H(12B)	107.7	C(15)-C(16)-H(16B)	110.9
C(14)-C(13)-C(12)	107.21(11)	H(16A)-C(16)-H(16B)	109.0
C(14)-C(13)-H(13A)	110.3	O(1)-C(17)-O(2)	125.37(13)
C(12)-C(13)-H(13A)	110.3	O(1)-C(17)-C(15)	125.87(13)
C(14)-C(13)-H(13B)	110.3	O(2)-C(17)-C(15)	108.74(11)
C(12)-C(13)-H(13B)	110.3	O(2)-C(18)-C(19)	108.76(12)
H(13A)-C(13)-H(13B)	108.5	O(2)-C(18)-H(18A)	109.9
C(9)-C(14)-C(13)	108.95(10)	C(19)-C(18)-H(18A)	109.9
C(9)-C(14)-C(15)	103.51(10)	O(2)-C(18)-H(18B)	109.9
C(13)-C(14)-C(15)	121.01(11)	C(19)-C(18)-H(18B)	109.9
C(9)-C(14)-H(14)	107.6	H(18A)-C(18)-H(18B)	108.3
C(13)-C(14)-H(14)	107.6	C(18)-C(19)-H(19A)	109.5
C(15)-C(14)-H(14)	107.6	C(18)-C(19)-H(19B)	109.5
C(20)-C(15)-C(17)	106.19(10)	H(19A)-C(19)-H(19B)	109.5

C(18)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5
O(3)-C(20)-O(4)	123.76(12)
O(3)-C(20)-C(15)	125.38(12)
O(4)-C(20)-C(15)	110.86(11)
O(4)-C(21)-C(22)	107.54(11)
O(4)-C(21)-H(21A)	110.2
C(22)-C(21)-H(21A)	110.2
O(4)-C(21)-H(21B)	110.2
C(22)-C(21)-H(21B)	110.2
H(21A)-C(21)-H(21B)	108.5
C(21)-C(22)-H(22A)	109.5
C(21)-C(22)-H(22B)	109.5
H(22A)-C(22)-H(22B)	109.5
C(21)-C(22)-H(22C)	109.5
H(22A)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5
C(17)-O(2)-C(18)	118.29(11)
C(20)-O(4)-C(21)	115.21(10)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for 2009src0660. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	23(1)	18(1)	15(1)	-5(1)	-6(1)	-2(1)
C(2)	26(1)	22(1)	17(1)	-4(1)	-3(1)	-3(1)
C(3)	37(1)	21(1)	19(1)	0(1)	-6(1)	-4(1)
C(4)	38(1)	19(1)	25(1)	-2(1)	-10(1)	5(1)
C(5)	28(1)	22(1)	25(1)	-6(1)	-7(1)	4(1)
C(6)	24(1)	18(1)	17(1)	-5(1)	-7(1)	0(1)
C(7)	17(1)	22(1)	18(1)	-6(1)	-5(1)	0(1)
C(8)	17(1)	20(1)	16(1)	-4(1)	-5(1)	-2(1)
C(9)	17(1)	17(1)	14(1)	-4(1)	-5(1)	-1(1)
C(10)	19(1)	19(1)	14(1)	-5(1)	-4(1)	-2(1)
C(11)	20(1)	21(1)	16(1)	-2(1)	-2(1)	-3(1)
C(12)	16(1)	23(1)	21(1)	-4(1)	-2(1)	-1(1)
C(13)	16(1)	19(1)	19(1)	-3(1)	-4(1)	-1(1)
C(14)	16(1)	17(1)	15(1)	-3(1)	-3(1)	-2(1)
C(15)	16(1)	17(1)	16(1)	-3(1)	-3(1)	-2(1)
C(16)	17(1)	20(1)	19(1)	-1(1)	-3(1)	-2(1)
C(17)	20(1)	18(1)	15(1)	-1(1)	-1(1)	-7(1)

C(18)	35(1)	30(1)	21(1)	-4(1)	-15(1)	-8(1)
C(19)	41(1)	29(1)	19(1)	-5(1)	-10(1)	-4(1)
C(20)	16(1)	19(1)	18(1)	-2(1)	-6(1)	-3(1)
C(21)	26(1)	15(1)	24(1)	1(1)	-4(1)	-3(1)
C(22)	37(1)	24(1)	25(1)	0(1)	1(1)	-6(1)
O(1)	30(1)	23(1)	24(1)	-10(1)	-3(1)	-2(1)
O(2)	26(1)	25(1)	18(1)	-3(1)	-10(1)	0(1)
O(3)	32(1)	20(1)	25(1)	-8(1)	-2(1)	-4(1)
O(4)	23(1)	15(1)	20(1)	-1(1)	0(1)	-3(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 2009src0660.

	x	y	z	U(eq)
H(2)	-1766	-2331	10450	27
H(3)	-306	-4232	11144	32
H(4)	3079	-4617	10329	34
H(5)	4947	-3101	8835	30
H(7)	5208	-1039	7358	23
H(11A)	-2745	-157	9959	24
H(11B)	-3175	-773	9024	24
H(12A)	-4511	1165	8556	25
H(12B)	-2884	1827	8876	25
H(13A)	-2100	947	6808	22
H(13B)	-2464	2404	6832	22
H(14)	315	2339	7568	19
H(16A)	4528	983	5554	24
H(16B)	4577	1856	6399	24

H(18A)	-2260	2447	3843	33
H(18B)	-561	1400	3616	33
H(19A)	208	4031	2848	44
H(19B)	-179	3234	2027	44
H(19C)	1733	2937	2514	44
H(21A)	4033	5522	4366	28
H(21B)	2293	5425	3791	28
H(22A)	6354	4845	2852	47
H(22B)	5237	6100	2337	47
H(22C)	4618	4759	2278	47

6.4 X-ray Crystal Structure Data for 121a

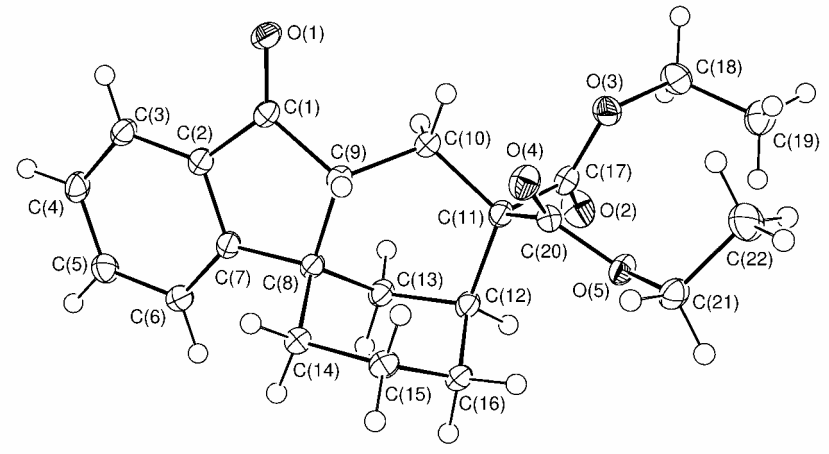


Table 1. Crystal data and structure refinement for 2008PD1.

Identification code	2008PD1	
Empirical formula	C_{22} H_{26} O_5	
Formula weight	370.43	
Temperature	120(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 8.6246(1) Å	α= 72.539(1)°.
	b = 10.2112(1) Å	β= 89.841(1)°.
	c = 11.4753(1) Å	γ = 76.897(1)°.
Volume	936.617(16) $Å^3$	
Z	2	

Density (calculated)	1.313 Mg/m^3
Absorption coefficient	0.751 mm^{-1}
F(000)	396
Crystal size	0.26 x 0.08 x 0.06 mm^3
Theta range for data collection	6.43 to 66.59°.
Index ranges	-10<=h<=10, -12<=k<=11, -13<=l<=13
Reflections collected	9695
Independent reflections	3238 [R(int) = 0.0196]
Completeness to theta = 66.59°	98.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9564 and 0.8288
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3238 / 0 / 246
Goodness-of-fit on F^2	1.070
Final R indices [I>2sigma(I)]	R1 = 0.0360, wR2 = 0.0948
R indices (all data)	R1 = 0.0389, wR2 = 0.0981
Largest diff. peak and hole	0.262 and -0.206 $e.Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)

for 2008PD1. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	5683(2)	2158(1)	6197(1)	17(1)
C(2)	7256(2)	2471(1)	6319(1)	17(1)
C(3)	7643(2)	3782(1)	6047(1)	20(1)
C(4)	9206(2)	3803(1)	6273(1)	22(1)
C(5)	10369(2)	2545(1)	6757(1)	23(1)
C(6)	9982(2)	1243(1)	7016(1)	21(1)
C(7)	8407(2)	1211(1)	6786(1)	17(1)
C(8)	7742(1)	-74(1)	6934(1)	17(1)
C(9)	5930(1)	551(1)	6545(1)	16(1)
C(10)	4828(1)	23(1)	7536(1)	18(1)
C(11)	5254(1)	-1612(1)	8124(1)	17(1)
C(12)	7107(1)	-2263(1)	8340(1)	19(1)
C(13)	7965(2)	-1077(1)	8255(1)	19(1)
C(14)	8563(2)	-892(1)	6079(1)	20(1)

C(15)	7887(2)	-2167(1)	6147(1)	22(1)
C(16)	7867(2)	-3083(1)	7467(1)	22(1)
C(17)	4494(2)	-1892(1)	9359(1)	19(1)
C(18)	1986(2)	-1934(2)	10235(1)	25(1)
C(19)	1717(2)	-3388(2)	10452(1)	30(1)
C(20)	4450(1)	-2307(1)	7362(1)	17(1)
C(21)	4109(2)	-4541(1)	7300(1)	22(1)
C(22)	2374(2)	-4531(2)	7409(2)	33(1)
O(1)	4401(1)	3010(1)	5906(1)	23(1)
O(2)	5191(1)	-2289(1)	10352(1)	30(1)
O(3)	2896(1)	-1574(1)	9164(1)	22(1)
O(4)	3790(1)	-1720(1)	6360(1)	23(1)
O(5)	4611(1)	-3681(1)	7974(1)	20(1)

—

Table 3. Bond lengths [Å] and angles [°] for 2008PD1.

C(1)-O(1)	1.2179(15)	C(11)-C(17)	1.5353(17)
C(1)-C(2)	1.4789(17)	C(11)-C(12)	1.5748(16)
C(1)-C(9)	1.5311(16)	C(12)-C(13)	1.5360(17)
C(2)-C(7)	1.3920(17)	C(12)-C(16)	1.5432(18)
C(2)-C(3)	1.3968(17)	C(12)-H(12)	1.0000
C(3)-C(4)	1.3804(19)	C(13)-H(13A)	0.9900
C(3)-H(3)	0.9500	C(13)-H(13B)	0.9900
C(4)-C(5)	1.3984(19)	C(14)-C(15)	1.5247(17)
C(4)-H(4)	0.9500	C(14)-H(14A)	0.9900
C(5)-C(6)	1.3898(18)	C(14)-H(14B)	0.9900
C(5)-H(5)	0.9500	C(15)-C(16)	1.5262(18)
C(6)-C(7)	1.3934(18)	C(15)-H(15A)	0.9900
C(6)-H(6)	0.9500	C(15)-H(15B)	0.9900
C(7)-C(8)	1.5127(16)	C(16)-H(16A)	0.9900
C(8)-C(13)	1.5382(17)	C(16)-H(16B)	0.9900
C(8)-C(14)	1.5428(17)	C(17)-O(2)	1.2002(16)
C(8)-C(9)	1.5582(16)	C(17)-O(3)	1.3458(16)
C(9)-C(10)	1.5322(16)	C(18)-O(3)	1.4545(15)
C(9)-H(9)	1.0000	C(18)-C(19)	1.502(2)
C(10)-C(11)	1.5572(16)	C(18)-H(18A)	0.9900
C(10)-H(10A)	0.9900	C(18)-H(18B)	0.9900
C(10)-H(10B)	0.9900	C(19)-H(19A)	0.9800
C(11)-C(20)	1.5317(17)	C(19)-H(19B)	0.9800

C(19)-H(19C)	0.9800
C(20)-O(4)	1.2005(15)
C(20)-O(5)	1.3424(15)
C(21)-O(5)	1.4636(15)
C(21)-C(22)	1.4996(19)
C(21)-H(21A)	0.9900
C(21)-H(21B)	0.9900
C(22)-H(22A)	0.9800
C(22)-H(22B)	0.9800
C(22)-H(22C)	0.9800

O(1)-C(1)-C(2)	126.75(11)	C(13)-C(8)-C(14)	109.01(10)
O(1)-C(1)-C(9)	125.28(11)	C(7)-C(8)-C(9)	104.06(9)
C(2)-C(1)-C(9)	107.95(10)	C(13)-C(8)-C(9)	110.00(10)
C(7)-C(2)-C(3)	121.58(11)	C(14)-C(8)-C(9)	111.38(10)
C(7)-C(2)-C(1)	109.48(11)	C(1)-C(9)-C(10)	110.92(10)
C(3)-C(2)-C(1)	128.94(11)	C(1)-C(9)-C(8)	105.88(9)
C(4)-C(3)-C(2)	118.17(11)	C(10)-C(9)-C(8)	114.06(10)
C(4)-C(3)-H(3)	120.9	C(1)-C(9)-H(9)	108.6
C(2)-C(3)-H(3)	120.9	C(10)-C(9)-H(9)	108.6
C(3)-C(4)-C(5)	120.74(12)	C(8)-C(9)-H(9)	108.6
C(3)-C(4)-H(4)	119.6	C(9)-C(10)-C(11)	113.55(10)
C(5)-C(4)-H(4)	119.6	C(9)-C(10)-H(10A)	108.9
C(6)-C(5)-C(4)	120.90(12)	C(11)-C(10)-H(10A)	108.9
C(6)-C(5)-H(5)	119.6	C(9)-C(10)-H(10B)	108.9
C(4)-C(5)-H(5)	119.6	C(11)-C(10)-H(10B)	108.9
C(5)-C(6)-C(7)	118.73(12)	H(10A)-C(10)-H(10B)	107.7
C(5)-C(6)-H(6)	120.6	C(20)-C(11)-C(17)	106.31(10)
C(7)-C(6)-H(6)	120.6	C(20)-C(11)-C(10)	110.51(10)
C(2)-C(7)-C(6)	119.86(11)	C(17)-C(11)-C(10)	105.72(10)
C(2)-C(7)-C(8)	112.47(11)	C(20)-C(11)-C(12)	111.60(10)
C(6)-C(7)-C(8)	127.62(11)	C(17)-C(11)-C(12)	109.56(10)
C(7)-C(8)-C(13)	113.18(10)	C(10)-C(11)-C(12)	112.77(10)
C(7)-C(8)-C(14)	109.17(10)	C(13)-C(12)-C(16)	108.06(10)

C(13)-C(12)-C(11)	109.05(10)	C(15)-C(16)-C(12)	114.53(10)
C(16)-C(12)-C(11)	116.57(10)	C(15)-C(16)-H(16A)	108.6
C(13)-C(12)-H(12)	107.6	C(12)-C(16)-H(16A)	108.6
C(16)-C(12)-H(12)	107.6	C(15)-C(16)-H(16B)	108.6
C(11)-C(12)-H(12)	107.6	C(12)-C(16)-H(16B)	108.6
C(12)-C(13)-C(8)	109.28(10)	H(16A)-C(16)-H(16B)	107.6
C(12)-C(13)-H(13A)	109.8	O(2)-C(17)-O(3)	124.34(12)
C(8)-C(13)-H(13A)	109.8	O(2)-C(17)-C(11)	126.24(12)
C(12)-C(13)-H(13B)	109.8	O(3)-C(17)-C(11)	109.39(10)
C(8)-C(13)-H(13B)	109.8	O(3)-C(18)-C(19)	109.83(11)
H(13A)-C(13)-H(13B)	108.3	O(3)-C(18)-H(18A)	109.7
C(15)-C(14)-C(8)	111.58(10)	C(19)-C(18)-H(18A)	109.7
C(15)-C(14)-H(14A)	109.3	O(3)-C(18)-H(18B)	109.7
C(8)-C(14)-H(14A)	109.3	C(19)-C(18)-H(18B)	109.7
C(15)-C(14)-H(14B)	109.3	H(18A)-C(18)-H(18B)	108.2
C(8)-C(14)-H(14B)	109.3	C(18)-C(19)-H(19A)	109.5
H(14A)-C(14)-H(14B)	108.0	C(18)-C(19)-H(19B)	109.5
C(14)-C(15)-C(16)	111.65(11)	H(19A)-C(19)-H(19B)	109.5
C(14)-C(15)-H(15A)	109.3	C(18)-C(19)-H(19C)	109.5
C(16)-C(15)-H(15A)	109.3	H(19A)-C(19)-H(19C)	109.5
C(14)-C(15)-H(15B)	109.3	H(19B)-C(19)-H(19C)	109.5
C(16)-C(15)-H(15B)	109.3	O(4)-C(20)-O(5)	124.75(11)
H(15A)-C(15)-H(15B)	108.0	O(4)-C(20)-C(11)	125.37(11)

O(5)-C(20)-C(11)	109.88(10)
O(5)-C(21)-C(22)	111.59(11)
O(5)-C(21)-H(21A)	109.3
C(22)-C(21)-H(21A)	109.3
O(5)-C(21)-H(21B)	109.3
C(22)-C(21)-H(21B)	109.3
H(21A)-C(21)-H(21B)	108.0
C(21)-C(22)-H(22A)	109.5
C(21)-C(22)-H(22B)	109.5
H(22A)-C(22)-H(22B)	109.5
C(21)-C(22)-H(22C)	109.5
H(22A)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5
C(17)-O(3)-C(18)	116.86(10)
C(20)-O(5)-C(21)	116.56(10)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for 2008PD1. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	21(1)	14(1)	15(1)	-3(1)	1(1)	-3(1)
C(2)	21(1)	16(1)	16(1)	-5(1)	2(1)	-4(1)
C(3)	24(1)	14(1)	20(1)	-5(1)	3(1)	-4(1)
C(4)	27(1)	17(1)	25(1)	-8(1)	6(1)	-10(1)
C(5)	20(1)	23(1)	28(1)	-9(1)	4(1)	-8(1)
C(6)	19(1)	18(1)	24(1)	-5(1)	1(1)	-3(1)
C(7)	20(1)	15(1)	16(1)	-4(1)	2(1)	-5(1)
C(8)	17(1)	13(1)	20(1)	-3(1)	0(1)	-4(1)
C(9)	18(1)	14(1)	17(1)	-4(1)	0(1)	-4(1)
C(10)	19(1)	14(1)	20(1)	-4(1)	1(1)	-3(1)
C(11)	18(1)	14(1)	18(1)	-3(1)	0(1)	-4(1)
C(12)	18(1)	14(1)	20(1)	-1(1)	-1(1)	-4(1)
C(13)	19(1)	16(1)	21(1)	-3(1)	-2(1)	-4(1)
C(14)	19(1)	16(1)	24(1)	-5(1)	4(1)	-4(1)
C(15)	23(1)	17(1)	28(1)	-10(1)	5(1)	-4(1)
C(16)	19(1)	13(1)	31(1)	-5(1)	2(1)	-3(1)
C(17)	24(1)	14(1)	20(1)	-5(1)	1(1)	-7(1)

C(18)	26(1)	29(1)	21(1)	-9(1)	8(1)	-6(1)
C(19)	34(1)	26(1)	27(1)	-2(1)	7(1)	-8(1)
C(20)	17(1)	16(1)	19(1)	-5(1)	4(1)	-5(1)
C(21)	24(1)	17(1)	27(1)	-10(1)	1(1)	-6(1)
C(22)	26(1)	32(1)	47(1)	-19(1)	4(1)	-12(1)
O(1)	21(1)	16(1)	28(1)	-3(1)	-2(1)	-1(1)
O(2)	30(1)	41(1)	19(1)	-6(1)	-1(1)	-12(1)
O(3)	21(1)	24(1)	19(1)	-4(1)	4(1)	-5(1)
O(4)	27(1)	22(1)	19(1)	-3(1)	-3(1)	-7(1)
O(5)	24(1)	15(1)	22(1)	-5(1)	-1(1)	-7(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 2008PD1.

	x	y	z	U(eq)
H(3)	6851	4635	5715	23
H(4)	9496	4683	6099	26
H(5)	11438	2581	6910	27
H(6)	10775	390	7344	25
H(9)	5673	302	5801	20
H(10A)	3716	330	7173	22
H(10B)	4882	467	8188	22
H(12)	7323	-2929	9193	22
H(13A)	9116	-1487	8494	23
H(13B)	7519	-547	8822	23
H(14A)	8413	-253	5226	24
H(14B)	9723	-1213	6312	24
H(15A)	8542	-2741	5684	26
H(15B)	6787	-1838	5758	26

H(16A)	8978	-3581	7787	26
H(16B)	7273	-3809	7473	26
H(18A)	946	-1237	10106	30
H(18B)	2575	-1901	10961	30
H(19A)	1184	-3431	9716	45
H(19B)	1045	-3601	11142	45
H(19C)	2745	-4083	10641	45
H(21A)	4753	-5525	7622	26
H(21B)	4308	-4173	6425	26
H(22A)	2174	-4902	8273	49
H(22B)	2080	-5124	6955	49
H(22C)	1732	-3561	7069	49

6.5 X-ray Crystal Structure Data for 128

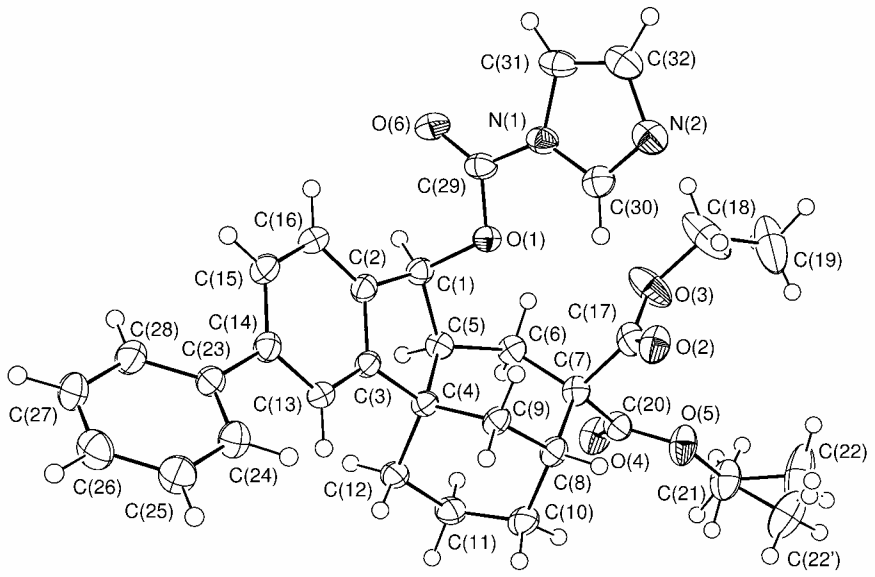


Table 1. Crystal data and structure refinement for DMC-B-469.

Identification code	DMC-B-469, 2010src0268	
Empirical formula	C_{32} H_{34} N_2 O_6	
Formula weight	542.61	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P c	
Unit cell dimensions	a = 11.5003(3) Å	α= 90°.
	b = 8.4551(3) Å	β= 108.961(2)°.
	c = 15.1907(4) Å	γ = 90°.

Volume	1396.94(7) $Å^3$
Z	2
Density (calculated)	1.290 Mg/m^3
Absorption coefficient	0.089 mm^{-1}
F(000)	576
Crystal size	0.30 x 0.17 x 0.15 mm^3
Theta range for data collection	3.05 to 27.48°.
Index ranges	-14<=h<=13, -10<=k<=10, -19<=l<=19
Reflections collected	27229
Independent reflections	3191 [R(int) = 0.0525]
Completeness to theta = 27.48°	99.4 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9867 and 0.9737
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3191 / 3 / 374
Goodness-of-fit on F^2	1.092
Final R indices [I>2sigma(I)]	R1 = 0.0443, wR2 = 0.1010
R indices (all data)	R1 = 0.0492, wR2 = 0.1036
Absolute structure parameter	?
Largest diff. peak and hole	0.360 and -0.342 $e.Å^{-3}$

Notes:

The absolute structure could not be determined from the diffraction data.

The methyl group C(22)/C(22') is disordered over two positions, at a percentage occupancy ratio of 58 (3) / 42 (3).

The hydrogen atoms were fixed as riding models.

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)

for DMC-B-469. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	5779(2)	7122(3)	1405(2)	26(1)
C(2)	5107(2)	6192(3)	1929(2)	26(1)
C(3)	5340(2)	4587(3)	1874(2)	24(1)
C(4)	6155(2)	4274(3)	1283(2)	24(1)
C(5)	6110(2)	5891(3)	789(2)	26(1)
C(6)	7206(2)	6302(3)	450(2)	28(1)
C(7)	8441(2)	5416(3)	901(2)	27(1)
C(8)	8306(2)	3762(3)	1302(2)	28(1)
C(9)	7473(2)	3890(3)	1901(2)	26(1)
C(10)	7827(3)	2451(4)	574(2)	33(1)
C(11)	6486(3)	2644(4)	-27(2)	34(1)
C(12)	5667(3)	2923(3)	582(2)	30(1)
C(13)	4850(2)	3494(3)	2337(2)	25(1)
C(14)	4099(2)	4021(3)	2846(2)	27(1)

C(15)	3869(3)	5633(3)	2886(2)	30(1)
C(16)	4370(3)	6728(3)	2431(2)	30(1)
C(17)	9355(3)	6386(4)	1680(2)	33(1)
C(18)	10407(4)	8874(6)	1997(3)	75(2)
C(19)	11425(4)	9191(8)	1661(3)	85(2)
C(20)	9055(3)	5201(3)	147(2)	29(1)
C(21)	10931(3)	4573(5)	-104(2)	45(1)
C(22)	12217(8)	4780(30)	375(7)	78(6)
C(21')	10931(3)	4573(5)	-104(2)	45(1)
C(22')	12092(15)	3780(30)	434(10)	62(4)
C(23)	3524(2)	2850(3)	3308(2)	28(1)
C(24)	4174(3)	1543(4)	3766(2)	34(1)
C(25)	3623(3)	447(4)	4190(2)	39(1)
C(26)	2410(3)	647(4)	4153(2)	40(1)
C(27)	1749(3)	1927(4)	3683(2)	41(1)
C(28)	2300(3)	3039(4)	3268(2)	36(1)
C(29)	6776(3)	9056(3)	2512(2)	29(1)
C(30)	8883(3)	8524(3)	3602(2)	31(1)
C(31)	8035(3)	10829(3)	3749(2)	34(1)
C(32)	9166(3)	10690(4)	4368(2)	38(1)
N(1)	7847(2)	9420(3)	3241(2)	29(1)
N(2)	9705(2)	9250(3)	4281(2)	36(1)
O(1)	6936(2)	7736(2)	2086(1)	27(1)

O(2)	9885(2)	5929(3)	2455(1)	38(1)
O(3)	9500(3)	7834(3)	1373(2)	53(1)
O(4)	8551(2)	5293(3)	-673(1)	40(1)
O(5)	10244(2)	4852(3)	538(1)	40(1)
O(6)	5870(2)	9851(2)	2324(2)	40(1)

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Table 3. Bond lengths [Å] and angles [°] for DMC-B-469.

C(1)-O(1)	1.488(3)	C(9)-H(9B)	0.9900
C(1)-C(2)	1.499(4)	C(10)-C(11)	1.525(4)
C(1)-C(5)	1.528(4)	C(10)-H(10A)	0.9900
C(1)-H(1)	1.0000	C(10)-H(10B)	0.9900
C(2)-C(16)	1.387(4)	C(11)-C(12)	1.537(4)
C(2)-C(3)	1.392(4)	C(11)-H(11A)	0.9900
C(3)-C(13)	1.386(4)	C(11)-H(11B)	0.9900
C(3)-C(4)	1.517(3)	C(12)-H(12A)	0.9900
C(4)-C(9)	1.536(4)	C(12)-H(12B)	0.9900
C(4)-C(12)	1.538(4)	C(13)-C(14)	1.407(3)
C(4)-C(5)	1.552(3)	C(13)-H(13)	0.9500
C(5)-C(6)	1.548(3)	C(14)-C(15)	1.394(4)
C(5)-H(5)	1.0000	C(14)-C(23)	1.487(4)
C(6)-C(7)	1.554(4)	C(15)-C(16)	1.387(4)
C(6)-H(6A)	0.9900	C(15)-H(15)	0.9500
C(6)-H(6B)	0.9900	C(16)-H(16)	0.9500
C(7)-C(17)	1.539(4)	C(17)-O(2)	1.200(3)
C(7)-C(20)	1.540(3)	C(17)-O(3)	1.340(4)
C(7)-C(8)	1.553(4)	C(18)-C(19)	1.447(4)
C(8)-C(9)	1.525(3)	C(18)-O(3)	1.455(4)
C(8)-C(10)	1.536(4)	C(18)-H(18A)	0.9900
C(8)-H(8)	1.0000	C(18)-H(18B)	0.9900
C(9)-H(9A)	0.9900	C(19)-H(19A)	0.9800

C(19)-H(19B)	0.9800	C(27)-H(27)	0.9500
C(19)-H(19C)	0.9800	C(28)-H(28)	0.9500
C(20)-O(4)	1.193(3)	C(29)-O(6)	1.194(4)
C(20)-O(5)	1.334(3)	C(29)-O(1)	1.333(3)
C(21)-C(22)	1.431(10)	C(29)-N(1)	1.397(4)
C(21)-O(5)	1.459(3)	C(30)-N(2)	1.304(4)
C(21)-H(21A)	0.9900	C(30)-N(1)	1.368(4)
C(21)-H(21B)	0.9900	C(30)-H(30)	0.9500
C(22)-H(22A)	0.9800	C(31)-C(32)	1.340(5)
C(22)-H(22B)	0.9800	C(31)-N(1)	1.398(4)
C(22)-H(22C)	0.9800	C(31)-H(31)	0.9500
C(22')-H(22D)	0.9800	C(32)-N(2)	1.392(4)
C(22')-H(22E)	0.9800	C(32)-H(32)	0.9500
C(22')-H(22F)	0.9800		
C(23)-C(24)	1.388(4)		
C(23)-C(28)	1.398(4)		
C(24)-C(25)	1.392(4)		
C(24)-H(24)	0.9500		
C(25)-C(26)	1.388(4)		
C(25)-H(25)	0.9500		
C(26)-C(27)	1.380(5)		
C(26)-H(26)	0.9500		
C(27)-C(28)	1.394(4)		

O(1)-C(1)-C(2)	108.2(2)	C(4)-C(5)-H(5)	105.4
O(1)-C(1)-C(5)	108.6(2)	C(5)-C(6)-C(7)	118.2(2)
C(2)-C(1)-C(5)	104.0(2)	C(5)-C(6)-H(6A)	107.8
O(1)-C(1)-H(1)	111.9	C(7)-C(6)-H(6A)	107.8
C(2)-C(1)-H(1)	111.9	C(5)-C(6)-H(6B)	107.8
C(5)-C(1)-H(1)	111.9	C(7)-C(6)-H(6B)	107.8
C(16)-C(2)-C(3)	121.0(2)	H(6A)-C(6)-H(6B)	107.1
C(16)-C(2)-C(1)	129.2(2)	C(17)-C(7)-C(20)	105.7(2)
C(3)-C(2)-C(1)	109.7(2)	C(17)-C(7)-C(8)	108.0(2)
C(13)-C(3)-C(2)	120.1(2)	C(20)-C(7)-C(8)	108.3(2)
C(13)-C(3)-C(4)	127.9(2)	C(17)-C(7)-C(6)	112.3(2)
C(2)-C(3)-C(4)	111.9(2)	C(20)-C(7)-C(6)	107.7(2)
C(3)-C(4)-C(9)	110.6(2)	C(8)-C(7)-C(6)	114.4(2)
C(3)-C(4)-C(12)	112.6(2)	C(9)-C(8)-C(10)	109.4(2)
C(9)-C(4)-C(12)	109.4(2)	C(9)-C(8)-C(7)	109.4(2)
C(3)-C(4)-C(5)	101.71(19)	C(10)-C(8)-C(7)	115.2(2)
C(9)-C(4)-C(5)	110.6(2)	C(9)-C(8)-H(8)	107.5
C(12)-C(4)-C(5)	111.8(2)	C(10)-C(8)-H(8)	107.5
C(1)-C(5)-C(6)	116.3(2)	C(7)-C(8)-H(8)	107.5
C(1)-C(5)-C(4)	106.2(2)	C(8)-C(9)-C(4)	109.7(2)
C(6)-C(5)-C(4)	117.1(2)	C(8)-C(9)-H(9A)	109.7
C(1)-C(5)-H(5)	105.4	C(4)-C(9)-H(9A)	109.7
C(6)-C(5)-H(5)	105.4	C(8)-C(9)-H(9B)	109.7

C(4)-C(9)-H(9B)	109.7	C(15)-C(14)-C(13)	119.5(2)
H(9A)-C(9)-H(9B)	108.2	C(15)-C(14)-C(23)	120.8(2)
C(11)-C(10)-C(8)	114.2(2)	C(13)-C(14)-C(23)	119.7(2)
C(11)-C(10)-H(10A)	108.7	C(16)-C(15)-C(14)	121.1(2)
C(8)-C(10)-H(10A)	108.7	C(16)-C(15)-H(15)	119.5
C(11)-C(10)-H(10B)	108.7	C(14)-C(15)-H(15)	119.5
C(8)-C(10)-H(10B)	108.7	C(15)-C(16)-C(2)	118.9(2)
H(10A)-C(10)-H(10B)	107.6	C(15)-C(16)-H(16)	120.6
C(10)-C(11)-C(12)	110.8(2)	C(2)-C(16)-H(16)	120.6
C(10)-C(11)-H(11A)	109.5	O(2)-C(17)-O(3)	123.7(3)
C(12)-C(11)-H(11A)	109.5	O(2)-C(17)-C(7)	125.8(3)
C(10)-C(11)-H(11B)	109.5	O(3)-C(17)-C(7)	110.5(2)
C(12)-C(11)-H(11B)	109.5	C(19)-C(18)-O(3)	111.9(3)
H(11A)-C(11)-H(11B)	108.1	C(19)-C(18)-H(18A)	109.2
C(4)-C(12)-C(11)	112.0(2)	O(3)-C(18)-H(18A)	109.2
C(4)-C(12)-H(12A)	109.2	C(19)-C(18)-H(18B)	109.2
C(11)-C(12)-H(12A)	109.2	O(3)-C(18)-H(18B)	109.2
C(4)-C(12)-H(12B)	109.2	H(18A)-C(18)-H(18B)	107.9
C(11)-C(12)-H(12B)	109.2	C(18)-C(19)-H(19A)	109.5
H(12A)-C(12)-H(12B)	107.9	C(18)-C(19)-H(19B)	109.5
C(3)-C(13)-C(14)	119.4(2)	H(19A)-C(19)-H(19B)	109.5
C(3)-C(13)-H(13)	120.3	C(18)-C(19)-H(19C)	109.5
C(14)-C(13)-H(13)	120.3	H(19A)-C(19)-H(19C)	109.5

H(19B)-C(19)-H(19C)	109.5	C(27)-C(26)-H(26)	120.2
O(4)-C(20)-O(5)	124.0(2)	C(25)-C(26)-H(26)	120.2
O(4)-C(20)-C(7)	125.7(3)	C(26)-C(27)-C(28)	120.5(3)
O(5)-C(20)-C(7)	110.2(2)	C(26)-C(27)-H(27)	119.8
C(22)-C(21)-O(5)	109.6(4)	C(28)-C(27)-H(27)	119.8
C(22)-C(21)-H(21A)	109.8	C(27)-C(28)-C(23)	120.2(3)
O(5)-C(21)-H(21A)	109.8	C(27)-C(28)-H(28)	119.9
C(22)-C(21)-H(21B)	109.7	C(23)-C(28)-H(28)	119.9
O(5)-C(21)-H(21B)	109.8	O(6)-C(29)-O(1)	127.1(3)
H(21A)-C(21)-H(21B)	108.2	O(6)-C(29)-N(1)	122.8(3)
H(22D)-C(22')-H(22E)	109.5	O(1)-C(29)-N(1)	110.1(2)
H(22D)-C(22')-H(22F)	109.5	N(2)-C(30)-N(1)	111.7(3)
H(22E)-C(22')-H(22F)	109.5	N(2)-C(30)-H(30)	124.2
C(24)-C(23)-C(28)	118.8(3)	N(1)-C(30)-H(30)	124.2
C(24)-C(23)-C(14)	121.2(2)	C(32)-C(31)-N(1)	104.7(3)
C(28)-C(23)-C(14)	120.0(3)	C(32)-C(31)-H(31)	127.7
C(23)-C(24)-C(25)	120.7(3)	N(1)-C(31)-H(31)	127.7
C(23)-C(24)-H(24)	119.7	C(31)-C(32)-N(2)	111.7(3)
C(25)-C(24)-H(24)	119.7	C(31)-C(32)-H(32)	124.1
C(26)-C(25)-C(24)	120.1(3)	N(2)-C(32)-H(32)	124.1
C(26)-C(25)-H(25)	119.9	C(30)-N(1)-C(29)	128.7(2)
C(24)-C(25)-H(25)	119.9	C(30)-N(1)-C(31)	107.0(2)
C(27)-C(26)-C(25)	119.6(3)	C(29)-N(1)-C(31)	124.3(2)

C(30)-N(2)-C(32)	104.9(3)
C(29)-O(1)-C(1)	113.3(2)
C(17)-O(3)-C(18)	118.0(3)
C(20)-O(5)-C(21)	115.9(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for DMC-B-469. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	26(1)	26(1)	26(1)	1(1)	7(1)	3(1)
C(2)	22(1)	28(1)	27(1)	0(1)	7(1)	2(1)
C(3)	22(1)	26(1)	25(1)	-3(1)	8(1)	2(1)
C(4)	26(1)	23(1)	26(1)	1(1)	11(1)	2(1)
C(5)	29(1)	28(1)	22(1)	0(1)	10(1)	-1(1)
C(6)	32(1)	31(1)	25(1)	3(1)	14(1)	0(1)
C(7)	29(1)	33(1)	22(1)	1(1)	12(1)	-1(1)
C(8)	27(1)	32(1)	28(1)	3(1)	13(1)	3(1)
C(9)	27(1)	28(1)	26(1)	3(1)	13(1)	4(1)
C(10)	37(2)	33(1)	39(1)	-2(1)	23(1)	2(1)
C(11)	38(2)	33(2)	35(2)	-11(1)	18(1)	-3(1)
C(12)	32(1)	28(1)	35(1)	-6(1)	18(1)	-3(1)
C(13)	26(1)	23(1)	29(1)	-2(1)	11(1)	1(1)
C(14)	25(1)	30(1)	28(1)	-1(1)	11(1)	0(1)
C(15)	28(1)	33(1)	32(1)	-4(1)	14(1)	2(1)
C(16)	31(1)	26(1)	36(1)	-3(1)	13(1)	4(1)
C(17)	30(1)	44(2)	30(1)	-5(1)	18(1)	-6(1)

C(18)	99(3)	83(3)	55(2)	-33(2)	41(2)	-61(3)
C(19)	48(2)	155(5)	60(3)	-48(3)	28(2)	-43(3)
C(20)	32(1)	33(1)	27(1)	-2(1)	16(1)	-4(1)
C(21)	38(2)	69(2)	38(2)	-2(2)	25(1)	1(2)
C(22)	31(3)	170(16)	34(4)	-16(7)	12(3)	7(6)
C(21')	38(2)	69(2)	38(2)	-2(2)	25(1)	1(2)
C(22')	47(6)	91(11)	55(6)	12(7)	26(5)	26(7)
C(23)	29(1)	30(1)	30(1)	-5(1)	15(1)	-3(1)
C(24)	31(1)	39(2)	35(2)	3(1)	13(1)	0(1)
C(25)	41(2)	38(2)	39(2)	7(1)	14(1)	1(1)
C(26)	47(2)	43(2)	39(2)	0(1)	24(1)	-10(1)
C(27)	36(2)	45(2)	53(2)	-6(2)	29(1)	-5(1)
C(28)	33(1)	35(2)	44(2)	1(1)	20(1)	3(1)
C(29)	39(2)	21(1)	31(1)	1(1)	16(1)	-1(1)
C(30)	36(1)	33(1)	30(1)	1(1)	17(1)	0(1)
C(31)	53(2)	26(1)	31(1)	-5(1)	22(1)	-5(1)
C(32)	50(2)	38(2)	29(1)	-5(1)	18(1)	-12(1)
N(1)	36(1)	26(1)	28(1)	-3(1)	15(1)	-3(1)
N(2)	43(1)	40(1)	28(1)	-4(1)	16(1)	-7(1)
O(1)	28(1)	23(1)	30(1)	-2(1)	11(1)	0(1)
O(2)	31(1)	57(1)	27(1)	-6(1)	10(1)	3(1)
O(3)	77(2)	53(1)	34(1)	-9(1)	25(1)	-37(1)
O(4)	39(1)	58(1)	26(1)	2(1)	15(1)	4(1)
O(5)	28(1)	67(2)	28(1)	-3(1)	14(1)	-1(1)

O(6)	41(1)	26(1)	51(1)	-4(1)	14(1)	6(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for DMC-B-469.

	x	y	z	U(eq)
H(1)	5260	7992	1030	31
H(5)	5378	5831	212	31
H(6A)	7369	7449	547	33
H(6B)	6944	6110	-229	33
H(8)	9139	3434	1718	33
H(9A)	7779	4734	2371	31
H(9B)	7482	2880	2232	31
H(10A)	8342	2427	163	40
H(10B)	7924	1420	899	40
H(11A)	6208	1680	-408	41
H(11B)	6408	3550	-455	41
H(12A)	4823	3182	177	36
H(12B)	5627	1939	924	36
H(13)	5020	2399	2309	31
H(15)	3361	5989	3229	36
H(16)	4211	7825	2463	36

H(18A)	10008	9885	2062	90
H(18B)	10722	8378	2620	90
H(19A)	11875	8207	1657	128
H(19B)	11979	9963	2069	128
H(19C)	11112	9617	1027	128
H(21A)	10774	3485	-356	54
H(21B)	10656	5323	-632	54
H(22A)	12376	5880	583	117
H(22B)	12680	4528	-46	117
H(22C)	12476	4075	915	117
H(21C)	11107	5588	-360	54
H(21D)	10450	3895	-627	54
H(22D)	12498	4382	1000	93
H(22E)	12635	3710	54	93
H(22F)	11911	2707	603	93
H(24)	5002	1394	3791	41
H(25)	4078	-440	4505	47
H(26)	2037	-92	4449	49
H(27)	912	2051	3642	49
H(28)	1843	3927	2957	43
H(30)	8991	7498	3386	38
H(31)	7482	11693	3673	41
H(32)	9553	11478	4813	45

Table 6. Torsion angles [°] for DMC-B-469.

O(1)-C(1)-C(2)-C(16)	80.2(3)
C(5)-C(1)-C(2)-C(16)	-164.5(3)
O(1)-C(1)-C(2)-C(3)	-98.3(2)
C(5)-C(1)-C(2)-C(3)	17.0(3)
C(16)-C(2)-C(3)-C(13)	-1.0(4)
C(1)-C(2)-C(3)-C(13)	177.7(2)
C(16)-C(2)-C(3)-C(4)	179.4(2)
C(1)-C(2)-C(3)-C(4)	-1.9(3)
C(13)-C(3)-C(4)-C(9)	-75.6(3)
C(2)-C(3)-C(4)-C(9)	104.0(3)
C(13)-C(3)-C(4)-C(12)	47.0(4)
C(2)-C(3)-C(4)-C(12)	-133.4(2)
C(13)-C(3)-C(4)-C(5)	166.9(3)
C(2)-C(3)-C(4)-C(5)	-13.6(3)
O(1)-C(1)-C(5)-C(6)	-42.3(3)
C(2)-C(1)-C(5)-C(6)	-157.3(2)
O(1)-C(1)-C(5)-C(4)	90.0(2)
C(2)-C(1)-C(5)-C(4)	-25.0(3)
C(3)-C(4)-C(5)-C(1)	23.4(2)
C(9)-C(4)-C(5)-C(1)	-94.1(2)
C(12)-C(4)-C(5)-C(1)	143.7(2)
C(3)-C(4)-C(5)-C(6)	155.3(2)

C(9)-C(4)-C(5)-C(6)	37.8(3)
C(12)-C(4)-C(5)-C(6)	-84.4(3)
C(1)-C(5)-C(6)-C(7)	106.4(3)
C(4)-C(5)-C(6)-C(7)	-20.7(3)
C(5)-C(6)-C(7)-C(17)	-97.8(3)
C(5)-C(6)-C(7)-C(20)	146.2(2)
C(5)-C(6)-C(7)-C(8)	25.8(3)
C(17)-C(7)-C(8)-C(9)	77.4(3)
C(20)-C(7)-C(8)-C(9)	-168.5(2)
C(6)-C(7)-C(8)-C(9)	-48.4(3)
C(17)-C(7)-C(8)-C(10)	-158.8(2)
C(20)-C(7)-C(8)-C(10)	-44.7(3)
C(6)-C(7)-C(8)-C(10)	75.4(3)
C(10)-C(8)-C(9)-C(4)	-59.4(3)
C(7)-C(8)-C(9)-C(4)	67.7(3)
C(3)-C(4)-C(9)-C(8)	-173.7(2)
C(12)-C(4)-C(9)-C(8)	61.8(3)
C(5)-C(4)-C(9)-C(8)	-61.8(3)
C(9)-C(8)-C(10)-C(11)	54.7(3)
C(7)-C(8)-C(10)-C(11)	-69.0(3)
C(8)-C(10)-C(11)-C(12)	-50.5(3)
C(3)-C(4)-C(12)-C(11)	178.8(2)
C(9)-C(4)-C(12)-C(11)	-57.9(3)
C(5)-C(4)-C(12)-C(11)	65.0(3)

C(10)-C(11)-C(12)-C(4)	51.6(3)
C(2)-C(3)-C(13)-C(14)	1.1(4)
C(4)-C(3)-C(13)-C(14)	-179.3(2)
C(3)-C(13)-C(14)-C(15)	-0.6(4)
C(3)-C(13)-C(14)-C(23)	177.2(2)
C(13)-C(14)-C(15)-C(16)	-0.1(4)
C(23)-C(14)-C(15)-C(16)	-177.9(3)
C(14)-C(15)-C(16)-C(2)	0.2(4)
C(3)-C(2)-C(16)-C(15)	0.3(4)
C(1)-C(2)-C(16)-C(15)	-178.0(3)
C(20)-C(7)-C(17)-O(2)	-114.5(3)
C(8)-C(7)-C(17)-O(2)	1.3(4)
C(6)-C(7)-C(17)-O(2)	128.4(3)
C(20)-C(7)-C(17)-O(3)	64.7(3)
C(8)-C(7)-C(17)-O(3)	-179.6(2)
C(6)-C(7)-C(17)-O(3)	-52.5(3)
C(17)-C(7)-C(20)-O(4)	-138.8(3)
C(8)-C(7)-C(20)-O(4)	105.6(3)
C(6)-C(7)-C(20)-O(4)	-18.6(4)
C(17)-C(7)-C(20)-O(5)	42.8(3)
C(8)-C(7)-C(20)-O(5)	-72.8(3)
C(6)-C(7)-C(20)-O(5)	163.1(2)
C(15)-C(14)-C(23)-C(24)	-141.0(3)
C(13)-C(14)-C(23)-C(24)	41.2(4)

C(15)-C(14)-C(23)-C(28)	40.4(4)
C(13)-C(14)-C(23)-C(28)	-137.4(3)
C(28)-C(23)-C(24)-C(25)	-0.8(4)
C(14)-C(23)-C(24)-C(25)	-179.4(3)
C(23)-C(24)-C(25)-C(26)	0.4(5)
C(24)-C(25)-C(26)-C(27)	0.9(5)
C(25)-C(26)-C(27)-C(28)	-1.7(5)
C(26)-C(27)-C(28)-C(23)	1.3(5)
C(24)-C(23)-C(28)-C(27)	0.0(4)
C(14)-C(23)-C(28)-C(27)	178.6(3)
N(1)-C(31)-C(32)-N(2)	-0.4(3)
N(2)-C(30)-N(1)-C(29)	179.8(3)
N(2)-C(30)-N(1)-C(31)	-0.8(3)
O(6)-C(29)-N(1)-C(30)	171.0(3)
O(1)-C(29)-N(1)-C(30)	-9.1(4)
O(6)-C(29)-N(1)-C(31)	-8.3(4)
O(1)-C(29)-N(1)-C(31)	171.6(2)
C(32)-C(31)-N(1)-C(30)	0.7(3)
C(32)-C(31)-N(1)-C(29)	-179.9(2)
N(1)-C(30)-N(2)-C(32)	0.6(3)
C(31)-C(32)-N(2)-C(30)	-0.1(3)
O(6)-C(29)-O(1)-C(1)	-9.6(4)
N(1)-C(29)-O(1)-C(1)	170.5(2)
C(2)-C(1)-O(1)-C(29)	-82.2(3)

C(5)-C(1)-O(1)-C(29)	165.6(2)
O(2)-C(17)-O(3)-C(18)	3.9(5)
C(7)-C(17)-O(3)-C(18)	-175.3(3)
C(19)-C(18)-O(3)-C(17)	113.3(5)
O(4)-C(20)-O(5)-C(21)	0.0(4)
C(7)-C(20)-O(5)-C(21)	178.3(3)
C(22)-C(21)-O(5)-C(20)	159.3(12)

Symmetry transformations used to generate equivalent atoms:

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