DOCTOR OF PHILOSOPHY

Tandem Michael/Intramolecular Aldol reactions mediated by secondary amines, thiols and phosphines.

Richards, Elinor Louise

Award date:
2002

Awarding institution:
University of Wales, Bangor

Tandem Michael/Intramolecular Aldol Reactions Mediated by Secondary Amines, Thiols and Phosphines

Elinor Louise Richards BSc (Hons)

A thesis submitted to the

University of Wales

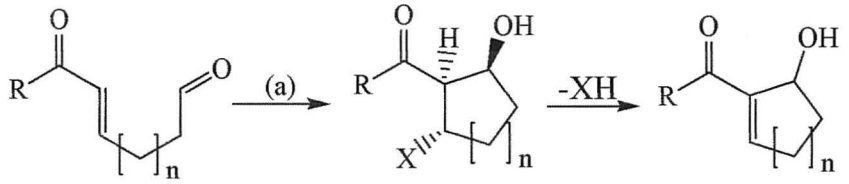
in candidature for the degree

of Philosophiae Doctor

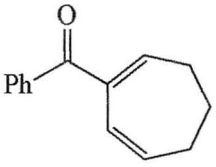
2002

Abstract

The secondary amine mediated Baylis-Hillman reaction of substrates **1** have been found to proceed *via* a tandem Michael addition/intramolecular aldol followed by a slow elimination step; it was also observed that similar processes could be effected using phosphines and thiols as mediators. These reactions are highly substrate dependent, with the best results being obtained for the formation of 5 and 6-membered products **2** and **3** using thiol or thiolate nucleophiles. Amine and phosphine mediated cyclisations were found to be problematic in several cases but were still effective methods for the formation of 5-7 membered compounds for example **4**.



1 **2** **3**

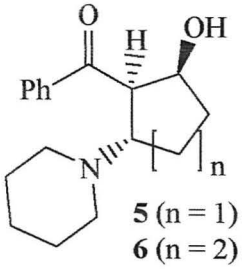


4

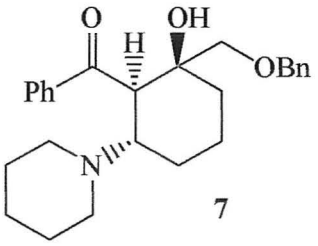
(a) Piperidine, TolSH or PR_3; $CDCl_3$ or $CHCl_3$; r.t. to reflux

R = Ph, EtO or TolS; X = Piperidyl, TolS or PR_3; n = 1, 2, 3, 4 or 5

Mechanistic investigations into the reaction of amines found that piperidine was the most effective catalyst of the amines investigated. Intermediates **5** and **6** were shown to be stable long-lived species by NMR and X-ray crystallographic data for **7** was also obtained.



5 (n = 1)
6 (n = 2)



7

I Mam, Dad, Caryl, Mamgu a Dylan

Acknowledgements

Firstly, I must express my gratitude to Dr Patrick J. Murphy for guidance and supervision throughout the research project.

I am also indebted to the technical staff at the chemistry department especially the NMR experts, Mr Eric Lewis and Mr Glyn Connolly.

I am grateful to the University of Wales Bangor for my funding.

In addition to the staff at Bangor, I am grateful to the staff at the EPSRC X-ray Crystallography Centre at Cardiff (now Southampton) and the Mass Spectrometry Centre at Swansea.

I would like to thank all members of our research group, past and present, for providing many a distraction in the form of cocktail evenings, formal dinners and the endless leaving do's!

For the holiday that made my final year the most memorable, many thanks to Claire, Dan, Dylan, Hankey, Kevin, Paul and Will (fellow discoverers of the Flaming Lamborghinis: Tenerife's legendary beverage!)

For friendship and support, thanks to Alison, Karen, Clark, Mari, Robert, Emma, Louise, Donna, Marie, Christine and Claire.

Finally, but most importantly, I am grateful to my parents, grandmother, sister and fiancé, to whom I dedicate this thesis, for their constant support and encouragement. *Diolch am bopeth. Mae eich cariad a'ch cefnogaeth yn golygu llawer i mi.*

Abbreviations

app	Apparent
(-)-CAMP	*o*-Anisylcyclohexylmethylphosphine
(-)-PAMP	*o*-Anisylphenylmethylphosphine
Ar	Aromatic
AIBN	Azobisisobutyronitrile
BINOL	(±)-1,1'-Bi-2-naphthol
(S)-BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
B. pt.	Boiling point
br	Broad
TBSCl	*tert*-Butyldimethylchlorosilane
CSA	Camphorsulfonic acid
CI	Chemical ionisation
δ	Chemical shift downfield from TMS, given as ppm
mCPBA	3-Chloroperbenzoic acid
J	Coupling constant, in Hz
Dec	Decomposition
°C	Degrees celsius
d.e.	Diastereomeric excess
DABCO	1, 4-Diazabicyclo[2.2.2]octane
DCM	Dichloromethane
DCC	Dicyclohexylcarbodiimide
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
d	Doublet
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
dt	Doublet of triplets
EI	Electron impact
EWG	Electron withdrawing group
e.e.	Enantiomeric excess
(E)	Entegen (*trans*): opposite sides

ν	Frequency
Hz	Hertz (sec^{-1} or cycles per second)
HRMS	High resolution mass spectrum
h/hr(s)	Hour(s)
HMPA	Hexamethylphosphoric acid triamide
ImH	Imidazole
IR	Infrared
LDA	Lithium diisopropylamide
MS	Mass spectrum
MHz	Megahertz
M. pt.	Melting point
Min/s	Minute(s)
M	Molar
Mol/mmol	Moles/millimoles
m	Multiplet
NMR	Nuclear magnetic resonance
ppm	Parts per million
PhSTMS	Phenyl trimethylsilyl sulfide
q	Quartet
r.t.	Room temperature
s	Singlet
Δ	Symbol for heat supplied to a reaction
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Tol	Tolyl
Trt	Trityl
Ts	Tosyl or *p*-toluenesulfonyl group
P(*n*Bu$_3$) or *n*-Bu$_3$P	Tributylphosphine
TMEDA	Trimethylethylenediamine
t	Triplet
TDAP	Trisdimethylaminophosphine
cm^{-1}	Wavenumbers
(Z)	Zusammen (*cis*): same side

Contents

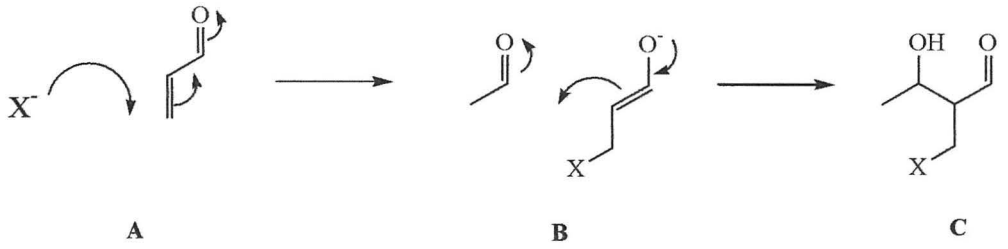
1 Introduction

1.1 Tandem reactions

The tandem organic reaction, which results in several organic transformations, is defined as "a combination of two or more reactions whose occurrence is in a specific order, and if they involve sequential addition of reagents, the secondary reagents must be integrated into the products."[1] Put simply, tandem reactions are those that occur in succession and the second stage of the reaction must be triggered by the first stage.

1.2 Tandem Michael-aldol reactions

Tandem Michael-aldol reactions are 1,4 additions of carbanions to α,β-unsaturated carbonyl systems followed by an aldol condensation of the generated enol. A general outline of this reaction is given in Scheme 1. At **A**, a nucleophilic attack on the β-carbon of an α, β-unsaturated alkene *via* 1,4-addition leads to the formation of the enolate anion in **B**, which then reacts with an aldehyde to give the aldol product in **C**.

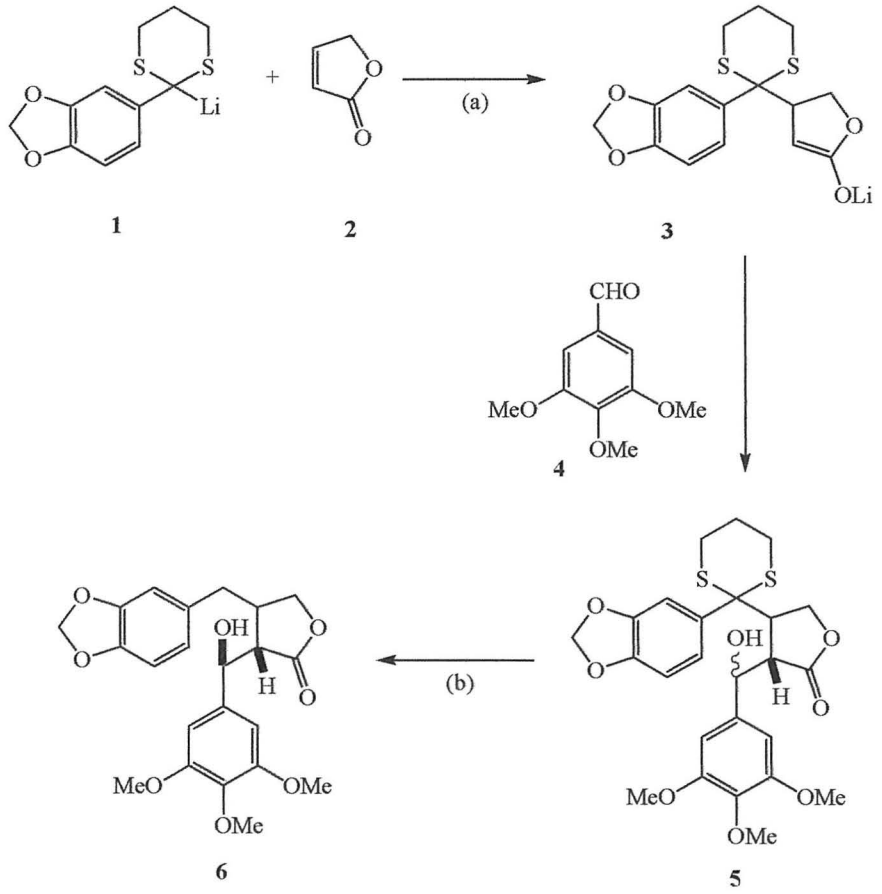


Scheme 1: X = Nucleophile e.g. C, P, N or S

1.3 Tandem Michael-aldol reactions mediated by carbon nucleophiles

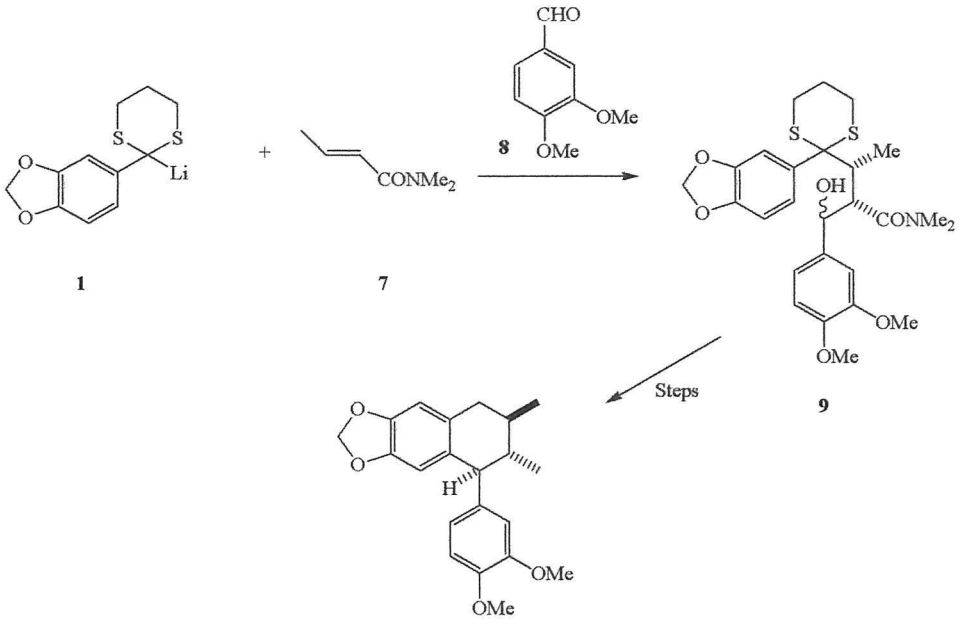
1.3.1 Intermolecular reactions

An intermolecular version of this sequence is found in the synthesis of lignans such as podorhizol[2] and galactin[3] (Schemes 2 and 3). In these examples, 2-aryl-1,3-dithian-2-yllithiums **1** behave as Michael donors towards the α, β-unsaturated lactone **2** leading to the intermediate enolate **3**, which undergoes an aldol reaction with aldehyde **4** yielding **5**, a key precursor in the synthesis of podorhizol, **6**.



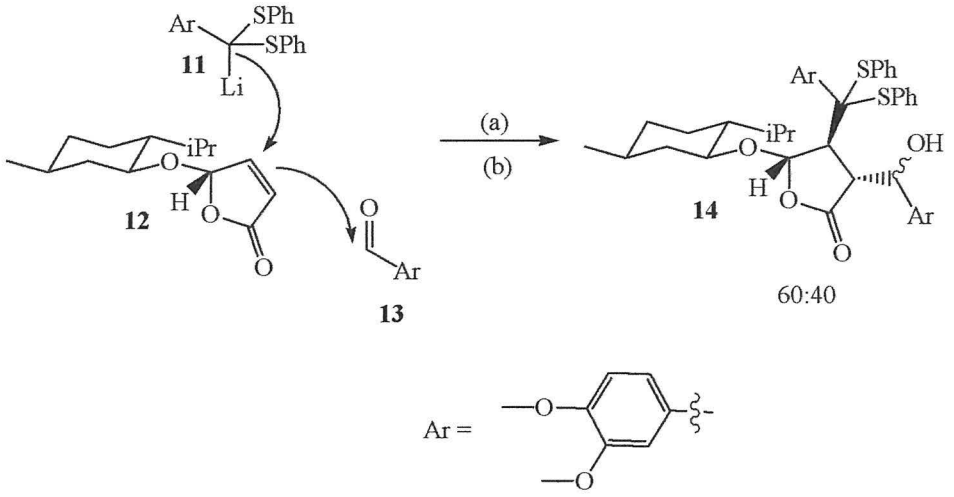
Scheme 2: (a) THF; (b) Ni, EtOH

In a similar fashion, reaction of **1** with an amide **7** and an aldehyde **8** led to the formation of **9**, a synthetic precursor of galactin, **10**.



Scheme 3

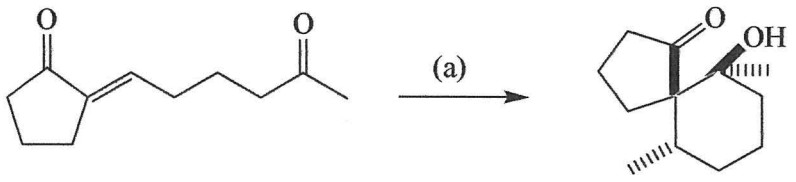
Work published by Jansen and Feringa[4] gave details of the enantioselective Michael addition of the aryldithiane of 3,4-dimethoxybenzaldehyde **11** to (5S)-menthyloxy-2-[5H]-furanone **12** to give the optically pure adduct **14** in 62% yield. The reaction is a tandem Michael addition-aldol condensation of **12** with a benzyllithium derivative and an arylaldehyde (Scheme 4).



Scheme 4: (a) –90°C, THF; (b) –20°C

1.3.2 Intramolecular reactions

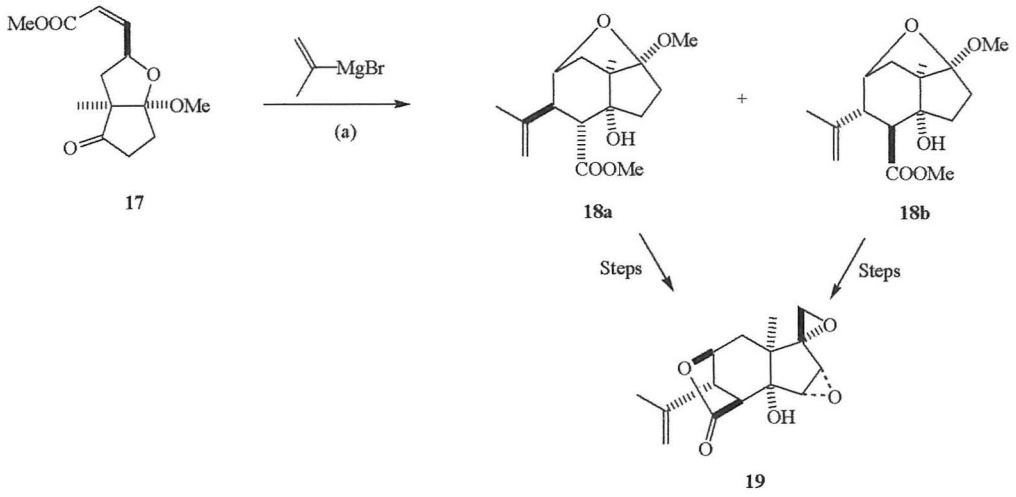
Several groups have reported investigations into the intramolecular Michael-aldol reaction where the two reactive moieties are present in the same molecule. Näf *et al* utilised the intramolecular Michael-aldol reaction to form the spirocyclic compound **16** from the ξ-oxo-α,β-enone **15** in a stereoselective manner[5] (Scheme 5).



15 **16**

Scheme 5: (a) Me_2CuLi

A similar reaction was also used as an effective ring formation method in the copper catalysed Michael addition of Grignards to the α, β-unsaturated ester **17**. The alcohols obtained, **18a** and **18b**, were then modified to give the naturally occurring metabolite, coriamyrtin **19**[6] (Scheme 6).

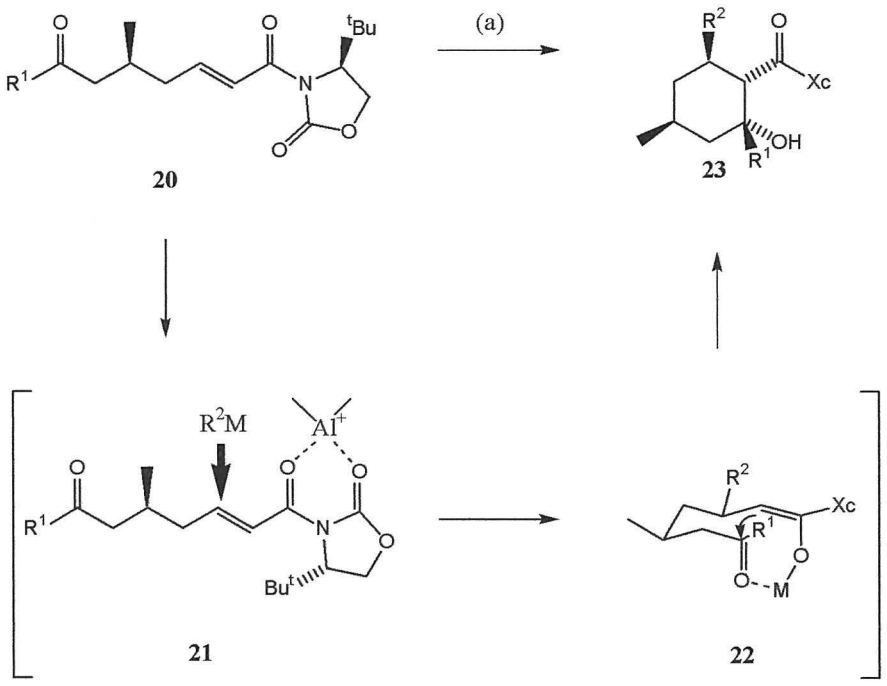


Scheme 6: (a) CuI, THF, -50°C

Schneider[7-14] reported the preparation of poly-functionalised cyclohexanes by domino Michael/aldol and Michael/Mannich reactions. The reactions involved a nucleophilic addition of organometallic reagents to α, β-unsaturated imides in a stereocontrolled manner followed by an intramolecular aldol or Mannich reaction leading to these functionalised cyclohexanes. Examples included carbon, sulfur and nitrogen-containing nucleophiles; the use of sulfur and nitrogen-containing nucleophiles will be discussed later.

Thus, the α, β-unsaturated imide **20** was treated with a range of organometallic reagents[15, 16] (Scheme 7, Table 1), generally in the presence of Me_2AlCl, leading to the formation of the imide enolate **22**, which underwent cyclisation to form the cyclohexanes **23** in good to excellent yields.[7-14] It was found that the bulky 4-*t*Bu-2-oxazolidinone was by far the best chiral auxiliary for conjugate addition reactions to α, β-unsaturated imides giving 1,4-addition products with usually >20:1 diastereoselectivity.[8] Excellent stereoselectivity was seen with

this reaction despite the formation of two new σ-bonds and three chiral centres. It is thought that the reaction between the Lewis acid, Me_2AlCl, and the imide carbonyl groups forms a cationic chelate complex, **21**.[17, 18] The cuprate then attacks the upper face of the conjugate double bond *anti* to the *t*Bu-group. An imide enolate is formed which is then trapped by the aldehyde in the chair-like transition structure, **22**, transposing the metal cation from the enolate oxygen to the aldehyde oxygen intramolecularly, leading to the homogeneous *syn*-stereochemistry of the aldol structure of the products.



Scheme 7: (a) R^2M, Me_2AlCl, THF, -78°C to -30°C

R^1 = H or CH_3; R^2M = *n*BuCu-LiI; $EtCuMgBr_2$; $AllylCu\text{-}MgBr_2$; X_c = Chiral auxiliary

Table 1

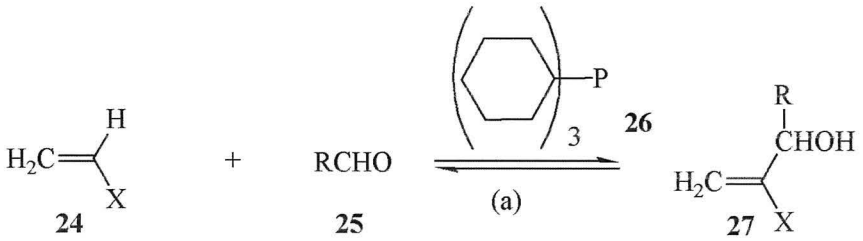
Entry	Cuprate (R^2M)	R^2	R^1	Yield (%)
1	$CH_3Cu.LiI$	CH_3	CH_3	54
2	$C_2H_5Cu.MgBr_2$*	C_2H_5	CH_3	71
3	$C_4H_9Cu.LiI$	C_4H_9	CH_3	83
4	$AllylCu.MgBr_2$*	Allyl	CH_3	81
5	$C_6H_{13}Cu.LiI$	C_6H_{13}	CH_3	62
6	$Ph_2Cu.MgBr$	Ph	CH_3	53
7	$BuCu.LiI$	Bu	H	41

* = In these cases, Me_2AlCl was omitted.

1.4 Tandem Michael-aldol reactions mediated by phosphine nucleophiles

1.4.1 Intermolecular reactions

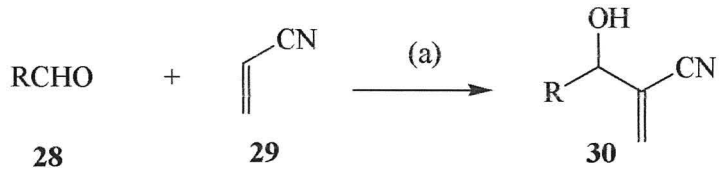
The first reported use of phosphines in the Michael-aldol reaction was by Morita *et al*[19] who utilised tricyclohexylphosphine **26** as a catalyst for the coupling of activated olefins **24** with aldehydes **25**. The reaction went to completion after 2 hours at 120-130°C. 2-Hydroxyalkyl derivatives **27** of acrylate and related systems were isolated. Unfortunately, low yields were obtained. The name "carbinol reaction" was suggested for the conversion (Scheme 8).



Scheme 8: (a) 120-130°C, 2 hrs

X = CO_2R or CN; R = alkyl, Ph or substituted Ph

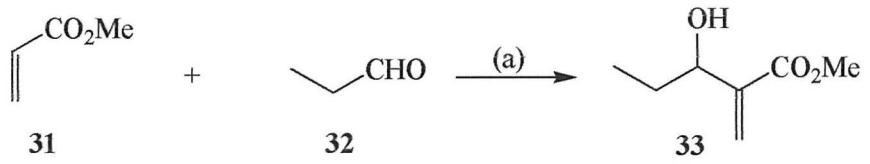
Imagawa *et al*[20] obtained higher yields in the case of acrylonitrile by using tributylphosphine and triethylaluminium as catalysts at elevated temperatures (80°C for 22 hours). The role of the Lewis acid is to coordinate to the carbonyl oxygen of the aldehyde, thereby enhancing the reactivity (Scheme 9).



Scheme 9: (a) P(nBu$_3$)-AlEt$_3$, 80°C, 22 hrs

R = alkyl, aryl

During Leahy's investigation into the base-promoted Baylis-Hillman reaction[21], the main problem noted was the formation of self-aldol products from the initial aldehyde; thus, it was necessary to find a good catalyst to allow Michael addition to the acrylate without forming the aldol product. The best catalyst for this particular reaction was tributylphosphine, giving the product in an 80% yield over 2 days. The catalysts used in this particular investigation and the results obtained are summarised in Table 2 (Scheme 10).



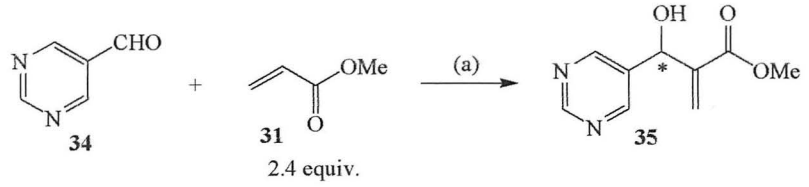
31 **32** **33**

Scheme 10: (a) P(nBu$_3$), r.t., 2 days

Table 2

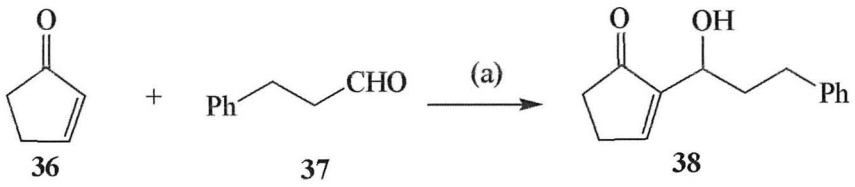
Catalyst	Time	Yield (%)
Me_3P	No reaction	------
$(Cyclohexyl)_3P$	6d	20
Bu_3P	2d	80

Soai[22] investigated the use of the chiral phosphine, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl ((S)-BINAP, an axially chiral bidentate phosphine), to catalyse the enantioselective Baylis-Hillman reaction between pyrimidine-5-carbaldehyde **34** and methyl acrylate **31** to provide the chiral α-methylene β-hydroxyester **35** in 44% e.e. (24% yield) together with several other examples[21, 23-24] (Scheme 11).



Scheme 11: (a) 20 mol% (S)-BINAP, $CHCl_3$, 20°C

Yamada & Ikegami[25] investigated the promotion of Baylis-Hillman reactions by mild, cooperative Lewis base catalysts such as tributylphosphine with phenols or naphthols such as (±)-1,1'-bi-2-naphthol (BINOL) acting as a mild Brønsted acid. Proton NMR studies suggested that BINOL activates the carbonyl group of an aldehyde **37** and a polarised alkene **36** (Scheme 12).

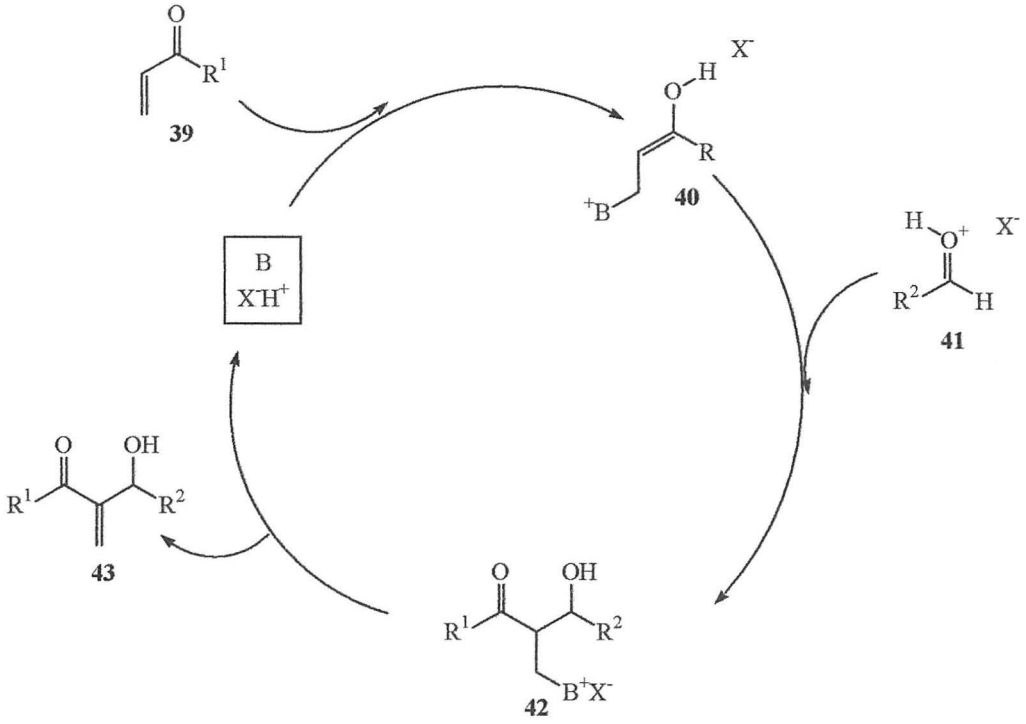


Scheme 12: (a) P(nBu$_3$), BINOL, THF, r.t., 1 hour

The investigation found that the use of DABCO (20 mol%) as the catalyst in this reaction was unsuccessful. Tributylphosphine alone did give the Baylis-Hillman product, but only in a low yield (23%). The best results were those where tributylphosphine (20 mol%) and BINOL (10 mol%) were used in combination leading to **38** in quantitative yield.

The mechanism of the reaction is shown in Scheme 13. The conjugated addition of a Lewis base, tributylphosphine, to the polarised alkene **39** affords the

enol **40**, which reacts with the aldehyde **41** (under acid catalysis) to give the aldol-type intermediate **42**. This then undergoes β-elimination to give the α-methylene-β-hydroxyalkanone **43**. Several other examples are known where a mild Brønsted acid, such as a phenol or naphthol, functions as a co-catalyst to activate the carbonyl groups of an enolate and an aldehyde in Baylis-Hillman reactions.[20, 26-28]

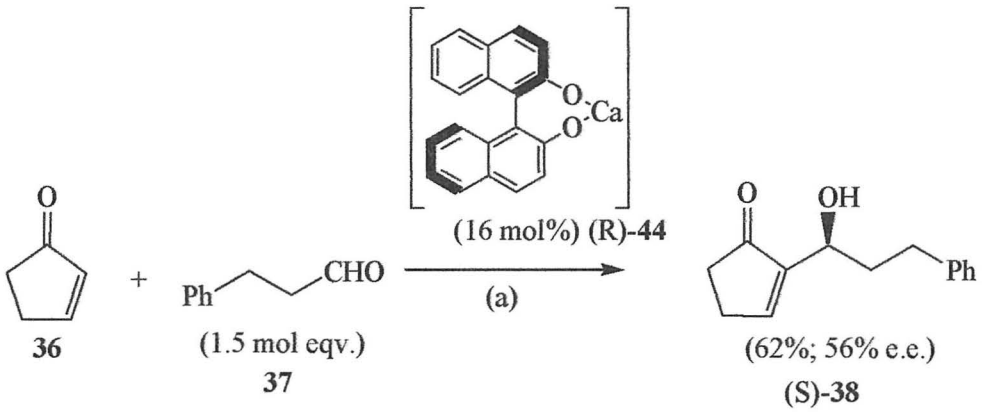


Scheme 13: X^-H^+ = Brønsted acid (phenol or naphthol)

B = Lewis base (tributylphosphine)

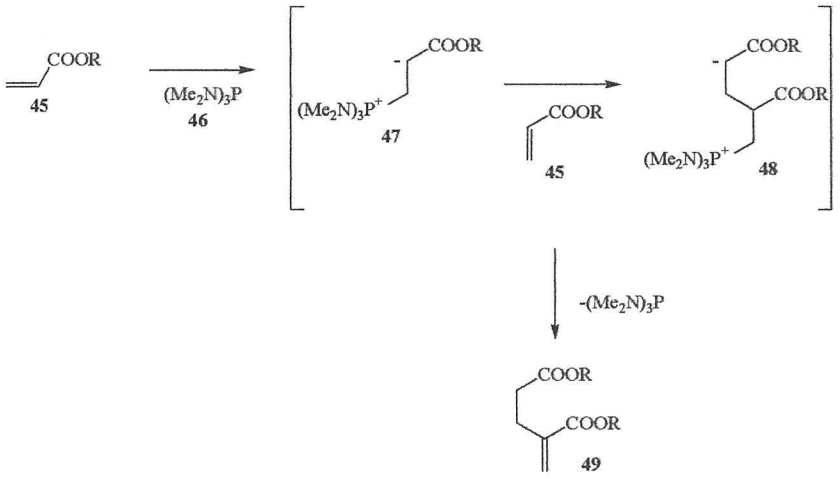
R^1, R^2 = alkyl or aryl

Ikegami and co-workers also developed an asymmetric version of the reaction with the optically active calcium catalyst (R)-**44** acting as a chiral Lewis acid, with tributylphosphine as an achiral Lewis base. This creates an effective method for a catalytic asymmetric Baylis-Hillman reaction[25] (Scheme 14).



Scheme 14: (a) P(nBu)$_3$ (10 mol%), THF, r.t., 7 hrs

It is probably worthy of note that only one example of a tandem Michael/Michael reaction has been reported.[29] It was found that trisdimethylaminophosphine (TDAP) **46** is an excellent catalyst for the preparation of 2-methyleneglutaric esters **49**, from acrylates **45**. This reaction proceeds *via* a similar mechanism to the Baylis-Hillman reaction in that the phosphine undergoes a Michael addition to generate a reactive enolate **47** which then reacts with a further equivalent of acrylate in a Michael fashion. Elimination of the phosphine leads to the product **49** (Scheme 15).



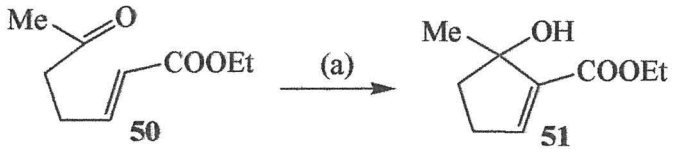
Scheme 15: R = C_2H_5 or ^tBu

1.4.2 Intramolecular reactions

Phosphines were found to be efficient catalysts for intramolecular Michael-aldol reactions, again, better than tertiary amines, as was demonstrated by Roth *et al.*[24] They carried out intramolecular reactions with (2E)-6-oxohept-2-enoate **50** in the presence of the usual Baylis-Hillman catalysts, DABCO and quinidine and found them to be ineffective.

They turned their attention to the use of phosphines as catalysts, which were found to be very effective (Scheme 16, Table 3). Tributylphosphine was found to be the most effective catalyst leading to a 75% conversion of **50** into the cyclised product **51** (entry 1). Other phosphines gave mixed results (entries 2-5), particularly those with aryl substituents, which were inactive.

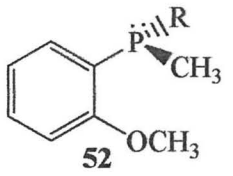
They also investigated the use of chiral phosphines and again the diaryl substituted phosphine (-)-PAMP was inactive, whereas the mono aryl phosphine (-)-CAMP did catalyse the reaction slowly and gave a product with a low e.e.



Scheme 16: (a) Phosphine (PBu_3, $PPhMe_2$, $Me_2PhPMeCN$, P(*i*-Bu)MePh or (-)-CAMP), see Table 3

Table 3

Entry	Catalyst	Time	Mol% cat.	% 50	% 51	Isolated
1	$(n\text{Bu})_3\text{P}$	1d	25	25	75 (GC)	39 %
2	$(CH_3)_2(C_6H_5)\text{P}$	1d	25	35	65 (GC)	
3	$(CH_3)_2(C_6H_5)\text{PCH}_3\text{CN}$	5d	30	70	30 (GC)	
4	(i-Bu, CH_3, C_6H_5)P	30d	25	50	50	
5	CH_3 $(C_6H_5)_2\text{P}$	40d	25	100	------	
6	(-) PAMP (78% e.e.)	20d	20	100	------	
7	(-) CAMP (62% e.e.)	10d	18	25	75 (GC)	40% of **51** (14% e.e.)



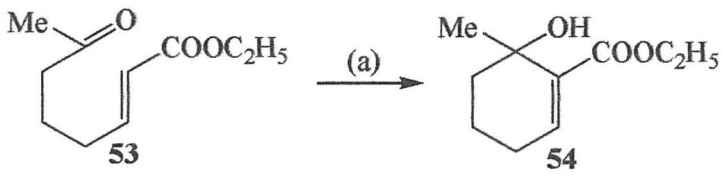
52

(-) PAMP: R = C_6H_5

(-) CAMP: R = c-C_6H_{11}

Figure 1

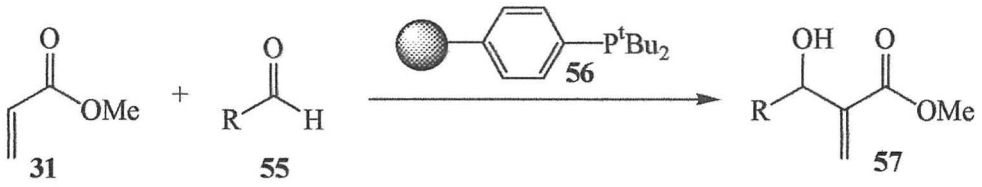
The enoate **53**, unfortunately gave disappointing results when treated under similar conditions to those used for **50**. Curiously, only Me_2PhP gave any appreciable levels of cyclisation with **54** being isolated in 17% yield (Scheme 17).



53 **54**

Scheme 17: (a) Phosphine ($PPhMe_2$), 6 days

More recently, Leadbeater *et al* have investigated the use of resin-bound phosphine complexes as catalysts in the Baylis-Hillman reaction.[30] It was found that the reaction yields obtained for both polymer-supported and solution-phase catalysts were similar, however the polymer-supported catalyst required longer reaction times to effect completion (Scheme 18). This could be due to the different steric effects and reaction kinetics associated with the use of polymer-supported catalysts. The resin-bound phosphine reagent **56** was easily removed at the end of the reaction by filtration and was shown to be reusable.



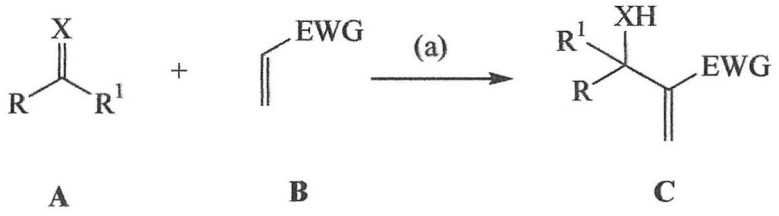
31 **55** **56** **57**

Scheme 18: R = Me, Et, $PhCH_2CH_2$ or Ph

1.5 Tandem Michael-aldol reactions mediated by nitrogen nucleophiles

1.5.1 Intermolecular reactions

The Baylis-Hillman reaction is a well studied[31, 32-37] C-C bond forming reaction, which involves the coupling of activated alkenes with carbon electrophiles under the influence of tertiary amines. The reaction is chemo-, regio-, diastereo- and enantioselective.[38] It is economical in atom count[39] and requires mild conditions, producing synthetically useful multifunctional molecules. The reaction was defined in a German patent as a reaction that results in the formation of a carbon-carbon bond between the α-position of activated alkenes and carbon electrophiles containing an electron-deficient sp^2 carbon atom under the influence of a suitable catalyst, particularly a tertiary amine, producing multifunctional molecules[40] (Scheme 19).



Scheme 19: (a) 3° amine

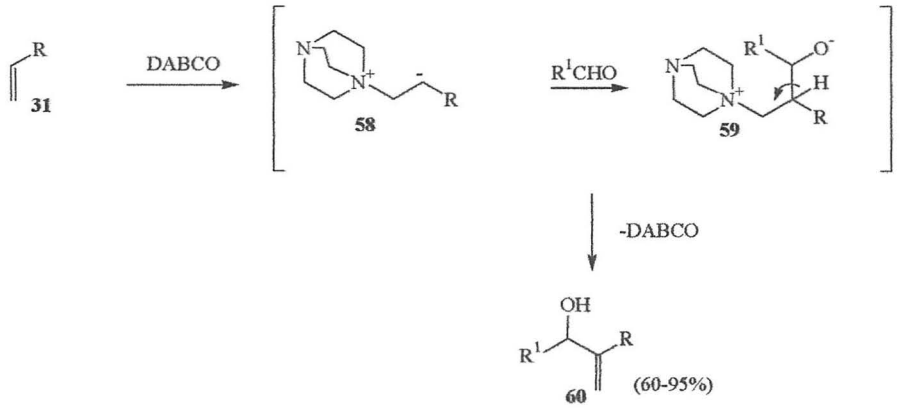
X = O, NR_2; EWG = Electron withdrawing group; R, R^1 = H, alkyl or aryl

Examples of activated alkenes used in the Baylis-Hillman reaction include acrylic esters, acrylonitrile, vinyl ketones, phenylvinyl sulphone, phenyl vinyl sulphonate, vinyl phosphonate, allenic acid ester, and acrolein.[32, 41-52] Examples of aldehydes used in the Baylis-Hillman reaction include aliphatic, aromatic, heteroaromatic, α, β-unsaturated aldehydes, paraformaldehyde (or formalin) and functionalised aldehydes, all being employed as electrophiles.[32, 53-61]

As well as DABCO, the usual Baylis-Hillman catalyst, other catalysts have been employed including various tertiary amines e.g. 3-hydroxyquinuclidine[62], triethylamine[52], and quinidine.[31]

It is a well known fact that reaction times are long, commonly one week or more and even up to one month in some cases.[19, 31, 63-64] Reaction half-lives are reduced in three ways: the addition of methanol or any other alcohol, by increasing the proportion of catalyst or by using electrophilic heterocyclic aldehydes.[31] It has also been found that many aldehydes, for example aromatic aldehydes, are reluctant to serve as substrates because of their low reactivity.[65-66] In order to combat this problem, techniques such as microwave irradiation or high pressure reactions have been used but these have given mixed results at best.[65, 67-69]

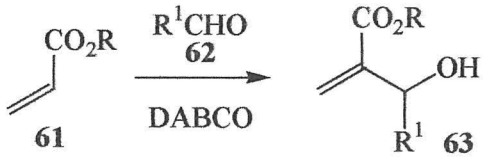
A classic example of this reaction reported by Hoffman[53] is shown in Scheme 20. The synthesis of 2-(hydroxyalkyl)-2-propenoic esters **60** is catalysed by DABCO (diazabicyclo [2.2.2] octane), coupling an aldehyde with methyl acrylate **31** (R = COOMe) *via* the formation of a zwitterionic adduct of DABCO and the acrylic ester **58**. This intermediate reacts with the aldehyde, and the catalyst is regenerated by elimination from the aldol product **59**. Amri and Villieras[43] similarly reported the use of DABCO to catalyse the reaction of methyl vinyl ketone **31** (R = COMe) and acrylonitrile **31** (R = CN) with aldehydes. These reactions can be described as tandem Michael-aldol-elimination processes and their major drawback is that typical reaction times are between 7 and 10 days.



Scheme 20: R = COOMe, COMe or CN; R^1 = alkyl or substituted alkyl

In an improvement on this reaction, Hill and Isaacs[52], reported that similar, tertiary amine catalysed Baylis-Hillman reactions can be catalysed under high pressure and reactions that normally took 4-5 days were accelerated by pressures of 2-3 kbar over 1 hour to give yields of up to 95%. Augé *et al*[67] also reported acceleration in the rate of the Baylis-Hillman reaction when carried out in aqueous media. The DABCO catalysed coupling reaction of benzaldehyde with acrylonitrile (in the presence of 0.15 eqv. of DABCO) in water, formamide or ethylene glycol was studied at room temperature. The reaction had gone to completion in 7-8 hours leading to a 90-98% yield of the product.

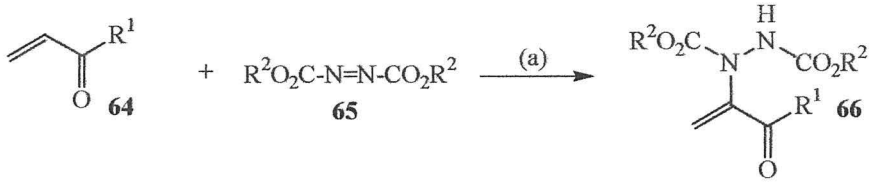
Perlmutter[70] reported the first investigation into the reactions of aryl acrylates under Baylis-Hillman conditions. It became apparent that aryl acrylates react faster when compared with methyl acrylate. For example, the reaction of benzaldehyde, **62** (R^1 = Ph), with methyl acrylate, **61** (R = Me), takes 6 days at room temperature giving **63** in 39% yield; the same yield is obtained when reacting phenyl acrylate, **61** (R = Ph), at 0°C for only 8 hours. The best yield obtained was when R = Ph and R^1 = 3-pyridyl. A yield of 54% was achieved in 10 minutes at 0°C (Scheme 21).



61 63

Scheme 21: R = Ph, 4-nitrophenyl, 2,6-dimethylphenyl, 4-methoxyphenyl or Me; R^1 = Ph, 3-pyridyl or 2-furyl

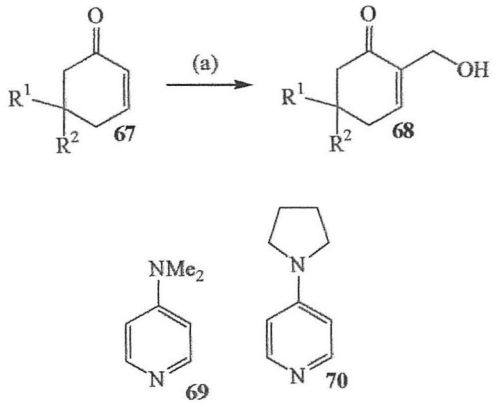
Kamimura[71] has more recently prepared α-hydrazino-α, β-unsaturated ketones *via* the aza-Baylis-Hillman reaction.[31, 40, 63] Imines had previously been used as electrophiles in the reaction to give β-amino-α-methylene compounds,[72] but there had been no examples of the use of other nitrogen electrophiles. With this idea in mind, the group devised a method to prepare α-(N, N'-bisalkoxycarbonyl)hydrazino-α, β-unsaturated ketones **66** in one step from alkyl vinyl ketones **64** and azodicarboxylates **65** under Baylis-Hillman conditions. DABCO was found to be the most effective catalyst giving good yields (34-90%) over fairly short time periods i.e. 8-24 hours (Scheme 22).



Scheme 22: (a) DABCO, THF, r.t. to 40°C, 8-24 hrs

R^1 = Me, Et, C_6H_{13}, C_7H_{15}, PhCH=CH-, OMe; R^2 = Et, ^{t}Bu

El Gaied[73] reported DMAP-catalysed direct α-hydroxymethylation of 2-cyclohexenones in aqueous media through Baylis-Hillman reactions. It was found that the reaction of **67** with HCHO in THF catalysed by DABCO[21, 24, 74] led to the recovery of starting materials; so, they modified the conditions by using a catalytic amount (10 mol%) of 4-(dimethylamino)pyridine **69** or 4-(pyrrolidine)pyridine **70** at room temperature. The α, β-unsaturated ketone **67** reacted with aqueous formaldehyde (2 equiv.) in THF to give 2-(hydroxymethyl)-2-cyclohexenone **68** in 68-82% yield. This was the first Baylis-Hillman reaction of cyclic enones with aldehydes catalysed by a pyridine derivative to be reported (Scheme 23).

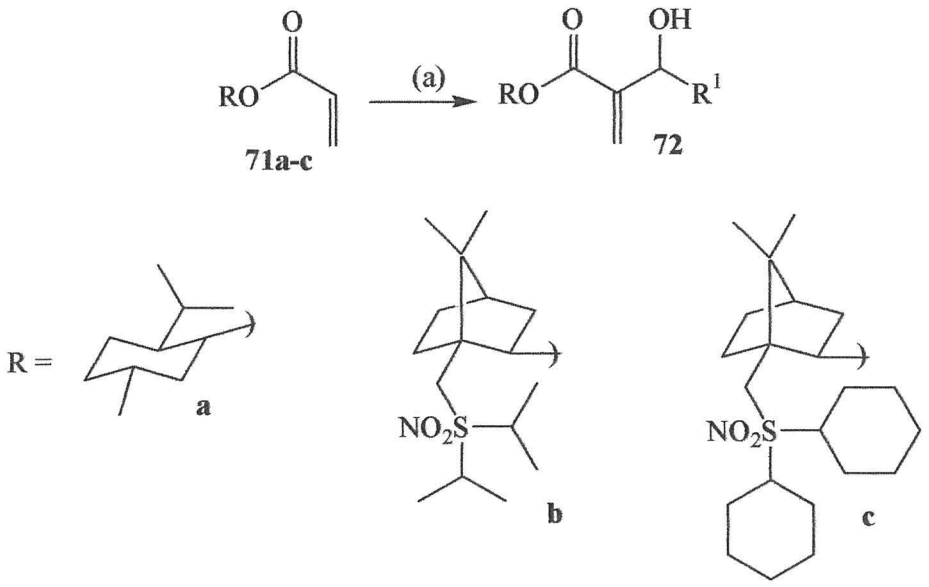


Scheme 23: (a) HCHO aq. (4-6 eqv.), **69** or **70** (10-20 mol%), THF, r.t. to 60°C, 3-6 days

R^1 = H or Me; R^2 = H, Me or Ph

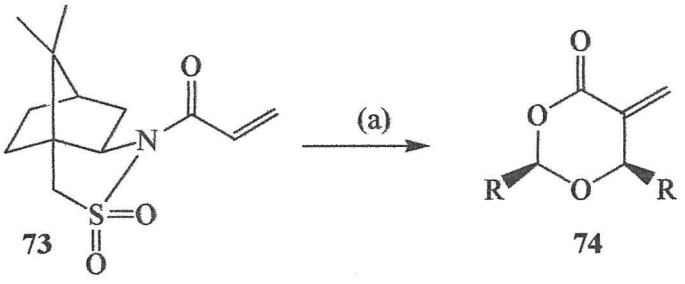
The Baylis-Hillman reaction provides intermediates with various synthetically useful functionalities[31, 63, 75] which have great potential in organic synthesis.[76-80] The drive to find an asymmetric variant of the reaction is obviously of importance and attempts have been made to introduce stereoselectivity into the reaction using optically pure amine catalysts[81], aldehydes[82] and acrylates.[37, 83-88, 89-92]

An effective method to introduce stereochemistry into a molecule is by using a chiral auxiliary.[88] Basavaiah *et al*[83] used chiral acrylates **71** as substrates in the Baylis-Hillman reaction in an asymmetric version of the reaction. DABCO was used to induce the diastereoselective (7-70%) coupling of chiral acrylates with aldehydes, producing the corresponding optically active 2-(1-hydroxyalkyl) acrylates **72**. Three chiral acrylates (**71a-c**) were studied in a coupling reaction with propionaldehyde under the influence of DABCO. The best d.e. (70%) was obtained when propionaldehyde was reacted with **71c** over 10 days giving **72** in 45% yield (Scheme 24).



Scheme 24: (a) R^1CHO (R^1 = CH_3, CH_3CH_2, $(CH_3)_2CH$, C_4H_3O or C_6H_5), DABCO (100 mol%), 0.75-15 days

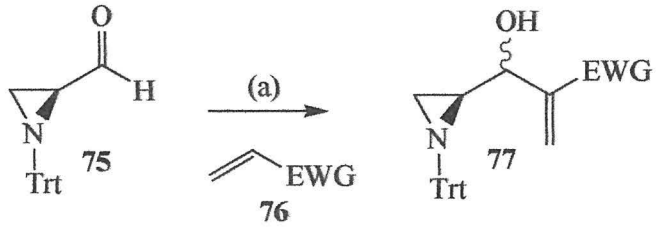
Oppolzer's sultam derivative **73** also gave excellent transfer of chirality in a Baylis-Hillman reaction, giving the cyclic acetal products **74** in excellent yields and essentially optically pure.[89-91] The best results were obtained when R = ethyl, the yield of product **74** being 98% (>99% e.e.) (Scheme 25).



Scheme 25: (a) RCHO, DABCO, CH_2Cl_2, 0°C

R = CH_3, CH_3CH_2, $CH_3CH_2CH_2$, $(CH_3)_2CH$, $PhCH_2CH_2$, $ArOCH_2$ or $(CH_3)_2CHCH_2$

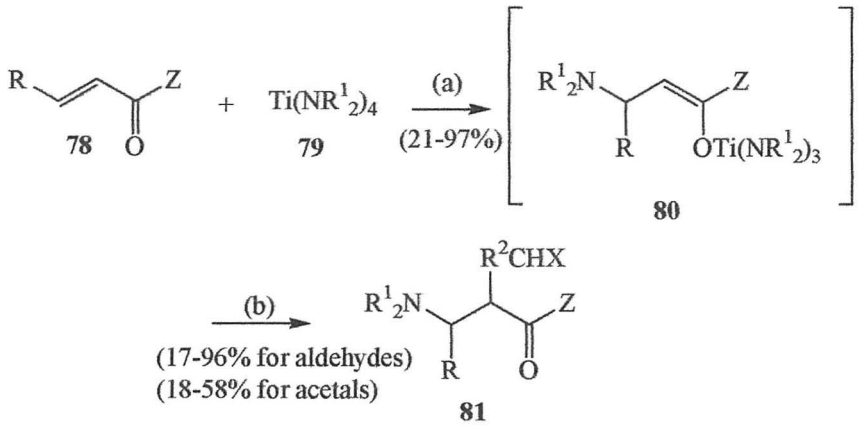
Chiral aldehydes can also be used in the asymmetric Baylis-Hillman reaction [35, 82, 93-97] however the reaction has met with limited success. Zwanenburg[96] for example, reported the Baylis-Hillman reaction of N-trityl aziridine-2-(S)-carboxaldehyde **75** with a variety of acceptors **76** in the presence of a catalytic amount of DABCO giving corresponding adducts **77** in good yields but as a mixture of *syn* and *anti*-diastereomers (Scheme 26).



Scheme 26: (a) DABCO, r.t., 3-45 days, 28-83%

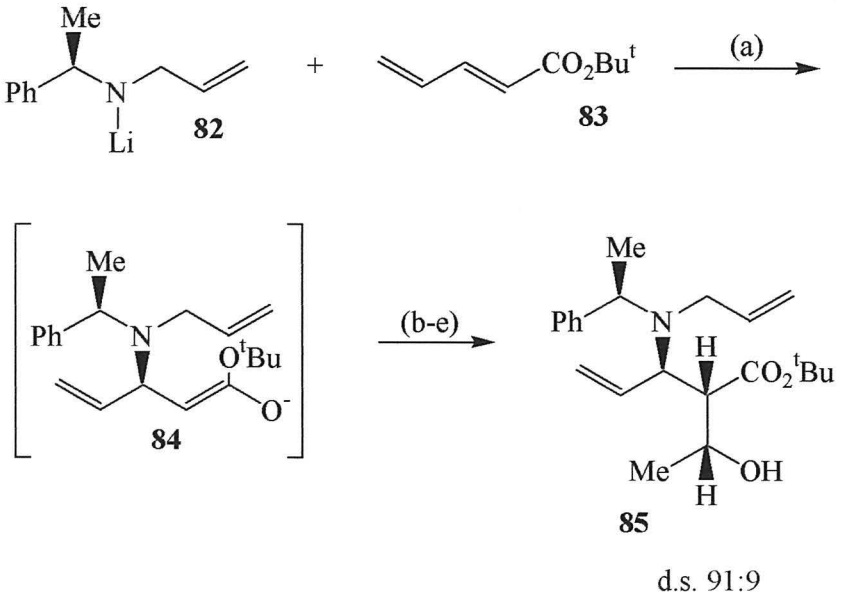
EWG = CO_2Me, CO_2Et, CN, C(O)Me or SO_2Ph

Metal derivatives of amides are also effective in tandem Michael-aldol reactions, for example Hosomi[98] reported the conjugate addition of titanium amides **79** to α, β-unsaturated esters and ketones **78**, and the successive crossed-aldol reaction of the resulting enolates **80** with aldehydes and acetals. Yields of up to 96% were achieved for adducts **81** (Scheme 27).



Scheme 27: (a) $BF_3{:}OEt_2$, CH_2Cl_2, –20°C to reflux, 30 mins-64 hrs; (b) R_2CHO or $R^2CH(OR^3)_2$; Z = alkoxy or alkyl; X = OH or OR^3; R = H, Me or Ph; R^1 = Me or Et; R^2 (aldehydes) = Ph, *p*-$CH_3C_6H_4$, 1-naphthyl, C_4H_3O, Me, *n*-Pr, *t*-Bu, C_5H_9 or PhC_2H_2; R^2 (acetals) = Ph, $CH_3(CH_2)_5$, $PhCH_2$ or $Ph(CH_2)_2$; R^3 = Me

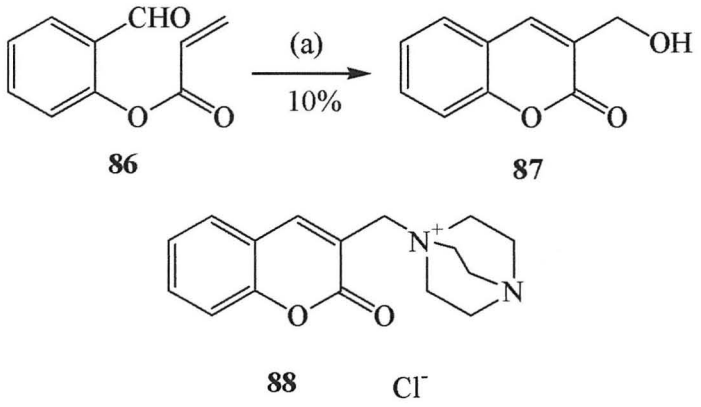
Davies and Fenwick[99] also reported the use of lithium (α-methylbenzyl)allylamide **82** in a formal asymmetric synthesis of thienamycin. This was achieved by preparing the synthetic intermediate **85** *via* a highly stereoselective conjugate addition of **82** to (E)-*t*-butyl penta-2,4-dienoate **83**, followed by the stereoselective aldol reaction of the enolate **84** with acetaldehyde to give **85**[100, 101] (Scheme 28).



Scheme 28: (a) Aqueous NH_4Cl, 87%; (b) LDA, THF, 0°C, 2 hrs then –78°C; (c) $B(OMe)_3$; (d) MeCHO; (e) aqueous NH_4Cl, 82%

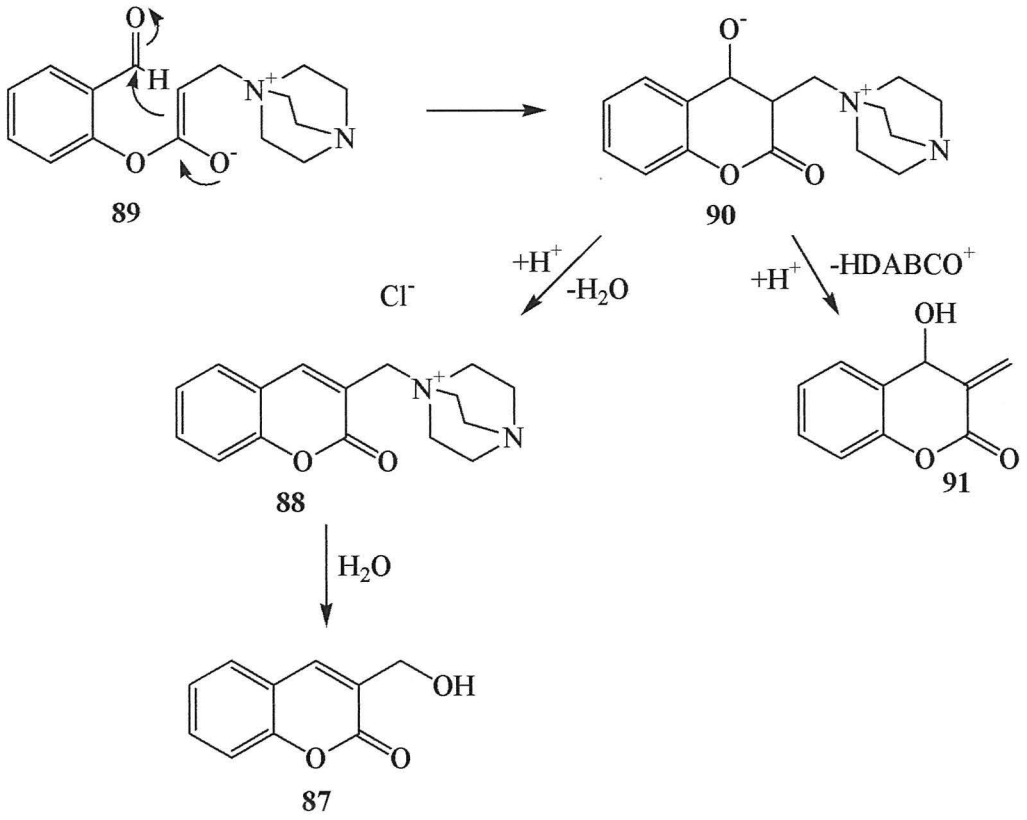
1.5.2 Intramolecular reactions

Only a few examples of intramolecular tandem Michael-aldol reactions have been reported. Drewes *et al*[102] investigated the reaction of 2-acrylyloxybenzaldehyde **86** in the presence of DABCO in DCM which gave 3-hydroxymethylcoumarin **87** in only 10% yield. The major product isolated was the quaternary ammonium salt **88** (Scheme 29).



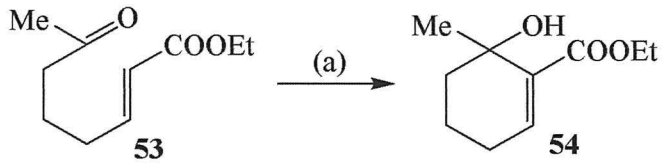
Scheme 29: (a) DABCO, CH_2Cl_2

The mechanism initially involves the formation of the Michael adduct **89** which then undergoes aldol cyclisation to give **90**. This intermediate then preferentially undergoes dehydration to give **88** rather than eliminate the base to give **91**. Compound **87** probably arises from the hydrolysis of **88** (Scheme 30).



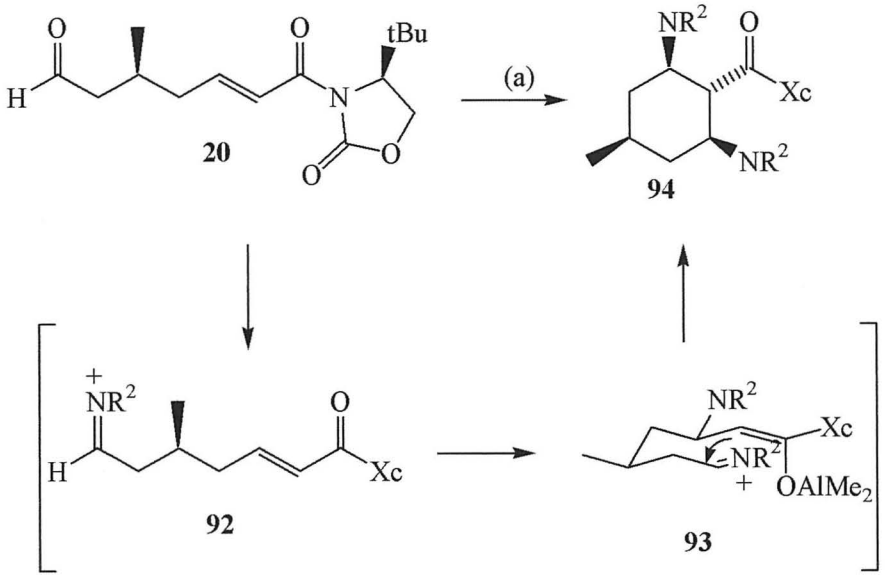
Scheme 30

Fráter's group[24] carried out investigations into the reaction of (2E)-7-oxooct-2-enoate with lithium quinidate, which gave the cyclised product **54** in 23% yield. No asymmetric induction was observed in this process (Scheme 31).



Scheme 31: (a) Li-quinidate, catalyst (25 mol%), r.t., 2 hrs, HMPA

In addition to his work on the tandem Michael-aldol addition of cuprates, Schneider also reported the domino Michael-Mannich reactions[10] of adducts **20** with aluminium amides in the presence of secondary amines. Instead of the usual cyclohexanols, this reaction gave the diamino cyclohexanes **94a-d** in good yields as single stereoisomers. The results are summarised in Table 4 (Scheme 32).



Scheme 32: (a) Me_2AlCl, $2HNR^2$, CH_2Cl_2, 0°C

X_c = Chiral auxiliary

R^2 = Morpholine, piperidine, Bn_2NH or Et_2NH

Table 4

Product	Amine	Yield (%)
94a	Morpholine	69
94b	Piperidine	57
94c	$(Bn)_2NH$	65
94d	Et_2NH	46

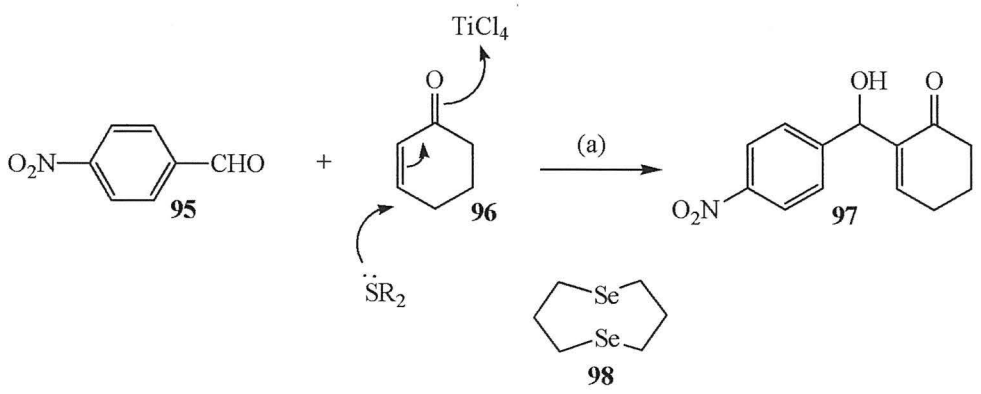
Initially, N, O-hemiacetals are formed, which collapsed to the iminium salts **92** leading to **93**, which, after the Michael addition of a second equivalent of Me_2AlNR_2, were trapped by the imine in a Mannich reaction.[103] A complete reversal of stereochemistry was observed when compared to the aldol reaction. The intramolecular transposition of metal ion is prohibited because of the inability of the iminium nitrogen atom to co-ordinate to the aluminium ion, due to lack of vacant co-ordination sites; so, the large iminium group occupies a sterically more favourable pro-equatorial position in the transition structure, which eventually results in the *anti*-configuration of the Mannich products.

1.6 Tandem Michael-aldol reactions mediated by chalcogen nucleophiles

Recently, there has been a surge of interest in what has been referred to as the "chalcogeno-Baylis-Hillman reaction", essentially this reaction uses a chalcogen derivative, typically of S or Se in the presence of a Lewis acid to effect a Baylis-Hillman reaction.

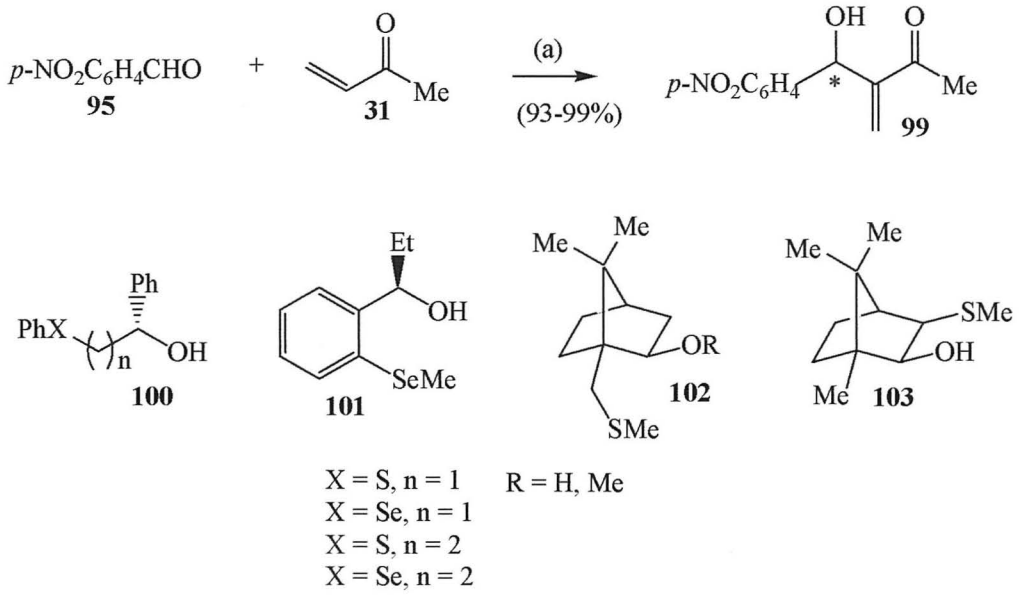
1.6.1 Intermolecular reactions

Kataoka[104-106] and co-workers have developed an effective method for chalcogeno-Baylis-Hillman reactions, employing dialkylsulfides and dialkylselenides as catalysts in the presence of Lewis acids. For example, the reaction of *p*-nitrobenzaldehyde **95** with 3 equivalents of 2-cyclohexen-1-one **96** in the presence of dimethyl sulfide and 1 equivalent of $TiCl_4$, gave a 62% yield of the product **97** after 1 hour at room temperature.[104] A variety of chalcogenide catalysts were tested in this reaction with the best results being obtained when the bis-selenide **98** was utilised (85% yield).[104] The reaction was found to be generally applicable to several activated alkenes, for example acrylonitrile, methyl acrylate, phenyl vinyl sulfone and phenyl vinylsulfonate as well as β-substituted enones[104-105, 107] (Scheme 33).



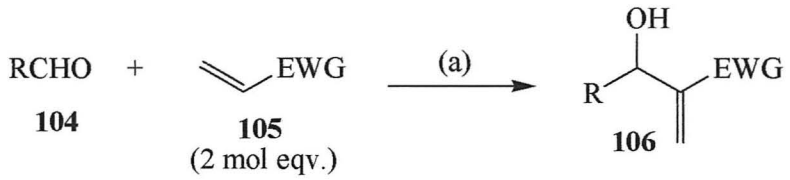
Scheme 33: (a) Me_2S (0.1-1.0 eqv.), Lewis acid: $TiCl_4$ (0.1-1 eqv.), $AlCl_3$, $EtAlCl_2$, Et_2AlCl, $HfCl_4$ or $Hf(OTf)_4$ (1.0 eqv.), CH_2Cl_2, r.t. to reflux, 10 min-5 days, 11-62%

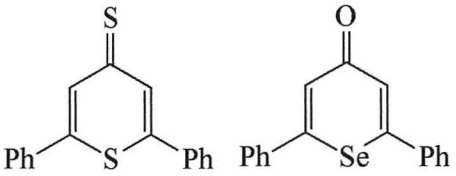
Kataoka[106] also investigated a similar reaction using chiral hydroxy-chalcogenide-$TiCl_4$ complexes. Asymmetric induction in the reaction is enabled because the hydroxy-chalcogenide forms a four-component complex with the enone **31**, the aldehyde **95** and $TiCl_4$ (Scheme 34). They investigated a range of catalysts **100-103** with the best e.e. being given by 10-methylthioisobornenol **102** (R = H), which gave the product **99** in 72% e.e.



Scheme 34: (a) Aldehyde (1 eqv.), enone (3 eqv.), chalcogenide (0.1–1.0 eqv.) (**100-103**), $TiCl_4$ (1 eqv.), CH_2Cl_2, -78 to -20°C, 1-24 hrs

Further catalysts have also been utilised[108] including 2,6-diphenyl-4H-thiopyran-4-thione, **107** and 2,6-diphenyl-4H-selenopyran-4-one, **108**. The catalysts gave adducts **106** under identical reaction conditions in moderate to high yields and were found to be more efficient catalysts than Me_2S (Scheme 35).



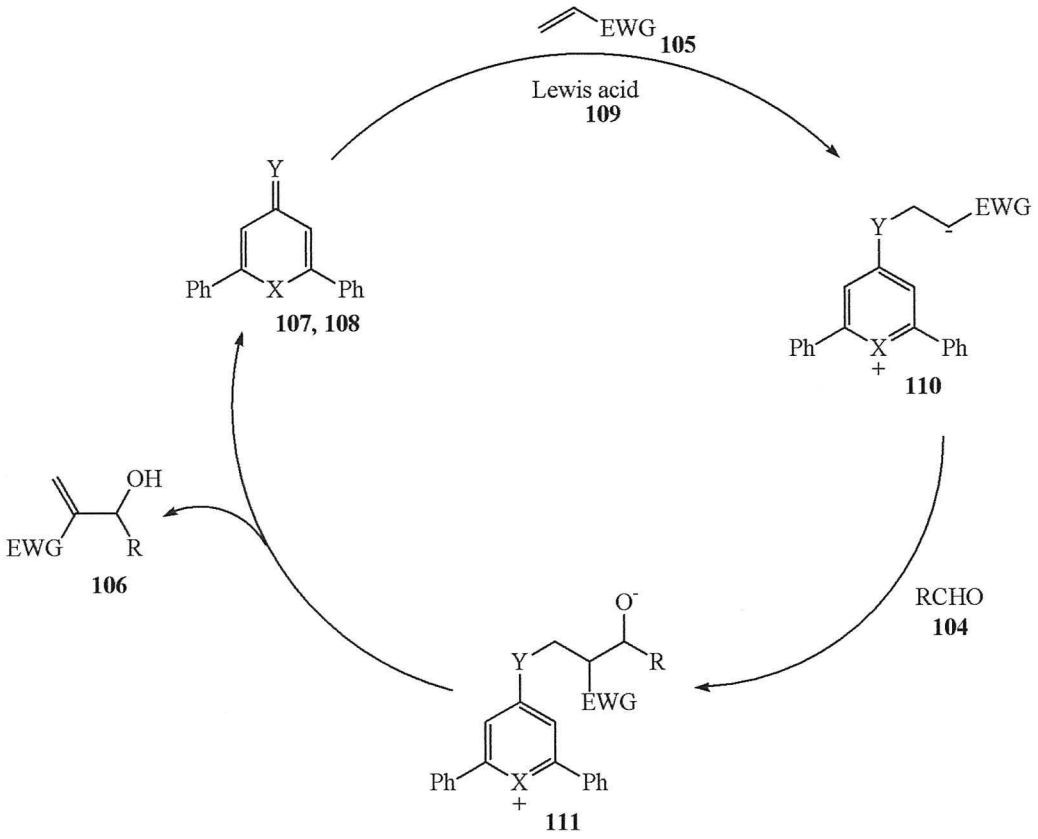


107 108

Scheme 35: (a) Catalyst (**107** or **108**, 0.1 mol eqv.), $TiCl_4$ (1 mol eqv.), CH_2Cl_2, 0°C to reflux, 1-24 hrs, 32-95%

R = *p*-ClC_6H_4, Ph, *p*-MeC_6H_4, $PhCH_2CH_2$, *i*Pr or *p*-$NO_2C_6H_4$; EWG = COMe, C_6H_8O, C_5H_6O, COSEt, COH or CN

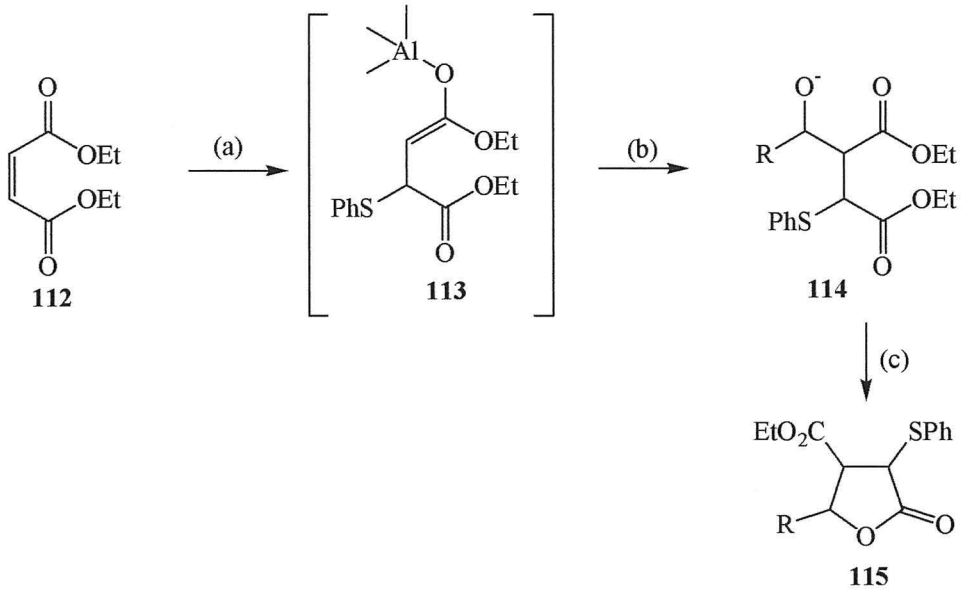
The mechanism of this reaction is somewhat different to that supposed for the simple dialkylchalcogens, in that it is thought that the reaction proceeds *via* intermediates **110** and **111**, which, despite the fact that they were not isolated, were found to be present by proton NMR studies of the reaction (Scheme 36).



Scheme 36: X = S; Y = S or X = Se; Y = O

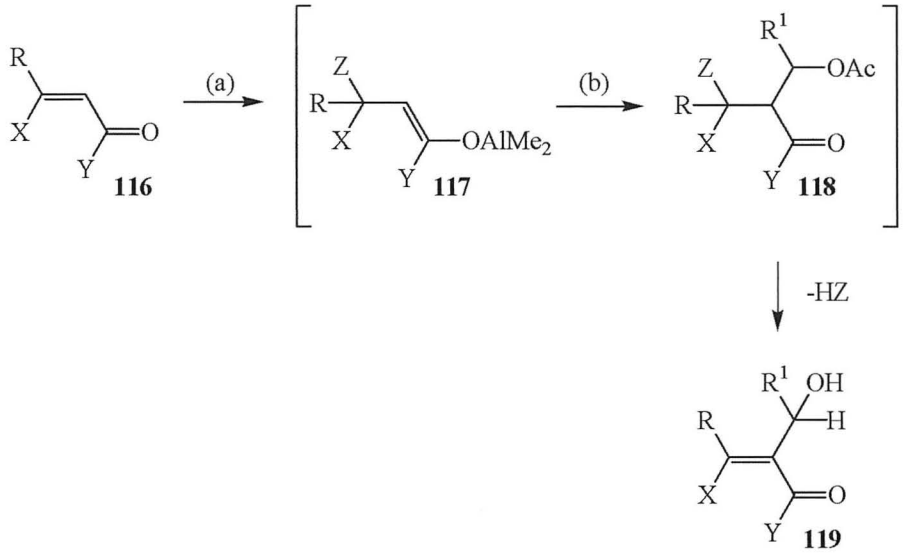
R and EWG = see previous page

Metal thiolates have also been applied to tandem Michael/aldol processes, for example, Levin[109] developed an efficient, general route to α-thiophenyl-γ-butyrolactones **115** using an aluminium thiophenoxide mediated Stobbe condensation, achieving a yield of between 51 and 85% (Scheme 37).



Scheme 37: (a) $(CH_3)_3AlLiSPh$; (b) RCHO; (c) *p*-TsOH, CH_2Cl_2, reflux, 16 hrs
R = Aryl or heteroaryl

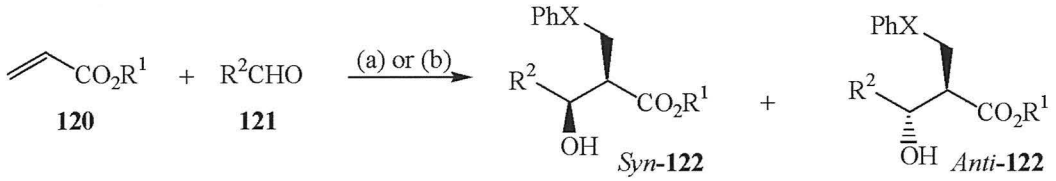
Oshima[110] studied the aldol reaction of aluminium enolates **117**, which result from a 1,4-addition of Me_2AlSPh or $Me_2AlSeMe$ to an α, β-unsaturated carbonyl compound. The resulting aluminium enolates react with aldehydes to give adducts of the anion after formal PhSH or MeSeH elimination. Yields of up to 97% for **118** and 92% for **119** were achieved (Scheme 38).



Scheme 38: (a) Me_2AlX; (b) R^1CHO

R = H or Me; R^1 = Me, $CH_3(CH_2)_7$, methacrolein, H or Ph; Z = SPh or SeMe; X, Y = $-(CH_2)_3-$, H and H, $-(CH_2O)-$ or H and CH_3

Kamimura[111] also investigated the stereoselective Michael/aldol tandem reaction triggered by thiolate anion or analogues. The α, β-unsaturated ester **120**, aldehyde **121** and lithium thiophenolate were reacted in CH_2Cl_2 and underwent a reaction to give the α-phenyl-thiomethyl-β-hydroxy esters **122**, in good yield (92%) with high *syn*-selectivity (88:12) (Scheme 39).

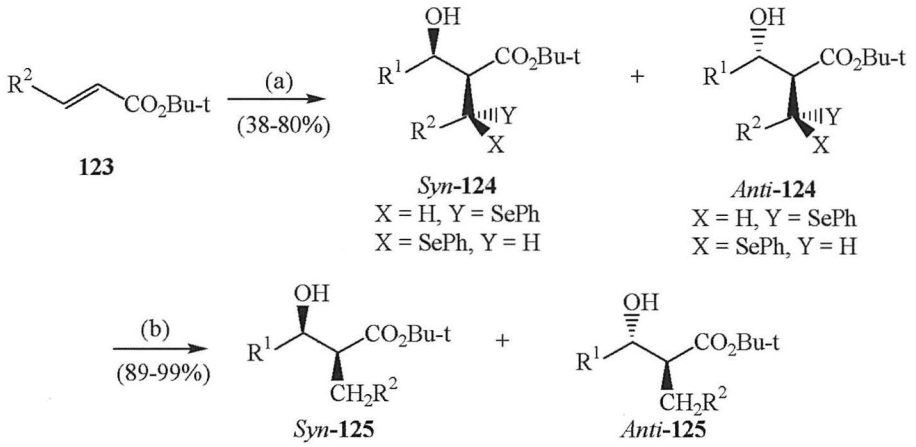


120 **121** *Syn*-**122** *Anti*-**122**

Scheme 39: (a) PhSLi, CH_2Cl_2, -78°C then –50°C; (b) PhSeSePh, MeLi.LiBr, Et_2O, -78°C then r.t.

R^1 = Me, Et or *t*Bu; R^2 = Ph, *p*-ClC_6H_4, 1-naphthyl, PhCH=CH, C_5H_{11} or C_9H_{19}; X = S, Se or O

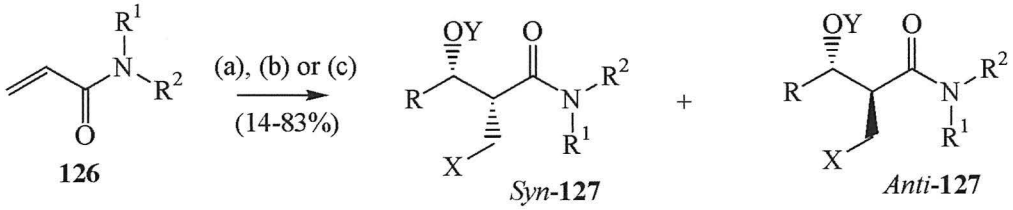
Kamimura[112] further reported a magnesium selenoate-induced Michael/aldol tandem reaction resulting in *anti*-aldol selective formation of β-hydroxy-α-(phenylseleno) alkyl esters **124**. They found that use of magnesium thiolate or selenoate promotes tandem reaction with high (98:2) *anti*-aldol selectivity. Reductive removal of the seleno group gives *anti*-aldols in high stereoselectivity. This was found to be the opposite of the result given by the lithium cation investigated previously[111] (Scheme 40).



Scheme 40: (a) PhSeSePh/MeMgBr, R^1CHO, -50°C to r.t.; (b) Bu_3SnH/AIBN, toluene, 110°C

R^1 = Ph, *p*-MeC_6H_4, *p*-ClC_6H_4, *m*-$MeOC_6H_4$, *p*-$MeOC_6H_4$ or C_5H_{11}; R^2 = Me or C_3H_7

Kamimura[113] also employed thiolates and selenoates to induce Michael-aldol tandem reactions, converting α, β-unsaturated amides **126** to α-phenylthio or α-phenylseleno-methyl-β-hydroxy amides **127** with *syn*-stereoselectivity and in yields of up to 83%, the best results being obtained when both R^1 and R^2 are benzyl groups (Scheme 41). These tandem adducts can be reduced or oxidised and eliminated leading to NH-amide aldols or amide-Baylis-Hillman adducts which are difficult to prepare in good yield under normal conditions.[31, 63, 75]



Scheme 41: (a) PhSLi, CH_2Cl_2, RCHO, -30°C to r.t., 15 hrs

R^1 = H, Bn, *t*Bu, *i*-Pr, -$(CH_2)_5$-; R^2 = H, Bn, *i*-Pr, -$(CH_2)_5$-, *t*Bu

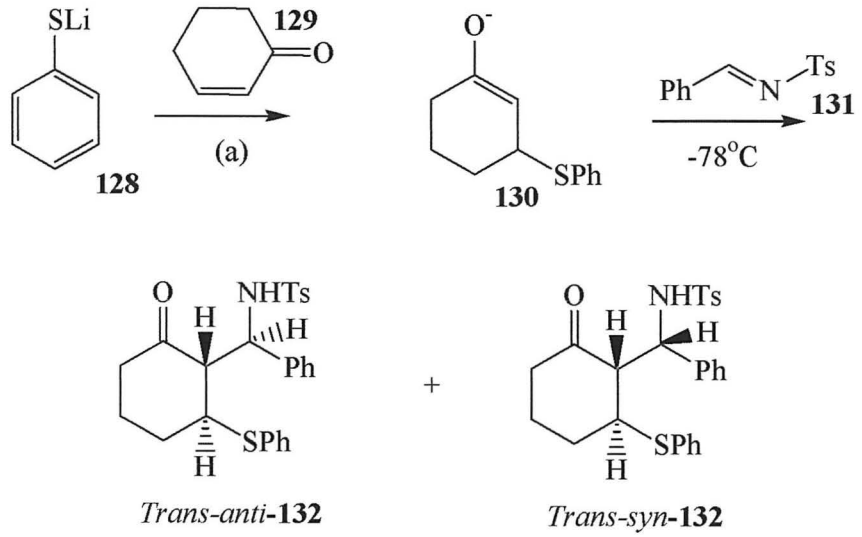
(b) PhSeLi, ether, RCHO, -10°C to r.t., 15 hrs; (c) PhSeLi, ether, RCHO, -10°C to r.t., 15 hrs then TBSCl, ImH, DMF

X = S or Se

Y = H or TBS

R = *p*-ClC_6H_4-, *p*-$MeOC_6H_4$-, 2-furyl, $C_{10}H_7$-, C_5H_{11}-, Ph

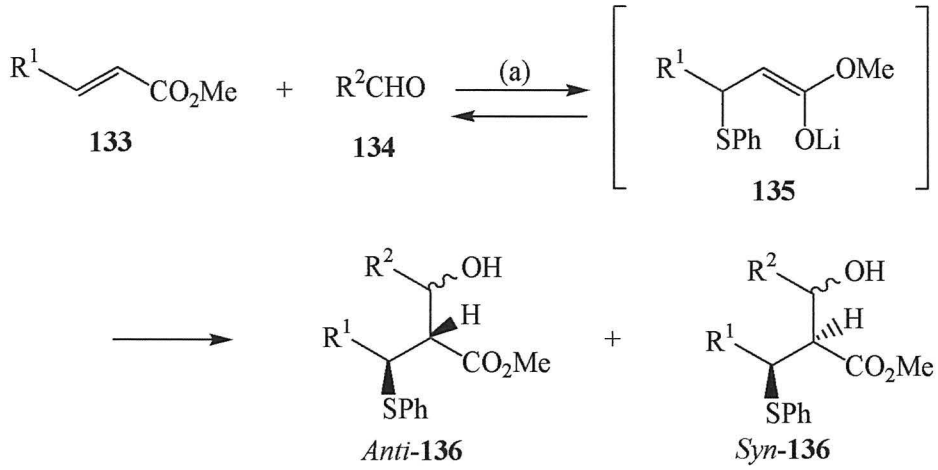
Hou *et al*[114] prepared Michael-aza-aldol adducts with high *trans-anti* stereoselectivity. Phenylthiolate **128** was reacted with cyclohexenone **129** giving enolate **130**, which was then trapped by imine **131** to give the corresponding β-amino ketone **132** as the final product in high yield (93%) and excellent stereoselectivity (94:6) (Scheme 42).



Trans-anti-**132** *Trans-syn*-**132**

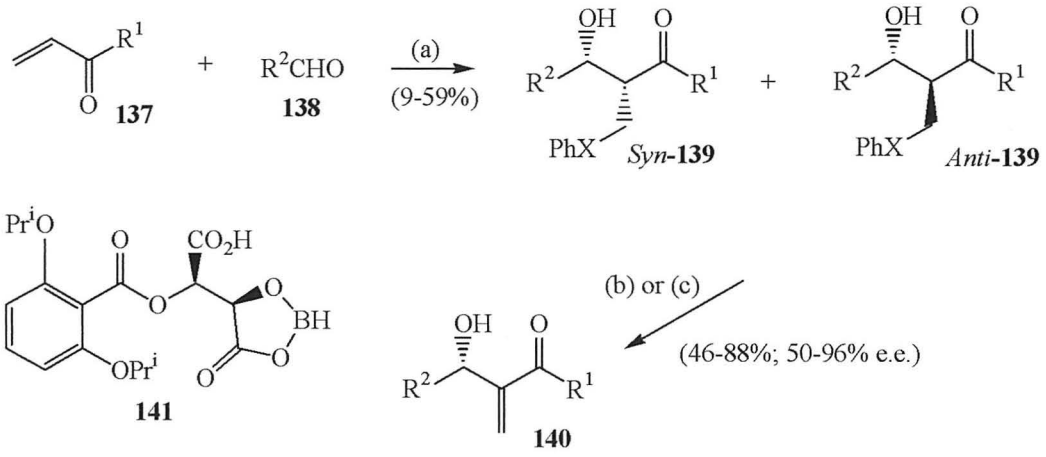
Scheme 42: (a) Base: (*n*-BuLi, NaH or EtMgBr), Solvent: (CH_2Cl_2, hexane or THF), Additive: none, HMPA (2, 4 or 10 eqv.), 12-crown-4 (1 eqv.) or TMEDA (2 eqv.), -78°C

Tomioka and co-workers[115-119] have also extensively studied the stereoselective tandem conjugate addition reaction of catalytic amounts of lithium arylthiolates to enoates in the presence of phenyl trimethylsilyl sulfide. For example, enoates **133** gave the 3-arylsulfanylalkanoates **136** in high yield (56-97%) with d.e. as high as 99:1 (*anti:syn*) (Scheme 43).



Scheme 43: (a) PhSLi (0.2 eqv.), phenyl trimethylsilyl sulfide (2 eqv.), THF, r.t., 2h
R^1 = Me, Bu, Bn or Ph; R^2 = Ph, 4-MeOPh, 4-ClPh, 2-py, 2-furyl, *t*-Bu or cHex

Barrett and Kamimura[120] reported the catalytic asymmetric synthesis of α-methylene-β-hydroxy-ketones **140** by reaction of methyl vinyl ketone **137**, acetaldehyde **138** and trimethylsilyl phenyl sulfide catalysed by chiral (acyloxy)borane **141** (20 mol%). The adducts **139** were obtained predominantly as the *syn*-diastereomers in yields ranging from 9-59% with as high as >98:2 selectivity and 97% e.e. Similar reactions using trimethylsilylphenylselenide gave the adducts **139** in better yield, however the e.e's were lower than for corresponding sulfide examples (Scheme 44).

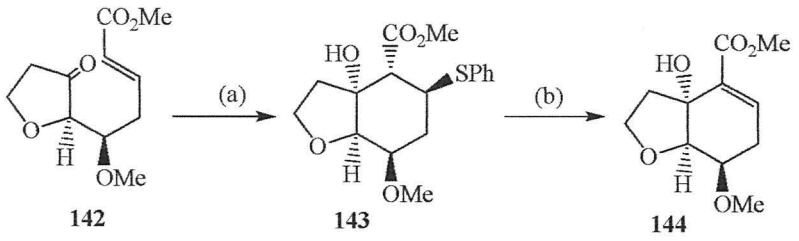


Scheme 44: (a) Me_3SiSPh or $Me_3SiSePh$, **141** (20 mol%), C_2H_5CN, -78°C; (b) *m*-chloroperbenzoic acid, CH_2Cl_2, -10°C then 130-150°C; (c) H_2O_2, CH_2Cl_2, 25°C

R^1 = Me, Et or OMe; R^2 = Me, Et, *i*Pr, Bu, Ph or Pr; X = S or Se

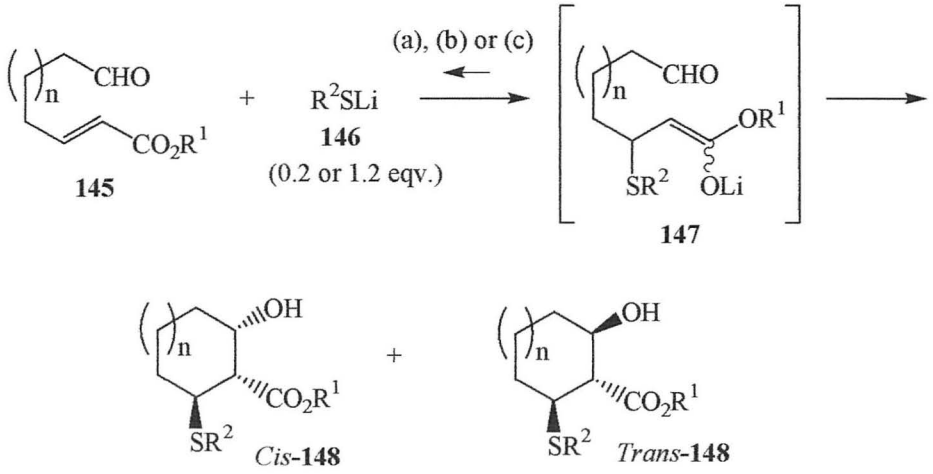
1.6.2 Intramolecular reactions

Armistead and Danishefsky[121] reported the first intramolecular Michael-aldol sequence of an enolate-ketone triggered by the action of an aluminium thiophenoxy "ate" complex in their synthesis of the oxahydrindene subunit of the avermectins. Thus the substrate **142** reacted with the "ate" species generated from the reaction of trimethylaluminium with lithium thiophenoxide producing a high yield (89%) of **143** as a single diastereomer. Oxidative de-sulfenylation afforded a 94% yield of **144**[110, 122] (Scheme 45).



Scheme 45: (a) $Me_3AlSPhLi$, THF, 0°C; (b) mCPBA, 110°C

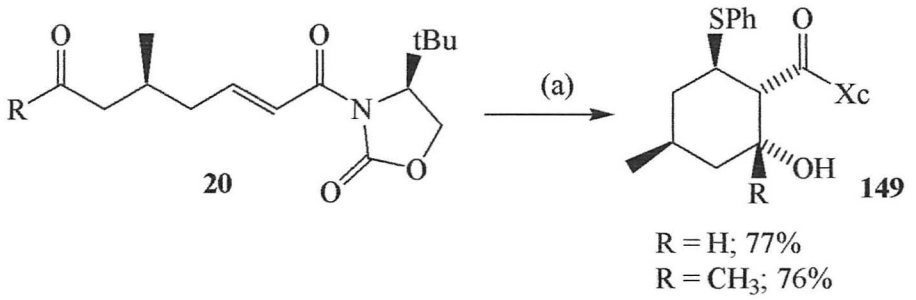
As was previously discussed (Section 1.6.1), Tomioka *et al* reported a lithium benzenethiolate initiated Michael addition-intermolecular aldol tandem reaction of enoates with aldehydes.[115] They broadened the scope of the process to an intramolecular reaction of ω-oxo-α, β-unsaturated esters **145** with lithium thiolates leading to the cyclisation product **148** via ω-formylenolate **147**. They reported the synthesis of 5, 6 and 7-membered carbocycles with predominantly *cis*-selectivity and in good to excellent yields (Scheme 46).



Scheme 46: (a) 2.0 eqv. PhSTMS; (b) 1.2 eqv. $AlMe_3$; (c) No additive; -20 to 0°C, 0.5-6 hrs

R^1 = Me or Et; R^2 = Ph or $PhCH_2$; n = 0, 1 or 2

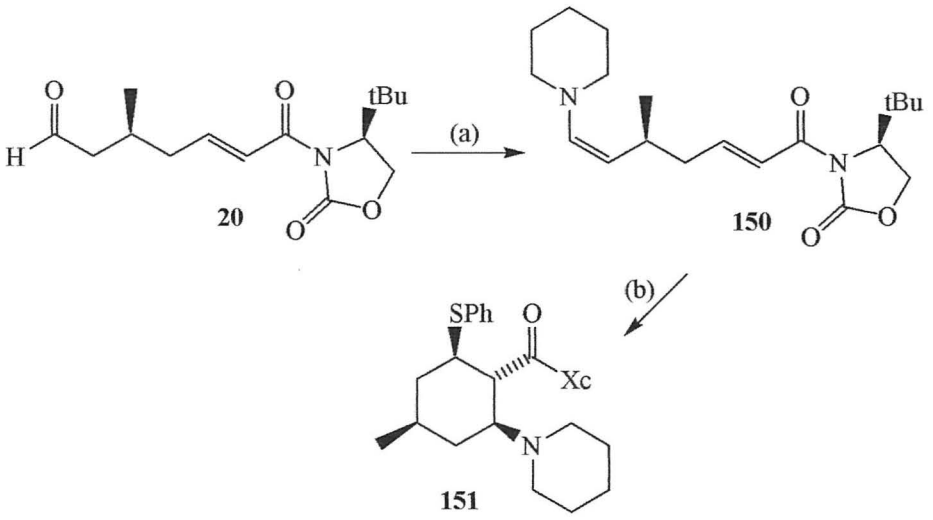
Schneider[7] used the dimethylaluminium phenylthiolate to effect cyclisation of the substrates **20** to the cyclohexanols **149**, which were obtained as single stereoisomers in excellent yield (Scheme 47).



Scheme 47: (a) Me_2AlSPh, THF, -78°C

R = H or CH_3

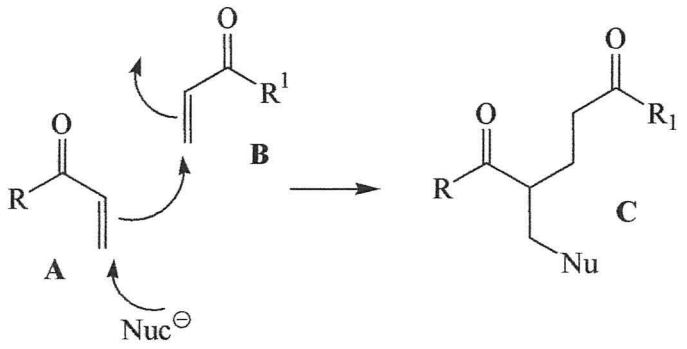
They also reported that 7-oxo-2-enimide **20** could be converted into the enamine **150**, which, on reaction with Me_2AlSPh and Me_2AlCl at –78°C, formed the highly functionalised cyclohexane **151** in moderate yield but with complete stereocontrol (Scheme 48).



Scheme 48: (a) Piperidine, $MgSO_4$; (b) Me_2AlSPh, Me_2AlCl, CH_2Cl_2, -78°C, (50%), 2 steps

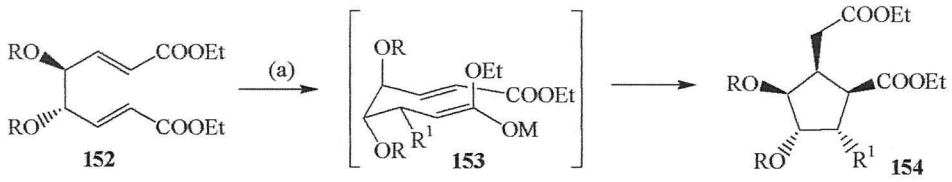
1.7 Tandem Michael-Michael reactions

The tandem Michael-Michael reaction as it suggests is a conjugate addition of a nucleophile to a Michael acceptor, generating an enolate, which then undergoes a second Michael reaction. A general reaction scheme is shown in Scheme 49.



Scheme 49: R, R^1 = alkyl or aryl

For example, 2,6-octadienoic diesters **152** are cyclised on treatment with alkyl magnesium Grignards leading to the cyclopentane derivatives **154**.[123] The Michael addition of several Grignard reagent-cuprous iodide (1:1) complexes to **152** were investigated, and a single enantiomer was obtained in each case (Scheme 50).

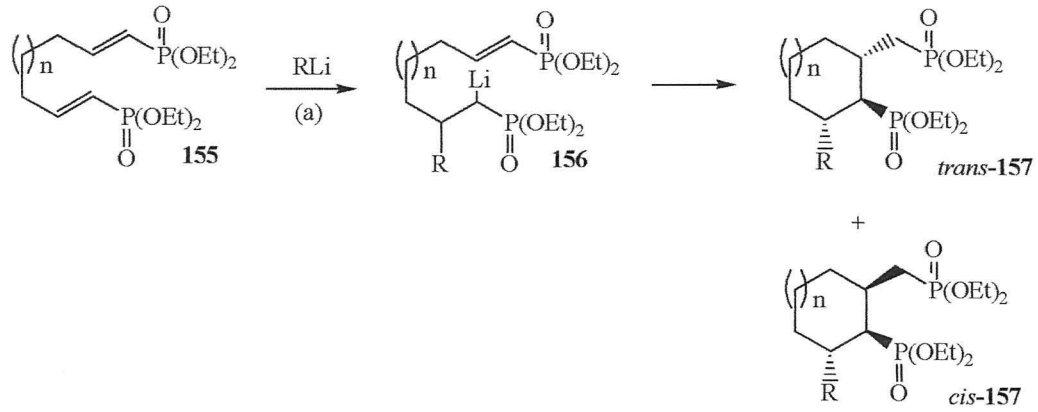


(40-94%; >99% d.e.)

Scheme 50: (a) R^1MgBr-CuI (6 mol eqv.), ether, -20°C, 1 hr

R = TBS; R^1 = CH_2CH, CH_3, CH_3CH_2 or C_6H_5

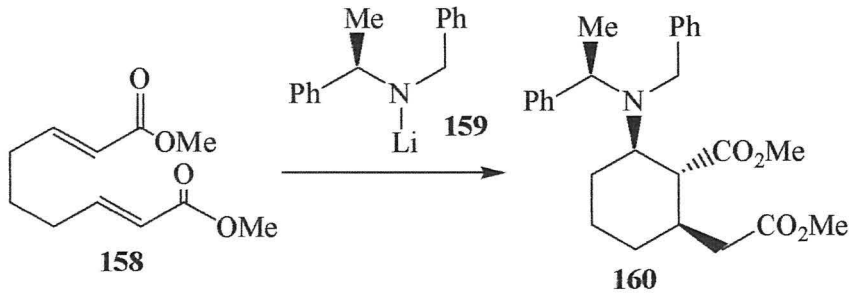
Tomioka *et al*[124] also utilised this method in the reaction of α, β, ψ, ω-unsaturated bisphosphonates with organolithiums. This reaction of the α, β-unsaturated bisphosphonates **155** with organolithiums (RLi) give the carbocycles **157** in high yield (94% overall; *trans*-58%, *cis*-0%) and in good selectivity (Scheme 51).



Scheme 51: (a) THF, -78°C

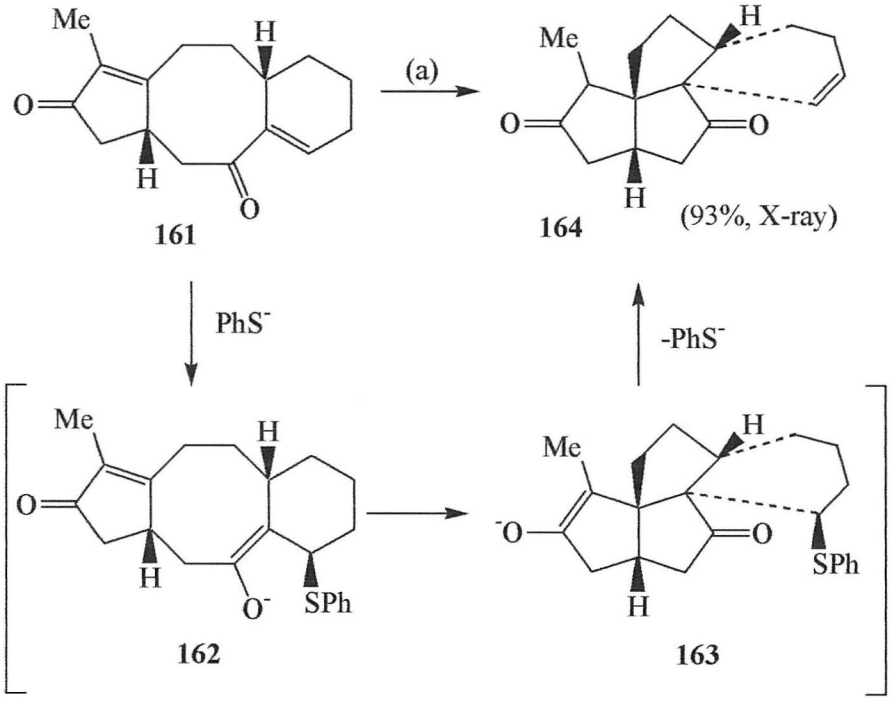
R = Ph, 1-naphthyl, 2-naphthyl or Bu; n = 5 or 6

Davies also reported the tandem Michael-Michael cyclisation of the bis-enoate **158** by the addition of the chiral lithium amide **159**. The reaction proceeded in high yield and gave **160** as a single diastereoisomer[125] (Scheme 52).



Scheme 52

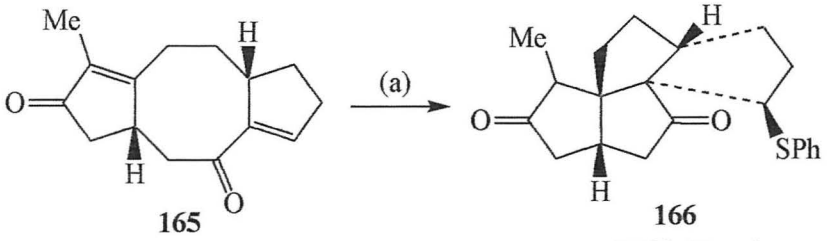
Moore[126] also reported a tandem reaction sequence leading to angularly fused polyquinanes from squaric acid-derived bicyclo [6.3.0]-undecadienediones. Thus when a THF solution of **161** and thiophenol together with a catalytic amount of sodium thiophenolate were refluxed for 12 hours, the reaction resulted in the rearrangement of **161** to the angularly fused tetraquinane **164** in 93% yield. The process involves a sequence of reactions; firstly, Michael addition of thiolate to **161** from the β-face gives enolate **162**, which undergoes a transannular ring closure to give **163**. The enolate in **163** induces an intramolecular E2 *trans*-diaxial elimination giving product **164** and the thiophenolate catalyst is regenerated (Scheme 53).



Scheme 53: (a) PhSH (1.0 eqv.), PhSNa (0.1 eqv.), THF, reflux, 12 hrs

Evidence for this reaction was found when the homologue **165** was subject to the same conditions: little reaction was observed. However, when a stoichiometric amount of thiophenol was employed with a catalytic amount of sodium

thiophenolate, the angularly fused tetraquinane **166** (homologous to the protonated form of **163**) was obtained in 76% isolated yield (Scheme 54).



165 **166**
(76%, X-ray)

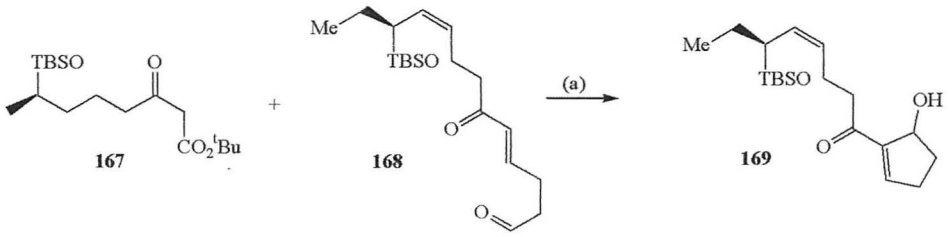
Scheme 54: (a) PhSH (1.0 eqv.), PhSNa (cat.), THF, reflux, 2 hrs

1.8 Conclusion

As can be seen from the work presented in the introduction, the potential for tandem Michael-aldol and Michael-Michael reactions in organic synthesis and in asymmetric synthesis is significant. In the next section, the work from our own group will be discussed, much of which predates some of the referenced material in the introduction as does the work presented in this thesis.

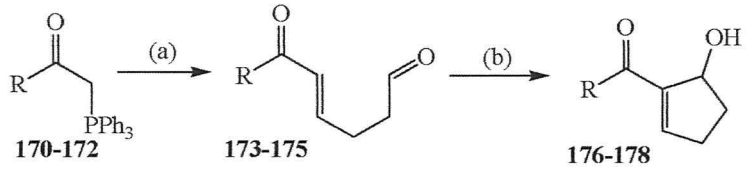
2 Background

Within our research group, as part of a programme directed towards the synthesis of naturally occurring guanidine alkaloids,[127-130] there is significant interest in the Knoevenagel condensation of β-ketoesters and aldehydes. One of these syntheses involved a condensation between β-ketoester **167** and aldehyde **168** in the presence of piperidine or piperidinium acetate. Despite considerable effort, it was found that this reaction was very difficult to effect and the only product formed was not that of dehydration, as expected, but the product **169** in which an intramolecular Baylis-Hillman reaction has occurred[130] (Scheme 55).



Scheme 55: (a) Morpholine, piperidine or piperidinium acetate, CH_2Cl_2, -20 to 0°C, 24-48 hrs

Further investigations into this reaction[130-131] were performed using the three substrates **173-175** prepared from succinaldehyde *via* a Wittig reaction with the corresponding phosphorane. These substrates were then treated with the catalysts piperidine, piperidinium acetate and DABCO to give the cyclopentenols **176-178** (Scheme 56, Table 5).



170-172 **173-175** **176-178**

R = C_9H_{19} (**170**, **173**, **176**); R = Ph (**171**, **174**, **177**); R = OEt (**172**, **175**, **178**)

Scheme 56: (a) Succinaldehyde (1.4 eqv.), CH_2Cl_2, 48 hrs; (b) Catalyst (30 mol%) (see Table 5), $CDCl_3$

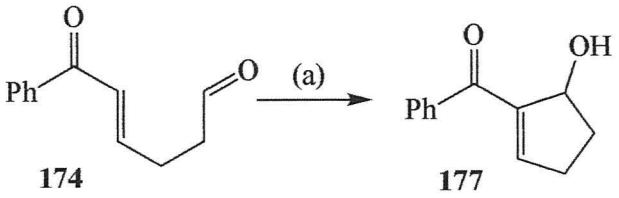
Table 5

	R	**Yield (173-175)**	**Yield (176-178)** [a] **Piperidine**	**Yield (176-178)** [a] **Piperidinium acetate**	**Yield (176-178)** [a] **DABCO**
170	C_9H_{19}	67% **173**	50% (30 hrs) **176**	45% (30 hrs) **176**	No reaction
171	Ph	48% **174**	50% (144 hrs) **177**	28% (72 hrs) **177**	No reaction
172	OEt	58% **175**	(b)	(b)	No reaction

(a) Isolated. (b) Only products of aldol condensation and polymerisation were observed.

The yields for this process were reasonable for the ketonic substrates **173** and **174**, when either piperidinium acetate or piperidine were employed as catalysts, with the latter giving the best yield in both cases. Interestingly, the ester substrate **175** gave only products of aldol condensation and polymerisation on treatment with either catalyst. The common Baylis-Hillman catalyst DABCO gave no reaction for any of the three examples, even after prolonged periods of time (30 days). In order to

investigate further, the reaction of substrate **174** with a series of secondary amines was also performed[130-131] (Scheme 57, Table 6).



174 **177**

Scheme 57: (a) Catalyst (30 mol%), $CDCl_3$, r.t., 7 days

Table 6

Amine (a)	% Conversion	% Yield (b)
Piperidine	93	55 (50)
2-Methylpiperidine	97	30 (26)
2,6-Dimethylpiperidine	75	0
Morpholine	74	16
Piperazine	94	28
N-methylpiperazine	83	21
Pyrrolidine	82	15
Di-*n*-butylamine	100	15

(a) Conditions: Catalyst (30 mol%), $CDCl_3$ (0.35 M), r.t., 7 days.

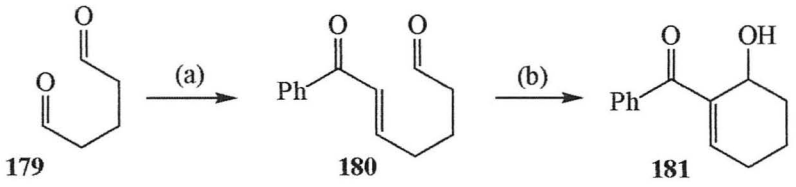
(b) Yields (+/-5%) are calculated from ^1H NMR data. Yields in brackets are isolated yields.

With the exception of the hindered 2,6-dimethylpiperidine, all secondary amines gave the expected cyclised product, however, none of the catalysts showed an improvement in yield compared to piperidine. In addition, a trend was observed in the series piperidine, 2-methylpiperidine and 2,6-dimethylpiperidine, in that the yield of product decreases as steric bulk increases.

To further investigate this reaction, a series of experiments were performed in which the concentration of substrate **174** was varied. The previous experiments were all performed at a concentration of 0.35M. On repeating at 0.18M and 0.09M, a

slight increase in yield (ca. 5% for 0.09M) was observed for the formation of **177**, however, reaction time was increased for both reactions (10 and 15 days for 95% conversion, respectively).

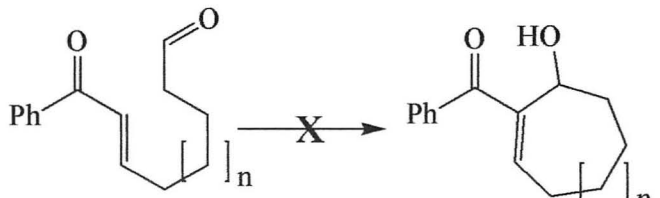
In order to study the effects of ring size on this reaction, pentane-1,5-dialdehyde **179** (formed from the ozonolysis of cyclopentene) was converted to the adduct **180** in 70% yield, which, on treatment with piperidine under identical conditions, gave the cyclohexenol **181** in 24% yield (0.38M, 95% conversion, 14 days). Once again, the yield could be increased slightly (to 30%) by performing the reaction at a higher dilution (0.19M) but the time scale for the reaction was increased to 28 days for 95% conversion (Scheme 58).



179 **180** **181**

Scheme 58: (a) $PhCOCHPPh_3$, CH_2Cl_2, 48 hrs, 70%; (b) Piperidine (30 mol%), $CDCl_3$, r.t., 14 days, 24%

Further to this reaction, the substrates **182-184** were prepared and attempts to cyclise these compounds under the standard conditions failed, indicating that the method may have limitations in the synthesis of medium ring carbocyles[131] (Scheme 59).

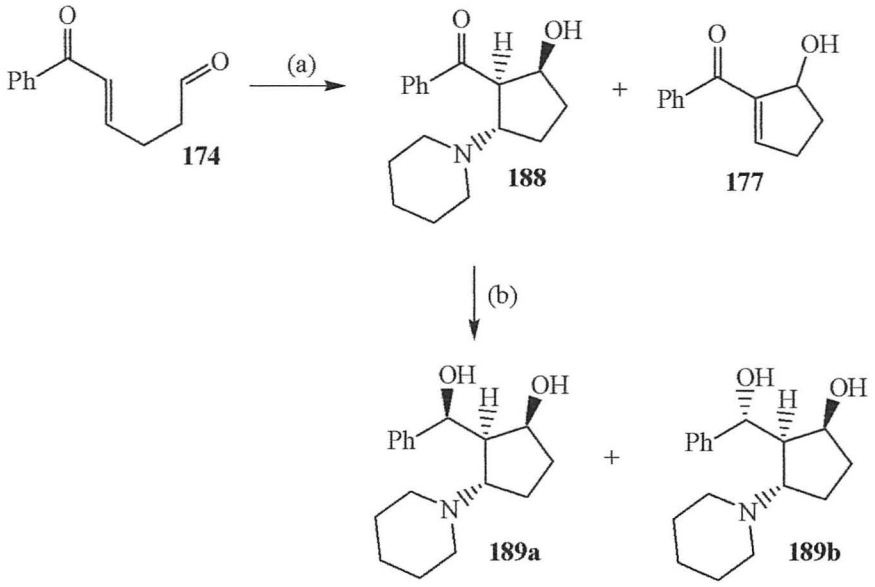


182-184 **185-187**

Scheme 59: n = 1-3

Some initial efforts[130] were made to elucidate the mechanism of this reaction and to this end, the aldehyde **174** was treated with an excess of piperidine in chloroform, which resulted in a rapid reaction yielding **188** together with a small

amount of the cyclopentenol **177** (ca. 5%). It was observed that the intermediate **188** was stable for long periods of time (> 7 days) in chloroform and very little further conversion to **177** was observed (Scheme 60).



Scheme 60: (a) Piperidine (1.3 eqv.), $CHCl_3$, r.t., 10 mins; (b) $NaBH_4$, MeOH, 0°C

In addition, evaporation of the chloroform followed by treatment of a methanolic solution of **188** with sodium borohydride gave a separable 1:1.3 mixture of the diols **189a** and **189b** in 67% overall yield, the former providing crystals suitable for X-ray analysis which confirmed the relative stereochemistry of the intermediate **188** as that shown.[131] All this information was suggestive of an addition-aldol-elimination sequence leading to the formation of **177** *via* the intermediate **188**.

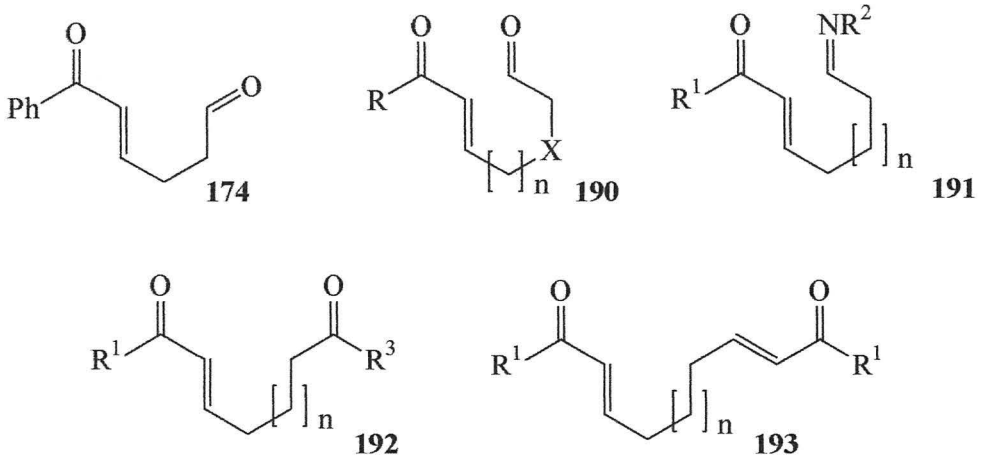
3 Aims

The overall aim of my research was to investigate this new variant of the Baylis-Hillman reaction and in particular to focus on several specific aspects.

Mechanistic considerations: Whilst the mechanism of the reaction had been established to some extent, a more detailed investigation of the reaction leading to the formation of the cyclohexenol products was to be performed to establish if the trend is general.

Other heteronucleophiles: The application of other heteronucleophiles to this reaction, such as thiols and phosphines, was to be investigated.

The scope of the reaction: To date, the most successful reactions have been those performed on substrates such as **174**. It was intended to investigate extensions to this reaction, hopefully to include the generalised structures **190-193** (Scheme 61).



Scheme 61: R = Alkyl, aryl, OR, SR or CN; R^1 = Alkyl, aryl, OR or SR; R^2 = Protecting group; R^3 = Alkyl, aryl or COOR; X = CH_2, O, S or NR; n = 0-?

Investigation of these proposed substrates would increase the scope of the reaction by allowing the reaction to be applied to enoates and thiolenoates and to

expand the scope to other electrophilic acceptor groups such as imines **191**, ketones **192** and enones **193**. We also intended to investigate the use of other nucleophilic mediators including thiols and phosphines.

Asymmetric variants of the process: It is apparent from the consideration of the mechanism of this reaction that the formation of the intermediate is a highly stereoselective process. It is thus likely that the reaction is an ideal candidate for asymmetric development and this was a major aim of the project. Initial approaches were to concentrate on an investigation of the use of chiral amines including 2-methylpiperidine and 2-phenylpiperidine. The possibility of investigating internal stereocontrol (ie. a chiral substrate) was also to be considered.

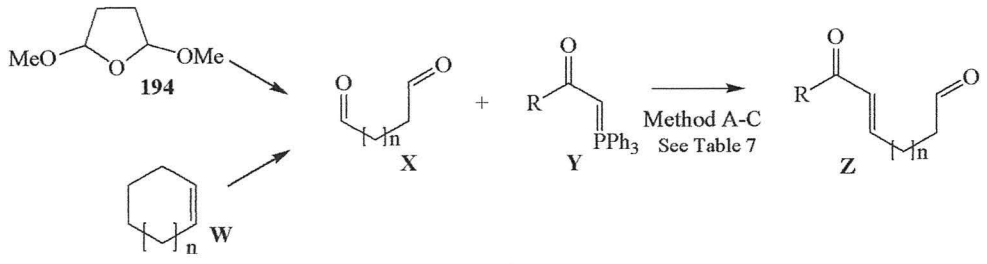
Synthetic applications: Although a long term aim, the methodology developed above might be applicable to the synthesis of interesting natural products.

4 Results and discussion

4.1 Introduction

The basic remit of the project was to investigate the intramolecular, tandem Michael-aldol-elimination reaction of a range of substrates containing an activated alkene and an aldehyde. In order to attempt this, we required a reliable method for the preparation of substrates for our cyclisations; the preparation of these will be discussed independently.

4.2 The preparation of the substrates *via* the Wittig reaction



Scheme 62

The substrates **Z** for the investigation were prepared by reaction of a suitable phosphorus ylid **Y**, with a dialdehyde **X** prepared by either hydrolysis of 2,5-dimethoxytetrahydrofuran **194** in the case of succinaldehyde (X, n = 1) (Method A)[132], ozonolysis of a cycloalkene (Method B) or using an aqueous solution of glutaric dialdehyde **179** (X, n = 2) (Method C) (Table 7). The crude products were purified by column chromatography and a bis-enone obtained by double Wittig reaction on the dialdehyde was generally obtained as a by-product of the reaction,[129] which led to diminished yield. In the case of reactions in aqueous media, the yields are generally low and the Z-alkene isomers were also isolated in significant amounts. Despite these drawbacks, the reactions were easy to perform and gave gram quantities of the precursors for investigation.

Table 7

Entry	R	n	Method	Yield (%)
1	Ph	1	A	48
2	Ph	2	B/C	70/73
3	Ph	3	B	41
4	Ph	4	B	47
5	Ph	5	B	49
6	OEt	1	A	58
7	OEt	2	C	E-41, Z-23
8	OEt	3	B	38
9	STol	1	A	46
10	STol	2	C	32

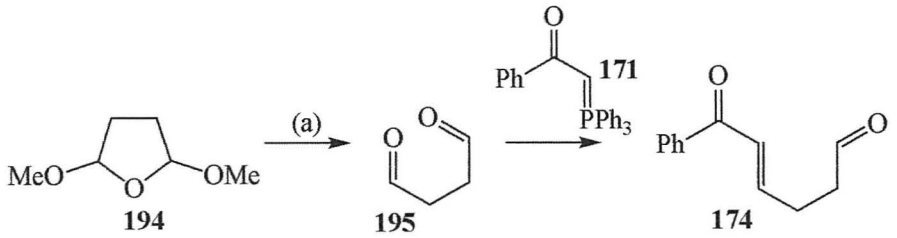
Method A: $RCOCHPPh_3$, Succinaldehyde (2.0 eqv.), CH_2Cl_2 or THF.

Method B: (i) Cycloalkene (5-20 eqv.), O_3, CH_2Cl_2, -78°C (ii) PPh_3, -78°C (iii) 1 eqv. $RCOCHPPh_3$.

Method C: Glutaric dialdehyde (25% w/v in H_2O) (20 eqv.), EtOH or THF, r.t., $RCOCHPPh_3$.

4.2.1 Preparation of the phenyl-containing substrates

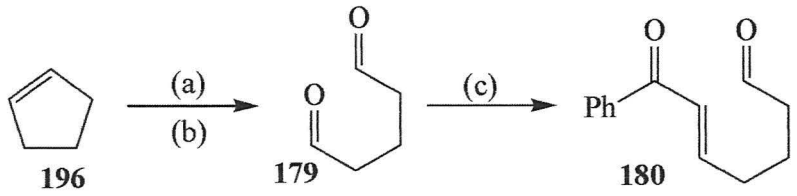
The preparation of substrate **174** was achieved by the reaction of phosphorane **171** with succinaldehyde, **195**. Succinaldehyde was prepared by the aqueous hydrolysis of 2,5-dimethoxytetrahydrofuran,[132] **194**, followed by extraction and distillation. This process was not an efficient one as the aldehyde is prone to rapid decomposition and invariably is obtained as a mixture of compounds, however purity can be estimated from proton NMR and the Wittig reaction performed on these mixtures. Thus a 2:1 mixture of succinaldehyde and **171** was stirred for 16 hours to give **174** in 48% yield. The structure was confirmed by proton NMR with signals at δ = 6.90-7.10 ppm for the alkene protons, 7.60-8.00 ppm for the phenyl group and at 9.82 ppm for the aldehyde (Scheme 63).



Scheme 63: Method A: (a)$PhCOCHPPh_3$ **171**, succinaldehyde **195** (2.0 eqv.), CH_2Cl_2, HCl (aq).

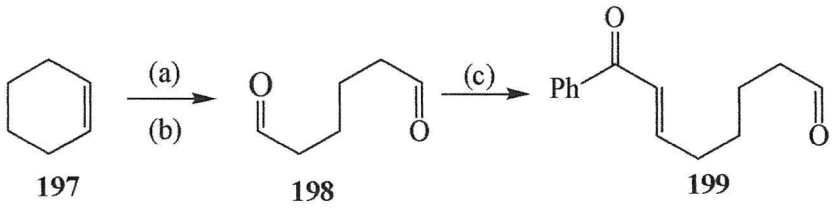
Our next target was the previously prepared[130] *E*-7-phenyl-7-oxohept-5-enal **180,** which we envisaged as being easily prepared from the reaction of phosphorane **171** with glutaric dialdehyde, **179**, prepared by the ozonolysis of cyclopentene, **196**. Several attempts were made to effect this transformation, but on each occasion we were unable to isolate significant quantities of the required product **180**. We believe the reason for this was insufficient amounts of ozone being generated during the ozonolysis step of the reaction. We next attempted the reaction by using an aqueous solution of the aldehyde, which is available commercially. Our initial attempts involved the reaction of an ethanolic solution of phosphorane **171** with an excess (20 eqv.) of aqueous aldehyde for 48 hours. This gave the required product in 24% yield, however, considerable decomposition was evident from TLC analysis.

On repeating this reaction over the shorter time period of 16 hours, we obtained a considerably improved yield of 73% (Scheme 64). These observations would suggest that the substrate **180** and related structures are unstable to the reaction conditions over prolonged reaction times, possibly suggesting that they are decomposed by ethanol-water mixtures. The structure was confirmed by the presence of signals in the proton NMR at δ = 6.70-7.10 ppm for the alkene protons, at 7.40-8.00 ppm for the phenyl group and 9.80 ppm for the aldehyde.



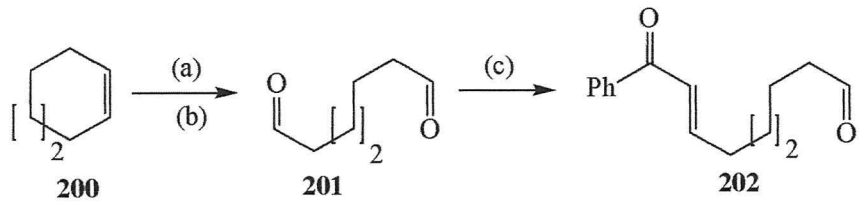
Scheme 64: Method B: (a) Cyclopentene **196** (5 eqv.), O_3, CH_2Cl_2, -78°C; (b) PPh_3, -78°C; (c) $PhCOCHPPh_3$ (1 eqv.) **171** or Method C: (c) Glutaric dialdehyde (25% w/v in H_2O) (20 eqv.) **179**, EtOH, r.t., $PhCOCHPPh_3$ **171**

Preparation of higher homologues of the compounds **174** and **180** was also straightforward and involved the ozonolysis of the required cycloalkene, followed by a Wittig reaction. Thus *E*-8-phenyl-8-oxo-6-octenal **199** was prepared from cyclohexene **197** in 41% overall yield (Scheme 65). The structure was confirmed by the presence of signals in the proton NMR at $\delta = 6.90$ ppm (d) and 7.03 ppm (dt) for the alkene protons, and at 7.43 and 7.95 ppm for the phenyl group and 9.78 ppm for the aldehyde.



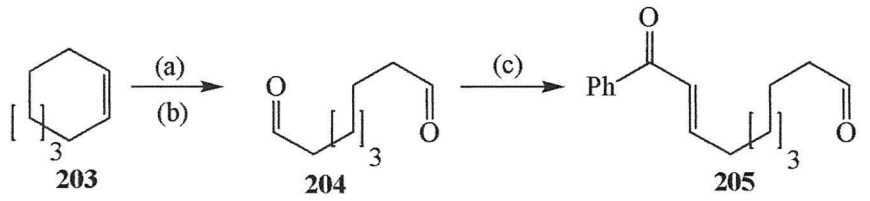
Scheme 65: Method B: (a) Cyclohexene **197** (20 eqv.), O_3, CH_2Cl_2, -78°C; (b) PPh_3, -78°C; (c) $PhCOCHPPh_3$ **171** (1 eqv.)

Similarly, the substrate **202** was prepared using the same methodology. Ozone was bubbled through a solution of cycloheptene **200** and the resulting dialdehyde **201** was reacted with phosphorane **171** to produce **202** in 31% yield (Scheme 66). Again, the structure was confirmed by signals at $\delta = 6.88$ ppm (d) and 7.05 ppm (m) for the alkene protons, 7.45 and 7.95 ppm for the phenyl group and an aldehyde signal at 9.78 ppm.



Scheme 66: Method B: (a) Cycloheptene **200** (5 eqv.), O_3, CH_2Cl_2, -78°C; (b) PPh_3, -78°C; (c) $PhCOCHPPh_3$ **171** (1 eqv.)

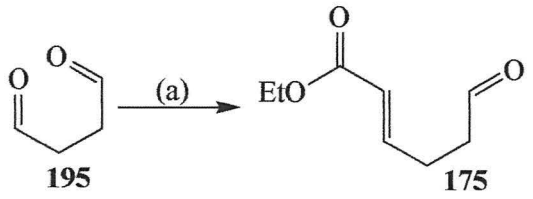
Similarly, substrate **205** was prepared from cyclooctene **203**, which was ozonised, and the resultant dialdehyde **204** reacted with phosphorane **171**. The product **205** was obtained in a 26% yield (Scheme 67). The structure was confirmed by the presence of signals in the proton NMR at $\delta = 6.85$ ppm (d) and 7.06 ppm (dt) for the alkene protons, 7.40 and 7.95 ppm for the phenyl group and an aldehyde signal at 9.75 ppm.



Scheme 67: Method B: (a) Cyclooctene **203** (10 eqv.), O_3, CH_2Cl_2, -78°C; (b) PPh_3, -78°C; (c) $PhCOCHPPh_3$ **171** (1 eqv.)

4.2.2 Preparation of the ester-containing substrates

Our next target was *E*-6-ethoxy-6-oxo-4-hexenal **175**, which was prepared by the reaction of phosphorane **172** with succinaldehyde in THF over 16 hours giving the product **175** in 27% yield (Scheme 68). The structure was confirmed by proton NMR with signals at δ = 1.30 ppm for the CH_3, 4.19 ppm for the CH_2-O, 5.85 ppm (d) and 6.94 ppm (dt) for the alkene protons and at 9.70 ppm for the aldehyde.

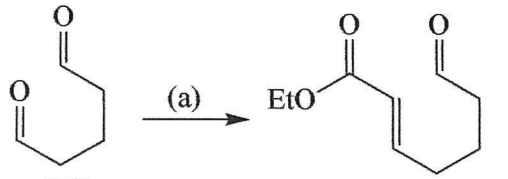


195 **175**

Scheme 68: Method A: (a) $EtOCOCHPPh_3$ **172**, succinaldehyde **195** (2.0 eqv.), THF

The phosphorane, **172**, was also treated with glutaric dialdehyde, **179**, in THF/H_2O over 16 hours (Scheme 69). The product **206** was isolated as a separable mixture of *cis* (23%) and *trans* (41%) isomers. The structure of the Z-isomer was confirmed by the presence of signals in the proton NMR at δ = 1.18 ppm for the CH_3, 2.60 ppm for the CH_2-O, 5.72 ppm (d) and 6.11 ppm (dt) for the alkene protons and an aldehyde signal at 9.28 ppm.

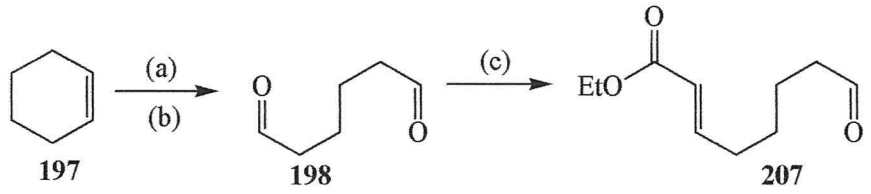
The structure of the E-isomer was confirmed by signals at δ = 1.05 ppm for the CH_3, 2.05 ppm for the CH_2-O, 5.61 ppm (d) and 6.69 ppm (dt) for the alkene protons and an aldehyde signal at 9.54 ppm.



179 **206**

Scheme 69: Method C: (a) Glutaric dialdehyde **179** (25% w/v in H_2O) (20 eqv.), THF, r.t., $EtOCOCHPPh_3$ **172**

Substrate **207** was prepared by ozonolysis of cyclohexene, **197**, followed by Wittig reaction with carboethoxymethylenetriphenylphosphorane, **172** (Scheme 70). The product was formed in a 38% yield and signals in the proton NMR at $\delta = 1.29$ ppm for the CH_3, 2.23 ppm for the CH_2-O, 5.83 ppm (d) and 6.92 ppm (dt) for the alkene protons and 9.78 ppm for the aldehyde confirmed the structure as **207**.

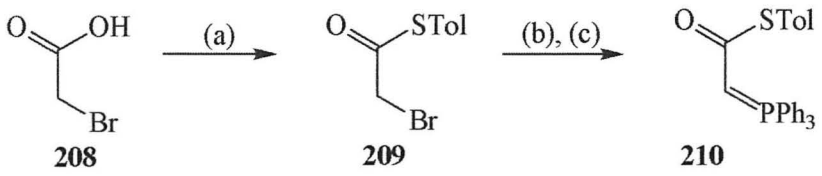


197 **198** **207**

Scheme 70: Method B: (a) Cyclohexene **197** (20 eqv.), O_3, CH_2Cl_2, -78°C; (b) PPh_3, -78°C; (c) $EtOCOCHPPh_3$ **172** (1 eqv.)

4.2.3 Preparation of the thiolester-containing substrates

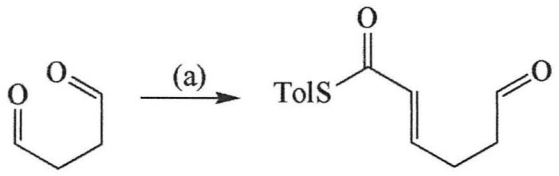
In order to investigate the reaction of α,β-unsaturated thiolesters on the intramolecular Baylis-Hillman reaction, we needed to prepare the phosphorane **210**. This was accomplished by the reaction of bromoacetic acid, **208**, with toluene-4-thiol under DCC coupling conditions,[133] followed by reaction of the thiolester **209** with triphenylphosphine and treatment of the intermediate phosphonium salt with sodium carbonate (Scheme 71).



208 **209** **210**

Scheme 71: (a) MeC_6H_4SH, DMAP, DCC, CH_2Cl_2, 0°C, 3 hrs; (b) PPh_3, toluene, r.t., 48hrs; (c) Na_2CO_3, H_2O, CH_2Cl_2, 30 mins

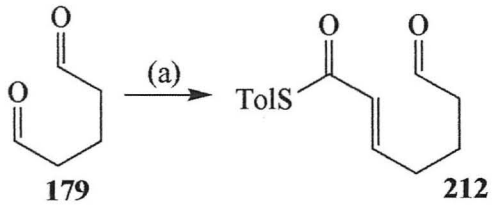
With phosphorane **210** in hand, we investigated its reaction with 2 equivalents of succinaldehyde in THF to give, after purification, adduct **211** in 46% yield (Scheme 72). The structure of the product was confirmed by analysis of the proton NMR which contained signals at δ = 2.42 ppm for the tolyl CH_3, 2 methylene groups at 2.50 and 2.62 ppm, together with alkene protons at 6.22 and 6.95 ppm, an AA'BB' pattern at 7.25 ppm and an aldehyde signal at 9.85 ppm.



195 **211**

Scheme 72: Method A: (a) $TolSCOCHPPh_3$ **210**, succinaldehyde **195** (2.0 eqv.), THF

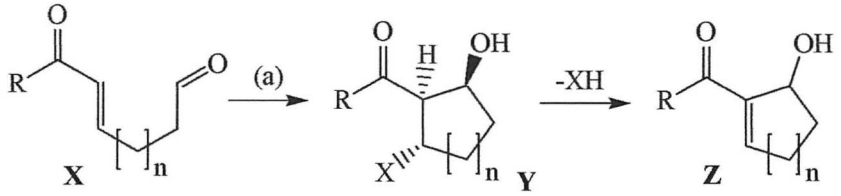
Similarly, **210** was reacted with glutaric dialdehyde, **179**. Thus treatment of **210** with 20 equivalents of glutaric dialdehyde in ethanol and stirring for 16 hours gave a 32% yield of the desired substrate **212** (Scheme 73). The structure of the product was confirmed by the presence of signals in the proton NMR at δ = 2.39 ppm corresponding to the tolyl CH_3, methylene groups at 1.84, 2.30 and 2.52 ppm together with alkene protons at 6.20 and 6.90 ppm, an AA'BB' pattern at 7.25 ppm and an aldehyde signal at 9.75 ppm. The yield for this reaction was somewhat poor, which again may be due to instability of the product to the reaction conditions, particularly the solvent.



Scheme 73: Method C: (a) Glutaric dialdehyde **179** (25% w/v in H_2O) (20 eqv.), EtOH, r.t., TolSCOCHPPh_3 **210**

4.3 Tandem intramolecular Michael-aldol cyclisation reactions

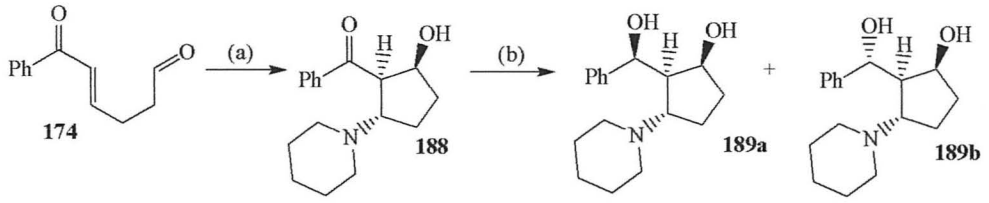
There have been several investigations into the tandem intermolecular and intramolecular Michael-aldol cyclisations, particularly those mediated by phosphine, nitrogen and chalcogen nucleophiles as discussed in the introduction and background. Our objective was to continue studies into the intramolecular version of this reaction, focusing on the reactions of the substrates prepared in section 4.2 with secondary amines, thiols and phosphines as catalysts, thereby increasing the scope of the reaction. It was found that a range of nucleophiles, including secondary amines, thiols and phosphines effect a tandem intramolecular Michael-aldol cyclisation of enones **X** leading to either adducts **Y** or the eliminated Baylis-Hillman type product **Z** (Scheme 74). [130, 134] Following these preliminary studies we were keen to assess the scope of this reaction taking into account such variables as the nature of the nucleophile and the R group and the potential for variations in the ring size of the product formed. We were also interested in studying the mechanistic aspects of this reaction in more detail than before. This section brings together our preliminary findings on these matters and our further studies on the process.



Scheme 74: (a): Piperidine, TolSH or PR_3; $CDCl_3$ or $CHCl_3$; r.t. to reflux
R = Ph, EtO or TolS; X = Piperidyl, TolS or PR_3; n = 1, 2, 3, 4, 5

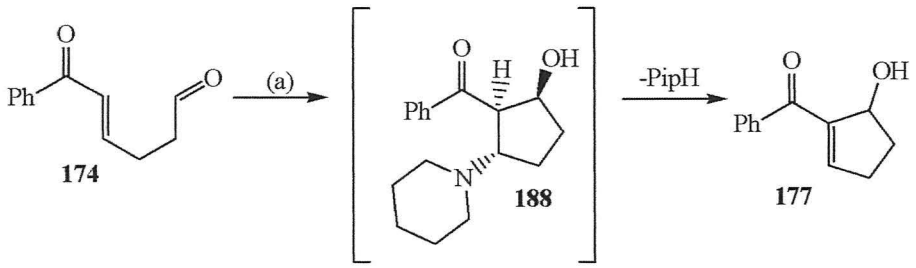
4.4 Mechanistic studies on the Baylis-Hillman reaction mediated by secondary amines

Our preliminary investigation stemmed from the observations that a suitable catalyst for effecting the conversion of the substrate **174** into the cyclised product **177** was the secondary amine piperidine. The formation of **177** is concentration dependent, however, on closer inspection of the NMR data for these reactions, it was apparent that the reaction was proceeding through a long-lived and fairly stable intermediate which we presumed to be the product of 1,4-addition and intramolecular aldol condensation, **188**. As was shown in the background (pages 55-56), treatment of aldehyde **174** with an excess of piperidine in chloroform effected a complete transformation of the starting material to the intermediate **188**, which was stable for long periods of time, together with a small amount of **177**. Also, evaporation of the chloroform, followed by reduction with sodium borohydride gave a separable 1:1.3 mixture of the diols **189a** and **189b** in 67% overall yield. (Scheme 75). [130, 131, 135]



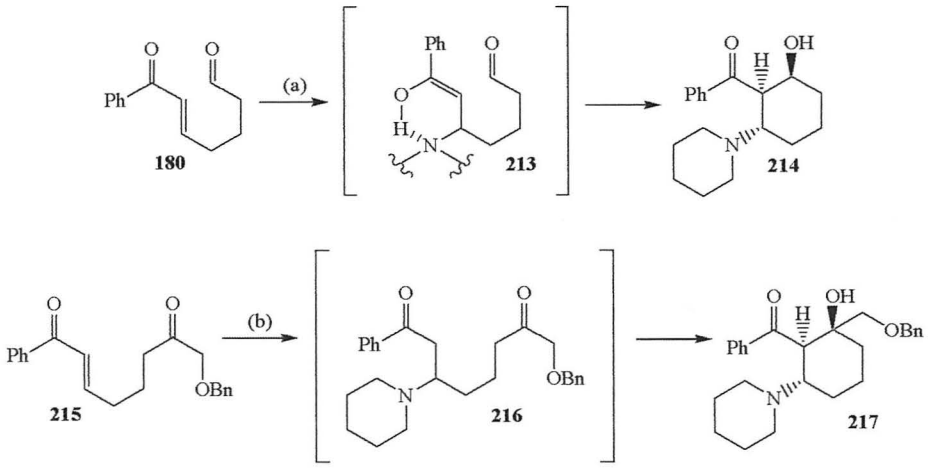
Scheme 75: (a) Piperidine (1.3 eqv.), $CHCl_3$, 10 min., r.t.; (b) $NaBH_4$, MeOH, 0°C

In addition, the mechanism for the formation of cyclopentenol **177** was shown to proceed *via* an addition-aldol-elimination sequence, which has structure **188** as an intermediate (Scheme 76).



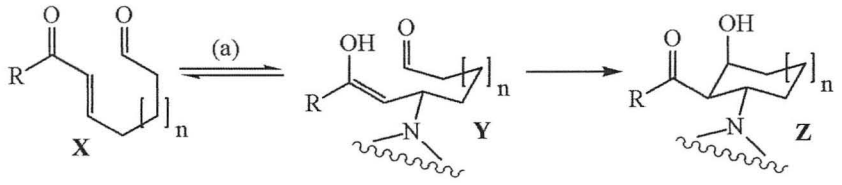
Scheme 76: (a) Piperidine, $CDCl_3$

To elucidate the mechanism of the formation of cyclohexenols, we repeated this reaction using the enone **180** and found that the adduct **214** was formed very rapidly. The presence of signals at δ 3.2 (1H, ddd, J = 3, 12, 12 Hz), 3.6 (1H, dd, J = 2, 12 Hz) and 4.2 (1H, br m), indicated that the relative stereochemistry of **214** is as illustrated. In addition, it was apparent that the reaction leading to **214** was proceeding *via* an intermediate enol, possibly of structure **213**, as indicated by signals at δ 4.3 (1H, dt, J = 14, 7.5 Hz) and 5.8 (1H, d, J = 14 Hz). Again, **214** was found to be stable in solution for prolonged periods of time with only ~10% conversion to the cyclohexenol **181** being observed over 28 days. We also attempted to eliminate piperidine from **214** by treatment with excess CSA at both room temperature and at reflux with no noticeable reaction occurring after a prolonged period. We were also able to isolate the adduct **217** which arose from the addition of piperidine to ketone **215**[136] and found that this compound gave suitable crystals for X-ray structure determination confirming the stereochemistry as that shown below.[134] Interestingly, this cyclisation took considerably longer to effect that the previous case, requiring six days for complete reaction, possibly reflecting the lower reactivity of ketones. We were also able to observe, by NMR with signals at δ = 0.73-1.87 (12H, m, 6 x CH_2), 2.24 (2H, m, 2 x $C\underline{H}_aH_bN$), 2.47 (2H, m, 12H, $CH_a\underline{H}_bN$), 3.26 (3H, m, $C\underline{H}N$ + $C\underline{H}_2O$), 3.86 (1H, d, J = 11.6 Hz, CH), 4.33 (2H, s, $OC\underline{H}_2Ph$), 5.00 (1H, br s, $CHO\underline{H}$), 7.14-7.94 (10H, m, Ph) the intermediate conjugate adduct **216** in the reaction mixture and, as in other cases, the Michael-aldol sequence proceeded to give a single diastereomer by NMR and we were unable to isolate any minor diastereomeric products (Scheme 77).



Scheme 77: (a) Piperidine (1.3 eqv.), $CHCl_3$; (b) Piperidine (1.3 eqv.), $CHCl_3$; 60%

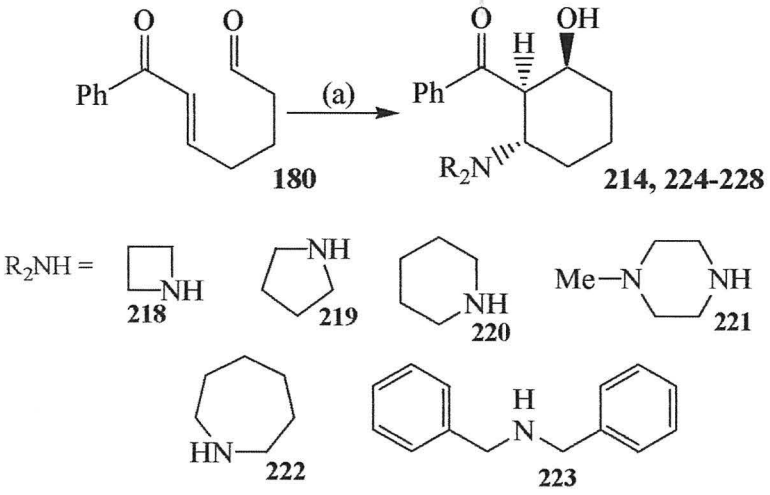
All of these observations seem to suggest that the reaction indeed proceeds *via* a conjugate addition of the amine to the enone yielding an intermediate, possibly **Y**, (n = 0,1) followed by an intramolecular aldol cyclisation *via* the conformation shown (Scheme 78).



Scheme 78: (a) Piperidine, n = 0,1; R = alkyl, aryl

This mechanism might explain the slow rate of formation of the Baylis-Hillman products from this reaction, as the rate determining step must be the elimination of the piperidine from intermediates such as **214**, which is obviously a stereoelectronically unfavourable process, particularly in the case of the cyclohexane intermediate (n = 1).

As it was apparent that the intermediates **188**, **214** and **217** are easily formed, we decided to investigate their presence in the reactions of a variety of amines to gauge structural features required in the amine to effect conversion to the intermediates, **214** and **224-228**. The efficiency of various amines in the formation of the cycloalkenes had already been investigated and piperidine had been found to be the most efficient. We treated substrate **180** with an excess of the amines azetidine, pyrrolidine, 1-methylpiperazine, homopiperidine and dibenzylamine and observed the region δ = 3.0-4.5 to estimate the formation of intermediates **214** and **224-228**. The results are listed in Table 8. Reaction of **180** with a 1.3 molar excess of the amine whilst following the reaction by NMR and observing the signal in the intermediate **214** and **224-228** for H_1, H_2, and H_3 illustrated that again piperidine was the best base for effecting the transformation (Scheme 79).



Scheme 79: (a) R_2NH (1.3 eqv.) (Table 8), $CDCl_3$, 0-7 days

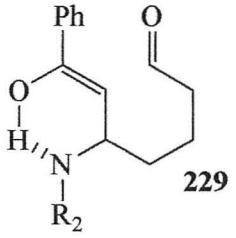
Table 8

Amine	Time	Yield (%)	Decomposition	H_1 (J)	H_2 (J)	H_3 (J)
Azetidine **218**	2 h	0 (**224**)	100%	------	------	------
Pyrrolidine **219**	24 h	~25% (**225**)	~75%	4.18 (br m)	3.57 (dd, 2, 11)	3.47 (ddd, 3, 11, 11)
Piperidine **220**	10-15 min	>90% (**214**)	<10%	4.20 (br m)	3.60 (dd, 2, 12)	3.20 (ddd, 3, 12, 12)
1-Methylpiperazine **221**	3 h	>85% (**226**)	<15%	4.14 (br m)	3.68 (dd, 2, 11)	3.47 (ddd, 3, 11, 11)
Homopiperidine **222**	24 h	~5% (**227**)	~95%	4.17 (br m)	3.58 (dd, 2, 11)	3.30 (obscured)
Dibenzylamine **223**	7 days	Trace (**228**)	>95%	------	------	------

As can be seen, the only amines leading to the intermediate adduct **214** and **224-228** with a good conversion are the 6-membered amines piperidine and 1-methylpiperazine. 1-Methylpiperazine, gave in essence the same reaction profile as observed for piperidine in that within 3 hours almost all the substrate **180** had been consumed and the product **226** which was formed was stable in solution for prolonged periods of time (>20 days). The 4, 5 and 7-membered cyclic amines together with dibenzylamine predominantly gave products of decomposition arising from self-aldol condensations of the substrate **180**. The formation of a Michael intermediate similar in nature to the enol **229** (Figure 2) was observed with the use of di-*n*-benzylamine as a catalyst, as judged by signals at $\delta = 4.15$ (1H, dt, J = 14.6, 6.9 Hz) and 6.15 (1H, d, J = 14.6 Hz) ppm, however, after a prolonged period of time only decomposition was observed.

The reason for the success of the reaction only with 6-membered amines is unclear but it is likely to be differences in basicity owing to the similarity in structure of the amines employed. As previously stated, it is likely that the reaction is proceeding *via* an intermediate enol similar in structure to **229** (Figure 2) and it may be that the propensity to form this moiety is the key to the success or failure of the

reactions. It is possible that changes in the structure of the base have a significant influence on the stability of this intermediate or even its ability to be formed. Whatever this reason might be, it is obvious that the reaction is quite susceptible to changes in structure of the amine and it is apparent that 6-membered cyclic amines give the best results.



229

Figure 2

4.5 Systematic modification of substrates and catalysts

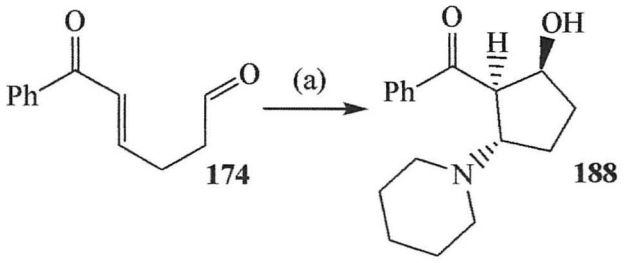
Following the mechanistic studies, we embarked upon a systematic study of the cyclisation process and chose to investigate the use of different electron withdrawing groups in the Michael substrate and to couple these modifications with variation in ring size and the use of other nucleophiles.

4.6 5-Membered substrates

Our first area of investigation focused on the formation of the 5-membered adducts or the corresponding cyclopentenols using either the piperidine-based methodology described earlier, or by the use of thiolate or phosphine based catalysts. Our investigations on the 5-membered series focused on the use of an aryl ketone, ester or thiolester acceptor group and the reactions with piperidine were attempted first.

4.6.1 Piperidine catalysis

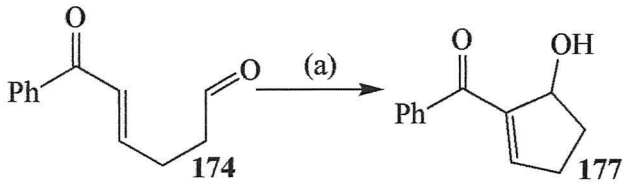
Reaction of ketone **174** with 1.3 equivalents of piperidine was carried out previously[130] and gave adduct **188** in an excellent 90% yield in 10 minutes as judged by proton NMR (Scheme 80).



Scheme 80: (a) Piperidine (1.3 eqv.), $CDCl_3$, r.t., 10 mins

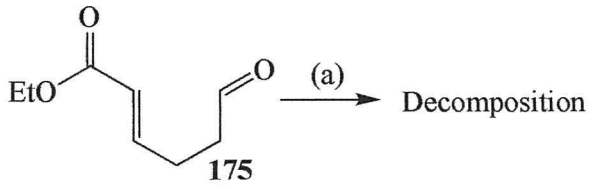
When a catalytic amount of piperidine (0.3 equivalents) was utilised in a similar reaction, the cyclised product **177** was obtained in 50% yield after purification. Proton NMR gave signals at δ = 3.33 (1H, br s, OH), 5.30 (1H, m,

CHOH) and 6.71 (1H, t, J = 1.5 Hz, CH), confirming the structure as **177** (Scheme 81).



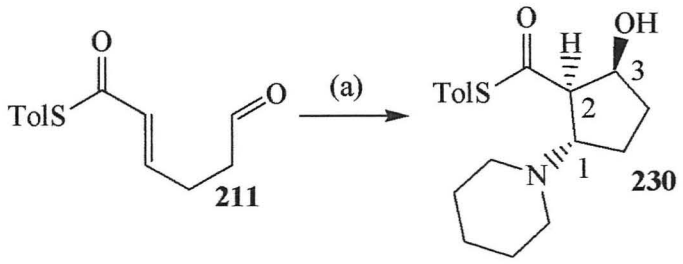
Scheme 81: (a) Piperidine (0.3 eqv.), $CDCl_3$, r.t., 144 hrs

On application of these conditions to the ester-containing substrate **175**, a different outcome was observed in that only products derived from aldol condensation of the aldehyde function were obtained. This possibly reflects a lower reactivity of α,β-unsaturated esters towards Michael addition reactions (Scheme 82).



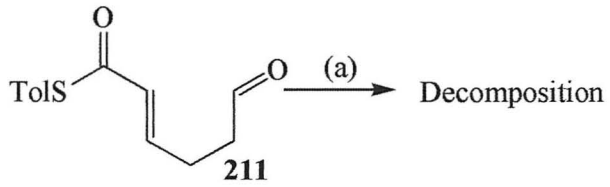
Scheme 82: (a) Piperidine (1.3 or 0.3 eqv.), $CDCl_3$, r.t., 2 days

One of the major problems that arose in the previous investigations was the inability to effect an intramolecular reaction utilising an ester as the activating group on the alkene. To alleviate this problem, we decided to attempt an intramolecular reaction on the thiolester substrate **211**, with the amine, phosphine and thiolester catalysts. Similar reactions of the thiolester-containing substrate **211** with piperidine were also complicated by considerable decomposition, including some evidence of amide formation and aldol reaction processes. Only a low yield (10%) of the intermediate adduct **230** was observed with an excess of piperidine as judged by proton NMR. The proton NMR of **230** gave diagnostic signals at δ = 3.10 (1H, app t, J = 7.7 Hz, CH) for the C-2 proton, δ = 3.50 (1H, m, CH) for the C-1 proton and at δ = 3.75 (1H, m, CHOH) for the C-3 proton (Scheme 83).



Scheme 83: (a) Piperidine (1.3 eqv.), $CDCl_3$, r.t., 2 days

Similarly, reaction with a catalytic amount of piperidine led to the formation of decomposition products of aldol condensation (Scheme 84).

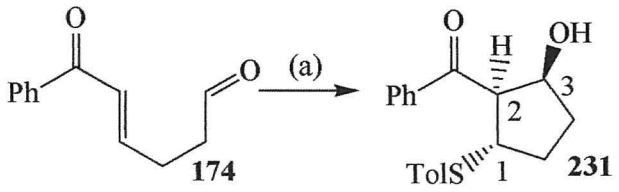


Scheme 84: (a) Piperidine (0.3 eqv.), $CDCl_3$, r.t., 2 days

From this preliminary investigation, we can conclude that piperidine is a good catalyst for the tandem, intramolecular Michael-aldol reaction and the intramolecular Baylis-Hillman reaction but only when the acceptor is an enone. The cases in which enoate or thioenoate acceptors were used are prone to decomposition, either through an aldol type process or *via* reaction of the thioenoate function with the catalyst.

4.6.2 Thiol-based catalysis

As both amines and phosphines are in essence weak nucleophiles, we felt that the use of a thiol might be of more advantage to us. We thus treated enone **174** with 1.3 equivalents of toluene-4-thiol under our standard conditions and we were pleased to observe the conversion of the starting material into a new product, the adduct, **231** in an excellent 77% isolated yield (Scheme 85). Careful analysis of the NMR of the crude reaction mixture failed to show the presence of any significant amounts of isomeric compounds. The proton NMR of **231** gave diagnostic signals at δ = 3.89 (1H, dd, J = 5.3, 8.3 Hz, CH) for the C-2 proton, δ = 4.19 (1H, ddd, J = 6.3, 8.3, 8.3 Hz, CH) for the C-1 proton and at δ = 4.59 (1H, m, C<u>H</u>OH) for the C-3 proton.



Scheme 85: (a) *p*-TolSH (1.3 eqv.), $CHCl_3$, r.t., 16 hrs

Similar treatment of the ester-substituted **175** failed to effect this transformation even at reflux in chloroform. The reaction was attempted several times varying the amounts of the catalyst from 2 to 3 equivalents with no success. However, if the reaction was performed with 2 equivalents of *p*-TolSH and a catalytic quantity of *p*-TolSNa[126], the adduct **232** was obtained in 72% yield as well as the addition product **233** in 10% yield (Scheme 86). We were able to grow crystals of **232**, which were suitable for X-ray analysis (see Appendix A) and this confirmed the structure to be as illustrated in Figure 3. Again the proton NMR of **232** gave diagnostic signals at δ = 2.76 (1H, dd, J = 5.0, 9.0 Hz, CH), 3.97 (1H, m, CH) and at δ = 4.47 (1H, m, C<u>H</u>OH) enabling a correlation to be made between **232** and **231** and supporting the assignment of the stereochemistry of compound **231**.

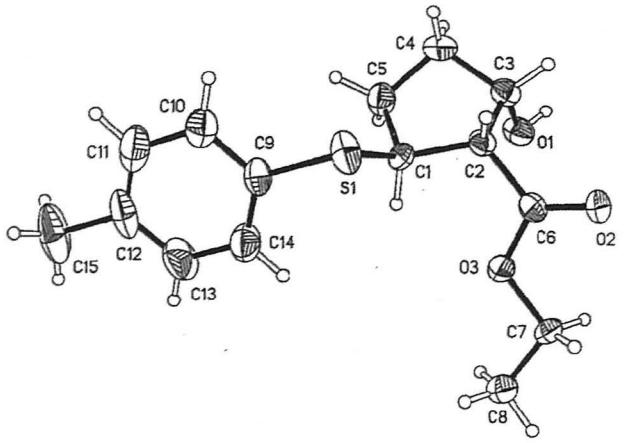
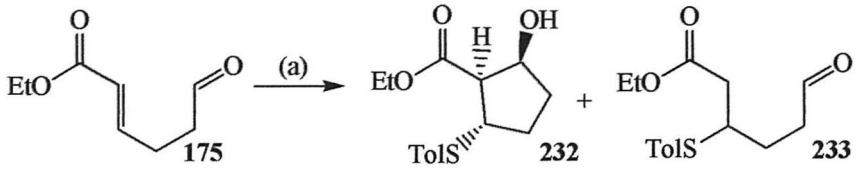


Figure 3: X-ray structure of **232**

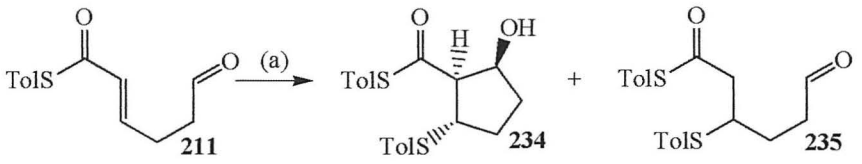


Scheme 86: (a) *p*-TolSH (2.0 eqv.), *p*-TolSNa (0.2 eqv.), $CHCl_3$, Δ, 16 hrs

When the thiolester substrate **211** was investigated, it was found that the reaction proceeded without the use of the sodium thiolate catalyst, however it was necessary to reflux the reaction for 12 hours to effect a reasonable conversion. We found that without reflux, the conversion was slow and after 3 days in $CDCl_3$ at room temperature, only ca. 10% of the substrate had been converted to the cyclised material **234**.

Increasing the amount of thiol present in the reaction to 3 equivalents and heating the reaction under reflux for 12 hours effected a 65% conversion to the cyclic product **234** as judged by proton NMR together with the formation of the intermediate Michael adduct **235**. Further reflux failed to convert **235** into **234** and this might indicate that equilibrium exists between these two species. Again, careful analysis of the NMR of the crude reaction mixture seemed to suggest that the reaction gave essentially a single stereoisomer of the cyclised product (Scheme 87).

The proton NMR of **234** supports the stereochemistry when compared to the previously prepared adducts **231** and **232** in that signals at δ = 3.14 (1H, dd, J = 4.8, 8.8 Hz, CH), 4.04 (1H, ddd, J = 6.2, 8.8, 8.8 Hz, CH) and 4.55 (1H, m, C<u>H</u>OH) ppm correlate with those observed in these other adducts. The by-product **235** was identified by the presence of the AB of an ABX pattern at δ = 2.80 (dd, J = 8.0, 15.7 Hz) and 2.97 (dd, J = 6.0, 15.7 Hz) ppm for the methylene protons of C<u>H</u>$_2$COSTol and the presence of an aldehyde signal at 9.79 ppm.



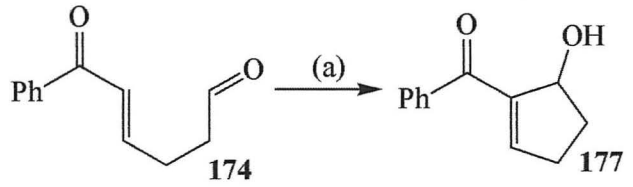
Scheme 87: (a) *p*-TolSH (3.0 eqv.), $CHCl_3$, Δ, 12 hrs

We can conclude that the thiolate method for the cyclisation of these adducts is a very powerful methodology as it appears to be general for these substrates, high yielding (56-77%) and gives the required compounds as essentially single diastereoisomers.

4.6.3 Phosphine-based catalysis

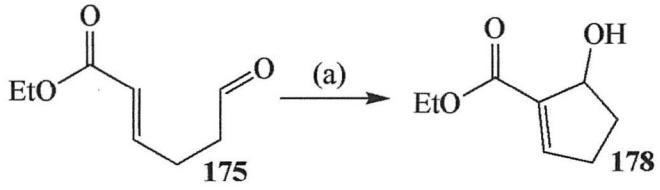
We next moved our investigation to the use of phosphines in these tandem cyclisations and took as our catalyst tributylphosphine, as this appeared to have been successful in one previous case[24] and is commercially available in high purity.

We thus treated substrate **174** with a catalytic amount of tri-*n*-butylphosphine (0.2 equivalents) and were pleased to find that it was converted to the previously prepared cyclopentenol **177** in a modest 20% yield. Spectroscopic data was identical to the previously prepared material (Scheme 88).



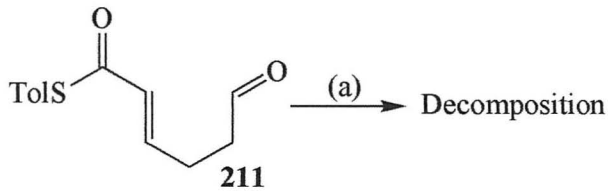
Scheme 88: (a) *n*-Bu_3P (0.2 eqv.), $CDCl_3$, r.t., 17 hrs

Similar treatment of the enoate substrate **175** under these conditions led to the formation of **178** in 40% yield, however a prolonged reaction time was required to effect complete consumption of **175** (Scheme 89). Diagnostic proton NMR signals were obtained at δ = 2.85 (1H, br s, OH), 5.08 (1H, m, C<u>H</u>OH) and 6.71 (1H, t, J = 2.5 Hz, CH) confirming the structure as **178**.



Scheme 89: (a) *n*-Bu_3P (0.4 eqv.), $CDCl_3$, r.t., 28 days

Finally, treatment of thioenoate substrate **211** with tri-*n*-butylphosphine was attempted and it was found that this gave a different outcome in that only products of decomposition were obtained. This was a rapid process and might suggest that the phosphine catalyst is incompatible with thiolester functionalities (Scheme 90).



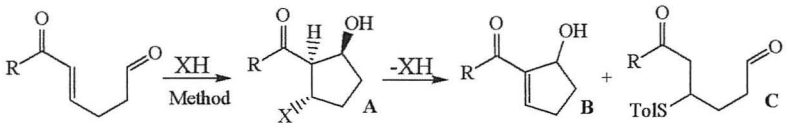
Scheme 90: (a) *n*-Bu_3P (0.4 eqv.), $CDCl_3$, r.t., 1 hr

In conclusion, the phosphine catalysis studies proved to be a reasonable success in that the reaction is applicable to enone and enoate containing substrates, however is not applicable to thioenoates as the thiolester function appears to react preferentially with the phosphine.

4.6.4 Conclusions

Our overall conclusions from the reactions of the 5-membered substrates are that the thiolate catalysed reactions are very successful leading to high yields of the cyclised products in all cases. Reactions catalysed by phosphines gave mixed results and piperidine only performed well as a catalyst with the phenyl-containing substrates. One conclusion that is apparent from this work is that the ester substrates require more forcing conditions or prolonged reaction times than the corresponding ketones. This is possibly because of a lower reactivity in the initial Michael step or may be due to a lower acidity of the α-protons in the intermediate Michael adduct formed, when compared to ketonic substrates.

The overall results of this work are summarised in Table 9.



Scheme 91

Table 9

Entry	Subs	R =	Method[a]	X	A	B	C
1	**174**	Ph	1.3 eqv. Piperidine, 10 min.	Piperidyl	**188**, 90%[b]	------	------
2	**174**	Ph	0.3 eqv. Piperidine, 144 h.	Piperidyl	------	**177**, 50%	------
3	**174**	Ph	1.3 eqv. *p*-TolSH, 16 h.	TolS	**231**, 77%	------	Trace
4	**174**	Ph	0.2 eqv. *n*-Bu_3P, 17 h.	------	------	**177**, 20%	------
5	**175**	OEt	1.3 eqv. Piperidine, 2 days.	Piperidyl	Dec[c]	------	------
6	**175**	OEt	0.3 eqv. Piperidine, 2 days.	Piperidyl	Dec[c]	------	------
7	**175**	OEt	2 eqv. *p*-TolSH, 0.2 eqv. *p*-TolSNa, Δ, 16 h.	TolS	**232**, 72%	------	**233**, 10%
8	**175**	OEt	0.4 eqv. *n*-Bu_3P, 28 days.	------	------	**178**, 40%	------
9	**211**	STol	1.3 eqv. Piperidine, 2 days.	Piperidyl	**230**, 10%[b]	------	------
10	**211**	STol	0.3 eqv. Piperidine, 2 days.	Piperidyl	Dec[c]	------	------
11	**211**	STol	3 eqv. *p*-TolSH, Δ, 12 h.	TolS	**234**, 56%	------	**235**, Trace
12	**211**	STol	0.4 eqv. *n*-Bu_3P, 1 h.	------	Dec[d]	------	------

(a) All reactions performed in $CHCl_3$ or $CDCl_3$ at r.t. unless specified.

(b) As observed by NMR of the progress of the reaction.

(c) Largely composed of products derived from aldol condensation.

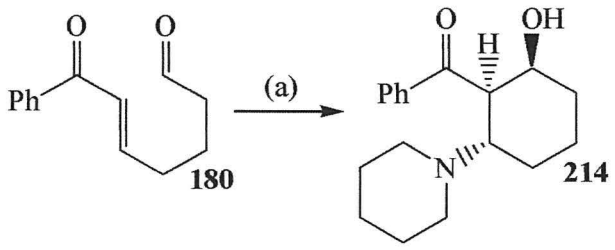
(d) Unidentified decomposition products.

4.7 6-Membered substrates

Having investigated the reaction of the 5-membered substrates with amines, thiols and phosphines, we next attempted similar reactions with the 6-membered substrates. Again, our investigation focused on the use of an aryl ketone, ester and thiolester acceptor group.

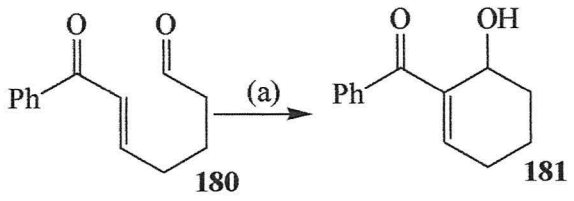
4.7.1 Piperidine catalysis

We turned our attention to the reactions of enone substrate **180**, the ester **206** and the thiolester **212** which, on cyclisation, would lead to 6-membered adducts or cyclohexenes. As previously reported, the reaction of ketone **180** gave adduct **214** with excess piperidine in a 90% yield (Scheme 92).



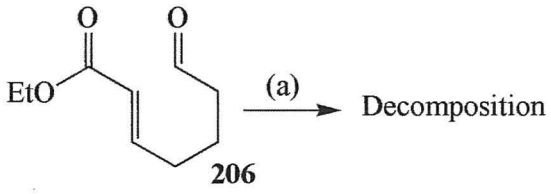
Scheme 92: (a) Piperidine (1.3 eqv.), $CDCl_3$, r.t., 10 mins

If the conditions were modified to employ only 0.3 equivalents of piperidine, the cyclised product **181** was obtained in a 30% yield (Scheme 93). Diagnostic NMR data included signals at $\delta = 3.53$ (1H, br s) corresponding to the hydroxyl proton and at $\delta = 4.75$ (1H, m) for the C<u>H</u>OH proton and $\delta = 6.73$ (1H, t, J = 4.0 Hz) for the alkene proton.



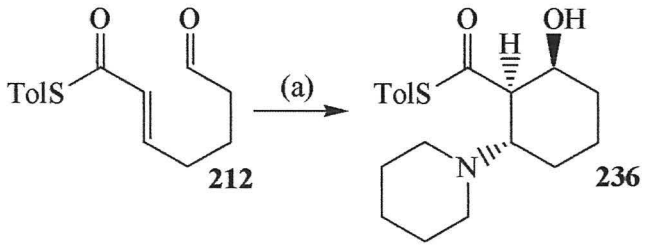
Scheme 93: (a) Piperidine (0.3 eqv.), $CDCl_3$, r.t., 14-28 days

We next applied these conditions to the enoate-containing substrate **206** and as was observed with the 5-membered series, only products derived from aldol condensation of the aldehyde function were formed (Scheme 94).



Scheme 94: (a) Piperidine (1.3 or 0.3 eqv.), $CDCl_3$, r.t.

Similarly, reaction of the thiolester-containing substrate **212** with piperidine were complicated by considerable decomposition, including amide formation and aldol condensations with only a low yield (ca. 5%) of the intermediate adduct **236** being observed by NMR (Scheme 95).

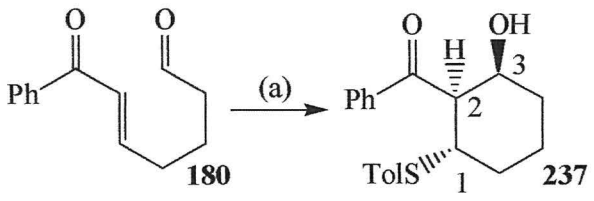


Scheme 95: (a) Piperidine (1.3 or 0.3 eqv.), $CDCl_3$, r.t., 2 days

The conclusions for this investigation mirror those of the 5-membered series in that the enone substrate undergoes tandem Michael-aldol cyclisation or Baylis-Hillman cyclisation depending on the conditions employed, whilst the enoate and thioenoate substrates lead only to decomposition.

4.7.2 Thiol-based catalysis

We next investigated a thiol as the nucleophile in the reaction of the enoate substrate **180** and found that the addition of an excess of *p*-TolSH to a chloroform solution of **180** at room temperature effected a cyclisation to give the adduct **237** in 93% isolated yield as the sole product (Scheme 96), together with a trace of the aldol product. Analysis of the proton NMR spectrum for **237** indicated that the signal at δ = 3.77 ppm is a dd with J = 2.5 and 11.5 Hz. This signal suggests a large *trans*-diaxial coupling to an adjacent proton and a smaller axial-equatorial coupling for CH-2. This is indicative of the relative stereochemistry shown in Scheme 96. In addition, the proton at C-3 resonates at δ = 4.20 and is a broad multiplet, whereas the proton for C-1 resonates at δ = 4.22 as a ddd with J = 4.0, 11.5 and 11.5 Hz. These signals are again consistent with the stereochemistry shown.

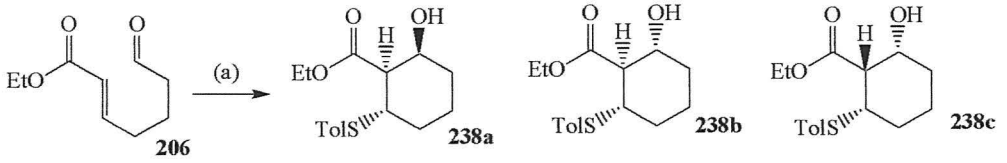


180 **237**

Scheme 96: (a) *p*-TolSH (1.3 eqv.), $CHCl_3$, r.t., 16 hrs

In common with the additions of the secondary amines, in all these reactions the Michael addition-aldol cyclisation step proceeds to give a single diastereomer by NMR and again we have been unable to isolate any minor diastereomeric products.

Treatment of the ester substituted (E)-**206** under the previous conditions failed to effect cyclisation, even on refluxing in chloroform. However, if the reaction was performed with 2 equivalents of *p*-TolSH and a catalytic quantity of *p*-TolSNa, adduct **238a** was obtained in 75% yield (Scheme 97).



Scheme 97: (a) *p*-TolSH (2.0 eqv.), *p*-TolSNa (0.2 eqv.), $CHCl_3$, reflux, 16 hrs

On analysis of the proton NMR of **238a**, we observed very similar signals and coupling constants to those found in **237**, specifically δ = 2.53 (1H, dd, J = 1.9, 10.6 Hz, CH), 3.48 (1H, ddd, J = 4.0, 11.3, 11.3 Hz, SCH) and 4.18 (1H, m, CHOH). We can thus conclude that the relative stereochemistry is identical to that found in **236**. A trace of the aldol product was also detected in the proton NMR spectrum.

In addition to the main product, further chromatographic purification of the crude column fractions enabled us to isolate two compounds **238b** and **238c** in 7% and 5% yield respectively. The stereochemistry of **238b** was easily determined from the proton NMR as the C-2 methine proton displayed two large *trans*-diaxial coupling constants at δ = 2.33 ppm, J = 11.5, 12.0 Hz, indicating the relative stereochemistry shown. The stereochemistry of **238c** was assigned by X-ray crystallography (Figure 4) (see Appendix A) and has a diagnostic signal for the C-2 methine proton at δ = 2.98 ppm which gave coupling constants of J = 3.7, 4.5 Hz.

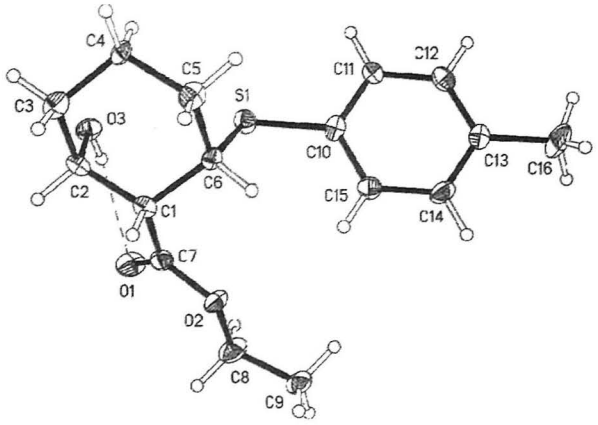
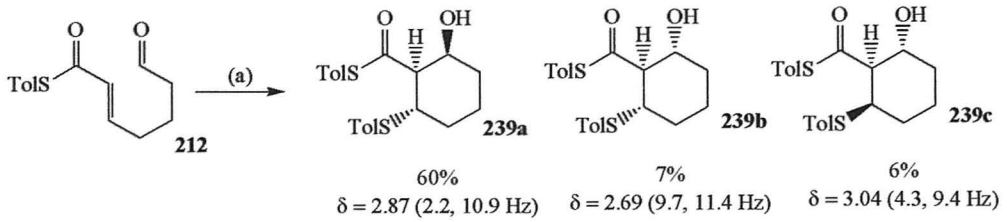


Figure 4: X-ray structure of **238c**

We then moved on to an investigation of the thiolester-containing substrate **212** and employed identical conditions to those used previously and found that this led to the formation of adduct **239a** in 60% yield, together with a trace of the aldol product. Again, two minor by-products **239b** and **239c** were isolated in 7% and 6% yield respectively (Scheme 98).



Scheme 98: (a) *p*-TolSH (2.0 eqv.), *p*-TolSNa (0.2 eqv.), $CHCl_3$, reflux, 16 hrs

Analysis of the proton NMR of **239a** again gave very similar signals and coupling constants to those found in **237** and **238a**, specifically δ = 2.87 (1H, dd, J = 2.2, 10.9 Hz, CH), 3.60 (1H, ddd, J = 4.0, 10.9, 11.7 Hz, C<u>H</u>S) and 4.30 (1H, m, C<u>H</u>OH) and we can thus conclude that the relative stereochemistry is as shown.

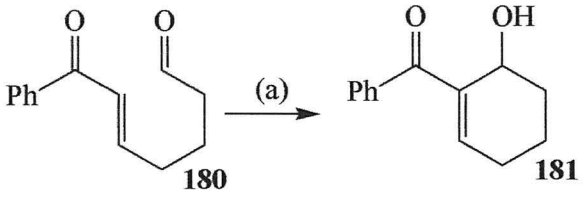
The stereochemistry of **239b** was again determined from proton NMR as the C-2 methine proton displayed two large *trans*-diaxial coupling constants (δ = 2.69 ppm, J = 9.7, 11.5 Hz) indicative of all the substituents having equatorial positions. Finally, the stereochemistry of **239c** was assigned again based on the signal for the

C-2 methine proton at δ = 3.04 ppm which gave coupling constants of very similar magnitude to **239a** (J = 4.3, 9.5 Hz). This suggests that as with **239a**, the thiol ester is in an equatorial position and one of the adjacent functionalities must be axially arranged to give the smaller J value. We can thus tentatively assign the structure shown in which the S-tolyl is formally adopting an axial position.

The conclusion from this part of the work is that the thiol/thiolate catalysed reactions are as successful as those for the 5-membered cases discussed in the previous chapter with high yields (60-93%) and excellent stereocontrol. The reason for the formation of the minor by-products in the thiolate cases is unclear, however they may be arising from an equilibrium process occurring in the reaction. As to why different isomers are obtained in these two processes we have no clear rationale, however it may be due to steric factors (the S-tolyl group being considerably more bulky than the OEt group).

4.7.3 Phosphine-based catalysis

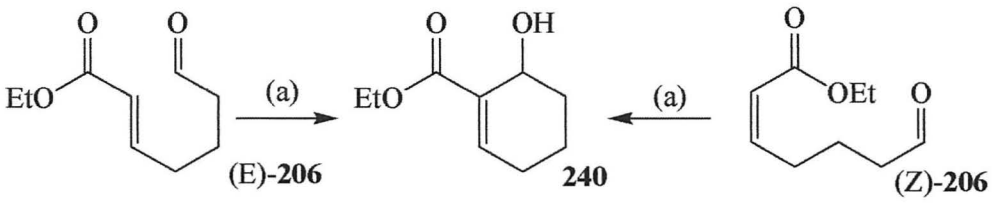
We next turned our attention to the use of phosphines in these cyclisations and found that treatment of a chloroform solution of enone **180** with a catalytic amount of *n*-Bu_3P led to the rapid formation of the previously prepared enone **181** in an excellent (75%) yield (Scheme 99).



Scheme 99: (a) *n*-Bu_3P (0.2 eqv.), $CDCl_3$, r.t., 2 hrs

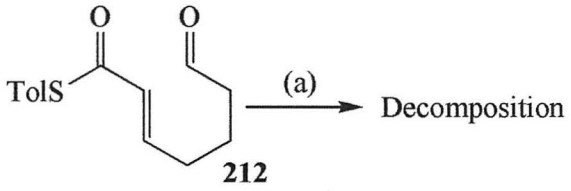
The reasons for this improved reaction yield and rate when compared with the equivalent 5-membered cyclisation are unclear. However, it is possible to speculate that as the chain length separating the two reactive centres increases in length, increased flexibility might give this system a conformational bias leading to a more rapid reaction.

Following this, we investigated the cyclisation of the enoate substrate (E)-**206**, which, on treatment under the same conditions, gave the cyclohexene product **240** in a satisfying 50% yield. Interestingly, the isomeric compound (Z)-**206** also underwent cyclisation to **240** in an improved 70% yield; the exact reason for this higher yield is unclear (Scheme 100). Diagnostic proton NMR data for **240** include a multiplet at δ = 4.55, which corresponds to the methine proton adjacent to the hydroxyl and a triplet at δ = 7.11 (J = 2.0 Hz) for the alkene proton.



Scheme 100: (a) *n*-Bu_3P (0.2 eqv.), $CDCl_3$, r.t., 24 hrs

Again, unsurprisingly, it was found that treatment of thiolester **212** with phosphine under similar conditions led to a rapid decomposition of the substrate to a mixture of unidentifiable products (Scheme 101).



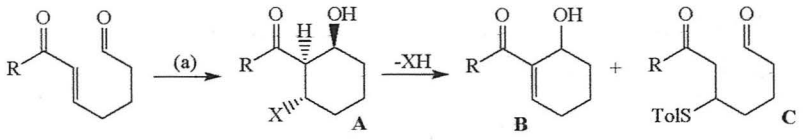
Scheme 101: (a) *n*-Bu_3P (0.4 eqv.), $CDCl_3$, r.t., 17 hrs

Our conclusion from this work is that both the enone and enoate substrates give excellent yields in the cyclisation process which are better than those for the corresponding 5-membered series. The thioenoate substrate, however underwent a similar decomposition to that already observed for the 5-membered series.

4.7.4 Conclusions

Our overall conclusions from the reactions of the 6-membered substrates are that the thiolate catalysed reactions are very successful leading to high yields of the cyclised products in all cases, as was found in the 5-membered series. Reactions catalysed by phosphines gave excellent results for the enone and enoate substrates whilst piperidine only performed well as a catalyst for cyclising the enone-containing substrate. Again, it is apparent from this work that the enoate substrates require more forcing conditions or prolonged reaction times than the corresponding enones.

The overall results are summarised in Table 10.



Scheme 102

Table 10

Entry	Subs	R =	Method[a]	X	A	B	C
1	**180**	Ph	1.3 eqv. Piperidine, 10 min.	Piperidyl	**214**, 90%[b]	------	------
2	**180**	Ph	0.3 eqv. Piperidine, 14-28 days.	Piperidyl	------	**181**, 24-30%	------
3	**180**	Ph	1.3 eqv. *p*-TolSH, 16 h, r.t.	TolS	**237**, 93%	------	Trace
4	**180**	Ph	0.2 eqv. *n*-Bu_3P, 2 h.	------	------	**181**, 75%	------
5	(E)-**206**	OEt	1.3 eqv. Piperidine.	Piperidyl	Dec[c]	------	------
6	(E)-**206**	OEt	0.3 eqv. Piperidine.	Piperidyl	Dec[c]	------	------
7	(E)-**206**	OEt	2 eqv. *p*-TolSH, 0.2 eqv. *p*-TolSNa, Δ, 16 h.	TolS	**238**[d], 75%	------	Trace
8	(E)-**206**	OEt	0.2 eqv. *n*-Bu_3P, 24 h.	------	------	**240**, 50%	------
9	(Z)-**206**	OEt	0.2 eqv. *n*-Bu_3P, 24 h.	------	------	**240**, 70%	------
10	**212**	STol	1.3 eqv. Piperidine, 2 days.	Piperidyl	**236**[b], ca. 5%	------	------
11	**212**	STol	0.3 eqv. Piperidine, 2 days.	Piperidyl	**236**[b], ca. 5%	------	------
12	**212**	STol	2 eqv. *p*-TolSH, 0.2 eqv. *p*-TolSNa, Δ, 16 h.	TolS	**239**[d], 60%	------	Trace
13	**212**	STol	0.4 eqv. *n*-Bu_3P, 17 h.	------	Rapid dec[e]	------	------

(a) All reactions performed in $CHCl_3$ or $CDCl_3$ at r.t. unless specified.

(b) As observed by NMR of the progress of the reaction.

(c) Largely composed of products derived from aldol condensation.

(d) Major isomer; see text.

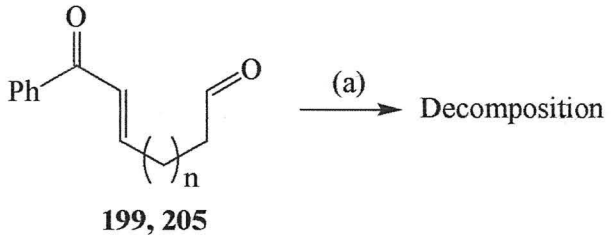
(e) Unidentified decomposition products.

4.8 Reactions involving the formation of larger ring systems

The previous work has demonstrated that our methodology is ideal for the formation of 5 and 6-membered carbocyclic rings. We next wished to investigate the formation of medium ring carbocycles using the easily prepared substrates **199** and **205** (prepared from cyclohexene and cyclooctene).

4.8.1 Piperidine catalysis

We firstly treated the substrates **199** and **205** with both stoichiometric and catalytic amounts of piperidine at differing concentrations and it was apparent from these reactions that the expected intermediate Michael-aldol adducts or the cycloalkenols which arise from a Baylis-Hillman process were not formed even on prolonged reaction times. The main outcome of these reactions appeared to be decomposition, which was occurring *via* an aldol type process (Scheme 103).

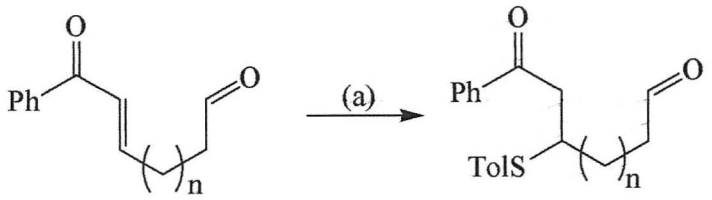


199, 205

Scheme 103: (a) Piperidine (1.3 or 0.3 eqv.); n = 3 or 5

4.8.2 Thiol-based catalysis

We next investigated the reaction of **199** and **205** with *p*-TolSH at room temperature and at reflux and with the presence of *p*-TolSNa as catalyst and found that the only products obtained were the Michael adducts **241** and **242** (both in 79% yield) (Scheme 104).



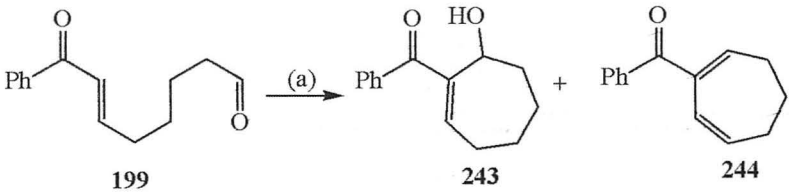
199, 205 **241, 242**

Scheme 104: (a) *p*-TolSH (2.0 eqv.), *p*-TolSNa (0.2 eqv.), $CHCl_3$, Δ, 16 hrs; n = 3 or 5

4.8.3 Phosphine-based catalysis

With these disappointing results, we proceeded to investigate the phosphine mediated cyclisations and were pleased when these reactions met with more success. We found that treatment of **199** with 0.2 equivalents of *n*-Bu_3P for 48 hours in chloroform led to the formation of a trace amount of the cycloheptenol **243**, as evidenced by NMR with a signal at δ = 4.70 ppm (m, CHOH).

However, the main product from this reaction was shown to be, somewhat surprisingly, the cycloheptadiene **244**, which was obtained in 77% isolated yield (Scheme 105).

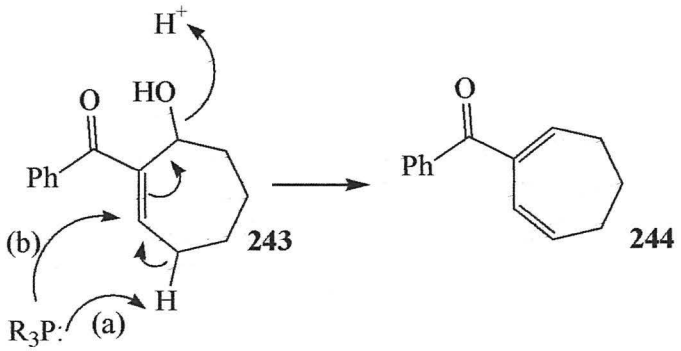


Scheme 105: (a) *n*-Bu_3P (0.2 eqv.), $CDCl_3$, 2 days or *n*-Bu_3P (0.2 eqv.), C_6D_6, 2 days

This product was unexpected as similar products were not observed in any previous *n*-Bu_3P catalysed cyclisation reactions. In order to determine if this elimination was occurring due to an interaction between the phosphine and the chloroform, we repeated the reaction in D_6-benzene with comparable results being obtained, in that **244** was the major product formed (46% yield). The mechanism of

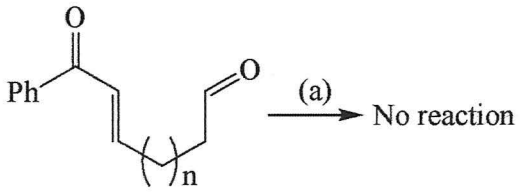
this reaction is most probably a simple elimination of water, possibly mediated by the phosphine catalyst acting as a base (route a) as shown in Scheme 106. Further evidence for this was that the signal for water in the proton NMR at $\delta = 1.90$ ppm increased steadily during the monitoring of the progress of the reaction. However, why this is occurring in only this particular ring size is not known but the more flexible conformation of the 7-membered ring might be a factor. It is also possible that a nucleophilic attack of the phosphine to the enone, followed by elimination of water is occurring (route b).

Diagnostic proton NMR data for **244** includes signals at $\delta = 6.06$ (1H, dt, J = 5.2, 11.9 Hz, CH), 6.33 (1H, dd, J = 1.2, 11.9 Hz, CH) and 6.57 (1H, br t, J = 5.2 Hz, CH) which correspond to the three alkene protons.



Scheme 106

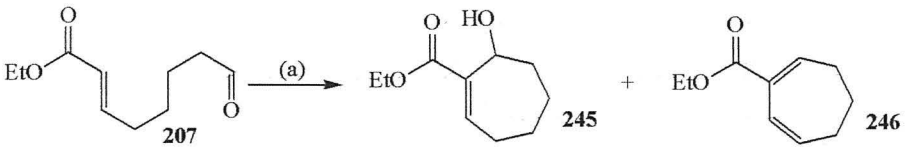
Similar reactions were attempted on the enone substrates **202** and **205** which, if successful, would generate 8 and 9-membered rings respectively, however these proved completely unreactive toward the reaction conditions and no cyclisations were observed even on prolonged reaction times (Scheme 107).



202, 205

Scheme 107: (a) *n*-Bu_3P (0.2 eqv.), 6 days; n = 4 or 5

We were keen to investigate the elimination process observed in the formation of **244** further and thus treated the enoate substrate **207** under identical conditions. We found that this also led to the formation of the cycloheptadiene **246** but in much lower yield (10%). In this case, however, the expected Baylis-Hillman product **245** was obtained in a slightly higher yield (16%). The other noteable feature of this reaction was the much shorter time required for complete consumption of the starting material and the larger amount of decomposition that was observed (Scheme 108). Diagnostic NMR data for the two products includes, for **245**, signals at δ = 3.13 ppm (1H, br s) for the CHOH, 4.81 ppm (1H, m) for the CHOH proton and at δ = 7.11 ppm (1H, t, J = 6.4 Hz) for the alkene proton. Data for **246** included signals at δ = 5.98 (1H, dt, J = 5.4, 11.6 Hz, CH), 6.38 (1H, br d, J = 1.5, 11.6 Hz, CH) and 7.14 (1H, t, J = 5.5 Hz, CH) ppm for the three alkene signals.



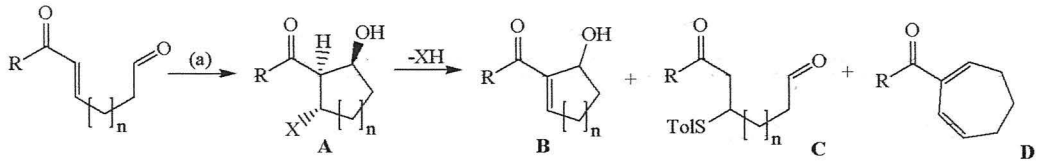
207 **245** **246**

Scheme 108: (a) *n*-Bu_3P (0.2 eqv.), 6 days

4.8.4 Conclusions

The conclusions from this work are that firstly, the methodology involving piperidine and thiol/thiolates are ineffective and appear limited to 5 and 6-membered systems. The phosphine catalysed processes are of more interest in that they appear to offer the potential for the synthesis of 7-membered systems in very high yields; a process that might be of considerable synthetic interest. The phosphine catalysis was limited to this ring size and no reaction was observed when larger ring sizes were attempted.

The overall results are summarised in Table 11.



Scheme 109

Table 11

Entry	Subs	R =	n =	Method[a]	X	A	B	C	D
1	**199**	Ph	3	1.3 eqv. Piperidine.	Piperidyl	Dec[b]	------	------	------
2	**199**	Ph	3	0.3 eqv. Piperidine.	Piperidyl	Dec[b]	------	------	------
3	**205**	Ph	5	1.3 eqv. Piperidine.	Piperidyl	Dec[b]	------	------	------
4	**205**	Ph	5	0.3 eqv. Piperidine.	Piperidyl	Dec[b]	------	------	------
5	**199**	Ph	3	2 eqv. *p*-TolSH, 0.2 eqv. *p*-TolSNa, Δ, 16 h.	TolS	------	------	**241** 79%	------
6	**205**	Ph	5	2 eqv. *p*-TolSH, 0.2 eqv. *p*-TolSNa, Δ, 16 h.	TolS	------	------	**242** 79%	------
7	**199**	Ph	3	0.2 eqv. *n*-Bu_3P, 2 days.	------	Trace[c]	------	------	**244** 77%
8	**199**	Ph	3	0.2 eqv. *n*-Bu_3P, C_6D_6, 2 days.	------	Trace[c]	------	------	**244**, 46%
9	**202**	Ph	4	0.2 eqv. *n*-Bu_3P, 6 days.	------	No reaction	------	------	------
10	**205**	Ph	5	0.2 eqv. *n*-Bu_3P, 6 days.	------	No reaction	------	------	------
11	**207**	OEt	3	0.2 eqv. *n*-Bu_3P, 6 days.	------	Trace[c]	**245**, 16%	------	**246**, 10%

(a) All reactions performed in $CHCl_3$ or $CDCl_3$ at r.t. unless specified.

(b) Largely composed of products derived from aldol condensation.

(c) As observed by NMR of the progress of the reaction.

4.9 Overall conclusions

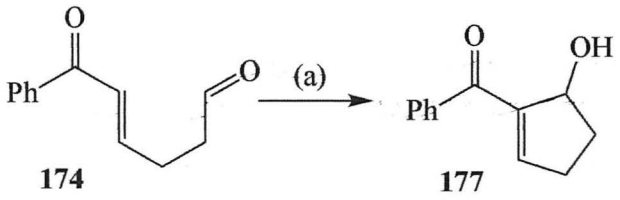
It is apparent from the results of sections 4.6-4.8, that the amine cyclisations are limited in scope to the 5 and 6-membered cyclisations with enones as the Michael acceptors, yields for the stoichiometric processes being very high and those for the catalytic being less so.

The phosphine mediated cyclisations seem to work well for both the enone and enoate cyclisations, with the best yields being obtained for substrates leading to 6 and 7-membered products, leading either to Baylis-Hillman products or the eliminated cycloheptadienes.

But the major achievements of this work are the studies on the thiol and thiolate mediated cyclisations. These were by far the most successful reactions, proceeding for all the 5 and 6-membered substrates in 56-93% yield and giving one major product in all cases with excellent stereoselectivity. These results are comparable with stoichiometric methods such as those using dimethyaluminiumthiophenylates[10] or lithium thiophenoxide in their yield and stereoselectivity.[138]

4.10 Investigation into the use of chiral amines in tandem Michael-aldol cyclisations

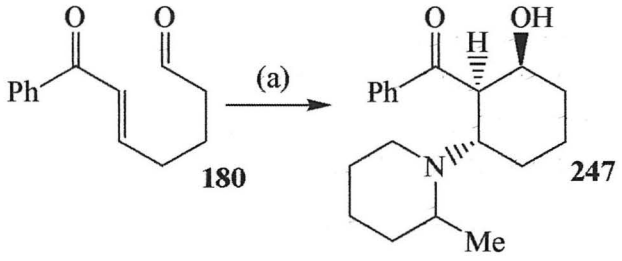
Within the remit of the project, we intended to investigate the use of chiral amines as mediators of the Baylis-Hillman cyclisation, as this might lead to the possibility of an asymmetric reaction process. It had previously[130] been shown that 2-methylpiperidine was effective to some extent in effecting a Baylis-Hillman cyclisation of the enone substrate **174** in 30% yield (Scheme 110).



174 **177**

Scheme 110: (a) 2-Methylpiperidine (30 mol%), $CDCl_3$, r.t., 7 days

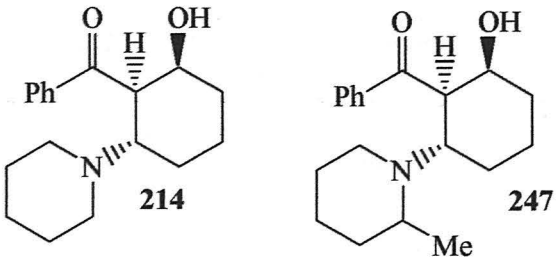
For our purposes, we treated enone **180** with an excess of this amine and observed a slow conversion of the substrate to the product **246** over the course of 3 days, as evidenced by proton NMR (Scheme 111).



180 **247**

Scheme 111: (a) 2-Methyl piperidine (1.3 eqv.), $CDCl_3$, 3 days, r.t.

Evidence for this compound was given by the appearance of a similar set of signals to those observed previously for **214** (Scheme 112, Table 12).



Scheme 112

Table 12

R_2NH	H_1 (J)	H_2 (J)	H_3 (J)
247	4.19 (br m)	3.62 (dd, 3, 11 Hz)	3.80 (ddd, 3, 11, 11 Hz)
214	4.20 (br m)	3.60 (dd, 2, 12 Hz)	3.20 (ddd, 3, 12, 12 Hz)

As can be seen in Figure 5, the crude NMR displayed one major set of signals and several minor by-products. Initially, we felt that these were diastereomeric with **247**, however on close inspection of the ^{13}C spectrum, the presence of only one set of signals with none of the characteristic "twinning" of signals for diastereomeric mixtures has led us to believe that the reaction proceeded to essentially a single diastereomeric product.

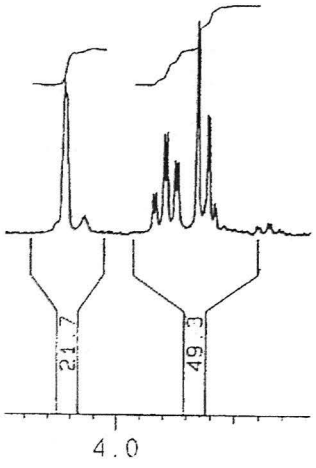
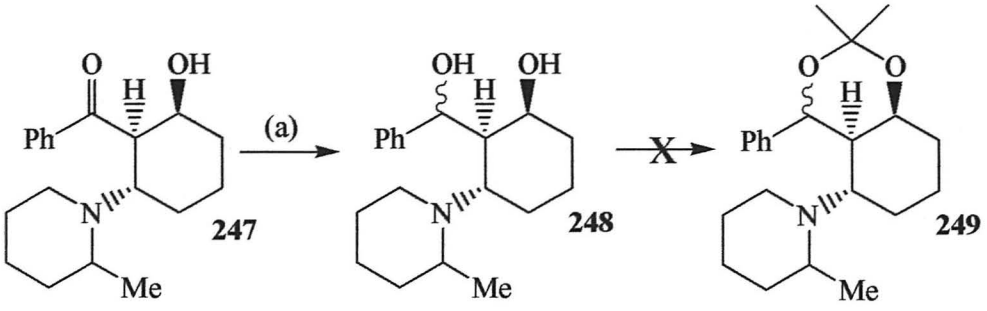


Figure 5

In order to elucidate the relative stereochemistry of the above product, we treated a methanolic solution of the product with sodium borohydride to effect a reduction of the benzoyl group to give the benzylic alcohol **248** (Scheme 113).



Scheme 113: (a) $NaBH_4$, MeOH, 0°C

This was isolated in an overall yield of 61% from the substrate **180** and again was isolated as a single diastereomer as illustrated by the proton and carbon NMR (Figure 6).

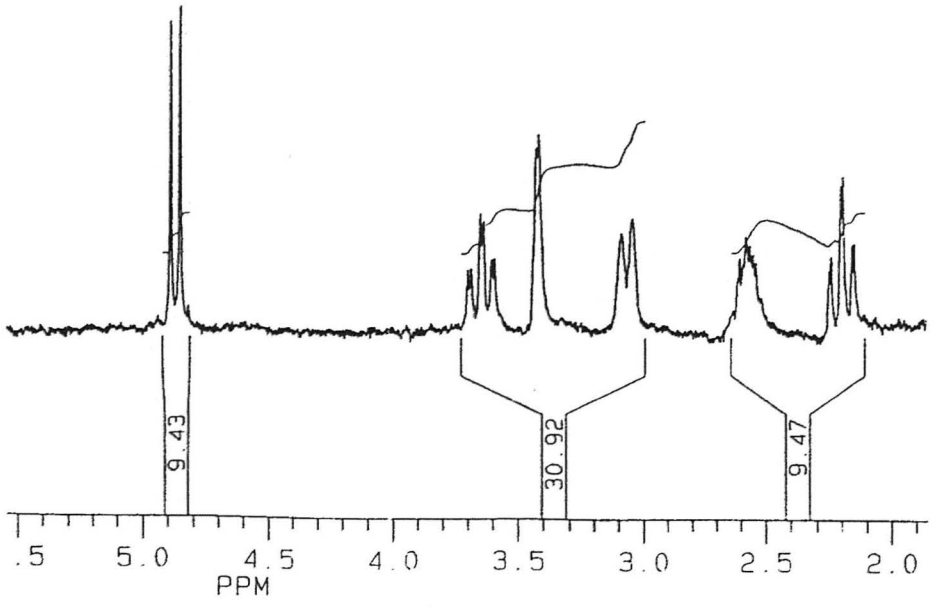


Figure 6

Again it was apparent from the carbon spectrum of this compound that only a single diastereomer of this compound had been formed, as only one methyl signal α-to piperidine was observable (δ = 21.14). Unfortunately, we were unable to obtain any crystals of **248** despite trying a range of solvents and thus attempts to elucidate the relative stereochemistry of both the piperidine methyl and the benzylic alcohol positions proved difficult.

The formation of derivatives of **248** also proved to be difficult. Attempted acetylation using acetyl chloride gave only an inseparable mixture of compounds and the attempted formation of the dimethylacetone derivative **249** using 2-methoxypropene was also unsuccessful.

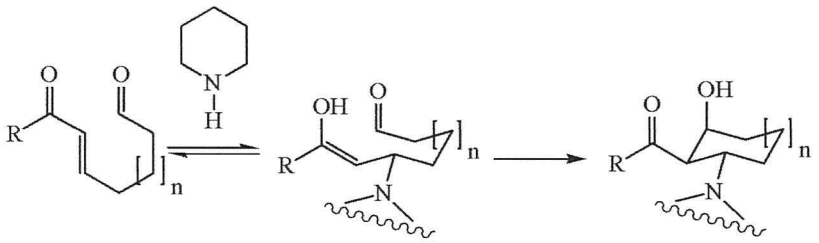
These results were disappointing as the reaction appears to be stereoselective and a determination of the relative stereochemistry would possibly give an insight into the reaction in general. Possible future work on this area might focus on using other groups on the amine to increase the crystallinity of the products obtained and aid structure determination.

5 Conclusions and further work

At the outset of the project, the aim was to investigate further the intramolecular Michael-aldol reaction using a range of substrates and catalysts. This was achieved through a range of studies and each will be summarised and commented on in turn.

The preparation of substrates: Initially, there were some problems encountered in the preparation of the substrates required for the cyclisation studies, however methods were developed to overcome this and we were able to prepare gram quantities of these materials.

Mechanistic studies on the Baylis-Hillman reaction: This was a very successful aspect of the work and from a combination of NMR studies and the use of X-ray crystallography, we determined the nature of the reaction sequence and the relative stereochemistry of the intermediates involved in this cyclisation process. (Scheme 114).



Scheme 114: n = 0,1; R = alkyl, aryl

The use of a range of amine investigations in this reaction, illustrated that this reaction pathway was common for most of the secondary amines we employed, however the use of a 6-membered amine gave by far the best results. As yet we have no explanation for this observation.

Investigation of new catalysts and substrates: The use of phosphines and thiols as catalysts for this reaction proved very effective with high yields being

observed in several cases. The use of a thiolester as an activating group for the alkene was not easily applicable to the use of phosphines and amines, but was very effective under the thiol/thiolate conditions. Again, the reactions appear highly stereoselective. In summary, the conclusions from this work are as follows:

i) Piperidine is only useful for Michael-aldol and Baylis-Hillman cyclisations of 5 and 6-membered enone substrates.

ii) Thiol/thiolate cyclisations are applicable to Michael-aldol cyclisations of the 5 and 6-membered substrates.

iii) Tri-*n*-butyl phosphine is applicable to the Baylis-Hillman cyclisations of 5, 6 and 7-membered enone and ester substrates.

Investigation into the use of chiral amines in tandem Michael-aldol cyclisations: One very important observation from our work is that we have been able to effect a diastereoselective variant of the Michael-aldol cyclisation using 2-methylpiperidine as a chiral amine catalyst. This opens up significant possibilities for the use of chiral amines, phosphines and thiols in this reaction and may prove the most fruitful area of investigation in the future.

Further developments: In addition to the further studies mentioned above, other work might involve the application of this methodology to synthesis. The intermediates generated by amine or thiol addition may be transformed in several ways (for example Cope or Hoffman elimination, oxidative sulfoxide elimination or desulfurisation) to give useful synthetic precursors. The synthesis of heterocycles and fused systems by these methods is also a possibility.

In conclusion, this work has continued to develop during this investigation and offers potential as a new and viable synthetic methodology.

6 Experimental

6.1 General experimental details

Reagents: All reagents were obtained from commercial suppliers and were used without further purification.

Solvents: Solvents were purified when necessary using the methods described in 'Advanced Practical Organic Chemistry' by M. Casey, J. Leonard, B. Lygo and G. Procter. In particular, dichloromethane (DCM) was distilled over calcium hydride and diethyl ether (ether) and tetrahydrofuran (THF) were distilled over sodium wire and benzophenone. Petrol refers to the fraction of petroleum spirit boiling in the range 40-60°C.

Chromatography: The purity of compounds was assessed by thin layer chromatography (TLC). Unless otherwise stated, all new compounds were homogeneous as indicated by TLC. TLC was performed on BDH glass silica plates coated with Kieselgel 60 F254 (Art. 5554, Merck). Compounds were visualised by examination under ultraviolet light or staining by contact with a solution of phosphomolybdic acid (PMA) in ethanol and heating to 180°C. Column chromatography was performed using Merck 7736 silica gel under medium pressure with the eluting solvent specified in each case.

Analytical methods: Melting points were determined using a Gallenkamp capillary apparatus and are uncorrected. Infra-red (IR) spectra were recorded as thin films on NaCl plates (oils) or KBr discs (solids) using a Perkin-Elmer 1600 FTIR spectrometer. Microanalyses were obtained using a Carbo-Erba Model 1106 CHN analyser. Electron impact (EI), chemical ionisation (CI), fast atom bombardment and high resolution mass spectra were recorded using a VG Masslab Model 12/253 spectrometer by the EPSRC Mass Spectrometry Service at Swansea. In some cases, high resolution mass spectra could not be obtained due to limited access to this service. Proton NMR spectra were recorded at 250 MHz using a Bruker AC250

spectrometer. Carbon NMR spectra were recorded using the Bruker AC250 spectrometer at 62.5 MHz and were broadband-decoupled. All spectra were recorded in $CDCl_3$ unless otherwise stated. Chemical shifts are reported as δ values relative to tetramethylsilane.

Miscellaneous: All non-aqueous reactions were performed using oven-dried glassware (250°C) under a static atmosphere of argon. The term 'concentrated' refers to the removal of solvent on a Büchi rotary evaporator under reduced pressure (~15 mm Hg). All yields quoted are for purified compounds unless otherwise stated.

6.2 General conditions for the Wittig reaction with dialdehydes

Preparation of succinaldehyde (195)

A mixture of 2,5-dimethoxytetrahydrofuran (11 g; 0.083 mol) and aqueous acetic acid solution (22 ml 1% v/v) was refluxed for 20 minutes. After cooling and neutralising with saturated sodium bicarbonate solution (volume until neutral on pH paper), the mixture was saturated with NaCl (solid) and extracted with ethyl acetate (50 ml x 3) and chloroform (50 ml). Drying and evaporation of the combined extracts was followed by vacuum distillation, yielding succinaldehyde (2.70 g, 78% pure; B.pt: 70°C at 8.6 mbar), the purity of which was determined by NMR.

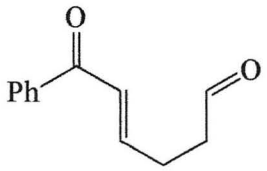
Method A: The relevant phosphorane (1 equivalent) was dissolved in dry dichloromethane (10 ml per gram of phosphorane) and added dropwise to a solution of succinaldehyde (2 equivalents) as a cooled (0°C) solution in dichloromethane or THF (3 x the volume employed for the phosphorane) and the resulting solution stirred for 48 hours. The solution was then washed with a large volume of water (typically 250 ml x 3 for each 100 ml of reaction solvent) and after drying and evaporation of the solvent, the resulting solid mass was triturated with ether (ca. 50-100 ml) then diluted with petrol (ca. 25-50 ml) and the supernatant liquid decanted with filtration. After repeating this process a further three times, the combined filtrates were then dried ($MgSO_4$), evaporated and subjected to chromatography (ether/petrol) to yield the products.

Method B: The cycloalkene (5-20 equivalents) was dissolved in dry dichloromethane (15 ml per gram) and cooled to -78°C whereupon ozone was bubbled in the flask until the solution became blue in colour and at this point, the reaction was flushed with nitrogen gas and triphenylphosphine (equivalent to the amount of cycloalkene) was added in one portion and the reaction stirred until it dissolved and for a further 30 minutes. The phosphorane (1 equivalent) was then added and the reaction stirred to room temperature overnight. The reaction solvent was evaporated and the solid mass remaining was triturated with ether (ca. 100 ml x

3) and the triturates filtered, combined and washed with a large volume of water (ca. 250 ml x 3), then dried ($MgSO_4$) and evaporated. Silica gel chromatography (ether/petrol) gave the products.

Method C: The relevant phosphorane (1 equivalent) was dissolved in ethanol or THF (20 ml per gram of phosphorane) at room temperature whereupon aqueous glutaric dialdehyde solution (20 equivalents) was added and the reaction stirred overnight at room temperature. Water (ca. 50 ml per gram of phosphorane) was added and the reaction extracted with ether (typically 200 ml x 3) and the combined ether extracts washed with aqueous HCl solution (0.2 M, ca. 300 ml x 3), followed by brine (ca. 50 ml x 3). After drying ($MgSO_4$) and evaporation, silica gel chromatography (ether/petrol) gave the products.

***E*-6-Phenyl-6-oxohex-4-enal (174)**



See: General conditions for the Wittig reaction with dialdehydes.

Method A: Phosphorane **171** (3.55 g; 9.4 mmol) gave **174** (840 mg, 48%); 20-50% ether in petrol, $R_f = 0.29$ (50% ether in petrol).

^{1}H NMR: (250MHz) δ = 2.65 (4H, m, 2 x CH_2), 6.90-7.10 (2H, m, 2 x CH), 7.60-8.00 (5H, m, Ph), 9.82 (1H, s, CHO).

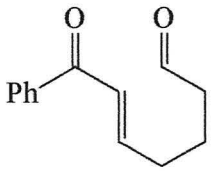
^{13}C NMR: (62.5MHz) δ = 24.97 (CH_2), 41.92 (CH_2), 126.74 (CH), 128.48 (CH), 128.54 (CH), 132.78 (CH), 137.64 (C), 146.67 (CH), 190.33 (C=O), 200.37 (CHO).

IR (NaCl): ν_{max} = 3058, 2897, 2826, (C-H), 2725 (CHO), 1722 (C=O), 1670 (C=O), 1621 (C=C) cm^{-1}.

MS (CI): 206 (100%, $[M+NH_4]^+$), 189 (70%, $[M+H]^+$).

HRMS: $C_{12}H_{13}O_2$ ($[M+H]^+$) requires 189.0916, found 189.0916.

***E*-7-Phenyl-7-oxohept-5-enal (180)**



See: General conditions for the Wittig reaction with dialdehydes.

Method B: Cyclopentene, **196** (8.9 g; 0.13 mol) and phosphorane **171** (5.0 g; 13.2 mmol) gave **180** (1.87 g, 70%).

Method C: Phosphorane **171** (4.02 g; 10.6 mmol) gave **180** (1.54 g, 73%); 30% ether in petrol, $R_f = 0.10$ (30% ether in petrol).

^{1}H NMR: (250MHz) δ = 1.90 (2H, quintet, J = 7.3 Hz, CH_2), 2.37 (2H, dt, J = 6.7, 7.3 Hz, CH_2), 2.50 (2H, dt, J = 0.8, 7.3 Hz, CH_2), 6.70-7.10 (2H, m, 2 x CH), 7.40-8.00 (5H, m, Ph), 9.80 (1H, t, J = 0.8 Hz, CHO).

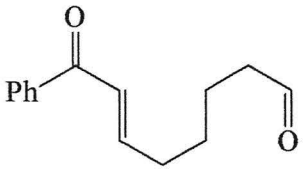
^{13}C NMR: (62.5MHz) δ = 20.49 (CH_2), 31.83 (CH_2), 42.99 (CH_2), 126.64 (2 x CH), 128.49 (2 x CH), 128.52 (CH), 132.72 (CH), 137.77 (C), 147.97 (CH), 190.55 (C=O), 201.55 (CHO).

IR (NaCl): ν_{max} = 3056, 2930, (C-H), 2726 (CHO), 1722 (C=O), 1669 (C=O), 1620 (C=C) cm^{-1}.

MS (CI): 220 (80%, $[M+NH_4]^+$), 203 (100%, $[M+H]^+$).

HRMS: $C_{13}H_{15}O_2$ ($[M+H]^+$) requires 203.1072, found 203.1072.

***E*-8-Phenyl-8-oxo-6-octenal (199)**



See: General conditions for the Wittig reaction with dialdehydes.

Method B: Cyclohexene, **197** (16.4 g; 200 mmol) and phosphorane **171** (3.88 g; 10 mmol) gave **199** (0.878 g, 41%); 20% ether in petrol, $R_f = 0.17$ (20% ether in petrol).

^{1}H NMR: (250MHz) δ = 1.50-1.70 (4H, m, 2 x CH_2), 2.37 (2H, app q, J = 6.4 Hz, CH_2), 2.49 (2H, dt, J = 1.5, 7.0 Hz, CH_2), 6.90 (1H, d, J = 14.5 Hz, CH), 7.03 (1H, dt, J = 6.4, 14.5 Hz, CH), 7.43-7.95 (5H, m, Ph), 9.78 (1H, d, J = 1.5 Hz, CHO).

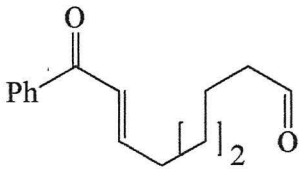
^{13}C NMR: (62.5MHz) δ = 21.58 (CH_2), 27.61 (CH_2), 32.49 (CH_2), 43.58 (CH_2), 126.24, 128.51, 132.67 (6 x CH), 137.85 (C), 148.88 (CH), 190.26 (C=O), 202.15 (CHO).

IR (NaCl): ν_{max} = 2935 (C-H), 2724 (CHO), 1722 (C=O), 1668 (C=O), 1619 (C=C) cm^{-1}.

MS (CI): 234 (100%, $[M+NH_4]^+$), 217 (70%, $[M+H]^+$).

HRMS: $C_{14}H_{17}O_2$ ($[M+H]^+$) requires 217.1229, found 217.1226.

***E*-9-Phenyl-9-oxo-7-nonenal (202)**



See: General conditions for the Wittig reaction with dialdehydes.

Method B: Cycloheptene, **200** (4.81 g; 50 mmol) and phosphorane **171** (3.04 g; 8.0 mmol) gave **202** (0.858 g, 47%); 20% ether in petrol, $R_f = 0.16$ (20% ether in petrol).

^{1}H NMR: (250MHz) δ = 1.30-1.80 (6H, m, 3 x CH_2), 2.34 (2H, app q, J = 7.0 Hz, CH_2), 2.46 (2H, t, J = 7.3 Hz, CH_2), 6.88 (1H, d, J = 16.5 Hz, CH), 7.05 (1H, m, CH), 7.45-7.95 (5H, m, Ph), 9.78 (1H, br s, CHO).

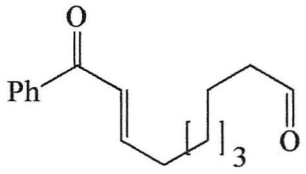
^{13}C NMR: (62.5MHz) δ = 21.78 (CH_2), 27.92 (CH_2), 28.69 (CH_2), 32.54 (CH_2), 43.73 CH_2), 126.08, 128.51, 132.63 (6 x CH), 138.00 (C), 149.40 (CH), 190.81 (C=O), 202.44 (CHO).

IR (NaCl): ν_{max} = 2930 (C-H), 2721 (CHO), 1721 (C=O), 1668 (C=O), 1618 (C=C) cm^{-1}.

MS (CI): 248 (100%, $[M+NH_4]^+$), 231 (55%, $[M+H]^+$).

HRMS: $C_{15}H_{19}O_2$ ($[M+H]^+$) requires 231.1385, found 231.1385.

***E*-10-Phenyl-10-oxo-8-decenal (205)**



See: General conditions for the Wittig reaction with dialdehydes.

Method B: Cyclooctene, **203** (11.0 g; 0.10 mol) and phosphorane **171** (3.82 g; 10.0 mmol) gave **205** (1.19 g, 49%); 25% ether in petrol, $R_f = 0.16$ (25% ether in petrol).

^{1}H NMR: (250MHz) δ = 1.30-1.70 (8H, m, 4 x CH_2), 2.32 (2H, app q, J = 7.0 Hz, CH_2), 2.45 (2H, dt, J = 1.0, 6.7 Hz, CH_2), 6.85 (1H, d, J = 15.3 Hz, CH), 7.06 (1H, dt, J = 7.0, 15.3 Hz, CH), 7.40-7.95 (5H, m, Ph), 9.75 (1H, d, J = 1.0 Hz, CHO).

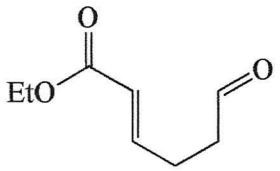
^{13}C NMR: (62.5MHz) δ = 21.90 (CH_2), 27.94 (CH_2), 28.90 (CH_2), 28.93 (CH_2), 32.70 (CH_2), 43.80 (CH_2), 125.99, 128.50, 132.60 (6 x CH), 137.96 (C), 149.71 (CH), 190.87 (C=O), 202.65 (CHO).

IR (NaCl): ν_{max} = 2931, 2856 (C-H), 2720 (CHO), 1722 (C=O), 1669 (C=O), 1619 (C=C) cm^{-1}.

MS (CI): 262 (100%, $[M+NH_4]^+$), 245 (80%, $[M+H]^+$).

HRMS: $C_{16}H_{21}O_2$ ($[M+H]^+$) requires 245.1542, found 245.1542.

***E*-6-Ethoxy-6-oxo-4-hexenal (175)**



See: General conditions for the Wittig reaction with dialdehydes.

Method A: Phosphorane **172** (2.84 g; 8.1 mmol) gave **175** (730 mg, 58%); 50% ether in petrol, $R_f = 0.30$ (50% ether in petrol).

^{1}H NMR: (250MHz) δ = 1.30 (3H, t, J = 7.1 Hz, CH_3), 2.50-2.70 (4H, m, 2 x CH_2), 4.19 (2H, q, J = 7.1 Hz, CH_2), 5.85 (1H, d, J = 15.7 Hz, CH), 6.94 (1H, dt, J = 6.4, 15.7 Hz, CH), 9.70 (1H, d, J = 0.7 Hz, CHO).

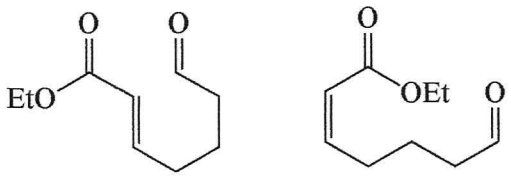
^{13}C NMR: (62.5MHz) δ = 14.23 (CH_3), 24.41 (CH_2), 41.83 (CH_2), 60.34 (CH_2), 122.46 (CH), 146.26 (CH), 166.26 (C=O), 200.33 (CHO).

IR (NaCl): ν_{max} = 2981, 2832 (C-H), 2727 (CHO), 1721 (C=O), 1657 (C=C) cm^{-1}.

MS (CI): 174 (100%, $[M+NH_4]^+$).

HRMS: $C_8H_{16}NO_3$ ($[M+NH_4]^+$) requires 174.1130, found 174.1129.

***E*- and *Z*-7-Ethoxy-7-oxo-5-heptenal ((E)-206 and (Z)-206)**



See: General conditions for the Wittig reaction with dialdehydes.

Method C: Phosphorane **172** (3.66 g; 10.5 mmol) gave (Z)-**206** (410 mg, 23%) and (E)-**206** (737 mg, 41%); 10% ether in petrol, R_f = 0.14 and 0.07 (10% ether in petrol).

Data for (Z)-**206.** **^{1}H NMR:** (250MHz) δ = 1.18 (3H, t, J = 7.1 Hz, CH_3), 1.70 (2H, app pentet, J = 7.3 Hz, CH_2), 2.40 (2H, t, J = 7.2 Hz, CH_2), 2.60 (2H, app q, J = 7.4 Hz, CH_2), 4.05 (2H, q, J = 7.1 Hz, CH_2), 5.72 (1H, d, J = 11.4 Hz, CH), 6.11 (1H, dt, J = 7.4, 11.4 Hz, CH), 9.28 (1H, s, CHO).

^{13}C NMR: (62.5MHz) δ = 14.12 (CH_3), 21.17 (CH_2), 27.98 (CH_2), 43.05 (CH_2), 59.73 (CH_2), 120.67 (CH), 148.44 (CH), 166.05 (C=O), 201.83 (CHO).

IR (NaCl): ν_{max} = 3038, 2982, 2937, 2826, (C-H), 2724 (CHO), 1722 (C=O), 1644 (C=C) cm^{-1}.

MS (CI): 188 (100%, $[M+NH_4]^+$), 171 (30%, $[M+H]^+$).

HRMS: $C_9H_{15}O_3$ ($[M+H]^+$) requires 171.1021, found 171.1018.

Data for (E)-**206.** **^{1}H NMR:** (250MHz) δ = 1.05 (3H, t, J = 7.1 Hz, CH_3), 1.57 (2H, app pentet, J = 7.3 Hz, CH_2), 2.05 (2H, app q, J = 7.1 Hz, CH_2), 2.27 (2H, t, J = 7.0 Hz, CH_2), 3.93 (2H, q, J = 7.1 Hz, CH_2), 5.61 (1H, d, J = 15.6 Hz, CH), 6.69 (1H, dt, J = 6.8, 15.6 Hz, CH), 9.54 (1H, s, CHO).

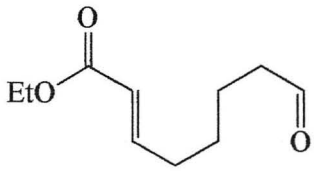
^{13}C NMR: (62.5MHz) δ = 14.24 (CH_3), 20.30 (CH_2), 31.22 (CH_2), 42.93 (CH_2), 60.27 (CH_2), 122.25 (CH), 147.53 (CH), 167.50 (C=O), 201.62 (CHO).

IR (NaCl): ν_{max} = 2982, 2938, (C-H), 2724 (CHO), 1716 (C=O), 1653 (C=C) cm^{-1}.

MS (CI): 188 (100%, $[M+NH_4]^+$), 171 (25%, $[M+H]^+$).

HRMS: $C_9H_{15}O_3$ ($[M+H]^+$) requires 171.1021, found 171.1023.

***E*- 8-Ethoxy-8-oxo-6-octenal (207)**



See: General conditions for the Wittig reaction with dialdehydes.

Method B: Cycloheptene, **197** (16.4 g; 171 mmol) and phosphorane **172** (3.48 g; 10.0 mmol) gave **207** (700 mg, 38%); 40% ether in petrol, R_f = 0.22 (40% ether in petrol).

^{1}H NMR: (250MHz) δ = 1.29 (3H, t, J = 7.0 Hz, CH_3), 1.48-1.70 (4H, m, 2 x CH_2), 2.23 (2H, app q, J = 7.0 Hz, CH_2), 2.47 (2H, t, J = 7.0 Hz, CH_2), 4.19 (2H, q, J = 7.0 Hz, CH_2), 5.83 (1H, d, J = 15.9 Hz, CH), 6.92 (1H, dt, J = 6.7, 15.9 Hz, CH), 9.78 (1H, s, CHO).

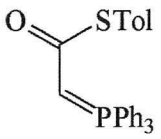
^{13}C NMR: (62.5MHz) δ = 14.24 (CH_3), 21.47 (CH_2), 27.45 (CH_2), 31.83 (CH_2), 43.56 (CH_2), 60.20 (CH_2), 121.79 (CH), 148.25 (CH), 166.56 (C=O), 202.11 (CHO).

IR (NaCl): ν_{max} = 2981, 2937, 2862 (C-H), 2721 (CHO), 1719 (C=O), 1654 (C=C) cm^{-1}.

MS (CI): 202 (100%, $[M+NH_4]^+$).

HRMS: $C_{10}H_{20}NO_3$ ($[M+NH_4]^+$) requires 202.1443, found 202.1444.

Preparation of phosphorane (210)[133]



Toluene-4-thiol (12.20 g; 0.098 mol) was placed in DCM (450 ml) together with bromoacetic acid (13.93 g; 0.10 mol) and DMAP (1.22 g; 0.01 mol). The solution was stirred and cooled (0°C) whereupon DCC (21.71 g; 0.105 mol) was added in 3 portions. After stirring for 48 hrs at r.t., the solution was filtered through celite and the resulting cake was washed several times with DCM (5 x 50 ml). The filtrate was then washed with $NaHCO_3$ (sat. 50 ml), water (500 ml) and brine (100 ml) then dried ($MgSO_4$), concentrated *in vacuo* to give the product **209** (23.48 g) as a brown oil.

^{1}H NMR: (250MHz) δ = 2.40 (3H, s, CH_3), 4.10 (2H, s, CH_2), 7.25 (4H, m, 4 x CH).

This oil was dissolved in toluene (150 ml) and triphenylphosphine (26.3g, 0.10 mol) was added after standing for 2 days at room temperature to give, after filtration and washing with toluene, the intermediate phosphonium salt (38.33 g, 77%).

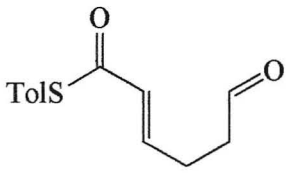
^{1}H NMR: (250MHz) δ = 2.30 (3H, s, CH_3), 6.05 (2H, d, J_{P-H} = 15 Hz, CH_2), 7.00 - 8.00 (19H, m, 4 x CH and 3 x Ph).

These crystals were dissolved in DCM (150 ml) and vigorously stirred with a solution of Na_2CO_3 (100 ml, 10% solution w/v) for 30 minutes. The organic layer was separated and the aqueous layer was extracted with further DCM (50 ml x 2) The combined organic phases were dried ($MgSO_4$) and partially concentrated *in vacuo* (to ca. 100 ml) and then diluted with pentane to precipitate the phosphorane **210** (28.78 g, 69% overall yield).

M. pt.: 179°C.

^{1}H NMR: (250MHz) δ = 2.30 (3H, s, CH_3), 3.64 (1H, d, J_{P-H} = 22.2 Hz, CH), 7.12 (2H, d, J = 7.9 Hz, 2 x CH), 7.40-7.70 (17H, m, 3 x Ph and 2 x CH).

6-(S-*p*-Tolyl)-6-oxohept-4-enal (211)



See: General conditions for the Wittig reaction with dialdehydes.

Method A: Phosphorane **210** (2.14 g; 5.02 mmol) gave **211** (540 mg, 46%); 20-30% ether in petrol, $R_f = 0.22$ (30% ether in petrol). M. pt.: 31-33°C.

^{1}H NMR: (250MHz) δ = 2.42 (3H, s, CH_3), 2.50-2.62 (4H, m, 2 x CH_2), 6.22 (1H, dt, J = 15.5, 1.5 Hz, CH), 6.95 (1H, dt, J = 15.5, 6.5 Hz, CH), 7.20-7.40 (4H, m, Ph), 9.85 (1H, t, J = 0.8 Hz, CHO).

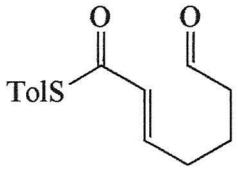
IR (NaCl): ν_{max} = 3035, 2942, 2872 (C-H), 2756 (CHO), 1709 (C=O), 1680 (C=O), 1634 (C=C) cm^{-1}.

MS (CI): 252 (50%, $[M+NH_4]^+$), 235 (40%, $[M+H]^+$).

HRMS: $C_{13}H_{14}O_2S$ ($[M]^+$) requires 234.0715, found 234.0716.

Microanalysis: found C = 66.27; H = 5.75, $C_{13}H_{14}O_2S$ requires C = 66.64; H = 6.02.

7-(S-*p*-Tolyl)-7-oxohept-5-enal (212)



See: General conditions for the Wittig reaction with dialdehydes.

Method B: Phosphorane **210** (4.47 g; 10.5 mmol) gave **212** (840 mg, 32%); 30% ether in petrol, $R_f = 0.16$ (30% ether in petrol). M. pt.: 32-34°C.

^{1}H NMR: (250MHz) δ = 1.84 (2H, app quintet, J = 7.3 Hz, CH_2), 2.30 (2H, ddt, J = 7.3, 6.9, 1.4 Hz, CH_2), 2.39 (3H, s, CH_3), 2.52 (2H, dt, J = 7.3, 1.3 Hz, $C\underline{H_2}CHO$), 6.20 (1H, dt, J = 15.5, 1.4 Hz, CH), 6.90 (1H, dt, J = 15.5, 6.9 Hz, CH), 7.25 (4H, AA'BB', J = 8.0 Hz, tolyl), 9.75 (1H, t, J = 1.3 Hz, CHO).

IR (NaCl): ν_{max} = 2976, 2952, 2857 (C-H), 2738 (CHO), 1715 (C=O), 1680 (C=O), 1633 (C=C) cm^{-1}.

MS (CI): 266 (100%, $[M+NH_4]^+$), 249 (40%, $[M+H]^+$).

HRMS (EI): $C_{14}H_{16}O_2S$ ($[M]^+$) requires 248.0871, found 248.0861.

Microanalysis: found C = 67.86; H = 6.38, $C_{14}H_{16}O_2S$ requires C = 67.71; H = 6.49.

6.3 Cyclisation reactions

6.3.1 General conditions for the addition reactions of secondary amines

The aldehyde (typically 100 mg) was weighed into an NMR tube and diluted to the correct concentration with $CDCl_3$. The relevant amine or amine salt (0.3 or 1.3 equivalents) was then added (either neat or as a solution in $CDCl_3$) and the tube agitated. The reaction was followed by NMR and on completion (to ca. 95%), the solvent was removed and the cyclisation products isolated by chromatography (ether/petrol). For larger scale reactions, chloroform was employed as the solvent and the reaction was carried out in a round bottom flask. For yields see Tables 9, 10 and 11.

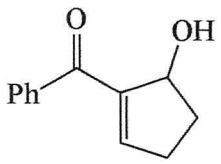
6.3.2 General method for thiol and thiolate reactions

The aldehyde (typically 100-250 mg) was placed in either a round bottom flask in the case of reactions that were heated to reflux or into an NMR tube and diluted with $CHCl_3$ or $CDCl_3$. The *p*-TolSH (1.3-2.0 equivalents either neat or as a solution in $CHCl_3/CDCl_3$) and the catalyst, *p*-TolSNa (0.2 equivalents) were then added. The reaction was followed to completion by NMR or TLC, at which point the solvent was removed and the products obtained by chromatography. For specific conditions, see Tables 9, 10 and 11.

6.3.3 General method for phosphine reactions

The aldehyde (typically 100 mg) was weighed into an NMR tube and diluted to the correct concentration with $CDCl_3$. The tri-*n*-butylphosphine (0.05-0.4 equivalents) was then added neat and the tube agitated. The reaction was followed by NMR and on completion (to ca. 5%), the solvent was removed and the products were obtained by column chromatography. For specific conditions, see Tables 9, 10 and 11.

2-Benzoyl-1-hydroxycyclopent-2-ene (177)



See: General conditions for the addition reactions of secondary amines and the general method for phosphine reactions.

Column solvent: 35% ether in petrol, $R_f = 0.10$ (50% ether in petrol).

^{1}H NMR: (250MHz) δ = 1.94 (1H, m, C$\underline{H}_a$H$_b$), 2.30-2.85 (3H, m, CH$_a\underline{H}_b$ + C$\underline{H}_2$), 3.33 (1H, br s, OH), 5.30 (1H, m, C$\underline{H}$OH), 6.71 (1H, t, J = 1.5 Hz, CH), 7.42-7.78 (5H, m, Ph).

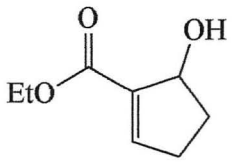
^{13}C NMR: (62.5MHz) δ = 31.40 (CH_2), 31.74 (CH_2), 76.51 (CH), 128.35 (2 x CH), 128.92 (2 x CH), 132.44 (CH), 138.13 (C), 144.54 (C), 149.05 (CH), 194.86 (C=O).

IR (NaCl): ν_{max} = 3460 (O-H), 3058, 2940 (C-H), 1639 (C=O) cm^{-1}.

MS (CI): 206 (45%, $[M+NH_4]^+$), 189 (100%, $[M+H]^+$).

HRMS: $C_{12}H_{13}O_2$ ($[M+H]^+$) requires 189.0916, found 189.0916.

2-Carboethoxy-1-hydroxycyclopent-2-ene (178)



See: General method for phosphine reactions.

Column solvent: 20% ether in petrol, $R_f = 0.04$ (20% ether in petrol).

^{1}H NMR: (250MHz) δ = 1.36 (3H, t, J = 7.1 Hz, CH_3), 1.89 (1H, m, $C\underline{H}_aH_b$), 2.27-2.67 (3H, m, $CH_a\underline{H}_b + CH_2$), 2.85 (1H, br s, OH), 4.24 (2H, q, J = 7.1 Hz, CH_2), 5.08 (1H, m, C<u>H</u>OH), 6.71 (1H, t, J = 2.5 Hz, CH).

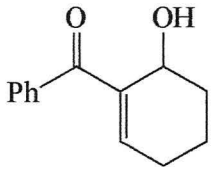
^{13}C NMR: (62.5MHz) δ = 14.25 (CH_3), 31.80 (CH_2), 31.78 (CH_2), 60.46 (CH_3), 75.54 (CH), 138.00 (C), 146.24 (CH), 165.06 (C=O).

IR (NaCl): ν_{max} = 3583, 3440 (O-H), 2924 (C-H), 1713 (C=O), 1634 (C=C) cm^{-1}.

MS (CI): 174 (60%, $[M+NH_4]^+$).

HRMS: $C_8H_{16}NO_3$ ($[M+NH_4]^+$) requires 174.1130, found 174.1130.

2-Benzoyl-1-hydroxycyclohex-2-ene (181)



See: General conditions for the addition reactions of secondary amines and the general method for phosphine reactions.

Column solvent: 20% ether in petrol, $R_f = 0.11$ (25% ether in petrol).

^{1}H NMR: (250MHz) δ = 1.67 (1H, m, C$\underline{H}_a$H$_b$), 1.90 (3H, m, CH$_a\underline{H}_b$ + C$\underline{H}_2$), 2.31 (2H, m, CH$_a$H$_b$), 3.53 (1H, br s, OH), 4.75 (1H, m, C$\underline{H}$OH), 6.73 (1H, t, J = 4.0 Hz, CH), 7.40-7.68 (5H, m, Ph).

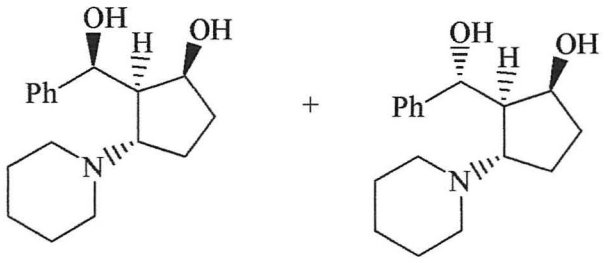
^{13}C NMR: (62.5MHz) δ = 17.29 (CH_2), 26.23 (CH_2), 29.60 (CH_2), 63.83 (CH), 128.03 (2 x CH), 129.10 (2 x CH), 131.77 (CH), 137.69 (C), 140.00 (C), 146.79 (CH), 199.38 (C=O).

IR (NaCl): ν_{max} = 3436 (O-H), 3058, 2938, 2864 (C-H), 1636 (C=O) cm^{-1}.

MS (CI): 220 (15%, $[M+NH_4]^+$), 203 (100%, $[M+H]^+$), 202 (35%, $[M+]^+$).

HRMS: $C_{13}H_{15}O_2$ ($[M+H]^+$) requires 203.1072, found 203.1072.

Preparation of 189a and 189b from 6-Phenyl-6-oxo-4-hexen-1-al (174)



Substrate **174** (200 mg; 1.064 mmol) was dissolved in chloroform (3 ml), cooled (0°C) and piperidine (118 mg; 1.383 mmol) was added to the solution with stirring. After 10 minutes, a solution of sodium borohydride (202 mg; 5.32 mmol) in methanol (5 ml) was added to the mixture and stirring continued for 1 hour. The reaction was evaporated to dryness and the solid mass that resulted was triturated with chloroform and the triturates filtered through a cotton wool plug. On evaporation, silica gel chromatography (methanol in ethyl acetate 1-10%) gave **189a** and **189b** as crystalline solids. **Data for 189a:** Yield: 0.083 g, 29%. M. pt: 180-183°C (ethyl acetate), R_f = 0.12 (10% methanol in ethyl acetate).

^{1}H NMR: (250MHz) δ = 1.24 (1H, d, J = 3.4 Hz, C$\underline{H}_a$H$_b$), 1.49-1.79 (11H, m, 4 x CH_2 + 2 x C$H_a\underline{H}_b$ + 2 x OH), 1.99 (1H, ddd, J = 4.7, 9.8, 10.6 Hz, CH), 2.57 (2H, m, 2 x C$\underline{H}_a$H$_b$N), 2.73 (2H, m, 2 x C$H_a\underline{H}_b$N), 3.59 (1H, m, C$\underline{H}$N), 3.76 (1H, m, C$\underline{H}$OH), 5.00 (1H, d, J = 9.8 Hz, PhC$\underline{H}$OH), 7.24-7.50 (5H, m, Ph).

^{13}C NMR: (62.5MHz) δ = 17.98, 20.28, 24.63, 26.31, 32.75 (7 x CH_2), 51.37 (CH), 69.47 (CH), 71.70 (CH), 75.72 (CH), 126.60, 127.43, 128.36 (5 x CH), 143.93 (C).

IR (NaCl): ν_{max} = 3407 (O-H), 3018, 2932 (C-H), cm^{-1}.

MS (CI): 276 (40%, $[M+H]^+$), 86 (100%, $[C_5H_{12}N]^+$).

HRMS: $C_{17}H_{26}NO_2$ ($[M+H]^+$) requires 276.1964, found 276.1964.

Data for 189b: Yield: 0.110 g, 38%. M. pt: 77-80°C (ethyl acetate), R_f = 0.07 (10% methanol in ethyl acetate).

^{1}H NMR: (250MHz) δ = 1.46-2.09 (13H, m, 5 x CH_2 + CH + 2 x OH), 2.54 (2H, m, 2 x C$\underline{H}_a$H$_b$N), 2.79 (2H, m, 2 x C$H_a\underline{H}_b$N), 2.98 (1H, m, C$\underline{H}$N), 3.81 (1H, ddd, J = 5.0, 6.7, 8.0 Hz, C$\underline{H}$OH), 4.61 (1H, d, J = 9.6 Hz, PhC$\underline{H}$OH), 7.28-7.45 (5H, m, Ph).

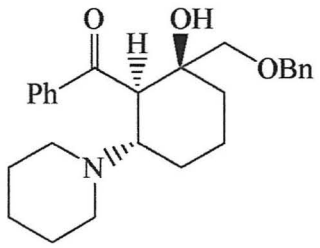
^{13}C NMR: (62.5MHz) δ = 19.16, 24.54, 26.27, 31.04 (7 x CH_2), 54.75 (CH), 71.84 (CH), 72.02 (CH), 80.16 (CH), 126.68, 128.17, 128.90 (5 x CH), 143.80 (C).

IR (NaCl): ν_{max} = 3372 (O-H), 3017, 2935 (C-H), cm^{-1}.

MS (CI): 276 (100%,$[M+H]^+$).

HRMS: $C_{17}H_{26}NO_2$ ($[M+H]_+$) requires 276.1964, found 276.1964.

1S, 2R, 3S/1R, 2S, 3R-2-Benzoyl-1-benzyloxymethyl-3-(N-piperidyl)cyclohexan-1-ol (217)



Substrate **215** (81.4 mg; 0.253 mmol) in $CDCl_3$ (0.5 ml) with piperidine (25.8 mg; 0.303 mmol) after 6 days gave **217** (61.5 mg, 60%; 15% ether in petrol, R_f = 0.12 (15% ether in petrol). M. pt: 154°C (petrol).

^{1}H NMR: (250MHz) δ = 0.73-1.87 (12H, m, 6 x CH_2), 2.24 (2H, m, 2 x $C\underline{H_a}H_bN$), 2.47 (2H, m, 12H, $CH_a\underline{H_b}N$), 3.26 (3H, m, $C\underline{H}N$ + $C\underline{H_2}O$), 3.86 (1H, d, J = 11.6 Hz, CH), 4.33 (2H, s, $OC\underline{H_2}Ph$), 5.00 (1H, br s, $CHO\underline{H}$), 7.14-7.94 (10H, m, Ph).

^{13}C NMR: (62.5MHz) δ = 19.72 (CH_2), 23.62 (CH_2), 24.57 (CH_2), 25.71 (CH_2), 29.63 (CH_2), 49.23 (CH_2), 49.23 (CH), 50.07 (CH_2), 65.73 (CH), 73.39 (CH_2), 74.58 (C), 77.87 (CH_2), 125.96-128.50 (9 x CH), 132.44 (CH), 137.82 (C), 139.87 (C), 210.09 (C=O).

IR (NaCl): ν_{max} = 3451 (O-H), 2926, 2851, 2801 (C-H), 1646.4 (C=O) cm^{-1}.

MS (CI): 409 (2%, $[M + H]^+$, 408 (5%, $[M]^+$, 86 (100%, $[C_5H_{12}N]^+$.

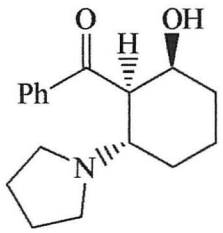
HRMS: $C_{26}H_{33}O_3N$ ($[M]^+$) requires 407.2460, found 407.2464.

Microanalysis: found C = 76.33; H = 8.47; N = 3.43, $C_{26}H_{33}O_3N$ requires C = 76.62; H = 8.16; N = 3.57.

6.3.4 General conditions for the addition reactions of secondary amines to 180

The substrate **180** (typically 100 mg) was dissolved in $CDCl_3$ (1 ml) and the required secondary amine (1.1 equivalents) added. After agitation, the reaction was followed by proton NMR. For results see Table 8.

1S, 2R, 3S/1R, 2S, 3R-2-Benzoyl-3-(N-pyrrolidinyl)cyclohexan-1-ol (225)

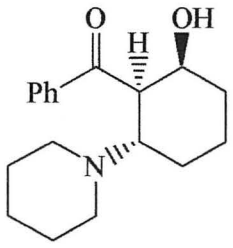


See: General method for addition reaction of secondary amines to **180**.

Partial NMR data (as in Table 8, page 73):

^{1}H NMR: (250MHz) δ = 3.47 (1H, ddd, J = 3, 11, 11 Hz, CH), 3.57 (1H, dd, J = 2, 11 Hz, CH), 4.18 (1H, br m, CH).

1S,2R,3S/1R,2S,3R-2-Benzoyl-3-(N-piperidyl)cyclohexan-1-ol (214)

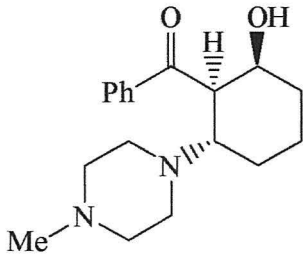


See: General method for addition reaction of secondary amines to **180**.

Partial NMR data (as in Table 8, page 73):

^{1}H NMR: (250MHz) δ = 3.20 (1H, ddd, J = 3, 12, 12 Hz, CH), 3.60 (1H, dd, J = 2, 12 Hz, CH), 4.20 (1H, br m, CH).

1S, 2R, 3S/1R, 2S, 3R-2-Benzoyl-3-(N-methylpiperazinyl)cyclohexan-1-ol (226)

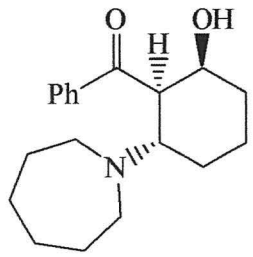


See: General method for addition reaction of secondary amines to **180**.

Partial NMR data (as in Table 8, page 73):

^{1}H NMR: (250MHz) δ = 3.47 (1H, ddd, J = 3, 11, 11 Hz, CH), 3.68 (1H, dd, J = 2, 11 Hz, CH), 4.14 (1H, br m, CH).

1S, 2R, 3S/1R, 2S, 3R-2-Benzoyl-3-(N-homopiperidinyl)cyclohexan-1-ol (227)

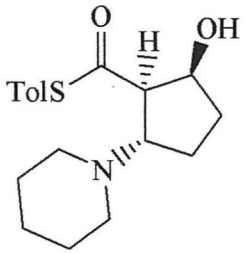


See: General method for addition reaction of secondary amines to **180**.

Partial NMR data (as in Table 8, page 73):

^{1}H NMR: (250MHz) δ = 3.30 (obscured), 3.58 (1H, dd, J = 2, 11 Hz, CH), 4.17 (1H, br m, CH).

1S, 2R, 3S/1R, 2S, 3R-(S-Tolylthiocarboxy)-3-(N-piperidinyl)cyclopentan-1-ol (230)



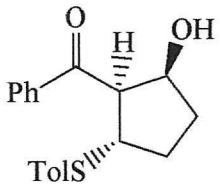
See: General conditions for the addition reactions of secondary amines.

Substrate **211** (100.4 mg; 0.427 mmol) and piperidine (46.90 mg; 0.556 mmol) gave the product **230** (13.6 mg, 10%) after chromatography in 10% ether in petrol (R_f = 0.74).

The product was tentatively identified by proton NMR.

^{1}H NMR: (250MHz) δ = 3.10 (1H, t, J = 7.7 Hz, CH), 3.50 (1H, m, CH), 3.75 (1H, m, C<u>H</u>OH).

1S, 2R, 3S/1R, 2S, 3R-2-Benzoyl-1-(S-tolyl)cyclopentan-3-ol (231)



See: General method for thiol and thiolate reactions.

Substrate **174** (100 mg; 0.53 mmol) and *p*-TolSH (85 mg; 0.69 mmol) gave the product **231** (127.6 mg, 77%) after chromatography in 15% EtOAc in petrol (R_f = 0.2) as an oil.

^{1}H NMR: (250MHz) δ = 1.86 (2H, m, CH_2), 2.13 (1H, m, $C\underline{H}_aH_b$), 2.26 (3H, s, CH_3), 2.48 (1H, m, $CH_a\underline{H}_b$), 2.69 (1H, br s, OH), 3.89 (1H, dd, J = 5.3, 8.3 Hz, CH), 4.19 (1H, ddd, J = 6.3, 8.3, 8.3 Hz, CH), 4.59 (1H, m, CH), 6.96-7.88 (9H, m, 9 x ArCH).

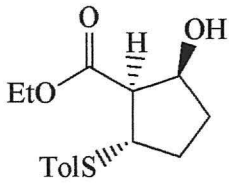
^{13}C NMR: (62.5MHz) δ = 20.85 (CH_3), 30.88 (CH_2), 34.93 (CH_2), 48.28 (CH), 57.79 (CH), 75.15 (CH), 128.20, 128.38, 129.44, 132.44, 133.28 (9 x ArCH), 130.77, 137.10 (C), 137.19 (C), 200.76 (C).

IR (NaCl): ν_{max} = 3372 (O-H), 2920 (C-H), 1677 (C=O) cm^{-1}.

MS (CI): 330 (3%, $[M+NH_4]^+$), 313 (10%, $[M+H]^+$).

HRMS (EI): $C_{19}H_{20}O_2S$ ($[M]^+$) requires 312.1184, found 312.1171.

1S, 2R, 3S/1R, 2S, 3R-2-Carboethoxy-1-(S-tolyl)cyclopentan-3-ol (232)



See: General method for thiol and thiolate reactions.

Substrate **175** (206.6 mg; 1.324 mmol), *p*-TolSH (328 mg; 2.7 mmol) and *p*-TolSNa (40 mg; 0.27 mmol) gave the product **232** (283 mg, 72%) after chromatography in 30% ether in petrol (R_f= 0.06) as crystals. M. pt: 39-42°C (ether/petrol).

^{1}H NMR: (250MHz) δ = 1.23 (3H, t, J = 7.1 Hz, CH_3), 1.60-2.00 (3H, m, CH_2 + $C\underline{H}_aH_b$), 2.33 (3H, s, CH_3), 2.36 (1H, m, $CH_a\underline{H}_b$), 2.76 (1H, dd, J = 5.0, 9.0 Hz, CH), 2.86 (1H, br s, CHO$\underline{H}$), 3.97 (1H, m, CH), 4.10 (2H, m, CH_2), 4.47 (1H, m, CH), 7.10 (2H, d, J = 8.0 Hz, 2 x CH), 7.33 (2H, d, J = 8.0 Hz, 2 x CH).

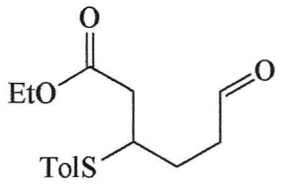
^{13}C NMR: (62.5MHz) δ = 14.08 (CH_3), 21.05 (CH_3), 30.84 (CH_2), 33.64 (CH_2), 47.30 (CH), 56.41 (CH), 61.05 (CH_2), 74.10 (CH), 129.56 (2 x CH), 130.90 (CH), 132.70 (2 x CH), 137.40 (C), 173.40 (C).

IR (NaCl): ν_{max} = 3429 (O-H), 2973, 2927 (C-H), 1735 (C=O) cm^{-1}.

MS (CI): 298 (20%, $[M+NH_4]^+$), 281 (10%, $[M+H]^+$).

HRMS (CI): $C_{15}H_{21}O_3S$ ($[M+H]^+$) requires 281.1211, found 281.1212.

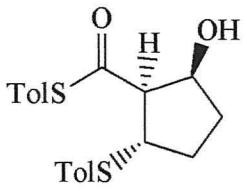
3-(4-Methyl-cyclohexylsulfanyl)-6-oxo-hexanoic acid ethyl ester (233)



See: General method for thiol and thiolate reactions and reaction conditions for **232**.

^{1}H NMR: (250MHz) δ = 1.23 (3H, t, J = 7.1 Hz, CH_3), 1.60-2.00 (2H, m, CH_2), 2.33 (3H, s, CH_3), 2.36-2.76 (4H, m, 2 x CH_2), 3.50 (1H, m, CHS), 4.20 (2H, q, J = 7.1 Hz, CH_2), 7.00-7.50 (4H, m, Ph), 9.80 (1H, s, CHO).

1S, 2R, 3S/1R, 2S, 3R-1-(S-Tolyl)-2-(S-tolylthiocarboxy)cyclopentan-3-ol (234)



See: General method for thiol and thiolate reactions.

Substrate **211** (149.1 mg; 0.637 mmol) and *p*-TolSH (232 mg; 1.91 mmol) gave the product **234** (128 mg, 56%) after chromatography in 30% ether in petrol (R_f = 0.04) as an oil which solidified on standing. M. pt: 63-69°C.

^{1}H NMR: (250MHz) δ = 1.68-2.16 (4H, m, 2 x CH_2), 2.35 (3H, s, CH_3), 2.86 (1H, br s, CHOH), 3.14 (1H, dd, J = 4.8, 8.8 Hz, CH), 4.04 (1H, ddd, J = 6.2, 8.8, 8.8 Hz, CHS), 4.55 (1H, m, CHOH), 7.00-7.40 (8H, m, 8 x CH).

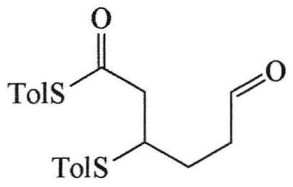
^{13}C NMR: (62.5MHz) δ = 21.15 (CH_3), 21.36 (CH_3), 30.86 (CH_2), 33.83 (CH_2), 47.64 (CH), 64.52 (CH), 75.19 (CH), 123.52 (C), 128.52 (2 x CH), 129.79 (2 x CH), 130.61 (C), 132.91 (2 x CH), 134.34 (2 x CH), 137.57 (C), 139.98 (C), 199.09 (C).

IR (NaCl): ν_{max} = 3349 (O-H), 2920 (C-H), 1711 (C=O) cm^{-1}.

MS (CI): 359 (30%, $[M+NH_4]^+$), 376 (100%, $[M+H]^+$).

HRMS (CI): $C_{20}H_{23}O_2S_2$ ($[M+H]^+$) requires 359.1139, found 359.1140.

4,6-Di-(S-tolyl)-6-oxoheptanal (235)



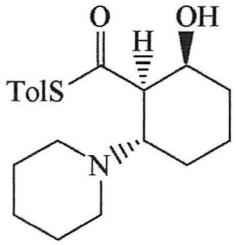
See: General method for thiol and thiolate reactions and reaction conditions for **234**.

Scale: 0.427 mol, 16.2 mg, 11%. Chromatography in 30% ether in petrol, $R_f = 0.21$.

^{1}H NMR (250 MHz): δ = 1.85 (1H, m, CH), 2.03 (1H, m, CH), 2.35, 2.38 (6H, 2 x s, 2 x CH_3), 2.70 (2H, m, CH_2), 2.80 (1H, dd, J = 8.0, 15.7 Hz, CH), 2.97 (1H, dd, J = 6.0, 15.7 Hz, CH), 3.48 (1H, m, C<u>H</u>S), 7.04-7.41 (8H, m, 4 x ArCH), 9.79 (1H, t, J = 1 Hz, CHO).

IR (NaCl): ν_{max} = 3022, 2919 (C-H), 2727 (CHO), 1721, 1703 (2 x C=O) cm^{-1}.

1S, 2R, 3S/1R, 2S, 3R-(S-Tolylthiocarboxy)-3-(N-piperidinyl)cyclohexan-1-ol (236)

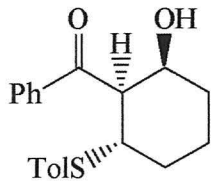


See: General conditions for the addition reactions of secondary amines.

Substrate **211** (105.0 mg; 0.427 mmol) and piperidine (48.20 mg; 0.556 mmol) gave the product **236** (ca. 5% as observed by proton NMR).

^{1}H NMR (250 MHz): δ = 1.19 (2H, m, CH_2), 1.37 (2H, m, CH_2), 1.51 (8H, m, 4 x CH_2), 2.11 (1H, br s, OH), 2.76-2.81 (1H, dd, J = 2.1, 11.3 Hz, CH), 2.28 (3H, s, CH_3), 2.32 (4H, m, 2 x CH_2), 3.47-3.57 (1H, ddd, J = 3.9, 11.5, 11.5 Hz, CH), 4.21 (1H, br m, C<u>H</u>OH), 7.01-7.35 (4H, m, Ph).

1S, 2R, 3S/1R, 2S, 3R-2-Benzoyl-1-(S-tolyl)cyclohexan-3-ol (237)



See: General method for thiol and thiolate reactions.

Substrate **180** (60 mg; 0.297 mmol) and *p*-TolSH (40 mg; 0.322 mmol) gave the product **237** (89.6 mg, 93%) after chromatography in 10% EtOAc in petrol (R_f = 0.13) as an oil.

^{1}H NMR: (C_6D_6, 250MHz) δ = 1.35 (1H, m, C$\underline{H}_a$H$_b$), 1.59 (2H, m, CH_2), 1.73 (1H, m, CH$_a\underline{H}_b$), 2.18 (1H, m, C$\underline{H}_a$H$_b$), 2.25 (3H, s, CH_3), 2.43 (1H, s, CH$_a\underline{H}_b$), 3.77 (1H, dd, J = 2.5, 11.5 Hz, CH), 3.93 (1H, br s, CHO$\underline{H}$), 4.20 (1H, m, CH), 4.22 (1H, ddd, J = 4.0, 11.5, 11.5 Hz, CHS), 7.03 (2H, d, J = 8.2 Hz, 2 x CH), 7.25-7.57 (5H, m, Ph), 8.18 (2H, d, J = 8.2 Hz, 2 x CH).

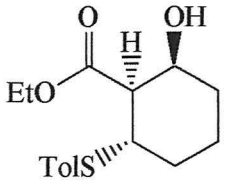
^{13}C NMR: (62.5MHz) δ = 19.57 (CH_2), 20.94 (CH_3), 31.10 (CH_2), 33.54 (CH_2), 44.97 (CH), 52.13 (CH), 67.11 (CH), 128.48, 128.57, 129.39, 133.51, 133.61 (9 x ArCH), 129.60, 137.00, 137.50 (3 x ArC), 204.50 (C).

IR (NaCl): ν_{max} = 3475 (O-H), 2950, 2900 (C-H), 1663 (C=O) cm^{-1}.

MS (EI): 326 (10%, $[M]^+$).

HRMS: $C_{20}H_{22}O_2S$ ($[M]^+$) requires 326.1341, found 326.1325.

1S, 2R, 3S/1R, 2S, 3R-2-Carboethoxy-1-(S-tolyl)cyclohexan-3-ol (238a)



See: General method for thiol and thiolate reactions.

Substrate (E)-**206** (213 mg; 1.253 mmol), *p*-TolSH (314 mg; 2.51 mmol) and *p*-TolSNa (37 mg; 0.25 mmol) gave the product **238a** (276 mg, 75%) after chromatography in 20 % ether in petrol ($R_f = 0.17$) as an oil.

^{1}H NMR: (250MHz) δ = 1.28 (2H, m, CH_2), 1.34 (3H, t, J = 7.0 Hz, CH_3), 1.52 (1H, m, $C\underline{H}_aH_b$), 1.83 (2H, m, CH_2), 2.30 (1H, m, $C\underline{H}_aH_b$), 2.35 (3H, s, CH_3), 2.53 (1H, dd, J = 1.9, 10.6 Hz, CH), 3.35 (1H, br s, CHO$\underline{H}$), 3.48 (1H, ddd, J = 4.0, 11.3, 11.3 Hz, SC$\underline{H}$), 4.18 (1H, m, C$\underline{H}$OH), 4.23 (2H, m, CH_2), 7.12 (2H, d, J = 8.0 Hz, 2 x CH), 7.38 (2H, d, J = 8.0 Hz, 2 x CH).

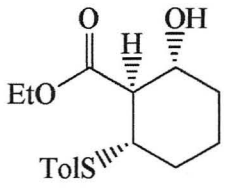
^{13}C NMR: (62.5MHz) δ = 14.16 (CH_3), 19.76 (CH_2), 21.11 (CH_3), 30.75 (CH_2), 32.68 (CH_2), 44.13 (CH), 52.54 (CH), 61.12 (CH_2), 67.23 (CH), 129.02 (C), 129.57 (2 x CH), 134.28 (2 x CH), 137.90 (C), 174.72 (C=O).

IR (NaCl): ν_{max} = 3508 (O-H), 2977, 2936, 2864 (C-H), 1724 (C=O) cm^{-1}.

MS (CI): 312 (100%, $[M+NH_4]^+$), 295 (45%, $[M+H]^+$).

HRMS (CI): $C_{16}H_{23}O_3S$ ($[M+H]^+$) requires 295.1368, found 295.1375.

1S, 2R, 3R/1R, 2S, 3S-2-Carboethoxy-1-(S-tolyl)cyclohexan-3-ol (238b)



See: General method for thiol and thiolate reactions.

A small quantity of **238b** (25.8 mg, 7%) was isolated as an oil by careful chromatography of the recovered column residues of the reaction to prepare **238a**.

^{1}H NMR: (250MHz) δ = 1.22 (2H, m, CH_2), 1.35 (3H, t, J = 7.0 Hz, CH_3), 1.74 (2H, m, CH_2), 1.98 (2H, m, CH_2), 2.33 (1H, dd, J = 11.5, 12.0 Hz, CH), 2.35 (3H, s, CH_3), 3.01 (1H, ddd, J = 3.6, 12.0, 12.0 Hz, SC<u>H</u>), 3.80 (1H, ddd, J = 4.3, 11.5, 11.5 Hz, CHOH), 4.26 (2H, m, CH_2), 7.13 (2H, d, J = 8.0 Hz, 2 x CH), 7.40 (2H, d, J = 8.0 Hz, 2 x CH).

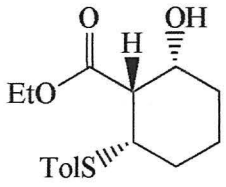
^{13}C NMR: (62.5MHz) δ = 14.27 (CH_3), 21.14 (CH_3), 23.19 (CH_2), 32.41 (CH_2), 33.85 (CH_2), 47.31 (CH), 57.91 (CH), 60.88 (CH_2), 72.53 (CH), 128.48 (C), 129.55 (2 x CH), 134.97 (2 x CH), 138.20 (C), 173.46 (C=O).

IR (NaCl): ν_{max} = 3442 (O-H), 2924, 2853 (C-H), 1732 (C=O) cm^{-1}.

MS (CI): 312 (100%, $[M+NH_4]^+$), 295 (10%, $[M+H]^+$).

HRMS (CI): $C_{16}H_{23}O_3S$ ($[M+H]^+$) requires 295.1368, found 295.1367.

1S, 2S, 3R/1R, 2R, 3S-2-Carboethoxy-1-(S-tolyl)cyclohexan-3-ol (238c)



See: General method for thiol and thiolate reactions.

A small quantity of **238c** (18.5 mg, 5%) was isolated as a solid by careful chromatography of the recovered column residues of the reaction to prepare **238a**. M. pt: 63-68°C.

^{1}H NMR: (250MHz) δ = 1.20-1.70 (3H, m, CH_2 + $C\underline{H}_a\underline{H}_b$), 1.27 (3H, t, J = 7.0 Hz, CH_3), 1.85-2.20 (3H, m, CH_2 + $CH_a\underline{H}_b$), 2.29 (3H, s, CH_3), 2.92 (1H, br s, CHO$\underline{H}$), 2.98 (1H, dd, J = 3.7, 4.5 Hz, CH), 3.44 (1H, m, C$\underline{H}$S), 4.08 (1H, m, C$\underline{H}$OH), 4.22 (2H, m, CH_2), 7.07 (2H, d, J = 8.0 Hz, 2 x CH), 7.30 (2H, d, J = 8.0 Hz, 2 x CH).

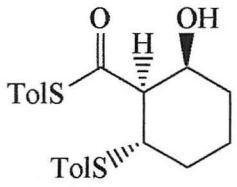
^{13}C NMR: (62.5MHz) δ = 14.24 (CH_3), 18.14 (CH_2), 21.05 (CH_3), 29.98 (CH_2), 30.56 (CH_2), 48.04 (CH), 50.57 (CH), 60.89 (CH_2), 67.72 (CH), 129.57 (C), 129.63 (2 x CH), 132.40 (2 x CH), 137.19 (C), 174.00 (C=O).

IR (NaCl): ν_{max} = 3436 (O-H), 2927, 2855 (C-H), 1730 (C=O) cm^{-1}.

MS (CI): 312 (75%, $[M+NH_4]^+$), 295 (35%, $[M+H]^+$).

HRMS (CI): $C_{16}H_{23}O_3S$ ($[M+H]^+$) requires 295.1368, found 295.1365.

1S, 2R, 3S/1R, 2S, 3R-2-(S-Tolylthiocarboxy)-1-(S-tolyl)cyclohexan-3-ol (239a)



See: General method for thiol and thiolate reactions.

Substrate **212** (72.3 mg; 0.292 mmol), *p*-TolSH (73.4 mg; 0.58 mmol) and *p*-TolSNa (8.6 mg; 0.06 mmol) gave the product **239a** (69 mg, 60%) after chromatography in 20% ether in petrol ($R_f = 0.16$) as an oil.

^{1}H NMR: (250MHz) δ = 1.22-2.21 (6H, m, 3 x CH_2), 2.36 (3H, s, CH_3), 2.40 (3H, s, CH_3), 2.87 (1H, dd, J = 2.2, 10.9 Hz, CH), 2.88 (1H, br s, OH), 3.60 (1H, ddd, J = 4.0, 10.9, 11.7 Hz, C<u>H</u>S), 4.30 (1H, m, C<u>H</u>OH), 7.11-7.42 (8H, m, 8 x CH).

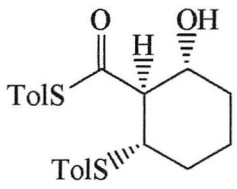
^{13}C NMR: (62.5MHz) δ = 19.62 (CH_2), 21.14 (CH_3), 21.37 (CH_3), 30.93 (CH_2), 33.15 (CH_2), 43.96 (CH), 60.49 (CH), 67.86 (CH), 123.56 (C), 129.57 (2 x CH), 130.10 (2 x CH), 133.84 (2 x CH), 134.27 (2 x CH), 137.80 (C), 140.08 (2 x C), 201.35 (C=O).

IR (NaCl): ν_{max} = 3520 (O-H), 3021, 2937, 2864 (C-H), 1706/1679 (C=O) cm^{-1}.

MS (CI): 390 (100%, $[M+NH_4]^+$), 373 (20%, $[M+H]^+$).

HRMS (CI): $C_{21}H_{25}O_2S_2$ ($[M+H]^+$) requires 373.1296, found 373.1295.

1S, 2R, 3R/1R, 2S, 3S-2-(S-Tolylthiocarboxy)-1-(S-tolyl)cyclohexan-3-ol (239b)



See: General method for thiol and thiolate reactions.

A small quantity of **239b** (8 mg, 7%) was isolated as an oil by careful chromatography of the recovered column residues of the reaction to prepare **239a**.

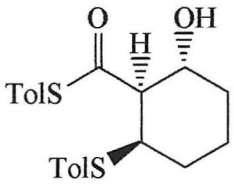
^{1}H NMR: (250MHz) δ = 1.20-2.10 (7H, m, 3 x CH_2 + OH), 2.35 (3H, s, CH_3), 2.39 (3H, s, CH_3), 2.69 (1H, dd, J = 9.7, 11.4 Hz, CH), 3.14 (1H, ddd, J = 2.5, 11.4, 11.6 Hz, CHS), 3.88 (1H, ddd, J = 4.0, 9.0, 9.8 Hz, C<u>H</u>OH), 7.00-7.55 (8H, m, 8 x CH).

IR (NaCl): ν_{max} = 3440 (O-H), 2921, 2844 (C-H), 1703 (C=O) cm^{-1}.

MS (CI): 390 (50%, $[M+NH_4]^+$), 373 (5%, $[M+H]^+$).

HRMS (CI): $C_{21}H_{28}NO_2S_2$ ($[M+NH_4]^+$) requires 390.1561, found 390.1562.

1R, 2R, 3R/1S, 2S, 3S-2-(S-Tolylthiocarboxy)-1-(S-tolyl)cyclohexan-3-ol (239c)



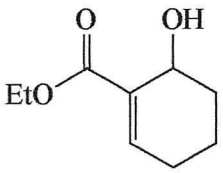
See: General method for thiol and thiolate reactions.

A small quantity of **239c** (ca. 7 mg, ca. 6%) contaminated with **239a** was isolated by careful chromatography of the recovered column residues of the reaction to prepare **239a**.

Selected data:

^{1}H NMR: (250MHz) δ = 3.04 (1H, dd, J = 4.3, 9.4 Hz, CH), 3.95 (1H, br m, CHS), 4.22 (1H, m, C<u>H</u>OH).

Carboethoxy-1-hydroxycyclohex-2-ene (240)



See: General method for phosphine reactions.

Column solvent: 30% ether in petrol, $R_f = 0.10$ (30% ether in petrol).

^{1}H NMR: (250MHz) $\delta = 1.31$ (3H, t, J = 7.1 Hz, CH_3), 1.43-1.85 (5H, m, 2 x CH_2 + OH), 2.09-2.32 (2H, m, CH_aH_b), 4.23 (2H, q, J = 7.1 Hz, CH_2), 4.55 (1H, m, C<u>H</u>OH), 7.11 (1H, t, J = 2.0 Hz, CH).

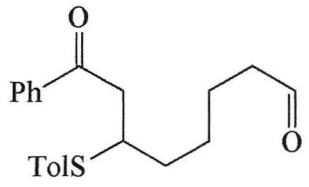
^{13}C NMR: (62.5MHz) δ = 14.19 (CH_3), 17.42 (CH_2), 26.05 (CH_2), 29.82 (CH_2), 60.55 (CH_2), 63.41 (CH), 132.37 (C), 142.78 (CH), 167.50 (C=O).

IR (NaCl): ν_{max} = 3460 (O-H), 2971, 2938, 2867 (C-H), 1712 (C=O), 1646 (C=C) cm^{-1}.

MS (CI): 188 (70%, $[M+NH_4]^+$), 171 (100%, $[M+H]^+$).

HRMS: $C_9H_{15}O_3$ ($[M+H]^+$) requires 171.1021, found 171.1020.

6-(4-Methyl-cyclohexylsulfanyl)-8-oxo-8-phenyl-octanal (241)

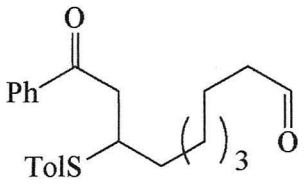


See: General method for thiol and thiolate reactions.

Substrate **199** (261.6 mg; 1.211 mmol), *p*-TolSH (309.1 mg; 2.422 mmol) and *p*-TolSNa (36.3 mg; 0.242 mmol) gave the product **241** (323.1 mg, 79%) after chromatography in 20% ether in petrol ($R_f = 0.08$) as an oil.

^{1}H NMR: (250MHz) δ = 1.50-1.80 (6H, m, CH_2), 2.30 (3H, s, CH_3), 2.40-2.50 (2H, m, CH_2), 3.10 (1H, dd, J = 5.9, 14.7 Hz, CH) 3.30 (1H, dd, J = 7.4, 14.7 Hz, CH), 3.65-3.80 (1H, br m, CHS), 7.00-7.90 (9H, m, Ph), 9.70 (1H, s, CHO).

8-(4-Methyl-cyclohexylsulfanyl)-10-oxo-10-phenyl-decanal (242)



See: General method for thiol and thiolate reactions.

Substrate **205** (272.7 mg; 1.118 mmol), *p*-TolSH (280.1 mg; 2.235 mmol) and *p*-TolSNa (34.80 mg; 0.224 mmol) gave the product **242** (324.6 mg, 79%) after chromatography in 20% ether in petrol ($R_f = 0.15$) as an oil.

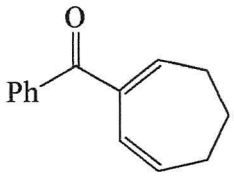
^{1}H NMR: (250MHz) δ = 1.35 (4H, 2 x s, 2 x CH_2), 1.52-1.67 (4H, m, 2 x CH_2), 2.33 (3H, s, CH_3), 2.38-2.45 (2H, m, CH_2), 3.10 (1H, dd, J = 5.1, 17.1 Hz, CH), 3.29 (1H, dd, J = 6.8, 17.1 Hz, CH), 3.72 (1H, br s, C<u>H</u>S), 7.09-7.90 (9H, m, Ph), 9.75-9.77 (3H, t, J = 1.8 Hz, CHO).

IR (NaCl): ν_{max} = 3024, 2930, 2855 (C-H), 2719 (CHO), 1723 (C=O), 1682 (C=O) cm^{-1}.

MS (CI): 386.3 (40%, $[M+NH_4]^+$), 369.3 (10%, $[M+H]^+$), 262.3 (100%, M^+-PhCOH), 245.2 (90%, M^+-TolS).

HRMS: $C_{23}H_{28}O_2S$ ($[M+NH_4]^+$) requires 386.2154, found 386.2153.

2-Benzoylcyclo-1,3-heptadiene (244)



See: General method for phosphine reactions.

Substrate **199** (200.8 mg; 0.930 mmol) and tributylphosphine (37.62 mg; 0.186 mmol) gave the product **243** (142.6 mg, 77%) after chromatography in 20% ether in petrol ($R_f = 0.13$) as an oil.

^{1}H NMR: (250MHz) δ = 1.94 (2H, m, CH_2), 2.37-2.53 (4H, m, 2 x CH_2), 6.06 (1H, dt, J = 5.2, 11.9 Hz, CH), 6.33 (1H, dd, J = 1.2, 11.9 Hz, CH), 6.57 (1H, br t, J = 5.2 Hz, CH), 7.38-7.58 (3H, m, Ph), 7.66-7.76 (2H, m, Ph).

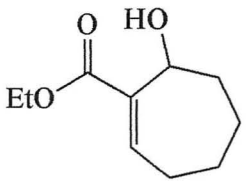
^{13}C NMR: (62.5MHz) δ = 25.70 (CH_2), 30.98 (CH_2), 31.71 (CH_2), 123.29 (CH), 128.04 (2 x CH), 129.58 (2 x CH), 131.75 (CH), 135.33 (CH), 137.89 (C), 138.21 (C), 145.34 (CH), 198.22 (C=O).

IR (NaCl): ν_{max} = 3027, 2926, 2881 (C-H), 1651 (C=O/C=C) cm^{-1}.

MS (CI): 216 (100%, $[M+NH_4]^+$), 199 (70%, $[M+H]^+$).

HRMS: $C_{14}H_{15}O$ ($[M+H]^+$) requires 199.1123, found 199.1122.

2-Carboethoxy-1-hydroxycyclohept-2-ene (245)



See: General method for phosphine reactions.

Column solvent: 10% ether in petrol, $R_f = 0.05$.

^{1}H NMR: (250MHz) δ = 1.31 (3H, t, J = 7.3 Hz, CH_3), 1.50-2.10 (6H, m, 3 x CH_2), 2.20-2.55 (2H, m, CH_2), 3.13 (1H, br s, CHOH), 4.22 (2H, q, J = 7.3 Hz, CH_2), 4.81 (1H, m, CHOH), 7.11 (1H, t, J = 6.4 Hz, CH).

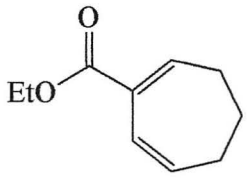
^{13}C NMR: (62.5MHz) δ = 14.19 (CH_3), 23.50 (CH_2), 25.66 (CH_2), 27.28 (CH_2), 32.36 (CH_2), 60.82 (CH_2), 68.70 (CH), 136.77 (C), 145.17 (CH), 168.40 (C=O).

IR (NaCl): ν_{max} = 3450 (O-H), 2981, 2930, 2857 (C-H), 1702 (C=O), 1642 (C=C) cm^{-1}.

MS (CI): 202 (90%, $[M+NH_4]^+$), 185 (100%, $[M + H]^+$.

HRMS: $C_{10}H_{17}O_3$ ($[M+H]^+$) requires 185.1178, found 185.1179.

2-Carboethoxy-1,3-heptadiene (246)



See: General method for phosphine reactions.

Column solvent: 5% ether in petrol, $R_f = 0.48$ (20% ether in petrol).

^{1}H NMR: (250MHz) δ = 1.30 (3H, t, J = 7.0 Hz, CH_3), 1.90 (2H, m, CH_2), 2.35 (2H, m, CH_2), 2.45 (2H, m, CH_2), 4.23 (2H, q, J = 7.0 Hz, CH_2), 5.98 (1H, dt, J = 5.4, 11.6 Hz, CH), 6.38 (1H, br d, J = 1.5, 11.6 Hz, CH), 7.14 (1H, t, J = 5.5 Hz, CH).

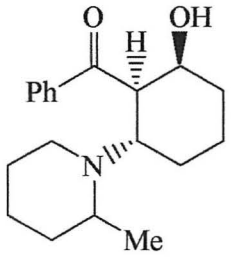
^{13}C NMR: (62.5MHz) δ = 14.21 (CH_3), 25.89 (CH_2), 30.62 (CH_2), 31.39 (CH_2), 60.67 (CH_2), 122.88 (CH), 128.39 (C), 134.66 (CH), 143.61 (CH), 167.72 (C=O).

IR (NaCl): ν_{max} = 3023, 2981, 2932 (C-H), 1708 (C=O), 1607 (C=C) cm^{-1}.

MS (CI): 184 (70%, $[M+NH_4]^+$).

HRMS: $C_{10}H_{18}NO_2$ ($[M+NH_4]^+$) requires 184.1338, found 184.1339.

1S,2R,3S/1R,2S,3R-2-Benzoyl-3-(N-2'-methylpiperidyl)cyclohexan-1-ol (247)



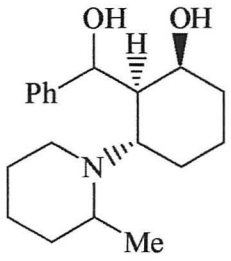
See: General method for the Baylis-Hillman reactions with secondary amines.

^{1}H NMR (250 MHz): δ = key signals: 3.20 (1H, ddd, J = 3.0, 11.0, 11.0 Hz, CH), 3.62 (1H, dd, 2.5, 11.0 Hz, CH), 4.19 (1H, br m, CH).

^{13}C NMR (62.5 MHz): δ = 19.17 (CH_2), 20.78 (CH_3), 23.67 (CH_2), 24.92 (CH_2), 25.46 (CH_2), 31.78 (CH_2), 35.86 (CH_2), 46.53 (CH_2), 49.50 (CH), 53.94 (CH), 55.19 (CH), 68.02 (CH), 127.65, 128.42, 132.64 (5 x ArCH), 209.10 (C).

This was used in the next reaction (page 149) without further purification.

1S,2R,3S/1R,2S,3R-2-(Benzyl-1-hydroxy)-3-(N-2'-methylpiperidyl)cyclohexan-1-ol (248)



2-Methylpiperidine (135.0 mg; 1.361 mmol) in chloroform (1.5 ml) was added to enone **180** (250 mg; 1.237 mmol) dissolved in chloroform (1.5 ml) and the solution was allowed to stir for 4 days. Sodium borohydride (234 mg; 6.185 mmol) was then dissolved in methanol (10 ml) and this was added to the cooled (0°C) reaction mixture. After stirring overnight, the reaction was adsorbed onto silica gel (4 g) and the product eluted by column chromatography in (100% ether, 50% ether in EtOAc and 100% ethyl acetate) to give **248** (227.6 mg, 61%) as a solid.

M. pt: 138°C.

^{1}H NMR: (250MHz) δ = 1.08-1.82 (15 H, m,), 1.27 (3H, d, J = 6.3 Hz, CH_3), 2.27 (1H, ddd, J = 11.6, 9.4, 2.4 Hz, CH), 2.66 (1H, m, CH), 3.14 (1H, br m, CH), 3.49 (br d, J = 1.0 Hz, OH), 3.72 (1H, ddd, J = 3.3, 11.6, 11.6 Hz, CH), 4.94 (1H, d, J = 9.4 Hz, CH), 7.27-7.69 (5H, m, Ph).

^{13}C NMR (62.5 MHz): δ = 19.09 (CH_2), 21.14 (CH_3), 23.48 (CH_2), 24.93 (CH_2), 25.91 (CH_2), 33.60 (CH_2), 36.25 (CH_2), 46.48 (CH_2), 47.24 (CH), 53.74 (CH), 56.06 (CH), 67.73 (CH), 77.89 (CH), 127.26, 127.41, 128.14 (5 x ArCH), 143.12 (C).

IR (NaCl): ν_{max} = 3420 (O-H), 3064, 2934, 2858 (C-H) cm^{-1}.

MS(CI): 304 (5%, $[M+H]^+$).

HRMS: $C_{19}H_{30}O_2N$ ($[M+H]^+$) requires 304.2277, found 304.2298.

7 References

1. T. –L. Ho, *Tandem Organic Reactions*, 1992, 1.

2. K. E. Ziegler, J. A. Schwartz, *Tetrahedron Lett.*, 1975, 4643.

3. G. B. Mpango, V. Snieckus, *Tetrahedron Lett.*, 1980, **21**, 4827.

4. J. F. G. A. Jansen, B. L. Feringa, *Tetrahedron Lett.*, 1991, **32**, 27, 3239.

5. F. Näf, R. Decorzant, W. Thommen, *Helv. Chim. Acta.*, 1975, **58**, 1808.

6. K. Tanaka, F. Uchiyama, K. Sakamoto, Y. Inubushi, *J. Am. Chem. Soc.*, 1982, **104**, 4965.

7. C. Schneider, *Synlett*, 2001, 13.

8. C. Schneider, O. Reese, *Synthesis*, 2000, 1689.

9. C. Schneider, O. Reese, *Angew. Chem.*, 2000, **112**, 3074.

10. C. Schneider, O. Reese, *Angew. Chem. Int. Ed. Engl.*, 2000, **39**, 2948.

11. C. Schneider, *Synlett*, 1997, 815.

12. C. Schneider, A. Schuffenhauer, *Eur. J. Org. Chem.*, 2000, 73.

13. C. Schneider, C. Börner, *Synlett*, 1998, 652.

14. C. Schneider, C. Börner, A. Schuffenhauer, *Eur. J. Org. Chem.*, 1999, 3353.

15. Y. Yamamoto, K. Maruyama, *J. Am. Chem. Soc.*, 1978, **100**, 3240.

16. Y. Yamamoto, S. Yamamoto, H. Yatagai, Y. Ishihara, K. Maruyama, *J. Org. Chem.*, 1982, **47**, 119.

17. D. A. Evans, K. T. Chapman, J. Bisaha, *J. Am. Chem. Soc.*, 1988, **110**, 1238.

18. S. Castellino, W. J. Dwight, *J. Am. Chem. Soc.*, 1993, **115**, 2986.

19. K. Morita, Z. Suzuki, H. Hirose, *Bull. Chem. Soc. Jpn.*, 1968, **41**, 2815.

20. T. Imagawa, K. Uemura, Z. Nagai, M. Kawanisi, *Synth. Commun.*, 1984, **14**, 1267.

21. S. Rafel, J. W. Leahy, *J. Org. Chem.*, 1997, **62**, 1521.

22. T. Hayase, T. Shibata, K. Soai, Y. Wakatsuki, *Chem. Commun.*, 1998, 1271.

23. S. Bertenshaw, M. Kahn, *Tetrahedron Lett.*, 1989, **30**, 2731.

24. F. Roth, P. Gygax, G. Frater, *Tetrahedron Lett.*, 1992, **33**, 1045.

25. Y. M. A. Yamada, S. Ikegami, *Tetrahedron Lett.*, 2000, **41**, 2165.

26. V. K. Aggarwal, G. J. Tarver, R. McCague, *Chem. Commun.*, 1996, 2713.

27. T. Kataoka, T. Iwama, S. Tsujiyama, *Chem. Commun.*, 1998, 197.

28. M. Kawamura, S. Kobayashi, *Tetrahedron Lett.*, 1999, **40**, 1539.

29. H. Amri, M. Rambaud, J. Villieras, *Tetrahedron Lett.*, 1989, **30**, 7381.

30. N. E. Leadbeater, 1999, King's College London, unpublished results (personal communication).

31. S. E. Drewes, G. H. P. Roos, *Tetrahedron*, 1988, **44**, 4653.

32. H. M. R. Hoffmann, J. Rabe, *Angew. Chem. Int. Ed. Engl.*, 1983, **22**, 795.

33. P. Perlmutter, M. Tabone, *J. Org. Chem.*, 1995, **60**, 6515.

34. E. M. Campi, A. Holmes, P. Perlmutter, C. C. Teo, *Aust. J. Chem.*, 1995, **48**, 1535.

35. T. Manickum, G. Roos, *Afr. J. Chem.*, 1994, **47**, 1.

36. P. Kündig, L. H. Xu, P. Romanens, G. Bernardinelli, *Tetrahedron Lett.*, 1993, **34**, 7049.

37. A. Gilbert, T. W. Heritage, N. S. Isaacs, *Tetrahedron:Asymmetry*, 1991, **2**, 969.

38. B. M. Trost, *Science*, 1983, **219**, 245.

39. B. M. Trost, *Science*, 1991, **256**, 1471.

40. A. B. Baylis, M. E. D. Hillman, German Patent, **2155113**, 1972, *Chem. Abstr.*, 1972, **77**, 34174q.

41. S. E. Drewes, N. D. Emslie, *J. Chem. Soc., Perkin Trans I*, 1982, 2079.

42. D. Basavaiah, V. V. L. Gowriswari, *Synth. Commun.*, 1987, **17**, 587.

43. H. Amri, J. Villieras, *Tetrahedron Lett.*, 1986, **27**, 36, 4307.

44. D. Basavaiah, V. V. L. Gowriswari, *Tetrahedron Lett.*, 1986, **27**, 2031.

45. D. Basavaiah, T. K. Bharathi, V. V. L. Gowriswari, *Synth. Commun.*, 1987, **17**, 1893.

46. P. Auvray, P. Knochel, J. F. Normant, *Tetrahedron Lett.*, 1986, **27**, 5095.

47. A. Weichert, H. M. R. Hoffmann, *J. Org. Chem.*, 1991, **56**, 4098.

48. S. –Z. Wang, K. Yamamoto, H. Yamada, T. Takahashi, *Tetrahedron*, 1992, **48**, 2333.

49. H. Amri, M. M. El Gaied, J. Villieras, *Synth. Commun.*, 1990, **20**, 659.

50. S. Tsuboi, S. Takatsuka, M. Utaka, *Chemistry Letters*, 1988, 2003.

51. S. Tsuboi, H. Kuroda, S. Takatsuka, T. Fukawa, T. Sakai, M. Utaka, *J. Org. Chem.*, 1993, **58**, 5952.

52. J. S. Hill, N. S. Isaacs, *Tetrahedron Lett.*, 1986, **27**, 5007.

53. H. M. R. Hoffmann, J. Rabe, *J. Org. Chem.*, 1985, **50**, 3849.

54. W. Poly, D. Schomburg, H. M. R. Hoffmann, *J. Org. Chem.*, 1988, **53**, 3701.

55. P. Perlmutter, T. D. McCarthy, *Aust. J. Chem.*, 1993, **46**, 253.

56. R. Fikentscher, E. Hahn, A. Kud, A. Oftring, *Chem. Abstr.*, 1987, **107**, 77815.

57. S. E. Drewes, G. Loizou, G. H. P. Roos, *Synth. Commun.*, 1987, **17**, 291.

58. H. –S. Byun, K. C. Reddy, R. Bittman, *Tetrahedron Lett.*, 1994, **35**, 1371.

59. C. R. Strauss, M. N. Galbraith, A. F. Faux, *Chem. Abstr.*, 1992, **116**, 128185v.

60. T. Janecki, *Synth. Commun.*, 1993, **23**, 641.

61. S. E. Drewes, N. D. Emslie, A. A. Khan, G. H. P. Roos, *Synth. Commun.*, 1989, **19**, 959.

62. F. Ameer, S. E. Drewes, S. Freese, P. T. Kaye, *Synth. Commun.*, 1988, **18**, 495.

63. D. Basavaiah, P. D. Rao, R. S. Hyma, *Tetrahedron*, 1996, **52**, 8001.

64. T. Jenn, D. Heissler, *Synlett.*, 1995, 607.

65. W. P. Almeida, F. Coelho, *Tetrahedron Lett.*, 1998, **39**, 8609.

66. Y. Fort, M. C. Berthe, P. Caubere, *Tetrahedron*, 1992, **48**, 6371.

67. J. Auge, N. Lubin, A. Lubineau, *Tetrahedron Lett.*, 1994, **35**, 7947.

68. M. K. Kundu, S. B. Mukherjee, N. Balu, R. Padmakumar, S. V. Bhat, *Synlett.*, 1994, 444.

69. J. S. Hill, N. S. Isaacs, *J. Chem. Res. Synop.*, 1988, 330.

70. P. Perlmutter, E. Puniani, G. Westman, *Tetrahedron Lett.*, 1996, **37**, 10, 1715.

71. A. Kamimura, Y. Gunjigake, H. Mitsudera, S. Yokoyama, *Tetrahedron Lett.*, 1998, **39**, 7323.

72. P. Perlmutter, C. C. Teo, *Tetrahedron Lett.*, 1984, **25**, 5951.

73. F. Rezgui, M. M. El Gaied, *Tetrahedron Lett.*, 1998, **39**, 5965.

74. J. R. Hwu, G. H. Hakimelahi, C. –T. Chou, *Tetrahedron Lett.*, 1992, **33**, 6469.

75. E. Ciganek, *Org. React.*, 1997, **51**, 201.

76. A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev.*, 1993, **93**, 1307.

77. R. S. Atkinson, J. Fawcett, D. R. Russell, P. J. Williams, *J. Chem. Soc., Chem. Commun*, 1994, 2031.

78. D. Basavaiah, A. K. D. Bhavani, S. Pandiaraju, P. K. S. Sarma, *Synlett.*, 1995, 243.

79. R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, L. Raimondi, *J. Org. Chem.*, 1995, **60**, 4697.

80. L. J. Brzezinski, S. Rafel, J. W. Leahy, *Tetrahedron*, 1997, **53**, 16423.

81. T. Oishi, H. Oguri, M. Hirama, *Tetrahedron:Asymmetry*, 1995, **6**, 1241.

82. S. E. Drewes, A. A. Khan, K. Rowland, *Synth. Commun.*, 1993, **23**, 183.

83. D. Basavaiah, V. V. L. Gowriswari, P. K. S. Sarma, P. D. Rao, *Tetrahedron Lett.*, 1990, **31**, 1621.

84. S. E. Drewes, N. D. Emslie, A. A. Khan, *Synth. Commun.*, 1993, **23**, 1215.

85. A. A. Khan, N. D. Emslie, S. E. Drewes, J. S. Field, N. Ramesar, *Chem. Ber.*, 1993, **126**, 1477.

86. S. E. Drewes, N. D. Emslie, N. Karodia, A. A. Khan, *Chem. Ber.*, 1990, **123**, 1447.

87. K. N. Jensen, G. H. P. Roos, *Afr. J. Chem.*, 1992, **45**, 112.

88. D. J. Ager, I. Prakash, D. R. Schaad, *Chem. Rev.*, 1996, **96**, 835.

89. M. C. Weismiller, J. C. Towson, F. A. Davis, *Org. Synth.*, 1990, **69**, 154.

90. J. C. Towson, M. C. Weismiller, G. S. Lal, A. C. Sheppard, F. A. Davis, *Org. Synth.*, 1990, **69**, 158.

91. G. J. Ho, D. J. Mathre, *J. Org. Chem.*, 1995, **60**, 2271.

92. K. S. Yang, K. Chen, *Organic Letters*, 2000, **2**, 729.

93. S. E. Drewes, T. Manickum, G. H. P. Roos, *Synth. Commun.*, 1988, **18**, 1065.

94. S. E. Drewes, O. L. Njamela, G. H. P. Roos, *Chem. Ber.*, 1990, **123**, 2455.

95. T. Manickum, G. H. P. Roos, *Synth. Commun.*, 1991, **21**, 2269.

96. S. K. Nayak, L. Thijs, B. Zwanenburg, *Tetrahedron Lett.*, 1999, **40**, 981.

97. B. Alcaide, P. Almendros, C. Aragoncillo, *Tetrahedron Lett.*, 1999, **40**, 7537.

98. A. Hosomi, T. Yanagi, M. Hojo, *Tetrahedron Lett.*, 1991, **32**, 2371.

99. S. G. Davies, D. R. Fenwick, *Chem. Commun.*, 1997, 565.

100. K. Hattori, M. Miyata, H. Yamamoto, *J. Am. Chem. Soc.*, 1993, **115**, 1151.

101. Y. Ito, Y. Kobayashi, T. Kawabata, M. Takase, S. Terashima, *Tetrahedron*, 1989, **45**, 5767.

102. S. E. Drewes, O. L. Njamela, N. D. Emslie, N. Ramesar, J. S. Field, *Synth. Commun.*, 1993, **23**, 2807.

103. M. Arend, B. Westermann, N. Risch, *Angew. Chem.*, 1998, **110**, 1096. *Angew. Chem. Int. Ed. Engl.*, 1998, **37**, 1044.

104. T. Kataoka, T. Iwama, S. –i. Tsujiyama, T. Iwamura, S. –i. Watanabe, *Tetrahedron*, 1998, **54**, 11813.

105. T. Kataoka, T. Iwama, S. –i. Tsujiyama, K. Kanematsu, T. Iwamura, S. –i. Watanabe, *Chemistry Letters,* 1999, 257.

106. T. Kataoka, T. Iwama, H. Kinoshita, S. Tsujiyama, Y. Tsurukami, T. Iwamura, S. Watanabe, *Synlett.*, 1999, 197.

107. D. Basavaiah, K. Muthukumaran, B. Sreenivasulu, *Synlett.*, 1999, 1249.

108. T. Iwama, H. Kinoshita, T. Kataoka, *Tetrahedron Lett.*, 1999, **40**, 3741.

109. J. I. Levin, *Synth. Commun.*, 1992, **22** (7), 961.

110. A. Itoh, S. Ozawa, K. Oshima, H. Nozaki, *Tetrahedron Lett.*, 1980, **21**, 361.

111. A. Kamimura, H. Mitsudera, S. Asano, A. Kakehi, M. Noguchi, *Chem. Commun.*, 1998, 1095.

112. H. Mitsudera, A. Kakehi, A. Kamimura, *Tetrahedron Lett.*, 1999, **40**, 7389.

113. A. Kamimura, Y. Omata, H. Mitsudera, A. Kakehi, *J. Chem. Soc. Perkin Trans I*, 2000, 4499.

114. X. –F. Yang, X. –L. Hou, L. –X. Dai, *Tetrahedron Lett.*, 2000, **41**, 4431.

115. M. Ono, K. Nishimura, Y. Nagaoka, K. Tomioka, *Tetrahedron Lett.*, 1999, **40**, 1509.

116. K. Nishimura, T. Ono, Y. Nagaoka, K. Tomioka, *J. Am. Chem. Soc.*, 1997, **119**, 12974.

117. K. Tomioka, M. Okuda, K. Nishimura, S. Manabe, M. Kanai, Y. Nagaoka, K. Koga, *Tetrahedron Lett.*, 1998, **39**, 2141.

118. O. Miyata, T. Shinada, I. Ninomiya, T. Naito, T. Date, K. Okamura, S. Inagaki, *J. Org. Chem.*, 1991, **56**, 6556.

119. R. Clauss, W. Hinz, R. Hunter, *Synlett.*, 1997, 57.

120. A. G. M. Barrett, A. Kamimura, *J. Chem. Soc., Chem. Commun.*, 1995, 1755.

121. D. M. Armistead, S. L. Danishefsky, *Tetrahedron Lett.*, 1987, **28**, 4959.

122. A. Itoh, S. Ozawa, K. Oshima, H. Nozaki, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 274.

123. S. Saito, Y. Hirohara, O. Narahara, T. Moriwake, *J. Am. Chem. Soc.*, 1989, **111**, 4533.

124. Y. Nagaoka, K. Tomioka, *Organic Letters*, 1999, **1**, 9, 1467.

125. J. G. Urones, N. M. Garrido, D. Diez, S. H. Dominguez, S. G. Davies, *Tetrahedron:Asymmetry*, 1999, **10**, 1637.

126. J. –K. Ergüden, H. W. Moore, *Organic Letters*, 1999, **1**, 3, 375.

127. P. J. Murphy, H. L. Williams, K. A. Malik, *J. Chem. Soc., Chem. Commun.*, 1993, 119.

128. P. J. Murphy, H. L. Williams, *J. Chem. Soc., Chem. Commun.*, 1993, 819.

129. P. J. Murphy, H. L. Williams, D. E. Hibbs, M. B. Hursthouse, K. M. A. Malik, *Tetrahedron*, 1996, **52**, 8315.

130. G. P. Black, F. Dinon, S. Fratucello, P. J. Murphy, M. Nielsen, H. L. Williams, *Tetrahedron Lett.*, 1997, **38**, 8561.

131. F. Dinon, *Erasmus Report*, Bangor, 1997.

132. J. Fakstorp, D. Raleigh, L. E. Schniepp, *J. Am. Chem. Soc.*, 1950, **72**, 869.

133. G. E. Keck, E. P. Boden, S. A. Mabury, *J. Org. Chem.*, 1985, **50**, 709.

134. F. Dinon, E. Richards, P. J. Murphy, D. E. Hibbs, M. B. Hursthouse, K. M. A. Malik, *Tetrahedron Lett.*, 1999, **40**, 3279.

135. E. L. Richards, P. J. Murphy, F. Dinon, S. Fratucello, P. M. Brown, T. Gelbrich, M. B. Hursthouse, *Tetrahedron*, 2001, **57**, 7771.

136. This material was prepared from cyclopent-1-ene-1-methanol[137] which was benzylated (NaH, BnBr, TBAI, THF; 69%), ozonised (O_3, -78°C then PPh_3) and treated with benzoylmethylenetriphenylphosphorane (1.3 eqv., CH_2Cl_2, r.t., 24 hrs; 97%).

137. J. B. Brown, H. B. Henbest, E. R. H. Jones, *J. Chem. Soc.*, 1950, 3634.

138. M. Ono, K. Nishimura, Y. Nagaoka, K. Tomioka, *Tetrahedron Lett.*, 1999, **40**, 6979.

Appendix A

X-ray crystallographic data for compound **217**.

University of Southampton · Department of Chemistry

EPSRC National Crystallography Service

EPSRC Engineering and Physical Sciences Research Council

Table 1. Crystal data and structure refinement.

Identification code	**97SRC262**	
Empirical formula	$C_{26}H_{33}NO_3$	
Formula weight	407.53	
Temperature	293(2) K	
Wavelength	0.71069 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 5.8680(10) Å	α = 85.930(9)°
	b = 10.7490(10) Å	β = 87.6200(10)°
	c = 17.301(2) Å	γ = 84.5800(10)°
Volume	1083.0(2) $Å^3$	
Z	2	
Density (calculated)	1.250 Mg / m^3	
Absorption coefficient	0.081 mm^{-1}	
F(000)	440	
Crystal	?; ?	
Crystal size	? x ? x ? mm^3	
θ range for data collection	2.17 – 24.72°	
Index ranges	$-5 \le h \le 6, -11 \le k \le 11, -20 \le l \le 14$	
Reflections collected	4022	
Independent reflections	2763 [R_{int} = 0.0971]	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2763 / 0 / 272	
Goodness-of-fit on F^2	0.461	
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0423, *wR2* = 0.0674	
R indices (all data)	*R1* = 0.1403, *wR2* = 0.0897	
Largest diff. peak and hole	0.165 and –0.154 e $Å^{-3}$	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details:

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
O1	2775(4)	694(3)	3800(2)	28(1)	1
O2	–482(4)	–1019(3)	2562(2)	31(1)	1
O3	–2462(4)	1367(3)	2331(2)	28(1)	1
N1	1582(5)	1775(4)	899(2)	20(1)	1
C1	840(7)	1656(4)	125(3)	25(1)	1
C2	282(7)	2949(5)	–289(3)	36(2)	1
C3	2290(7)	3749(5)	–276(3)	33(1)	1
C4	3088(7)	3777(4)	541(3)	28(1)	1
C5	3616(6)	2456(4)	878(3)	30(1)	1
C6	1783(6)	584(4)	1376(3)	25(1)	1
C7	3933(6)	–300(4)	1220(3)	26(1)	1
C8	3977(7)	–1500(4)	1751(3)	34(2)	1
C9	3594(6)	–1245(4)	2599(3)	29(1)	1
C10	1456(6)	–381(4)	2756(3)	19(1)	1
C11	1537(6)	836(4)	2252(3)	19(1)	1
C12	1181(6)	–131(4)	3603(3)	28(1)	1
C13	2482(7)	971(5)	4588(3)	29(1)	1
C14	4016(7)	1960(4)	4778(3)	22(1)	1
C15	3685(7)	2499(5)	5466(3)	32(1)	1
C16	5080(8)	3374(5)	5679(3)	41(2)	1
C17	6829(8)	3717(5)	5189(3)	38(2)	1
C18	7176(7)	3195(5)	4490(3)	38(2)	1
C19	5767(7)	2312(4)	4284(3)	28(1)	1
C20	–553(7)	1766(5)	2355(3)	23(1)	1
C21	–357(7)	3089(4)	2465(3)	22(1)	1
C22	1536(7)	3507(4)	2765(3)	28(1)	1
C23	1646(7)	4762(5)	2885(3)	37(2)	1
C24	–152(8)	5619(5)	2673(3)	40(2)	1
C25	–2046(7)	5219(5)	2366(3)	35(2)	1
C26	–2143(7)	3980(5)	2261(3)	33(2)	1

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

O1–C12	1.416(5)	C10–C11	1.523(6)
O1–C13	1.417(5)	C11–C20	1.519(6)
O2–C10	1.445(4)	C13–C14	1.517(6)
O3–C20	1.240(4)	C14–C15	1.360(6)
N1–C1	1.443(5)	C14–C19	1.373(5)
N1–C5	1.455(4)	C15–C16	1.382(6)
N1–C6	1.471(5)	C16–C17	1.365(6)
C1–C2	1.531(6)	C17–C18	1.369(6)
C2–C3	1.525(5)	C18–C19	1.390(6)
C3–C4	1.509(6)	C20–C21	1.465(6)
C4–C5	1.506(6)	C21–C22	1.371(5)
C6–C7	1.533(5)	C21–C26	1.390(6)
C6–C11	1.558(6)	C22–C23	1.387(6)
C7–C8	1.528(6)	C23–C24	1.378(6)
C8–C9	1.516(6)	C24–C25	1.370(6)
C9–C10	1.516(5)	C25–C26	1.363(6)
C10–C12	1.508(6)		

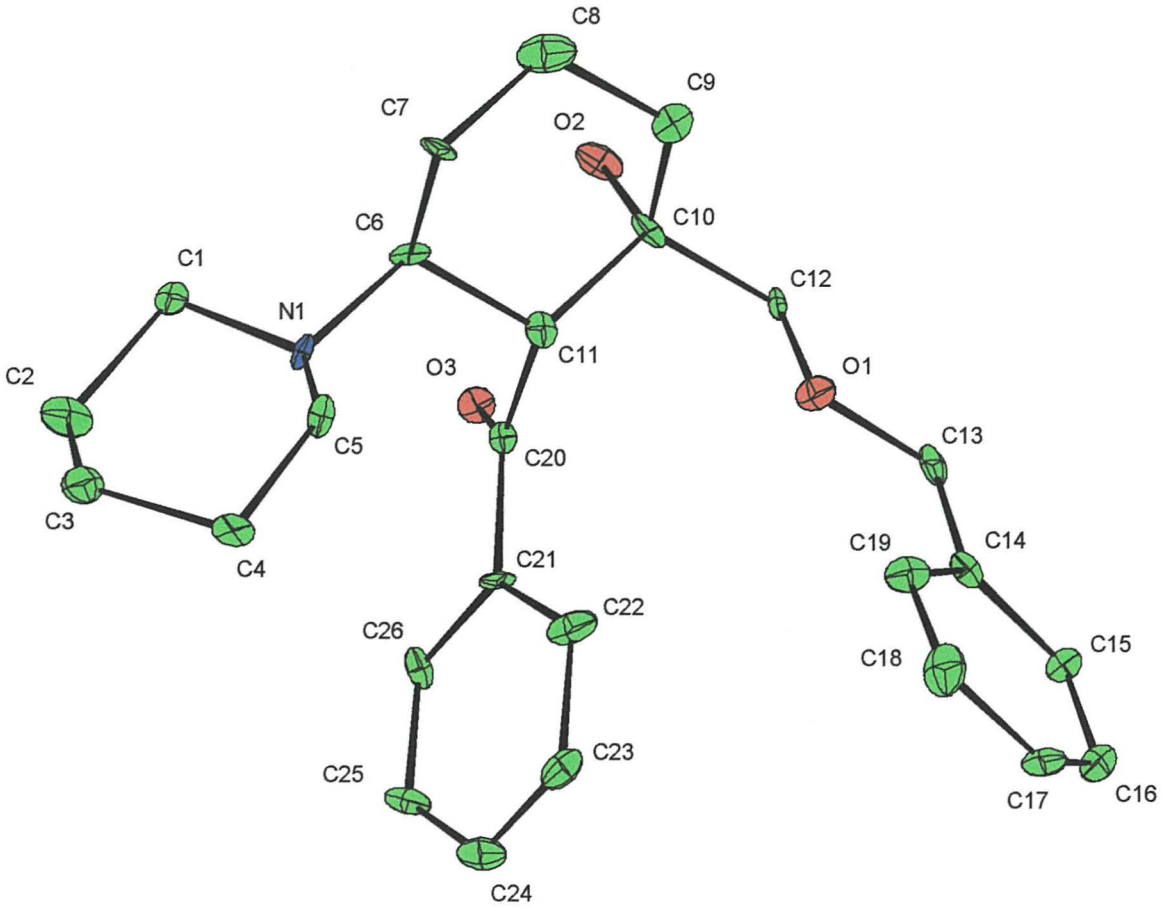
C12–O1–C13	111.1(3)	C10–C11–C6	111.2(4)
C1–N1–C5	110.8(3)	O1–C12–C10	110.6(3)
C1–N1–C6	113.5(4)	O1–C13–C14	111.1(4)
C5–N1–C6	114.1(3)	C15–C14–C19	118.6(5)
N1–C1–C2	110.5(4)	C15–C14–C13	119.2(4)
C3–C2–C1	111.2(4)	C19–C14–C13	122.2(5)
C4–C3–C2	110.5(4)	C14–C15–C16	121.6(5)
C5–C4–C3	109.4(4)	C17–C16–C15	119.7(5)
N1–C5–C4	110.4(4)	C16–C17–C18	119.6(5)
N1–C6–C7	116.1(4)	C17–C18–C19	120.2(5)
N1–C6–C11	110.1(4)	C14–C19–C18	120.3(5)
C7–C6–C11	110.3(4)	O3–C20–C21	120.4(4)
C8–C7–C6	111.7(4)	O3–C20–C11	117.5(4)
C9–C8–C7	112.7(4)	C21–C20–C11	122.1(4)
C10–C9–C8	113.2(4)	C22–C21–C26	117.3(5)
O2–C10–C12	107.5(4)	C22–C21–C20	122.8(4)
O2–C10–C9	107.2(4)	C26–C21–C20	119.8(4)
C12–C10–C9	111.2(4)	C21–C22–C23	121.6(5)
O2–C10–C11	110.0(4)	C24–C23–C22	119.4(5)
C12–C10–C11	111.0(4)	C25–C24–C23	119.6(5)
C9–C10–C11	109.8(4)	C26–C25–C24	120.2(5)
C20–C11–C10	114.2(4)	C25–C26–C21	121.7(5)
C20–C11–C6	107.3(4)		

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

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O1	28(2)	35(2)	23(3)	−5(2)	4(2)	−9(2)
O2	30(2)	19(2)	47(3)	7(2)	−5(2)	−15(2)
O3	16(2)	33(2)	35(3)	−6(2)	0(2)	−5(2)
N1	20(2)	18(3)	22(3)	1(2)	0(2)	−3(2)
C1	20(3)	31(4)	23(4)	−7(3)	0(2)	3(2)
C2	38(3)	37(4)	34(4)	−3(3)	−13(3)	−4(3)
C3	36(3)	27(4)	35(4)	−3(3)	−2(3)	−4(2)
C4	33(3)	23(4)	27(4)	2(3)	2(3)	−9(2)
C5	24(3)	33(4)	33(4)	1(3)	−5(2)	−13(2)
C6	16(3)	22(3)	38(4)	−8(3)	−1(2)	−2(2)
C7	20(3)	18(3)	40(4)	−5(3)	−4(2)	0(2)
C8	25(3)	23(4)	54(5)	−6(3)	−4(3)	4(2)
C9	26(3)	27(4)	34(4)	−5(3)	0(3)	0(2)
C10	18(3)	15(3)	24(4)	−2(3)	3(2)	−4(2)
C11	8(2)	27(3)	21(3)	−1(3)	4(2)	0(2)
C12	19(3)	28(4)	37(4)	−1(3)	3(3)	−5(2)
C13	27(3)	39(4)	20(4)	−5(3)	2(3)	3(2)
C14	25(3)	22(3)	17(4)	6(3)	−1(3)	6(2)
C15	37(3)	41(4)	18(4)	−1(3)	−2(3)	−5(3)
C16	57(4)	32(4)	34(4)	−4(3)	−8(3)	−4(3)
C17	49(4)	33(4)	34(4)	−8(3)	0(3)	−16(3)
C18	16(3)	50(4)	46(5)	2(4)	4(3)	−4(3)
C19	33(3)	28(4)	24(4)	−3(3)	−3(3)	2(3)
C20	23(3)	31(4)	14(3)	−3(3)	0(2)	2(2)
C21	25(3)	16(3)	26(4)	−4(3)	3(2)	−3(2)
C22	26(3)	22(4)	38(4)	−11(3)	8(3)	−8(2)
C23	30(3)	31(4)	53(5)	−14(3)	4(3)	−5(3)
C24	51(3)	25(4)	45(5)	−13(3)	11(3)	−11(3)
C25	37(3)	24(4)	44(4)	−2(3)	1(3)	−3(3)
C26	23(3)	31(4)	45(4)	−3(3)	2(3)	−1(3)

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H2	–369(40)	–1734(14)	2765(22)	47	1
H1A	–508(7)	1195(4)	150(3)	30	1
H1B	2040(7)	1190(4)	–167(3)	30	1
H2A	–80(7)	2852(5)	–822(3)	44	1
H2B	–1054(7)	3369(5)	–37(3)	44	1
H3A	3542(7)	3409(5)	–604(3)	39	1
H3B	1826(7)	4595(5)	–479(3)	39	1
H4A	4447(7)	4226(4)	536(3)	33	1
H4B	1903(7)	4209(4)	856(3)	33	1
H5A	4821(6)	2032(4)	566(3)	36	1
H5B	4158(6)	2471(4)	1399(3)	36	1
H6	470(6)	137(4)	1261(3)	30	1
H7A	3980(6)	–513(4)	684(3)	31	1
H7B	5282(6)	125(4)	1300(3)	31	1
H8A	2798(7)	–2001(4)	1601(3)	41	1
H8B	5445(7)	–1981(4)	1682(3)	41	1
H9A	3478(6)	–2034(4)	2901(3)	35	1
H9B	4911(6)	–874(4)	2772(3)	35	1
H11	2887(6)	1235(4)	2388(3)	23	1
H12A	–363(6)	234(4)	3713(3)	33	1
H12B	1418(6)	–915(4)	3916(3)	33	1
H13A	2842(7)	214(5)	4917(3)	35	1
H13B	895(7)	1268(5)	4695(3)	35	1
H15	2492(7)	2273(5)	5802(3)	38	1
H16	4828(8)	3728(5)	6154(3)	49	1
H17	7780(8)	4302(5)	5330(3)	45	1
H18	8358(7)	3430(5)	4153(3)	45	1
H19	6012(7)	1959(4)	3809(3)	34	1
H22	2775(7)	2935(4)	2892(3)	34	1
H23	2924(7)	5022(5)	3105(3)	45	1
H24	–81(8)	6466(5)	2739(3)	48	1
H25	–3271(7)	5794(5)	2228(3)	42	1
H26	–3438(7)	3725(5)	2049(3)	40	1


C8
C9
C7
O2
C10
C6
C1
C12
N1
C11
O3
O1
C2
C5
C20
C13
C3
C19
C14
C4
C21
C22
C26
C18
C15
C23
C25
C17
C16
C24

X-ray crystallographic data for compound **232**.

Table 1. Crystal data and structure refinement.

Identification code	**00src179**	
Empirical formula	$C_{15}H_{20}O_3S$	
Formula weight	280.37	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	$a = 8.9143(6)$ Å	$\alpha = 90°$
	$b = 4.9923(3)$ Å	$\beta = 95.936(2)°$
	$c = 16.7387(15)$ Å	$\gamma = 90°$
Volume	740.93(9) Å^3	
Z	2	
Density (calculated)	1.257 Mg / m^3	
Absorption coefficient	0.220 mm^{-1}	
F(000)	300	
Crystal	Needle; colourless	
Crystal size	$0.70 \times 0.03 \times 0.03$ mm^3	
θ range for data collection	3.18 – 25.24°	
Index ranges	$-10 \le h \le 10, -5 \le k \le 5, -16 \le l \le 20$	
Reflections collected	3879	
Independent reflections	2475 [$R_{int} = 0.0398$]	
Completeness to $\theta = 25.24°$	98.7 %	
Max. and min. transmission	0.9934 and 0.8613	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2475 / 1 / 190	
Goodness-of-fit on F^2	0.985	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0493$, $wR2 = 0.0885$	
R indices (all data)	$R1 = 0.0784$, $wR2 = 0.0964$	
Absolute structure parameter	0.05(9)	
Largest diff. peak and hole	0.226 and –0.201 e Å^{-3}	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Data collection and cell refinement:** *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction:** *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426 **Program used to solve structure:** *DIRDIF-96* (P. T. Beurskens, G. Beurskens, W. P. Bosman, R. de Gelder, S. Garcia-Granda, R. O. Gould, R. Israël & J. M. M. Smits (1996). Crystallography Laboratory, University of Nijmegen, The Netherlands. **Program used to refine structure:** *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).

Further information: http://www.soton.ac.uk/~xservice/strat.htm

Special details:

Hydrogen bonds (Table 6, Fig. 2) lead to infinite chains parallel to the *b* axis (Figure)

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

Atom	x	y	z	U_{eq}	*S.o.f.*
S1	2200(1)	121(1)	2880(1)	41(1)	1
O1	−240(3)	−5680(4)	914(1)	37(1)	1
O2	2542(2)	−2433(4)	233(1)	37(1)	1
O3	3325(2)	−4899(4)	1307(1)	30(1)	1
C1	1376(3)	−2734(5)	2315(2)	25(1)	1
C2	1263(3)	−1972(6)	1412(2)	26(1)	1
C3	−317(4)	−2873(6)	1070(2)	32(1)	1
C4	−1242(4)	−2341(6)	1765(2)	36(1)	1
C5	−233(4)	−3380(7)	2495(2)	37(1)	1
C6	2421(4)	−3079(6)	924(2)	27(1)	1
C7	4419(4)	−6183(7)	840(2)	35(1)	1
C8	5351(4)	−8036(6)	1389(2)	39(1)	1
C9	2358(4)	−1118(6)	3875(2)	35(1)	1
C10	1593(4)	140(9)	4443(2)	51(1)	1
C11	1799(5)	−662(9)	5237(2)	59(1)	1
C12	2738(5)	−2728(9)	5480(2)	54(1)	1
C13	3463(5)	−4041(8)	4908(2)	62(1)	1
C14	3292(4)	−3229(7)	4118(2)	49(1)	1
C15	2994(6)	−3584(11)	6357(2)	84(2)	1

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

S1–C9	1.768(3)
S1–C1	1.823(3)
O1–C3	1.428(4)
O1–H1O	0.8400
O2–C6	1.215(3)
O3–C6	1.334(3)
O3–C7	1.460(3)
C1–C5	1.530(4)
C1–C2	1.551(4)
C1–H1	1.0000
C2–C6	1.488(4)
C2–C3	1.532(4)
C2–H2	1.0000
C3–C4	1.517(4)
C3–H3	1.0000
C4–C5	1.531(4)
C4–H4A	0.9900
C4–H4B	0.9900
C5–H5A	0.9900
C5–H5B	0.9900
C7–C8	1.495(4)
C7–H7A	0.9900
C7–H7B	0.9900
C8–H8A	0.9800
C8–H8B	0.9800
C8–H8C	0.9800
C9–C10	1.378(5)
C9–C14	1.378(5)
C10–C11	1.382(5)
C10–H10	0.9500
C11–C12	1.364(6)
C11–H11	0.9500
C12–C13	1.376(6)
C12–C15	1.522(5)
C13–C14	1.377(4)
C13–H13	0.9500
C14–H14	0.9500
C15–H15A	0.9800
C15–H15B	0.9800
C15–H15C	0.9800
C15–H15D	0.9800
C15–H15E	0.9800
C15–H15F	0.9800
C9–S1–C1	101.79(14)
C3–O1–H1O	109.5
C6–O3–C7	116.5(2)
C5–C1–C2	106.0(2)
C5–C1–S1	113.5(2)
C2–C1–S1	107.23(19)
C5–C1–H1	110.0
C2–C1–H1	110.0
S1–C1–H1	110.0
C6–C2–C3	110.4(2)
C6–C2–C1	117.7(3)
C3–C2–C1	104.9(2)
C6–C2–H2	107.8
C3–C2–H2	107.8
C1–C2–H2	107.8

O1–C3–C4	110.6(2)
O1–C3–C2	107.3(3)
C4–C3–C2	102.4(3)
O1–C3–H3	112.0
C4–C3–H3	112.0
C2–C3–H3	112.0
C3–C4–C5	103.4(3)
C3–C4–H4A	111.1
C5–C4–H4A	111.1
C3–C4–H4B	111.1
C5–C4–H4B	111.1
H4A–C4–H4B	109.1
C1–C5–C4	104.9(3)
C1–C5–H5A	110.8
C4–C5–H5A	110.8
C1–C5–H5B	110.8
C4–C5–H5B	110.8
H5A–C5–H5B	108.8
O2–C6–O3	121.9(3)
O2–C6–C2	124.0(3)
O3–C6–C2	114.1(3)
O3–C7–C8	107.6(2)
O3–C7–H7A	110.2
C8–C7–H7A	110.2
O3–C7–H7B	110.2
C8–C7–H7B	110.2
H7A–C7–H7B	108.5
C7–C8–H8A	109.5
C7–C8–H8B	109.5
H8A–C8–H8B	109.5
C7–C8–H8C	109.5
H8A–C8–H8C	109.5
H8B–C8–H8C	109.5
C10–C9–C14	118.2(3)
C10–C9–S1	119.6(3)
C14–C9–S1	122.1(3)
C9–C10–C11	120.4(4)
C9–C10–H10	119.8
C11–C10–H10	119.8
C12–C11–C10	121.5(4)
C12–C11–H11	119.3
C10–C11–H11	119.3
C11–C12–C13	118.1(4)
C11–C12–C15	121.7(4)
C13–C12–C15	120.2(4)
C12–C13–C14	121.0(4)
C12–C13–H13	119.5
C14–C13–H13	119.5
C13–C14–C9	120.8(4)
C13–C14–H14	119.6
C9–C14–H14	119.6
C12–C15–H15A	109.5
C12–C15–H15B	109.5
H15A–C15–H15B	109.5
C12–C15–H15C	109.5
H15A–C15–H15C	109.5
H15B–C15–H15C	109.5
C12–C15–H15D	109.5
H15A–C15–H15D	141.1
H15B–C15–H15D	56.3
H15C–C15–H15D	56.3

C12–C15–H15E	109.5
H15A–C15–H15E	56.3
H15B–C15–H15E	141.1
H15C–C15–H15E	56.3
H15D–C15–H15E	109.5
C12–C15–H15F	109.5
H15A–C15–H15F	56.3
H15B–C15–H15F	56.3
H15C–C15–H15F	141.1
H15D–C15–H15F	109.5
H15E–C15–H15F	109.5

Symmetry transformations used to generate equivalent atoms:

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

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S1	64(1)	26(1)	30(1)	1(1)	–4(1)	–7(1)
O1	39(2)	33(1)	37(2)	–8(1)	–8(1)	1(1)
O2	42(2)	45(1)	23(1)	9(1)	7(1)	7(1)
O3	31(1)	32(1)	26(1)	3(1)	6(1)	6(1)
C1	28(2)	23(2)	25(2)	–5(1)	5(2)	1(1)
C2	29(2)	24(2)	25(2)	1(1)	1(2)	3(1)
C3	33(2)	31(2)	33(2)	4(2)	1(2)	2(2)
C4	28(2)	31(2)	47(2)	–3(2)	2(2)	2(2)
C5	39(2)	44(2)	29(2)	1(2)	6(2)	–3(2)
C6	29(2)	23(2)	28(2)	2(1)	–1(2)	–1(1)
C7	32(2)	42(2)	32(2)	4(2)	12(2)	13(2)
C8	35(2)	44(2)	39(2)	4(2)	7(2)	9(2)
C9	46(2)	34(2)	25(2)	2(2)	3(2)	–9(2)
C10	59(2)	54(2)	39(2)	–8(2)	2(2)	6(2)
C11	60(3)	83(3)	35(2)	–13(2)	11(2)	–16(2)
C12	61(3)	75(3)	24(2)	7(2)	–4(2)	–33(2)
C13	79(3)	65(3)	39(3)	18(2)	–5(2)	7(2)
C14	62(3)	51(2)	34(2)	2(2)	7(2)	5(2)
C15	97(4)	126(4)	28(2)	15(2)	2(2)	–48(3)

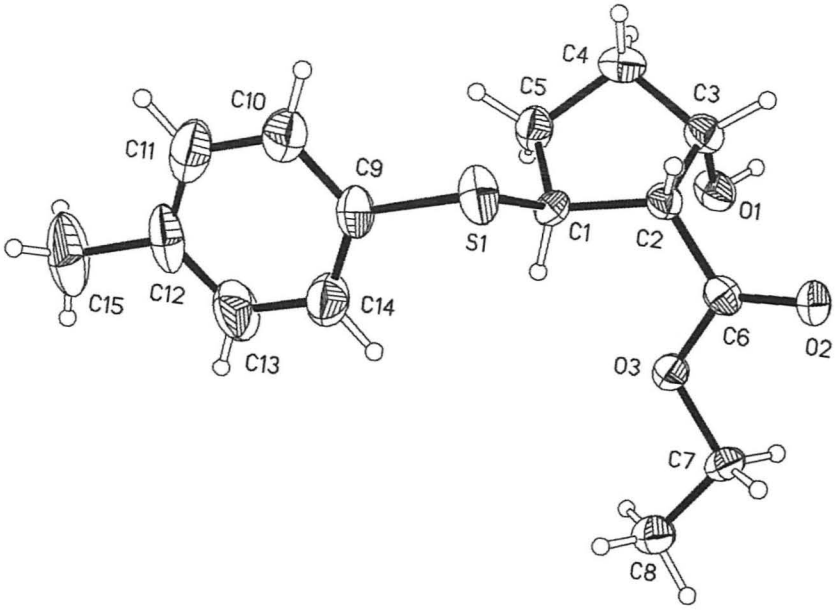
Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

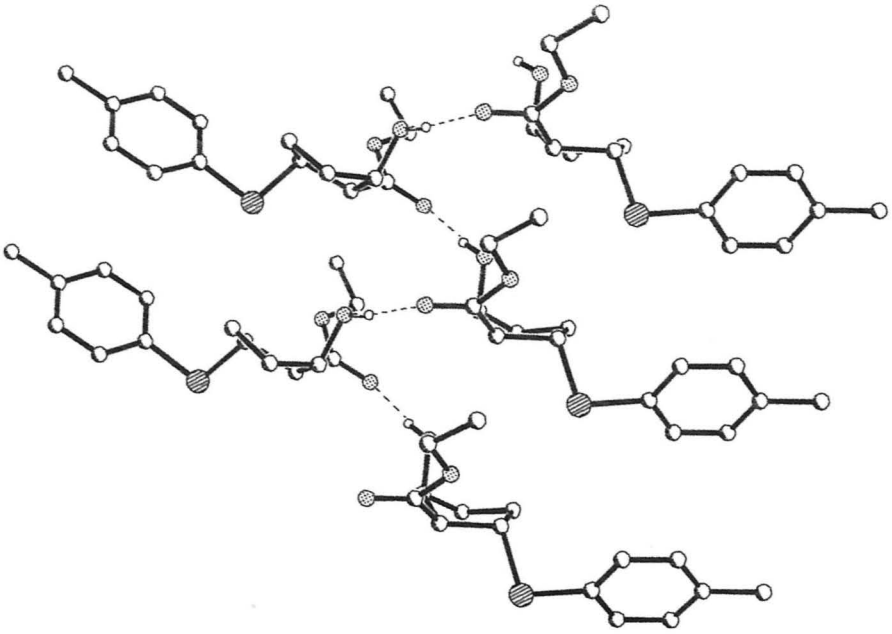
Atom	x	y	z	U_{eq}	*S.o.f.*
H1O	–905	–6094	542	37(10)	1
H1	2034	–4345	2417	35(8)	1
H2	1302	26	1375	33(7)	1
H3	–697	–1838	579	29(8)	1
H4A	–2212	–3324	1695	32(8)	1
H4B	–1449	–404	1817	25(8)	1
H5A	–471	–2467	2991	52(10)	1
H5B	–366	–5334	2560	48(10)	1
H7A	5069	–4817	620	44(9)	1
H7B	3892	–7197	386	58(12)	1
H8A	6097	–8934	1092	58(11)	1
H8B	4697	–9379	1603	48(9)	1
H8C	5871	–7010	1834	60(12)	1
H10	920	1567	4289	75(14)	1
H11	1274	245	5623	91(15)	1
H13	4091	–5531	5060	53(11)	1
H14	3825	–4135	3735	47(10)	1
H15A	3704	–5089	6410	126	0.35(5)
H15B	2033	–4137	6541	126	0.35(5)
H15C	3411	–2079	6684	126	0.35(5)
H15D	2395	–2448	6680	126	0.65(5)
H15E	4066	–3400	6549	126	0.65(5)
H15F	2687	–5457	6406	126	0.65(5)

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*DHA*)
O1–H1O···O2^{i}	0.84	1.97	2.802(3)	172.5

Symmetry transformations used to generate equivalent atoms:
(i) −x,y−1/2,−z


C4
C5
C3
C10
C11
C9
O1
S1
C1
C2
C15
C12
C14
C6
O2
C13
O3
C7
C8



X-ray crystallographic data for compound **238c**

Table 1. Crystal data and structure refinement.

Identification code	**00src431**	
Empirical formula	$C_{16}H_{22}O_3S$	
Formula weight	294.40	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$Pca2_1$	
Unit cell dimensions	a = 15.8301(2) Å	α = 90°
	b = 5.62760(10) Å	β = 90°
	c = 33.8340(6) Å	γ = 90°
Volume	3014.12(8) Å^3	
Z	8	
Density (calculated)	1.298 Mg / m^3	
Absorption coefficient	0.220 mm^{-1}	
F(000)	1264	
Crystal	Prism; colourless	
Crystal size	0.10 × 0.07 × 0.07 mm^3	
θ range for data collection	3.14 – 25.09°	
Index ranges	$-18 \le h \le 18$, $-6 \le k \le 6$, $-40 \le l \le 36$	
Reflections collected	21408	
Independent reflections	5060 [R_{int} = 0.0696]	
Completeness to θ = 25.09°	99.6 %	
Max. and min. transmission	0.9848 and 0.9784	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5060 / 1 / 408	
Goodness-of-fit on F^2	1.036	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0431, $wR2$ = 0.0629	
R indices (all data)	$R1$ = 0.0806, $wR2$ = 0.0689	
Absolute structure parameter	0.05(12)	
Extinction coefficient	0.00055(19)	
Largest diff. peak and hole	0.217 and –0.190 e Å^{-3}	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Data collection and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. **A51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Program used to solve structure**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Program used to refine structure**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).

Further information: http://www.soton.ac.uk/~xservice/strat.htm

Special details:

The asymmetric unit of the structure contains two molecules.
Intramolecular hydrogen bonds (Table 6)

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
S1	8294(2)	5324(2)	9105(1)	26(1)	1
O1	10372(4)	5333(6)	8605(2)	36(1)	1
O2	10049(1)	1718(4)	8843(1)	27(1)	1
O3	8917(2)	7839(5)	8360(1)	27(1)	1
C1	9048(3)	3522(8)	8419(2)	20(1)	1
C2	8924(4)	5613(9)	8150(2)	21(1)	1
C3	8086(5)	5465(9)	7931(3)	30(2)	1
C4	7361(6)	5174(7)	8212(2)	24(2)	1
C5	7468(2)	3015(6)	8482(1)	29(1)	1
C6	8307(2)	3083(6)	8708(1)	20(1)	1
C7	9889(3)	3660(7)	8629(1)	26(1)	1
C8	10848(2)	1732(7)	9060(2)	38(1)	1
C9	10862(7)	−283(8)	9336(3)	33(2)	1
C10	8025(2)	3576(6)	9518(1)	22(1)	1
C11	7453(5)	4534(7)	9790(2)	20(1)	1
C12	7287(2)	3312(6)	10141(1)	26(1)	1
C13	7651(2)	1140(7)	10226(1)	23(1)	1
C14	8218(6)	198(8)	9955(3)	29(3)	1
C15	8398(2)	1400(6)	9602(1)	26(1)	1
C16	7443(6)	−150(8)	10616(3)	47(3)	1
S2	787(2)	9705(2)	6565(1)	26(1)	1
O1'	2871(4)	9680(6)	7055(2)	31(1)	1
O2'	2556(1)	13246(4)	6802(1)	27(1)	1
O3'	1408(2)	7232(6)	7309(1)	29(1)	1
C1'	1557(3)	11534(8)	7238(2)	20(1)	1
C2'	1431(4)	9415(9)	7524(2)	27(1)	1
C3'	611(6)	9676(8)	7744(3)	25(2)	1
C4'	−145(6)	9890(7)	7456(3)	36(3)	1
C5'	−11(2)	12039(6)	7191(1)	27(1)	1
C6'	813(2)	11935(7)	6960(1)	21(1)	1
C7'	2390(3)	11315(7)	7025(1)	23(1)	1
C8'	3352(2)	13218(7)	6589(2)	36(1)	1
C9'	3340(7)	15301(9)	6311(3)	44(2)	1
C10'	518(2)	11440(6)	6142(1)	21(1)	1
C11'	−41(5)	10516(8)	5867(2)	26(1)	1
C12'	−214(2)	11649(6)	5521(1)	26(1)	1
C13'	158(2)	13850(7)	5431(1)	29(1)	1
C14'	704(6)	14802(8)	5710(3)	24(2)	1
C15'	899(2)	13619(6)	6053(1)	27(1)	1
C16'	−22(4)	15127(6)	5058(2)	28(2)	1

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

S1–C10	1.761(5)
S1–C6	1.843(5)
O1–C7	1.216(6)
O2–C7	1.335(4)
O2–C8	1.462(4)
O3–C2	1.439(6)
O3–H3O	0.81(4)
C1–C2	1.500(7)
C1–C7	1.510(6)
C1–C6	1.548(6)
C1–H1	1.0000
C2–C3	1.521(10)
C2–H2	1.0000
C3–C4	1.500(12)
C3–H3A	0.9900
C3–H3B	0.9900
C4–C5	1.528(7)
C4–H4A	0.9900
C4–H4B	0.9900
C5–C6	1.534(5)
C5–H5A	0.9900
C5–H5B	0.9900
C6–H6	1.0000
C8–C9	1.470(8)
C8–H8A	0.9900
C8–H8B	0.9900
C9–H9A	0.9800
C9–H9B	0.9800
C9–H9C	0.9800
C10–C15	1.389(5)
C10–C11	1.397(8)
C11–C12	1.398(7)
C11–H11	0.9500
C12–C13	1.381(5)
C12–H12	0.9500
C13–C14	1.390(11)
C13–C16	1.541(9)
C14–C15	1.401(11)
C14–H14	0.9500
C15–H15	0.9500
C16–H16A	0.9800
C16–H16B	0.9800
C16–H16C	0.9800
S2–C10'	1.785(5)
S2–C6'	1.835(5)
O1'–C7'	1.199(6)
O2'–C7'	1.351(4)
O2'–C8'	1.452(4)
O3'–C2'	1.427(6)
O3'–H3O'	0.74(4)
C1'–C7'	1.506(6)
C1'–C6'	1.524(6)
C1'–C2'	1.549(7)
C1'–H1'	1.0000
C2'–C3'	1.504(11)
C2'–H2'	1.0000
C3'–C4'	1.546(13)
C3'–H3'1	0.9900
C3'–H3'2	0.9900

C4'–C5'	1.521(8)
C4'–H4'1	0.9900
C4'–H4'2	0.9900
C5'–C6'	1.522(5)
C5'–H5'1	0.9900
C5'–H5'2	0.9900
C6'–H6'	1.0000
C8'–C9'	1.503(8)
C8'–H8'1	0.9900
C8'–H8'2	0.9900
C9'–H9'1	0.9800
C9'–H9'2	0.9800
C9'–H9'3	0.9800
C10'–C11'	1.384(8)
C10'–C15'	1.399(5)
C11'–C12'	1.362(8)
C11'–H11'	0.9500
C12'–C13'	1.405(5)
C12'–H12'	0.9500
C13'–C14'	1.387(11)
C13'–C16'	1.481(8)
C14'–C15'	1.372(11)
C14'–H14'	0.9500
C15'–H15'	0.9500
C16'–H16D	0.9800
C16'–H16E	0.9800
C16'–H16F	0.9800

C10–S1–C6	101.50(17)
C7–O2–C8	115.6(3)
C2–O3–H3O	105(3)
C2–C1–C7	111.1(4)
C2–C1–C6	114.1(4)
C7–C1–C6	112.3(4)
C2–C1–H1	106.2
C7–C1–H1	106.2
C6–C1–H1	106.2
O3–C2–C1	112.6(4)
O3–C2–C3	106.3(4)
C1–C2–C3	111.5(5)
O3–C2–H2	108.7
C1–C2–H2	108.7
C3–C2–H2	108.7
C4–C3–C2	111.4(7)
C4–C3–H3A	109.3
C2–C3–H3A	109.3
C4–C3–H3B	109.3
C2–C3–H3B	109.3
H3A–C3–H3B	108.0
C3–C4–C5	112.3(5)
C3–C4–H4A	109.1
C5–C4–H4A	109.1
C3–C4–H4B	109.1
C5–C4–H4B	109.1
H4A–C4–H4B	107.9
C4–C5–C6	112.0(4)
C4–C5–H5A	109.2
C6–C5–H5A	109.2
C4–C5–H5B	109.2
C6–C5–H5B	109.2
H5A–C5–H5B	107.9

C5–C6–C1	110.1(3)
C5–C6–S1	111.8(3)
C1–C6–S1	111.1(3)
C5–C6–H6	107.9
C1–C6–H6	107.9
S1–C6–H6	107.9
O1–C7–O2	123.4(5)
O1–C7–C1	124.3(5)
O2–C7–C1	112.3(4)
O2–C8–C9	109.2(5)
O2–C8–H8A	109.8
C9–C8–H8A	109.8
O2–C8–H8B	109.8
C9–C8–H8B	109.8
H8A–C8–H8B	108.3
C8–C9–H9A	109.5
C8–C9–H9B	109.5
H9A–C9–H9B	109.5
C8–C9–H9C	109.5
H9A–C9–H9C	109.5
H9B–C9–H9C	109.5
C15–C10–C11	118.8(4)
C15–C10–S1	123.5(3)
C11–C10–S1	117.5(3)
C10–C11–C12	119.3(5)
C10–C11–H11	120.3
C12–C11–H11	120.3
C13–C12–C11	122.4(4)
C13–C12–H12	118.8
C11–C12–H12	118.8
C12–C13–C14	117.9(5)
C12–C13–C16	120.5(4)
C14–C13–C16	121.5(5)
C13–C14–C15	120.6(5)
C13–C14–H14	119.7
C15–C14–H14	119.7
C10–C15–C14	120.9(5)
C10–C15–H15	119.6
C14–C15–H15	119.6
C13–C16–H16A	109.5
C13–C16–H16B	109.5
H16A–C16–H16B	109.5
C13–C16–H16C	109.5
H16A–C16–H16C	109.5
H16B–C16–H16C	109.5
C10'–S2–C6'	102.47(16)
C7'–O2'–C8'	115.9(3)
C2'–O3'–H3O'	110(4)
C7'–C1'–C6'	113.3(4)
C7'–C1'–C2'	110.3(4)
C6'–C1'–C2'	113.6(4)
C7'–C1'–H1'	106.4
C6'–C1'–H1'	106.4
C2'–C1'–H1'	106.4
O3'–C2'–C3'	108.2(5)
O3'–C2'–C1'	110.4(4)
C3'–C2'–C1'	110.2(5)
O3'–C2'–H2'	109.3
C3'–C2'–H2'	109.3
C1'–C2'–H2'	109.3
C2'–C3'–C4'	111.4(8)

C2'–C3'–H3'1	109.3
C4'–C3'–H3'1	109.3
C2'–C3'–H3'2	109.4
C4'–C3'–H3'2	109.3
H3'1–C3'–H3'2	108.0
C5'–C4'–C3'	109.0(5)
C5'–C4'–H4'1	109.9
C3'–C4'–H4'1	109.9
C5'–C4'–H4'2	109.9
C3'–C4'–H4'2	109.9
H4'1–C4'–H4'2	108.3
C4'–C5'–C6'	113.1(4)
C4'–C5'–H5'1	109.0
C6'–C5'–H5'1	109.0
C4'–C5'–H5'2	109.0
C6'–C5'–H5'2	109.0
H5'1–C5'–H5'2	107.8
C5'–C6'–C1'	110.6(3)
C5'–C6'–S2	112.4(3)
C1'–C6'–S2	111.4(3)
C5'–C6'–H6'	107.4
C1'–C6'–H6'	107.4
S2–C6'–H6'	107.4
O1'–C7'–O2'	122.8(5)
O1'–C7'–C1'	125.4(5)
O2'–C7'–C1'	111.8(4)
O2'–C8'–C9'	106.9(5)
O2'–C8'–H8'1	110.4
C9'–C8'–H8'1	110.3
O2'–C8'–H8'2	110.3
C9'–C8'–H8'2	110.4
H8'1–C8'–H8'2	108.6
C8'–C9'–H9'1	109.5
C8'–C9'–H9'2	109.5
H9'1–C9'–H9'2	109.5
C8'–C9'–H9'3	109.5
H9'1–C9'–H9'3	109.5
H9'2–C9'–H9'3	109.5
C11'–C10'–C15'	117.4(4)
C11'–C10'–S2	119.0(3)
C15'–C10'–S2	123.3(3)
C12'–C11'–C10'	122.0(5)
C12'–C11'–H11'	119.0
C10'–C11'–H11'	119.0
C11'–C12'–C13'	121.0(4)
C11'–C12'–H12'	119.5
C13'–C12'–H12'	119.5
C14'–C13'–C12'	117.1(5)
C14'–C13'–C16'	120.9(5)
C12'–C13'–C16'	122.1(4)
C15'–C14'–C13'	121.8(5)
C15'–C14'–H14'	119.1
C13'–C14'–H14'	119.1
C14'–C15'–C10'	120.7(5)
C14'–C15'–H15'	119.7
C10'–C15'–H15'	119.7
C13'–C16'–H16D	109.5
C13'–C16'–H16E	109.5
H16D–C16'–H16E	109.5
C13'–C16'–H16F	109.5
H16D–C16'–H16F	109.5

H16E–C16'–H16F	109.5	

Symmetry transformations used to generate equivalent atoms:

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

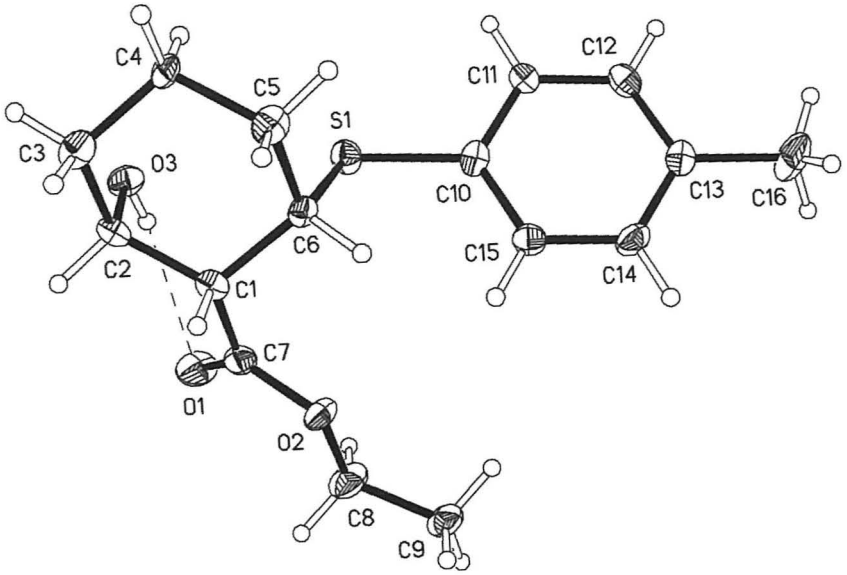
Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S1	34(1)	22(1)	24(1)	−2(1)	5(1)	0(1)
O1	20(3)	34(2)	54(3)	6(2)	−3(3)	−6(2)
O2	27(2)	21(2)	32(2)	7(1)	−5(1)	3(1)
O3	27(2)	20(2)	34(2)	−1(2)	−2(1)	1(2)
C1	20(2)	19(3)	23(3)	−6(2)	0(2)	−2(2)
C2	18(2)	21(2)	25(3)	−5(3)	4(2)	−2(3)
C3	36(4)	26(3)	28(4)	0(4)	−6(3)	3(3)
C4	24(6)	32(5)	14(4)	4(2)	−7(4)	1(2)
C5	29(2)	26(2)	33(3)	3(2)	−4(2)	−5(2)
C6	28(2)	11(2)	19(2)	−1(2)	0(2)	2(2)
C7	29(3)	19(3)	30(3)	1(2)	6(2)	5(2)
C8	30(3)	42(3)	42(3)	9(2)	−13(2)	5(2)
C9	37(5)	37(3)	25(4)	3(3)	−8(4)	12(3)
C10	29(2)	18(2)	19(2)	−1(2)	−5(2)	−7(2)
C11	21(3)	20(2)	20(3)	−4(3)	1(2)	−2(3)
C12	26(2)	29(3)	21(2)	−7(2)	4(2)	−2(2)
C13	24(2)	24(3)	21(2)	0(2)	−5(2)	−8(2)
C14	31(5)	18(4)	37(6)	4(2)	−2(4)	4(2)
C15	28(2)	22(3)	26(3)	−3(2)	2(2)	2(2)
C16	73(6)	42(6)	26(6)	12(2)	−9(5)	9(3)
S2	33(1)	22(1)	23(1)	0(1)	−4(1)	4(1)
O1'	34(3)	21(2)	37(3)	10(2)	3(2)	9(2)
O2'	26(1)	24(2)	31(2)	6(1)	7(1)	−1(1)
O3'	34(2)	22(2)	32(2)	−1(2)	6(2)	1(2)
C1'	23(2)	16(3)	21(3)	2(2)	0(2)	−4(2)
C2'	37(3)	19(2)	24(3)	4(3)	−5(3)	−3(3)
C3'	35(4)	21(3)	20(4)	5(3)	2(3)	−5(2)
C4'	27(6)	31(5)	51(6)	−1(2)	4(5)	−5(2)
C5'	22(2)	27(2)	33(2)	−6(2)	−3(2)	4(2)
C6'	27(2)	14(2)	24(3)	−2(2)	0(2)	1(2)
C7'	27(2)	26(3)	17(2)	−1(2)	−1(2)	−11(2)
C8'	30(3)	38(3)	40(3)	−1(2)	7(2)	−4(2)
C9'	44(6)	40(4)	47(5)	5(3)	12(5)	−10(3)
C10'	19(2)	20(2)	22(2)	0(2)	2(2)	1(2)
C11'	27(3)	24(2)	28(3)	1(3)	6(2)	−8(3)
C12'	26(2)	26(2)	24(3)	−1(2)	−1(2)	−1(2)
C13'	26(2)	33(3)	26(3)	4(2)	8(2)	4(2)
C14'	23(5)	26(4)	24(5)	5(2)	8(4)	−1(2)
C15'	21(2)	30(3)	30(3)	−5(2)	−4(2)	−4(2)
C16'	14(3)	38(5)	31(5)	7(2)	−6(4)	−4(2)

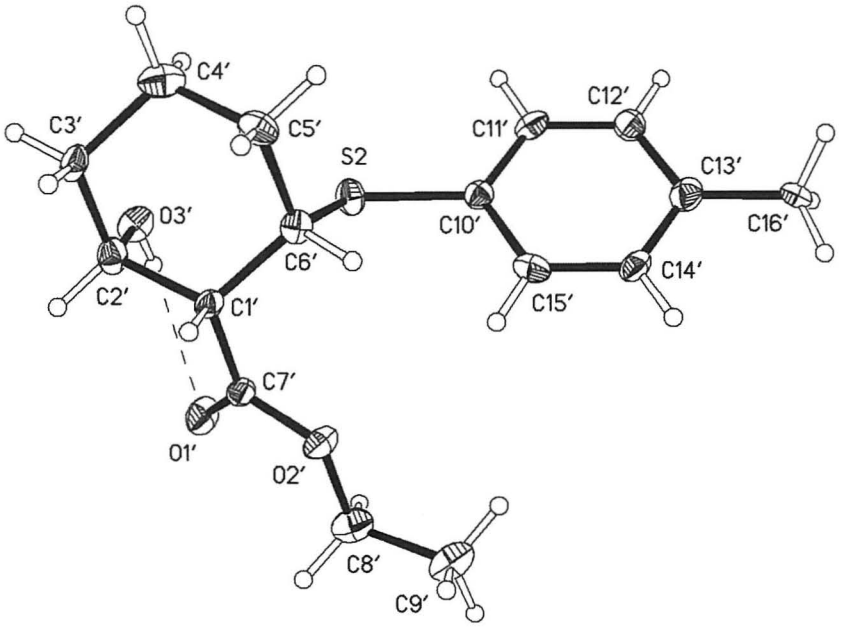
Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H3O	9350(20)	7840(70)	8485(12)	40	1
H1	9077	2091	8244	24	1
H2	9392	5642	7952	13(8)	1
H3A	8004	6930	7774	29(10)	1
H3B	8099	4101	7747	31(14)	1
H4A	6831	5001	8059	40(30)	1
H4B	7310	6621	8377	33(16)	1
H5A	7445	1549	8320	22(10)	1
H5B	6995	2962	8673	48(12)	1
H6	8393	1491	8833	6(8)	1
H8A	10906	3242	9207	59(14)	1
H8B	11326	1605	8872	60(14)	1
H9A	11394	–268	9485	39(16)	1
H9B	10817	–1773	9188	37(17)	1
H9C	10386	–152	9520	35(19)	1
H11	7180	6002	9736	24	1
H12	6911	3999	10327	27(10)	1
H14	8487	–1276	10009	17(11)	1
H15	8780	718	9418	52(13)	1
H16A	7039	798	10769	69(14)	1
H16B	7962	–363	10770	69(13)	1
H16C	7196	–1707	10557	120(20)	1
H3O'	1800(20)	7070(70)	7195(13)	38(13)	1
H1'	1599	12988	7406	24	1
H2'	1909	9369	7717	17(9)	1
H3'1	636	11109	7913	33(13)	1
H3'2	527	8279	7917	35(11)	1
H4'1	–190	8433	7294	10(12)	1
H4'2	–676	10075	7608	60(40)	1
H5'1	–15	13494	7355	20(9)	1
H5'2	–488	12151	7002	8(8)	1
H6'	895	13521	6832	16(9)	1
H8'1	3414	11715	6440	36(11)	1
H8'2	3831	13358	6776	21(9)	1
H9'1	3858	15303	6152	57(19)	1
H9'2	3307	16779	6463	60(20)	1
H9'3	2848	15180	6136	90(30)	1
H11'	–313	9048	5922	41(11)	1
H12'	–591	10940	5337	31(10)	1
H14'	949	16317	5662	32(13)	1
H15'	1297	14286	6231	7(8)	1
H16D	311	16593	5048	45(10)	1
H16E	–625	15520	5046	70(13)	1
H16F	127	14114	4833	76(15)	1

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*DHA*)
O3–H3O···O1	0.81(4)	2.19(4)	2.825(7)	137(4)
O3'–H3O'···O1'	0.74(4)	2.29(5)	2.829(7)	131(4)


C4
C5
C3
O3
C2
C1
C6
S1
C11
C12
C10
C13
C16
C15
C14
C7
O1
O2
C8
C9


C4′
C3′
C5′
S2
C11′
C12′
C13′
C16′
O3′
C10′
C6′
C14′
C2′
C1′
C15′
C7′
O1′
O2′
C8′
C9′

Pergamon

Tetrahedron Letters 40 (1999) 3279–3282

TETRAHEDRON LETTERS

Tandem Michael/intramolecular aldol reactions mediated by secondary amines, thiols and phosphines

Francesca Dinon, Elinor Richards and Patrick J. Murphy.*

Department of Chemistry, University of Wales, Bangor, Gwynedd, UK, LL57 2UW.

David E. Hibbs, Michael B. Hursthouse and K. M. Abdul Malik.

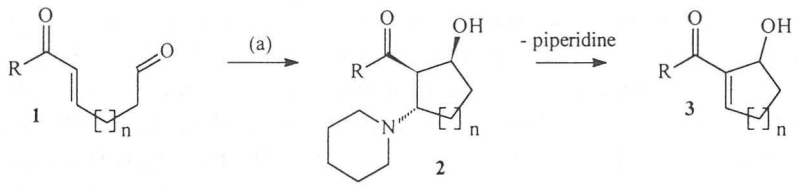
Department of Chemistry, University of Wales, Cardiff, PO Box 912, Cardiff, UK, CF1 3TB.

Received 4 November 1998; revised 15 February 1999; accepted 23 February 1999

Abstract: The secondary amine mediated Baylis-Hillman reaction has been found to proceed *via* a tandem Michael addition/intramolecular aldol followed by a slow elimination step; it was also observed that similar processes can be effected using phosphines and thiols as mediators.

Keywords: Cyclisation, Michael reactions, aldols.

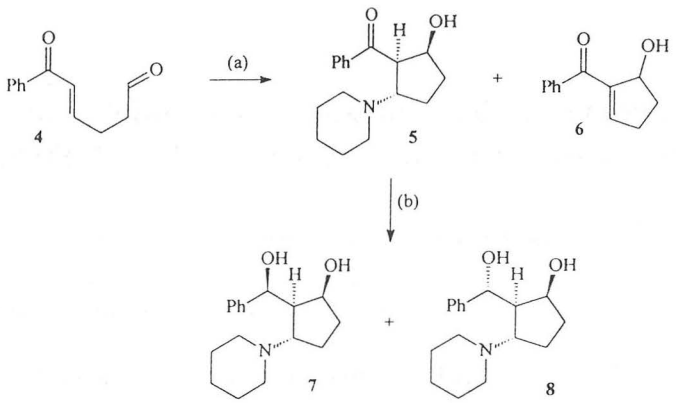
We have previously reported the preparation of substituted cyclopentenols and cyclohexenols **3** from the enone-aldehydes **1** catalysed by secondary amines in a process reminiscent of the Baylis-Hillman reaction.[1] Preliminary evidence suggested that the reaction was proceeding *via* a tandem Michael addition/intramolecular aldol process giving intermediates such as **2**, which was followed by a slow elimination step. We were thus eager to investigate the mechanism of this process further and to ascertain the generality of this reaction by employing other nucleophiles.



(a) Piperidine, $CDCl_3$, rt., 20-50% 3-5 days, R = Ph, alkyl; n = 1, 2.

To this end, we treated aldehyde **4** with an excess of piperidine in chloroform and found that the reaction proceeded to completion rapidly (ca 10 min) to give a product with ^1H nmr signals indicative of **5**, together with a small amount of the cyclopentenol **6** (ca 5%). We found that the intermediate **5** was stable for long periods of time (>7 days) in chloroform solution and very little further conversion to **6** was observed.

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00419-0



(a) 1.3 eqv. piperidine, $CHCl_3$, 10 min, rt., (b) $NaBH_4$, MeOH, 0°C.

In addition, evaporation of the chloroform, followed by treatment of a methanolic solution of **5** with sodium borohydride gave a separable 1:1.3 mixture of the diols **7** and **8** in 67% overall yield, the former providing crystals suitable for X-ray analysis[2] which confirmed the relative stereochemistry of the intermediate **5**, as that illustrated (Fig 1).

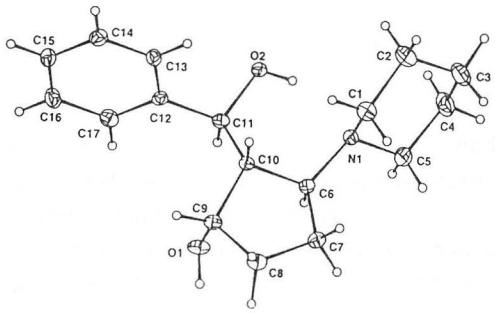


Figure 1.

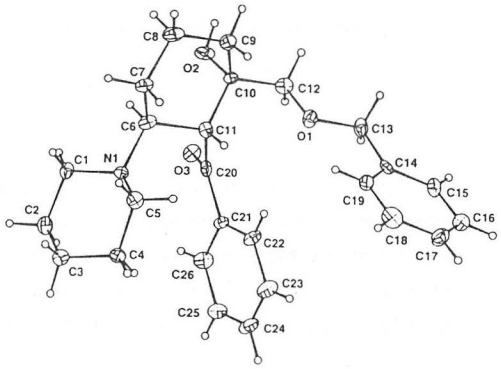
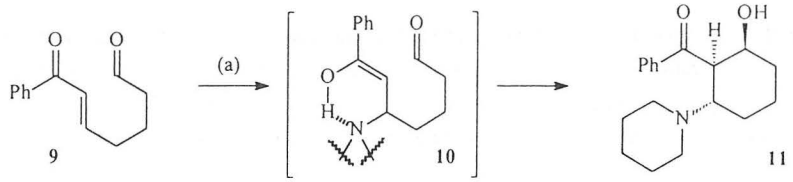


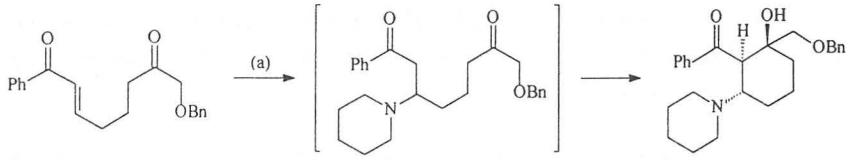
Figure 2.

We repeated this reaction with the enone **9** and were pleased to find conversion of this material into a compound with similar ^1H nmr data to **5**; the presence of signals at δ = 3.2 (1H, ddd, J = 3, 12, 12 Hz), 3.6 (1H, dd, 1.8, 12 Hz) and 4.2 (1H, br m) ppm, indicating the stereochemisty illustrated in structure **11**. In addition, it was apparent that the reaction leading to **11** was proceeding *via* an intermediate enol, possibly of structure **10**, as indicated by signals at δ = 4.3 (1H, dt, J = 14, 7.5 Hz), 5.8 (1H, d, 14 Hz) ppm. Again **11** was found to be stable in solution for prolonged periods with only ca ~ 10% conversion to the cyclohexenol **3** (R = Ph, n = 2) being observed over 28 days. An analogous sequence of reactions also occurred with N-methylpiperazine.



(a) 1.3 eqv. piperidine, $CHCl_3$, >90%.

More direct evidence for the stereochemical outcome of this reaction comes from the piperidine mediated cyclisation of **12**[6] leading to the cyclohexane **14** *via* the observed (nmr) intermediate **13**. Interestingly this cyclisation took considerably longer to effect, requiring six days for complete reaction, possibly reflecting the lower reactivity of ketones as electrophiles. In addition we were able to isolate (60% yield) and obtain crystals of **14** suitable for X-ray analysis[2] which again confirmed the stereochemistry as that illustrated. (Fig 2).

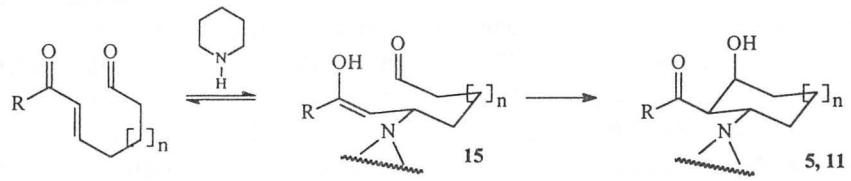


12 **13** **14**

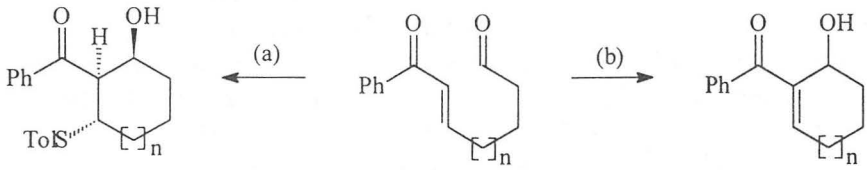
(a) 1.3 eqv.. piperidine, $CHCl_3$; 60%

It is worth emphasising that in all these reactions the Michael-addition/aldol cyclisation step proceeded to give a single diastereomer by nmr and as yet we have been unable to isolate any minor diastereomeric products.

All of these observations seem to suggest that the reaction indeed proceeds *via* a conjugate addition of the amine to the enone yielding an intermediate enol, followed by an intramolecular aldol cyclisation *via* the conformation shown (**15**, n = 0,1). This mechanism might explain the slow rate of formation of the Baylis-Hillman products from this reaction, as the key step must be the elimination of piperidine from intermediates **5** and **11**, which is obviously a stereoelectronically unfavourable process particularly in the case of the cyclohexane intermediate (n = 1).



With these result in hand we were keen to see if this cyclisation could be effected using other nucleophiles. It is known that metal thiolates and selenates,[8] or metallated amines[9] can be used in tandem Michael-aldol reactions, including some cyclisations,[10] and that phosphines can catalyse intramolecular Baylis-Hillman reactions,[11] albeit in poor isolated yield. We were thus pleased to find that the substrates **5** and **9** could be converted into either the adducts **16a,b** on treatment with excess *p*-tolylthiol or to the cyclic alkenols **3** and **6** by treatment with a catalytic amount of *n*-Bu_3P.



16a; n = 0, 77% **5**; n = 0 **3**; n = 0, 20%

16b; n = 1, 93% **9**; n = 1 **6**; n = 1, 75%

(a) 1.3 eqv. TolSH, $CHCl_3$, 16 hrs rt., (b) 0.05-0.2 eqv. n-Bu_3P, $CHCl_3$, 2-16 hrs, rt.

Again the reactions leading to **16a,b** proceed to a single diastereomer which can be equated to the amine case. The reaction involving the tri-*n*-butylphosphine proceeded well for the formation of the cyclohexene product **3**, however the corresponding cyclopentene case gave a somewhat disappointing yield, with a great deal of polymerisation being apparent. This may reflect differences in the conformation of the two intermediate enols at the point of cyclisation.

In conclusion, we have reported a mild, effective and potentially very versatile route to substituted cycloalkanes and alkenes, which is mediated in a predictable manner by a range of nucleophiles. We are currently developing this methodology to allow access to a range of substituted carbocycles and are assessing the scope of the reaction as a synthetic procedure.

Acknowledgements: Thanks are given to the ERASMUS (FD) and the European Social Fund (ER) for funding and to Mr E. Lewis for nmr studies; the EPSRC Mass spectrometry centre at Swansea is also acknowledged.

References

1. G. P. Black, F. Dinon, S Fratucello, P J. Murphy, M. Nielsen, H. L Williams and N. D. A. Walshe, *Tetrahedron Lett.* 1997, **38**, 8561.
2. Crystallographic measurements for both compounds were made using a FAST area detector diffractometer and Mo-K_α radiation (λ = 0.71069 Å), following previously described procedures.[3] The structures were solved by direct methods (SHELX-S)[4] and refined on F^2 by full-matrix least-squares (SHELXL-93)[5] using all unique data to final *wR* (on F^2) = 0.0897 (**7**) and 0.0641 (**14**) and R (on F) = 0.0423 (**7**) and 0.0323 (**14**) [hydrogen atoms riding on the parent atoms, non-H atoms anisotropic]. Full details of data collection and structure refinement, atomic co-ordinates, thermal parameters, and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre.
Crystal data for **7**: $C_{17}H_{25}NO_2$, M_r = 275.38, orthorhombic $P2_12_12_1$, a = 5.6790(5), b = 13.1960(10), c = 20.1710(10) Å, U = 1511.6(2) Å^3, Z = 4, D_c = 1.210 g cm^{-3}, μ(Mo-Kα) = 0.78 cm^{-1}, F(000) = 600, T = 150K. *Crystal data for* **14**: $C_{26}H_{33}NO_3$, M_r = 407.53, triclinic P 1, a = 5.8680(10), b = 10.7490(10), c = 17.301(2) Å, α = 85.930 (9), β = 87.620(10), γ = 85.580(10)°, U = 1083.0(2) Å^3, Z = 2, D_c = 1.250 g cm^{-3}, μ(Mo-Kα) = 0.81 cm^{-1}, F(000) = 440, T = 150K.
3. J. A. Darr, S. R. Drake, M. B. Hursthouse and K. M. A. Malik, *Inorg. Chem.* 1993, **32**, 5704.
4. G. M. Sheldrick, *Acta Crystallogr., Sect. A*. 1990, **46**, 467.
5. G. M. Sheldrick, SHELXL-93 Program for Crystal Structure Refinement, University of Gottingen, Germany, 1993.
6 This material was prepared from cyclopent-1-ene-1-methanol[7] which was benzylated (NaH/BnBr/TBAI/THF), ozonised and treated with benzoylmethylenetriphenylphosphorane (1.3 eqv., DCM, rt., 24hrs).
7. J. B. Brown, H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.* 1950, 3634.
8. a) A. G. M. Barrett and A. Kamimura, *J. Chem. Soc. Chem. Commun.* 1995, 1755.
b) A. Kamimura, H. Mitsudera, S. Asano, A. Kakehi and M. Noguchi, *Chem. Commun.* 1998, 1095.
c) M. Ono, K. Nishimura, Y. Nagaoka and K. Tomioka, *Tetrahedron Lett.* 1999, **40**, 1509.
9. S, G. Davies and D. R. Fenwick, *J. Chem. Soc. Chem. Commun.* 1997, 565.
10. a) A. Itoh, S. Ozawa, K. Oshima and H. Nozaki, *Tetrahedron Lett.* 1980, **21**, 361.
b) D. M. Armistead and S. J. Danishefsky, *Tetrahedron Lett.* 1987, **28**, 4959.
c) M. J. Wanner and G-J. Koomen, *Tetrahedron.* 1992, **48**, 3935.
11. F. Roth, P. Gygax and G. Frater, *Tetrahedron Lett.* 1992, **33**, 1045.

Pergamon

Tetrahedron 57 (2001) 7771–7784

TETRAHEDRON

Assessing the scope of the tandem Michael/intramolecular aldol reaction mediated by secondary amines, thiols and phosphines

Elinor L. Richards,[a] Patrick J. Murphy,[a,*] Francesca Dinon,[a] Silvia Fratucello,[a] Paul M. Brown,[a] Thomas Gelbrich[b] and Michael B. Hursthouse[b]

[a]*Department of Chemistry, University of Wales, Bangor, Gwynedd LL57 2UW, UK*
[b]*Department of Chemistry, University of Southampton, Highfield, Southampton SO17 1BJ, UK*

Received 2 March 2001; revised 20 June 2001; accepted 12 July 2001

Abstract—The outcome of a tandem Michael/intramolecular aldol reaction which is mediated by secondary amines, thiols and phosphines has been found to be highly substrate dependent, with the best results being obtained for the formation of 5 and 6-membered rings using thiol or thiolate nucleophiles. Amine and phosphine mediated cyclisations were found to be problematic in several cases but were still effective methods for the formation of 5–7 membered rings. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

In our preliminary communications,[1] we described the ability of a range of nucleophiles, including secondary amines, thiols and phosphines to effect a tandem intramolecular Michael/aldol cyclisation of enones **1** leading to either the adducts **2** or the eliminated Baylis–Hillman type product **3**[1] (Scheme 1).

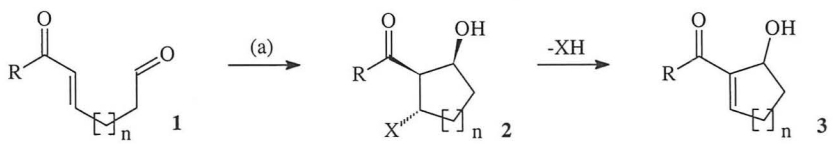
Following these preliminary studies we were keen to assess the scope of this reaction taking into account such variables as the nature of the nucleophile and the group R and the potential for variations in the ring size of the product formed. We were also interested in studying the mechanistic aspects of this reaction and this paper brings together our preliminary findings on these matters and our further studies on the process.

2. Preparation of aldehydes 1

The substrates (**1a–j**) for the investigation were prepared by reaction of a suitable phosphorus ylid with a dialdehyde prepared by either hydrolysis of 2,5-dimethoxytetrahydrofuran in the case of succinaldehyde (method A),[2] ozonolysis of a cycloalkene (method B) or using an aqueous solution of glutaraldehyde (method C) (Table 1). The crude products are purified by column chromatography and a *bis*-enone, obtained by double Wittig reaction on the dialdehyde, is generally obtained as a by-product of the reaction[3] which can lead to diminished yield. In the case of reactions in aqueous media, the yields are generally low and the *Z*-alkene isomers are also isolated in significant amounts (Scheme 2).

3. Reactions involving secondary amines

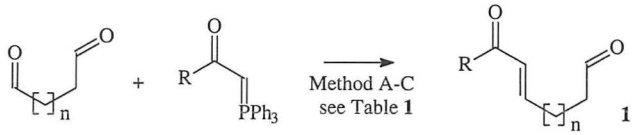
Our preliminary investigation stemmed from the observations that a suitable catalyst for effecting the conversion of the substrate **1a** into the cyclised product **3a** was the secondary amine piperidine. We thus performed a preliminary study of the reaction of other amines and it was apparent that piperidine was by far the superior choice of catalyst for effecting this transformation. The results in Table 2 illustrate that, with the exception of the hindered amine 2,6-dimethylpiperidine, all the secondary amines gave the expected cyclised product, however none of the



Scheme 1. (a) X=R_2N, R_3P^+, PhS; n=1,2; R=Alkyl, Ph.

Keywords: tandem Michael/intramolecular aldol reaction; secondary amine; thiols; phosphines.
* Corresponding author. Tel.: +44-01248-382392; e-mail: paddy@bangor.ac.uk

0040–4020/01/$ - see front matter
PII: S0040-4020(01)00744-X



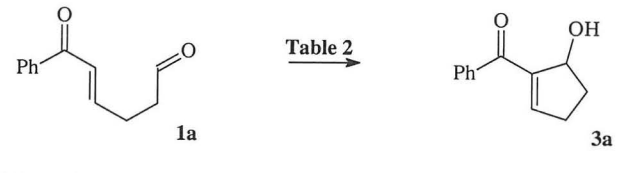
Scheme 2.

Table 1.

Entry	R	*n*	Method	Yield (%)
1a	Ph	1	A	48
1b	Ph	2	B/C	70/73
1c	Ph	3	B	41
1d	Ph	4	B	47
1e	Ph	5	B	49
1f	OEt	1	A	58
1g	OEt	2	C	*E*-41, *Z*-23
1h	OEt	3	B	38
1i	STol	1	A	46
1j	STol	2	C	32

Method A: $RCOCHPPh_3$, 2.0 equiv. succinaldehyde, CH_2Cl_2. Method B: (i) 10–20 equiv. cycloalkene, O_3, CH_2Cl_2, −78°C, (ii) PPh_3, −78°C, (iii) 1 equiv. $RCOCHPPh_3$. Method C: 20 equiv. glutaric dialdehyde (25% w/v in H_2O), EtOH, rt, $RCOCHPPh_3$.

catalysts showed an improvement in yield compared to piperidine. In addition, a trend was observed in the series piperidine, 2-methylpiperidine and 2,6-dimethylpiperidine, in that the yield of product decreases as steric bulk of the amine increases. To further investigate this reaction, we performed a series of experiments in which the concentra tion of substrate **1a** was varied. The previous experiment were all performed at a concentration of 0.35 M, on repeat ing at 0.18 and 0.09 M a slight increase in yield (ca. 5% fo 0.09 M) was observed for the formation of **3a**, howeve reaction time was increased for both reactions (10 an 15 days for 95% conversion, respectively) (Scheme 3).



Scheme 3.

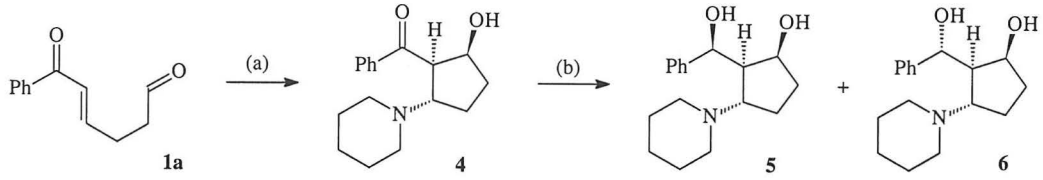
These observations suggest that the reaction for the forma tion of **3a** is concentration dependent, however on close inspection of the NMR data for these reactions, it wa apparent that the reaction was proceeding through a long lived and fairly stable intermediate which we presumed t be the product of 1,4-addition and intramolecular aldo condensation (**4**). This was indeed shown to be true, a treatment of aldehyde **1a** with an excess of piperidine i chloroform effected a complete transformation of the start ing material to the intermediate **4** (together with a sma amount of **3a**). In addition, **4** was stable for long period of time (>7 days) in chloroform solution and very littl further conversion to **3a** was observed. Furthermore evaporation of the chloroform, followed by treatment of methanolic solution of **4** with sodium borohydride gave separable 1:1.3 mixture of the diols **5** and **6** in 67% overal yield, the former providing crystals suitable for X-ray analy sis[1b] which confirmed the relative stereochemistry of th intermediate **4**, as that depicted (Scheme 4).

We repeated this reaction using the enone **1b** and found tha the adduct **8** was formed very rapidly. The presence o signals at δ 3.2 (1H, ddd, J=3, 12, 12 Hz), 3.6 (1H, dd J=2.0, 12 Hz) and 4.2 (1H, m), indicated that the relativ stereochemistry of **8** is as illustrated. In addition, it wa apparent that the reaction leading to **8** was proceeding vi an intermediate enol, possibly of structure **7**, as indicated b signals at δ 4.3 (1H, dt, J=14, 7.5 Hz) and 5.8 (1H, d J=14 Hz). Again, **8** was found to be stable in solution fo prolonged periods of time with only ca. ~10% conversio

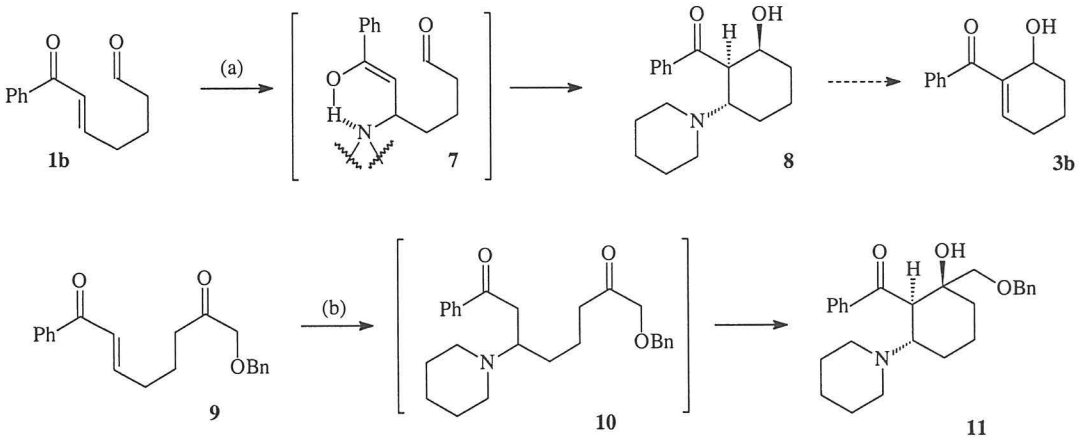
Table 2.

Amine[a]	% Conversion	% **3a**[b]	% Recovery	% Dec.
Piperidine	93	55 (50)	7	38
2-Methylpiperidine	97	30 (26)	3	67
2,6-Dimethylpiperidine[c]	63	0	37	63
Morpholine	74	16	39	45
Piperazine	94	28	9	63
N-Methylpiperazine	83	21	25	54
Pyrrolidine	82	15	18	67
Di-*n*-butylamine	100	15	0	85

[a] Conditions: catalyst (30 mol%), $CDCl_3$ (0.35 M), rt, 7 days.
[b] Yields are calculated from ^1H NMR data, with yields in brackets being isolated yields.
[c] A mixture of the *cis*- and *trans*-amines was used.



Scheme 4. (a) 1.3 equiv. piperidine, $CHCl_3$, 10 min, rt, (b) $NaBH_4$, MeOH, 0°C.

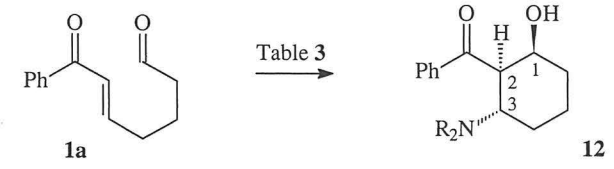


Scheme 5. (a) 1.3 equiv. piperidine, $CHCl_3$, (b) 1.3 equiv. piperidine, $CHCl_3$; 60%.

to the cyclohexenol **3b** being observed over 28 days. We were also able to isolate the adduct **11** which arose from the addition of piperidine to ketone **9**[4] and found that this compound gave suitable crystal for X-ray structure determination which confirmed the stereochemistry as that shown below.[1b] Interestingly, this cyclisation took considerably longer to effect than the previous case, requiring six days for complete reaction, possibly reflecting the lower reactivity of ketones. We were also able to observe (NMR) the intermediate conjugate adduct **10** in the reaction mixture and, as in other cases, the Michael/aldol sequence proceeded to give a single diastereoisomer by NMR and as yet we have been unable to isolate any minor diastereomeric products (Scheme 5).

As it was apparent that the intermediates **4**, **8** and **11** are easily formed, we decided to investigate their presence in the reactions of a variety of amines (Table 3). Reaction of **1b** with a 1.3 molar excess of the amine, whilst following the reaction by NMR and observing the signals in the intermediate **12** for H_1, H_2 and H_3, illustrated that again piperidine was the best base for effecting this transformation (Scheme 6).

As can be seen, the only amines leading to the intermediate adduct **12** in a good yield are the 6-membered cyclic amines piperidine and 1-methylpiperazine. The 4-, 5- and 7-membered cyclic amines together with dibenzylamine predominantly gave products of decomposition arising from self-aldol condensations of the substrate **1b**. The reason for the success of the reaction only with 6-membered amines is unclear but it is unlikely to be differences in basicity owing to the similarity in structure of the amines employed. As previously stated, it is likely that the reaction is proceeding via an intermediate enol similar in structure to **7** and it may be that the propensity to form this moiety is the key to the success or failure of the reactions. It is possible that changes in the structure of the base have a significant influence on the stability of this intermediate or even its ability to be formed. Whatever this reason might be, it is obvious that the reaction is susceptible to changes in structure of the amine and it is likely that progress with this methodology is best focused on the development of further 6-membered cyclic amine systems.



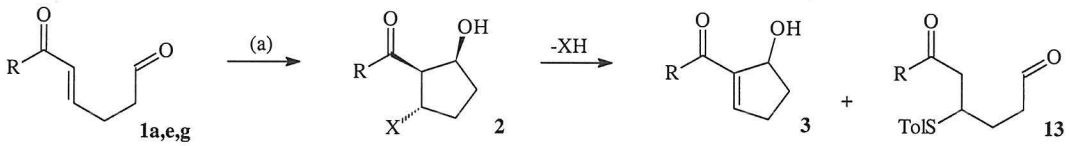
Scheme 6. (a) 1.3 equiv. $R_2NH/CDCl_3$, 0–7 days.

4. Systematic modification of substrates and catalyst

With these preliminary studies in hand, we next embarked upon a systematic study of the cyclisation process and chose to investigate the use of different electron withdrawing groups in the Michael substrate and to couple these modifications with variation in ring size and the use of other nucleophiles. This decision was based upon literature reports that metal thiolates and selenates,[6] or metallated amines[7] can be used in tandem Michael-aldol reactions, including some cyclisations,[8] and that phosphines can catalyse intramolecular Baylis–Hillman reactions,[9] albeit in poor isolated yield. Our first area of investigation focused on the formation of the 5-membered adducts **2** or the corresponding cyclopentenols **3** using either the

Table 3.

Amine	Time	**12** (%)	Decomp. (%)	H_1 (J)	H_2 (J)	H_3 (J)
Azetidine	2 h	0	100	–	–	–
Pyrrolidine	24 h	~25	~75	4.18 (br m)	3.57 (dd, 2, 11)	3.47 (ddd, *J*=3, 11, 11)
Piperidine	10–15 min	>90	<10	4.20 (br m)	3.60 (dd, 2, 12)	3.20 (ddd, *J*=3, 12, 12)
1-Methylpiperazine	3 h	>85	<15	4.14 (br m)	3.68 (dd, 2, 11)	3.47 (ddd, *J*=3, 12, 12)
Homopiperidine	24 h	~5	~95	4.17 (br m)	3.58 (dd, 2, 11)	3.30 (obscured)
Dibenzylamine	7 days	Trace	>95	–	–	–



Scheme 7.

Table 4.

Entry	Substrate	R	Method	X	2[a]	3	13[a]
1	**1a**	Ph	1.3 equiv. piperidine, $CDCl_3$, 10 min	Piperidyl	**4**, 90%[b]	–	–
2	**1a**	Ph	0.3 equiv. piperidine, $CDCl_3$, 144 h	Piperidyl	–	**3a**, 50%	–
3	**1a**	Ph	1.3 equiv. TolSH, $CHCl_3$, 16 h	TolS	**2aT**, 77%	–	Trace
4	**1a**	Ph	0.2 equiv. *n*-Bu_3P, $CDCl_3$, 17 h	–	–	**3a**, 20%	–
5	**1f**	OEt	1.3 equiv. piperidine, $CDCl_3$ 2 days	Piperidyl	Dec[c]	–	–
6	**1f**	OEt	0.3 equiv. piperidine, $CDCl_3$ 2 days	Piperidyl	Dec[c]	–	–
7	**1f**	OEt	2 equiv. TolSH, 0.2 TolSNa, Δ, 16 h	TolS	**2fT**, 72%	–	**13fT**, 10%
8	**1f**	OEt	0.4 equiv. *n*-Bu_3P, $CDCl_3$, 28 days	–	–	**3f**, 40%	–
9	**1i**	STol	1.3 equiv. piperidine, $CDCl_3$, 2 days	Piperidyl	**2iP**, 10%[b]	–	–
10	**1i**	STol	0.3 equiv. piperidine, $CDCl_3$, 2 days	Piperidyl	Dec[c]	–	–
11	**1i**	STol	3 equiv. TolSH, Δ, $CHCl_3$, 12 h	TolS	**2iT**, 56%	–	Trace
12	**1i**	STol	0.4 equiv. *n*-Bu_3P, $CDCl_3$, 1 h	–	Dec[d]	–	–

[a] **P** refers to adducts derived from piperidine, **T** from *p*-TolSH.
[b] As observed by NMR of the progress of the reaction.
[c] Largely composed of products derived from aldol condensation.
[d] Unidentified decomposition products.

piperidine-based methodology described earlier, or by the use of thiolate or phosphine-based catalyst; these results are summarised in Table 4 (Scheme 7).

Our investigations on the 5-membered series focused on the use of an aryl ketone (**1a**), ester (**1f**) or thiolester (**1i**) acceptor group and the reactions with piperidine were attempted first. Reaction of the ketone **1a** gave, as previously noted, the adduct **4** with excess piperidine (entry 1) and the cyclised product **3a** with 0.3 equiv. (entry 2). However, application of these conditions (entries 5 and 6) to the ester-containing substrate **1f** gave only products derived from aldol condensation of the aldehyde function, possibly reflecting the lower reactivity of α,β-unsaturated esters towards Michael reactions. Similar reactions of the thiolester-containing substrate **1i** with piperidine (entries 9 and 10) were also complicated by considerable decomposition, including some evidence of amide formation (by displacement of the thiotolyl group) and aldol reaction processes, and only a low yield (10%) of the intermediate adduct **2iP** was observed to be formed.

Turning our attention to the use of a thiol as the nucleophile in the reaction, we were pleased to observe that the addition of an excess of *p*-TolSH to a chloroform solution of **1a** at room temperature effected the cyclisation to the adduct **2aT** in 77% isolated yield (entry 3). Careful analysis of the NMR of the crude reaction mixture failed to show the presence of any other isomeric compounds. Similar treatment of the ester-substituted **1e** failed to effect this transformation even at reflux in chloroform. However, if the reaction was performed with 2 equiv. of *p*-TolSH and a catalytic quantity of *p*-TolSNa[10], the adduct **2fT** was obtained in 72% yield (entry 7) as well as the addition product **13fT** in 10% yield. We were able to grow crystals of **2fT** which were suitable for X-ray analysis[11] and this confirmed the structure to be as illustrated in Fig. 1. Cyclisation of the thiolester substrate **1i** did not require the use of sodium thiolate as a catalyst, however refluxing the reaction for 12 h was essential to

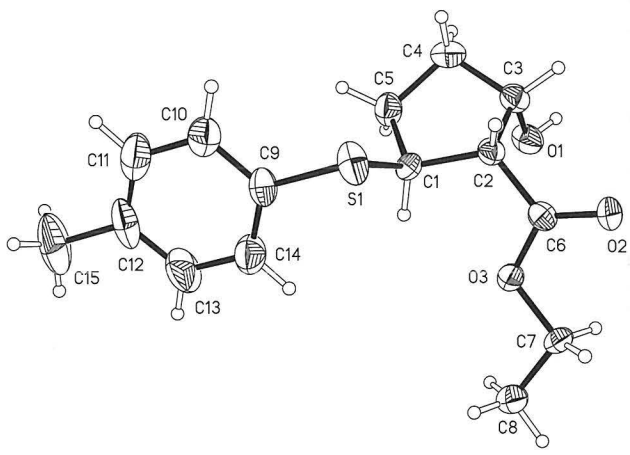


Figure 1. X-Ray structure of **2fT**.

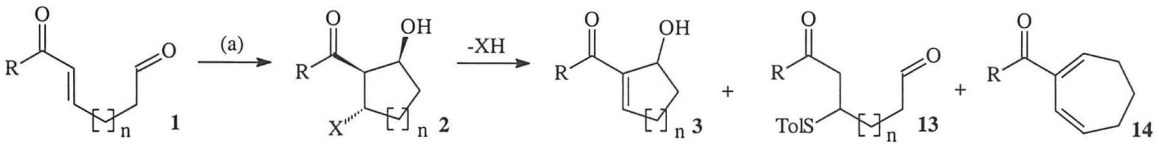
ffect the formation of the adduct **2iT** in 56% yield (entry 1). Again, careful analysis of the NMR of the crude eaction mixture seemed to suggest that the reaction gave ssentially a single product.

/e next investigated the use of phosphines and found that eatment of a solution of enone **1a** in chloroform with a atalytic amount of *n*-Bu_3P led to the formation of the reviously prepared enone **3a** in a mediocre 20% yield ntry 4) and similar treatment of **1f** led to the formation f **3f** in 40% yield, however a prolonged reaction time was equired (entry 8). Not surprisingly, treatment of thiolester i under these conditions led to a rapid complete ecomposition.

/e turned our attention to the reactions of enone substrate **b**, the ester **1g** and the thioester **1j** which, on cyclisation, ould lead to 6-membered adducts **2** or cyclohexenes **3**. The esults of these investigations together with the results of ur cyclisation attempts to give 7- and 9-membered ring ystems are reported in Table 5 (Scheme 8).

As previously reported,[1] reaction of the ketone **1b** with excess piperidine gave the adduct **2bP** (entry 1) and the cyclised product **3b** using 0.3 equiv. (entry 2). However, as with the 5-membered series, application of these conditions (entries 5 and 6) to the ester-containing substrate ***E*-1g** gave only products derived from aldol condensation of the aldehyde function. Similarly, reaction of the thiolester-containing substrate **1j** with piperidine (entries 10 and 11) was complicated by considerable decomposition, including amide formation and aldol condensations with only a low yield (ca. 5%) of the intermediate adduct **2jP** being observed by NMR.

The use of a thiol as the nucleophile in the reaction was again very successful and we were pleased to observe that the addition of an excess of *p*-TolSH to a chloroform solution of **1b** at room temperature effected the cyclisation to the adduct **2bT** in 93% isolated yield as the sole cyclisation product (entry 3). A similar treatment of the ester-substituted ***E*-1g** failed to effect the transformation even at reflux in chloroform, however, if the reaction was



cheme 8.

able 5.

ntry	Substrate	R	*n*	Method[a]	X	2[b]	3	13	14
	1b	Ph	2	1.3 equiv. piperidine, 10 min	Piperidyl	**2bP**, 90%[c]	–	–	–
	1b	Ph	2	0.3 equiv. piperidine, 14–28 days	Piperidyl	–	**3b**, 24–30%	–	–
	1b	Ph	2	1.3 equiv. TolSH, 16 h rt	TolS	**2bT**, 93%	–	Trace	
	1b	Ph	2	0.2 equiv. nBu_3P, 2 h	–	–	**3b**, 75%	–	–
	***E*-1g**	OEt	2	1.3 equiv. piperidine	Piperidyl	Dec[d]	–	–	–
	***E*-1g**	OEt	2	0.3 equiv. piperidine	Piperidyl	Dec[d]	–	–	–
	***E*-1g**	OEt	2	2 equiv. TolSH, 0.2 TolSNa, Δ, 16 h	TolS	**2gT**,[e] 75%	–	Trace	–
	***E*-1g**	OEt	2	0.2 equiv. *n*-Bu_3P, 24 h	–	–	**3g**, 50%	–	–
	***Z*-1g**	OEt	2	0.2 equiv. *n*-Bu_3P, 24 h	–	–	**3g**, 70%	–	–
)	**1j**	STol	2	1.3 equiv. piperidine, 2 days	Piperidyl	**2jP**,[c] ca. 5%	–	–	–
l	**1j**	STol	2	0.3 equiv. piperidine, 2 days	Piperidyl	**2jP**,[c] ca. 5%	–	–	–
2	**1j**	STol	2	2 equiv. TolSH, 0.2 TolSNa, Δ, 16 h	TolS	**2jT**,[e] 60%	–	Trace	–
3	**1j**	STol	2	0.4 equiv. *n*-Bu_3P, 17 h	–	Rapid dec[f]	–	–	–
4	**1c**	Ph	3	1.3 equiv. piperidine	Piperidyl	Dec[d]	–	–	–
5	**1c**	Ph	3	0.3 equiv. piperidine	Piperidyl	Dec[d]	–	–	–
6	**1e**	Ph	5	1.3 equiv. piperidine	Piperidyl	Dec[d]	–	–	–
7	**1e**	Ph	5	0.3 equiv. piperidine	Piperidyl	Dec[d]	–	–	–
8	**1c**	Ph	3	2 equiv. TolSH, 0.2 TolSNa, Δ, 16 h	TolS	–	–	**13cT**, 79%	–
9	**1e**	Ph	5	2 equiv. TolSH, 0.2 TolSNa, Δ, 16 h	TolS	–	–	**13eT**, 79%	–
0	**1c**	Ph	3	0.2 equiv. *n*-Bu_3P, 2 days	–	Trace[c]	–	–	**14c**, 77%
1	**1c**	Ph	3	0.2 equiv. nBu_3P, 2 days, C_6D_6	–	Trace[c]	–	–	**14c**, 46%
2	**1d**	Ph	4	0.2 equiv. *n*-Bu_3P, 6 days	–	No reaction	–	–	–
3	**1e**	Ph	5	0.2 equiv. *n*-Bu_3P, 6 days	–	No reaction	–	–	–
4	**1h**	OEt	3	0.2 equiv. *n*-Bu_3P, 6 days	–	Trace[c]	**3h**, 16%	–	**14h**, 10%

All reactions performed in $CHCl_3$ or $CDCl_3$ at rt unless specified.
P refers to adducts from piperidine, **T** from *p*-TolSH.
As observed by NMR of the progress of the reaction.
Largely composed of products derived from aldol condensation.
Major isomer; see text.
Unidentified decomposition products.

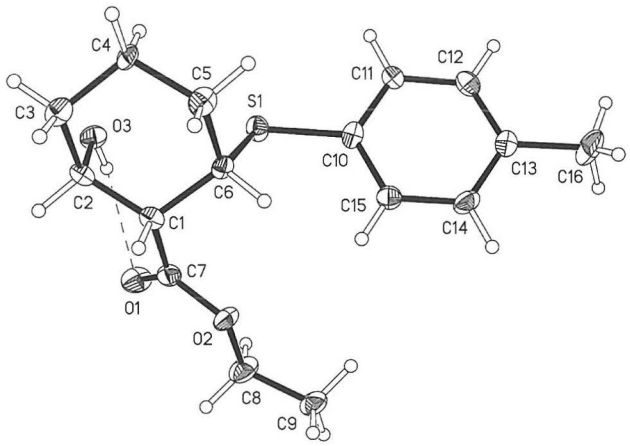


Figure 2. X-Ray structure of **2gTb**.

performed with 2 equiv. of *p*-TolSH and a catalytic quantity of *p*-TolSNa,[12] the adduct **2gT** was obtained in 75% yield (entry 7). Interestingly, we were able to isolate two further compounds **2gTa** and **2gTb** from this reaction in 7 and 5% yield, respectively. The stereochemistry of **2gTa** was determined by proton NMR, as the C-2 methine proton displayed two large *trans*-diaxial coupling constants (δ=2.33 ppm, J=11.5, 12 Hz) whilst the stereochemistry of **2gTb** was assigned using X-Ray analysis[11] (Fig. 2). Similarly, treatment of the thiolester-containing substrate **1j** under identical conditions led to the formation of the adduct **2jT** in 60% yield (entry 11). Again, two minor by-products **2jTa** and **2jTb** were isolated in 7 and 6% yield, respectively. The stereochemistry of **2jTa** was again determined from proton NMR as the C-2 methine proton displayed two large *trans*-diaxial coupling constants (δ=2.69 ppm, J=11.5, 9.7 Hz) whilst the stereochemistry of **2jTb** was tentatively assigned, based on the signal for the C-2 methine proton (δ=3.04 ppm, J=4.3, 9.4 Hz) (Scheme 9).

We next investigated the use of phosphines and found that treatment of a solution of enone **1b** in chloroform with a catalytic amount of *n*-Bu_3P led to the formation of the previously prepared enone **3b** in an excellent (75%) yield (entry 4). We also found that treatment of ***E*-1g** gave the cyclised product **3g** in 50% yield (entry 8) and the corresponding compound ***Z*-1g** gave the same compound in a improved 70% yield; the exact reason for this higher yie is unclear. Again, unsurprisingly, treatment of thiolest **1j** under these conditions led to a rapid comple decomposition.

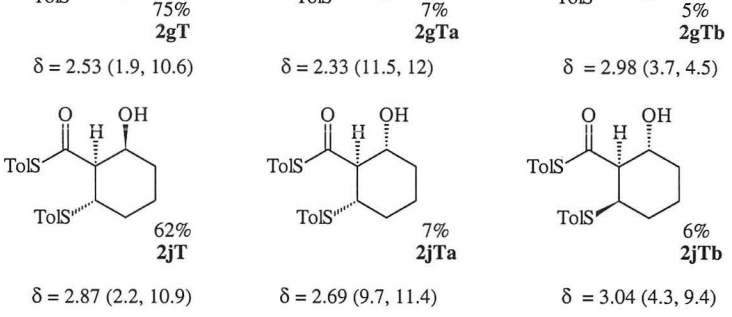
With these results in hand, we decided to investigate th formation of medium ring carbocycles using the substrat **1c** and **1e**. We firstly treated the substrates **1c** and **1e** wi both stoichiometric and catalytic amounts of piperidine differing concentrations (entries 14–17) and it was appare from these reactions that intermediate adducts **2c** and **2e** cycloalkenols **3c** and **3e** were not formed, even prolonged reaction time. Again the formation of ald related products was the major reaction pathway. Reactio of **1c** and **1e** with *p*-TolSH and *p*-TolSNa under th previously detailed conditions led to the formation of th Michael adducts **13c** and **13e** as the only products even reflux for long periods (entries 18, 19).

More success was obtained with the use of phosphines ar treatment of **1c** with 0.2 equiv. of *n*-Bu_3P for 48 h led to th formation of a trace amount of the cycloheptenol **3c**, evidenced by NMR, together with the cycloheptadien **14c** as the major product in 77% isolated yield (entry 20 This product was unexpected and similar products were n observed in any previous *n*-Bu_3P catalysed cyclisatio reaction. In order to determine if this elimination was occu ring due to an interaction between the phosphine and th deuterochloroform, we repeated the reaction in D_6-benzer with comparable results (entry 21). Treatment of th substrates **1d** and **1e** under identical conditions failed give the corresponding cycloocta- or cyclononadienes indeed any reaction product (entry 22, 23).

Treatment of the ester-containing substrate **1h** under thes conditions also led to the formation of the cycloheptadien **14h** but in much lower yield, in this case however, th expected Baylis–Hillman product **3h** was also obtained low yield (entry 24).

5. Conclusion

It is apparent from these results that the amine catalyse



Scheme 9.

yclisations are limited in scope to the 5- and 6-membered yclisations with enones as the Michael acceptors; yields or the tandem processes being high in both cases. ields for the formation of the eliminated products using catalytic amount of piperidine are satisfactory with none substrates, however, enoate and thioenoate xamples lead only to decomposition. The phosphine ediated cyclisations work best for the 6- and 7-membered nones and for the 6-membered enoate substrates leading the Baylis–Hillman products or the eliminated ycloheptadiene **14c** in high yield. Less success was bserved with the 5-membered enone and enoate substrates, hilst the thioenoates were totally unsuitable for this eaction. In contrast, the thiol and thiolate mediated yclisations were by far the most successful reactions roceeding for all the 5- and 6-membered substrates in 6–93% yield for the formation of the major adduct ith excellent stereoselectivity which is comparable ith stoichiometric methods such as those using dimethyluminiumthiophenylates[8a] or lithium thiophenoxide.[8b] Ve are currently investigating synthetic applications of nese reactions and will report our findings in due ourse.

6. Experimental

eagents: All reagents were obtained from commercial uppliers and were used without further purification.

olvents: Solvents were purified when necessary using tandard methods, in particular, dichloromethane (DCM) as distilled over calcium hydride. Petrol refers to the raction of petroleum spirit boiling in the range 40–60°C. *hromatography:* The purity of compounds was assessed y thin layer chromatography (TLC). Unless otherwise tated, all new compounds were homogeneous as indicated y TLC. TLC was performed on BDH glass silica plates oated with Kieselgel 60 F254 (Art. 5554, Merck). ompounds were visualised by examination under ultraiolet light or staining by contact with a solution of phoshomolybdic acid (PMA) in ethanol and heating to 180°C. olumn chromatography was performed using Merck 7736 ilica gel under medium pressure with the eluting solvent pecified in each case.

nalytical methods: Melting points were determined using a allenkamp capillary apparatus and are uncorrected. Infraed (IR) spectra were recorded as thin films on NaCl plates oils) or KBr discs (solids) using a Perkin–Elmer 1600 FTIR pectrometer. Microanalyses were obtained using a Carbo–rba Model 1106 CHN analyser. Electron impact (EI), hemical ionisation (CI), fast atom bombardment and high esolution mass spectra were recorded using a VG Masslab odel 12/253 spectrometer by the EPSRC Mass Spectroetry Service at Swansea. Proton NMR spectra were ecorded at 250 MHz using a Bruker AC250 spectrometer. arbon NMR spectra were recorded using the Bruker C250 spectrometer at 62.9 MHz and were broadbandecoupled. All spectra were recorded in $CDCl_3$ unless therwise stated. Chemical shifts are reported as δ values elative to tetramethylsilane.

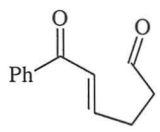
6.1. General conditions for the Wittig reaction with dialdehydes

Method A: The required phosphorane (1 equiv.) was dissolved in dry DCM (10 ml per gram of phosphorane) and added dropwise to a solution of succinaldehyde (4 equiv.) as a cooled (0°C) solution in DCM (3×the volume employed for the phosphorane) and the resulting solution stirred for 48 h. The solution was then washed with a large volume of water (typically 3×250 ml for each 100 ml of reaction solvent) and after drying and evaporation of the solvent, the resulting solid mass was triturated with ether (ca. 50–100 ml) then diluted with petrol (ca. 25–50 ml) and the supernatant liquid decanted with filtration. After repeating this process a further three times, the combined filtrates were dried ($MgSO_4$), evaporated and subjected to chromatography (ether/petrol) to yield the products **1**.

Method B: The cycloalkene (10–20 equiv.) was dissolved in dry dichloromethane (15 ml per g) and cooled to −78°C whereupon ozone was bubbled in the flask until the solution became blue in colour and at this point, the reaction was flushed with nitrogen gas and triphenylphosphine (equivalent to the amount of cycloalkene) was added in one portion and the reaction stirred until it dissolved and for a further 30 min. The phosphorane (1 equiv.) was then added and the reaction stirred to room temperature overnight. The reaction solvent was evaporated and the solid mass remaining was triturated with ether (ca. 3×100 ml). The triturates were then filtered, combined and washed with a large volume of water (ca. 3×250 ml), then dried ($MgSO_4$) and evaporated. Silica gel chromatography (ether/petrol) gave the products **1**.

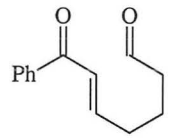
Method C: The required phosphorane (1 equiv.) was dissolved in EtOH (20 ml per g of phosphorane) at room temperature whereupon aqueous glutaric dialdehyde solution (20 equiv.) was added and the reaction stirred overnight at room temperature. Water (ca. 50 ml per g of phosphorane) was added and the reaction extracted with ether (typically 3×200 ml) and the combined ether extracts washed with aqueous HCl solution (0.2 M, ca. 3×300 ml), followed by brine (ca. 3×50 ml). After drying ($MgSO_4$) and evaporation, silica gel chromatography (ether/petrol) gave the products **1**.

6.1.1. *E*-6-Phenyl-6-oxohex-4-enal (1a).



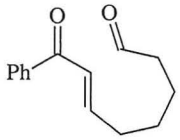
Method A: Phosphorane (3.55 g; 9.4 mmol) gave 840 mg, 48%; 20–50% ether in petrol, R_f=0.29 (50% ether in petrol). ^{1}H NMR: δ=2.65 (4H, m, 2×CH_2), 6.90–7.10 (2H, m, 2×CH), 7.6–8.0 (5H, m, Ph), 9.82 (1H, s, CHO). ^{13}C NMR: δ=24.97 (CH_2), 41.92 (CH_2), 126.74 (CH), 128.48 (CH), 128.54 (CH), 132.78 (CH), 137.64 (C), 146.67 (CH), 190.33 (C=O), 200.37 (CHO). IR: ν_{max}=3058, 2897, 2826, (C–H), 2725 (CHO), 1722 (C=O), 1670 (C=O), 1621 (C=C) cm^{-1}. MS (CI): 206 (100%, $[M+NH_4]^+$), 189 (70%, $[M+H]^+$). HRMS: $C_{12}H_{13}O_2$ ($[M+H]^+$) requires 189.0916, found 189.0916.

6.1.2. *E*-7-Phenyl-7-oxohept-5-enal (1b).



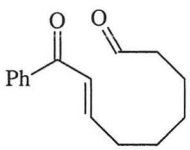
Method B: Cyclopentene (8.9 g, 0.13 mol) and phosphorane (5.0 g; 13.2 mmol) gave 1.87 g, 70%. Method C: Phosphorane (4.02 g; 10.6 mmol) gave 1.54 g, 73%; 30% ether in petrol, R_f=0.10 (30% ether in petrol). ^{1}H NMR: δ=1.90 (2H, quintet, J=7.3 Hz, CH_2), 2.37 (2H, dt, J=6.7, 7.3 Hz, CH_2), 2.50 (2H, dt, J=0.8, 7.3 Hz, CH_2), 6.70–7.10 (2H, m, 2×CH), 7.40–8.00 (5H, m, Ph), 9.80 (1H, t, J=0.8 Hz, CHO). ^{13}C NMR: δ=20.49 (CH_2), 31.83 (CH_2), 42.99 (CH_2), 126.64 (2×CH), 128.49 (2×CH), 128.52 (CH), 132.72 (CH), 137.77 (C), 147.97 (CH), 190.55 (C=O), 201.55 (CHO). IR: ν_{max}=3056, 2930 (C–H), 2726 (CHO), 1722 (C=O), 1669 (C=O), 1620 (C=C) cm^{-1}. MS (CI): 220 (80%, $[M+NH_4]^+$), 203 (100%, $[M+H]^+$). HRMS: $C_{13}H_{15}O_2$ ($[M+H]^+$) requires 203.1072, found 203.1072.

6.1.3. *E*-8-Phenyl-8-oxo-6-octenal (1c).



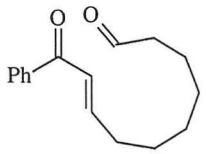
Method B: Cyclohexene (16.4 g, 200 mmol) and phosphorane (3.88 g, 10 mmol) gave 0.878 g, 41%; 20% ether in petrol, R_f=0.17 (20% ether in petrol). ^{1}H NMR: δ=1.50–1.70 (4H, m, 2×CH_2), 2.37 (2H, app q, J=6.4 Hz, CH_2), 2.49 (2H, dt, J=1.5, 7.0 Hz, CH_2), 6.90 (1H, d, J=14.5 Hz, CH), 7.03 (1H, dd, J=6.4, 14.5 Hz, CH), 7.43–7.95 (5H, m, Ph), 9.78 (1H, d, J=1.5 Hz, CHO). ^{13}C NMR: δ=21.58 (CH_2), 27.61 (CH_2), 32.49 (CH_2), 43.58 (CH_2), 126.24, 128.51, 132.67 (6×CH), 137.85 (C), 148.88 (CH) 190.26 (C=O), 202.15 (CHO). IR: ν_{max}=2935 (C–H), 2724 (CHO), 1722 (C=O), 1668 (C=O), 1619 (C=C) cm^{-1}. MS (CI): 234 (100%, $[M+NH_4]^+$), 217 (70%, $[M+H]^+$). HRMS: $C_{14}H_{17}O_2$ ($[M+H]^+$) requires 217.1229, found 217.1226.

6.1.4. *E*-9-Phenyl-9-oxo-7-nonenal (1d).



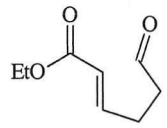
Method B: Cycloheptene (4.81 g, 50 mmol) and phosphorane (3.04 g, 8.0 mmol) gave 0.858 g, 47%; 20% ether in petrol, R_f=0.16 (20% ether in petrol). ^{1}H NMR: δ=1.30–1.80 (6H, m, 3×CH_2), 2.34 (2H, app q, J=7.0 Hz, CH_2), 2.46 (2H, t, J=7.3 Hz, CH_2), 6.88 (1H, d, J=16.5 Hz, CH), 7.05 (1H, m, CH), 7.45–7.95 (5H, m, Ph), 9.78 (1H, s, CHO). ^{13}C NMR: δ=21.78 (CH_2), 27.92 (CH_2), 28.69 (CH_2), 32.54 (CH_2), 43.73 (CH_2), 126.08, 128.51, 132.63 (6×CH), 138.00 (C), 149.40, (CH) 190.81 (C=O), 202.44 (CHO). IR: ν_{max}=2930 (C–H), 2721 (CHO), 1721 (C=O), 1668 (C=O), 1618 (C=C) cm^{-1}. MS (CI): 248 (100%, $[M+NH_4]^+$), 231 (55%, $[M+H]^+$). HRMS: $C_{15}H_{19}O$ ($[M+H]^+$) requires 231.1385, found 231.1385.

6.1.5. *E*-10-Phenyl-10-oxo-8-decenal (1e).



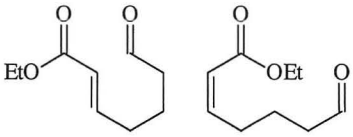
Method B: Cyclooctene (11.0 g, 0.10 mol) and phosphoran (3.82 g, 10.0 mmol) gave 1.19 g, 49%; 25% ether in petro R_f=0.16 (25% ether in petrol). ^{1}H NMR: δ=1.30–1.70 (8H m, 4×CH_2), 2.32 (2H, app q, J=7.0 Hz, CH_2), 2.45 (2H, d J=1.0, 6.7 Hz, CH_2), 6.85 (1H, d, J=15.3 Hz, CH), 7.0 (1H, dd, J=7.0, 15.3 Hz, CH), 7.40–7.95 (5H, m, Ph 9.75 (1H, d, J=1.0 Hz, CHO). ^{13}C NMR: δ=21.90 (CH_2 27.94 (CH_2) 28.90 (CH_2), 28.93 (CH_2), 32.70 (CH_2), 43.8 (CH_2), 125.99, 128.50, 132.60 (6×CH), 137.96 (C), 149.7 (CH) 190.87 (C=O), 202.65 (CHO). IR: ν_{max}=2931, 285 (C–H), 2720 (CHO), 1722 (C=O), 1669 (C=O), 161 (C=C) cm^{-1}. MS (CI): 262 (100%, $[M+NH_4]^+$), 24 (80%, $[M+H]^+$. HRMS: $C_{16}H_{21}O_2$ ($[M+H]^+$) require 245.1542, found 245.1542.

6.1.6. *E*-6-Ethoxy-6-oxo-4-hexenal (1f).



Method A: Phosphorane (2.84 g; 8.1 mmol) gave 730 mg 58 %; 50% ether in petrol, R_f=0.30 (50% ether in petrol). ^{1}H NMR: 1.30 (3H, t, J=7.1 Hz, CH_3), 2.50–2.70 (4H, m 2×CH_2), 4.19 (2H, q, J=7.1 Hz, CH_2), 5.85 (1H, d J=15.7 Hz, CH), 6.94 (1H, dd, J=6.4, 15.7 Hz, CH), 9. (1H, d, J=0.7 Hz, CHO). ^{13}C NMR: δ=14.23 (CH_3), 24.4 (CH_2), 41.83 (CH_2), 60.34 (CH_2), 122.46 (CH), 146.2 (CH), 166.26 (C=O), 200.33 (CHO). IR: ν_{max}=298 2832 (C–H), 2727 (CHO), 1721 (C=O), 165 (C=C) cm^{-1}. MS (CI): 174 (100%, $[M+NH_4]^+$). HRMS $C_8H_{16}NO_3$ ($[M+NH_4]^+$) requires 174.1130, foun 174.1129.

6.1.7. *E*- and *Z*-7-Ethoxy-7-oxo-5-heptenal (*E*-1g an *Z*-1g).



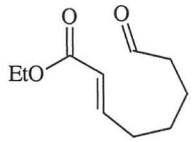
Method C: Phosphorane (3.66 g, 10.5 mmol) gave ***Z*-1g** 410 mg, 23% and ***E*-1g**, 737 mg, 41%; 10% ether in petro R_f=0.14 and 0.07 (10% ether in petrol).

Data for ***Z*-1g**. ^{1}H NMR: 1.18 (3H, t, J=7.1 Hz, CH_3), 1.7 (2H, app quintet, J=7.3 Hz, CH_2), 2.40 (2H, t, J=7.2 H CH_2), 2.60 (2H, app q, J=7.4 Hz, CH_2), 4.05 (2H, d J=7.1 Hz, CH_2), 5.72 (1H, d, J=11.4 Hz, CH), 6.11 (1H dd, J=7.4, 11.4 Hz, CH) 9.28 (1H, s, CHO). ^{13}C NMR δ=14.12 (CH_3), 21.17 (CH_2), 27.98 (CH_2), 43.05 (CH_2 59.73 (CH_2), 120.67 (CH), 148.44 (CH), 166.05 (C=O

01.83 (CHO). IR: ν_{max}=3038, 2982, 2937, 2826 (C–H), 724 (CHO), 1722 (C=O), 1644 (C=C) cm^{-1}. MS (CI): 88 (100%, $[M+NH_4]^+$), 171 (30%, $[M+H]^+$). HRMS: $_9H_{15}O_3$ ($[M+H]^+$) requires 171.1021, found 171.1018.

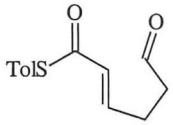
Data for ***E-1g***. ^{1}H NMR: 1.05 (3H, t, J=7.1 Hz, CH_3), 1.57 2H, app quintet, J=7.3 Hz, CH_2), 2.05 (2H, app q, =7.1 Hz, CH_2), 2.27 (2H, t, J=7.0 Hz, CH_2), 3.93 (2H, , J=7.1 Hz, CH_2), 5.61 (1H, d, J=15.6 Hz, CH), 6.69 1H, dd, J=6.8, 15.6 Hz, CH), 9.54 (1H, s, CHO). ^{13}C NMR: δ=14.24 (CH_3), 20.30 (CH_2), 31.22 (CH_2), 42.93 CH_2), 60.27 (CH_2), 122.25 (CH), 147.53 (CH) 167.50 C=O), 201.62 (CHO). IR: ν_{max}=2982, 2938 (C–H), 724 (CHO), 1716 (C=O), 1653 (C=C) cm^{-1}. MS (CI): 88 (100%, $[M+NH_4]^+$), 171 (25%, $[M+H]^+$). HRMS: $_9H_{15}O_3$ ($[M+H]^+$) requires 171.1021, found 171.1023.

.1.8. *E*-8-Ethoxy-8-oxo-6-octenal (1h).



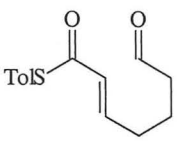
Method B: Cycloheptene (16.4 g, 171 mmol) and phosphorane (3.48 g, 10.0 mmol) gave 700 mg, 38%; 40% ether in petrol, R_f=0.22 (40% ether in petrol). ^{1}H NMR: 1.29 (3H, t, =7.0 Hz, CH_3), 1.48–1.70 (4H, m, 2×CH_2), 2.23 (2H, app , J=7.0 Hz, CH_2), 2.47 (2H, t, J=7.0 Hz, CH_2), 4.19 (2H, , J=7.0 Hz, CH_2), 5.83 (1H, d, J=15.9 Hz, CH), 6.92 (1H, d, J=6.7, 15.9 Hz, CH), 9.78 (1H, s, CHO). ^{13}C NMR: =14.24 (CH_3), 21.47 (CH_2), 27.45 (CH_2), 31.83 (CH_2), 3.56 (CH_2), 60.20 (CH_2), 121.79 (CH), 148.25 (CH), 66.56 (C=O), 202.11 (CHO). IR: ν_{max}=2981, 2937, 862 (C–H), 2721 (CHO), 1719 (C=O), 1654 C=C) cm^{-1}. MS (CI): 202 (100%, $[M+NH_4]^+$). HRMS: $_{10}H_{20}NO_3$ ($[M+NH_4]^+$) requires 202.1443, found 02.1444.

.1.9. 6-(*S*-*p*-Tolyl)-6-oxohept-4-enal (1i).



Method A: Phosphorane[12] (2.14 g; 5.02 mmol) gave 40 mg, 46% yield; 25–30% ether in petrol, R_f=0.22 30% ether in petrol), mp 31–33°C. ^{1}H NMR: δ=2.42 3H, s, CH_3), 2.50–2.62 (4H, m, 2×CH_2), 6.22 (1H, dt, =15.5, 1.5 Hz, CH), 6.95 (1H, dt, J=15.5, 6.5 Hz, CH), .2–7.4 (4H, m, Ph), 9.85 (1H, t, J=0.8 Hz, CHO). IR: $_{max}$=3035, 2942, 2872 (C–H), 2756 (CHO), 1709 C=O), 1680 (C=O), 1634 (C=C) cm^{-1}. MS (CI): 252 60%, $[M+NH_4]^+$), 235 (40%, $[M+H]^+$). HRMS (EI): $_{13}H_{14}O_2S$ ($[M]^+$) requires 234.0715, found 234.0716.

.1.10. 7-(*S*-*p*-Tolyl)-7-oxohept-5-enal (1j).

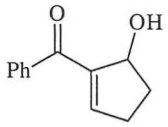


Method B: Phosphorane[12] (4.47 g; 10.5 mmol), gave 840 mg, 32%; 30% ether in petrol, R_f=0.16 (30% ether in petrol), mp 32–34°C. ^{1}H NMR: δ=1.84 (2H, app quintet, J=7.3 Hz, CH_2), 2.30 (2H, ddt, J=7.3, 6.9, 1.4 Hz, CH_2), 2.39 (3H, s, CH_3), 2.52 (2H, dt, J=7.3, 1.3 Hz, CH_2CHO), 6.20 (1H, dt, J=15.5, 1.4 Hz, CH), 6.90 (1H, dt, J=15.5, 6.9 Hz, CH), 7.25 (4H, AA′BB′, J=8.0 Hz, tolyl), 9.75 (1H, t, J=1.3 Hz, CHO). IR: ν_{max}=2976, 2952, 2857 (C–H), 2738 (CHO), 1715 (C=O), 1680 (C=O), 1633 (C=C) cm^{-1}. MS (CI): 266 (100%, $[M+NH_4]^+$), 249 (40%, $[M+H]^+$). HRMS (EI): $C_{14}H_{16}O_2S$ ($[M]^+$) requires 248.0871, found 248.0861. Microanalysis: found C=67.86; H=6.38, $C_{14}H_{16}O_2S$ requires C=67.71; H=6.49.

6.2. General conditions for the addition reactions of secondary amines

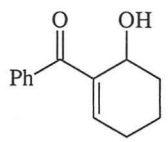
The aldehyde (typically 100 mg) was placed into a NMR tube and diluted to the correct concentration with $CDCl_3$. The required amine (0.3 or 1.3 equiv.) was then added (either neat or as a solution in $CDCl_3$) and the tube agitated. The reaction was followed by NMR and on completion (to ca. 95%) the solvent was removed and the cyclisation products isolated by chromatography (ether/petrol). For larger scale reactions, chloroform was employed as the solvent and the reaction was carried out in a round bottom flask. For yields, see Tables 4 and 5.

6.2.1. 2-Benzoyl-1-hydroxycyclopent-2-ene (3a).



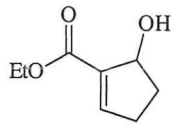
Column solvent: 35% ether in petrol, R_f=0.10 (50% ether in petrol). ^{1}H NMR: δ=1.94 (1H, m, CH_aH_b), 2.30–2.85 (3H, m, CH_aH_b+CH_2), 3.33 (1H, br s, OH), 5.30 (1H, m, C*H*OH), 6.71 (1H, t, J=1.5 Hz, CH), 7.42–7.78 (5H, m, Ph). ^{13}C NMR: δ=31.40 (CH_2), 31.74 (CH_2), 76.51 (CH), 128.35 (2×CH), 128.92 (2×CH), 132.44 (CH), 138.13 (C), 144.54 (C), 149.05 (CH), 194.86 (C=O). IR: ν_{max}=3460 (O–H) 3058, 2940 (C–H), 1639 (C=O) cm^{-1}. MS (CI): 206 (45%, $[M+NH_4]^+$), 189 (100%, $[M+H]^+$). HRMS: $C_{12}H_{13}O_2$ ($[M+H]^+$) requires 189.0916, found 189.0916.

6.2.2. 2-Benzoyl-1-hydroxycyclohex-2-ene (3b).



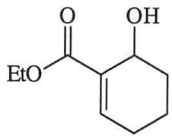
Column solvent: 20% ether in petrol, R_f=0.11 (25% ether in petrol). ^{1}H NMR: δ=1.67 (1H, m, CH_aH_b), 1.90 (3H, m, CH_aH_b+CH_2), 2.31 (2H, m, CH_aH_b), 3.53 (1H, br s, OH), 4.75 (1H, m, C*H*OH), 6.73 (1H, t, J=4.0 Hz, CH), 7.40–7.68 (5H, m, Ph). ^{13}C NMR: δ=17.29 (CH_2), 26.23 (CH_2), 29.60 (CH_2), 63.83 (CH), 128.03 (2×CH), 129.10 (2×CH), 131.77 (CH), 137.69 (C), 140.00 (C), 146.79 (CH), 199.38 (C=O). IR: ν_{max}=3436 (O–H) 3058, 2938, 2864 (C–H), 1636 (C=O) cm^{-1}. MS (CI): 220 (15%, $[M+NH_4]^+$), 203 (100%, $[M+H]^+$), 202 (35%, $[M]^+$). HRMS: $C_{13}H_{15}O_2$ ($[M+H]^+$) requires 203.1072, found 203.1072.

6.2.3. 2-Carboethoxy-1-hydroxycyclopent-2-ene (3f).



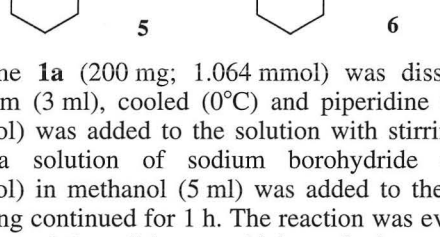
Column solvent: 20% ether in petrol, R_f=0.04 (20% ether in petrol). ^{1}H NMR: δ=1.36, (3H, t, J=7.1 Hz, CH_3), 1.89 (1H, m, CH_aH_b), 2.27–2.67 (3H, m, CH_aH_b+CH_2), 2.85 (1H, br s, OH), 4.24 (2H, q, J=7.1 Hz, CH_2), 5.08 (1H, m, CHOH), 6.71 (1H, t, J=2.5 Hz, CH). ^{13}C NMR: δ=14.25 (CH_3), 31.80 (CH_2), 31.78 (CH_2), 60.46 (CH_2), 75.54 (CH), 138.00 (C), 146.24 (CH), 165.06 (C=O). IR: ν_{max}=3583/3440 (O–H), 2924 (C–H), 1713 (C=O), 1634 (C=C) cm^{-1}. MS (CI): 174 (60%, $[M+NH_4]^+$) HRMS: $C_8H_{16}NO_3$ ($[M+NH_4]^+$) requires 174.1130, found 174.1130.

6.2.4. 2-Carboethoxy-1-hydroxycyclohex-2-ene (3g).



Column solvent: 30% ether in petrol, R_f=0.10 (30% ether in petrol). ^{1}H NMR: δ=1.31, (3H, t, J=7.1 Hz, CH_3), 1.43–1.85 (5H, m, 2×CH_2+OH), 2.09–2.32 (2H, m, CH_aH_b), 4.23 (2H, q, J=7.1 Hz, CH_2), 4.55 (1H, m, CHOH), 7.11 (1H, t, J=2.0 Hz, CH). ^{13}C NMR: δ=14.19 (CH_3), 17.42 (CH_2), 26.05 (CH_2), 29.82 (CH_2), 60.55 (CH_2), 63.41 (CH), 132.37 (C), 142.78 (CH), 167.31 (C=O). IR: ν_{max}=3460 (O–H), 2971, 2938, 2867 (C–H), 1712 (C=O), 1646 (C=C) cm^{-1}. MS (CI): 188 (70%, $[M+NH_4]^+$), 171 (100%, $[M+H]^+$). HRMS: $C_9H_{15}O_3$ ($[M+H]^+$) requires 171.1021, found 171.1020.

6.2.5. Preparation of 5 and 6 from 6-phenyl-6-oxo-4-hexen-1-al (1a).

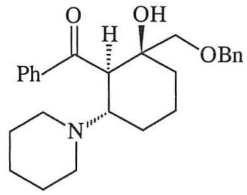


The enone **1a** (200 mg; 1.064 mmol) was dissolved in chloroform (3 ml), cooled (0°C) and piperidine (118 mg; 1.38 mmol) was added to the solution with stirring. After 10 min a solution of sodium borohydride (202 mg; 5.32 mmol) in methanol (5 ml) was added to the mixture and stirring continued for 1 h. The reaction was evaporated to dryness and the solid mass which resulted was triturated with chloroform and the triturates filtered through a cotton wool plug. On evaporation, silica gel chromatography (methanol in ethyl acetate 1–10%) gave **5** and **6** as crystalline solids.

Data for **5**: Yield: 0.083 g, 29%. Mp 180–183°C (ethyl acetate); R_f=0.12 (10% methanol in ethyl acetate). ^{1}H NMR: δ=1.24 (1H, d, J=3.4 Hz, CH_aH_b), 1.49–1.79 (11H, m, 4×CH_2+2×CH_aH_b+2×OH), 1.99 (1H, ddd, J=4.7, 9.8, 10.6 Hz, CH), 2.57 (2H, m, 2×CH_aH_bN), 2.7 (2H, m, 2×CH_aH_bN), 3.59 (1H, m, CHN), 3.76 (1H, m CHOH), 5.00 (1H, d, J=9.8 Hz, PhCHOH), 7.24–7.5 (5H, m, Ph). ^{13}C NMR: δ=17.98, 20.28, 24.63, 26.3 32.75 (7×CH_2), 51.37 (CH), 69.47 (CH), 71.70 (CH 75.72 (CH), 126.60, 127.43, 128.36 (5×CH), 143.93 (C IR: ν_{max}=3407 (O–H) 3018, 2932 (C–H) cm^{-1}. MS (CI 276 (40%, $[M+H]^+$), 86 (100%, $[C_5H_{12}N]^+$). HRMS $C_{17}H_{26}NO_2$ ($[M+H]^+$) requires 276.1964, found 276.1964

Data for **6**: Yield: 0.110 g, 38%. Mp 77–80°C (ethy acetate), R_f=0.07 (10% methanol in ethyl acetate). ^{1} NMR: δ=1.46–2.09 (13H, m, 5×CH_2+CH+2×OH), 2.5 (2H, m, 2×CH_aH_bN), 2.79 (2H, m, 2×CH_aH_bN), 2.98 (1H m, CHN), 3.81 (1H, ddd, J=5.0, 6.7, 8.0, CHOH), 4.61 (1H d, J=9.6 Hz, PhCHOH), 7.28–7.45 (5H, m, Ph). ^{13}C NMR δ=19.16, 24.54, 26.27, 26.30, 31.04 (7×CH_2), 54.75 (CH 71.84 (CH), 72.02 (CH), 80.16 (CH), 126.68, 128.1 128.90 (5×CH), 143.80 (C). IR: ν_{max}=3372 (O–H) 301 2935 (C–H) cm^{-1}. MS (CI): 276 (100%, $[M+H]^+$ HRMS: $C_{17}H_{26}NO_2$ ($[M+H]^+$) requires 276.1964, foun 276.1964.

6.2.6. 1*S*,2*R*,3*S*/1*R*,2*S*,3*R*-2-Benzoyl-1-benzyloxymethyl-3-(*N*-piperidyl)cyclohexan-1-ol (11).

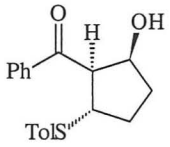


Enone **9** (81.4 mg, 0.253 mmol) in $CDCl_3$ (0.5 ml) wit piperidine (25.8 mg; 0.303 mmol) after 6 days gave **1** (61.5 mg, 60%, 15% ether in petrol, R_f=0.12 (15% ethe in petrol)). Mp 154°C (petrol). ^{1}H NMR: δ=0.73–1.8 (12H, m, 6×CH_2), 2.24 (2H, m, 2×CH_aH_bN), 2.47 (2H, m CH_aH_bN), 3.26 (3H, m, CHN+CH_2O), 3.86 (1H, d J=11.6 Hz, CH), 4.33 (2H, s, OCH_2Ph), 5.00 (1H, br s CHOH), 7.14–7.94 (10H, m, Ph). ^{13}C NMR: δ=19.7 (CH_2), 23.62 (CH_2), 24.57 (CH_2), 25.71 (CH_2), 29.6 (CH_2), 49.23 (CH_2), 49.23 (CH), 50.07 (CH_2), 65.73 (CH 73.39 (CH_2), 74.58 (C), 77.87 (CH_2), 125.96–128.5 (9×CH), 132.44 (CH), 137.82 (C), 139.87 (C), 210.0 (C=O). IR: ν_{max}=3451 (O–H), 2926, 2851, 2801 (C–H 1646.4 (C=O) cm^{-1}. MS (CI): 409 (2%, $[M+H]^+$), 40 (5%, $[M]^+$), 86 (100%, $[C_5H_{12}N]^+$). HRMS: $C_{26}H_{33}O_3$ ($[M]^+$) requires 407.2460, found 407.2464. Microanalysi found C=76.33; H=8.47; N=3.43, $C_{26}H_{33}O_3N$ require C=76.62; H=8.16; N=3.57.

6.3. General method for thiol and thiolates reactions

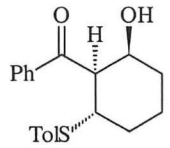
The aldehyde (typically 100–250 mg) was placed in either RBF in the case of reactions that were heated to reflux into an NMR tube and diluted with $CHCl_3$ or $CDCl_3$. Th TolSH (1.3–2 equiv. either neat or as a solution in CHCl $CDCl_3$) and the catalyst, TolSNa (0.2 equiv.) were the added. The reaction was followed to completion by NM or TLC at which point the solvent was removed and th products were obtained by chromatography. For specif conditions, see Tables 4 and 5.

3.1. 1*S*,2*R*,3*S*/1*R*,2*S*,3*R*-2-Benzoyl-1-(*S*-tolyl)cyclopen-n-3-ol (2aT).



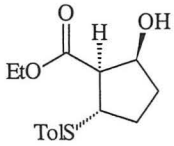
none **1a** (100 mg; 0.53 mmol) and TolSH (85 mg; 69 mmol) gave the product **57** (127.6 mg, 77%) after romatography in 15% EtOAc in petrol (R_f=0.2) as an l. ^{1}H NMR: δ=1.86 (2H, m, CH_2), 2.13 (1H, m, CH_aH_b), 2.26 (3H, s, CH_3), 2.48 (1H, m, CH_aH_b), 2.69 H, br s, OH), 3.89 (1H, dd, J=5.3, 8.3 Hz, CH), 4.19 H, ddd, J=6.3, 8.3, 8.3 Hz, CH), 4.59 (1H, m, CH), 96–7.88 (9H, m, 9×ArCH). ^{13}C NMR: δ=20.85 (CH_3), 0.88 (CH_2), 34.93 (CH_2), 48.28 (CH), 57.79 (CH), 75.15 CH), 128.20, 128.38, 129.44, 132.44, 133.28 (9×ArCH), 30.77 (C), 137.10 (C), 137.19 (C), 200.76 (C). IR: ν_{max}=3372 (O–H), 2920 (C–H), 1677 (C=O) cm^{-1}. MS CI): 330 (3%, $[M+NH_4]^+$), 313 (10%, $[M+H]^+$). RMS (EI): $C_{19}H_{20}O_2S$ ($[M]^+$) requires 312.1184, found 12.1171.

3.2. 1*S*,2*R*,3*S*/1*R*,2*S*,3*R*-2-Benzoyl-1-(*S*-tolyl)cyclohexan-ol (2bT).



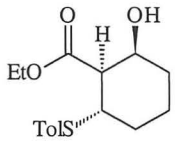
none **1b** (60 mg; 0.297 mmol) and TolSH (40 mg; 322 mmol) gave the product (89.6 mg 93%) after romatography in 10% EtOAc in petrol (R_f=0.13) as an l. ^{1}H NMR (C_6D_6): δ=1.35 (1H, m, CH_aH_b), 1.59 H, m, CH_2), 1.73 (1H, m, CH_aH_b), 2.18 (1H, m, CH_aH_b), 2.25 (3H, s, CH_3), 2.43 (1H, s, CH_aH_b), 3.77 H, dd, J=11.5, 2.5 Hz, CH), 3.93 (1H, br s, CHO*H*), 20 (1H, m, CH), 4.22 (1H, ddd, J=4.0, 11.5, 11.5 Hz, HS), 7.03 (2H, d, J=8.2 Hz, 2×CH), 7.25–7.57 (5H, , Ph), 8.18 (2H, d, J=8.2 Hz, 2×CH). ^{13}C NMR: =19.57 (CH_2), 20.94 (CH_3), 31.10 (CH_2), 33.54 CH_2), 44.97 (CH), 52.13 (CH), 67.11 (CH), 128.48, 28.57, 129.39, 133.51, 133.61 (9×ArCH), 129.60, 37.00, 137.50 (3×ArC), 204.50 (C). IR: ν_{max}=3475 O–H), 2950, 2900 (C–H), 1663 (C=O) cm^{-1}. MS EI): 326 (10%, $[M]^+$). HRMS: $C_{20}H_{22}O_2S$ ($[M]^+$) quires 326.1341, found 326.1325.

3.3. 1*S*,2*R*,3*S*/1*R*,2*S*,3*R*-2-Carboethoxy-1-(*S*-tolyl)cyclo-entan-3-ol (2fT).



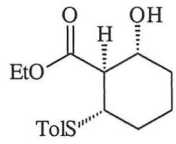
none **1f** (206.6 mg; 1.324 mmol), TolSH (328 mg; 70 mmol) and TolSNa (40 mg, 0.27 mmol) gave the oduct **57** (283 mg, 72%) after chromatography in 30% her in petrol (R_f=0.06) as crystals. Mp 39–42°C (ether/ trol). ^{1}H NMR: δ=1.23 (3H, t, J=7.1 Hz, CH_3), 1.60–2.00 (3H, m, CH_2+CH_aH_b), 2.33 (3H, s, CH_3), 2.36 (1H, m, CH_aH_b), 2.76 (1H, dd, J=5.0, 9.0 Hz, CH), 2.86 (1H, br s, CHO*H*), 3.97 (1H, m, CH), 4.10 (2H, m, CH_2), 4.47 (1H, m, CH), 7.10 (2H, d, J=8.0 Hz, 2×CH), 7.33 (2H, d, J=8.0 Hz, 2×CH). ^{13}C NMR: δ=14.08 (CH_3), 21.05 (CH_3), 30.84 (CH_2), 33.64 (CH_2), 47.30 (CH), 56.41 (CH), 61.05 (CH_2), 74.10 (CH), 129.56 (2×CH), 130.9 (CH), 132.7 (2×CH), 137.4 (C), 173.40 (C). IR: ν_{max}=3429 (O–H), 2973, 2927 (C–H), 1735 (C=O) cm^{-1}. MS (CI): 298 (20%, $[M+NH_4]^+$), 281 (10%, $[M+H]^+$). HRMS: $C_{15}H_{21}O_3S$ ($[M+H]^+$) requires 281.1211, found 281.1212.

6.3.4. 1*S*,2*R*,3*S*/1*R*,2*S*,3*R*-2-Carboethoxy-1-(*S*-tolyl)cyclohexan-3-ol (2gT).



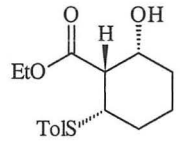
Enone ***E*-1g** (213 mg; 1.253 mmol) and TolSH (314 mg, 2.51 mmol) and TolSNa (37 mg, 0.25 mmol) gave the product (276 mg, 75%) after chromatography in 20% ether in petrol (R_f=0.17) as an oil. ^{1}H NMR: δ=1.28 (2H, m, CH_2), 1.34 (3H, t, J=7.0 Hz, CH_3), 1.52 (1H, m, CH_aH_b), 1.83 (2H, m, CH_2), 2.30 (1H, m, CH_aH_b), 2.35 (3H, s, CH_3), 2.53 (1H, dd, J=1.9, 10.6 Hz, CH), 3.35 (1H, br s, CHO*H*), 3.48 (1H, ddd, J=4.0, 11.3, 11.3 Hz, SC*H*), 4.18 (1H, m, C*H*OH), 4.23 (2H, m, CH_2), 7.12 (2H, d, J=8.0 Hz, 2×CH), 7.38 (2H, d, J=8.0 Hz, 2×CH). ^{13}C NMR: δ=14.16 (CH_3), 19.76 (CH_2), 21.11 (CH_3), 30.75 (CH_2), 32.68 (CH_2), 44.13 (CH), 52.54 (CH), 61.12 (CH_2), 67.23 (CH), 129.02 (C), 129.57 (2×CH), 134.28 (2×CH), 137.90 (C), 174.72 (C=O). IR: ν_{max}=3508 (O–H), 2977, 2936, 2864 (C–H), 1724 (C=O) cm^{-1}. MS (CI): 312 (100%, $[M+NH_4]^+$), 295 (45%, $[M+H]^+$). HRMS: $C_{16}H_{23}O_3S$ ($[M+H]^+$) requires 295.1368, found 295.1375.

6.3.5. 1*S*,2*R*,3*R*/1*R*,2*S*,3*S*-2-Carboethoxy-1-(*S*-tolyl)cyclohexan-3-ol (2gTa).



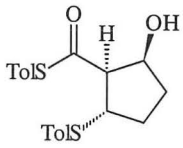
A small quantity of **2gTa** (25.8 mg, 7%) was isolated as an oil by careful chromatography of the recovered column residues of the reaction to prepare **2gT**. ^{1}H NMR: δ=1.22 (2H, m, CH_2), 1.35 (3H, t, J=7.0 Hz, CH_3), 1.74 (2H, m, CH_2), 1.98 (2H, m, CH_2), 2.33 (1H, dd, J=11.5, 12.0 Hz, CH), 2.35 (3H, s, CH_3), 3.01 (1H, ddd, J=3.6, 12.0, 12.0 Hz, SC*H*), 3.80 (1H, ddd, J=4.3, 11,5, 11.5 Hz, CHOH), 4.26 (2H, m, CH_2), 7.13 (2H, d, J=8.0 Hz, 2×CH), 7.40 (2H, d, J=8.0 Hz, 2×CH). ^{13}C NMR: δ=14.27 (CH_3), 21.14 (CH_3), 23.19 (CH_2), 32.41 (CH_2), 33.85 (CH_2), 47.31 (CH), 57.91 (CH), 60.88 (CH_2), 72.53 (CH), 128.48 (C), 129.55 (2×CH), 134.97 (2×CH), 138.20 (C), 173.46 (C=O). IR: ν_{max}=3442 (O–H), 2924, 2853 (C–H), 1732 (C=O) cm^{-1}. MS (CI): 312 (100%, $[M+NH_4]^+$), 295 (10%, $[M+H]^+$). HRMS: $C_{16}H_{23}O_3S$ ($[M+H]^+$) requires 295.1368, found 295.1367.

6.3.6. 1*S*,2*S*,3*R*/1*R*,2*R*,3*S*-2-Carboethoxy-1-(*S*-tolyl)cyclohexan-3-ol (2gTb).



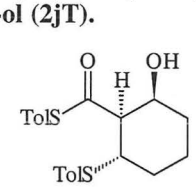
A small quantity of **2gTb** (18.5 mg, 5%) was isolated as a solid by careful chromatography of the recovered column residues of the reaction to prepare **2gT**. Mp 63–68°C. ^{1}H NMR: δ=1.20–1.70 (3H, m, CH_2+CH_aH$_b$), 1.27 (3H, t, J=7.0 Hz), 1.85–2.20 (3H, m, CH_2+CH$_a$H$_b$), 2.29 (3H, s, CH_3), 2.92 (1H, br s, CHO*H*), 2.98 (1H, dd, J=3.7, 4.5 Hz, CH), 3.44 (1H, m, C*H*S), 4.08 (1H, m, C*H*OH), 4.22 (2H, m, CH_2), 7.07 (2H, d, J=8.0 Hz, 2×CH), 7.30 (2H, d, J=8.0 Hz, 2×CH). ^{13}C NMR: δ=14.24 (CH_3), 18.14 (CH_2), 21.05 (CH_3), 29.98 (CH_2), 30.56 (CH_2), 48.04 (CH), 50.57 (CH), 60.89 (CH_2), 67.72 (CH), 129.57 (C), 129.63 (2×CH), 132.40 (2×CH), 137.19 (C), 174.00 (C=O). IR: ν_{max}=3436 (O–H), 2927, 2855 (C–H), 1730 (C=O) cm^{-1}. MS (CI): 312 (75%, $[M+NH_4]^+$), 295 (35%, $[M+H]^+$). HRMS: $C_{16}H_{23}O_3S$ ($[M+H]^+$) requires 295.1368, found 295.1365.

6.3.7. 1*S*,2*R*,3*S*/1*R*,2*S*,3*R*-1-(*S*-Tolyl)-2-(*S*-tolylthiocarboxy)cyclopentan-3-ol (2iT).



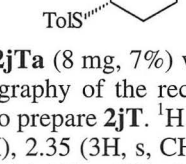
Enone **1i** (149.1 mg; 0.637 mmol) and TolSH (232 mg, 1.91 mmol) gave the product (128 mg, 56%) after chromatography in 30% ether in petrol (R_f=0.04) as an oil which solidified on standing. Mp 63–69°C. ^{1}H NMR: δ=1.68–2.16 (4H, m, 2×CH_2), 2.35 (3H, s, CH_3), 2.38 (3H, s, CH_3), 2.86 (1H, br s, CHO*H*), 3.14 (1H, dd, J=4.8, 8.8 Hz, CH), 4.04 (1H, ddd, J=8.8, 8.8, 6.2 Hz, C*H*S), 4.55 (1H, m, C*H*OH), 7.00–7.40 (8H, m, 8×CH). ^{13}C NMR: δ=21.15 (CH_3), 21.36 (CH_3), 30.86 (CH_2), 33.83 (CH_2), 47.64 (CH), 64.52 (CH), 75.19 (CH), 123.52 (C), 128.52 (2×CH), 129.79 (2×CH), 130.61 (C), 132.91 (2×CH), 134.34 (2×CH), 137.57 (C), 139.98 (C), 199.09 (C). IR: ν_{max}=3349 (O–H), 2920 (C–H), 1711 (C=O) cm^{-1}. MS (CI): 376 (100%, $[M+H]^+$), 359 (30%, $[M+NH_4]^+$). HRMS: $C_{20}H_{23}O_2S_2$ ($[M+H]^+$) requires 359.1139, found 359.1140.

6.3.8. 1*S*,2*R*,3*S*/1*R*,2*S*,3*R*-2-(*S*-Tolylthiocarboxy)-1-(*S*-tolyl)cyclohexan-3-ol (2jT).



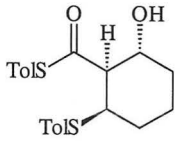
Enone **1j** (72.3 mg; 0.292 mmol) and TolSH (73.4 mg, 0.58 mmol) and TolSNa (8.6 mg, 0.06 mmol) gave the product (69 mg, 60%) after chromatography in 20% ether in petrol (R_f=0.16) as an oil. ^{1}H NMR: δ=1.22–2.21 (6H, m, 3×CH_2), 2.36 (3H, s, CH_3), 2.40 (3H, s, CH_3), 2.87 (1H, dd, J=2.2, 10.9 Hz, CH), 2.88 (1H, br s, OH), 3.60 (1H, dd J=4.0, 10.9, 11.7 Hz, C*H*S), 4.30 (1H, m, C*H*OH), 7.11 7.42 (8H, m, 8×CH). ^{13}C NMR: δ=19.62 (CH_2), 21.1 (CH_3), 21.37 (CH_3), 30.93 (CH_2), 33.15 (CH_2), 43.9 (CH), 60.49 (CH), 67.86 (CH), 123.56 (C), 129.5 (2×CH), 130.10 (2×CH), 133.84 (2×CH), 134.27 (2×CH 137.80 (C), 140.08 (2×C), 201.35 (C=O). IR: ν_{max}=352 (O–H), 3021, 2937, 2864 (C–H), 1706/1679 (C=O) cm^{-} MS (CI): 390 (100%, $[M+NH_4]^+$), 373 (20%, $[M+H]^+$ HRMS: $C_{21}H_{25}O_2S_2$ ($[M+H]^+$) requires 373.1296, four 373.1295.

6.3.9. 1*S*,2*R*,3*R*/1*R*,2*S*,3*S*-2-(*S*-Tolylthiocarboxy)-1-(*S*-tolyl)cyclohexan-3-ol (2jTa).



A small quantity of **2jTa** (8 mg, 7%) was isolated as an o by careful chromatography of the recovered column res dues of the reaction to prepare **2jT**. ^{1}H NMR: δ=1.20–2.1 (7H, m, 3×CH_2+OH), 2.35 (3H, s, CH_3) 2.39 (3H, s, CH 2.69 (1H, dd, J=9.7, 11.4 Hz, CH), 3.14 (1H, ddd, J=2. 11.4, 11.6 Hz, CHS), 3.88 (1H, ddd, J=4.0, 9.0, 9.8 H C*H*OH), 7.0–7.55 (8H, m, 8×CH). IR: ν_{max}=3440 (O–H 2921, 2844 (C–H), 1703 (C=O) cm^{-1}. MS (CI): 390 (50% $[M+NH_4]^+$), 373 (5%, $[M+H]^+$). HRMS: $C_{21}H_{28}NO_2$ ($[M+NH_4]^+$) requires 390.1561, found 390.1562.

6.3.10. 1*R*,2*R*,3*R*/1*S*,2*S*,3*S*-2-(*S*-Tolylthiocarboxy)-1-(*S*-tolyl)cyclohexan-3-ol (2jTb).

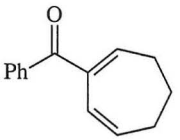


A small quantity of **2jTb** (ca. 7 mg, ca. 6%) contaminate with **2jT** was isolated by chromatography of the recovere column residues of the reaction to prepare **2jT**. Selecte data: ^{1}H NMR: δ=3.04 (1H, dd, J=4.3, 9.4 Hz, CH), 3.9 (1H, br m, CHS), 4.22 (1H, m, C*H*OH).

6.4. General method for phosphine reactions

The aldehyde (typically 100 mg) was weighed into an NM tube and diluted to the correct concentration with CDC The tri-*n*-butylphosphine (0.05–0.4 equiv.) was then adde neat and the tube agitated. The reaction was followed b NMR and on completion (to ca. 95%), the solvent w removed and the products were obtained by colum chromatography. For specific conditions, see Tables 4 and

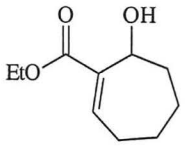
6.4.1. 2-Benzoylcyclo-1,3-heptadiene (14c).



Column solvent: 20% ether in petrol, R_f=0.13. ^{1}H NM δ=1.94 (2H, m, CH_2), 2.37–2.53 (4H, m, 2×CH_2), 6.

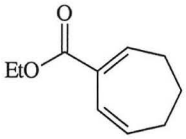
1H, dt, J=5.2, 11.9 Hz, CH), 6.33 (1H, dd, J=1.2, 11.9 Hz, CH), 6.57 (1H, br t, J=5.2 Hz, CH), 7.38–7.58 (3H, m, Ph), 7.66–7.76 (2H, m, Ph). ^{13}C NMR: δ=25.70 (CH_2), 30.98 (CH_2), 31.71 (CH_2), 123.29 (CH), 128.04 (2×CH), 129.58 (2×CH), 131.75 (CH), 135.33 (CH), 137.89 (C), 138.21 (C), 145.34 (CH), 198.22. (C=O). IR: ν_{max}=3027, 2926, 2881 (C–H), 1651 (C=O/C=C) cm^{-1}. MS (CI): 216 (100%, $[M+NH_4]^+$), 199 (70%, $[M+H]^+$). HRMS: $C_{14}H_{15}O$ ($[M+H]^+$) requires 199.1123, found 199.1122.

6.4.2. 2-Carboethoxy-1-hydroxycyclohept-2-ene (3h).



Column solvent: 10% ether in petrol, R_f=0.05. ^{1}H NMR: δ=1.31 (3H, t, J=7.3 Hz, CH_3), 1.50–2.10 (6H, m, 3×CH_2), 2.20–2.55 (2H, m, CH_2), 3.13 (1H, br s, CHO*H*), 4.22 (2H, q, J=7.3 Hz, CH_2), 4.81 (1H, m, C*H*OH), 7.11 (1H, t, J=6.4 Hz, CH). ^{13}C NMR: δ=14.19 (CH_3), 23.50 (CH_2), 25.66 (CH_2), 27.28 (CH_2), 32.36 (CH_2), 60.82 (CH_2), 68.70 (CH), 136.77 (C), 145.17 (CH), 168.40 (C=O). IR: ν_{max}=3450 (O–H), 2981, 2930, 2857 (C–H), 1702 (C=O), 1642 (C=C) cm^{-1}. MS (CI): 202 (90%, $[M+NH_4]^+$), 185 (100%, $[M+H]^+$). HRMS: $C_{10}H_{17}O_3$ ($[M+H]^+$) requires 185.1178, found 185.1179.

6.4.3. 2-Carboethoxy-1,3-heptadiene (14h).



Column solvent: 5% ether in petrol, R_f=0.48 (20% ether in petrol). ^{1}H NMR: δ=1.30 (3H, t, J=7.0 Hz, CH_3), 1.90 (2H, m, CH_2), 2.35 (2H, m, CH_2), 2.45 (2H, m, CH_2), 4.23 (2H, q, J=7.0 Hz, CH_2), 5.98 (1H, dt, J=5.4, 11.6 Hz, CH), 6.38 (1H, br d, J=1.5, 11.6 Hz, CH), 7.14 (1H, t, J=5.5 Hz, CH). ^{13}C NMR: δ=14.21 (CH_3), 25.89 (CH_2), 30.62 (CH_2), 31.39 (CH_2), 60.67 (CH_2), 122.88 (CH), 128.39 (C), 134.66 (CH), 143.61 (CH), 167.72 (C=O). IR: ν_{max}=3023, 2981, 2932 (C–H), 1708 (C=O), 1607 (C=C) cm^{-1}. MS (CI): 184 (70%, $[M+NH_4]^+$). HRMS: $C_{10}H_{18}NO_2$ ($[M+NH_4]^+$) requires 184.1338, found 184.1339.

Acknowledgements

Thanks are given to the EPSRC (PMB, GR/M50584), the ERASMUS scheme (F. D., S. F.), the European Social Fund (E. L. R.) and to the University of Wales for funding. The EPSRC Mass spectrometry centre at Swansea is also acknowledged.

References

1. (a) Black, G. P.; Dinon, F.; Fratucello, S.; Murphy, P. J.; Nielsen, M.; Williams, H. L.; Walshe, N. D. A. *Tetrahedron Lett.* **1997**, *38*, 8561–8564. (b) Dinon, F.; Richards, E.; Murphy, P. J.; Hibbs, D. E.; Hursthouse, M. B.; Malik, K. M. A. *Tetrahedron Lett.* **1999**, *40*, 3279–3282.
2. Fakstorp, J.; Raleigh, D.; Schniepp, L. E. *J. Am. Chem. Soc.* **1950**, *72*, 869–875.
3. Murphy, P. J.; Williams, H. L.; Hibbs, D. E.; Hursthouse, M. B.; Abdul Malik, K. M. A. *Tetrahedron* **1996**, *52*, 8315–8330.
4. This material was prepared from cyclopent-1-ene-1-methanol[5] which was benzylated (NaH, BnBr, TBAI, THF; 69%), ozonised (O_3, −78°C, then PPh_3) and treated with benzoylmethylenetriphenylphosphorane (1.3 equiv., DCM, rt, 24 h, 97%).
5. Brown, J. B.; Henbest, H. B.; Jones, E. R. H. *J. Chem. Soc.* **1950**, 3634–3641.
6. (a) Barrett, A. G. M.; Kamimura, A. *J. Chem. Soc., Chem. Commun.* **1995**, 1755–1756. (b) Kamimura, A.; Mitsudera, H.; Asano, S.; Kakehi, A.; Noguchi, M. *J. Chem. Soc., Chem. Commun.* **1998**, 1095–1096. (c) Kamimura, A.; Mitsudera, H.; Asano, S.; Kidera, S.; Kakehi, A. *J. Org. Chem.* **1999**, *64*, 6353–6360. (d) Mitsudera, H.; Kakehi, A.; Kamimura, A. *Tetrahedron Lett.* **1999**, *40*, 7389–7392. (e) Kamimura, A.; Omata, Y.; Mitsudera, H.; Kakehi, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4499–4504. (f) Ono, M.; Nishimura, K.; Nagaoka, Y.; Tomioka, K. *Tetrahedron Lett.* **1999**, *40*, 1509–1512.
7. Davies, S. G.; Fenwick, D. R. *J. Chem. Soc., Chem. Commun.* **1997**, 565–566.
8. (a) Schneider, C.; Reese, O. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2948–2950. (b) Ono, M.; Nishimura, K.; Nagaoka, Y.; Tomioka, K. *Tetrahedron Lett.* **1999**, *40*, 6979–6982. (c) Magnus, P.; Miknis, G. F.; Press, N. J.; Grandjean, D.; Taylor, G. M.; Harling, J. *J. Am. Chem. Soc.* **1997**, *119*, 6739–6748. (d) Armistead, D. M.; Danishefsky, S. J. *Tetrahedron Lett.* **1987**, *28*, 4959–4962. (e) Levin, J. I. *Synth. Commun.* **1992**, *22*, 961–970. (f) Wanner, M. J.; Koomen, G.-J. *Tetrahedron* **1992**, *48*, 3935–3944. (g) Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn* **1981**, *54*, 274–278. (h) Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1980**, *21*, 361–364.
9. Roth, F.; Gygax, P.; Frater, G. *Tetrahedron Lett.* **1992**, *33*, 1045–1048.
10. ErgUden, J.-K.; Moore, H. W. *Org. Lett.* **1999**, *1*, 375–377.
11. *X-ray structure determination*. The intensity data were collected on a Nonius Kappa CCD area-detector diffractometer at the window of a rotating anode FR591 generator (Mo-Kα radiation, =0.71073 Å). There structure was solved by direct methods and refined on F^2 by full-matrix least-squares refinements. Full details have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 150272 for **2eT** and CCDC 150990 for **2fTb**. **2eT**: $C_{15}H_{20}O_3S$. T=150 K, M=280.37, monoclinic space group $P2_1$, Z=2, a=8.9143(6) Å, b=4.9923(3) Å, c=16.7387(15) Å, β=95.936(2)°, V=740.93(9) Å^3, D_c=1.257 Mg m^{-3}, μ(Mo-Kα)=0.22 mm^{-1}. Colourless needle, crystal size 0.70×0.03×0.03 mm, range: 2.0–25.2°, 2475 unique data and 190 parameters, $R1[F^2 > 2\sigma(F^2)] = 0.049$, $wR2$(all data) = 0.096, Flack parameter=0.05(9). **2fTb**: $C_{16}H_{22}O_3S$. T=150 K, M=294.40, orthorhombic space group $Pca2_1$, Z=8, a=15.8301(2) Å, b=5.62760(10) Å, c=33.8340(6) Å, V=3014.12(8) Å^3, D_c=1.298 Mg m^{-3}, μ(Mo-Kα)=0.22 mm^{-1}. Colourless prism, crystal size 0.10×0.07×0.07 mm, range: 2.0–25.1°, 5060 unique data and 408

parameters, $R1[F^2 > 2\sigma(F^2)] = 0.043$, $wR2$(all data) = 0.069, Flack parameter=0.05(12).

12. The ylid TolSCOCHPPh$_3$ was prepared by coupling bromoacetic acid with toluene-4-thiol (DCC, DMAP, DCM, 0°C, 3 h) followed by reaction of the crude product thus obtained with triphenylphosphine (toluene, 48 h). This was followed by reaction of a DCM solution of the phosphonium salt formed with excess aqueous sodium carbonate solution followed by separation, drying and precipitation of the phosphorane with hexane; 69% Yield, mp 179°C. ^{1}H NMR: δ=2.30 (3H, s, CH_3), 3.64 (1H, d, J_{P-H}=22 Hz, CH), 7.12 (2H, d, J=7.9 Hz, 2×CH), 7.40–7.70 (17H, m, 3×Ph and 2×CH).