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C-H Insertion Approach to the Total Synthesis of Furofuran Lignans and their Heterocyclic Analogues

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To Sara.

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ABSTRACT

FACULTY OF SCIENCE

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C-H INSERTION APPROACH TO THE TOTAL SYNTHESIS OF FUROFURAN LIGNANS AND THEIR HETEROCYCLIC ANALOGUES

by Nigel Alan Swain

The synthesis of novel α-diazo-γ-butyrolactones was achieved *via* diazo-transfer reactions on activated lactones. These were subsequently found to undergo highly efficient regio- and stereo-selective C-H insertions to afford the *endo,exo*-furofuranone motif. This methodology was applied in the synthesis of various bicyclic furofuranone derivatives including two unsymmetrically substituted furofuran lignans, (±)-fargesin and (±)-epimagnolin A.

Further investigations into the enantioselective synthesis of furofuran(ones) highlighted 1-acetyl-4-aryl-3-oxabicyclo[3.1.0]hexanes as key intermediates. Optimisation of alcohol additions to these cyclopropanes under Lewis acidic conditions, with the development of a highly effective diazo-transfer protocol, was successful in the concise and diastereoselective preparation of *endo,exo*-furofuranones. Novel asymmetric synthesis of four *endo,exo*-furofuran lignans was also achieved when an enantiomerically enriched 1-aryl-allyl alcohol was employed. A significant contribution to the success of these asymmetric syntheses was the introduction of methanesulfonyl-protected phenols to increase the acid stability of several key intermediates. Furthermore, the convergent nature of this cyclopropane ring-opening approach permitted the formation of diverse structural furofuranone analogues.

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Abbreviations

Ac	acetyl
acac	acetylacetonate
AIBN	2,2'-azobisisobutyro-nitrile
aq	aqueous
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BP	boiling point
br	broad (spectral)
Bu	butyl
calcd	calculated
***c*AMP**	adenosine cyclic 3',5'-phosphate
CI	chemical ionisation
d	doublet (spectral)
DBU	1,8-diazabicyclo [5.4.0]undec-7-ene
DCC	*N*,*N*-dicyclohexylcarbo-diimide
de	diastereomeric excess
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
EI	electron impact
Et	ethyl
FT	Fourier transform
GOESY	gradient 1-D nuclear Overhauser effect spectroscopy
h	hour(s)
HMPA	hexamethylphosphoric triamide
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
Hz	hertz
IR	infrared
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazane
***m*-CPBA**	*m*-chloroperoxybenzoic acid
Me	methyl
MEM	(2-methoxyethoxy)methyl
MP	melting point
Ms	methanesulfonyl (mesyl)
NMR	nuclear magnetic resonance
Nu	nucleophile
obsc	obscured (spectral)
Ph	phenyl
Pr	propyl
py	pyridine
q	quartet (spectral)
s	singlet (spectral)
t	triplet (spectral)
TBDMS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl (tosyl)

Chapter 1

Rhodium Catalysed Intramolecular Cyclisations *via* C-H Insertion

Traditionally, carbon-carbon bond formation requires both organic fragments to be specifically activated (*e.g.* alkylation of an enolate anion with an alkyl halide). However, the development of transition metal stabilisation of reactive carbene intermediates meant alternative approaches could be considered, in which the carbon-carbon bond is formed by direct insertion into an unactivated C-H bond. Consequently, catalytic methods for the generation of metallocarbenes have attracted considerable attention in recent years and carbenoid mediated cyclisations have found numerous applications in organic synthesis. The following chapter will focus on rhodium carbene mediated C-H insertion reactions, particularly its use in heterocyclic and carbocyclic ring formations.

1.1 Transition Metal Complexation of Carbenes

By definition, carbenes[1] are neutral, bivalent carbon intermediates in which a carbon atom has two covalent bonds and two non-bonding orbitals containing two electrons between them. If these two electrons are spin paired, then the carbene is a *singlet* but if the spins are parallel, then the carbene is a *triplet*. A carbene in the lowest singlet state is planar with the empty p-orbital extending above and below the plane of the electron containing orbitals (resembling a carbonium ion) whereas the triplet form is tetrahedral in nature (Figure 1.1).

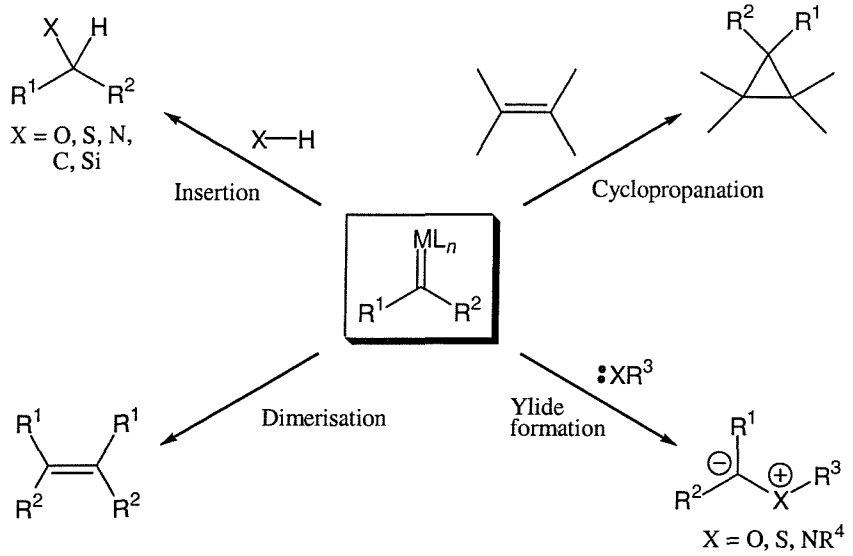
Figure 1.1 The two configurations of 'free' carbenes

Singlet carbene Triplet carbene

Carbenes, particularly the singlet form, are highly energetic species and can undergo reactions with unactivated functionalities acting as nucleophiles. The capability of free carbenes to insert into C-H bonds has long been acknowledged, although both low yields and lack of selectivity limited their value in organic synthesis.[2,3] However, complexation using transition metals is an effective way of stabilising a carbene such that its reactivity

may be controlled to an extent that makes it amenable to synthetic applications (Figure 1.2).[4,5]

Figure 1.2 Typical reactions of metallocarbenes

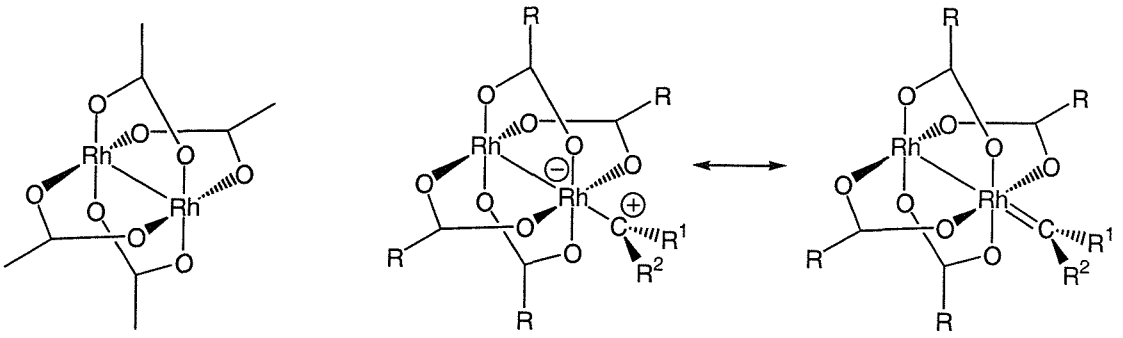


Early work in this area made use of insoluble catalysts (typically copper bronze and copper (II) sulphate) until Nozaki[6] and Moser[7] introduced homogeneous copper catalysts in the 1960s. Since then the effectiveness of a variety of transition metal catalysts have been investigated with the discovery that Rh^{II} carboxylates are superior for the generation of electrophilic metal carbenoids from α-diazocarbonyl compounds.[3,8-11]

1.2 Rhodium Catalysts for Carbenoid Generation

Teyssie and co-workers[12,13] were first to discover that dirhodium (II) tetraacetate (**1.1**) was highly active for diazo decomposition and its general applicability has seen it become one of the most widely used catalysts, especially in C-H insertion reactions. Rhodium (II) carboxylates are characterised by a bimetal unit strongly held together by four bridging carboxylate ligands.[14] This produces a compact and stable complex that resists substitution in the equatorial position. However, it leaves a single vacant axial site at each metal centre readily accessible for carbene co-ordination (Figure 1.3).

Figure 1.3 Carbene co-ordination to rhodium (II) carboxylates

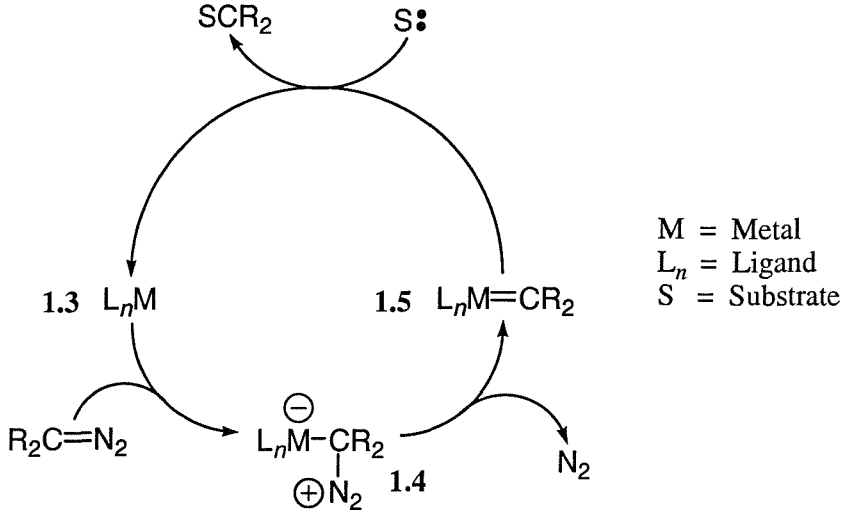


(**1.1**) Dirhodium (II) tetraacetate

1.2 Rhodium carbenoid resonance structure

In 1952, Yates[15] was first to suggest an electrophilic metal carbene complex of the type **1.2** but it was not until the 1980s that Doyle *et al.*[8] proposed a catalytic cycle explaining the fate of an α-diazo carbonyl compound upon exposure to a transition metal. They suggested the free co-ordination site at the metal centre allows it to react as an electrophile with the carbon of the diazo compound, providing complex **1.4** which eliminates nitrogen to afford carbenoid **1.5**. The metal carbene may then react with the various substrates present (*e.g.* a C-H bond) ultimately producing the observed product and regeneration of catalyst **1.3** completes the cycle (Figure 1.4).

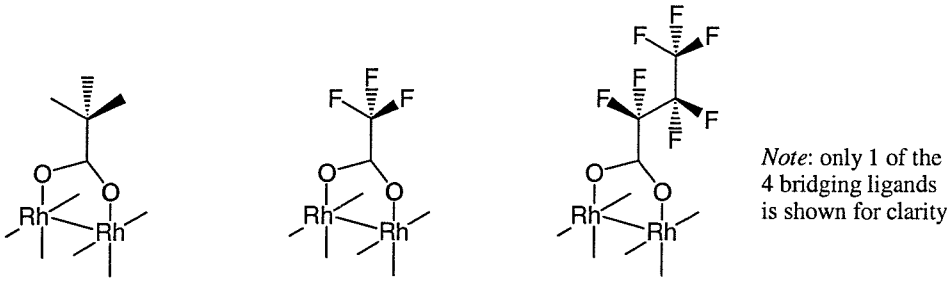
Figure 1.4 Catalytic cycle for transition metal catalysed reaction of diazo compounds



It is worth noting that a rhodium carbenoid species **1.2** is not well documented although strong evidence for the involvement of a carbenoid intermediate is provided by comparison with the reactivity/selectivity of well-characterised, stable metal carbene complexes with similar substrates.[16]

Since the first discovery of dirhodium (II) tetraacetate (**1.1**), a number of investigations have revealed the profound influence the electronic properties of the bridging dirhodium ligands play in the selectivity of the metal carbene transformation.[11,17-19] Conveniently, these complexes may be generated from dirhodium (II) tetraacetate itself *via* some rather harsh ligand exchanges or by direct synthesis from rhodium chloride with the appropriate carboxylate.[20] A large variety of alkyl and aryl derivatives have been prepared in this manner, for example, the pivalate complex[21] $[Rh_2(piv)_4]$ (**1.6**). However, complexes containing ligands with electronic properties differing from acetate are most commonly perfluorinated derivatives,[22] for example, the trifluoroacetate complex $[Rh_2(tfa)_4]$ (**1.7**) or the perfluorobutyrate complex $[Rh_2(pfb)_4]$ (**1.8**) (Figure 1.5). These catalysts may greatly differ from the rhodium alkyl carboxylates in terms of their reactivities.

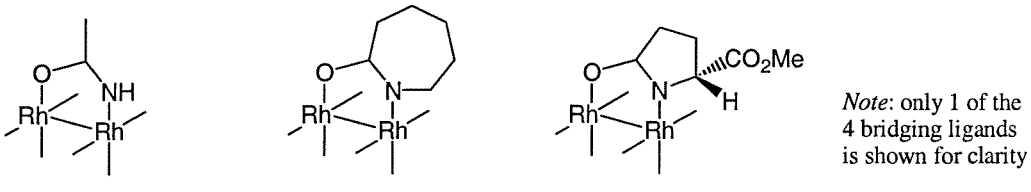
Figure 1.5 Examples from the dirhodium (II) carboxylate series of catalysts



$Rh_2(piv)_4$ (**1.6**) $Rh_2(tfa)_4$ (**1.7**) $Rh_2(pfb)_4$ (**1.8**)

Another important class of rhodium (II) dimers are those in which one of the two oxygen ligate atoms is replaced by a nitrogen atom, for example, acetamide complex[17] $[Rh_2(acam)_4]$ (**1.9**) or the caprolactam complex[18] $[Rh_2(cap)_4]$ (**1.10**). Catalysts incorporating chiral carboxamide ligands have become extremely important in enantioselective carbenoid reactions, for example, Doyles' pyrrolidone dirhodium catalyst[23,24] $[Rh_2(5R\text{-MEPY})_4]$ (**1.11**) (Figure 1.6) Recent advances in asymmetric catalytic metal carbene transformations have been extensively reviewed but will not be addressed in this report.[25-27]

Figure 1.6 Examples from the dirhodium (II) carboxamide series of catalyts



$Rh_2(acam)_4$ (**1.9**) $Rh_2(cap)_4$ (**1.10**) $Rh_2(5R\text{-MEPY})_4$ (**1.11**)

With uncertainty in the exact structure of rhodium carbenoid species **1.2**, the majority of these catalysts have been studied in an attempt to understand the mechanism of the C-H insertion reaction (*vide infra*).

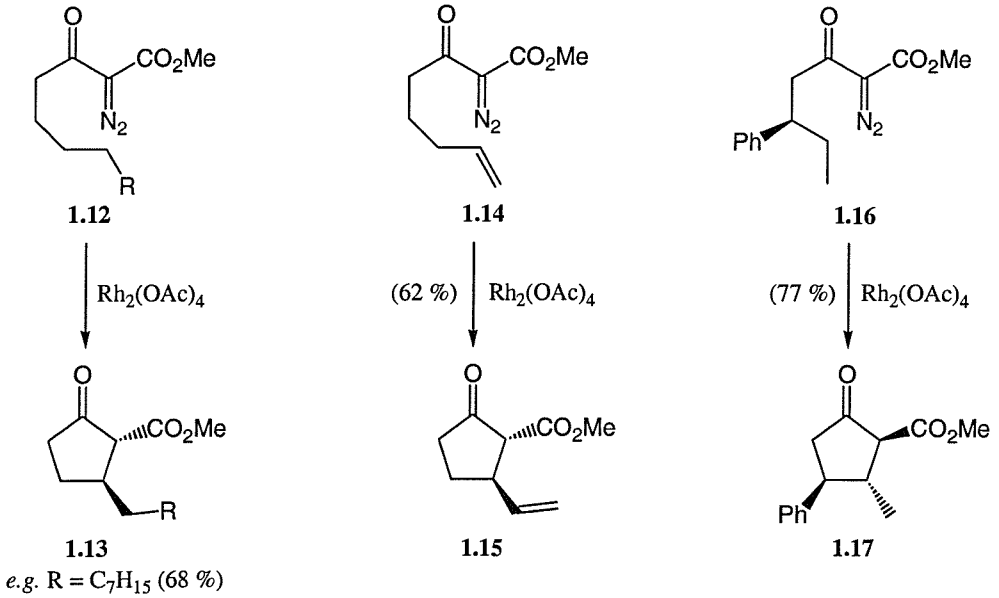
1.3 Rhodium Catalysed C-H Insertion Reactions

The development of rhodium catalysts (*vide supra*) has made a significant impact upon carbenoid insertion into C-H bonds.[3,8,10,25,26,28-30] To demonstrate the broad application of this transformation in organic synthesis, representative examples from literature are highlighted in the following sections. The reactions have been arranged into 3 categories according to regiochemistry of the insertion, electronic influences of the substrate and ligand effects of the rhodium catalyst, although some examples may overlap.

1.3.1 Regiochemistry

Independent work by both Taber[31] and Wenkert[32] in the early 1980s, pioneered the use of rhodium-catalysed carbenoid C-H insertions in an intramolecular fashion. Both groups found cyclisation of carbenoids derived from diazo-ketones or diazo-ketoesters preferentially formed 5-membered cyclopentanone carbocycles (*e.g.* **1.12** to **1.13**) (Figure 1.7).

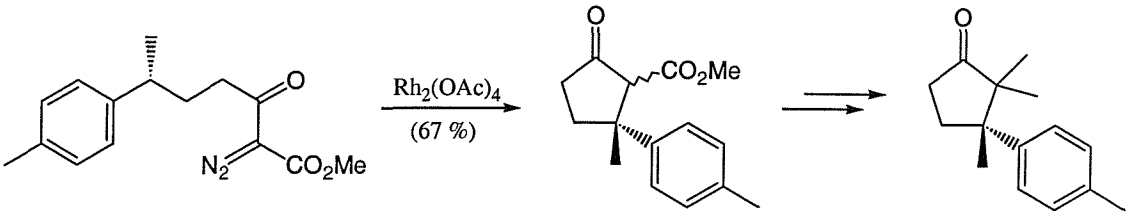
Figure 1.7 Intramolecular C-H insertion to 5-membered cyclopentanones



This highly facile ring formation provided cyclic ketones with *trans*-diastereoselectivity across the newly formed C-C bond and showed C-H insertion, even with freely rotating acyclic systems, to be an efficient process. Taber progressed to show that rhodium

catalysed C-H insertions could compete successfully against cycloadditions,[31] for example, diazo ketoester **1.14** afforded *trans*-cyclopentanone **1.15** over possible cyclopropanation[33] (a common product of copper mediated diazo decomposition). A further development by the Taber group[34,35] demonstrated the highly diastereoselective formation of *trans*-3,4-dialkyl cyclopentanone derivatives (*e.g.* **1.16** to **1.17**). All these observations re-enforced the existence of a highly ordered transition state geometry where unfavourable steric interactions were minimised.

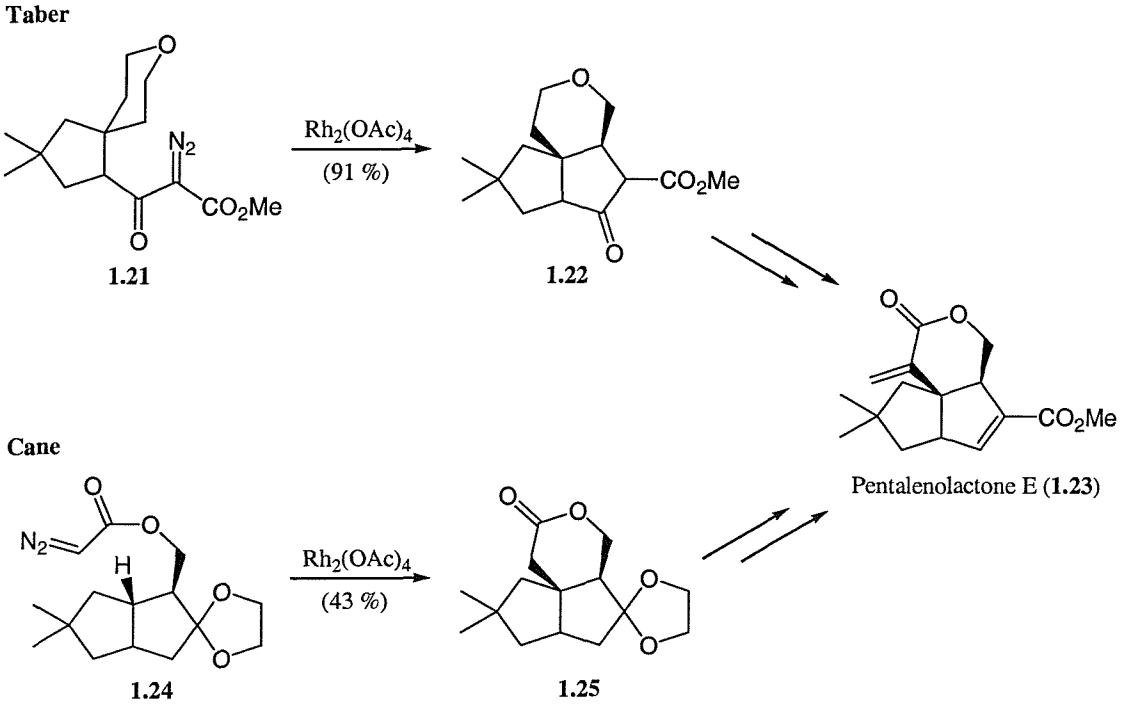
Figure 1.8 Synthesis of (+)-α-cuparenone



1.18 **1.19** (+)-α-Cuparenone (**1.20**)

Taber utilised this early methodology work in the synthesis of two natural products, (+)-α-cuparenone[36] (**1.20**) and pentalenolactone E[37] (**1.23**). He demonstrated that rhodium-mediated cyclisation of **1.18** to **1.19** proceeded with retention of absolute configuration in the synthesis of sesquiterpene, (+)-α-cuparenone (**1.20**) (Figure 1.8).[36] The transformation from an acyclic tertiary to a cyclic quaternary stereogenic centre reveals another powerful feature of the intramolecular C-H insertion reaction.

Figure 1.9 Two C-H insertion approaches to the synthesis of pentalenolactone E

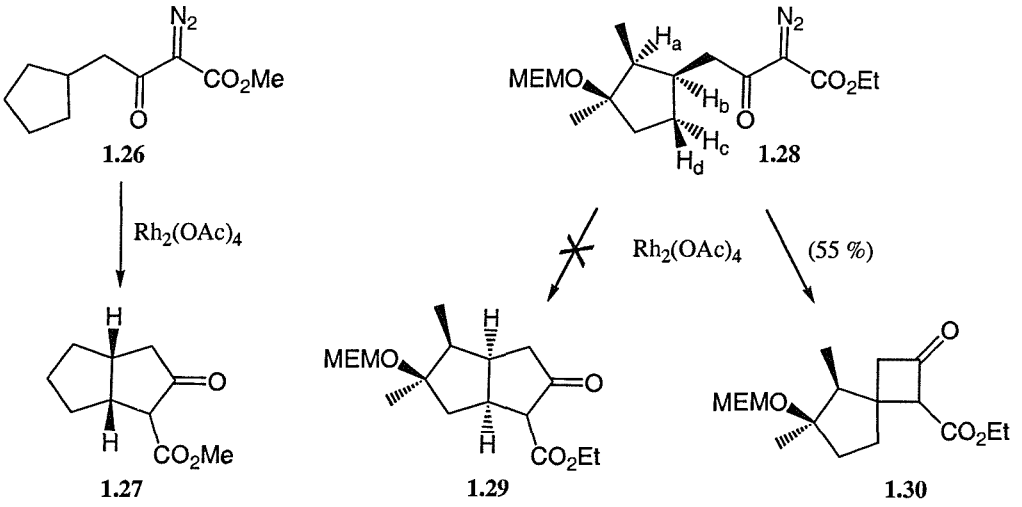


1.21 **1.22** Pentalenolactone E (**1.23**)

1.24 **1.25**

Interestingly, Cane and co-workers[38] reported an earlier approach towards pentalenolactone E (**1.23**) using a key carbenoid cyclisation step (Figure 1.9). By contrast, they utilised a C-H insertion to form the 6-membered lactone **1.25** from diazo precursor **1.24** (sterically the most accessible option over 5-membered ring formation). These two successful yet differing synthetic strategies illustrate the versatility of the intramolecular C-H insertion reaction.

Figure 1.10 Steric and conformational influences in C-H insertion



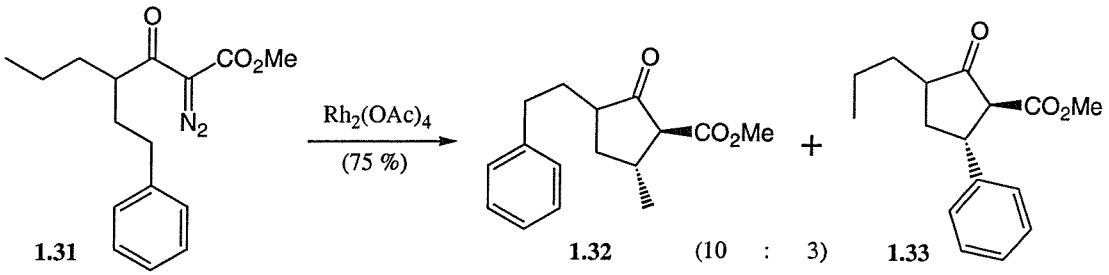
Steric factors play a crucial role in determining the regio- and stereo-chemical outcome of insertion products. Thus, insertion into C-H bonds of simple cyclopentanone derivatives gives only *cis*- fused bicyclic adducts[38] (*e.g.* **1.26** to **1.27**) (Figure 1.10). However, an excellent example of steric and conformational influences is also provided with results taken from work by Cane *et al.*[38] They reported that the catalytic decomposition of diazo-ester **1.28** resulted in spirocyclobutanone **1.30** whereas none of bicyclo[3.3.0]octanone **1.29** was isolated. Insertion at C-H_a or C-H_c is disfavoured by the strain imposed in forming a *trans*- ring junction. It is also probable that the combined 1,3 interactions of the MEM ether and β-methyl groups hinder approach of the carbenoid to the C-H_d bond, therefore promoting attack to be directed towards the opposite face of the cyclopentane ring. This leaves tertiary C-H_b as the only accessible site for insertion, leading to observed spirocycle **1.30**.

1.3.2 Substrate Electronic Effects

Taber and co-workers[34] have conducted systematic studies involving rhodium (II) tetraacetate catalysed intramolecular C-H insertions of α-diazo-β-ketoesters into aliphatic hydrocarbons. The results, not only showed that cyclisation to 5-membered rings was a

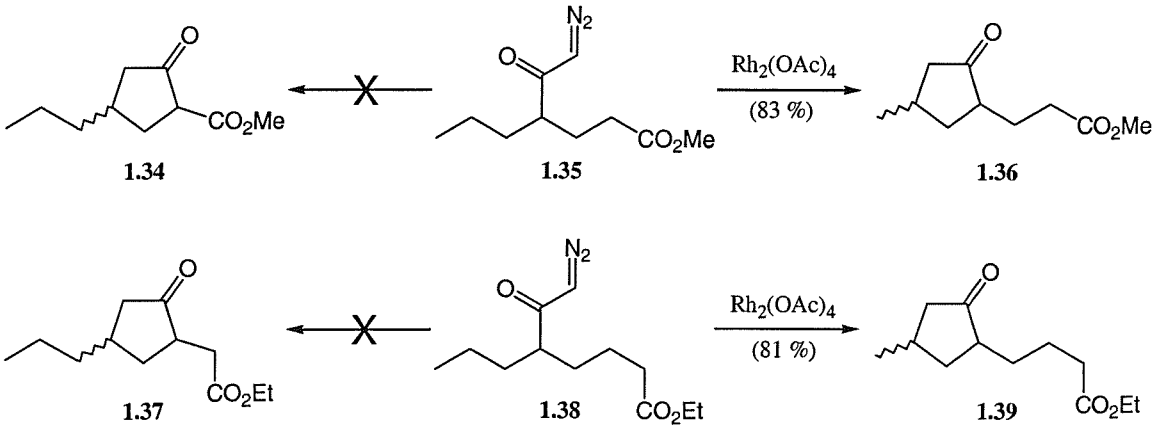
favoured process (*vide supra*), but also that the order of reactivity for C-H insertion increased along the series methyl to methylene to methine. Taber rationalised these regioselectivities were attributed to electronic influences of the electron donating alkyl groups and therefore by increasing the electron density in the C-H bond it becomes more susceptible to electrophilic carbenoid attack. Furthermore, it was determined that insertion into aliphatic methylenes was favoured over allylic and benzylic C-H bonds. The electron withdrawing phenyl substituent deactivates the benzylic methylene of **1.31** providing cyclopentanone **1.32** in preference to **1.33** (Figure 1.11).[34] In direct contrast, 'free' carbene insertion at these centres is a facile process,[39,40] supporting the theory that a rhodium carbenoid complex preferentially reacts with the most electron rich C-H bonds.

Figure 1.11 Benzylic *vs* aliphatic methylene C-H insertion



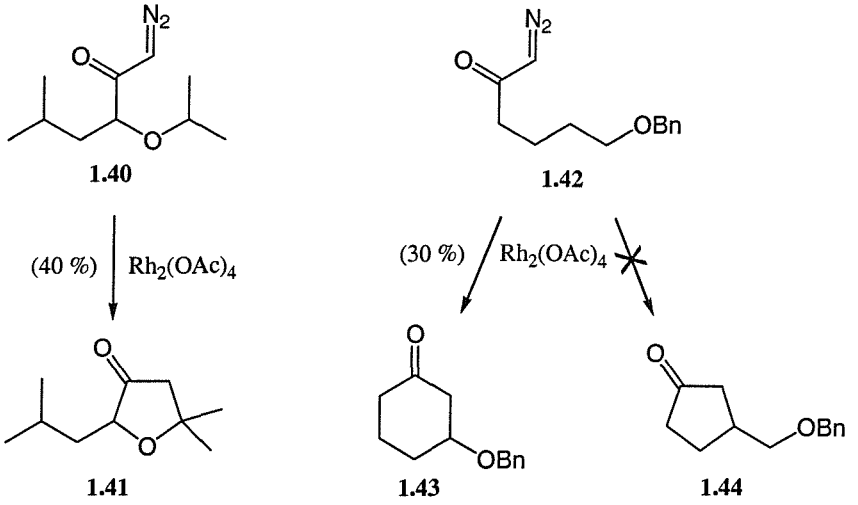
Further evidence of C-H insertion reactions under stereoelectronic control was observed in the work of Stork and Nakatani.[41] They reported that inductive effects of electron withdrawing ester groups deactivated the α or even β position towards C-H insertion. Rhodium mediated cyclisations of **1.35** and **1.38** was therefore directed towards an unactivated methylene C-H of a proximal aliphatic chain affording cyclopentanone esters **1.36** and **1.39** as a mixure of diastereoisomers (Figure 1.12).

Figure 1.12 Carboxyl group deactivation towards C-H insertion



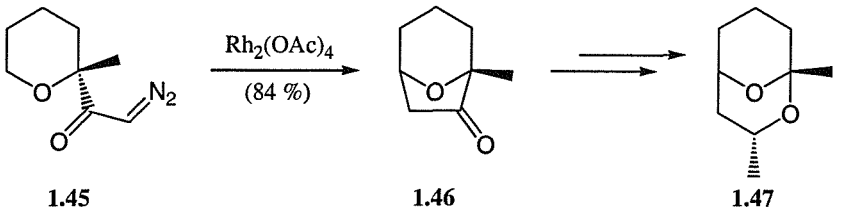
Taber's early suggestion that the most electron rich C-H bonds tend to be kinetically more reactive was a phenomenon also observed by Adams *et al.*[42,43] They recognised a preference for insertion into C-H bonds α to ether oxygens. For example, the rhodium catalysed reaction of diazo-ketone **1.40** afforded the corresponding furanone **1.41** as a single product (Figure 1.13). The affinity for insertion into C-H bonds α to oxygen is so pronounced that cyclisation of diazo ketone **1.42** formed 6-membered cyclic ether **1.43** with no cyclopentanone **1.44** observed.

Figure 1.13 Influence of α-heteroatom electron donation on C-H insertion



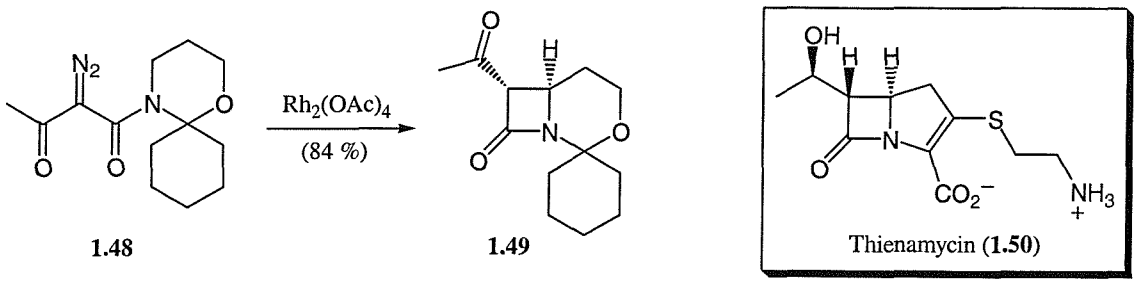
Adams exploited his knowledge of α-heteroatom activation in the total synthesis of insect pheromone **1.47**, in which C-H insertion α to the ether oxygen of **1.45** was the key step in forming bridged bicyclic ketone **1.46** (Figure 1.14).[44]

Figure 1.14 Synthesis of insect pheromone 1.47 *via* C-H insertion



Selective insertion into C-H bonds α to nitrogen atoms has also become an important transformation, particularly in the synthesis of β-lactam derivatives. Southgate and Ponsford[45] were first to report a rhodium carbenoid C-H insertion reaction of an α-diazo-β-ketoamide whereby **1.48** cyclised cleanly to provide β-lactam **1.49** (Figure 1.15). This proved a key strategy towards the synthesis of analogues of the carbapenem drug, thienamycin (**1.50**).[46,47]

Figure 1.15 β-Lactam synthesis *via* C-H insertion

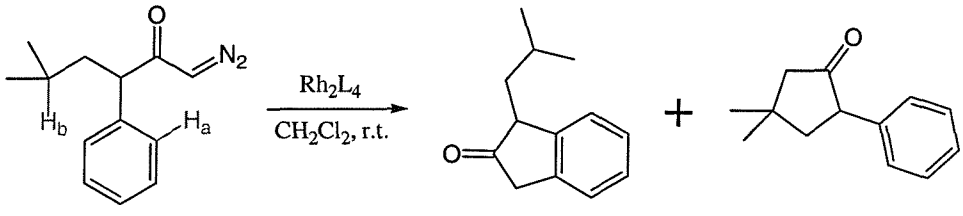


1.48 1.49 Thienamycin (**1.50**)

1.3.3. Rhodium Ligand Effects

Literature reports describe a variety of dirhodium (II) ligand modifications that influence chemoselectivity in metal-mediated transformations of α-diazo-carbonyl compounds.[11,18,19,34] In one selected example, the choice of catalyst exerted substantial control on competitive intramolecular aromatic C-H_a versus aliphatic C-H_b insertion (Figure 1.16).[48] A general trend of increasing preference for aromatic substitution was observed when the electron withdrawing capacity of the rhodium ligand was augmented. This may be attributed to enhanced formation of the metal stabilised carbocation resonance form of the metal carbene (**1.2**) upon removing electron density from the metal centre. Thus, electrophilic aromatic substitution (**1.51** to **1.52**) would be considered more favourable over insertion into the aliphatic C-H bond (**1.51** to **1.53**).

Figure 1.16 Intramolecular aromatic *vs* aliphatic C-H insertion



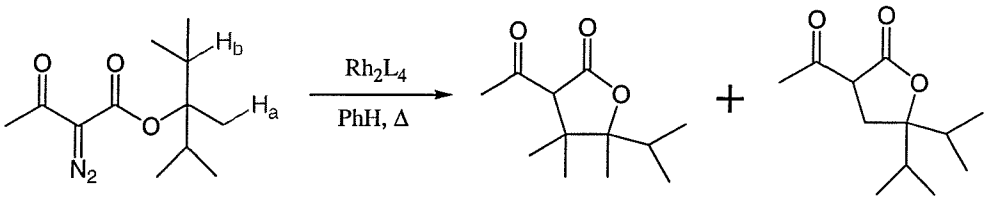
1.51 **1.52** **1.53**

Rhodium catalyst	% Yield	Product ratio	
		1.52	**1.53**
$Rh_2(cap)_4$	64	59	41
$Rh_2(OAc)_4$	97	65	35
$Rh_2(pfb)_4$	96	100	0

Doyle and co-workers[18] have extensively investigated carboxylate and carboxamide ligands on dirhodium (II) catalysts to modify regiocontrol in C-H insertion reactions of

diazoacetate esters. In one such experiment, the decomposition of diazo-β-ketoester **1.54**, a competition exists for primary C-H_a versus tertiary C-H_b insertion (Figure 1.17). With the prototypical acetate ligand, insertion into the more electron rich tertiary centre was observed, supporting Tabers earlier work (*vide supra*). This preference was further enhanced with the less electron withdrawing acetamide ligand complex (**1.55**:**1.56** = 99:1). However, with strongly electron withdrawing perfluorobutyrate ligands, the observed product ratio (**1.55**:**1.56** = 39:61) was almost exactly that of a predicted statistical product distribution based on the number and type (tertiary:primary) of carbon-hydrogen bonds available for insertion. These results were consistent with previous reports of reactivity/chemoselectivity in other catalytic carbenoid reactions that suggested decreased electron withdrawal by di-rhodium (II) ligands (acam < OAc < pfb) lowered the reactivity but increased selectivity.[17,48]

Figure 1.17 Effect of Rh ligand on primary *vs* tertiary C-H insertion

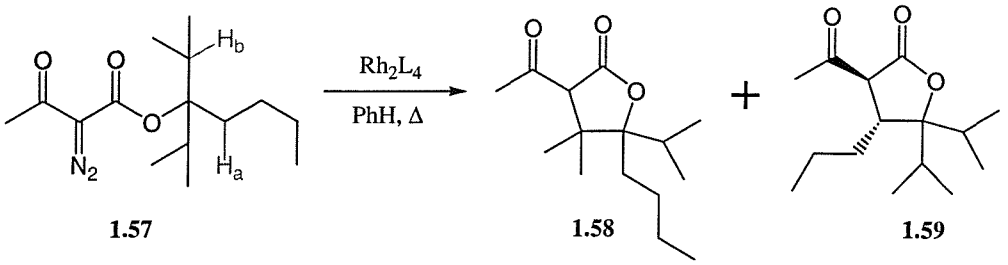


1.54 **1.55** **1.56**

Rhodium catalyst	% Yield	Product ratio	
		1.55	**1.56**
$Rh_2(pfb)_4$	61	39	61
$Rh_2(OAc)_4$	97	90	10
$Rh_2(acam)_4$	89	99	1

However, another set of experiments indicated the absence of any significant influence of the catalyst on regioselectivity for the C-H insertion reaction. Diazo decomposition of **1.57** significantly favoured insertion into the methylene C-H_a over methine C-H_b, with ligand changes providing a negligible effect (Figure 1.18). The formation of the electronically disfavoured insertion product suggested a strong conformational influence in either the transition state or reaction products. Doyle supported this theory with results of molecular modelling studies on the transition state and products resulting from the proposed C-H insertion of **1.57**. He estimated methylene insertion to be favoured over methine insertion by 4.6 kcal/mol in the transition states of **1.59** and **1.58**, with **1.59** also calculated to be more stable than **1.58** by 3.2 kcal/mol.

Figure 1.18 Insignificant effect of Rh catalysts on C-H insertion



1.57 1.58 1.59

Rhodium catalyst	% Yield	Product ratio	
		1.58	**1.59**
$Rh_2(pfb)_4$	74	5	95
$Rh_2(OAc)_4$	88	3	97
$Rh_2(cap)_4$	79	4	96

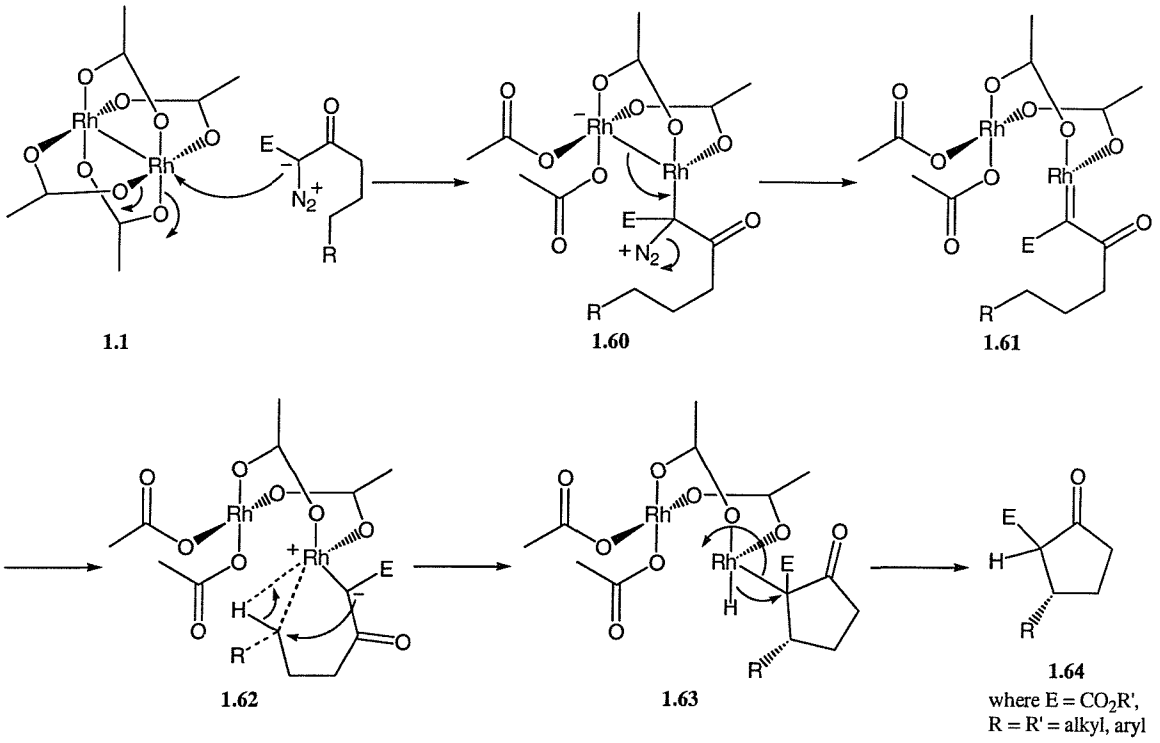
Doyle concluded that when the possible sites for insertion cannot present their C-H bonds to the carbene centre with equal probability then the regiochemical outcome is governed more by conformational than electronic preference. In such cases, selectivity for insertion into primary, secondary or tertiary C-H bonds may be random and changing the electrophilicity of the metal carbene will have little effect on selectivity.

1.4 Mechanistic Issues of the C-H Insertion Reaction

A detailed mechanism describing the role of the metal in a C-H insertion reaction was first proposed by Taber *et al.*[34] (Figure 1.19). This involved initial attack of an α-diazo-carbonyl compound at one of the vacant axial sites of the rhodium dimer (**1.1** shown for simplicity) resulting in dissociation of two bridging acetate ligands to provide intermediate **1.60**. Cleavage of the Rh-Rh bond, with subsequent loss of nitrogen, generates the metal carbene **1.61**. Taber was unsure whether the C-H insertion was a concerted 3-bond process (**1.62**) although ultimately he proposed a hydrogen atom ended up on rhodium. Reductive elimination of **1.63** regenerates the catalyst (upon reassociation of the bridging ligands) and affords the observed cyclopentanone C-H insertion product **1.64**. This highly speculative mechanism raised a number of interesting issues that were not properly addressed for several years (*vide infra*). Perhaps the most unusual and controversial feature of Taber's suggested mechanism was the cleavage of the Rh-Rh single bond. The high degree of stereoselectivity generally encountered in these reactions combined with his observation of retention of configuration implied a

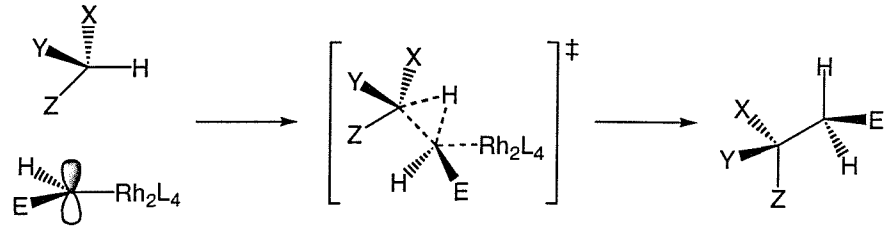
highly ordered transition state (*vide supra*). This was hard to imagine without a formal bond between the two rhodium atoms.

Figure 1.19 Mechanism of C-H insertion according to Taber *et al.*



Doyle and co-workers[24] later reported that a high degree of enantioselectivity was achieved in C-H insertion reactions utilising chiral dirhodium (II) carboxamides. Doyle felt this further supported the notion that ligands on the dirhodium complex remained intact throughout the reaction and consequently suggested a mechanism for C-H insertion[18] fundamentally different from Taber's original proposal (Figure 1.20).

Figure 1.20 Doyle's mechanism for C-H insertion



The Doyle mechanism involves overlap of the metal carbene's empty p-orbital with the σ-orbital of the reacting C-H bond. This leads to concerted C-C and C-H bond formation with loss of the rhodium complex, accounting for the observed high regioselectivities of the C-H insertion process and also providing a rationale for ligand modifications altering the stereochemical outcome. According to Doyle's model, electron withdrawing ligands

(*e.g.* perfluorobutyrate) increase the electrophilicity of the metal carbene and cause bond formation to take place at a greater distance from the reacting C-H bond (earlier transition state), thereby lowering selectivity but increasing reactivity. Ligands with decreased electron withdrawal (*e.g.* carboxamide ligands) lead to a later transition state with greater selectivity, an important feature of modern chiral ligand designs effecting enantioselective metal carbene transformations.[25]

Taber *et al.*[49,50] have added further thoughts regarding the exact nature of the transition state in an attempt to predict the diastereoselectivity of rhodium mediated intramolecular C-H insertion reactions. However, Doyle's mechanistic model for the C-H insertion process is still regarded as the most accurate and several groups have used it to explain their experimental observations.[51,52]

1.5 Conclusions

Dirhodium (II) catalysts have proved exceptionally effective for C-H insertion reactions of α-diazo-carbonyl compounds. The high yields obtained in these reactions, ability to form complex products from relatively simple starting materials and the remarkable degree of stereocontrol that can often be achieved makes C-H insertion a very powerful transformation available to the modern day synthetic chemist.

Although recent breakthroughs in chiral rhodium catalysts have shed increased light on the mechanistic issues surrounding the C-H insertion reaction, it is still not fully understood. However, the future design of rhodium ligands to enhance regio-, stereo- or enantio-control will certainly consider the architecture of the proposed metal carbene complex and its interaction with the reacting substrate.

Chapter 2

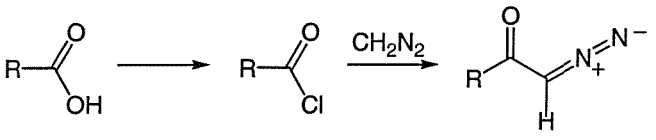
Diazo-Transfer Synthesis of α-Diazo Carbonyl Compounds

The preceding chapter discussed the synthetic applicability of rhodium catalysed C-H insertion reactions. However, the success of this reaction and many other carbenoid transformations relies heavily on the availability and synthesis of α-diazocarbonyl compounds. The following chapter will, therefore, appropriately summarise the most important methods towards preparation of these valuable synthetic intermediates.[29]

2.1 Early Approaches Towards α-Diazocarbonyl Synthesis

Independent work by Curtius[53] and Wolff[54] showed the synthesis of α-diazocarbonyl compounds was possible but it was not until the research of Arndt and Eistert,[55-57] in the late 1920s, that they became readily available. They demonstrated that acylation of diazomethane with an acid chloride was a viable route for the synthesis of α-diazo-ketones (Figure 2.1). Now, almost seventy-five years later, acylation of diazomethane probably remains the most important method for the synthesis of acyclic terminal α-diazo ketones.[58]

Figure 2.1 Synthesis of α-diazo-ketones *via* acylation of diazomethane



Although hugely successful, the pioneering preparation of α-diazocarbonyl derivatives *via* diazotisation of α-amino acids or diazomethane acylation had the obvious limitation of only being applicable to acyclic systems. Although many routes to α-diazocarbonyl compounds have been developed in an attempt to tackle this problem,[59,60] including the Bamford-Stevens approach,[61-63] their value has diminished substantially since the discovery of diazo-transfer techniques.

2.2 Diazo-Transfer Reactions

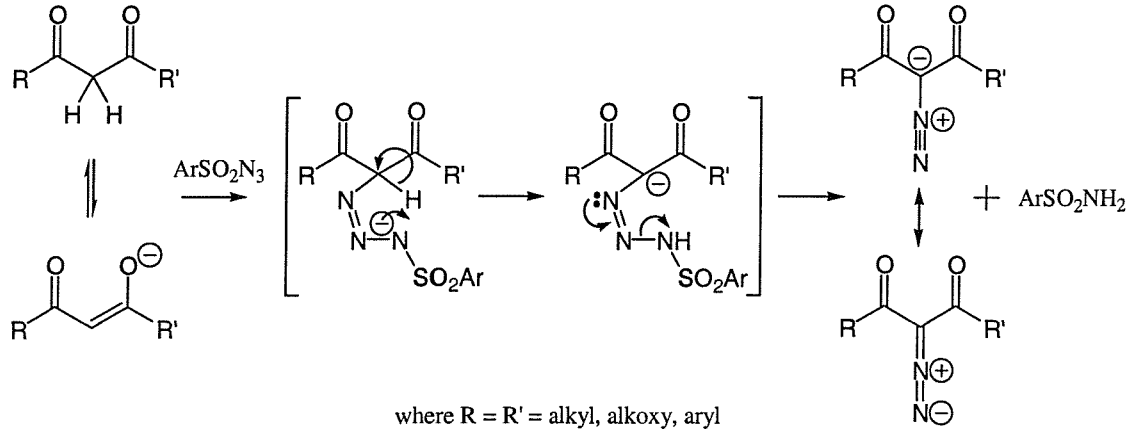
Since its introduction in 1967 by Regitz and co-workers,[64] diazo-transfer has become the standard methodology not only towards cyclic α-diazocarbonyl componds, but also to many acyclic systems inaccessible through diazoalkane acylation.[29] Diazo-transfer may be described as the transfer of a complete diazo group from a donor (most commonly a

sulfonyl azide) to an acid or ketone derived acceptor. For this transformation to take place at the α-carbonyl position requires the presence of a sufficiently strong base to deprotonate the substrate. Diazo-transfer can, therefore, be broadly divided into 2 categories depending on the acidity of the substrate: (a) direct diazo-transfer - the α-methylene position is sufficiently reactive toward attack onto an azide; (b) sacrificial activation – the substrate requires prior activation of the transfer centre with a group that will subsequently be lost upon formation of the diazo compound. Representative literature examples for each methodology are highlighted in the following sections.

2.2.1 Direct Diazo-Transfer

When an arenesulfonyl azide reacts, in the presence of base, with a compound containing a methylene position flanked by two carbonyl groups, it is smoothly converted into a 2-diazo-1,3-dicarbonyl product and an arenesulfonamide byproduct (Figure 2.2). Upon reaction with *p*-toluenesulfonyl azide, using triethylamine as base, Regitz *et al.*[64,65] utilised this method in the synthesis of diazo derivatives from a wide variety of 1,3-dicarbonyl systems, including malonic esters, β-keto esters and β-diketones. Although variations to the arenesulfonyl azide, base and solvent have been an area of continual investigation (*vide infra*), this general procedure still remains that most commonly used in the synthesis of α-diazo-dicarbonyl derivatives.

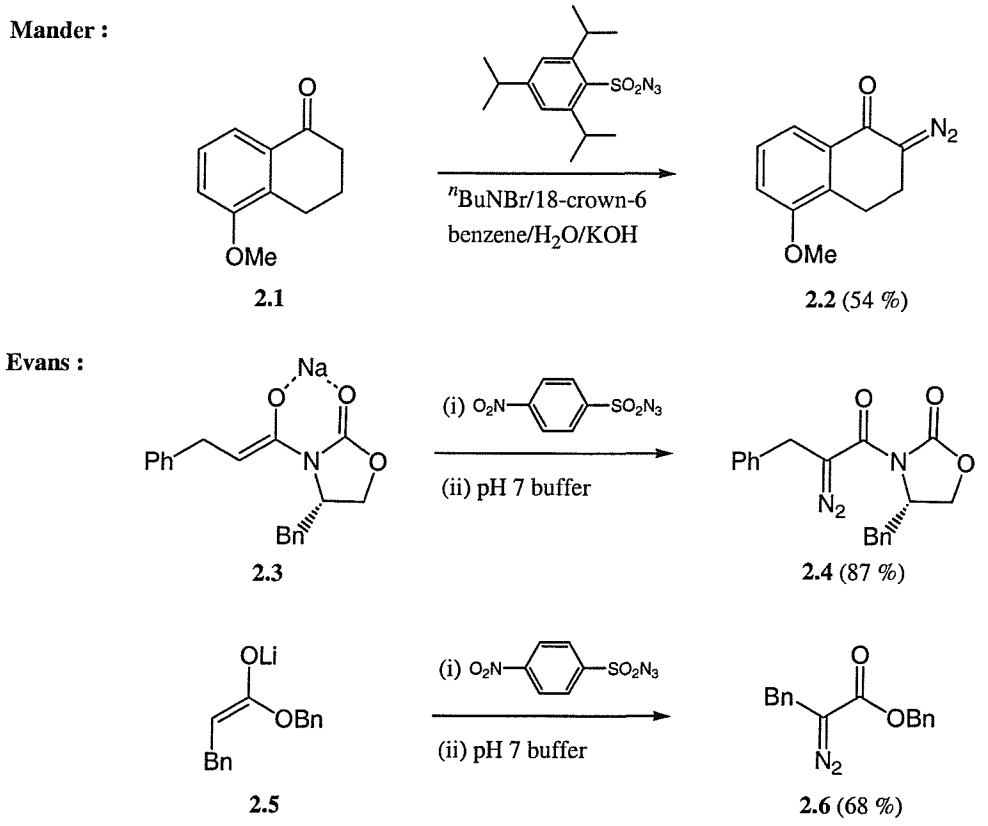
Figure 2.2 Diazo-transfer on 'doubly activated' methylene position



Whilst this strategy works extremely well for cases where the transfer site is activated by two carbonyl functionalities, direct diazo-transfer to singly activated methylene groups is scarce. Lombardo and Mander[66] have reported a one step synthesis of cyclic α-diazoketones under phase transfer conditions (Figure 2.3). When using 2,4,6-tri-*iso*propylbenzenesulfonyl azide in combination with catalytic quantities of tetra-*n*-

butylammonium bromide and 18-crown-6, this phase transfer method gave good results with a variety of cyclic ketones (*e.g.* **2.1** to **2.2**).

Figure 2.3 Examples of direct diazo-transfer to singly activated methylene groups



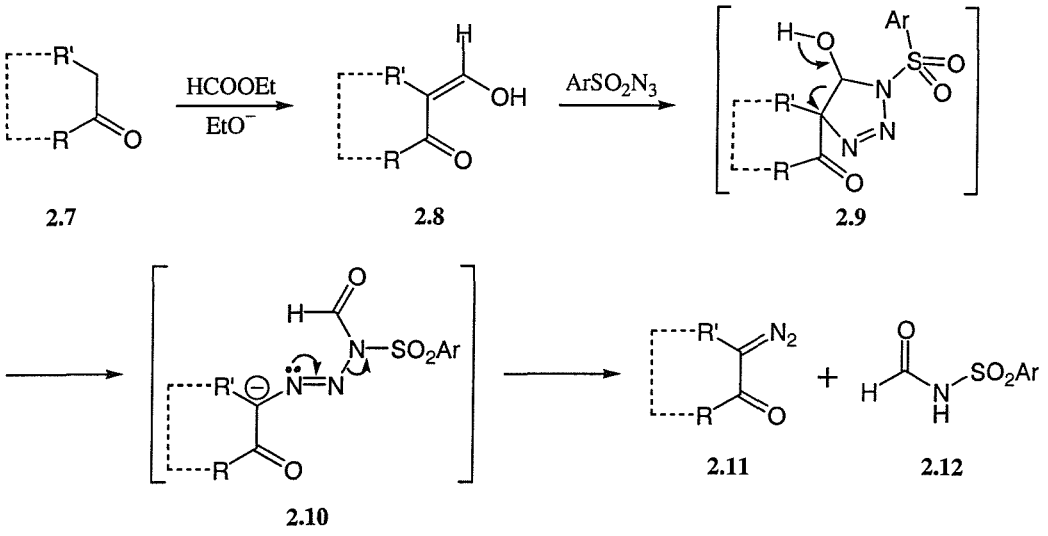
Upon investigating the synthesis of amino acids *via* electrophilic azidation of imide enolates **2.3**, Evans and co-workers[67] stumbled upon a set of conditions favouring the synthesis of α-diazo-imide **2.4**. They demonstrated that the course of the reaction was dependent on the sulfonyl azide, counterion of the enolate and 'quench' reagent used. In particular, the competing azidation reaction could be substantially reduced (and often eliminated) by the appropriate choice of electrophile. Thus, the highly electron deficient *p*-nitrobenzenesulfonyl azide predominantly formed the diazo-transfer product, whereas 2,4,6-tri-*iso*propylbenzenesulfonyl azide favoured an azide-transfer product – in stark contrast to results previously obtained by Mander and Lombardo (*vide supra*). Evans *et al.*[67] used their knowledge from these serendipitous observations to better synthetic value in the direct diazo-transfer of benzylester enolate **2.5**, affording α-diazoester **2.6** in good yield.

Although optimisation of reaction conditions with a single carbonyl compound activating the methylene group can, occasionally, provide diazo compounds in satisfactory yields (*vide supra*), better results are generally obtained upon activation of the transfer centre.

2.2.2 Sacrificial Activation

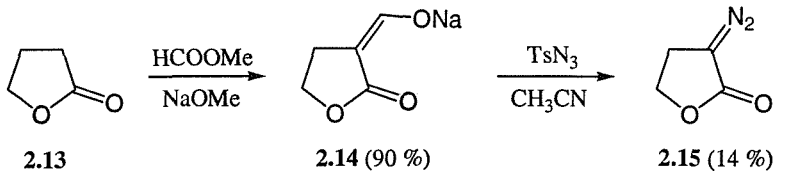
Diazo-transfer to simple ketones may be achieved through an indirect 'deformylative diazo-transfer' strategy first introduced by Regitz in 1967.[64] Ketone **2.7** is initially formylated under Claisen condensation conditions to provide keto aldehyde **2.8** (existing in its enol form) which is subsequently treated with a sulfonyl azide reagent, typically *p*-toluenesulfonyl azide, to afford triazoline intermediate **2.9** (Figure 2.4). This undergoes fragmentation, cleaving the introduced acyl moiety and following elimination of *N*-sulfonylamide **2.12** generates the desired α-diazocarbonyl compound **2.11**.

Figure 2.4 Deformylative diazo-transfer



The application of this method in the preparation of a variety of acyclic and cyclic α-diazocarbonyl compounds is now well documented.[65,68-72] This includes formylation of γ-butyrolactone (**2.13**) followed by diazo-transfer of **2.14** to provide the only known synthesis (before our work described hereafter) of α-diazolactone **2.15** (Figure 2.5).[73]

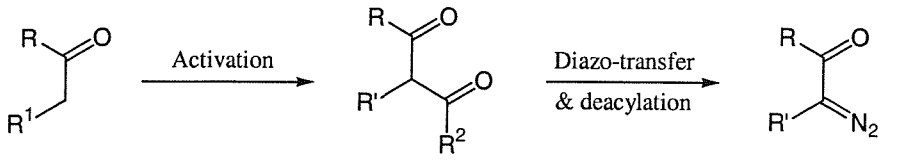
Figure 2.5 Synthesis of an α-diazo-γ-butyrolactone *via* deformylative diazo-transfer



In a number of crucial cases, as highlighted in the example above, deformylative diazo-transfer produces the desired diazocarbonyl compounds in relatively low yields. Particularly problematic are reactions involving base sensitive substrates such as esters and α,β-enones where the difficulties are mainly attributed to the harsh conditions

typically required for the Claisen condensation step. However, more recent work describes acylation as a superior method of activating carbonyl compounds towards diazo-transfer (Figure 2.6).

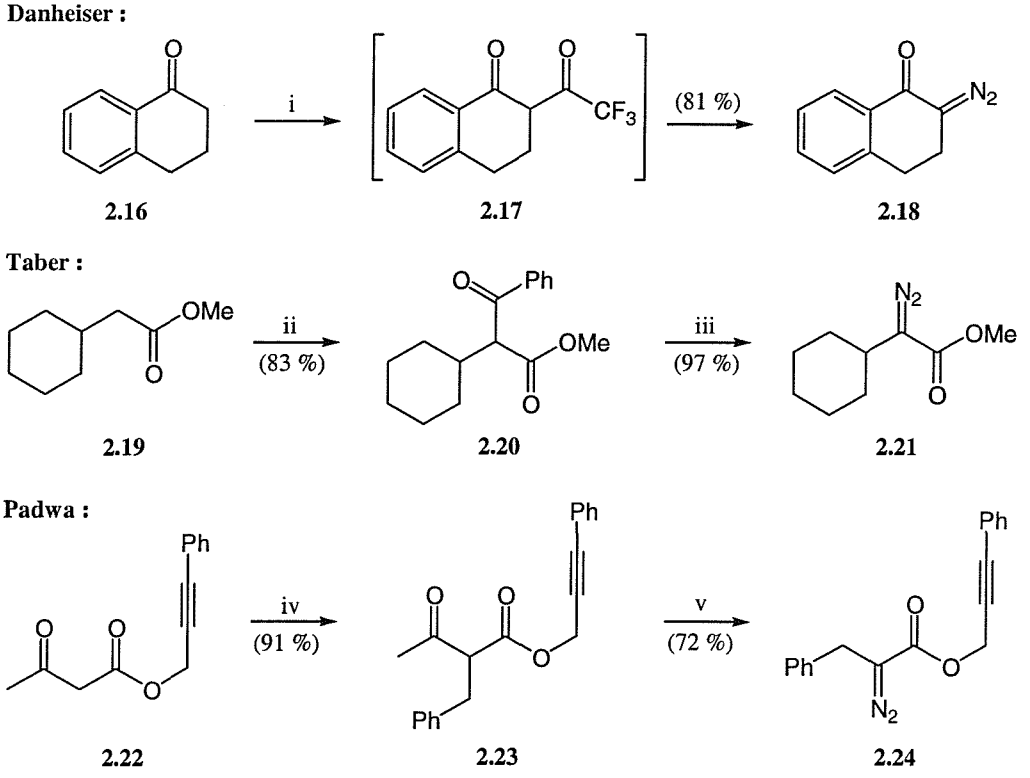
Figure 2.6 Deacylative diazo-transfer strategies



R = alkyl, alkoxy, aryl, R^1 = alkyl $R^2 = CH_3, CF_3$, Ph

Examples of synthetic applications utilising the most frequently used sacrificial activating carbonyl groups are represented below (Scheme 2.1). Danheiser and co-workers[74] reported a new protocol whereby activation of benylic and α,β-unsaturated ketone precursors (*e.g.* **2.16**) was achieved *via* trifluoroacetylation. Subsequent diazo-transfer of the α-trifluoroacetyl derivatives (*e.g.* **2.17**) provided dramatically improved yields of α-diazoketones over the conventional deformylative method.

Scheme 2.1



Reagents and conditions: (i) a) LiHMDS, $CF_3CO_2CH_2CF_3$, THF; b) MsN_3, Et_3N, CH_3CN; (ii) NaH, $PhCO_2Me$, DME; (iii) 4-nitrobenzenesulfonyl azide, DBU, CH_2Cl_2; (iv) NaH, BnBr, THF; (v) 4-nitrobenzenesulfonyl azide, DBU, CH_2Cl_2.

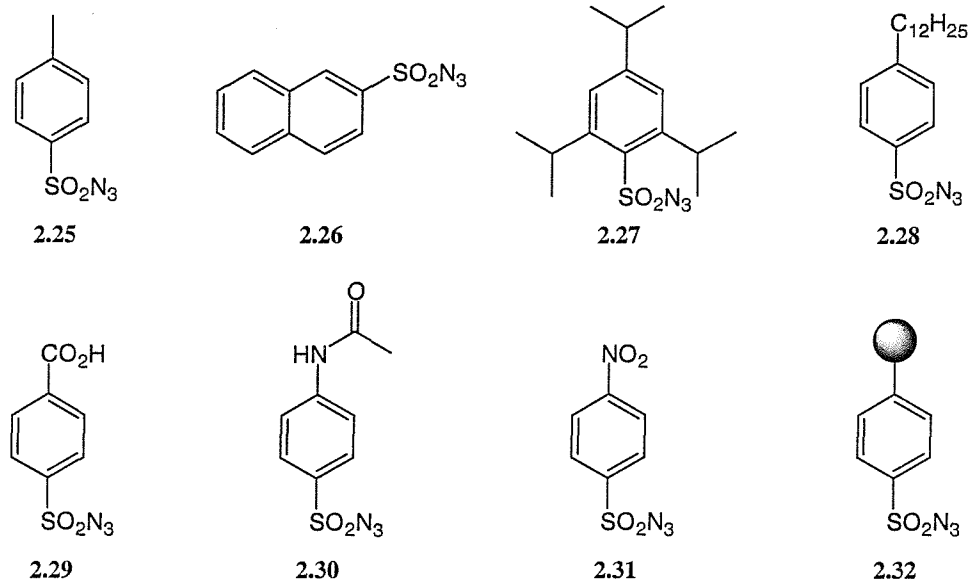
Taber and colleagues,[75] recognising the absence of a general procedure for diazo-transfer to the α-methylene of an ester, employed benzoylation (this methodology had already been described in the synthesis of α-diazoketones[76]) in the formation of a number of simple α-diazoesters (*e.g.* **2.21**). Padwa[77] investigated the use of acetoacetate derived acetyl moieties as sacrificial activators for diazo-transfer. Padwa found this methodology extensively more successful than Taber's benzoylation approach in the synthesis of a number of alkynyl substituted α-diazoesters (*e.g.* **2.24**).[77]

2.3 Diazo-Transfer Reagents

The reaction of activated methylene groups with tosyl azide in the presence of triethylamine generally provides the diazo compounds in good yields. Frequently, however, the reaction does not proceed to completion and gives rise to the problem of separating the product from unreacted tosyl azide and tosyl amide by-products.[70] Literature reports the use of tosyl azide as a transfer agent with a variety of bases to facilitate reaction work-up or promote deprotonation of the β-dicarbonyl substrates. These include; potassium carbonate in acetonitrile and filtration of the resulting inorganic salts;[78] potassium fluoride supported on alumina as a solid base;[79] potassium fluoride-crown ether combinations creating a 'naked' anion effect;[80] a phase-transfer method with aqueous base and ammonium salt;[81] use of DBU, particularly with hindered substrates.[82]

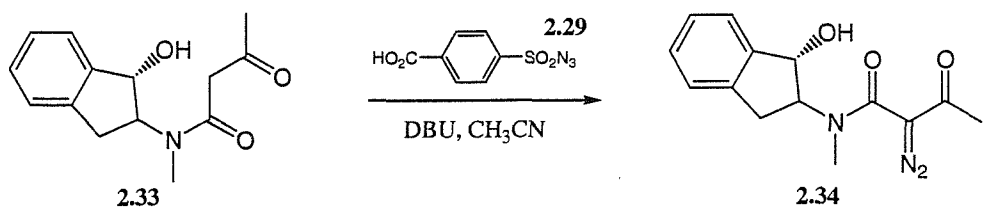
Although tosyl azide is by far the most frequently employed diazo donor, doubts have been raised regarding the safety aspect of this reagent.[83] When faced with the prospect of a large scale diazo transfer, Bollinger *et al.*[84] undertook a thorough investigation of benzenesulfonyl azides. Five reagents, **2.25** – **2.29**, were examined with regard to their thermal stability, ease of handling, safety and cost (Figure 2.7). Tosyl azide (**2.25**) was found to be most hazardous, combining the highest impact sensitivity with the largest heat of decomposition. With the lowest specific heat of decomposition and no impact sensitivity at the highest test level, *p*-dodecylbenzenesulfonyl azide[85] (**2.28**) was considered the 'safest' reagent of the group. Moreover, the sulfonamide by-product is non-crystalline, facilitating isolation of crystalline diazo compounds. If, however, the diazo- product is a liquid then naphthalene-2-sulfonyl azide (**2.26**) may be employed taking advantage of the resulting sulfonamides' insolubility.[84]

Figure 2.7 Examples of arenesulfonyl azides utilised in diazo-transfer reactions



Although Bollinger and co-workers found *p*-carboxybenezenesulfonyl azide (**2.29**) possessed good safety data they considered this reagent too expensive and furthermore, its use necessitated two moles of base per mole of substrate which was unsuitable for some of their base sensitive compounds.[84] However, the chemical handle offered by the carboxy group makes it a popular choice for a diazo donor. Hendrickson and Wolf[70] were first to take advantage of this solubility handle when they observed that the triethylamine salt of the *p*-carboxybenzenesulfonamide reaction by-product was essentially insoluble in acetonitrile. Filtration of this carboxyamide salt followed by an aqueous base work-up normally affords diazo compounds in relatively uncontaminated states. Precipitation of the salt proves an excellent visual indication as to whether the reaction is proceeding, demonstrated by an example taken from the work of McClure *et al.*[86] Diazo-transfer to acetoacetamide **2.33** was initially attempted with the standard *p*-carboxybenzenesufonyl azide/triethylamine methodology but no sulfonamide salt precipitating from solution was observed and indeed, no reaction had taken place (Figure 2.8). However, when the stronger DBU base was employed, a precipitate formed within seconds and the reaction to give diazo product **2.34** was complete within a few hours.

Figure 2.8 Use of *p*-carboxybenezenesulfonyl azide as a diazo-transfer reagent

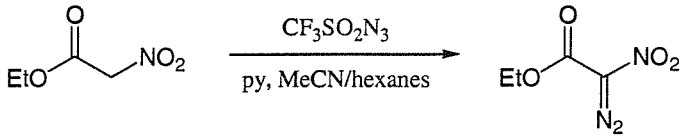


Baum and co-workers[87] report good stability data for *p*-acetamidobenzenesulfonyl azide (**2.30**) and claim it to be a practical and cost-effective reagent for diazo-transfer reactions. Similarly, Nickolaev *et al.*[80] and many other groups (*vide supra*) have found *p*-nitrobenzenesulfonyl azide (**2.31**) provides diazo compounds in very satisfactory yields. Both of these crystalline reagents offer a distinct advantage over tosyl- and *p*-dodecylbenzenesulfonyl azides due to the polarity differences in the azide, sulfonamide by-product and common substrates, thereby allowing ready monitoring of the reaction by TLC and simplified purification on silica gel.

Polymer supported sulfonyl azide (**2.32**) has been examined as a safe, easy to handle reagent with the convenience of a cleaner reaction work-up.[88-90] However, relatively large quantities of this expensive polystyrene based resin were required for diazo-transfer with reaction times seemingly longer than its homogeneous counterpart.

Although arenesulfonyl azides have traditionally been the reagent of choice for effecting diazo-transfer reactions there have been an increasing number of reports on the use of the more reactive methanesulfonyl azide and even trifluoromethanesulfonyl azide. Taber and colleagues[91] claim mesyl azide is a superior reagent with the advantage that any excess remaining after the reaction, together with the formamide by-product, may easily be removed by extraction into dilute aqueous base during work-up. Although extreme care must be taken when handling this low melting reagent, it is now commonly used in a variety of de-acylative diazo-transfers protocols (*vide supra*).[74,92,93]

Figure 2.9 Use of triflyl azide as a diazo-transfer reagent

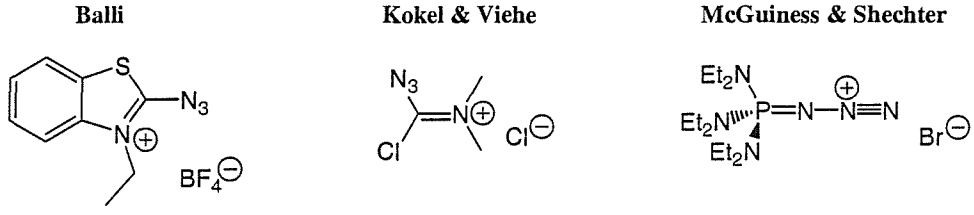


2.35 **2.36** (88 %)

After several failed attempts with tosyl azide, Norbeck and Kramer[94] managed to effect diazo-transfer to an enamine system using a solution of triflyl azide in 1,2-dichloroethane towards their synthesis of (-)-oxetanocin. Recently, Charette and co-workers[95] utilised this powerful reagent in the preparation of α-nitro-α-diazocarbonyl derivatives. They discovered that a hexane solution of triflyl azide reacted smoothly with ethyl nitroacetate (**2.35**) in acetonitrile and upon addition of pyridine generated ethyl-α-nitro-α-diazoacetate (**2.36**) in excellent yield (Figure 2.9).

The scope of diazo-transfer reagents has been considerably widened in recent years by the use of azidinium salts as diazo group donors. Balli and co-workers[96-98] were first to employ stable heterocyclic azidinium salts (*e.g.* **2.37**) as successful diazo-transfer reagents in the pH 0-8 range (Figure 2.10). Kokel and Viehe[99] report the more readily accessible iminium salt **2.38**, in acidic medium, as an effective diazo-transfer reagent with a variety of active methylene compounds. Both procedures prove beneficial in the preparation of base labile diazo derivatives, but their attractiveness is hampered by the high cost in forming the reagents themselves. Monteiro[100] partially circumvented this problem by generating the azididinium salt *in situ* and applied it to the preparation of several α-diazo-β-ketosulphones.

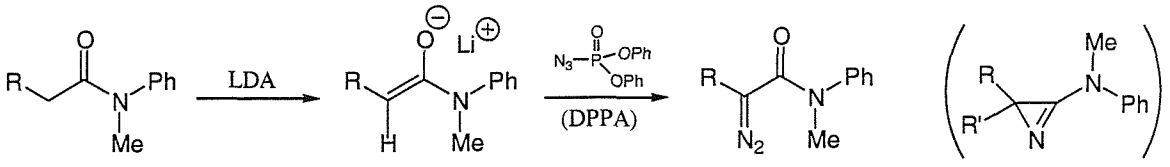
Figure 2.10 Azido- salts as diazo-transfer reagents



2.37 **2.38** **2.39**

McGuiness and Shechter[101] have reported azidotris(diethylamino)phosphonium bromide (**2.39**) as an exceptionally safe diazo-transfer reagent for 1,3 dicarbonyl compounds. Additionally, diazo-transfer generates a neutral leaving group, hexaethylphosphorimidic triamide, which is basic enough to deprotonate the starting material making the overall process catalytic in base. Unfortunately, azido- reagent **2.39** is extremely hydroscopic, requiring storage under vacuum, and has seen little synthetic application since its original description over a decade ago.

Figure 2.11 DPPA as a diazo-transfer reagent



2.40 **2.41** **2.42** (*e.g.* R = Ph, 65 %) **2.43**

Recently, Heimgartner *et al.*[102] reported diazo-transfer reactions with diphenyl phosphorazidate (DPPA). Whilst working on an aminoazirine synthesis they were surprised to isolate α-diazoamides **2.42** when enolates **2.41**, derived from 2-

monosubstituted amides **2.40**, were treated with DPPA (interestingly, enolates from 2,2-disubstituted amides formed the desired aziridines **2.43**) (Figure 2.11).

2.4 Conclusions

Diazo-transfer reactions have almost superseded other methodologies in the synthesis of stable α-diazocarbonyl compounds. Traditional reagents, such as arenesulfonyl azides, are routinely used to prepare diazo compounds from activated carbonyl derivatives. However, the more recently introduced azido salts have had little synthetic impact as diazo group donors, perhaps due to their cost but most probably the reluctance to stray from well-established methods.

Further improvements in diazo-transfer reactions almost certainly lie with a versatile diazo donor reagent(s) suitable for a wide range of substrates. It is the authors' belief that development of solid supported reagents holds the key to future advances in this area, both with regard to facilitating reaction work-up and safety.

Chapter 3

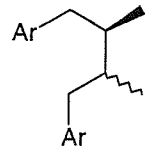
Furofuran Lignans: Structure, Biological Properties & Synthesis

The following chapter highlights the structural and biological properties of the furofuran series of lignan natural products. A summary of their previous synthetic approaches will also be included.

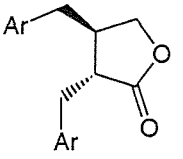
3.1 Introduction to Lignan Natural Products

Lignan natural products are produced by all vascular plants that use the polymer, lignin, to provide rigidity and strength in their cells. The widespread occurrence of lignans in the plant kingdom has led to the identification of a large number of structural types from various plant families (Figure 3.1).[103-107] Furthermore, novel lignans continue to be isolated at a steady rate with knowledge of their variety, structural diversity and natural abundance continually expanding.

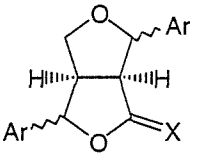
Figure 3.1 Representative structures of lignan natural products



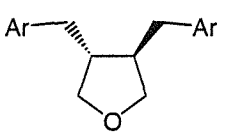
Dibenzylbutanes



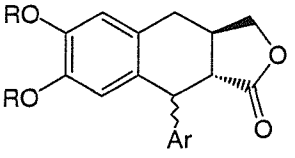
Dibenzylbutyrolactones



2,6-Diaryl-3,7-dioxabicyclo[3.3.0]octane-***8-one***
{furofuran(***ones***)} X = H_2 or ***O***



Substituted
tetrahydrofurans



Tetrahydronaphthalene
e.g. podophyllin lignans

Ar = various oxygenated aromatic rings and R = H-, Me- or -CH_2-

These natural products have attracted much interest over the years owing to their broad range of biological activities.[108,109] As a result of interesting pharmacological activities

many compounds and their synthetic derivatives have been assayed in an attempt to elucidate their mode of action and any structure-activity relationships. Indeed, analogues of the podophyllin class of lignan continue to be investigated in an effort to improve the anti-tumour activity of the clinical drug Etoposide.[110] Unfortunately, this has led to other classes of lignans all too often being overlooked, although it is worth noting that many of them also exhibit anti-cancer activity.[108] Although non conclusive, there is growing evidence that a lignan-rich diet may decrease the risk of contracting certain forms of cancer.[106]

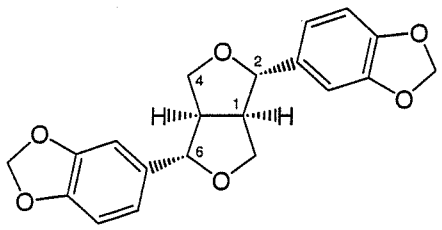
Recent advances in biological elucidation have identified a number of lignans as active ingredients in traditional Asian medicines.[111] For example, Deyama *et al.*[112-114] have isolated as many as 13 different lignans from *Cortex Eucommiae*, an anti-hypertensive medicine from China. The awareness for the significance of lignan natural products has prompted studies into their activities with the general recognition that the furofuran class remains one of the main attributers in the efficacy of these traditional drugs.

3.2 Structural and Biological Properties of the Furofuran Lignans

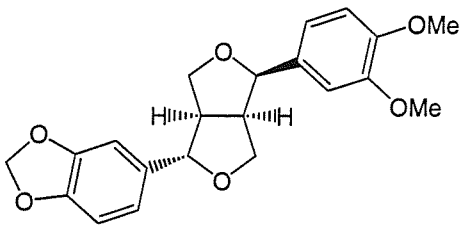
The furofurans are one of the largest subclass of lignan natural products and their isolation, characterisation, biosynthesis and biological activity have been extensively reviewed.[105-109] Structurally, the furofurans consist of a rigid dioxabicyclic core with appended electron-rich aromatic groups. The majority have their 2,6-diaryl substituents on the *exo* face of the bicyclic framework (*e.g.* **3.1**), although many compounds with *endo,exo*-configuration (*e.g.* **3.2–3.3**) and some with *endo,endo*-substitiution (*e.g.* **3.4**) are known (Figure 3.2).

A variety of biological activities have been attributed to the furofuran series, including: anti-tumour promotion,[115] anti-allergic activity,[116] antihypertensive activity,[117] anti-mitotic activity,[118] stress reducing activity,[108,111] *c*AMP phosphodiesterase inhibitory activity,[119] Ca^{2+} antagonist activity,[120] PAF antagonist activity[121,122] and toxicity enhancement in certain insecticides.[123,124] Recent bioassay-guided fractionation of traditional Asian medicines has facilitated identification of these biologically active furofurans. For example, the Chinese crude drugs, *shin-i* and *xinyi*, used to treat nausea and headaches, has unveiled the PAF and Ca^{2+} antagonist activity of fargesin[125,126] (**3.2**) and led to the isolation of a new furofuran displaying insecticidal activity, epimagnolin A[127] (**3.3**).

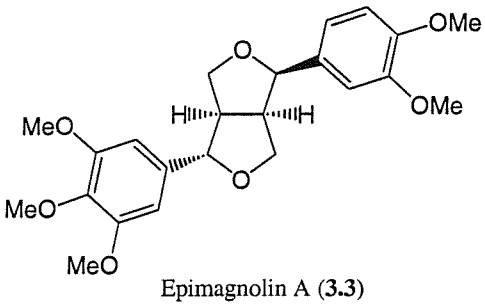
Figure 3.2 Structures of *exo,exo*-, *endo,exo*- and *endo,endo*-furofuran lignans



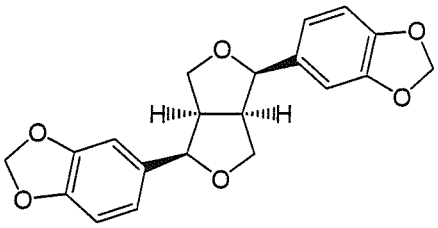
Sesamin (**3.1**)



Fargesin (**3.2**)
(also described as methyl pluviatilol)



Epimagnolin A (**3.3**)



Diasesamin (**3.4**)

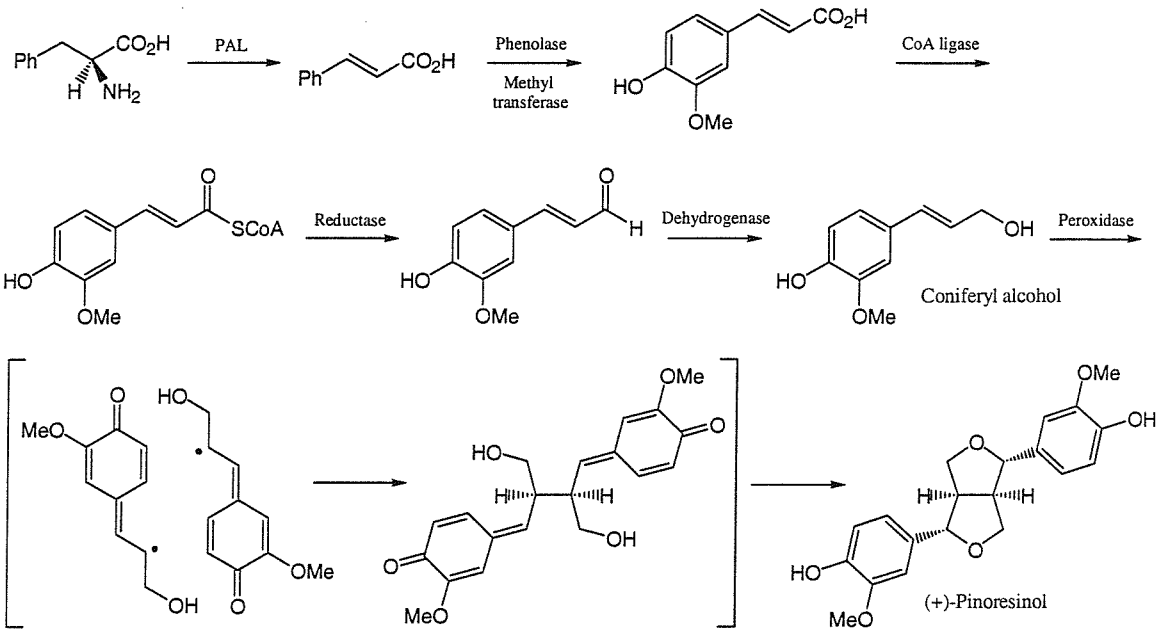
Although no furofuran derivative has reached the market as a medicinal agent, these compounds possess a wealth of biological activities (*vide supra*). It is reasonable to suggest, therefore, that structural modifications around the bicyclic skeleton may lead to significantly improved activities. Consequently, furofurans and their analogues have been and will continue to be, the subject of considerable synthetic interest.

3.3 Biosynthesis of Furofuran Lignans

The principle route to lignin and lignans commences with action of a lyase on phenylalanine to provide cinnamic acids. Stereospecific conversion of L-phenylalanine to the *E*-cinnamic derivatives is accomplished by a phenyl ammonia lyase (PAL) (Figure 3.3). A series of oxidases functionalise the aromatic ring (with or without methylation) before conversion to the coenzyme A esters is achieved. Ultimate reduction of cinnamic acids to the alcohols is performed with a combination of reductase and dehydrogenases.

Furofuran biosynthesis then proceeds *via* dimerisation of the alcohol monomers (*e.g.* coniferyl alcohol) with radical formation initiated by peroxidase enzymes. It has been proposed that the active site of the protein responsible for this transformation specifically recognises the radicals and only allows dimerisation to occur in a regio- and enantio-selective manner. Subsequent internal trapping of the quinone methides provides the final furofuran compounds.

Figure 3.3 Biosynthesis of furofuran lignans



The biosynthetic pathway discussed above uses pinoresinol as an example of the product obtained following coniferyl alcohol dimerisation. However, this route is equally applicable to other oxygenated aromatic systems. Furthermore, these dimerisation derivatives may be biochemically converted into other furofurans and also provide access to other classes of lignans.

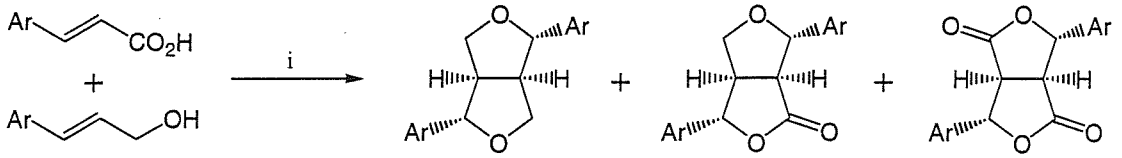
3.4 Synthesis of Furofuran Lignans

The following section details some of the existing methodologies available for the preparation of furofurans and their structurally related furofuranone and *bis*-lactone derivatives.

3.4.1 Synthetic Approaches Utilising Oxidative Coupling

The first literature methodologies for the synthesis of these classes of compounds involved oxidative dimerisation of cinnamyl derivatives in an attempt to mimic the biosynthesis.[128,129] Mixed oxidative phenolic couplings with cinnamic acids and cinnamyl alcohols, using ferric chloride as the oxidant[130,131] in air, generally provided a mixture of furofuran lignans **3.5**, furofuranones **3.6** and *bis*-lactones **3.7** (Scheme 3.1). Unfortunately, these oxidations required the cinnamyl derivatives to possess free OH groups at the *para*-position and is, therefore, unsuitable for the synthesis of compounds that incorporate, *e.g.* methylenedioxy groups, such as those derived from sesamin (**3.1**).

Scheme 3.1



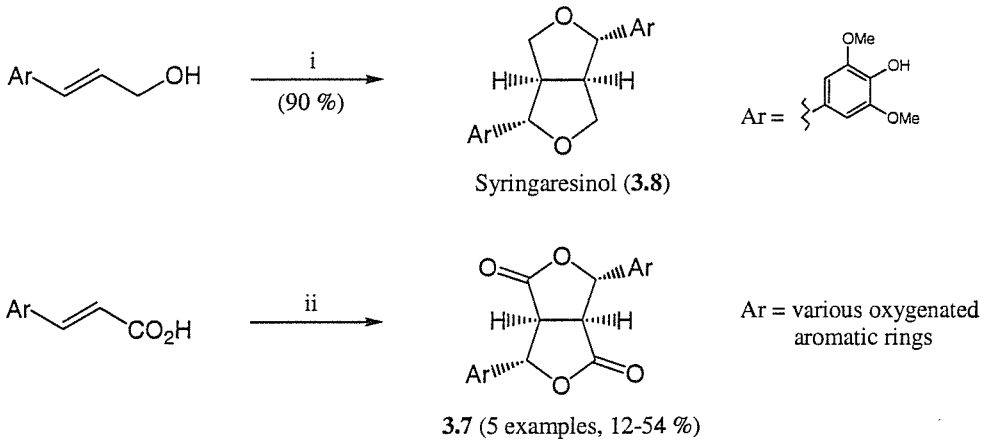
3.5 3.6 3.7

Ar = various oxygenated aromatic rings

Reagents and conditions: (i) $FeCl_3$, O_2, aq. acetone.

More recently, Vermes *et al.*[132] reported an oxidative dimerisation of sinapyl alcohol in the presence of air, light and a catalytic quantity of cupric sulfate to provide *exo,exo*-furofuran, syringaresinol (**3.8**) in excellent yield (Scheme 3.2). However, Taylor *et al.*[133,134] have shown that non-phenolic cinnamic acids may be converted into the corresponding *exo,exo*-bis-lactones **3.7**. They investigated the use of thallium (III) and cobalt (III) salts in the dimerisation of cinnamic acids to provide the desired lactones **3.7** in moderate to poor yields.

Scheme 3.2



Syringaresinol (**3.8**)

3.7 (5 examples, 12-54 %)

Ar = various oxygenated aromatic rings

Reagents and conditions: (i) $CuSO_4$, H_2O; (ii) $Tl(O_2CCF_3)_2$, $BF_3{\bullet}OEt_2$, TFA/CH_2Cl_2.

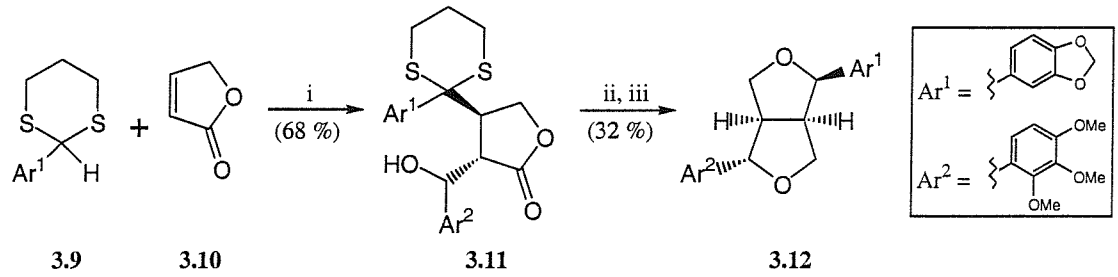
Possibly the overriding disadvantage with these strategies is their limitation to the synthesis of furofurans with symmetrically sustituted aromatic rings. Recent synthetic approaches have, therefore, been designed for the preparation of both symmetrically and the naturally more abundant unsymmetrically substituted furofuran lignans.

3.4.2 Synthetic Approaches Utilising Conjugate Addition to Butenolides

Mitra *et al.*[135] were first to utilise a tandem Michael addition-aldol condensation of a butenolide as the key step in furofuran synthesis (Scheme 3.3). Conjugate addition of a

sulfur-stabilised anion to unsubstituted butenolide **3.10** in the presence of an aromatic aldehyde gave *trans*-dithiane lactone **3.11**. Dethioacetylisation, exhaustive reduction and acid-catalysed cyclisation afforded furofuran lignan analogue **3.12** which they assigned as the *endo,exo* isomer on the basis of ^{13}C-NMR data.

Scheme 3.3

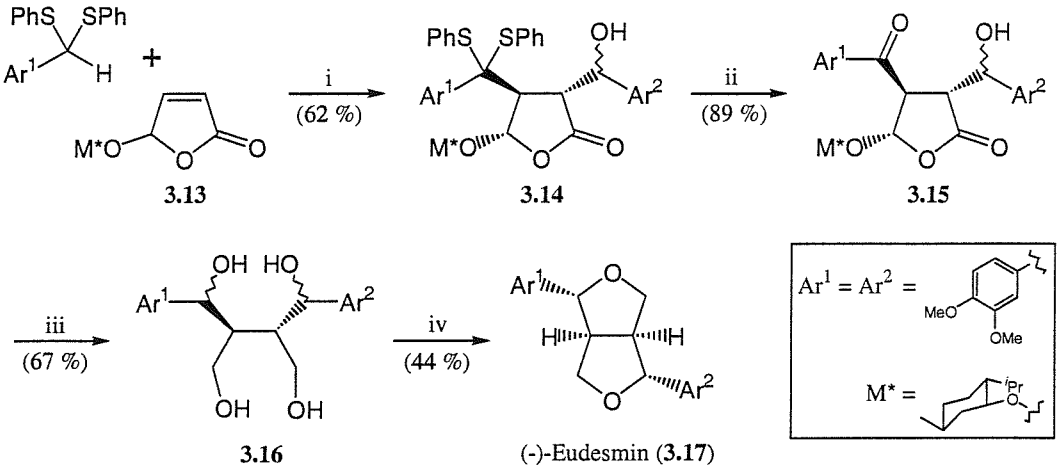


3.9 **3.10** **3.11** **3.12**

Reagents and conditions: (i) ^{n}BuLi, Ar^2CHO, THF; (ii) HgO, $BF_3{\bullet}OEt_2$; (iii) $NaBH_4$, MeOH; b) H_2SO_4 (aq).

Feringa *et al.*[136,137] extended this methodology with their expertise in conjugate addition to chiral butenolides and described the first asymmetric synthesis of (-)-eudesmin (**3.17**). Preparation of either diastereoisomer of butenolide **3.13** followed by Michael addition with a sulfur stabilised anion provided an intermediate ester enolate which was subsequently reacted *in situ* with an aromatic aldehyde to provide *trans* lactone **3.14** (Scheme 3.4). The epimers created at the hydroxyl substituted carbon was not a critical issue since both isomers were converted into (-)-eudesmin (**3.17**) in the final ring closure.

Scheme 3.4



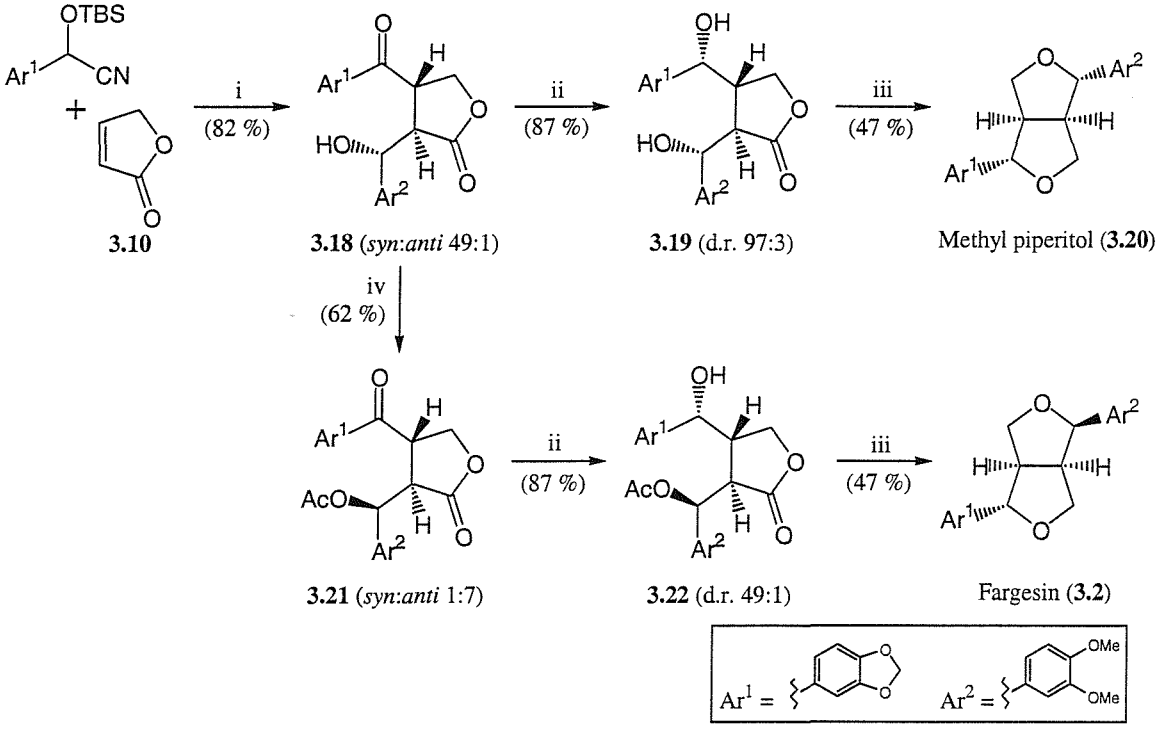
3.13 **3.14** **3.15** **3.16** (-)-Eudesmin (**3.17**)

Reagents and Conditions: (i) *n*BuLi, Ar^2CHO, THF; (ii) HgO, $BF_3{\bullet}OEt_2$, THF, H_2O; (iii) $LiAlH_4$, THF; (iv) $BF_3{\bullet}OEt_2$, THF.

These three component coupling reactions between butenolides, stabilised benzylic anions and aromatic aldehydes have subsequently been exploited by Ohmizu *et al.*[138,139]

to perform a stereocontrolled synthesis of both *exo,exo* and *endo,exo* furofuran lignans. Conjugate addition of a protected cyanohydrin-stabilised anion to butenolide **3.10**, followed by quenching of the lactone enolate with veratraldehyde afforded condensation product **3.18** (Scheme 3.5). Investigations into the effects of the enolate counter ion on reaction selectivity showed addition of zinc bromide resulted in the predominant formation of *syn*-isomer **3.18**. Selective reduction of the ketone functionality with L-Selectride resulted in diol **3.19**, arising from hydride delivery to the least hindered face. Reduction, followed by activation with mesyl chloride and spontaneous cyclisation gave methyl piperitol (**3.20**).

Scheme 3.5



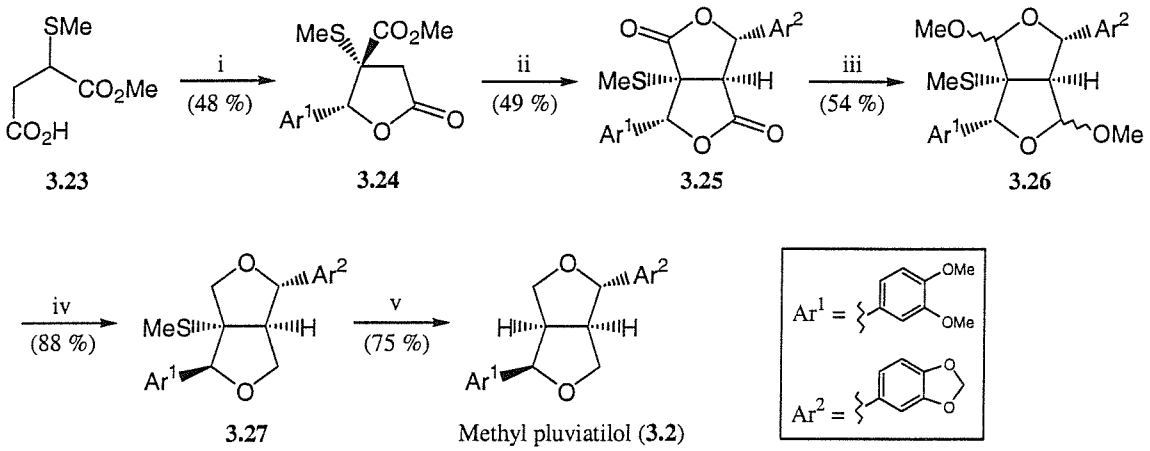
Reagents and Conditions: (i) a) LDA, Ar^2CHO, $ZnBr_2$, THF; b) separation of diastereoisomers; (ii) L-selectride, THF; (iii) a) $LiAlH_4$, THF; b) MsCl, py; (iv) TFA, AcOH, CH_2Cl_2 (1:10:1).

Attempts to selectively isolate the *anti*-aldol product failed but ultimately inversion of *syn*-alcohol **3.18** was effected by treatment with trifluoroacetic acid in acetic acid to provide acetate **3.21** with inversion of stereochemistry in reasonable selectivity (7:1). The *anti*-isomer was reduced in the manner described above and following cyclisation afforded *endo,exo*-furofuran, fargesin (**3.2**).

3.4.3 Synthetic Approaches Utilising Lactone Enolates

Pelter *et al.*[140] were first to describe a stereoselective synthesis towards *endo,exo*-isomers of the furofuran series. They utilised aldol chemistry to prepare lactones from 2-thiomethyl substituted succinnic half esters and appropriate aromatic aldehydes. Thus, condensation of **3.23** with veratraldehyde favoured diastereoisomer **3.24** in which the aryl and methylthio- functionality are *cis* to each other (2:1) (Scheme 3.6). This methylthio-group not only blocked deprotonation at C-4, but also ensured that subsequent aldol chemistry at C-3 introduced the electrophile with *trans*- relative strereochemistry. Spontaneous cyclisation provided *bis*-lactone **3.25** in moderate yield.

Scheme 3.6

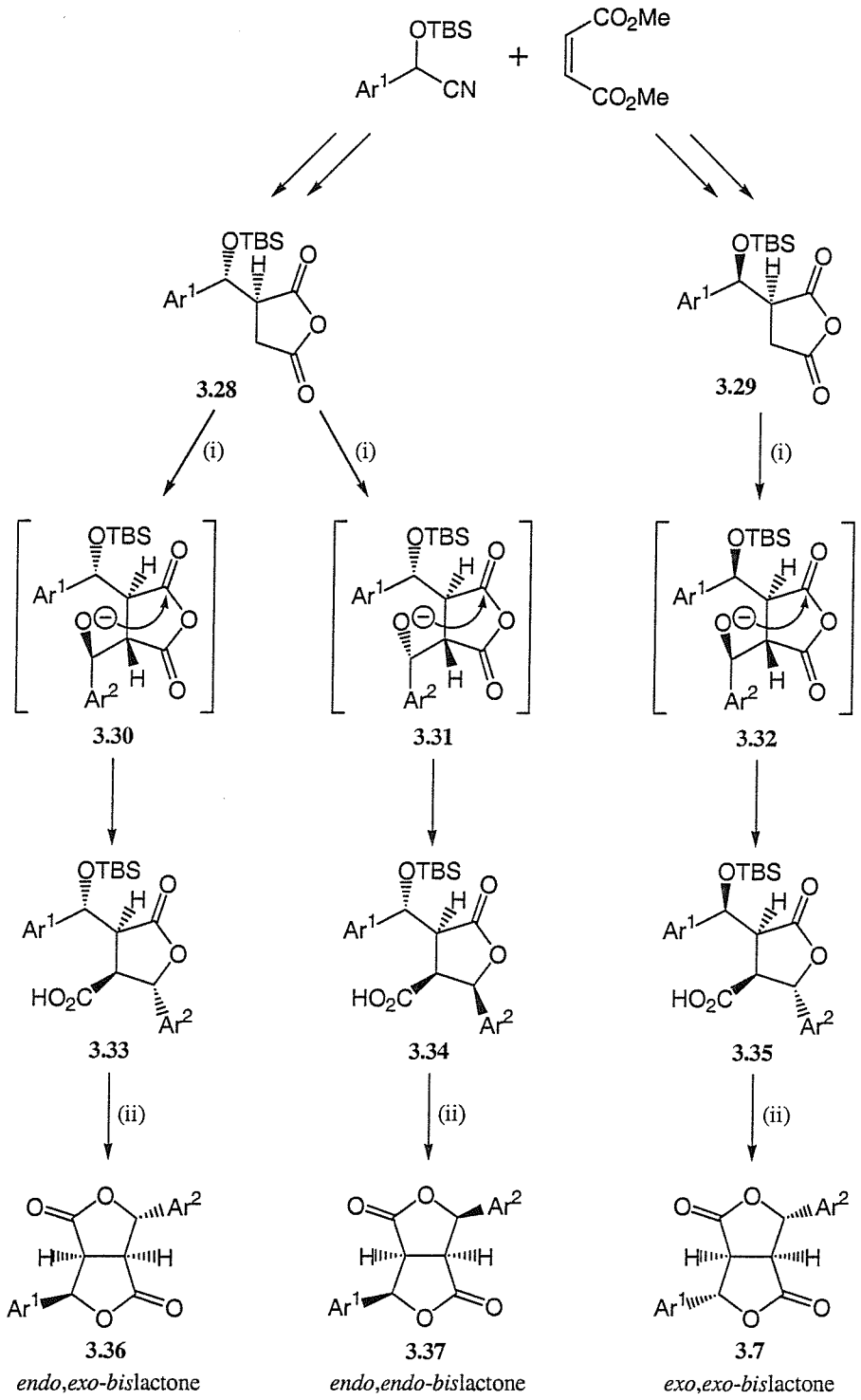


Reagents and Conditions: (i) a) LDA, Ar^1CHO, THF; b) separation of diastereoisomers; (ii) LDA, Ar^2CHO, THF; (iii) a) DIBAL, THF; b) MeOH, HCl; (iv) Et_3SiH, $BF_3 \bullet Et_2O$; (v) Raney nickel, EtOH.

Bis-lactone **3.25** was converted into its *bis*-dimethylacetal derivative **3.26** using Pelter's previously reported methodology.[141] Subsequent reduction of these hemiacetals was achieved *prior* to desulfurisation thereby avoiding isolation of mixtures. It was reasoned that the thiomethyl group directs the adjacent aryl group *trans* to itself during benzylic equilibration in the trifluoroborane-mediated reduction, consequently providing methyl pluviatilol (**3.2**) as a single diastereoisomer.

Ohmizu and co-workers have carried out extensive studies into the synthesis of *bis*-lactone furofuran analogues[142-144] and the scope of their investigations into conjugate additions of cyanohydrin anions has been excellently reviewed.[139] This more recent approach greatly resembles the butenolide route (*vide infra*) but instead involves the use of dimethyl maleate as a Michael acceptor. Although specific examples will not be discussed, a summary of their general strategy is illustrated below (Scheme 3.7).

Scheme 3.7

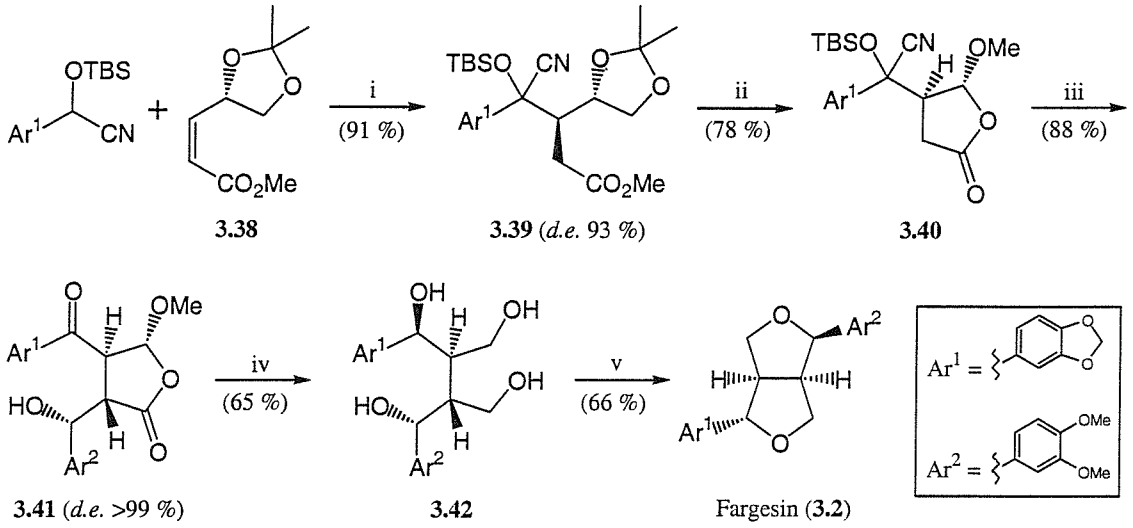


Reagents and Conditions: (i) Base, Ar^2CHO; (ii) a) nBu$_4$NF b) AcOH.

Ohmizu *et al.* have stereoselectively synthesised acid anhydrides **3.28** and **3.29** in good overall yields from the corresponding cyanohydrins. Aldol reaction of these derivatives with the desired aromatic aldehyde provided lactones **3.33-3.35** following cyclisation of the key hydroxy intermediates **3.30-3.32.** The degree of stereoselectivity was critically dependent on the enolate countercation and solvent used in the reaction but they generally

observed high selectivities (~ 95:5). The minor diastereoisomers were then removed by careful chromatography before deprotection and cyclisation gave the corresponding *bis*-lactones. Depending on the starting acid anhydride and conditions of the aldol condensation, this protocol has been successful in the preparation of *exo,exo-* *endo,exo-* and even *endo,endo-* *bis*-lactones. Furthermore, these are easily converted into the more naturally abundant furofurans through exhaustive reduction, primary alcohol mesylation and cyclisation (*vide supra*).

Scheme 3.8



Reagents and conditions: (i) LDA, HMPA, THF, -100 °C; (ii) $NaIO_4$, H_2SO_4, MeOH; (iii) a) LiHMDS, Ar^2CHO, THF; b) $n$$Bu_4NF$, AcOH; (iv) a) $NaBH_4$, MeOH; b) $LiAlH_4$, THF; (v) MsCl, py, CH_2Cl_2.

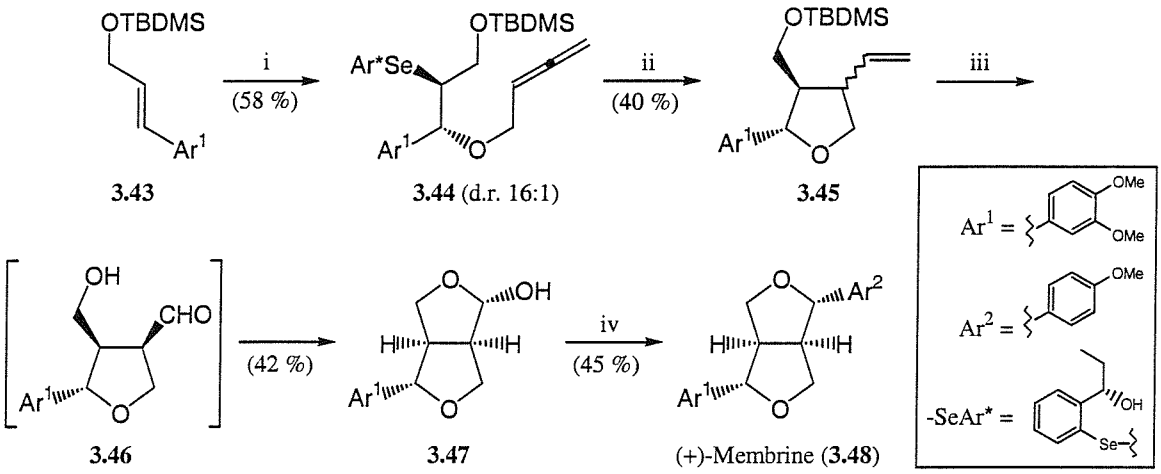
Ohmizu *et al.*[145,146] have also achieved an asymmetric synthesis of an *endo,exo*-furofuran utilising a novel diastereoselective 1,4 addition on enantiomerically pure α,β-unsaturated ester **3.38**. Exhaustive reduction of keto-lactone **3.41** and cyclisation of the resulting tetraol **3.42** provided (+)-fargesin (**3.2**) (Scheme 3.8).

3.4.4 Synthetic Approaches Utilising Radical Cyclisation

Wirth has described an asymmetric approach towards the construction of the lower tetrahydrofuran fragment in the furofurans using organoselenium mediated radical chemistry.[147] Thus, electrophilic addition of a chiral selenium triflate to protected cinnamyl alcohol derivative **3.43** provided a stabilised benzylic cation that upon quenching with an allenyl alcohol afforded **3.44** as a mixture of diastereoisomers (16:1) (Scheme 3.9). Radical cyclisation of the major isomer with triphenyltin hydride and AIBN gave tetrahydrofuran **3.45**, a common intermediate utilised in the methods of

several research groups. Oxidation of the vinylic double bond followed by periodate cleavage afforded aldehyde **3.46**. Under these reaction conditions loss of the TBDMS group and epimerisation at C-3 was also observed before hemiacetal formation provided **3.47**. This represented the dimethoxy analogue of (+)-samin (**3.78**), an unusual furofuran Wirth had previously synthesised using this method.[148] Transformation into (+)-membrine (**3.48**) was completed upon treatment with 4-methoxyphenylmagnesium bromide in refluxing THF.

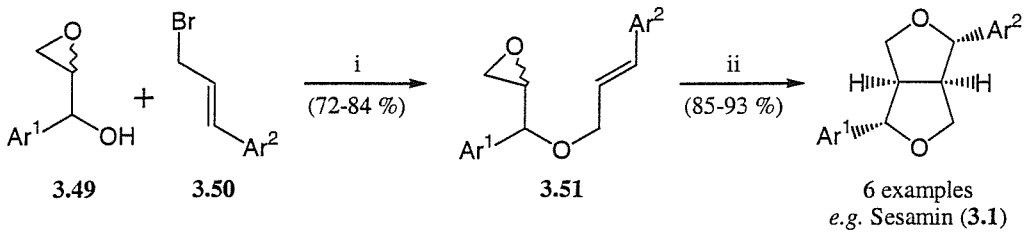
Scheme 3.9



Reagents and conditions: (i) Ar*SeOTf, 2,3-butadiene-1-ol, Et_2O; (ii) Ph_3SnH, AIBN, $PhCH_3$; (iii) a) cat. OsO_4, NMO, acetone, *t*BuOH, H_2O; b) H_5IO_6, THF; (iv) Ar^2MgBr, THF.

More recently, Roy *et al.*[149] have described a concise route to the *exo,exo*-furofuran class using a titanium (III) mediated radical cyclisation of epoxides. Epoxides **3.49** were prepared from the corresponding vinyl alcohols and *O*-alkylated upon treatment with the appropriate cinnamyl bromide **3.50** affording **3.51** as a mixture of diastereoisomers (1:1) (Scheme 3.10).

Scheme 3.10



Reagents and conditions: (i) NaH, THF, DMSO; (ii) a) Cp_2TiCl, THF; b) I_2, THF.

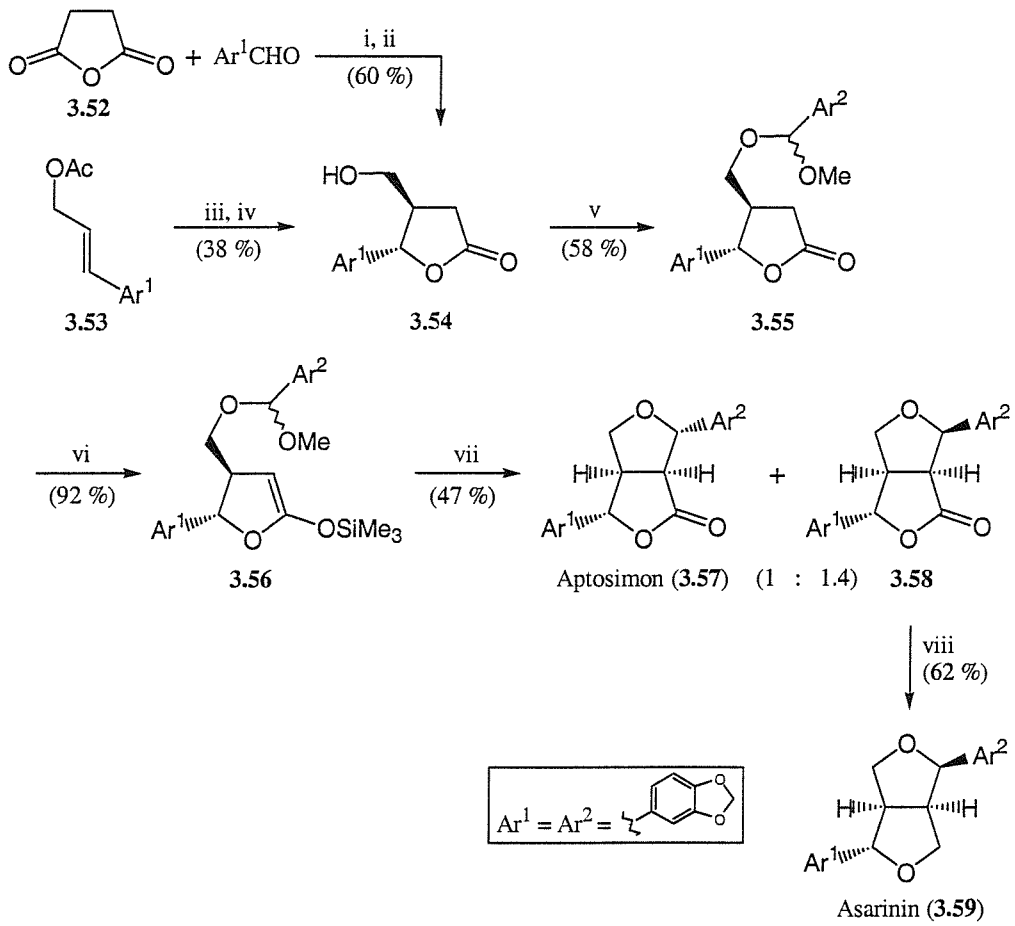
The racemic natural products were prepared directly from these epoxyolefinic ethers **3.51** following radical cyclisation and iodine-induced closure of the top ring. In the synthesis

of phenol containing lignans, benzyl protecting groups were used during the cyclisation and cleaved by controlled hydrogenolysis in the final step. A selection of both symmetrical and unsymmetrical furofuran lignans were formed in this manner, with the major *exo,exo*-isomer isolated in very respectable yields.

3.4.5 Synthetic Approaches Utilising Cationic Cyclisation

Whiting *et al.*[150] were first to employ an approach leading to the direct synthesis of furofuranone analogues.

Scheme 3.11



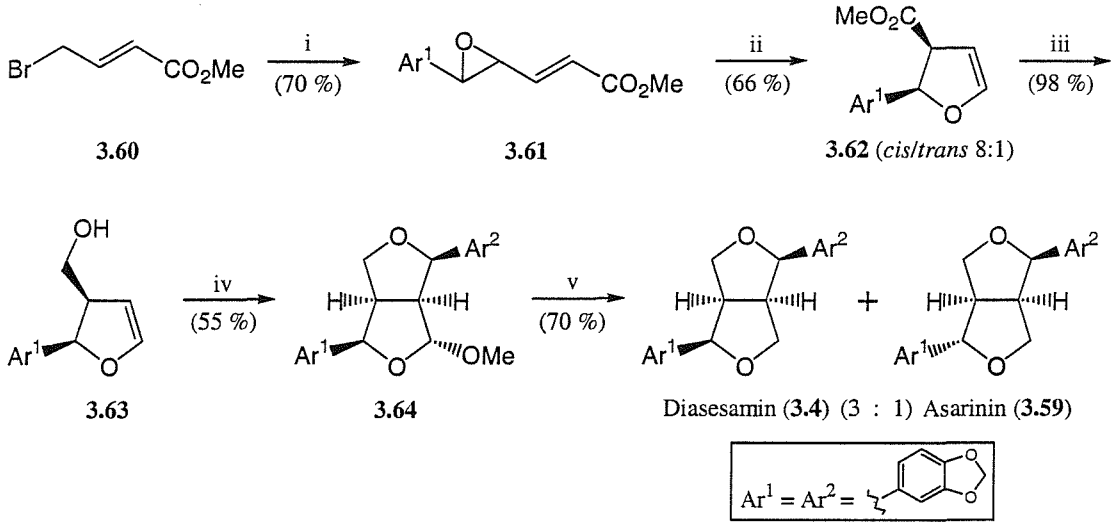
Reagents and Conditions: (i) $ZnCl_2$, NEt_3, CH_2Cl_2; (ii) $BH_3 \bullet Me_2S$; (iii) $Mn(OAc)_3$, KOAc, AcOH; (iv) HCl, THF; (v) $Ar^2CH(Cl)OMe$, NEt_3, CH_2Cl_2; (vi) LDA, TMSCl, THF; (vii) TMSOTf, NEt_3, THF; (viii) a) $LiAlH_4$, THF; b) HCl, MeOH.

The key 4,5-*trans*-disubstituted lactone intermediate **3.54** has two alternative routes of formation. Initial work involved the preparation of a lactone acid by reaction of an electron rich aromatic aldehyde with succinic anhydride **3.52** in the presence of a Lewis acid (Scheme 3.11).[151] Subsequent borane reduction provided *trans*-alcohol **3.54**. A later

strategy involved the manganese (III) oxidative radical addition of acetic acid to *trans*-cinnamyl acetate derivative **3.53** exclusively affording *trans*-lactone **3.54**.[152] Reaction with an aromatic α-haloether converted alcohol **3.54** into hemiacetal **3.55**, as a mixture of diastereoisomers (1:1). Formation of the silylketene acetal **3.56**, followed by treatment with a Lewis acid, brought about a Mukiayama condensation generating the furofuranones, aptosimon (**3.57**) and **3.58** (1 : 1.4 respectively) in moderate yield. Lactone **3.58** was subsequently converted to asarinin (**3.59**) through the reduction and cyclisation protocol previously discussed (*vide supra*).

More recently, Steel and co-workers[153] have described a similar approach to furofuran lignans where acetal formation and cationic cyclisation follow a cascade pathway in one pot. Vinyl epoxide **3.61** was prepared by Darzens condensation of bromocrotonate **3.60** before carrying out the critical alkenyl epoxide – dihydrofuran rearrangement using flash vacuum pyrolysis to afford dihydrofuryl ester **3.62** as a mixture of *cis/trans* isomers (8:1) (Scheme 3.12).

Scheme 3.12



Reagents and Conditions: (i) LDA, Ar^1CHO, THF; (ii) a) FVP, 500 °C, 0.04 mbar; b) separation of diastereoisomers; (iii) $LiAlH_4$, Et_2O; (iv) $Ar^2CH(OMe)_2$, TMSOTf, CH_2Cl_2; (v) Et_3SiH, $BF_3 \bullet Et_2O$, CH_2Cl_2.

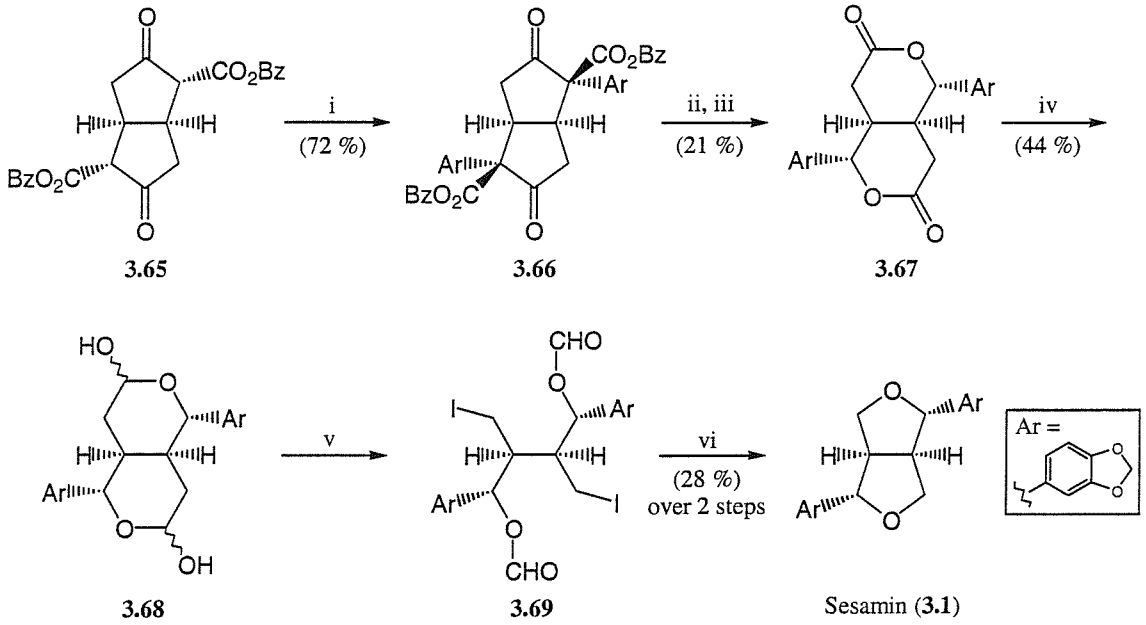
Reduction of the ester formed unstable alcohol **3.63** that was consequently combined, crude, with piperonal dimethyl acetal in the presence of a Lewis acid to provide methyl furofuryl acetal **3.64**. As with their preliminary model studies,[154] complete selectivity for the *endo,endo*-isomer **3.64** was observed provided the reaction was conducted at low temperature. Allowing the reaction to warm to room temperature resulted in a mixture of isomers in reduced yields. Following a detailed study of acetal reduction first described

by Pelter *et al.*,[141] it was determined that the stereochemistry of the diaryl product was critically dependent on the reaction temperature. Ultimately, the best set of conditions could only provide a mixture of *endo,endo*-furofuran, diasesamin (**3.4**) and *endo,exo*-furofuran, asarinin (**3.59**) in a 3:1 mixture, respectively.

3.4.6 Synthetic Approaches Utilising Rearrangements

An unusual strategy towards symmetrical *exo,exo*-furofurans involving the transformation of cyclopentanone rings into the tetrahydrofuran ring system of lignans has been described by Suginome *et al.*[155] Use of their aryl lead derivatives successfully incorporated the associated aromatic substituents onto **3.65** (Scheme 3.13). Hydrogenolysis of benzyl ester **3.66**, with spontaneous decarboxylation, followed by an extremely sluggish and low yielding Baeyer-Villiger rearrangement gave *bis*-δ-lactone **3.67**.

Scheme 3.13



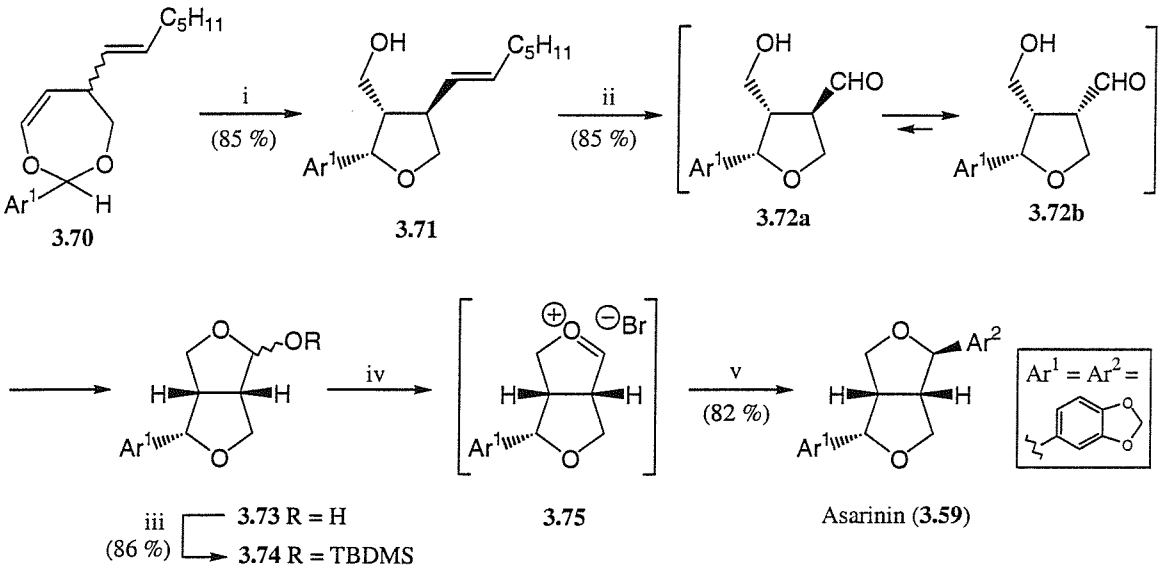
Reagents and conditions: (i) $ArPb(OAc)_3$, py., CH_2Cl_2; (ii) 10 % Pd/C, MeOH; (iii) *m*-CPBA, CH_2Cl_2; (iv) DIBAL, CH_2Cl_2; (v) a) HgO, I_2, PhH; b) hν; (vi) $NaBH_4$, MeOH.

Treatment of *bis*-lactol **3.68** with mercury (II) oxide and iodine prior to irradiation resulted in β-scission of the alkoxy radical and generation of *bis*-iodoformate **3.69**. Reductive cyclisation of crude **3.69** provided sesamin (**3.1**) in low overall yield.

Takano *et al.*[156] have described an interesting route towards furofuran lignans. The key trisubstituted tetrahydrofuran intermediate **3.71** was generated in a diastereoselective

manner *via* a Lewis acid catalysed rearrangement of 1,3-dioxepin derivative **3.70** generating an aldehyde intermediate that was subseqently reduced *in situ* (Scheme 3.14). It was found that the diastereoselectivity of the reaction was greatly dependent on the nature of the acid catalysts. Non-chelating conditions, followed by reduction, favoured formation of 2,3-*cis*-isomer **3.71** (d.r. 25:1) whereas chelating conditions (*e.g.* $(^{i}PrO)_2TiCl_2$) inverted the selectivity, preferentially providing a 2,3-*trans*-isomer (d.r. 30:1 - not shown). Oxidative cleavage of alkene **3.71** provided aldehyde **3.72a**, which, under basic conditions, equilibrated (**3.72a** - **3.72b**) and cyclised to provide *cis*-fused bicyclic lactol **3.73**. Treatment with trimethylsilyl bromide ultimately provided oxonium ion **3.75** which was selectively attacked by an aryl Grignard to provide racemic *endo,exo*-furofuran asarinin (**3.59**). Furthermore, the ability to vary the diastereoselective outcome of the oxepin rearrangement has also allowed them to target the *exo,exo*-furofuran derivatives as reported by their previous synthesis of (±)-samin (**3.78**).[157]

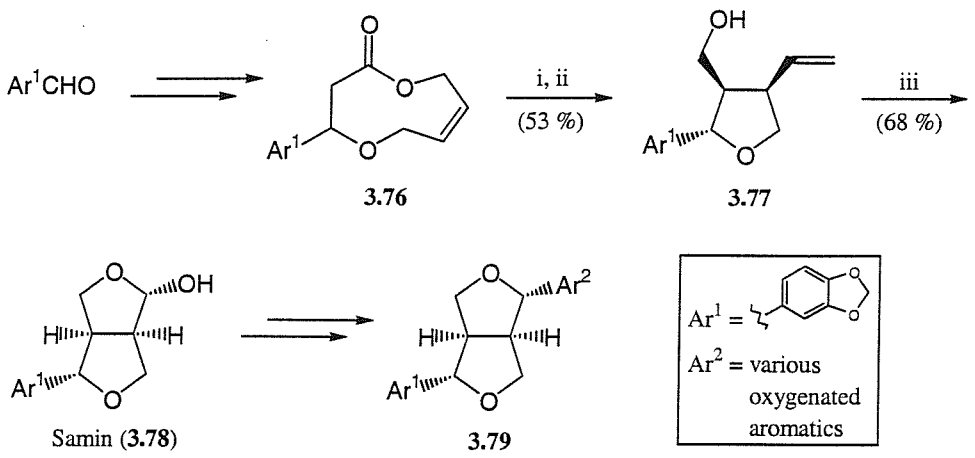
Scheme 3.14



Reagents and Conditions: (i) TBDMSOTf, CH_2Cl_2, $NaBH_4$; (ii) a) cat. OsO_4, Me_3NO, THF, H_2O; b) $NaIO_4$, $NaHCO_3$, THF, H_2O; c) NaOMe, MeOH; (iii) TBDMSCl, imidazole, DMF; (iv) TMSBr, CH_2Cl_2; (v) Ar^2MgBr, THF.

Recently the same group has elaborated this methodology towards an asymmetric approach by incorporating chiral centres in the alkene side chain of the starting dioxepin derivatives *via* a Heck reaction. Further transformations using the protocol described in Scheme 3.14 provided either (+)-sesamin or (-)-asarinin (depending on the oxepin rearrangement conditions) in reduced yields (*c.f.* racemic series) with e.e's of < 60 %.[158]

Scheme 3.15



Reagents and Conditions: (i) LDA, TMSCl, THF; (ii) $LiAlH_4$, Et_2O; (iii) a) cat. OsO_4, NMO, acetone, ^tBuOH, H_2O; b) $NaIO_4$, CH_2Cl_2, H_2O.

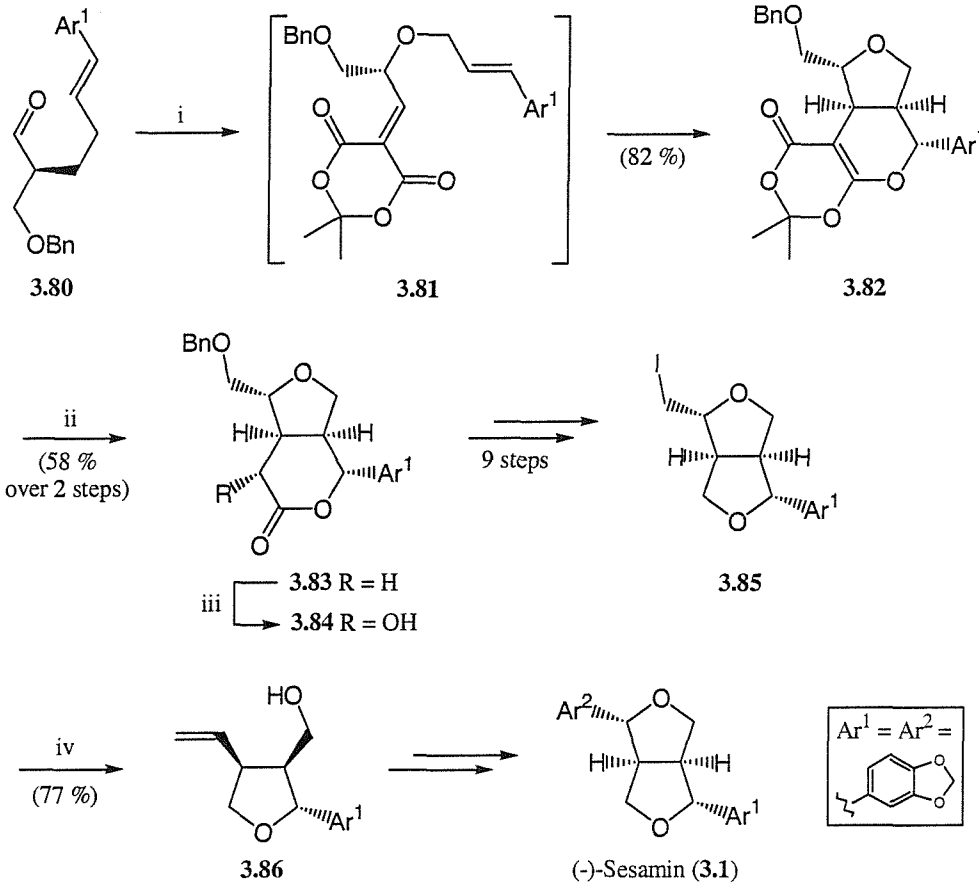
Knight *et al.*[159-161] have described a diastereoselective approach to furofuran lignans utilising an Ireland-Claisen rearrangement of oxamacrolides. Formation of a silyl enol ether of unsaturated macrocyclic lactone **3.76** induced rearrangement and following an *in situ* reduction provided 3,4-*cis*-substituted tetrahydrofuran **3.77** (Scheme 3.15). Studies into this transformation have shown that presence of a *Z*-alkene and generation of a *cis*-silyl enolate within the molecule imposes a boat-like transition state accounting for the observed 3,4-*cis*-stereochemistry. Subsequent oxidative cleavage of the vinyl group, using a related procedure to that employed by both Wirth and Takano, afforded (±)-samin (**3.78**), a precursor to both symmetrical and unsymmetrical *exo*,*exo*-furofuran lignans.

3.4.7 Synthetic Approaches Utilising a Diels-Alder Reaction

Takano *et al.*[162] were first to report an asymmetric synthesis of furofuran lignans in 1988 where an intramolecular hetero-Diels-Alder reaction proved the key process in a rather convoluted procedure totalling 24 steps.

Chiral ether **3.80** (7 steps from diethyl-L-tartrate) was condensed with Meldrum's acid and a resulting hetero-Diels-Alder reaction provided cyclo-adduct **3.82** (Scheme 3.16). Conversion to substituted δ-lactone **3.83** followed by incorporation of the α-hydroxy functionality, *via* a lactone enolate, afforded **3.84**. This intermediate was further subjected to a sequence of functional group interconversions eventually providing bicyclic ether **3.85**. A reductive ring opening yielded alkene **3.86** that was ultimately converted to (-)-sesamin (**3.1**) in the 4 steps subsequently used by Knight[159] (*vide supra*).

Scheme 3.16



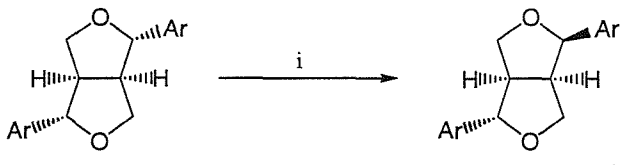
Reagents and conditions: (i) Meldrum's acid, DMAP, CH_2Cl_2; (ii) $MgCl_2$, DMA; (iii) LiHMDS, MoOPH; (iv) Zn, MeOH.

For such modest goals a significant number of synthetic operations were required but it was partially compensated for with the preparation of four separate chiral furofuran natural products originating from common intermediate **3.86**.

3.4.8 Synthetic Approaches Utilising Isomerisation

Das *et al.*[163] have recently examined the isomerisation of *exo,exo*-furofurans into their *endo,exo*-isomers (Scheme 3.17).

Scheme 3.17



exo,exo-isomer **3.5**

endo,exo-isomer **3.87**
4 examples (43-47 %)
e.g. asarinin (**3.59**)

Reagents and conditions: (i) Montmorillonite KSF, microwave, 466 W, 2 min.

The epimerisations of four symmetrical *exo,exo*-furofuran lignans **3.5** were induced with microwave irradiation in the presence of a clay catalyst. These mild conditions selectively epimerised the C-2 position to form the corresponding *endo,exo*-furofurans **3.87** in moderate yields. Although irradiation did not cause epimerisation at the C-6 position, unreacted *exo,exo*-furofurans were also isolated from the reaction mixture (typically 50 % recovery).

3.5 Conclusions

Given the varied biological activities and interesting structural features displayed by the furofuran lignans, their synthesis has attracted substantial interest. Although much effort has been devoted to establishing an efficient synthetic approach towards these natural products, there is clearly scope to progress further in this area. Many of the current routes suffer from being too long and complex and do not allow stereocontrolled entry to the furofurans. An acceptable synthetic strategy would permit the introduction of different diaryl substituents, allow control over the relative stereochemistry at the four contiguous centres and have potential for asymmetric induction. It is evident that the synthesis of the bicyclo[3.3.0]octane skeleton still remains a challenge to organic chemists. General methods capable of steric control coupled with good synthetic efficiency are, therefore, still viewed as particularly attractive.

Chapter 4

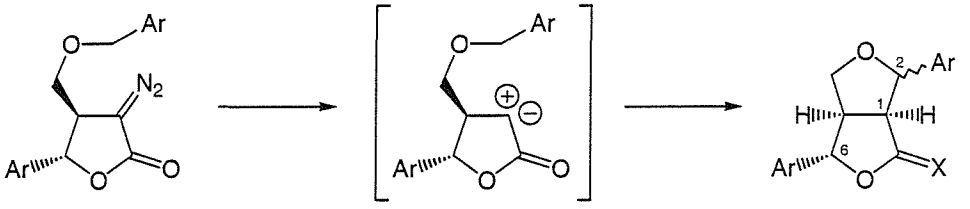
Southampton Approach to the Furofuran Lignans

The preceding chapter reviewed several synthetic approaches towards the furofuran lignans. It is therefore appropriate to describe our strategy for the preparation of these interesting natural products in the following chapter. A summary of previous work undertaken within the group towards furofurans will be discussed, in addition to future intentions stemming from these initial studies, the latter forming the major part of research carried out in this thesis.

4.1 Initial Aims of the Project

The original objective was the development of a new strategy towards the synthesis of furofuranones **4.3** and furofuran lignans **4.4** utilising an intramolecular C-H insertion reaction to close the C1-C2 σ-bond (Figure 4.1). It was hoped that this approach would introduce different aryl groups at the C-2 and C-6 positions and control the relative stereochemistry such that either C-2 epimer could be selectively generated.

Figure 4.1 Intramolecular C-H insertion approach to the furofuranones



4.1 **4.2** **4.3** X = O; **4.4** X = H_2

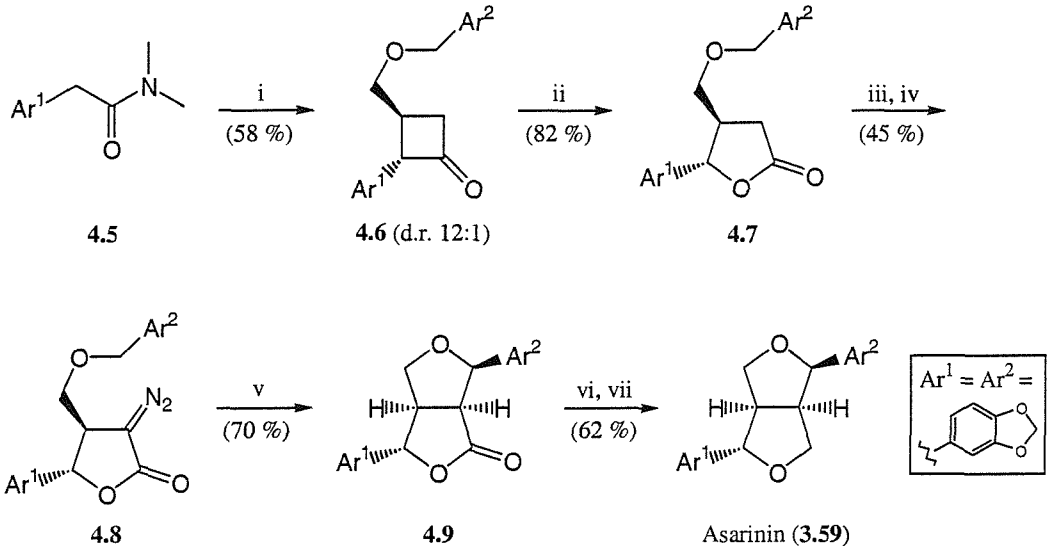
From the outset, there were many uncertainties with this proposed route including, potential decomposition pathways of a formal carbene intermediate **4.2**, stereoselectivity of the key C-H insertion and synthesis of the crucial α-diazo-γ-butyrolactones **4.1**.

4.2 Previous Work Towards *Endo,Exo*-Furofurans

Southampton researchers, Brown and Hinks,[164] described a short synthesis of the 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane framework *via* the described C-H insertion strategy (Scheme 4.1). A [2+2] keteniminium-olefin cycloaddition followed by regiospecific Baeyer-Villiger oxidation of the resulting cyclobutanone **4.6** successfully formed the desired *trans*-disubstituted lactone **4.7**. The most challenging aspect of this work proved to be the synthesis of α-diazo-γ-butyrolactone **4.8**, which required the development of a

modified direct diazo-transfer protocol. Although moderate yielding, this unoptimised procedure represented a significant improvement to other methods examined for effecting diazo-transfer to γ-butyrolactones.[73]

Scheme 4.1



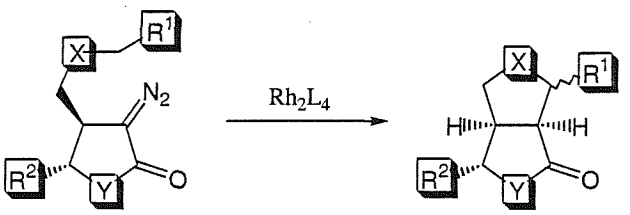
Reagents and Conditions: (i) a) Tf_2O, CH_2Cl_2; b) CH_2=$CHCH_2OCH_2Ar^2$, 2,6-di-*t*-butylpyridine, K_2CO_3, CH_2Cl_2; c) $NaHCO_3$ (aq); (ii) H_2O_2, AcOH; (iii) a) LiHMDS, THF; b) *p*-$NO_2C_6H_4SO_2N_3$, THF; c) AcCl; (iv) DMAP, THF; (v) 2 mol % $Rh_2(OAc)_4$, CH_2Cl_2; (vi) $LiAlH_4$, THF; (vii) MsCl, pyridine.

The key rhodium-catalysed C-H insertion of **4.8** proceeded with very high regio- and diastereo-selectivity providing, exclusively, *endo,exo*-furofuranone **4.9**. Furthermore, conversion to furofuran natural product, (±)-asarinin (**3.59**), demonstrated the utility of this approach in the synthesis of the naturally less common *endo,exo*-furofurans. This success opened up many new areas of exciting research centring on the remarkable efficiency of the carbenoid C-H insertion reaction.

4.3 Proposed Work

Although the rhodium-catalysed insertion reactions of diazo-lactones were highly regio- and diastereoselective, the factors responsible for the sense and magnitude of this outcome were unclear. The majority of research objectives, therefore, involved systematically varying substituents and spacer groups R^1, R^2, X and Y, in an attempt to examine and understand the regio- and diastereo-selectivity of the C-H insertion reaction (Figure 4.2). We also hoped to determine the scope and limitations of the carbenoid insertion approach for the construction of a range of bicyclo[3.3.0]octane ring systems **4.11**.

Figure 4.2 Effects of substituent and spacer groups on the C-H insertion reaction



4.10 4.11

R^1 = *e.g.* H, Me, *t*-Bu, Ph, 4-NO_2-C_6H_4, 4-MeO-C_6H_4
R^2 = *e.g.* H, alkyl, aryl
X = O, S, NR, CH_2
Y = O, NR

It is recognised that electron-donating groups activate neighbouring C-H bonds towards insertion.[34,42,43] Therefore, we intended to investigate a range of R^1 substituents, with varying steric and electronic properties, to explore the efficiency and diastereoselectivity of C-H insertion reactions. We were also curious whether variations made to the remote substituent R^2 would alter this stereoselection process.

We envisaged this type of annelation reaction would be of increased value if the scope of the C-H insertion could be broadened to allow for the synthesis of other classes of bicyclic compounds. In particular, replacement of linker heteroatoms X and Y could provide a convenient entry towards some novel bicyclic scaffolds. In addition, direct substitution of heteroatom X with a methylene group would disclose whether α-heteroatom activation of the adjacent C-H was required for efficient cyclisation.

Ultimately, we anticipated the existing methodology, or indeed a fresh approach, would be amenable to the enantioselective synthesis of furofuran lignans and their structural analogues.

4.4 Conclusions

Initial studies into cyclisations of α-diazo-γ-butyrolactones, *via* carbenoid C-H insertion, suggested it was an extremely effective approach towards the furofuran framework. This area of investigation also paved the way for future research, providing great potential for the synthesis of other carbocyclic and heterocyclic ring systems.

The following chapters will describe, in detail, the research undertaken in an attempt to accomplish some of the goals outlined in the section above.

Chapter 5

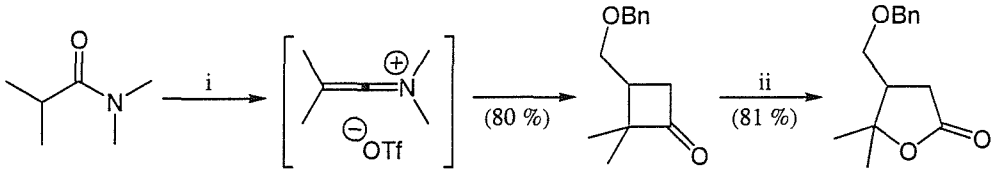
De-acylative Diazo-Transfer/Insertion Strategies Towards Furofuran(one) Lignans

The following chapter describes the attempted synthesis of a furofuranone analogue using the direct diazo-transfer methodology outlined in the preceding chapter. Subsequent investigations into a decarbonylative diazo-transfer strategy to some model lactone substrates will also be discussed. Finally, the effectiveness of this new approach will be demonstrated by the racemic synthesis of 2 furofuran lignan natural products.

5.1 Preparation of a Dimethylsubstituted Lactone and Attempted Diazo-Transfer

The [2+2] cycloaddition reaction between benzylallyl ether[165] and *N,N*-dimethyldimethyl-acetamide[166] (**5.1**) was carried out according to the method developed by Ghosez *et al.*[167] Initial treatment of disubstituted amide **5.1** with triflic anhydride and a non-nucleophilic base (2,6-di-*tert*-butylpyridine) generated the keteniminium triflate salt **5.2** *in situ*, *via O*-sulfonylation of the amide (Scheme 5.1). Addition of benzylallyl ether and subsequent hydrolysis of the resulting cyclic keteniminium salt provided the desired cyclobutanone **5.3** in good yield. The reaction could be conveniently monitored by IR spectroscopy given the characteristic absorption of both the cyclic keteniminium salt species (ν_{max} [C=N$^+$Me$_2$], 1728 cm^{-1}) and cyclobutanone **5.3** (ν_{max} [C=O], 1785 cm^{-1}).

Scheme 5.1



5.1 **5.2** **5.3** **5.4**

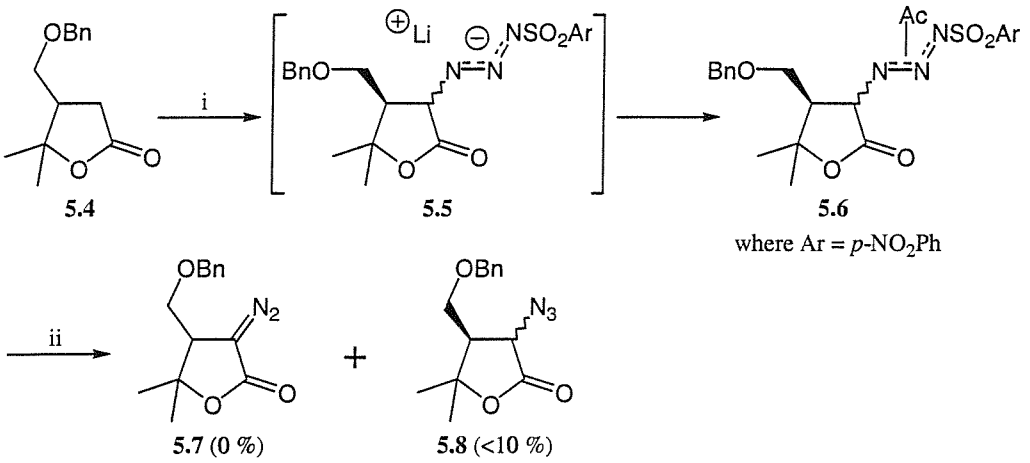
Reagents and conditions: (i) a) Tf_2O, CH_2Cl_2, -25 °C; b) 2,6-di-*t*-butylpyridine, allylbenzyl ether; c) $NaHCO_3$ (aq); (ii) H_2O_2, AcOH.

Regiospecific Baeyer-Villiger oxidation[168] of **5.3** to the corresponding trisubstituted lactone **5.4** was accomplished with either *m*-CPBA or peracetic acid generated *in situ*,[169] with the latter method returning consistently higher yields.

We then turned our attention to the crucial diazo-transfer reaction. Prior to research within the group, only one example of an α-diazo-γ-butyrolactone had been prepared in

low yield using a deformylative method.[73] However, previous work undertaken in our laboratories[164,170] and the existence of encouraging results from other groups[66,67] led us to initially pursue a direct diazo-transfer to the lactone enolate.

Scheme 5.2



Reagents and conditions: (i) a) LiHMDS, THF; b) 4-nitrobenzenesulfonyl azide; c) AcCl; (ii) DMAP, THF.

The formation of acylated triazene **5.6** proved ambiguous following reaction of lactone **5.4** with 4-nitrobenzenesulfonyl azide and attempted acylation at –78 °C. Decolouration of the red triazene anion **5.5** occurred prior to addition of acetyl chloride, suggesting decomposition of **5.5** before its stabilisation (Scheme 5.2). Indeed, analysis showed mainly starting lactone **5.4** and isolation of the triazene isomeric mixture **5.6** was not attempted due to its known instability on silica gel.[170] Instead the crude mixture was treated with DMAP and subsequent chromatography afforded only lactone **5.4** (10 % recovery) and azide **5.8** (predominately one diastereoisomer) as major products. None of the desired diazo lactone **5.7** was isolated.

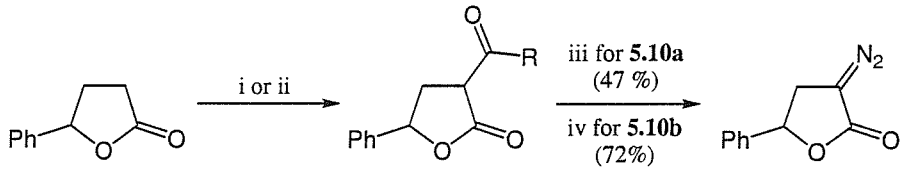
An identical reaction was run using NaHMDS as the base. Treatment of the sodium enolate of **5.4** with 4-nitrobenzenesulfonyl azide gave a deep purple triazene anion that, again, rapidly decolourised. Attempts to trap the anion with acetyl chloride failed and lactone **5.4** was the only material recovered in reasonable quantity.

5.2 Decarbonylative Diazo-Transfer Strategy on a Model Lactone

The inconsistency and poor efficiency of the direct diazo-transfer reactions described above imposed a considerable limitation on the overall approach to the desired diazo-lactones, not just in terms of yield but also purification from the azide and other decomposition by-products. To improve the diazo-transfer process, we decided to

conduct a survey of more recently introduced decarbonylative diazo-transfer methods[29] using 5-phenyl-γ-butyrolactone (**5.9**) as a model substrate (Scheme 5.3).

Scheme 5.3



5.9 **5.10a** R=Ph (53 %) **5.10b** R=CF_3 (84 %) **5.11**

Reagents and conditions: (i) NaH, $PhCO_2Me$, DME, MeOH cat.; (ii) NaH, $F_3CCH_2O_2CCF_3$, DME, MeOH cat.; (iii) 4-nitrobenzenesulfonyl azide, DBU, CH_2Cl_2; (iv) 4-nitrobenzenesulfonyl azide, Et_3N, CH_2Cl_2.

Acylation of **5.9** with either benzoyl[75] or trifluoroacetyl[74] groups was achieved using NaH as the base. Treatment of benzoyl derivative **5.10a** with 4-nitrobenzenesulfonyl azide, in the presence of DBU, afforded 3-diazo-5-phenyltetrahydro-2-furanone (**5.11**) in reasonable yield, although starting material **5.9** was recovered. Modifications made to the reaction conditions had little impact on driving the reaction towards completion. However, diazo-transfer with the more reactive trifluoroacetyl derivative **5.10b** was successful and complete conversion to diazo-lactone **5.11** was observed in good yield. On the basis of these unoptimised results we routinely settled on the use of triethylamine as base and methylene chloride as solvent.

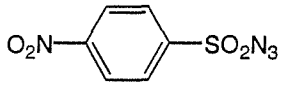
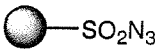
Recently, we have conducted a more thorough investigation into the de-trifluoro-acetylative diazo-transfer of model lactone **5.9** using analytical HPLC for reaction monitoring. Initial results showed that marginally faster reactions were obtained in acetonitrile compared to the previously employed methylene chloride and that alteration of both quantity and type of base had significant effects on the overall yield. In response to this, a set of diazo-transfer experiments was set up in acetonitrile with 1, 2, 5 and 10 equivalents of triethylamine (Table 5.1). Between one and two equivalents was seen as optimum whereas use of a large excess, up to 10 equivalents, appeared detrimental to the yield of **5.11**.

A set of experiments with a variety of bases was also undertaken and showed conversion of **5.10b** to diazo-lactone **5.11** with stronger bases (*e.g.* DBU) was achieved within a few hours, simple amine bases (*e.g.* Et_3N and Hünigs) within 24 hours and weak bases (*e.g.* imidazole) within a few days (entries 5-7, Table 5.1). Although DBU appeared

kinetically attractive, use of the 'weaker' bases, particularly the hindered Hünigs' base (di-*iso*-propylethylamine) provided cleaner reactions within a reasonable time scale. Control experiments indicated that the base, particularly DBU, caused substantial decomposition of 4-nitrobenzenesulfonyl azide effecting the overall purity of this step.

Table 5.1 Variation of base and sulfonyl azide on diazo-transfer methodology.

	Sulfonyl Azide	Equiv. Azide	Base	Equiv. Base	Rxn. Conditions	Isolated Yield of 5.11
1	A	1.2	Et_3N	1	MeCN, rt., 64 h.	89 %
2	A	1.2	Et_3N	2	MeCN, rt., 64 h.	92 %
3	A	1.2	Et_3N	5	MeCN, rt., 64 h.	80 %
4	A	1.2	Et_3N	10	MeCN, rt., 64 h.	53 %
5	A	1.2	Hünigs	1	MeCN, rt., 18 h.	94 %
6	A	1.2	DBU	1	MeCN, rt., 3 h.	75 %
7	A	1.2	Imidazole	1	MeCN, rt., 96 h.	78 %
8	B	4.0	Et_3N	4	CH_2Cl_2, rt., 136 h.	64 %

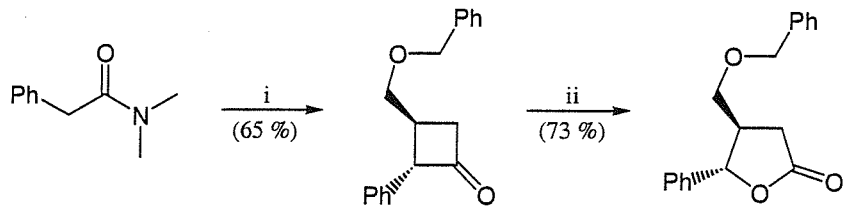
A =  B = 

We also examined the use of a supported diazo-transfer reagent to facilitate reaction workup and purification (entry 8, Table 5.1).[88-90] However, the sulfonyl azide resin, prepared following a reported method from 20 % cross-linked polystyrene, failed to effect diazo-transfer to the trifluoroacylated lactone **5.10b** or even ethyl acetoacetate.[88] Fortunately, sulfonyl azide resin prepared from commercial polystyrenesulfonyl chloride (Argonaut, 1 % cross-linked) was a successful diazo-transfer reagent affording **5.11** from **5.10b** in 64 % yield, although relatively large amounts of this expensive resin were required and the reaction was significantly slower than its homogeneous counterpart.

5.3 Synthesis of a *bis*-Phenyl Furofuranone Model

In an attempt to directly mimic the furofuran natural products with simple phenyl functionality, 3-benzyloxymethyl-2-phenylcyclobutanone (**5.13**) was prepared according to Ghosez's [2+2] keteniminium-olefin cycloaddition[167] procedure (Scheme 5.4). This cyclic ketone was obtained as a 9:1 mixture of diastereoisomers with the two pendent groups in a *trans*- disposition. Mechanistic justification for this is provided in Figure 5.1.[171]

Scheme 5.4

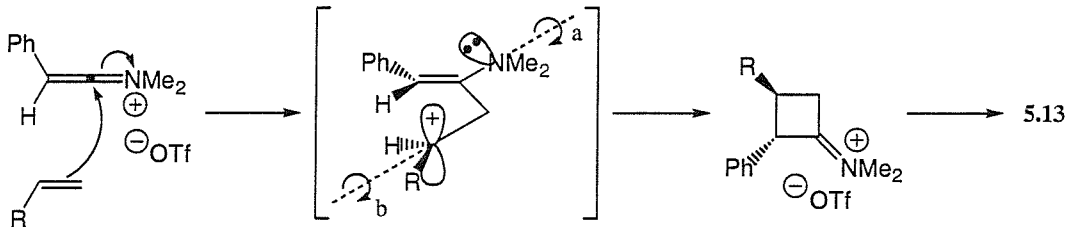


5.12 **5.13** (9:1) **5.14**

Reagents and conditions: (i) a) Tf_2O, CH_2Cl_2, -25 °C; b) 2,6-di-*t*-butylpyridine, allylbenzyl ether; c) $NaHCO_3$ (aq); (ii) H_2O_2, AcOH.

Initial nucleophilic attack by the olefin provides the stabilised carbonium ion **5.15**. To create the nucleophilic enamine system, and allow ring closure, rotation around the C-N bond (axis *a*) is necessary to ensure the nitrogen lone pair is planar with the conjugated π-system. Meanwhile, rotation around the C-C bond (axis *b*) favours placing the large groups remote from each other, forming a more stable cyclic transition state. Provided rotation around *b* is faster than *a* then the *trans*- isomer is expected to predominate in **5.16**. However, Ghosez has also proved that substantial α-keto isomerisation may occur during the hydrolysis of the keteniminium salt **5.16** to cyclobutanone **5.13**.

Figure 5.1 Mechanism for the keteniminium/olefin cycloaddition



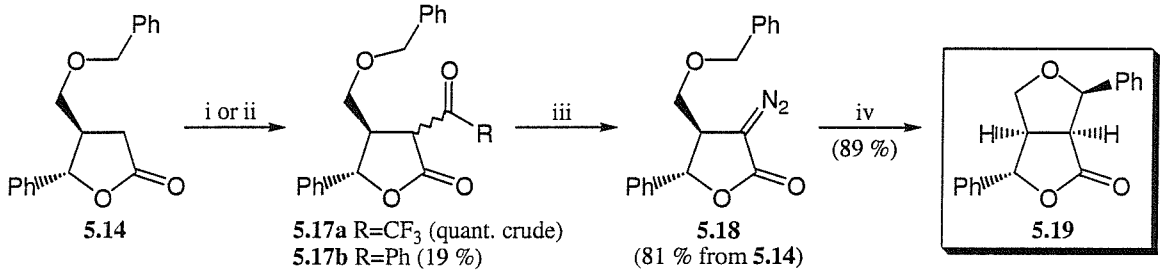
5.15 **5.16**
where R = CH_2OCH_2Ph

Separation of *trans*-cyclobutanone **5.13** was achieved by preparative normal-phase HPLC. However, it became apparent that the benzylic position underwent facile epimerisation so separation of the isomers was left until after the next step. Baeyer Villiger oxidation of **5.13** to the corresponding lactone **5.14** was accomplished using the peracetic acid methodology and any remaining minor diastereoisomer was removed by column chromatography.

Having established an efficient diazo-transfer protocol for model lactone **5.9**, we turned our attention to the 4-benzyloxymethyl substituted lactone **5.14** (Scheme 5.5). The acylated lactone **5.17a** was prepared with a quantitative crude mass recovery using NaH or LiHMDS as base. This trifluoroacyl lactone **5.17a** was unstable to column

chromatography and decomposed fairly rapidly on standing, requiring direct use in diazo-transfer reactions for optimum results. The more stable 3-benzoyl-5-phenylfuran-2-one **5.17b**, obtained in modest yield, did not react with the 4-nitrobenzenesulfonyl azide under the conditions developed for the model system and further investigations with this substrate were abandoned. However, the less stable trifluoroacyl derivative **5.17a** underwent the desired diazo-transfer efficiently, almost doubling the yield for the conversion of lactone **5.14** to **5.18** obtained using previous methods within the group.[164] Unfortunately, reaction of **5.17a** with the sulfonyl azide resin proved too slow to be practically useful for these more hindered substrates.

Scheme 5.5

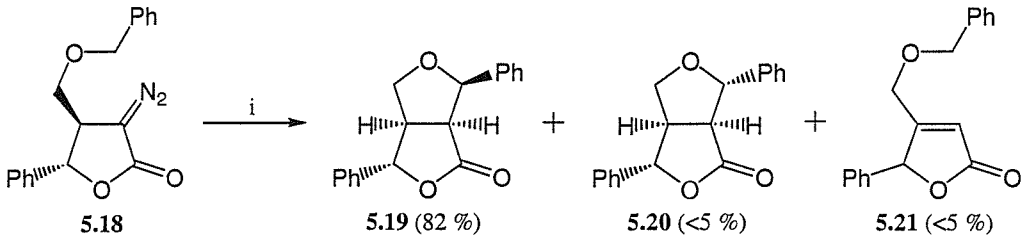


5.14 | **5.17a** R=CF_3 (quant. crude); **5.17b** R=Ph (19 %) | **5.18** (81 % from **5.14**) | **5.19**

Reagents and conditions: (i) LiHMDS (2 equiv), $F_3CCH_2O_2CCF_3$, THF; (ii) NaH, $PhCO_2Me$, DME, MeOH cat.; (iii) 4-nitrobenzenesulfonyl azide, Et_3N, CH_2Cl_2; (iv) $Rh_2(OAc)_4$, CH_2Cl_2.

The key C-H insertion reaction was then carried out using a catalytic quantity of rhodium (II) acetate dimer where the rapid and highly diastereoselective conversion of diazo-lactone **5.18** to furofuranone **5.19** was observed, with phenyl substituents bearing the *endo,exo* configuration.[164,172] The relative stereochemistry was supported by comparison of spectral data to that reported for analogous furofuranones[152] with final confirmation obtained from an X-ray structure of **5.19**.[173]

Scheme 5.6



5.18 | **5.19** (82 %) | **5.20** (<5 %) | **5.21** (<5 %)

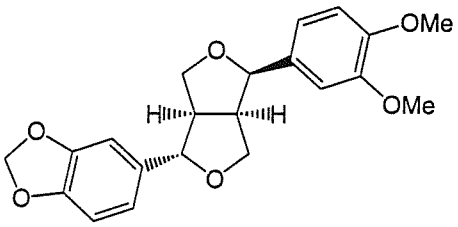
Reagents and conditions: (i) DCE, reflux.

The C-H insertion reaction was also achieved by refluxing diazo-lactone **5.18** in 1,2-dichloroethane for 24 hours, although thermal insertion did not proceed as cleanly as the

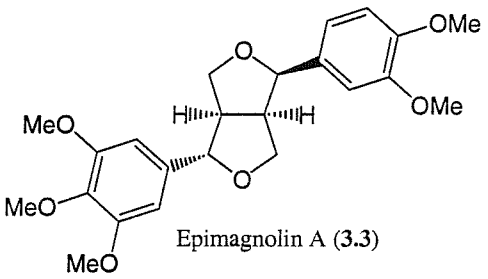
rhodium catalysed reaction (Scheme 5.6). Clean separation of minor components evident in the crude ^{1}H-NMR spectrum proved unsuccessful, however, we have tentatively assigned them as *exo,exo* furofuranone isomer **5.20** and butenolide **5.21** (the product arising from a competing 1,2-insertion).

5.4 Synthesis of (±)-Fargesin and (±)-Epimagnolin A

To demonstrate a more general utility of the decarbonylative diazo-transfer/insertion approach towards *endo,exo*-furofuran lignans, the synthesis of two unsymmetrically substituted natural products, (±)-fargesin (**3.2**) and (±)-epimagnolin A (**3.3**), was investigated (Scheme 5.7).



Fargesin (**3.2**)

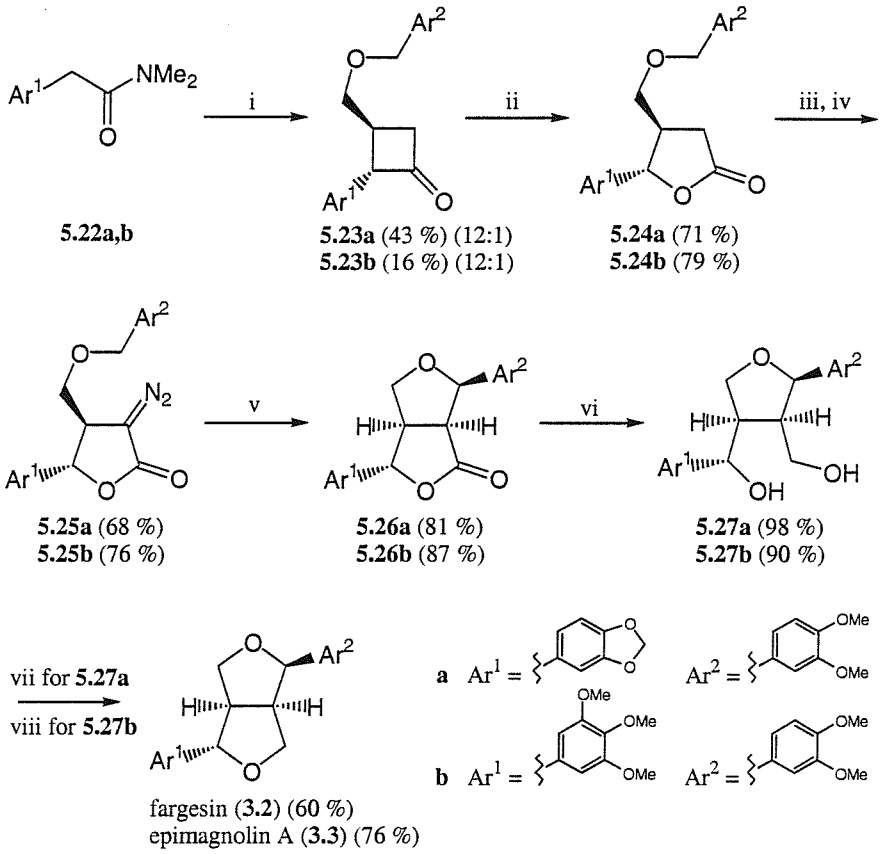


Epimagnolin A (**3.3**)

Even utilising a modification (developed within the Brown group) allowing the use of acid-sensitive substrates[164] (*e.g.* electron rich benzylic ethers), the initial [2+2] cycloaddition proved extremely problematic with highly oxgenated di- and tri-methoxy phenyl substituents. The buffering effect of anhydrous K_2CO_3 was essential in providing the desired cycloadducts **5.23a,b** albeit in moderate/poor yield. However, enough of cyclobutanones **5.23a,b** were produced to continue with the synthesis. Oxidation to lactones **5.24a,b** and diaxo-transfer proceeded in good yields to provide the C-H insertion precursors **5.25a,b**. Diazo-lactones **5.25a,b**, upon exposure to 2 mol % of the rhodium (II) catalyst, underwent efficient cyclisation with confirmation of stereochemistry for **5.26b** achieved by X-ray crystallography.[174]

Various methods for the final transformation of furofuranones to furofurans have been described.[144,152] Careful reduction of lactones **5.26a,b** with $LiAlH_4$ afforded the ring-opended diols **5.27a,b** in excellent yields. Reclosure of the lower tetrahydrofuran ring was achieved by treatment with excess methanesulfonyl chloride although starting diols **5.27a,b** were recovered in both cases. The syntheses of fargesin (**3.2**) and epimagnolin A (**3.3**) were thus completed in 10 % and 6 % overall yields, respectively.[172]

Scheme 5.7



Reagents and conditions: (i) a) Tf_2O, CH_2Cl_2, -25 °C; b) 2,6-di-*t*-butylpyridine, $CH_2{=}CHCH_2OCH_2Ar^2$ (**5.28**); K_2CO_3; c) $NaHCO_3$ (aq); (ii) H_2O_2, AcOH; (iii) LiHMDS (2 equiv), $CF_3CH_2OCOCF_3$, THF; (iv) 4-nitrobenzenesulfonyl azide, Et_3N, CH_2Cl_2; (v) $Rh_2(OAc)_4$, CH_2Cl_2; (vi) $LiAlH_4$, THF; (vii) MsCl, pyr, CH_2Cl_2; (viii) MsCl, Et_3N, DMAP, CH_2Cl_2.

5.5 Conclusions

Studies of diazo-transfer reactions conducted on a variety of γ-butyrolactones conclude that sacrificial activation with an α-trifluoroacyl group represents the most effective approach towards diazo-lactone synthesis. Together with the highly diastereoselective C-H insertion reaction, this powerful methodology was used to synthesise a simple *endo,exo-bis*-phenyl furofuranone **5.19** in an impressive 34 % yield over 5 steps. Finally, the success of these investigations culminated in the racemic synthesis of two unsymmetrically substituted furofuran lignans, (±)-fargesin and (±)-epimagnolin A.

Chapter 6

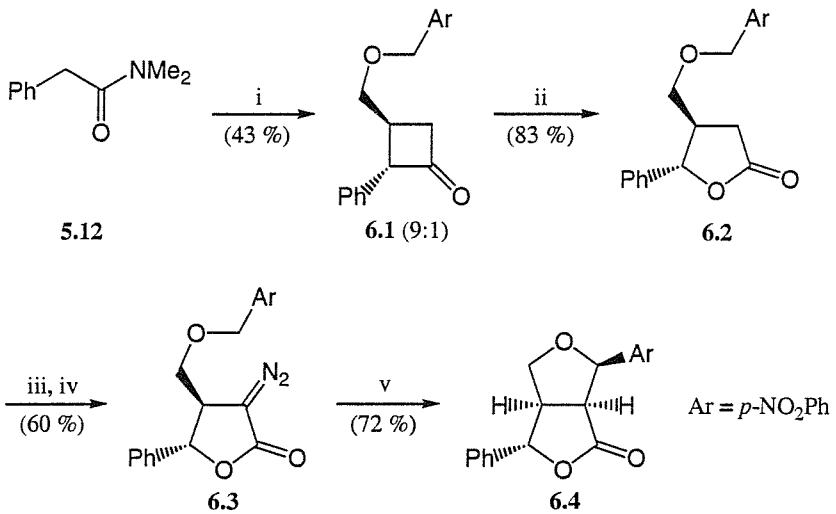
Furofuranone Analogues *via* Cyclobutanone Chemistry

The following chapter describes the synthesis of a variety of furofuranone structural analogues. These derivatives utilise the synthetic strategy outlined in the preceding chapter and, consequently, originate from a [2+2] cycloaddition.

6.1 Preparation of a *p*-Nitrophenyl Furofuranone Derivative

The [2+2] keteniminium-olefin cycloaddition between *N,N*-dimethylphenylacetamide[175] (**5.12**) and 4-nitrobenzylallyl ether[176] (**6.5**) was carried out using the method developed by Ghosez *et al.*[167] described in the preceding chapter (Scheme 6.1). Oxidation of cyclobutanone **6.1** and separation of the minor diastereoisomer afforded *trans*-lactone **6.2**. Diazo-transfer on **6.2** using the de-trifluoroacetylative approach gave diazo-lactone **6.3**, which upon treatment with dirhodium tetraacetate underwent cyclisation to yield **6.4** as a single diastereoisomer. The relative stereochemistry around the newly formed C-C bond was shown to be *cis* by interpretation of GOESY experiments, providing a further example of an *endo,exo*-furofuranone.

Scheme 6.1



Reagents and conditions: (i) a) Tf_2O, CH_2Cl_2, -25 °C; b) 2,6-di-*t*-butylpyridine, CH_2=$CHCH_2OCH_2Ar$ (**6.5**); c) $NaHCO_3$ (aq); (ii) H_2O_2, AcOH; (iii) LiHMDS (2 equiv), $CF_3CH_2OCOCF_3$, THF; (iv) 4-nitrobenzenesulfonyl azide, Et_3N, CH_2Cl_2; (v) $Rh_2(OAc)_4$, CH_2Cl_2.

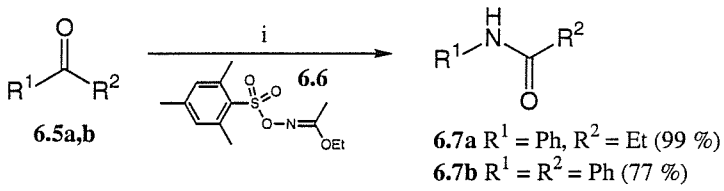
It is worth noting that insertion into the C-H bond α to electron neutral (unsubstituted phenyl), electron rich (*e.g.* 3,4-dimethoxy) and electron deficient (*e.g.* 4-nitro) phenyl rings has now been achieved. In all these examples a highly diastereoselective

conversion of diazo-lactones to the *endo,exo-* series of furofuranones was observed indicating that the electronic nature of the aromatic did not appear to alter the stereochemical outcome.

6.2 Preparation of a Lactam Furofuranone Derivative

Tamura's reagent, *O*-mesitylenesulfonylhydroxylamine (MSH)[177,178] has commonly been used to effect regio-selective ring expansions of unsymmetrical cyclobutanones.[179-181] MSH was successfully prepared by literature methods *via* sulfonylation of ethyl *N*-hydroxyacetimidate and subsequent removal of the protected amino group.[178] The resulting hydroxylamine was stored in the freezer following observations of a rapid and violent decomposition when left to stand for short periods at room temperature. We decided a much safer approach would be to generate MSH *in situ* averting the direct use of this highly reactive reagent.

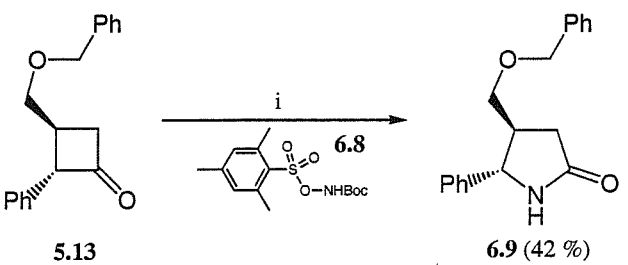
Scheme 6.2



Reagents and conditions: (i) $HClO_4$ (aq), CH_2Cl_2.

Treatment of some simple aryl ketones **6.5a,b** with MSH precursor ethyl *O*-(mesitylene-sulfonyl)-acetoxyhydroxamate (**6.6**) in acidic conditions successfully gave the desired amides **6.7a,b** in excellent yields (Scheme 6.2). Unfortunately, when applied to cyclobutanone **5.13** this protocol yielded none of the desired lactam. We speculated that use of strong aqueous acidic conditions were incompatible with our relatively sensitive cyclobutanone species. However, deprotection of the analogous *N*-Boc protected hydroxylamine[182,183] **6.8** followed by addition of cyclobutanone **5.13**, gave lactam **6.9** in moderate yield (Scheme 6.3).

Scheme 6.3

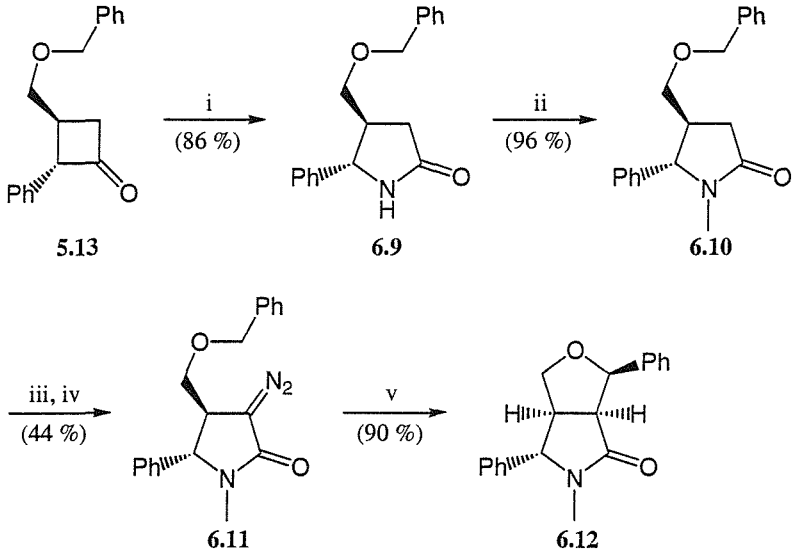


Reagents and conditions: (i) TFA, CH_2Cl_2.

This method also transformed aryl ketone **6.5a** to amide **6.7a** in good yield and demonstrated the potential for this modified one-pot procedure as a safer approach to Beckmann rearrangements on acid stable substrates.

Although we encountered some success with our one-pot strategy, the direct use of MSH consistently provided higher yields of desired lactam derivative **6.9**. Therefore, treatment of cyclobutanone **5.13** with excess MSH afforded lactam **6.9** that was subsequently *N*-methylated (Scheme 6.4). Activation of protected lactam **6.10** with the trifluoroacetyl-moiety prior to diazo-transfer provided diazo-lactam **6.11** in moderate yield. The increased polarity of these lactam derivatives (compared to the lactone series) hampered purification on silica gel with particularly difficult separations from 4-nitrobenzenesulfonyl azide related by-products encountered.

Scheme 6.4



Reagents and Conditions: (i) MSH, CH_2Cl_2; (ii) KO^{t}Bu, MeI, THF; (iii) LiHMDS (2 equiv), $F_3CCH_2OCOCF_3$, THF; (iv) 4-nitrobenzenesulfonyl azide, (i-Pr)$_2$EtN, MeCN; (v) $Rh_2(OAc)_4$, CH_2Cl_2.

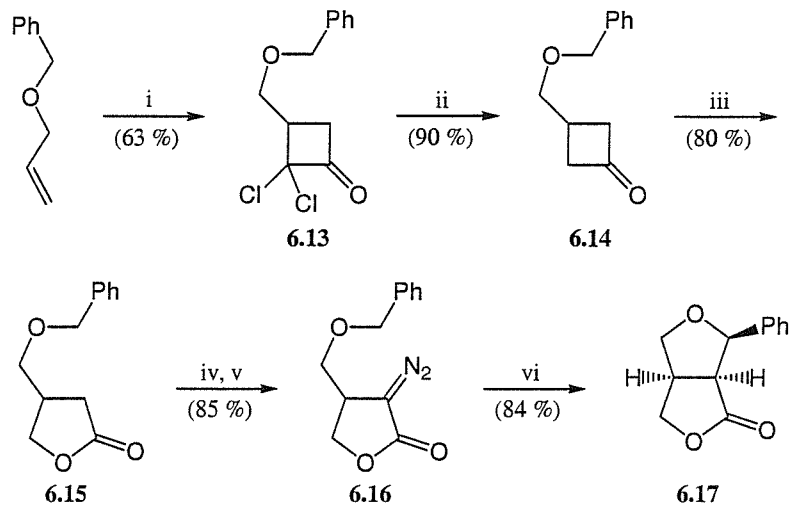
Gratifyingly, treatment of diazo-lactam **6.11** with dirhodium tetraacetate rapidly provided the cyclised product **6.12** as a single diastereoisomer in excellent yield. Interpretation of GOESY experiments and, more recently, an X-ray structure confirm the *endo,exo*-bicyclic ring system.

6.3 Furofuranone Formation of an 'Unsubstituted' Derivative

Addition of dichloroketene (generated from trichloroacetyl chloride and a zinc-copper couple[184]) to benzylallyl ether in a diethyl ether/1,2-dimethoxyethane solution[185] gave

dichlorocyclobutanone **6.13**[165] as a distillable liquid in 63 % isolated yield (Scheme 6.5). De-chlorination with zinc[185] proceeded smoothly to afford the corresponding cyclobutanone derivative **6.14**[165] and oxidation under the standard peracetic acid methodology provided lactone **6.15**.

Scheme 6.5



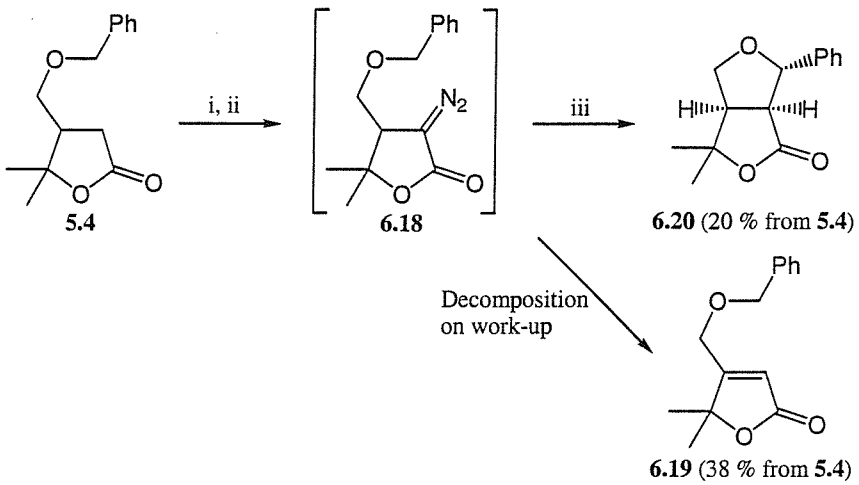
Reagents and Conditions: (i) Cl_3CCOCl, Zn/Cu, Et_2O, DME, reflux; (ii) Zn, MeOH, $NH_4^+Cl^-$; (iii) H_2O_2, AcOH; (iv) LiHMDS (2 equiv), $F_3CCH_2OCOCF_3$, THF; (v) 4-nitrobenzenesulfonyl azide, $(i\text{-}Pr)_2EtN$, MeCN; (vi) $Rh_2(OAc)_4$, CH_2Cl_2.

Activation of **6.15** and treatment of this crude material with 4-nitrobenzenesulfonyl azide gave diazo-lactone **6.16** in a pleasing yield over 2 steps. The crystalline nature of **6.16** allowed us to unequivocally confirm the structure of the diazo-lactone following results of an X-ray crystallographic study. The subsequent rhodium catalysed insertion reaction rapidly provided furofuranone **6.17** and stereochemical confirmation of the *endo*- isomer has been achieved on obtaining an X-ray crystal structure. Synthesis of furofuranone derivative **6.17** has, therefore, been achieved in a respectable 32 % overall yield.

6.4 Furofuranone Formation of a Gem-Dimethyl Derivative

Sacrificial activation of gem-dimethyl substituted lactone **5.4**, discussed in the previous chapter, and reaction with 4-nitrobenzenesulfonyl azide provided diazo-lactone **6.18** (Scheme 6.6). However, upon work-up employing a quick aqueous acid wash, complete decomposition of diazo derivative **6.18** was observed. The only compound successfully isolated from this degradation was 1,2-inserted product butenolide **6.19**. We were unsure as to whether the acidic wash, an unknown inorganic contaminant on the glassware or just general instability of the diazo-compound **6.18** was the cause of this unexpected result.

Scheme 6.6



Reagents and Conditions: (i) LiHMDS (2 equiv), $F_3CCH_2OCOCF_3$, THF; (ii) 4-nitrobenzenesulfonyl azide, $(i\text{-Pr})_2EtN$, MeCN; (iii) $Rh_2(OAc)_4$, CH_2Cl_2.

Treatment of crude diazo-lactone **6.18** with the rhodium catalyst provided a multi-component mixture from which furofuranone **6.20** was the only identified product, isolated as a colourless oil. A parallel programme of research within the Brown group re-investigated this transformation in more depth and discovered that diazo-intermediate **6.18** is, in fact, stable and that C-H insertion does provide a mixture of diastereoisomers. After a particularly tricky separation, the *exo*-furofuranone isomer **6.20** was successfully isolated as an oil and the minor *endo*- isomer as the usual crystalline solid (proved by an X-ray crystal structure). Comparison of spectral data confirmed we had originally isolated the *exo*-isomer **6.20**, this unexpected result had possibly been masked by that fact that we had taken the reaction crude over 3 steps. The exact reason why this 6,6-disubstituted derivative should alter the selectivity of the rhodium mediated C-H insertion has yet to be established. We have speculated that the gem dimethyl group must have a profound effect on the carbenoid transition state, either through steric interactions or as a result of substantial changes to the lactone ring conformation.

6.5 Conclusions

A number of furofuranone derivatives have been successfully synthesised from [2+2] cycloadducts. All these examples further demonstrated the flexibility of the diazo-transfer/C-H insertion methodology in forming bicyclic furanone scaffolds. Perhaps the most significant contribution involved the Beckmann cyclobutanone ring expansion to afford lactam intermediates that, subsequently, provided an *aza*- analogue to the furofuranones.

Chapter 7

Development of an Enantioselective Approach Towards the *Endo,Exo*-Furofuranone Framework

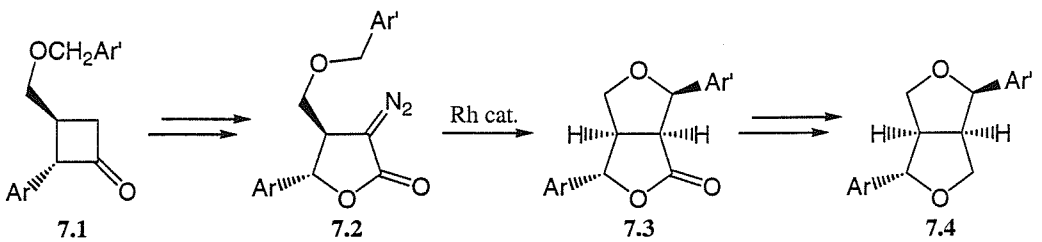
The two preceding chapters discussed an approach to the *endo,exo*-furofuran(one) series, including the racemic synthesis of two lignan natural products and a variety of their structural analogues.

The following chapter describes the development of an asymmetric synthesis of γ-butyrolactones in an attempt to synthesise enantiomerically pure furofurans. One new method incorporates nucleophilic ring openings of a cyclopropane intermediate to provide substrates for a novel diazo transfer reaction before C-H insertion affords the desired furofuranone framework.

7.1 The Demand for a New Route

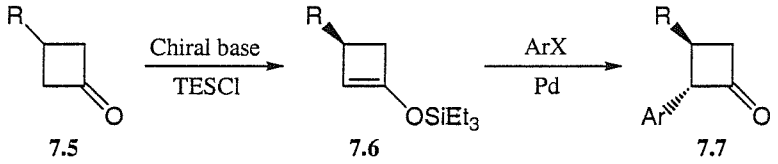
Although our original route (Scheme 7.1) provided an entry to furofuranones **7.3** and furofurans **7.4** it had its shortcomings.[172] The initial [2+2] cycloaddition was low yielding with electron rich aromatic systems that typify the natural products. Furthermore, this same step appeared unsuitable for the asymmetric synthesis of cycloadducts **7.1**. Even though Ghosez *et al.*[186,187] demonstrated that chiral amide derivatives can effect enantioselective cyclobutanone formation, they observed a poor level of chiral control with intermolecular reactions using proline derived auxilaries and substrates containing terminal double bonds. Although there was scope for developing an improved chiral amide derivative for the keteniminium-olefin cycloaddition we felt this would be time consuming and coupled with the moderate yields for the reaction, another approach would be more desirable.

Scheme 7.1



One feasible alternative to an asymmetric [2+2] cycloaddition involved the enantioselective deprotonation of achiral cyclobutanones[188] **7.5** to provide chiral precursors **7.6** for palladium-catalysed arylation[189,190] studies towards 3,4-disubstituted ketones **7.7** (Scheme 7.2).

Scheme 7.2



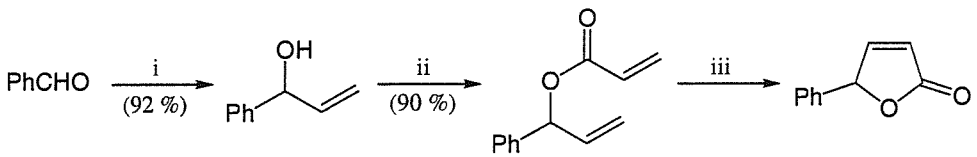
7.5 **7.6** **7.7**

However, at the time, we felt the most profitable area for investigation involved the preparation of enantiomerically pure 5-aryl substituted butenolides and stereoselective introduction of the required C-4 functionality. It was hoped this would avoid both the moderate yielding [2+2] cycloadditions and isolation of the resulting unstable cycloadducts.

7.2 Early Investigations into Butenolide Synthesis

The potential of 2(5H)-furanones (butenolides) as Michael acceptors in organic synthesis, allied with the number of naturally occurring compounds in which such functionality is present, has prompted great activity directed towards the synthesis of these molecules.[191,192] However, few 5-arylfuranones are known; their synthesis is complicated by ready isomerisation to the more stable 2(3H)-furanone isomer.[193] Available methods were either low yielding, or over-sophisticated for such modest targets.[192] We initially attempted the synthesis of butenolide **7.11** utilising ring-closing olefin metathesis[194] of acrylate ester **7.10**, derived from allylic alcohol **7.9**, in the presence of Grubbs' catalyst (Scheme 7.3).[195]

Scheme 7.3



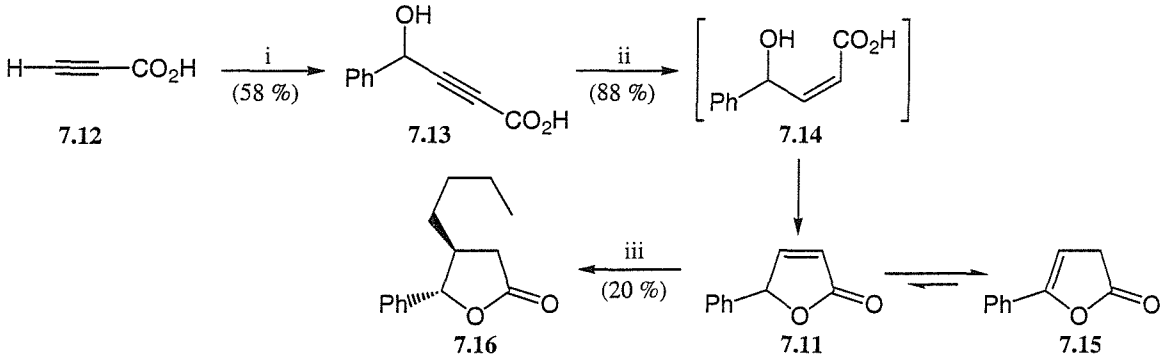
7.8 **7.9** **7.10** **7.11**

Reagents and Conditions: (i) Vinylmagnesium bromide, THF; (ii) Acryloyl chloride, NEt_3, DMAP, CH_2Cl_2; (iii) Grubbs' catalyst (10 mol %), $Ti(O^iPr)_4$, CH_2Cl_2.

Initial exposure of ester **7.10** to Grubbs' catalyst in the presence of titanium (IV) isopropoxide, at 40 °C for 15 hours, resulted in moderate conversion to 2(5H)-furanone

7.11 (60 % by ^{1}H-NMR) with a substantial amount of unreacted starting material. Purification attempts by flash chromatography were abandoned after the product appeared to degrade on silica gel. No further attempts were taken to improve this methodology as it was decided this route proved too expensive to produce butenolides on the multi-gram scale that would be required. The palladium-catalysed hydrogenation of alkyne **7.13** was, therefore, investigated as an alternative approach to the required 2(5H)-furanones (Scheme 7.4).

Scheme 7.4



Reagents and Conditions: (i) a) Methylmagnesium chloride, THF; b) PhCHO; c) 2N H_2SO_4 (aq); (ii) Lindlar catalyst, H_2, EtOAc; (iii) CuI, ^{n}BuLi, BF_3•Et_2O, THF, -78 °C.

Using a procedure described by Tishler *et al.*[196], conversion of alkyne **7.13** to butenolide **7.11**, *via* cyclisation of hydroxy olefinic acid **7.14**, was effected by Lindlar reduction. Purification was attempted by flash chromatography on silica gel treated with 1 % triethylamine in a bid to suppress the natural acidity of silica and avoid unwanted isomerisation or degradation of the desired butenolide. Ironically it had the effect of cleanly converting the crude (5H)-furanone to its more stable (3H) isomer **7.15**. Isomerisation also occurred upon attempted distillation of the crude product and under GC conditions. Therefore, it was decided that this material would be used crude with the few minor impurities most likely assigned to over reduced product in the hydrogenation.

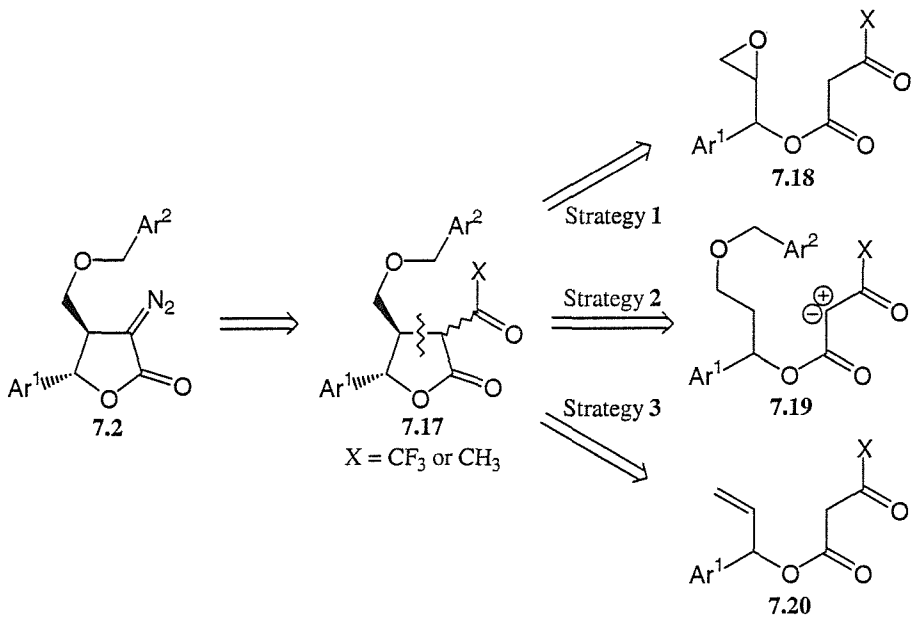
In an effort to introduce further functionality to butenolide **7.11** cuprate additions were examined (Scheme 7.4). The conjugate addition of lithium dibutyl cuprate using boron trifluoride etherate as a mediator[197] led to the successful isolation of *trans*-4,5-disubstituted lactone **7.16**, but only in 20 % yield (nucleophilic Michael additions to 5-monosubstituted butenolides have been studied extensively with a wide range of nucleophiles, including cuprates, and in all cases the nucleophile attacked from the opposite face to the substituent in the 5-position[198]).

Due to the disappointing results obtained in the butenolide synthesis we decided to investigate more robust and versatile routes towards γ-butyrolactones with the potential of an efficient chiral synthesis for furofuran lignans and their structural analogues.

7.3 A New Synthetic Target – A Fresh Approach

From the outset, the original synthesis was developed with the intention of utilising a direct diazo-transfer of a lactone enolate to provide the crucial diazo-lactones **7.2**. However, since the introduction of sacrificial activation at the lactone transfer centre, a new 1,3-dicarbonyl synthetic target **7.17** was envisaged. With the obvious C3-C4 disconnection we considered 3 main strategies for the desired 5-membered lactone ring closure (Figure 7.1). The first, a nucleophilic attack on epoxide **7.18**, the second a C-H insertion reaction of carbene intermediate **7.19** and finally, a radical or iodo cyclisation of alkene **7.20**.

Figure 7.1

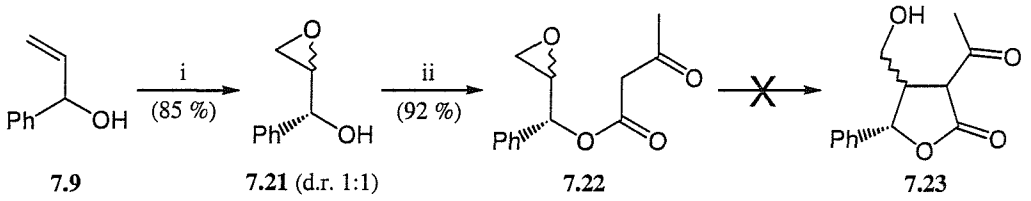


It was hoped that the β-ketoester derivatives **7.18-7.20** could be formed *via* acetoacetylation[199,200] of the corresponding benzylic alcohols. With respect to a chiral synthesis, we considered asymmetric epoxidations[201] or kinetic resolutions of secondary allylic alcohols;[202] enantioselective addition of organometallic reagents to the corresponding benzaldehydes;[203-205] and enzymatic resolutions[206,207] of racemic secondary benzylic alcohols. Uncertainties with the proposed strategies, aside from concerns over their success, involved the stereochemical issue surrounding the lactone ring closure towards the required *trans*-isomer.

7.3.1 Strategy 1 - Nucleophilic Closure of the Lactone Ring *via* an Epoxide

Epoxy alcohol **7.21** was prepared from the corresponding vinyl alcohol **7.9** following treatment with *m*-CPBA in chloroform[208] to give **7.21** as a 1:1 mixture of diastereoisomers based on ^{1}H-NMR signals. Acetoacetylation of secondary alcohol **7.21** was then effected with 2,2,6-trimethyl-4H-1,3-dioxin-4-one[200] providing acetoacetate ester **7.22** in excellent yield following short-path distillation (Scheme 7.5).

Scheme 7.5



7.9 **7.21** (d.r. 1:1) **7.22** **7.23**

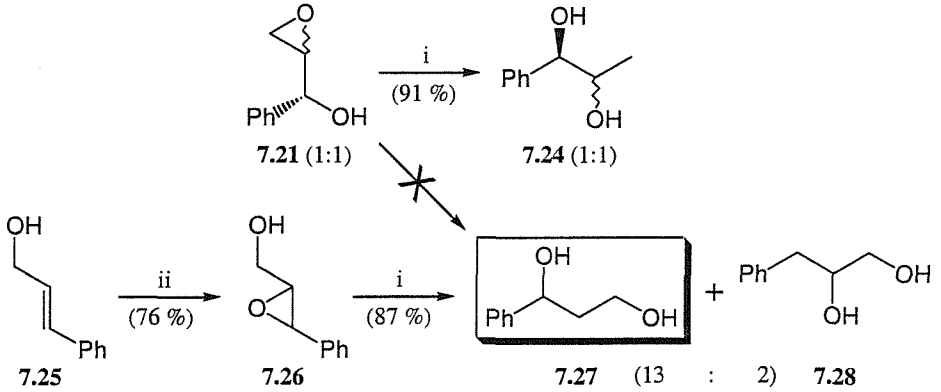
Reagents and Conditions: (i) *m*-CPBA, $CHCl_3$; (ii) 2,2,6-trimethyl-4H-1,3-dioxin-4-one, xylene, Δ.

Unfortunately, both base mediated and acid catalysed attempted ring closures of epoxide **7.22** failed to provide any of the desired primary alcohol **7.23** and in most cases starting material **7.22** was left unreacted.

7.3.2 Strategy 2 - Attempts at C-H insertion of a Carbene Intermediate

A key precursor towards the synthesis of an intermediate suitable for C-H insertion studies proved to be 1,3-diol **7.27**. Initially, we investigated the synthesis of diols from epoxy alcohols, which could be prepared through asymmetric synthesis or resolution.

Scheme 7.6



7.21 (1:1) **7.24** (1:1)

7.25 **7.26** **7.27** (13 : 2) **7.28**

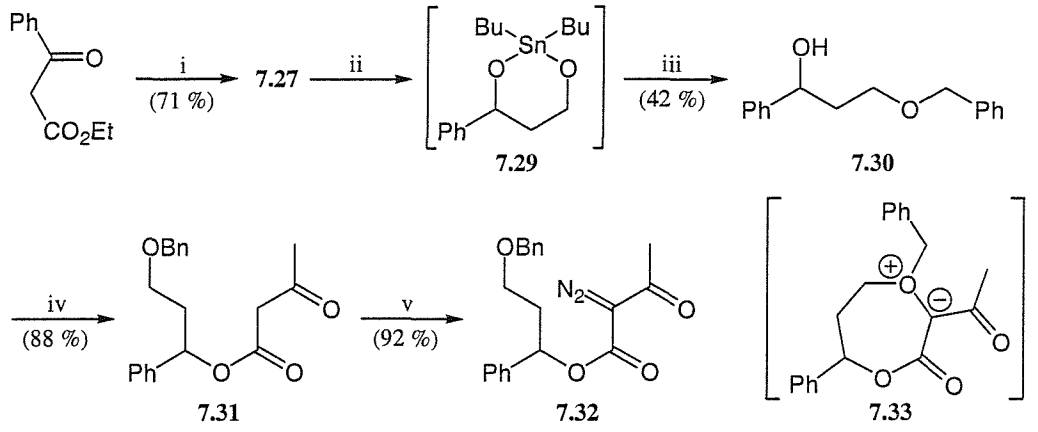
Reagents and Conditions: (i) RED-AL, THF; (ii) *m*-CPBA, $CHCl_3$.

Unsurprisingly, treatment of terminal epoxide **7.21** with RED-AL gave, exclusively, the unwanted 1,2-diol **7.24** (Scheme 7.6). However, opening of epoxide **7.26**, derived from

cinnamyl alcohol (**7.25**), under identical conditions provided a mixture of desired 1,3-diol **7.27** and 1,2-diol **7.28** in a 13:2 ratio respectively. Unfortunately, these diols co-eluted and although further synthesis was undertaken problems with separation were still encountered. Therefore, to ease analysis, a one-step reduction of ethyl benzoylacetate with sodium borohydride in THF/methanol provided **7.27** cleanly and in good yield (Scheme 7.7).[209]

Regioselective benzylation of 1,3-diol **7.27** was achieved upon formation of stannylene intermediate **7.29** prior to treatment with benzyl bromide.[210,211] Acetoacetylation of the resulting secondary alcohol **7.30**, using the previously mentioned dioxinone, provided acetoacetate ester **7.31** in good yield. Subsequent diazo-transfer, using commercially available sulfonyl azide to facilitate reaction work-up, gave diazo-ketoester **7.32** in excellent yield.

Scheme 7.7



Reagents and Conditions: (i) $NaBH_4$, THF/MeOH, reflux; (ii) Bu_2SnO, benzene, reflux; (iii) BnBr, $^nBu_4N^+Br^-$, reflux; (iv) 2,2,6-trimethyl-4H-1,3-dioxin-4-one, xylene, Δ; (v) 4-carboxybenzenesulfonyl azide, $^iPr_2EtN$, MeCN.

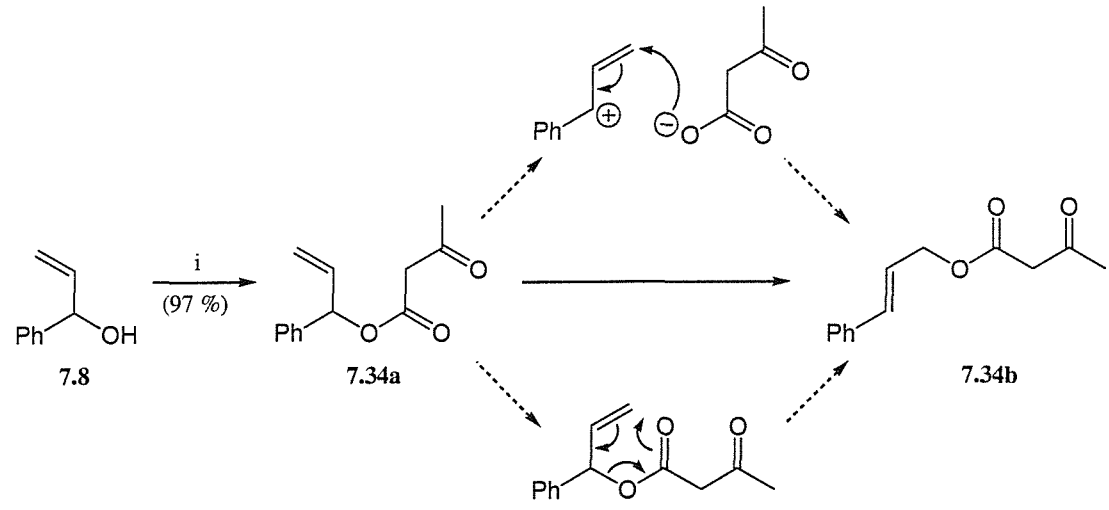
Several cyclisation attempts *via* carbenoid C-H insertion of **7.32** were made, but with little success. Exposure of diazo compound **7.32** with 2 mol % rhodium (II) tetraacetate in dichloromethane at room temperature showed little/no reaction and a substantial amount of starting material was recovered after 24 hours. However, decomposition was more rapid with 10 mol % rhodium catalyst in refluxing methylene chloride producing a multi-component mixture, although significant amounts of a more polar product were detected. Although this product proved too unstable to isolate and fully characterise, on the basis of NMR analysis of the partially purified material (exchangeable proton at ~ 5 ppm) we suggested that a hydroxy moiety was probably present. We suspected this could

be a direct result of quenching an oxonium ylide, of type **7.33**,[10] with water either under the reaction conditions or during work-up. Unfortunately, due to encouraging results from other areas of investigation, no further efforts were made to revisit and identify these potentially interesting reaction products.

7.3.3 Strategy 3 - Radical Cyclisations onto an Alkene

Acetoacetylation of 1-phenyl-prop-2-en-1-ol (**7.8**) under the conditions previously described provided acetoacetate ester **7.34a** following purification by distillation (Scheme 7.8). However, NMR analysis of the product showed a significant impurity that proved to be alkene **7.34b** resulting from either a [3,3] sigmatropic rearrangement (a common observation with allylic ketoesters[212]) or *via* an ionisation mechanism. We assumed the thermal conditions used in this synthesis and purification were promoting such a transformation. Therefore, the reaction time was reduced from 40 to 10 minutes at 150 °C and the product purified by flash chromatography (purification time also kept to a minimum as rearrangement was apparent on the silica surface). These modifications were successful in affording β-ketoester **7.34a** of satisfactory purity to investigate some radical cyclisations.

Scheme 7.8



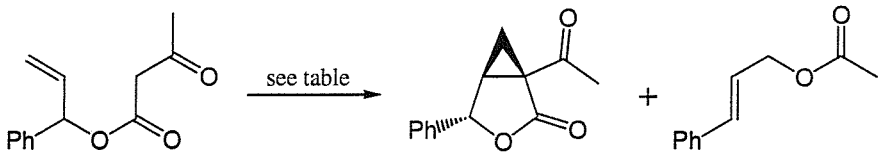
7.8 **7.34a** **7.34b**

Reagents and Conditions: (i) 2,2,6-Trimethyl-4H-1,3-dioxin-4-one, xylene, Δ.

Oxidative free-radical cyclisation[213] of allylic β-ketoester **7.34a** was first attempted with manganese (III) acetate dihydrate in the presence of copper (II) acetate in acetic acid at room temperature (Scheme 7.9). This left starting material **7.34a** unreacted and so the reaction temperature was increased to 50 °C. After 2 hours the dark brown colour of

Mn(III) was replaced with a blue-turquoise colouration and crude ^{1}H-NMR showed the presence of alkene **7.36** and what appeared to be cyclopropane **7.35** (entry 1, Table 7.1). The reaction was repeated at an elevated temperature of 70 °C, with the addition of potassium acetate and we were pleased to isolate cyclopropane **7.35** in moderate yield with excellent diastereoselectivity (*trans* / *cis* 22:1). The previously observed alkene by-product **7.36** was isolated (7 %) along with unreacted starting material **7.34a**.

Scheme 7.9



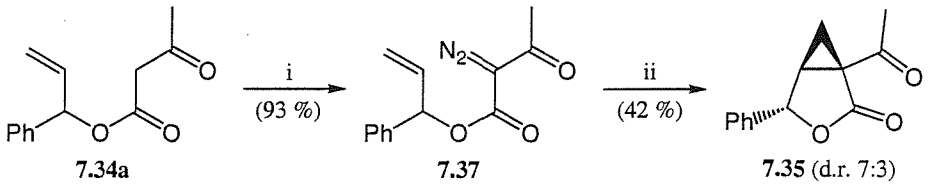
7.34a **7.35** (d.r. 22:1) **7.36**

Table 7.1 Effect of reaction conditions on the cyclisation of allylic ester **7.34a**.

	Equiv $Mn(OAc)_3$	Equiv $Cu(OAc)_2$	Equiv KOAc	Temp / °C	Time / min	Ratio cyclop:alke:SM	Yield of **7.35**	Yield of **7.36**
1	2	1	0	50	120	1 : 4 : 0	Not isolated	Not isolated
2	2	1	2	70	40	7 : 1 : 2	43 %	7 %
3	3	1.5	2.5	70	15	18 : 1 : 0	74 %	Not isolated

Model studies suggested radical cyclisation of **7.34a** was faster than any thermal rearrangement or nucleophilic attack of acetate onto the terminal double bond. In an effort to suppress these by-products the reaction was repeated with increased quantities of reagents pre-heated together, as a slurry in acetic acid, before addition of allylic ester **7.34a** to the mixture. This strategy proved very successful and reaction times were reduced to 15 minutes with no starting material and only minor amounts of alkene by-product **7.36** observed. This protocol also proved amenable to scale-up as demonstrated by a 20 g oxidation to provide cyclopropane **7.35** in an impressive 74 % yield (entry 3, Table 7.1). *trans*-Lactone **7.35** was obtained exclusively after recrystallisation with the stereochemical assignment unambiguously determined by X-ray crystallography. Surprisingly, very few cyclopropanations providing related bicyclo[3.1.0]lactones have been reported.[214-216]

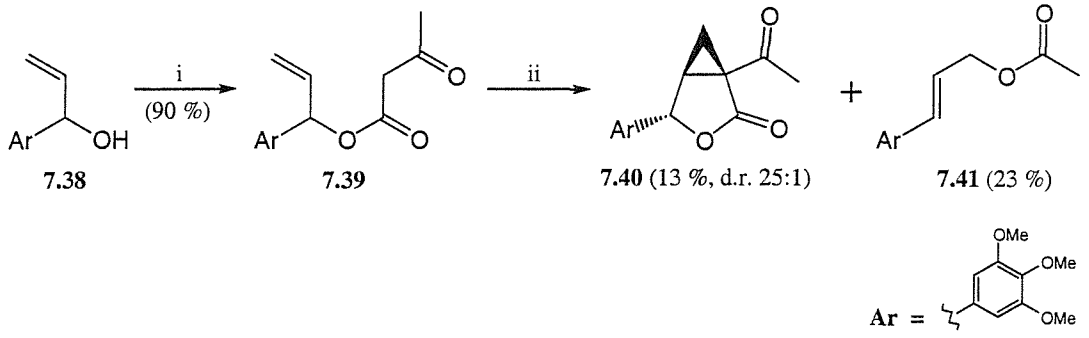
Scheme 7.10



Reagents and Conditions: (i) 4-Carboxybenzenesulfonyl azide, $^{i}Pr_2EtN$, MeCN; (ii) $CuSO_4$, $Cu(acac)_2$, toluene, reflux.

As an alternative to free-radical cyclisation of alkene **7.34a**, a carbenoid cylopropanation was attempted *via* copper mediated decomposition of diazo ketoester **7.37** (Scheme 7.10).[29,217] This was successful in providing cyclopropane **7.35** in moderate yield as a 7:3 mixture of *trans/cis* diastereoisomers, respectively. However, the methodology proved inferior to the Mn(III)-mediated cyclisation, both in terms of yield and diastereoselectivity, so no further attempts were made to optimise the reaction conditions (*e.g.* metal, ligand etc).

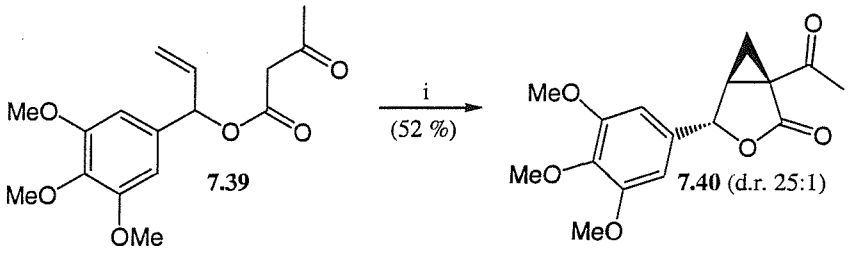
Scheme 7.11



Reagents and Conditions: (i) 2,2,6-Trimethyl-4H-1,3-dioxin-4-one, xylene, Δ; (ii) $Mn(OAc)_3$, $Cu(OAc)_2$, KOAc, AcOH, Δ.

The synthesis of furofuran natural products required this cyclopropanation methodology to be compatible with electron rich aromatic groups. Therefore, we investigated the oxidative cyclisation of 3,4,5-trimethoxyphenyl allylic ester **7.39** under the conditions described above (Scheme 7.11). We suspected that the highly activated benzylic ether may be incompatible with the acidic reaction medium and were, therefore, not surprised to isolate cyclopropane **7.40** in low yield with a significant quantity of alkene **7.41**. However, simple replacement of acetic acid with DMSO (or DMF)[218] as solvent was sufficient in eliminating these unwanted side products, providing **7.40** in a more respectable yield (Scheme 7.12).

Scheme 7.12

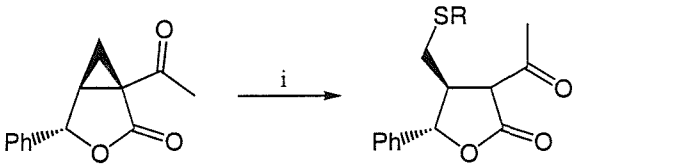


Reagents and Conditions: (i) $Mn(OAc)_3$, $Cu(OAc)_2$, DMSO, Δ.

7.4 Alcohol Additions to a Cyclopropane

We envisaged cyclopropane **7.35** as a key intermediate towards furofuranone derivatives due to its expected predisposition to undergo nucleophilic ring openings.[219] Indeed, addition of benzyl mercaptan and *p*-methoxythiophenol proceeded smoothly to give sulphides **7.42a,b** in excellent yields (Scheme 7.13).

Scheme 7.13



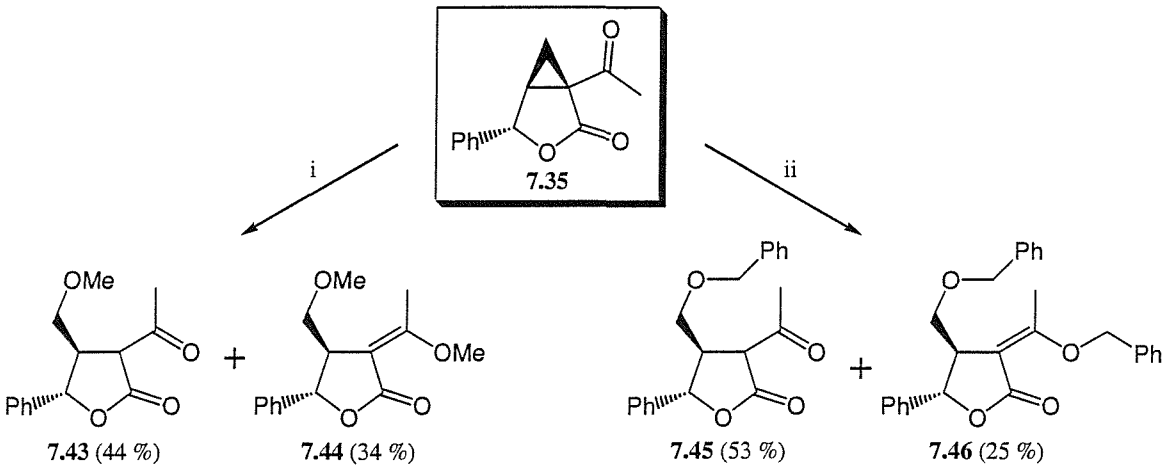
7.42a R = CH_2Ph (93 %)
7.42b R = 4-MeO-C_6H_4 (90 %)

Reagents and Conditions: (i) RSH, $NaHCO_3$, DMSO, Δ.

Although addition of soft nucleophiles (discussed further in Chapter 9) was very efficient, opening with alcohols proved more problematic.[220-222] Following disappointing results with acid and base mediated reactions, we turned our attention to Lewis acid assisted openings of cyclopropane **7.35** in neat methanol. However, even with a stoichiometric amount of zinc triflate at reflux for 24 hours, conversion to the desired product **7.43** was low (^{1}H-NMR ratio of starting cyclopropane **7.35** : product **7.43**, 5:2 respectively). Fortunately, access to a SmithSynthesizer™ microwave reactor allowed us to investigate a broader range of conditions with the conclusion that cyclopropane **7.35** could be opened, with methanol, effectively at 120 °C. Consumption of **7.35** was observed after just 30 minutes at this temperature to provide desired methyl ether product **7.43** and corresponding enol ether **7.44** (Scheme 7.14).

Due to their higher boiling points microwave conditions were not required for benzylic alcohol additions and following a brief screen of metal triflates, ytterbium triflate was identified as a superior catalyst. Reaction of cyclopropane **7.35** with five equivalents of benzyl alcohol in the presence of 10 mol % $Yb(OTf)_3$ at 120 °C provided both desired product **7.45** and corresponding benzyl enol ether **7.46** in 53 % and 25 % yield, respectively (Scheme 7.14). GOESY experiments carried out on **7.46** confirmed the *trans* relationship between the C4 and C5 substituents and the geometrical isomer of the enol ether.

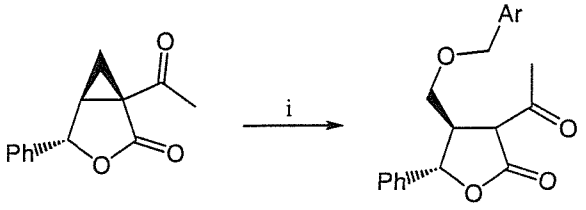
Scheme 7.14



Reagents and Conditions: (i) MeOH, $Zn(OTf)_2$, 120 °C, microwave radiation; (ii) BnOH, 10 mol% $Yb(OTf)_3$, 120 °C.

A more in-depth survey into common Lewis acids indicated improved results could be obtained when using magnesium perchlorate. Ultimately, optimisation of these conditions allowed opening of **7.35** with three equivalents of the appropriate alcohol, neat, at 120 °C with 10 mol% of Lewis acid, providing products **7.45** and **7.47b-d** in excellent yields with little enol ether formation observed (Scheme 7.15).

Scheme 7.15



7.35

7.45 Ar = Ph (80%)
7.47b Ar = 4-NO_2-C_6H_4 (88%)
7.47c Ar = 4-Br-C_6H_4 (91%)
7.47d Ar = 3-MeO-C_6H_4 (84%)

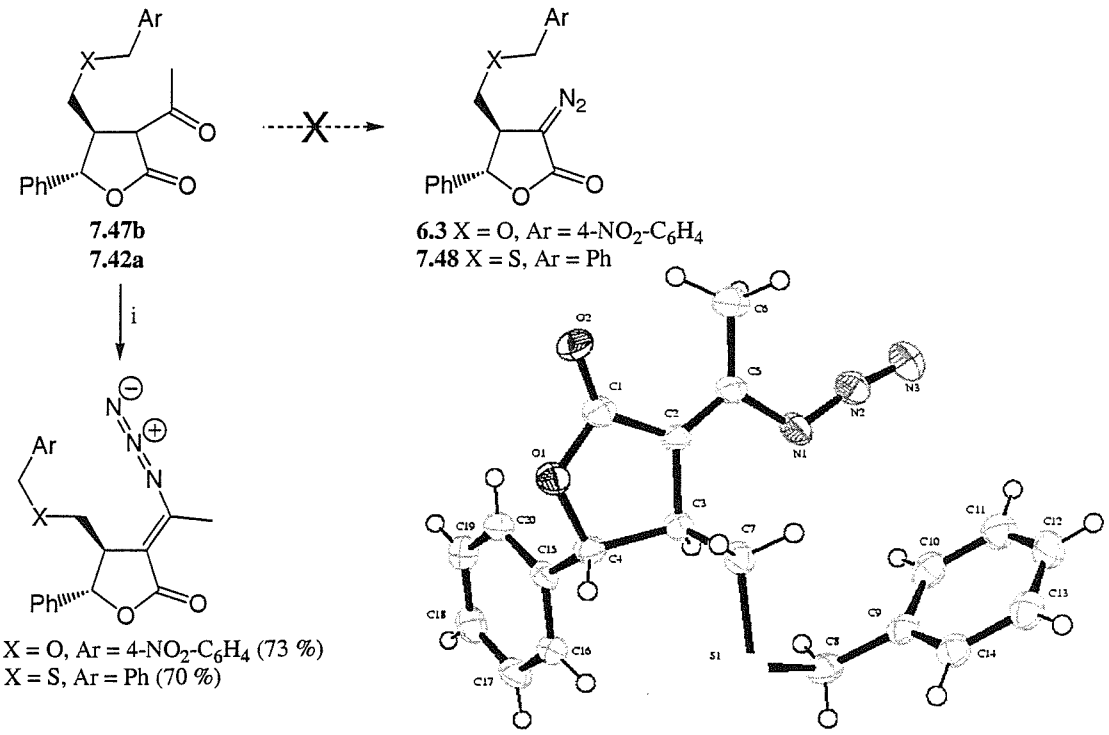
Reagents and Conditions: (i) $ArCH_2OH$, 10 mol % $Mg(ClO_4)_2$, 120 °C.

The success of nucleophilic alcohol additions to cyclopropane **7.35** was crucial in providing precursors for investigations into the de-acetylative diazo-transfer strategies required for the preparation of furofuranones.

7.5 Diazo-Transfer of α-Acetyl-γ-Butyrolactones

Acetylated lactone substrates **7.45** and **7.47b-d** proved inert to attempted de-acetylative diazo-transfer procedures utilising benzenesulfonyl azides, despite the fact that such transformations are well precedented.[29,77,92,93] Therefore, we decided to investigate the more reactive methanesulfonyl azide, prepared from mesyl chloride and sodium azide[223] and used in diazo-transfer reactions without further purification.[74,92,93] Although treatment of **7.47b** with MsN_3 and Hünigs' base provided none of the desired diazo-product, use of DBU was successful in converting lactone **7.47b** to, what we initially thought to be, diazo-adduct **6.3** (Scheme 7.16). Indeed, IR analysis showed an encouraging stretch (ν_{max}; 2110 cm^{-1}) consistent with that of a diazo lactone but we were baffled by NMR analysis that showed the presence of a methyl signal (resonances at 14.5 ppm - ^{13}C-NMR; three proton singlet at 2.6 ppm - ^{1}H-NMR). A thio-analogue was prepared in the same manner and found to have similar spectroscopic properties to that observed for its oxa analogue. Ultimately, this thio-derivative provided a satisfactory crystal for X-ray crystallographic studies that revealed it to be azido compound **7.49b**.

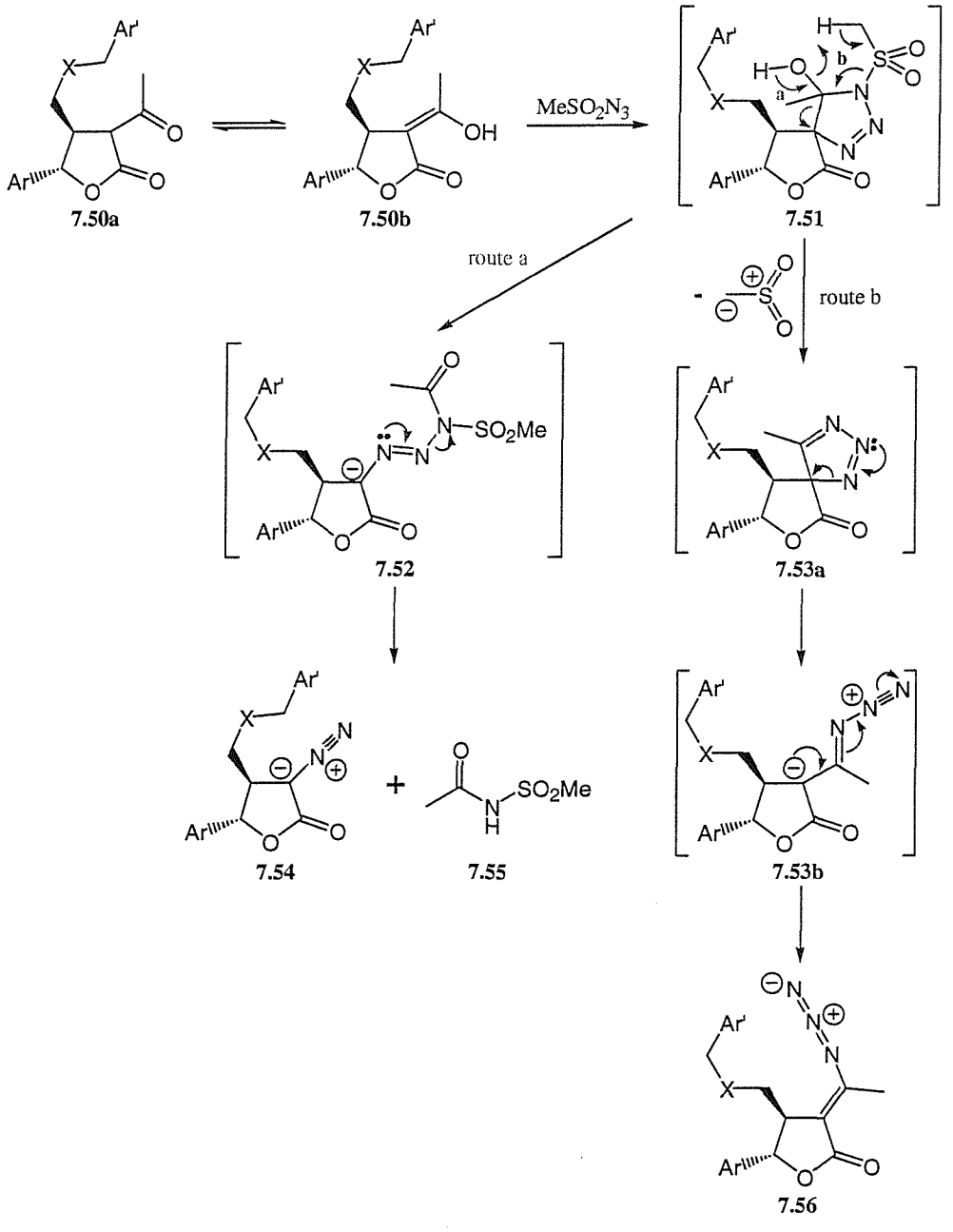
Scheme 7.16 and crystal structure of 7.49b



Reagents and Conditions: (i) MsN_3, DBU, MeCN.

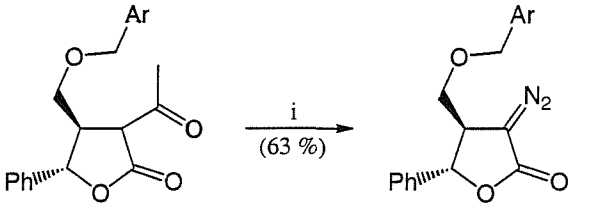
A proposed mechanism for this unusual transformation is shown in Figure 7.2. Reaction of acetyl-activated lactone **7.50a/b** with mesyl azide, in the presence of base, may provide cyclic triazene **7.51**.[64,68-70] Collapse of this intermediate *via* 'route a' would lead to diazo-transfer with concomitant acyl cleavage providing the expected diazo-lactone **7.54** and sulfonamide **7.55**. However, reaction of **7.51** *via* 'route b', with loss of water and dioxosulfonium methylide, would provide triazene spirocycle **7.53a** with subsequent rearrangement affording the observed azido derivative **7.56**. To the best of our knowledge, compounds of this type have never been isolated using mesyl azide as an azide donor and we can only assume that the lactone ring conformation makes this transformation a favourable process.

Figure 7.2 Mechanistic issues of diazo-transfer with mesyl azide



With the popular diazo-transfer reagents, including benzenesulfonyl azides and even mesyl azide failing to generate any of the desired α-diazo-γ-butyrolactones we began to wonder whether this was a feasible process. However, we reasoned that use of the extremely reactive trifluoromethanesulfonyl azide would prevent formation of azido derivatives **7.56** and provide access to the desired diazo-lactones **7.54**.[94,95,224] Gratifyingly, it was found that a hexane solution of triflyl azide reacted smoothly with α-acetyl lactone **7.47b** in acetonitrile to generate diazo compound **6.3** in moderate yield (Scheme 7.17).

Scheme 7.17



7.47b **6.3** Ar = 4-NO_2-C_6H_4

Reagents and Conditions: (i) a) DBU, MeCN; b) TfN_3, hexane.

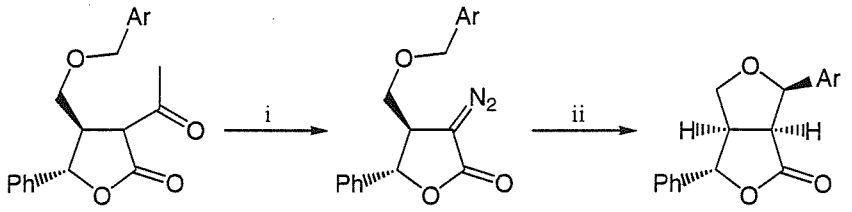
Having optimised nucleophilic ring openings of a cyclopropane intermediate and uncovered a suitable diazo-transfer reagent for the resulting α-acetyl lactone derivatives we decided to target some furofuranone derivatives.

7.6 Synthesis of *Endo,Exo*-Furofuranone Derivatives

Although no problems were encountered in the handling of triflyl azide solutions we, naturally, had some reservations on its frequent use in our diazo-transfer reactions. This led us to devise a facile and highly reactive one-pot method that successfully transformed acetyl-activated lactones **7.45** and **7.47b-d** into their corresponding diazo-lactones in good to excellent yields following the *in situ* generation of triflyl azide under phase-transfer catalysis (Scheme 7.18). Furthermore, these biphasic conditions may find applications in diazo-transfers to particularly difficult substrates that have previously proved challenging.

As expected, the C-H insertion reactions proceeded rapidly with high diastereoselectively upon treatment with a catalytic quantity of rhodium (II) acetate dimer to provide furofuranones **5.19**, **6.4** and **7.58c,d** bearing aryl substituents in an *endo,exo*-configuration.[172]

Scheme 7.18



7.45
7.47b-d

5.18 (92 %)
6.3 (80 %)
7.57c (83 %)
7.57d (84 %)

5.19 Ar = Ph (89 %)
6.4 Ar = 4-NO_2-C_6H_4 (78 %)
7.58c Ar = 4-Br-C_6H_4 (76 %)
7.58d Ar = 3-MeO-C_6H_4 (82 %)

Reagents and Conditions: (i) NaN_3, Tf_2O, $^nBu_4NBr$, 2 M NaOH/hexane/MeCN (2:1:1), 0 °C; (ii) 2 mol % $Rh_2(OAc)_4$, CH_2Cl_2.

Thus, the synthesis of **5.19** was completed in 5 steps with 47 % overall yield, demonstrating the excellent efficiency of this new approach.[225] Furthermore, the convergent nature of this route provides the opportunity to assemble diverse sets of structural furofuran lignan derivatives.

7.7 Conclusions

A concise and diastereoselective synthesis of a series of *endo,exo*-furofuranone analogues has been achieved. The most significant areas of contribution include optimisation of alcohol additions to cyclopropane **7.35** under Lewis acidic conditions and development of a highly effective diazo-transfer protocol to afford α-diazo-γ-butyrolactones. Although, more importantly we believe we have an approach, readily amenable, for the enantioselective synthesis of furofuran natural products.

Chapter 8

Asymmetric Synthesis of Furofuran Lignans

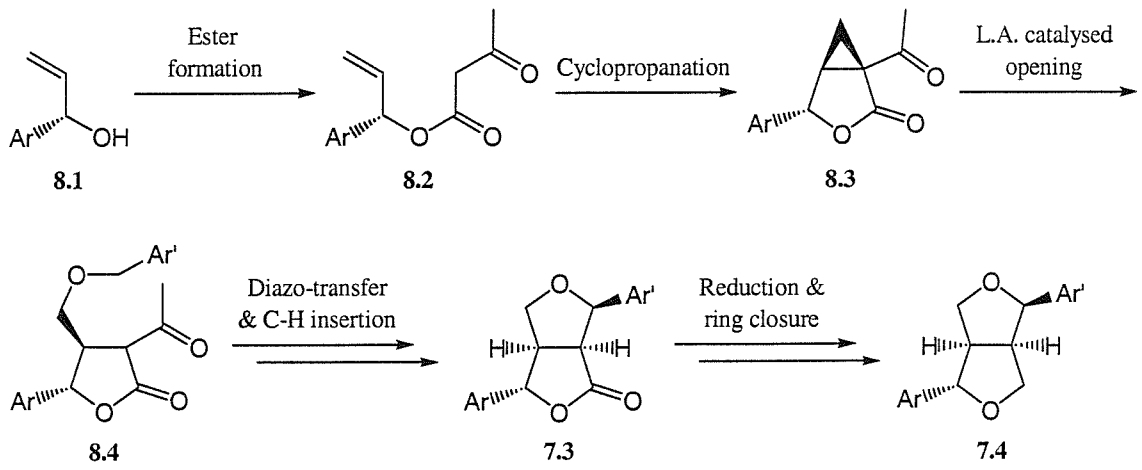
The preceding chapter discussed a novel cyclopropane ring opening approach towards a concise and diastereoselective preparation of *endo,exo*-furofuran(one) analogues. Furthermore, we believed this route could potentially provide a chiral synthesis, if enantiopure starting alcohols were employed.

The following chapter describes the asymmetric total synthesis of four furofuran lignans from an enantiomerically enriched 1-aryl-allyl alcohol.

8.1 Studies into Enzymatic Resolutions of Secondary Benzyl Alcohols

Previously we reported a new, more robust and higher yielding approach to furofuranone lignan derivatives **7.3**, centering on nucleophilic ring openings of a cyclopropane intermediate **8.3**.[225] We envisaged that if the synthesis originated from a chiral aryl-allyl alcohol **8.1** it would provide an entry to enantiopure furofurans **7.4**. The activated cyclopropane ring **8.3**, formed in the oxidative cyclisation of **8.2**, provides a means of introducing the top portion of the natural product using Lewis-acid catalysed 1,5-additions of electron rich benzylic alcohols.

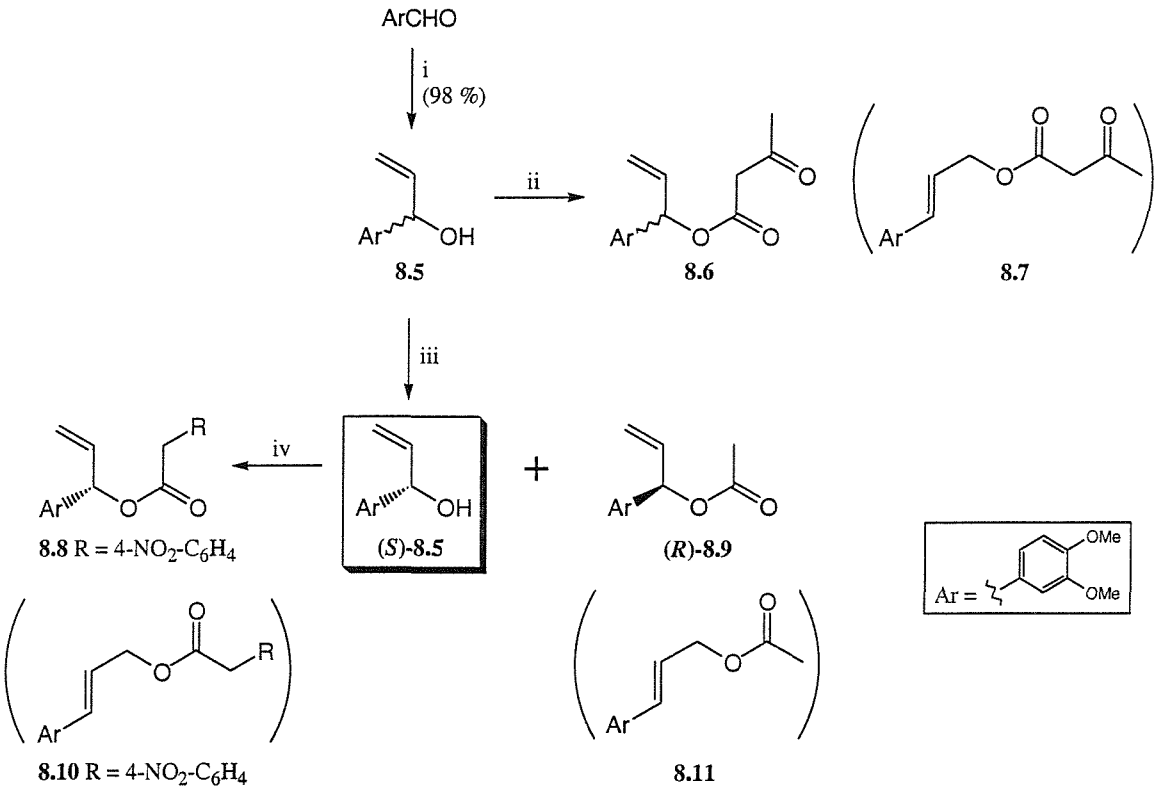
Figure 8.1 Enantioselective approach to the synthesis of endo,exo-furofurans



Although the preceding chapter outlined some elegant approaches towards the preparation of chiral secondary alcohols **8.1**, time constraints restricted us to examining the enzymatic resolution of racemates. Furthermore, the literature reports several encouraging results from lipase-mediated resolutions of secondary allylic alcohols on similar substrates.[226-228]

We had already shown that synthesis of cyclopropanes bearing electron rich aromatic substituents was possible, demonstrated by the preparation of the 3,4,5-trimethoxy derivative in the preceding chapter. However, we became interested in the synthesis of furofurans with a 3,4-dimethoxy-aryl group in the C-6 postion. Therefore, a lipase catalysed resolution of racemic 1-(3,4-dimethoxy)phenyl-prop-2-en-1-ol (±)-(**8.5**) was investigated using isopropenyl acetate as the acyl donor. The catalyst employed in our study was a lipase, Novozym 435,[228] derived from *Candida antartica*, immobilised on a macroporous resin to enable full recovery, easy handling and facile work-up.

Scheme 8.1



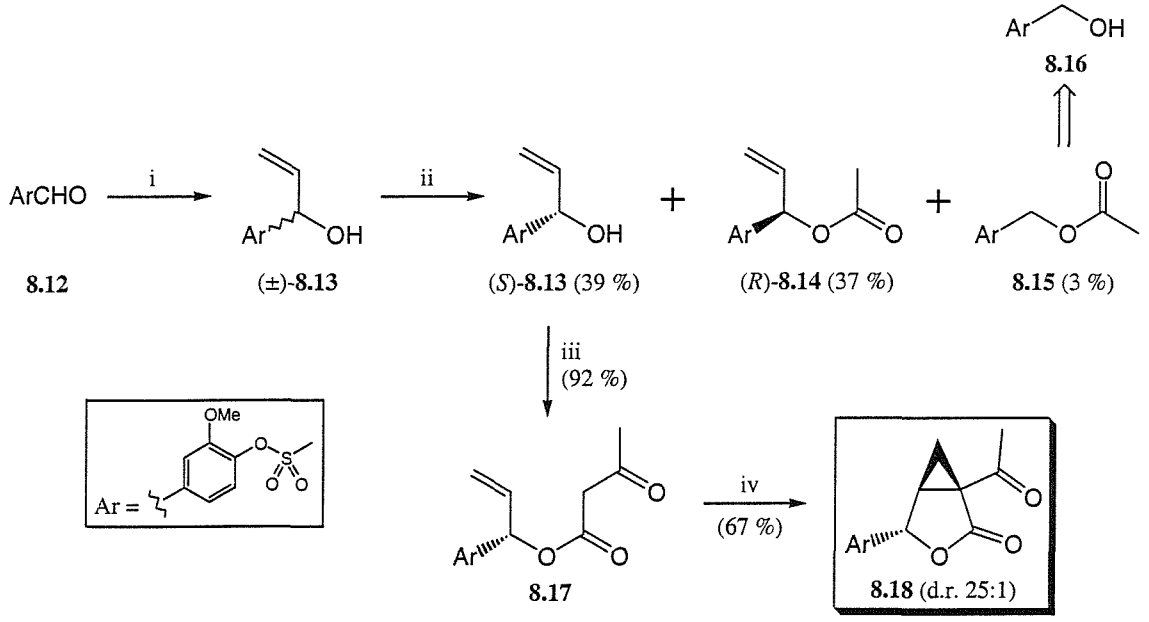
Reagents and conditions: (i) Vinylmagnesium bromide, THF; (ii) 2,2,6-trimethyl-4H-1,3-dioxin-4-one, xylene, Δ; (iii) Novozym 435, isopropenyl acetate; (iv) 4-nitrophenylacetic acid, DCC, DMAP, CH_2Cl_2.

Frustratingly, failure to resolve racemic alcohol (±)-**8.5**, using several normal-phase chiral columns and a variety of elution conditions, severely hampered reaction monitoring. However, partial separation of racemic acetate (±)-**8.9** was achieved and indicated good kinetic resolution of the allyl alcohol was possible (approx. 40 % conversion after 15 h at 40 °C). Unfortunately, under the reaction conditions and following purification on silica gel, some ester rearrangement ((*R*)-**8.9** to **8.11**) was evident, again preventing any accurate assessment of *e.e.* In an attempt to obtain a precise *e.e.* value for resolved alcohol (*S*)-**8.5**, the *para*-nitro benzyl derivative **8.8** was prepared (displaying full

separation on chiral HPLC). However, yet more problems were encountered upon purification and HPLC analysis. Silica seemingly promoted conversion of ester **8.8** to alkene **8.10**, the latter co-eluting with **8.8** complicating detailed analysis. This undesired transformation was further pronounced whilst attempting the acetoacetylation[200] of racemic dimethoxybenzyl alcohol (±)-**8.5**. High temperature conditions employed during the reaction resulted in almost entire conversion to alkene **8.7**, causing further concerns over the stability of these 3,4-dimethoxy esters.

With complications arising in the use of these highly activated benzyl derivatives so early on in the synthesis, a solution was required. One theory involved incorporation of an electron withdrawing methanesulfonyl group in an attempt to increase the acid stability of the benzylic ester intermediates. Therefore, repetition of this protocol, using a 4-methanesulfonyloxy-3-methoxy aryl substituent, was undertaken.

Scheme 8.2



Reagents and conditions: (i) Vinylmagnesium bromide, THF; (ii) Novozym 435, isopropenyl acetate; (iii) 2,2,6-trimethyl-4H-1,3-dioxin-4-one, xylene, Δ; (iv) $Mn(OAc)_3$, $Cu(OAc)_2$, KOAc, AcOH.

Careful addition of vinylmagnesium bromide to mesylated vanillin **8.12** was essential as use of Grignard reagents to deprotect phenolic mesylates has been reported (Scheme 8.2).[229,230] Enzymatic resolution of the crude racemate 1-(4-methanesulfonyloxy-3-methoxy)phenyl-prop-2-en-1-ol (±)-(**8.13**) was carried out with the supported lipase, Novozym 435. Gratifyingly, chiral normal-phase HPLC (Chiracel OD-H column – eluting with IPA/hexane, 1:9) successfully resolved racemate (±)-**8.13** and provided

essentially enantiomerically 'pure' alcohol (*S*)-**8.13**, with calculated e.e. >98 % (Rt (*S*)-alcohol = 25.2 min, Rt (*R*)-alcohol = 29.2 min). The transesterified by-product, acetate (*R*)-**8.14**, was also isolated along with minor amounts of benzyl acetate **8.15**. We postulated that minor quantities of **8.15** originated from the Grignard addition, whereby a reduction resulted in the formation of primary alcohol **8.16** that was subsequently acylated during the resolution step. King *et al.*[231] have also observed this reduction with vinylmagnesium bromide in the presence of an aryl aldehyde.

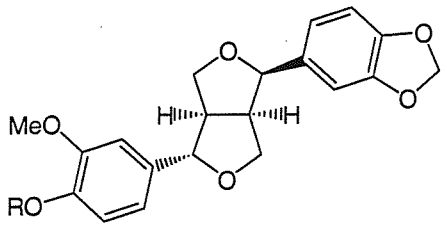
Enantiomerically enriched alcohol (*S*)-**8.13** then underwent acetoacetylation, with no detected racemisation or decomposition, to provide chiral β-ketoester **8.17** in excellent yield. We were extremely pleased that presence of the methanesulfonate group allowed the use of our optimised methodology for the Mn(III) mediated oxidative cyclisation with acetic acid as solvent (compared to DMSO or DMF required for the trimethoxy- system in Chapter 7). Cyclopropane **8.18** was, therefore, isolated in good yield with excellent diastereoselectivity (d.r. 25:1 by ^{1}H-NMR) and subsequent removal of the minor diastereomer was achieved by recrystallisation.

The methanesulfonate protection had now surpassed its main objective. It had increased the acid stability of the benzylic ester intermediate **8.17** to an extent that it allowed the cyclopropanation step to be conducted with the standard acetic acid methodology. Furthermore, we felt that this moiety could potentially allow the preparation of furofurans containing free phenolic groups. Therefore, with plenty of cyclopropane **8.18** to hand, we decided to target two phenolic furofuran lignans and their resulting *O*-methyl natural derivatives.

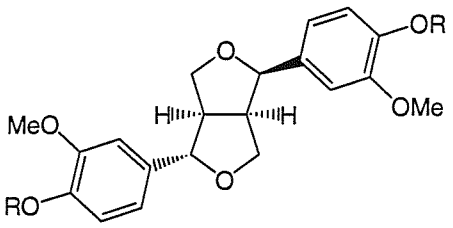
8.2 Total Synthesis of (+)-Xanthoxylol, (+)-Epipinoresinol, (+)-Methyl Xanthoxylol and (+)-Epieudesmin

The total synthesis of two *endo,exo*-phenolic furofuran lignans, (+)-xanthoxylol (**8.19**) and (+)-epipinoresinol (**8.20**), and their *O*-methylated counterparts, (+)-methyl xanthoxylol (**8.21**) and (+)-epieudesmin (**8.22**), was undertaken. A range of biological activities have been reported for these compounds with all four possessing PAF antagonist activity.[121,122] (+)-Epipinoresinol (**8.20**), perhaps the most studied of the four, also displays: Ca^{2+} antagonist activity (IC_{50} 38 μM);[120] moderate inhibition of *c*-AMP phosphodiesterase (IC_{50} 230 μM);[119] cytotoxic activity (IC_{50} 4.0 μg/mL)[232] and inhibitory histamine release (IC_{50} 39 μM).[233]

Figure 8.2 Structures of the furofuran lignans targeted for synthesis



R = H (+)-Xanthoxylol (**8.19**)
R = Me (+)-Methyl xanthoxylol (**8.21**)



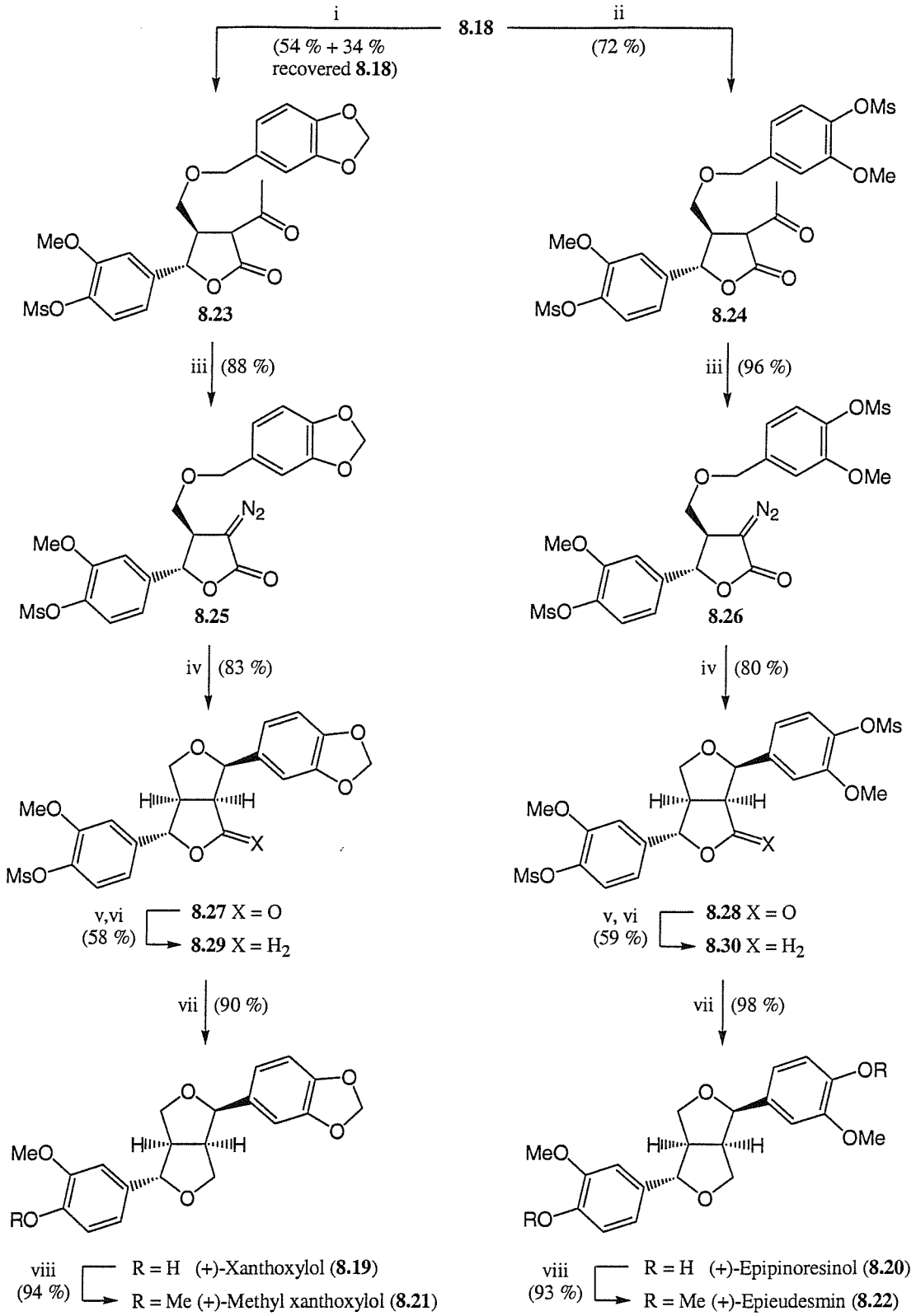
R = H (+)-Epipinoresinol (**8.20**)
R = Me (+)-Epieudesmin (**8.22**)

The synthesis proceeded with the ring openings of cyclopropane **8.18**, introducing the top portion of the natural products (Scheme 8.3). However, acid sensitivity of the electron rich benzyl systems continued to cause problems and attempted addition of 3,4-methylenedioxybenzyl alcohol (**8.31**) to **8.18** provided none of the desired lactone, the major reaction being the rapid condensation to the corresponding dibenzyl ether. Fortunately, formation of this by-product was suppressed by addition of 2,6-di-*tert*-butyl pyridine and a respectable yield of methylenedioxy adduct **8.23** was obtained, along with 34 % recovered cyclopropane **8.18**. The Lewis-acid catalysed opening with methanesulfonyl protected benzyl alcohol **8.32** proved more straightforward with the formation of ring-opened lactone **8.24**. A practical complication was encountered when excess alcohol **8.32** co-eluted with the desired product **8.24**. However, separation of alcohol **8.32** was readily achieved following its acylation under mild conditions with the supported lipase, Novozym 435.

Treatment of α-acetyl lactone derivatives **8.23** and **8.24** with triflyl azide generated *in situ via* our one pot method, was successful in returning the desired diazolactones **8.25** and **8.26** in excellent yields. Rhodium-catalysed C-H insertion then proceeded rapidly to afford *endo,exo*-furofuranones **8.27** and **8.28** as single diastereoisomers.

X-ray structures were obtained on compounds **8.18** and **8.28** and due to the presence of a heavy atom we were able to unambiguously determine their relative and absolute stereochemistry.

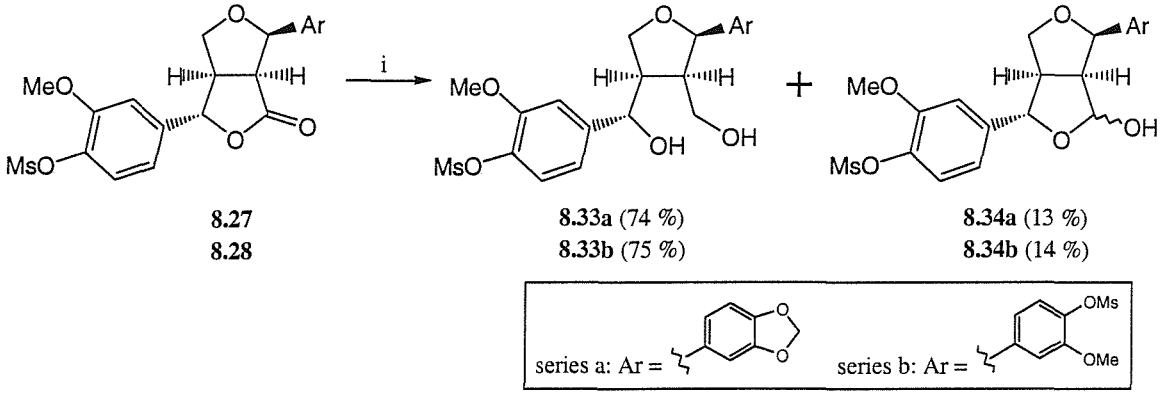
Scheme 8.3



Reagents and conditions: (i) 3,4-Methylenedioxy-benzyl alcohol (**8.31**), 10 mol % $Mg(ClO_4)_2$, 2,6-di*tert*butyl pyridine; (ii) a) 4-(methanesulfonyloxy)-3-methoxy-benzyl alcohol (**8.32**), 10 mol % $Mg(ClO_4)_2$, 2,6-di*tert*butyl pyridine; b) Novozym 435, isopropenyl acetate; (iii) NaN_3, Tf_2O, $^nBu_4NBr$, 2 N NaOH/hexane/MeCN (2:1:1); (iv) $Rh_2(OAc)_4$, CH_2Cl_2; (v) $LiAlH_4$, THF; (vi) Ms_2O, Et_3N, DMAP, CH_2Cl_2; (vii) 3 N KOH, MeOH/dioxane (1:1), Δ; (viii) MeI, Cs_2CO_3, acetone.

With furofuranones **8.27** and **8.28** to hand, completion of the synthesis proved relatively straightforward. Incomplete reduction of the lactone moiety provided diols **8.33a** and **8.33b** in slightly lower yields than expected, with lactols **8.34a** and **8.34b** also isolated in 13 % and 14 % yields, respectively (Scheme 8.4). Cyclisation of diols **8.33a/b**, in the presence of methanesulfonyl anhydride, successfully afforded furofuran analogues **8.29** and **8.30** in good yields.

Scheme 8.4



8.27
8.28

8.33a (74 %)
8.33b (75 %)

8.34a (13 %)
8.34b (14 %)

Reagents and conditions: (i) $LiAlH_4$, THF, 0 °C.

Now, all that remained to complete the natural product synthesis was deprotection of the sulfonate esters. Gratifyingly, the methanesulfonyl protection of the phenolic oxygens was readily removed upon treatment with 3N KOH in methanol/dioxane at 50 °C,[234] demonstrating the potential of this protecting group in lignan synthesis. (+)-Xanthoxylol (**8.19**) and (+)-epipinoresinol (**8.20**) displayed analytical data consistent with that reported and the synthesis of two additional furofuran lignans, (+)-methyl xanthoxylol (**8.21**) and (+)-epieudesmin (**8.22**), was completed by methylation of the phenolic hydroxyl groups present in **8.19** and **8.20**.

8.3 Conclusions

A new asymmetric approach to *endo,exo*-furofuran lignans, from enantiomerically enriched alcohol (*S*)-**8.13**, has been achieved. In addition to the key transformations previously developed, a significant contribution to the overall success stems from the ability of the methanesulfonyl group to increase the acid stability of the benzylic and ester intermediates.

Chapter 9

Furofuranone Analogues *via* Cyclopropane Ring-Openings

The following chapter describes the synthesis of a variety of furofuranone structural analogues. These derivatives utilise the synthetic strategy outlined in the two preceding chapters and, consequently, originate from cyclopropane ring openings.

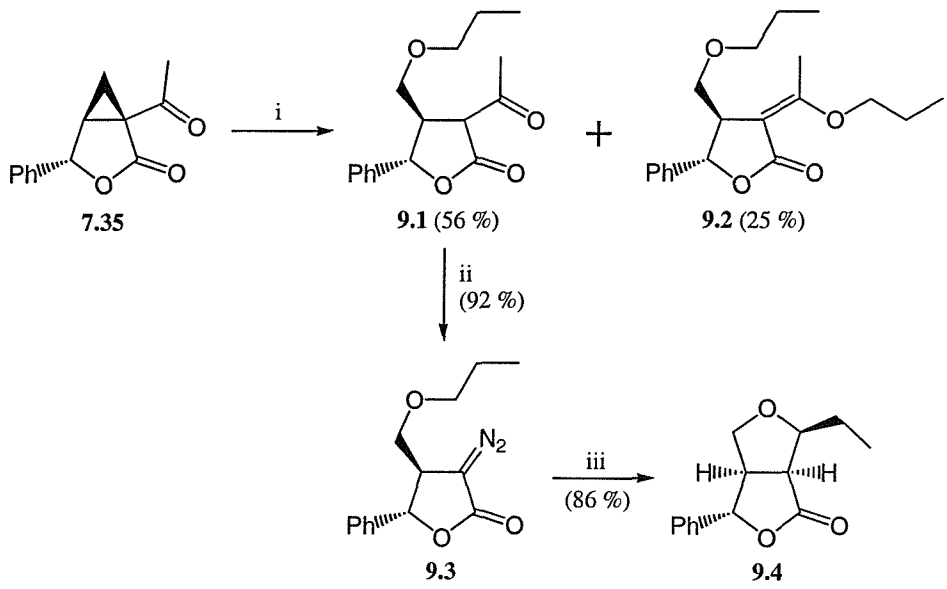
9.1 Cyclopropane Opening with Oxygen Based Nucleophiles

The following section describes the opening of cyclopropane intermediate **7.35** with both acetate and a variety of alcohols. Subsequent conversion to the corresponding diazolactone derivatives provided an opportunity to examine their decomposition pathway upon treatment with rhodium (II) tetraacetate.

9.1.1 Preparation of an Ethyl Furofuranone Derivative

Refluxing cyclopropane **7.35** in *n*-propyl alcohol, in the presence of magnesium perchlorate, successfully provided ring-opened adduct **9.1** and its corresponding propyl enol ether **9.2** (Scheme 9.1). De-acetylative diazo-transfer was carried out on lactone **9.1**, using the 'triflyl azide' protocol, to give diazo compound **9.3** in excellent yield.

Scheme 9.1



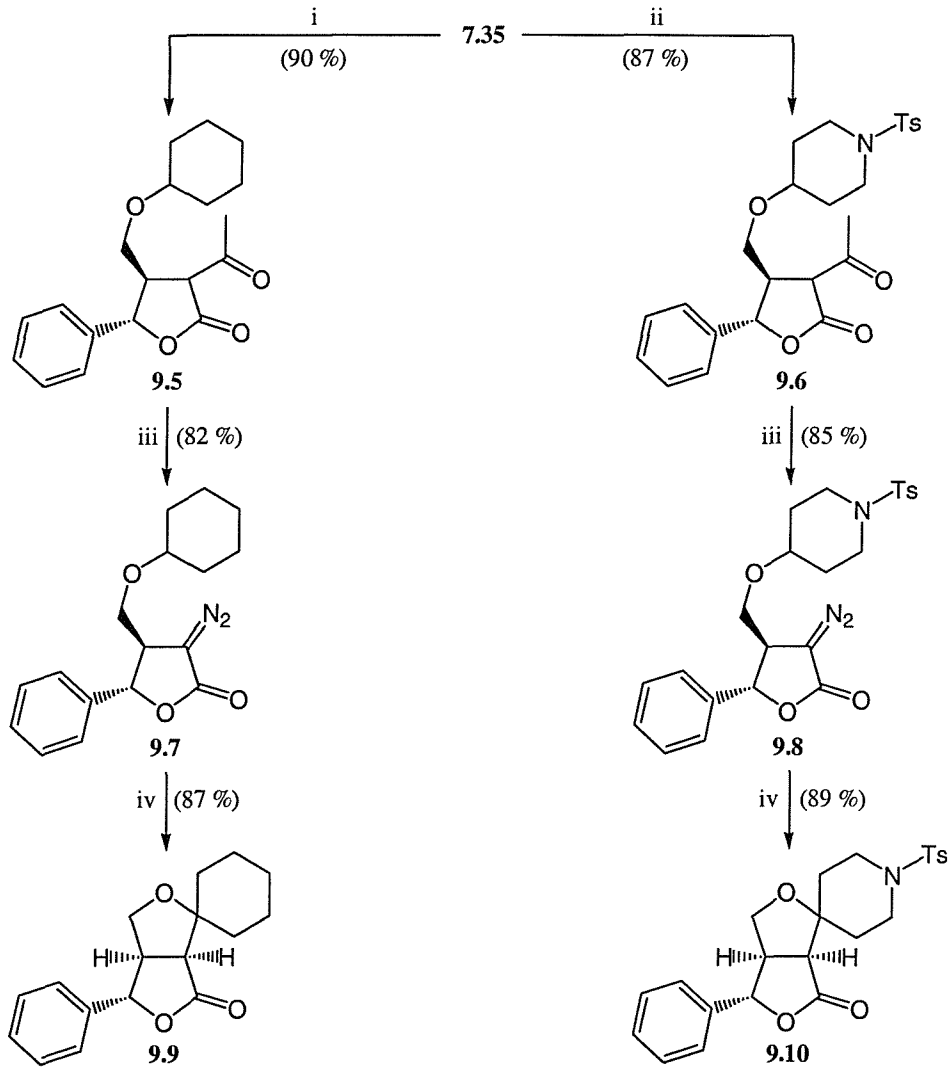
Reagents and conditions: (i) $CH_3(CH_2)_2OH$, 10 mol % $Mg(ClO_4)_2$, Δ; (ii) NaN_3, Tf_2O, $^nBu_4NBr$, 2 N NaOH/hexane/MeCN (2:1:1); (iii) 2 mol % $Rh_2(OAc)_4$, CH_2Cl_2.

Rhodium catalysed C-H insertion of **9.3** provided cyclised product **9.4** as a single diastereoisomer. Comparison of NMR data, with some of our previous analogues and those from literature,[152] suggested insertion had placed the ethyl group on the *endo*- face of the bicyclic core. Through interpretation of GOESY experiments the relative stereochemistry around the newly formed C-C bond was shown to be *cis* and provided a further example of an *endo,exo*-furofuranone.

9.1.2 Preparation of Spirocyclic Furofuranone Derivatives

The Lewis-acid catalysed additions of cyclohexanol and piperidinol **9.11** to cyclopropane **7.35** provided ring-opened adducts **9.5** and **9.6** in excellent yields (Scheme 9.2).

Scheme 9.2



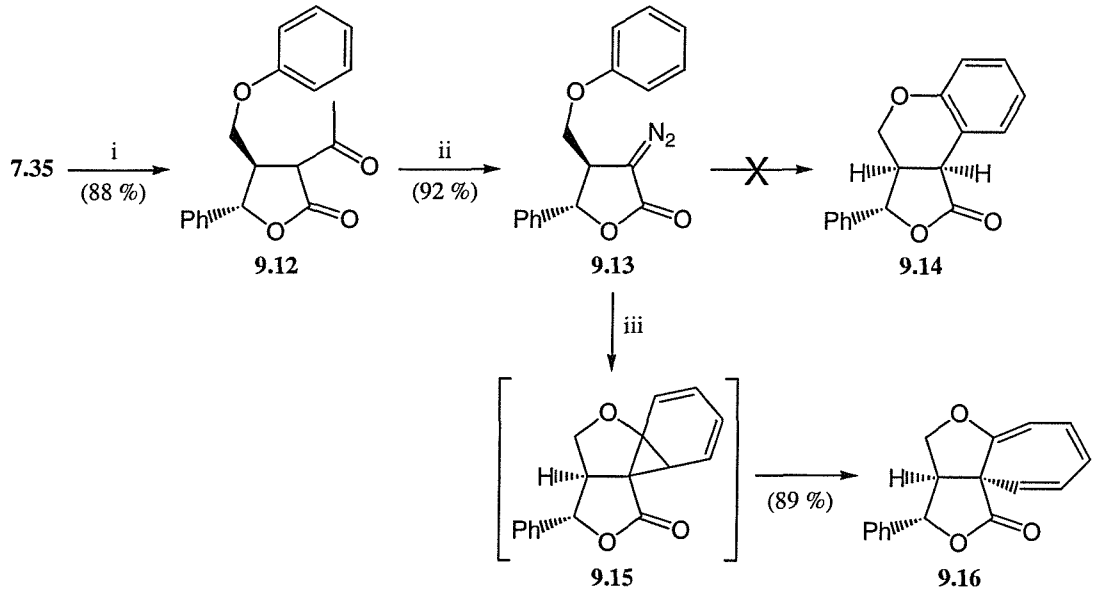
Reagents and conditions: (i) Cyclohexanol, 10 mol % $Mg(ClO_4)_2$, Δ; (ii) 1-(toluene-4-sulfonyl)-piperidin-4-ol (**9.11**), 10 mol % $Mg(ClO_4)_2$, Δ; (iii) NaN_3, Tf_2O, $^nBu_4NBr$, 2 N NaOH/hexane/MeCN (2:1:1); (iv) 2 mol % $Rh_2(OAc)_4$, CH_2Cl_2.

Treatment of diazolactones **9.7** and **9.8** with a catalytic quantity of dirhodium tetraacetate promoted rapid insertion into the methine C-H bond forming spirocyclic furofuranone derivatives **9.9** and **9.10** in 87 % and 89 % yields, respectively. Although time did not allow any further developments, aza- analogue **9.10** has the potential to provide an excellent tricyclic template for additional functionalisation.

9.1.3 Preparation of a Cycloheptatriene Furofuranone Derivative

Addition of caesium phenolate to cyclopropane **7.35** provided phenyloxy- ring opened adduct **9.12** in 88 % yield (Scheme 9.3). Our highly reactive diazo-transfer protocol remained efficient, successfully returning the desired diazolactone **9.13** in excellent yield.

Scheme 9.3



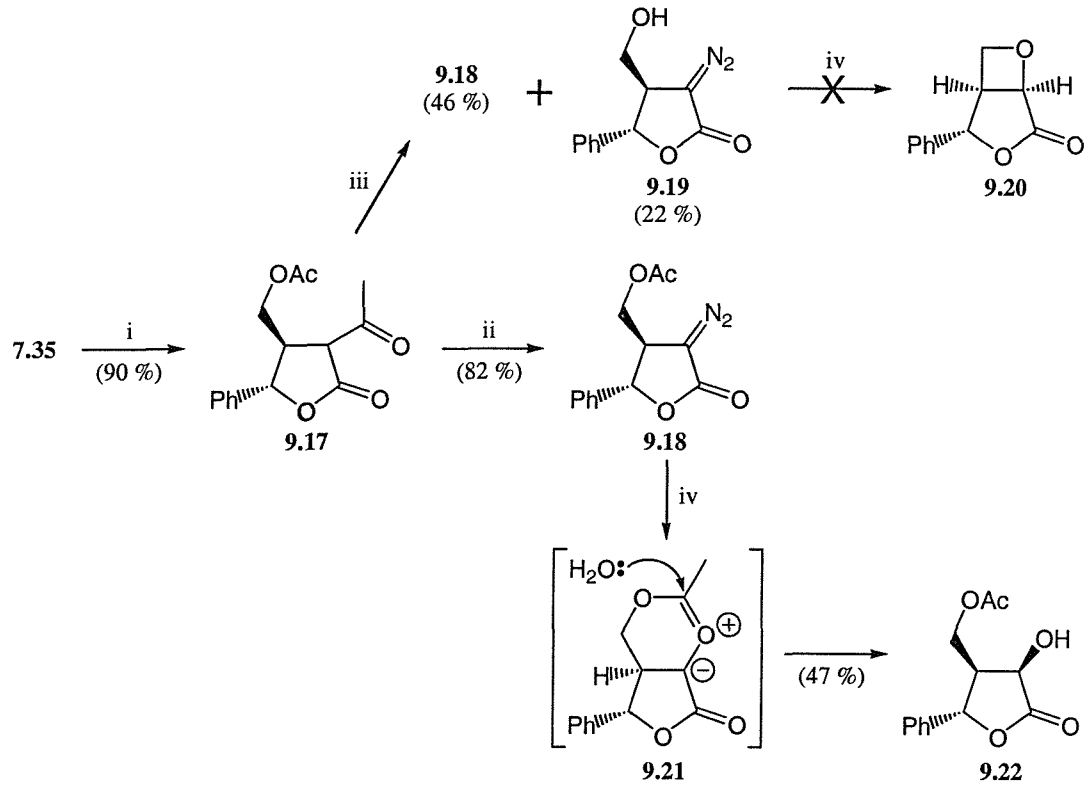
Reagents and conditions: (i) Phenol, Cs_2CO_3, DMSO, Δ; (ii) NaN_3, Tf_2O, $^nBu_4NBr$, 2 N NaOH/hexane/MeCN (2:1:1); (iii) 2 mol % $Rh_2(OAc)_4$, CH_2Cl_2.

The attempted rhodium-catalysed reaction of α-diazolactone **9.13** afforded a single product, but not that resulting from the expected aryl C-H insertion (**9.14**). More detailed NMR analysis indicated we had isolated cycloheptatriene **9.16**, formed *via* an intramolecular Büchner reaction.[235] Formally, this may be considered as an arene cyclopropanation followed by electrocyclic ring opening of the norcaradiene intermediate (**9.15**). The formation of this strained tricyclic system **9.16** provides another example of the unique transformations offered by these rhodium carbenoid reactions.

9.1.4 Acetate Cyclopropane Opening and Resulting Diazo Decomposition

Tanimori *et al.*[236] have shown that activated cyclopropanes fused onto cyclopentanone derivatives may be opened with potassium acetate and acetic acid in DMSO. Following their optimised conditions we were pleased to observe that lactone-derived cyclopropane **7.35** underwent this same transformation to provide acetate **9.17** in excellent yield (Scheme 9.4). Furthermore, use of our standard de-acetylative diazo-transfer protocol afforded diazolactone **9.18** in respectable yield. However, on one occasion **9.18** remained under basic phase-transfer conditions overnight resulting in the isolation of desired diazo adduct **9.18** and its corresponding de-acylated diazo-lactone **9.19** in 46 % and 22 % yields, respectively. Unfortunately, attempted rhodium catalysed O-H insertion of **9.19** resulted in a multi-component mixture and due to lack of time no purification was undertaken.

Scheme 9.4



Reagents and conditions: (i) KOAc, AcOH, DMSO, Δ; (ii) NaN_3, Tf_2O, $^nBu_4NBr$, 2 N NaOH/hexane/MeCN (2:1:1), 0 °C, 30 min; (iii) NaN_3, Tf_2O, $^nBu_4NBr$, 2 N NaOH/hexane/MeCN (2:1:1), 0 °C to r.t., 18 h; (iv) 5 mol % $Rh_2(OAc)_4$, CH_2Cl_2.

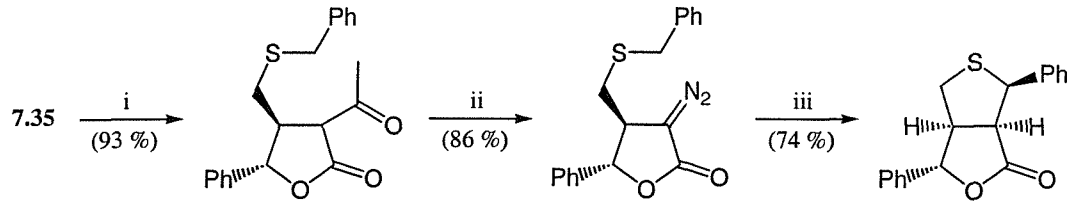
Treatment of diazolactone **9.18** with a catalytic quantity of rhodium (II) acetate and purification on silica gel provided alcohol **9.22** as the sole isolatable product. GOESY experiments confirmed the C3-C4 *cis*- relative stereochemistry and supported the

formation of intermediate carbonyl ylide **9.21**. Although 'dry and inert' conditions were employed, trapping of **9.21** with water either under the reaction conditions or during work-up, led to hydroxy acetate **9.22** with the observed *cis*- stereochemistry. Interestingly, the Padwa group utilised this strategy to prepare carbonyl ylides for subsequent use in some cycloaddition chemistry.[237,238] Employment of a similar cycloaddition methodology with our 1,3-dipole systems could potentially provide a number of novel ring systems.

9.2 Preparation of a Thio- Furofuranone Derivative

Addition of benzyl mercaptan to cyclopropane **7.35** proceeded smoothly to afford sulphide ring-opened adduct **7.42a** in excellent yield (Scheme 9.5). The key C-H insertion reaction was carried out using a catalytic quantity of dirhodium tetraacetate whereupon the rapid and highly diastereoselective conversion of diazo-lactone **7.48** to furofuranone **9.23** was observed. An X-ray structure of **9.23** confirmed the *endo,exo* configuration of the phenyl substituents.

Scheme 9.5



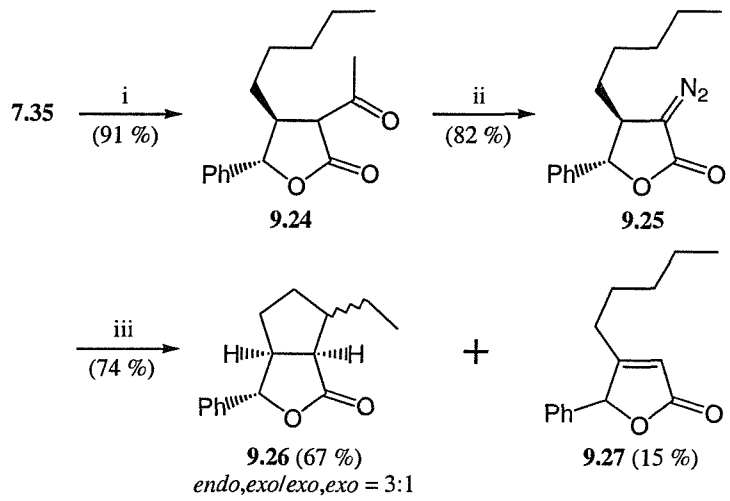
Reagents and conditions: (i) $PhCH_2SH$, $NaHCO_3$, DMSO, Δ; (ii) NaN_3, Tf_2O, $^nBu_4NBr$, 2 N NaOH/hexane/MeCN (2:1:1); (iii) 2 mol % $Rh_2(OAc)_4$, CH_2Cl_2.

We were slightly surprised to see such clean decomposition of diazo compound **7.48** as we expected to observe products arising from a 1,2-carbon shift (Stevens rearrangement) of an intermediate sulfide ylide.[10] This result represents a rare example where α-sulfur activated C-H insertion is exclusively favoured over ylide formation and rearrangement. Furthermore, we have demonstrated that sulfur can be introduced into the top ring of a furofuranone analogue with no noticeable rearrangement and with the high diastereoselectivity and yields that we have come to expect from these 2,6-diaryl systems.

9.3 Preparation of an Alkyl- Furofuranone Derivative

A simple cuprate addition to cyclopropane **7.35** with subsequent diazo-transfer provided alkyl substituted α-diazo-lactone **9.25** (Scheme 9.6). Unfortunately, rhodium catalysed C-H insertion of **9.25** showed less regio- and diastereo-selectivity than its α-heteroatom activated counterparts. As a result, diazo decomposition provided the bicyclo- furanone system **9.26** as an inseparable mixture of *endo,exo* and *exo,exo* isomers (3:1, respectively – based on ^{1}H-NMR analysis) and the 1,2 inserted product, butenolide **9.27**.

Scheme 9.6



Reagents and conditions: (i) (^{n}Bu)$_2$CuLi, THF; (ii) NaN_3, Tf_2O, ^{n}Bu$_4$NBr, 2 N NaOH/hexane/MeCN (2:1:1); (iii) 2 mol % $Rh_2(OAc)_4$, CH_2Cl_2.

We speculated that with absence of α-heteroatom activation, 1,2 insertion into the methine C-H of **9.25** competes with the familiar 1,5 methylene C-H insertion. Although there is still a clear preference for placing the ethyl group onto the *endo* face of the bicyclic core, presence of an α-heteroatom appears essential for high diastereoselectivity in this decomposition (*c.f.* **9.3** → **9.4**). Nevertheless, this strategy has been successful in the formation of a novel carbocyclic furofuranone analogue.

9.4 Conclusions

Cyclopropane **7.35** has proved a key intermediate towards the synthesis of several furofuranone analogues due to its predisposition to undergo nucleophilic ring openings. Furthermore, these examples demonstrate the flexibility of this novel diazo-transfer and C-H insertion methodology in forming diverse cyclic furanone scaffolds including carbo-, hetero- and spirocycles.

Chapter 10

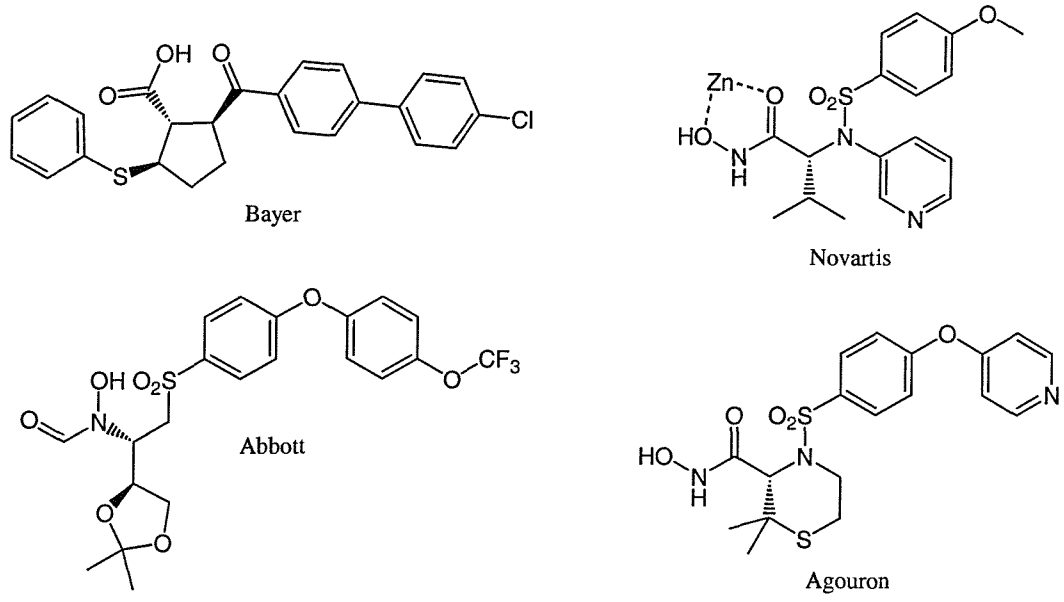
Progress Towards MMP Inhibitor Templates

The following chapter describes the attempted synthesis of furanone derived MMP inhibitor templates. Investigations towards establishing the desired ring system, *via* key C-H insertion reactions of α-diazo-β-ketosulphones, will be the principal area of discussion.

10.1 Introduction to MMP Inhibitors

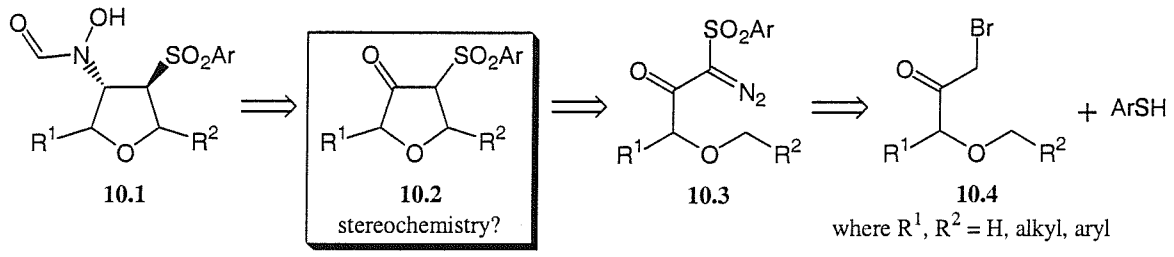
The matrix metalloproteinases (MMPs) are a family of zinc-containing enzymes capable of degrading most components in the extracellular matrix and have been implicated in several pathological processes including arthritis and tumour growth.[239-242] The discovery of potent and selective inhibitors of these enzymes is, therefore, highly attractive and the growing interest in this field is reflected by the increasing number of inhibitors discovered in various industrial and academic laboratories.[243,244] A number of MMP inhibitors have been developed and some examples are shown below (Figure 10.1).

Figure 10.1 Examples of MMP inhibitors



Our initial investigations were directed towards the synthesis of potential inhibitors with a substituted tetrahydrofuran ring template **10.2** *via* the key C-H insertion of diazosulfone precursor **10.3**. We envisaged these diazo intermediates could be synthesised from α-bromoketones **10.4** (derived from their readily available acids) and the desired benzene thiols (Figure 10.2).

Figure 10.2

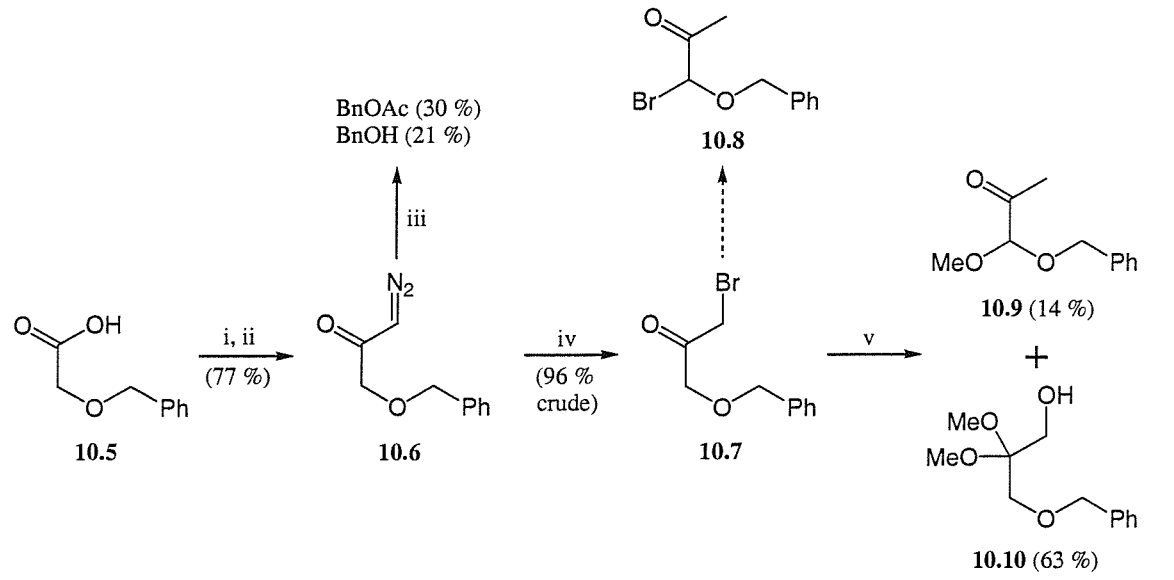


We hoped α-oxygen activation would promote C-H insertion towards forming the furanone, although stereoselectivity of this cyclisation was uncertain.

10.2 Investigations into MMP Inhibitor Templates

Conversion of benzyloxyacetic acid (**10.5**) to its acid chloride and treatment with trimethylsilyl diazomethane provided α-diazo-ketone **10.6**, stable enough to purify on silica gel (Scheme 10.1). Attempts to form α-bromo ketone **10.7** with hydrobromic acid in acetic acid resulted in cleavage of the benzyloxy group to give benzyl acetate and benzyl alcohol in 30 % and 21 % yield, respectively. However, repetition of this reaction with HBr in a milder aqueous/ether system cleanly provided the desired product **10.7**, although it was subsequently found to undergo rearrangement during purification or upon standing to what we have tentatively assigned 1-benzyloxy-1-bromo-2-propanone (**10.8**). Sondheimer and Bell have also reported this transformation with a similar substrate.[245]

Scheme 10.1

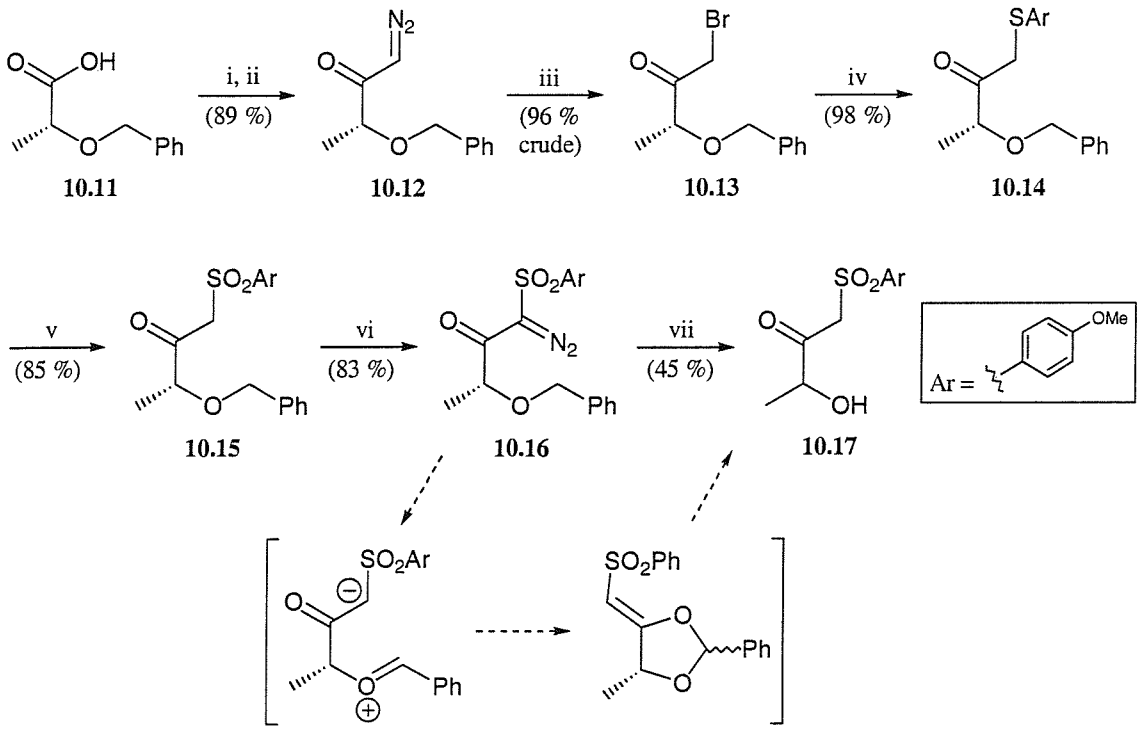


Reagents and Conditions: (i) Oxalyl chloride, DMF (cat), CH_2Cl_2; (ii) $TMSCHN_2$, THF/MeCN (1:1); (iii) HBr, AcOH; (iv) HBr (aq), Et_2O; (v) K_2CO_3, MeOH.

Coupling between crude bromide **10.7** and 4-methoxybenzenethiol, in the presence of potassium carbonate, was subsequently attempted. Surprisingly, we observed a multi-component mixture for this relatively 'simple' transformation. Control experiments showed α-bromo-ketone **10.7** readily reacted with K_2CO_3 in methanol to give a mixture of hydroxyacetal **10.10** and α-methoxy-ketone **10.9** in 63 % and 14 % yields, respectively. Further studies into the use of milder bases suggested sodium bicarbonate was a suitable replacement although with limited material available, due to the instability of the diazo and bromo intermediates in this series, we began to investigate other derivatives.

Chiral bromoketone **10.13** was prepared following the procedure devised for the synthesis of **10.7** (Scheme 10.2). This α-methyl derivative appeared more stable than its unsubstituted analogue **10.7**, tolerating potassium carbonate during the coupling with *p*-methoxybenzene thiol to provide sulphide **10.14** in excellent yield. Oxidation with *m*-CPBA and a standard diazo-transfer with *p*-carboxybenzenesulfonyl azide in acetonitrile[70] provided α-diazo-β-ketosulphone **10.16**.

Scheme 10.2

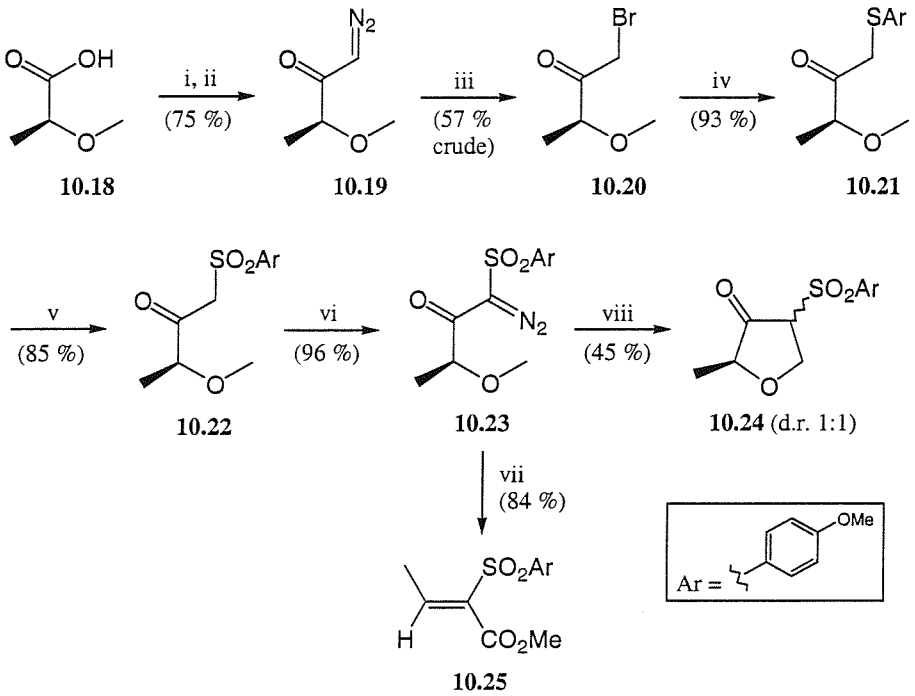


Reagents and Conditions: (i) Oxalyl chloride, DMF (cat), CH_2Cl_2; (ii) $TMSCHN_2$, THF/MeCN (1:1); (iii) HBr (aq), Et_2O; (iv) 4-methoxybenzenethiol, K_2CO_3, MeOH; (v) *m*-CPBA, CH_2Cl_2; (vi) 4-carboxybenzenesulfonyl azide, $^iPr_2EtN$, MeCN; (vii) 2 mol % $Rh_2(OAc)_4$, CH_2Cl_2.

We presumed α-heteroatom activation of the C-H bond and formation of a 5-membered ring system would promote smooth decomposition of diazosulfone **10.16** to the desired furanone derivative. However, when diazo compound **10.16** was treated with a catalytic quantity of dirhodium tetraacetate at room temperature the reaction was slow and after 24 hours gave a multi-component mixture. Following chromatography on silica gel, separation of the major (most polar) spot was eventually achieved and characterised as alcohol **10.17**. Benzaldehyde was also recovered along with an unidentified product isolated as a mixture of diastereoisomers. Further analysis of these diastereomers was abandoned as decomposition to alcohol **10.17** was observed within days standing at room temperature.

The decomposition of diazosulphone **10.16** was investigated using a series of rhodium and copper catalysts at room and elevated temperatures. However, these trials isolated the same components as mentioned above only in slightly varying ratios, with no 1,5 C-H insertion product observed. We postulated that formation of an oxonium ylide (*via* hydride transfer) could subsequently cyclise to form an unstable acetal intermediate (the most likely identity of our unknown mixture of diastereoisomers). Hydrolysis would provide the observed alcohol **10.17** and account for the isolation of benzaldehyde.

Scheme 10.3



Reagents and Conditions: (i) Oxalyl chloride, DMF (cat), DCM; (ii) $TMSCHN_2$, THF/MeCN (1:1); (iii) HBr (aq), Et_2O, 0 °C; (iv) 4-methoxybenzenethiol, K_2CO_3, MeOH; (v) *m*-CPBA, CH_2Cl_2; (vi) 4-carboxybenzenesulfonyl azide, $^iPr_2EtN$, MeCN; (vii) toluene, reflux; (viii) 15 mol % $Rh_2(OAc)_4$, CH_2Cl_2, rt.

Investigations into C-H insertion reactions of α-diazo-sulfone **10.23** began with attempted copper catalysed decompositions (Scheme 10.3). We were surprised to see that **10.23** could be left in methylene chloride at room temperature with 10 mol % copper (II) acetylacetonate for days without reacting! Furthermore, no major changes were observed when refluxing in dichloromethane or even dichloroethane for several hours. However, in refluxing toluene, this copper catalysed reaction showed consumption of diazo-sulfone **10.23** within 20 minutes. The major product isolated was assigned as alkene **10.25** (18:1 mixture of *Z/E* isomers, respectively). Although a mechanism for this transformation is unclear we suspected acyl bond migration had occurred to form a ketene intermediate (Wolff rearrangement) that was subsequently trapped by water/methoxide. Suspicions that thermal induced 'free' carbene decomposition was responsible were confirmed following a control experiment where absence of a metal catalyst, in refluxing toluene, provided alkene **10.25** in good yield.

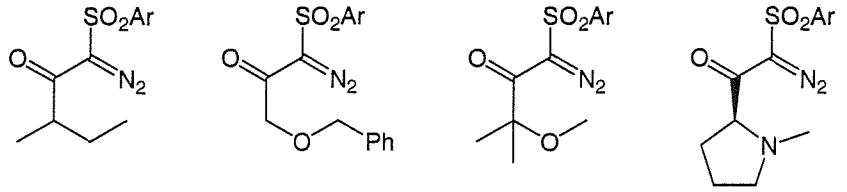
A rhodium-catalysed reaction of **10.23** in methylene chloride at room temperature for 3 days was finally successful in providing the desired furanone product **10.24** albeit as an approximate 1:1 mixture of diastereoisomers (^{1}H-NMR) with significant quantities of alkene **10.25** and alcohol **10.17** present.

10.3 Conclusions and Further Work

Unfortunately, synthesis of the required furanones did not proceed efficiently *via* the proposed C-H insertion approach. Furthermore, the mechanistic issues concerning the products isolated following diazo decomposition are still unclear.

Monteiro has reported that C-H insertion of α-diazo-β-keto-sulfones into a variety of alkyl side chains affords α-sulfonyl cyclopentanones in good yields.[246] We hoped that introduction of the ether functionality would, if anything, aid 1,5 insertion through activation of the adjacent C-H bond. However, this is clearly not the case and we have no conclusive evidence to explain why little to no furanone inserted products were observed, although stabilisation of an intermediate cation resulting from a hydride transfer to the carbene centre is likely to play a part.

Figure 10.3 Possible diazo-substrates for further decomposition analysis



10.26 **10.27** **10.28** **10.29**

The fact that these insertions were unsuccessful is interesting in its own right. Further understanding of the mechanism may be gained if the decomposition pathways of more diverse α-diazo-β-keto-sulfones are examined. Possibilities include: a substrate similar to that investigated by Monteiro **10.26**, one with no α-substitution **10.27**, one with no α-hydrogens **10.28** and finally **10.29**, a N-methyl-L-proline derived diazo sulphone in an attempt to form a bicyclic ring system.

Chapter 11

Concluding Remarks

The following chapter reviews the rhodium-catalysed C-H insertion approach towards furofuran natural products and their structural analogues. Our two main synthetic strategies for the construction of the *endo,exo*-furofuranone framework are summarised, in addition to a brief discussion on the selectivity of these C-H insertion reactions and the opportunities for future work in this area.

11.1 The Furofuran(one) Approaches Summarised

Initial studies into diazo-transfer reactions on a variety of γ-butyrolactones concluded that sacrificial activation at the lactone transfer centre represented the most effective approach towards the synthesis of α-diazo-lactones. This, together with the highly efficient and diastereoselective C-H insertion reaction, provided a powerful methodology in the preparation of the *endo,exo*-furofuranone bicyclic core, ultimately resulting in the racemic synthesis of two unsymmetrically substituted furofuran lignans, (±)-fargesin and (±)-epimagnolin A. These and a number of other furofuranone derivatives, all successfully prepared from [2+2] cycloadducts, are summarised in Figure 11.1.

Investigations into alternative routes for the enantioselective synthesis of furofuran(ones) highlighted 1-acetyl-4-aryl-3-oxabicyclo[3.1.0]hexanes as key intermediates. Optimisation of alcohol additions to cyclopropane **7.35** under Lewis acidic conditions with the development of a highly effective diazo-transfer protocol (forming triflyl azide under phase-transfer conditions) provided the pivotal α-diazo-γ-butyrolactones. This strategy was successful in the concise and diastereoselective synthesis of a series of *endo,exo*-furofuranones. A novel asymmetric approach towards the *endo,exo*-furofuran lignans was also achieved when an enantiomerically enriched benzylic alcohol was employed. A significant contribution to the success of these total syntheses was the introduction of methanesulfonyl-protected phenols to increase the acid stability of several key intermediates. Furthermore, the convergent nature of this cyclopropane ring-opening approach provided opportunities to assemble some diverse structural furofuranone analogues. A summary of this synthetic strategy is summarised in Figure 11.2.

Figure 11.1 Strategy 1: Synthesis of Furofuran Natural Products and Furofuranone Analogues *via* Cyclobutanone Chemistry

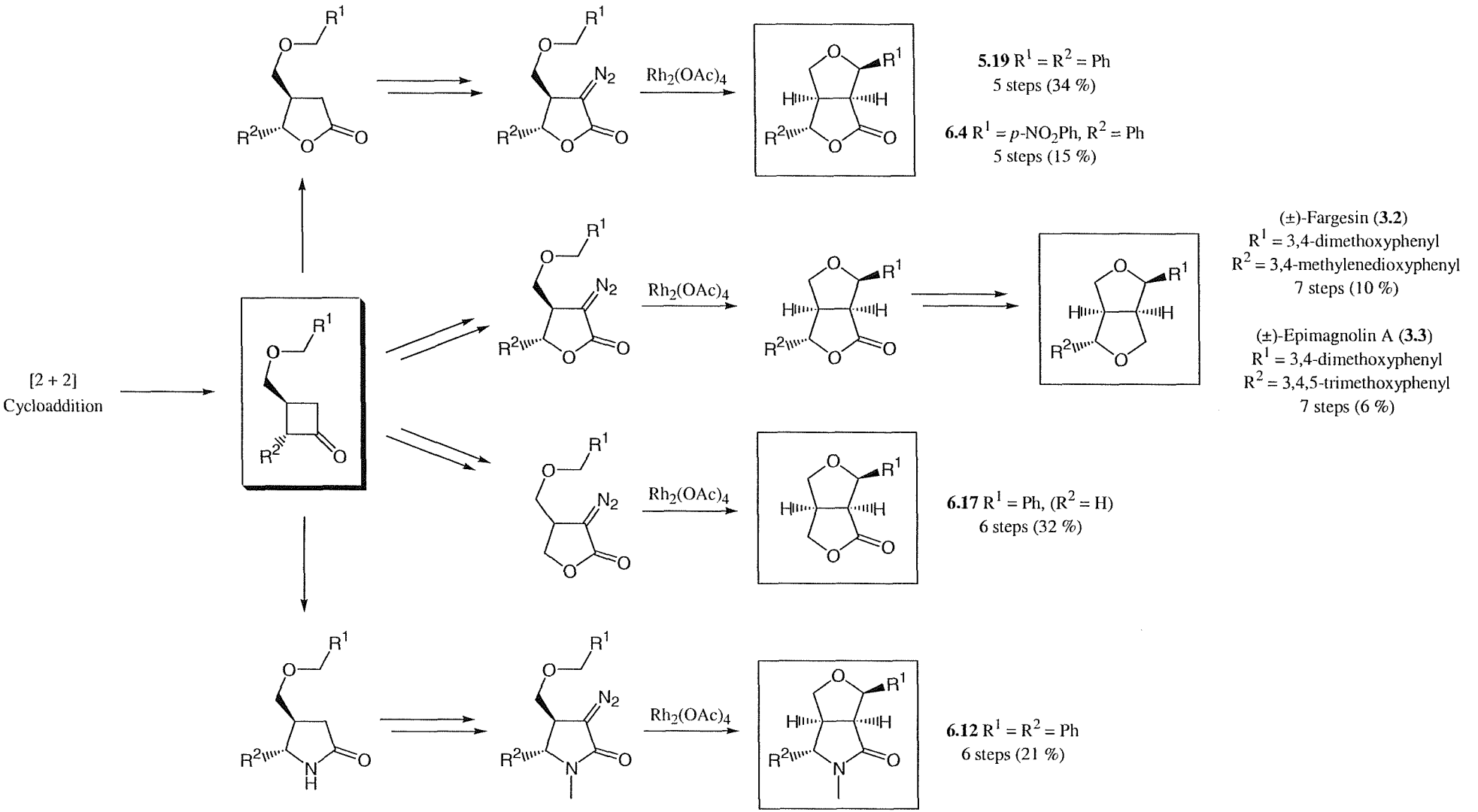
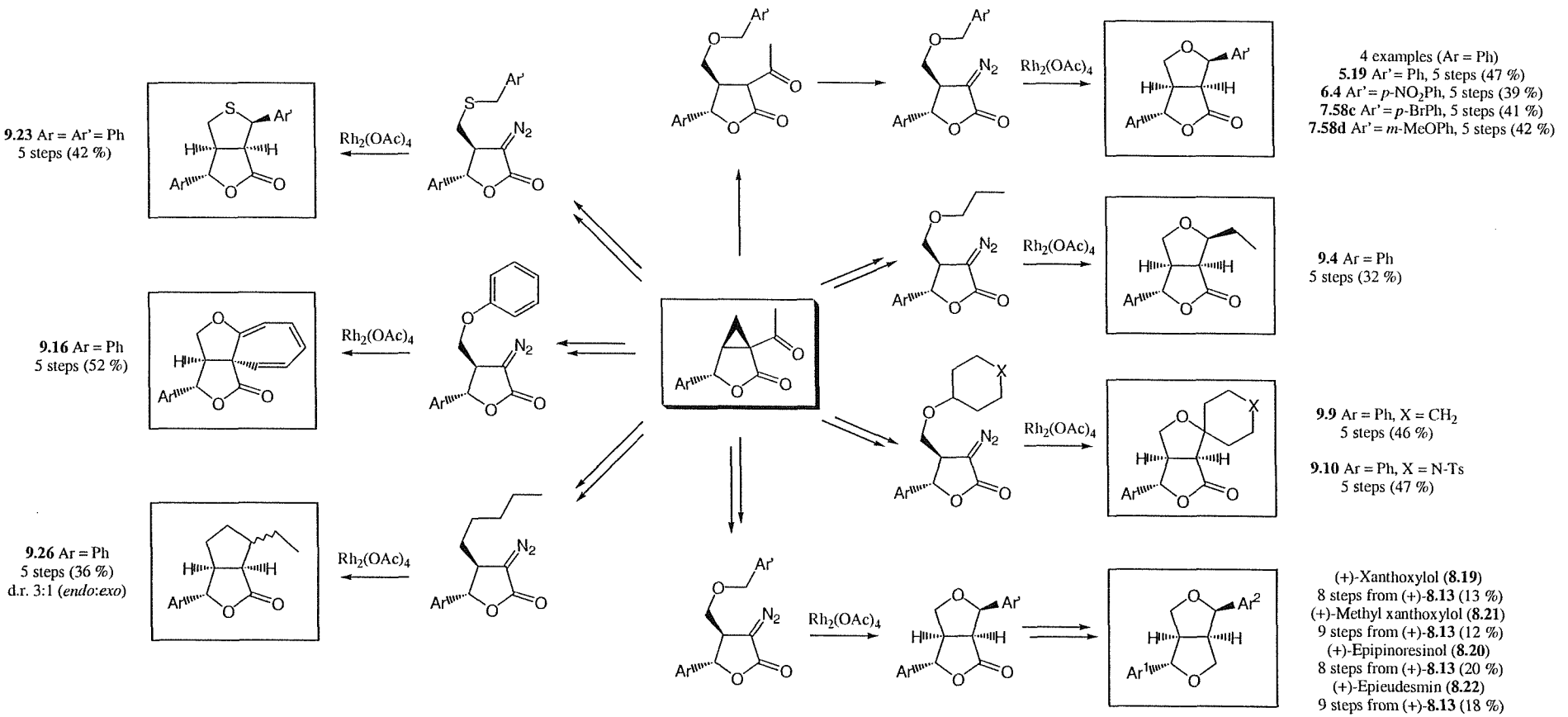


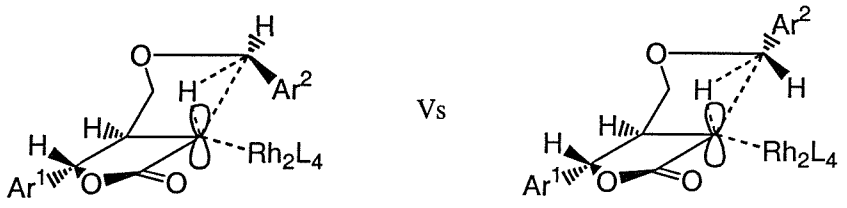
Figure 11.2 Strategy 2: Synthesis of Furofuran Natural Products and Furofuranone Analogues *via* Cyclopropane Ring-Openings



11.2 Attempts to Rationalise the Diastereoselectivity of the C-H Insertion Reaction

During our investigations, the majority of C-H insertion reactions on diazo-lactone substrates proceeded with very high diastereoselectivity. This is most pronounced with the 2,6-diaryl furofuranone analogues where carbenoid cyclisation to close the C1-C2 σ-bond exclusively formed the *endo,exo*-isomer. Using Doyle's proposed mechanism, two possible transition states for insertion into the diastereotopic methylene group have been proposed (Figure 11.3). On initial inspection the conformation established in the transition state of product **11.1** appears disfavoured as the aromatic substituent is directed over the pre-existing lactone.

Figure 11.3 Pseudo-transition states for insertion products using the Doyle model



11.1 *Endo* selectivity

11.2 *Exo* selectivity

If one considers a 3-D model physically incorporating a co-ordinated rhodium complex a different perspective may be gained. Two pseudo-transition states for the dirhodium (II) tetraacetate catalysed C-H insertion reaction of diazo-lactone **5.18** are illustrated in appendix 1. Although only a crude representation (*e.g.* the Rh-Rh bond length and Rh-C co-ordination distances are unknown) they still provide strong visual evidence to support *endo*-selectivity. Despite this favoured conformation placing the aryl group over the lactone core, this results in minimising any unfavourable steric interactions with the dirhodium complex. On the other hand, having the aryl substituent orientated on the *exo*-face leads to severe steric clash with the catalyst. Unfortunately, these models break down when attempting to rationalise the outcome for thermal C-H insertion reactions which, although not completely selective, also show strong preference for *endo,exo*-furofuranone formation.

There are some examples in this thesis where complete *endo*-selectivity upon rhodium-mediated C-H insertion is not observed. For example, the gem-dimethyl substituted diazo-lactone **6.18** undergoes C-H insertion to provide a mixture of *exo*- and *endo*-isomers. We speculate this may be the result of substantial changes in lactone ring conformation or steric interactions with the *endo* methyl group in the transition state. Comparison with C-H insertion into the methylenes of diazo-lactone substrates **9.3** and

9.25 highlight that α-heteroatom activation also plays an important role in the diastereoselective outcome of these reactions. We postulate that if the lone pair of the heteroatom activates the C-H bond undergoing insertion this may impart a conformational restriction on the transition state, therefore, influencing the diastereoselectivity.

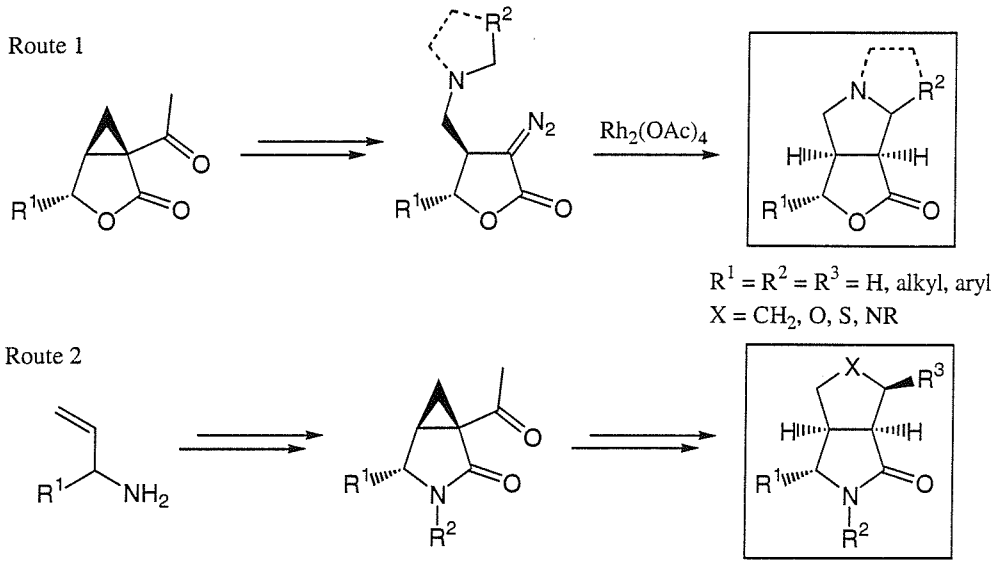
All these theories are extremely speculative and further work is needed to firmly establish the effects that govern the diastereoselctivity of C-H insertion reactions with our α-diazo-lactone substrates.

11.3 Further Work

Inspection of the initial research aims reveal significant progress has been made towards determining the scope of the carbenoid insertion in the construction of furofuranone derivatives. Unfortunately, factors responsible for the high diastereoselectivities observed in the majority of our rhodium catalysed insertion reactions of diazo-lactones still remain unclear. Further investigations are required to determine how the selectivity of the insertion reaction is effected upon changing the ligands attached to the rhodium centre, or even the metal itself.

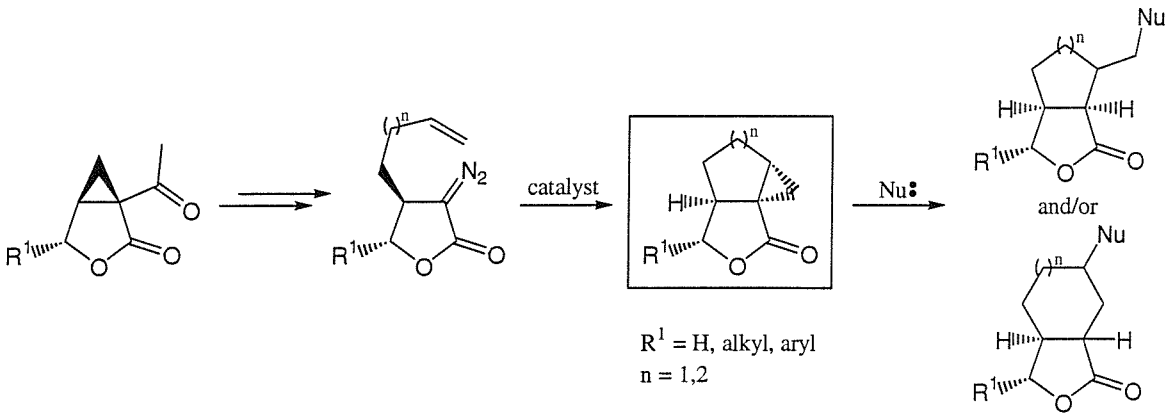
Introduction of the new cyclopropane ring-opening strategy has resulted in ever expanding possibilities for investigation. Certainly, the majority of future work will focus on the synthesis and subsequent reactions of these novel cyclopropane intermediates. With the number of research opportunities expanding in this area it is not possible to discuss them all. Therefore, the following section attempts to highlight those considered to be the most synthetically profitable. For example, the formation of novel aza-furofuranone templates provides a suitable handle for further functionalisation and is, therefore, a particularly attractive concept. Two main routes towards their synthesis may be considered; a) opening of a cyclopropane intermediate with amines b) direct formation of aza-cyclopropanes (Figure 11.4).

Figure 11.4 Formation of aza-analogues



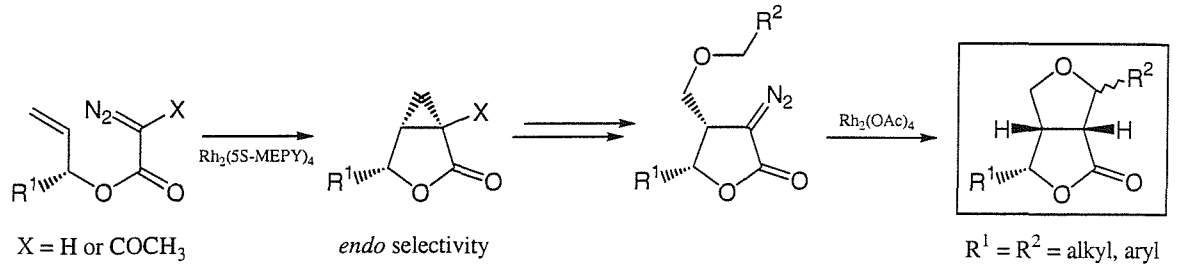
Another interesting area of investigation involves conducting a series of experiments to determine how the metal and ligands influence the competition between C-H insertion and cyclopropanation reactions in our α-diazo-lactone substrates (Figure 11.5). Furthermore, if intramolecular cyclopropanation prevails then additional functionalisation *via* a second cyclopropane opening may be attempted.

Figure 11.5 Carbenoid mediated intramolecular cyclopropanation



Chiral dirhodium (II) carboxamides have the amazing ability to react selectively with individual enantiomers of secondary allylic diazoacetates.[247] Martin and co-workers[248] describe the enhanced diastereoselectivity resulting from the configurational match between a chiral substrate and chiral catalyst. This methodology could be exploited in the synthesis of an *endo*-cyclopropane derivative, therefore allowing us to examine the selectivity of C-H insertion with a *cis*- C4-C5 substituted diazo-lactone (Figure 11.6).

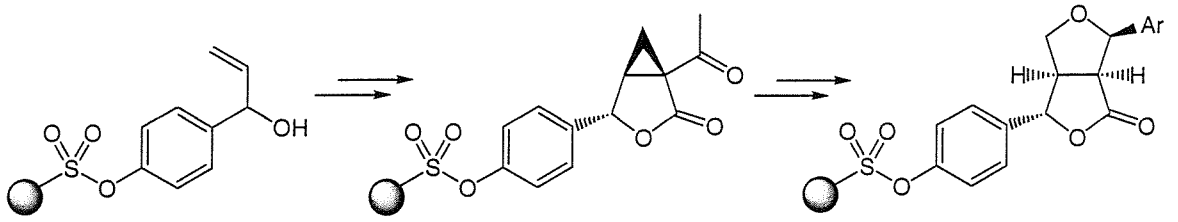
Figure 11.6 Opening of a *cis*-cyclopropane intermediate and C-H insertion



X = H or $COCH_3$ *endo* selectivity $R^1 = R^2$ = alkyl, aryl

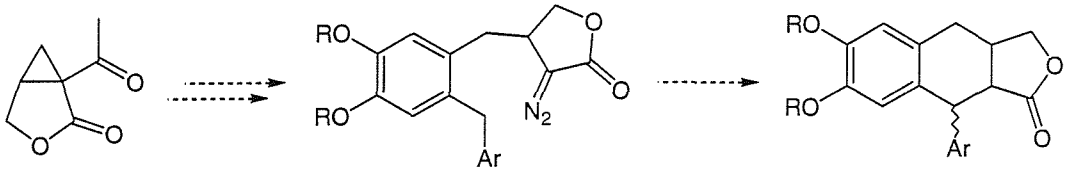
Successful use of a methanesulfonyl-protected phenol in the asymmetric synthesis of furofuran lignans led to questioning whether this moiety could be incorporated as a linker and immobilised on a resin to enable the solid-phase synthesis of furofuranone scaffolds (Figure 11.7).

Figure 11.7 A solid-phase approach to furofuranone derivatives



The ability to access α-diazo-lactones *via* cyclopropane intermediates may also prove useful in the synthesis of other natural products. For example, a C-H insertion to form a 6-membered ring could be utilised in the preparation of the podophyllin class of lignan natural products (Figure 11.8).

Figure 11.8 C-H insertion approach to the podophyllins



The possible scope for investigation has evolved into diverse new areas of research and hopefully some of these objectives will be examined, in due course, within the Brown group.

Chapter 12

Experimental Section

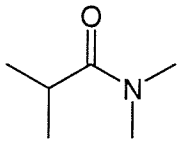
12.1 General Experimental

All air and/or moisture sensitive reactions were carried out under an inert atmosphere, in oven-dried glassware. "Brine" refers to a saturated aqueous solution of sodium chloride. Next to known compounds CAS registry numbers are written in parenthesis. Dichloromethane and dichloroethane were dried by distillation from CaH_2 and THF was distilled from Na/benzophenone prior to use. Where appropriate, all other solvents and reagents were purified according to standard methods.[249] Reactions were monitored by TLC using glass-backed plates coated with silica gel 60 containing a fluorescence indicator active at 254 nm; the chromatograms were visualised under UV light (254 nm) and by staining with, most commonly, 20 % phosphomolybdic acid in ethanol, cerium sulphate/ammonium molybdate in 2M H_2SO_4 (aq) or 10% aqueous $KMnO_4$. Flash column chromatography was performed with 40-63 μm silica gel (Merck) and column dimensions are quoted in cm (width x height).

^{1}H-NMR and ^{13}C-NMR were recorded on Bruker AM250, Bruker AC300, Bruker AM300 or Bruker DPX400 spectrometers in deuterated chloroform ($CDCl_3$) with chloroform (δ 7.26 ppm ^{1}H, δ 77.5 ppm ^{13}C) as the internal standard. IR spectra are reported in wavenumbers (cm^{-1}) and were collected on a) Nicolet Impact 400 as neat films or when fitted with a Thunderdome ATR sampling platform as solids or neat liquids b) Mattson Satellite fitted with a Specac Golden Gate ATR sampling platform as solids or neat liquids. Melting points were obtained in open capillary tubes and are uncorrected. Low-resolution mass spectra were obtained on a Fisons VG platform single quadropole mass spectrometer in either chemical ionisation or electron impact ionisation mode or a Micromass platform mass analyser with an electrospray ion source. Analytical HPLC was performed on a HP1090 Series II LC system using a reverse phase Phenomenex Sphereclone C_{18} column (4.6 x 250 mm, 5 μm) with 254, 230 and 215 nm detection, eluting with $MeCN/H_2O$ mixtures. Chiral analytical HPLC was performed on a HP1050 LC system using a normal phase Ciralcel OD-H column (4.6 x 250 mm, 5 μm) with 230 nm detection, eluting with IPA/hexane mixtures. Preparative normal phase HPLC was performed on a Perkin-Elmer Series 3B LC system using a normal phase Phenomenex Luna silica column (21.2 x 250 mm, 10 μm), eluting with either Et_2O/hexane or IPA/hexane mixtures.

12.2 Experimental Details

N,N,2-Trimethylpropanamide (21678-37-5) (5.1)



5.1

$C_6H_{13}NO$

m.w. = 115.18 g/mol

Colourless oil

A solution of isobutyryl chloride (5.24 mL, 50 mmol) in CH_2Cl_2 (50 mL) was treated with a solution of dimethylamine hydrochloride (9.78 g, 120 mmol) in NaOH (aq) (5.2 g of NaOH in 30 mL of H_2O) by dropwise addition over 10 min. The reaction was left stirring for 18 h and poured onto brine (30 mL). The organic layer was separated and the aqueous fully saturated by the addition of sodium chloride before extraction with CH_2Cl_2 (2 x 30 mL). The combined organic layers were washed with 2N HCl (aq) (30 mL) and brine (30 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield a pale yellow oil (6.7 g). Purification was accomplished by distillation under reduced pressure to give the title compound **5.1** (4.6 g, 40 mmol, 80 %) as a colourless oil. Spectroscopic details were consistent with those observed in the literature.[166]

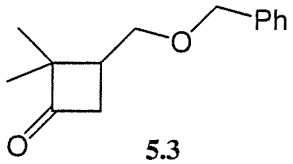
BP 33-34 °C (0.4 mbar).

FT-IR (neat) ν_{max} 2968 w, 1641 s, 1398 m, 1130 m, 1100 m cm^{-1}.

^{1}H NMR (300 MHz) δ 3.03 (3H, s, -NC**H**$_3$), 2.92 (3H, s, -NC**H**$_3$), 2.80 (1H, sept, J = 6.6 Hz, -C**H**-), 1.09 (6H, d, J = 6.6 Hz, -CH(C**H**$_3$)$_2$).

^{13}C NMR (75 MHz) δ 177.1 (**C**O), 37.2 (-N**C**H$_3$), 35.7 (-N**C**H$_3$), 30.3 (-**C**H-), 19.4 (-C(**C**H$_3$)$_2$).

3-[(Benzyloxy)methyl]-2,2-dimethyl-1-cyclobutanone (5.3)



5.3

$C_{14}H_{18}O_2$

m.w. = 218.30 g/mol

Pale yellow oil

The title compound was prepared according to the general method described by Ghosez *et al.*[167] Thus, to a solution of *N,N*,2-trimethylpropanamide (**5.1**) (1.0 g, 8.7 mmol) in CH_2Cl_2 (15 mL) at –25 °C (internal, CO_2(s)/acetone) was added freshly distilled Tf_2O (1.8 mL, 10.4 mmol) at such a rate that the temperature did not rise above –20 °C. The colourless homogeneous reaction mixture was stirred at –20 °C for 10 min before addition of a mixture of 2,6-di-*tert*-butylpyridine (2.3 mL, 10.4 mmol) and allylbenzylether[165] (2.7

mL, 17.4 mmol) in CH_2Cl_2 (15 mL) over a period of 10 min. The reaction was then allowed to warm to room temperature and stirred for 18 h (the formation of the cyclic iminium species was monitored by IR; υ_{max} 1728 cm^{-1}). The mixture was treated with sat. $NaHCO_3$ (aq) (30 mL) and warmed to reflux for 20 min. After cooling the mixture was diluted with CH_2Cl_2 (20 mL), the organic layer was separated and the aqueous extracted with CH_2Cl_2 (3 x 30 mL). The combined extracts were washed with water (40 mL) and brine (40 mL), dried with $MgSO_4$, and concentrated *in vacuo* to yield a yellow oil (7.4 g). Purification was accomplished by flash chromatography on silica gel (4.3 x 11) eluting with Et_2O/hexane (1:49 then 1:4) to give the title compound **5.3** (1.16 g, 5.3 mmol, 61 %) as a pale yellow oil.

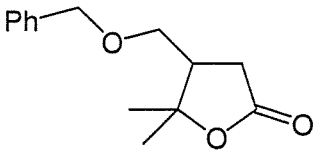
FT-IR (neat) ν_{max} 2964 m, 2930 m, 2869 m, 1785 s, 1459 m, 1098 s, 1070 s cm^{-1}.

^{1}H NMR (300 MHz) δ 7.41-7.23 (5H, m, PhH), 4.55 (2H, s, $PhCH_2$-), 3.60 (2H, m, -CH_2OBn), 3.15 (1H, dd, *J* = 17.9, 9.4 Hz, -COCHH-), 2.79 (1H, dd, *J* = 17.9, 7.0 Hz, -COCHH-), 2.46-2.34 (1H, m, -CH-), 1.25 (3H, s, -CH_3), 1.14 (3H, s, -CH_3).

^{13}C NMR (75 MHz) δ 214.6 (CO), 138.3 (C_{ar}), 128.6 (CH_{ar}), 127.9 (CH_{ar}), 127.8 (CH_{ar}), 73.4 (-CH_2OBn), 70.7 (-CH_2Ph), 61.0 (-CMe_2-), 45.8 (-CH-), 35.8 (-$COCH_2$-), 24.2 (-CH_3) and 16.9 (-CH_3).

LRMS (CI, NH_3) *m/z* (relative intensity) 219 (1) $[M+H]^+$, 236 (2) $[M+NH_4]^+$, 91 (100) $[PhCH_2]^+$, 127 (11) $[M-PhCH_2]^+$.

4-[(Benzyloxy)methyl]-5,5-dimethyltetrahydro-2-furanone (5.4)



5.4

$C_{14}H_{18}O_3$

m.w. = 234.28 g/mol

Colourless oil

The title compound was prepared by the general method described by Corey *et al.*[169] Thus, to a solution of cyclobutanone **5.3** (200 mg, 0.90 mmol) in glacial acetic acid (3 mL) at 0 °C (ice bath) was added a 30 % aqueous solution of hydrogen peroxide (0.31 mL, 2.8 mmol) and the reaction was maintained at 4 °C for 18 h. The reaction mixture was then diluted with Et_2O (15 mL) and quenched with sat. $NaHCO_3$ (aq) (15 mL) before extraction with Et_2O (3 x 20 mL). The combined extracts were washed with water (30 mL) and brine (30 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield a colourless oil (220 mg). Purification was accomplished by flash chromatography on silica gel (2.4 x

9) eluting with Et_2O/hexane (2:1) to give the title compound **5.4** (170 mg, 0.73 mmol, 81 %) as a colourless oil.

FT-IR (neat) ν_{max} 2981 m, 2873 m, 1774 s, 1379 m, 1276 s, 1138 s, 1087 s cm^{-1}.

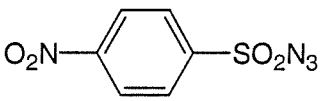
^{1}H NMR (300 MHz) δ 7.40-7.23 (5H, m, Ph**H**), 4.51 (2H, s, -C**H**$_2$Ph), 3.53-3.46 (2H, m, -C**H**$_2$OBn), 2.69-2.51 (2H, m, -COC**H**$_2$-), 2.46-2.34 (1H, m, -COCH$_2$C**H**-), 1.51 (3H, s, -C**H**$_3$), 1.32 (3H, s, -C**H**$_3$).

^{13}C NMR (75 MHz) δ 175.5 (**C**O), 137.8 (**C**$_{ar}$), 128.7 (**C**H$_{ar}$), 128.0 (**C**H$_{ar}$), 127.8 (**C**H$_{ar}$), 86.2 (-**C**Me$_2$), 73.5 (-**C**H$_2$Ph), 69.2 (-**C**H$_2$OBn), 44.9 (-**C**H-), 32.9 (-COCH$_2$-), 28.9 (-**C**H$_3$), 22.1 (-**C**H$_3$).

LRMS (CI, NH_3) *m/z* (relative intensity) 235 (60) $[M+H]^+$, 252 (100) $[M+NH_4]^+$.

HRMS (ES +ve) Calcd for $C_{14}H_{18}O_3Na$ 257.1148, found 257.1147.

4-Nitrobenzenesulphonyl azide (4547-62-0) (2.31)



2.31

$C_6H_4N_4SO_4$

m.w. = 228.18 g/mol

Pale brown needles

The title compound was prepared according to the method of Baum *et al.*[87] Thus, to a brown suspension of 4-nitrobenzenesulphonyl chloride (10 g, 45.1 mmol) containing tetra-*n*-butylammonium bromide (20 mg, cat.) in CH_2Cl_2 (80 mL) at 0 °C (ice/salt) was added a solution of NaN_3 (3.2 g, 49.6 mmol) in water (8 mL) dropwise over 20 min. The reaction mixture was allowed to warm slowly to room temperature and then left stirring for 18 h. The organic layer was separated and washed with water (2 x 30 mL) and brine (2 x 30 mL), dried with $MgSO_4$ and concentrated *in vacuo* (below 25 °C) until the solution appeared cloudy. A few drops of hexane were then added and the suspension left on ice for 30 min. The resulting precipitate was collected and washed with ice-cooled hexane to give the title compound (4.77 g, 20.9 mmol, 46 %) as tan coloured needles. Further recrystallisation of the crude filtrate provided the title compound (1.29 g, 5.7 mmol, 13 %) as a brown solid - overall yield (6.06 g, 26.6 mmol, 59 %).

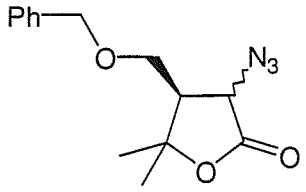
MP 101-102 °C CH_2Cl_2/hexane (lit. 101-102 °C[250]).

FT-IR (neat) ν_{max} 2142 s, 1529 s, 1376 s, 1350 s, 1177 s, 1159 s cm^{-1}.

^{1}H NMR (300 MHz) δ 8.48 (2H, d, J = 8.9 Hz, Ph**H**), 8.18 (2H, d, J = 8.9 Hz, Ph**H**).

^{13}C NMR (75 MHz) δ 143.9 (**C**$_{ar}$), 129.1 (**C**H$_{ar}$), 125.1 (**C**H$_{ar}$), (no **C**$_{ar}$ observed).

3-Azido-4-[(benzyloxy)methyl]-5,5-dimethyltetrahydro-2-furanone (5.8)



5.8

$C_{14}H_{17}N_3O_3$

m.w. = 275.31 g/mol

Colourless oil

LiHMDS (0.69 mL of a 1.0 M solution in THF, 0.69 mmol) was dissolved in THF (4 mL) and cooled to –78 °C (CO_2(s)/acetone). A pre-cooled solution of lactone **5.4** (155 mg, 0.66 mmol) in THF (3 mL) was added *via* a cannula and the reaction mixture stirred at –78 °C. After 1 h, a pre-cooled solution of *p*-nitrobenzenesulfonyl azide (157 mg, 0.69 mmol) in THF (3 mL) was added *via* a cannula giving an initial dark orange colouration that quickly returned to the original pale yellow colour. The reaction mixture was left stirring for 10 min before acetyl chloride (0.19 mL, 2.64 mmol) was added dropwise and the reaction allowed to warm slowly to room temperature over 90 min. The mixture was then diluted with Et_2O (30 mL) and washed with water (30 mL) and brine (30 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield a pale yellow oil (110 mg). Crude ^{1}H-NMR and TLC analysis showed this crude compound to be mainly starting lactone **5.4** and no attempts were made to isolate any of the possible triazene **5.6** products. Thus, to a solution of crude triazene **5.6** (110 mg) in THF (5 mL) was added DMAP (32 mg, 0.26 mmol) and the reaction maintained at 4 °C for 18 h. The solvent was removed and the crude material was purified by column chromatography on silica gel (2.2 x 6) eluting with Et_2O/hexane (1:4) to yield the title compound **5.8** (17 mg, 0.06 mmol, 9 %) as a colourless oil along with recovered starting material **5.4** (9 mg, 0.04 mmol, 6 %) as a colourless oil. Data for **5.8**.

FT-IR (neat) ν_{max} 2117 s, 1779 s, 1379 m, 1259 m, 1144 s, 1081 s cm^{-1}.

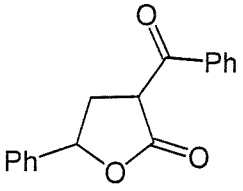
^{1}H NMR (300 MHz) δ 7.43-7.25 (5H, m, Ph**H**), 4.58 (1H, d, *J* = 11.9 Hz, PhC**H**H-), 4.52 (1H, d, *J* = 11.9 Hz, PhCH**H**-), 4.17 (1H, d, *J* = 11.4 Hz, -C**H**N_3), 3.70-3.55 (2H, m, -C**H**$_2$OBn), 2.41 (1H, ddd, *J* = 11.4, 7.9, 4.5 Hz, N_3CHC**H**-), 1.53 (3H, s, -C**H**$_3$), 1.33 (3H, s, -C**H**$_3$).

^{13}C NMR (75 MHz) δ 171.9 (**C**O), 137.4 (**C**$_{ar}$), 128.7 (**C**H$_{ar}$), 128.2 (**C**H$_{ar}$), 127.9 (**C**H$_{ar}$), 84.9 (-**C**Me$_2$), 73.7 (PhCH$_2$-), 66.9 (-**C**H$_2$OBn), 59.9 (-**C**HN_3), 51.1 (N_3**C**HCH-), 29.1 (-**C**H$_3$), 23.1 (-**C**H$_3$).

LRMS (CI, NH_3) *m/z* (relative intensity) 293 (50) $[M+NH_4]^+$, 248 (40) $[M+H(-N_2)]^+$, 106 (100).

HRMS (ES +ve) Calcd for $C_{14}H_{17}N_3O_3Na$ 298.1162, found 298.1162.

3-Benzoyl-5-phenyltetrahydro-2-furanone (5.10a)



5.10a

$C_{17}H_{14}O_3$

m.w. = 266.30 g/mol

White solid

The title compound was prepared according to the general method described by Taber *et al.*[75] Thus, NaH (1.53 g of a 60 % dispersion in mineral oil, 40.0 mmol) was washed with dry hexanes (2 x 10 mL) and then suspended in DME (freshly distilled over CaH_2, 25 mL). To this suspension at 0 °C (ice/salt) was added γ-phenyl-γ-butyrolactone (**5.9**) (1.40 mL, 10.0 mmol) in DME (8 mL). After 10 minutes at 0 °C, methyl benzoate (1.87 mL, 15.0 mmol) in DME (8 mL) was added dropwise. After the addition of four drops of methanol the mixture was allowed to warm to room temperature and left stirring for 4 h. The reaction mixture was then acidified to pH = 4 with 1N HCl (aq) and diluted with Et_2O (20 mL). The yellow organic layer was separated and the aqueous extracted with Et_2O (3 x 40 mL), dried with $MgSO_4$ and concentrated *in vacuo* to give a yellow oil that solidified on standing. This crude product was treated with ice-cold Et_2O and filtered to yield the product as a white powdery solid (0.87 g, 3.3 mmol, 33 %). The filtrate was concentrated *in vacuo* and purified by flash chromatography on silica (3.3 x 9) eluting with Et_2O/hexane (3:2) to provide the title compound **5.10a** (0.53 g, 2.1 mmol, 21 %) as an off-white solid (1:1 mixture of diastereoisomers) - overall yield of **5.10a** (1.40 g, 5.3 mmol, 53 %).

MP 95-97 °C (Et_2O/hexane).

FT-IR (neat) ν_{max} 1765 s, 1686 s, 1177 m, 1162 s cm^{-1}.

Both diastereoisomers reported for NMR analysis.

^{1}H NMR (300 MHz) δ 8.15 (2H, dd, *J* = 7.4, 1.5 Hz, PhH) and 8.08 (2H, dd, *J* = 7.4, 1.5 Hz, PhH), 7.70-7.59 (2 x 1H, m, PhH), 7.57–7.48 (2 x 2H, m, PhH), 7.45-7.32 (2 x 5H, m, PhH), 5.80 (1H, dd, *J* = 8.5, 7.0 Hz, PhCH-) and 5.57 (1H, dd, *J* = 10.4, 6.5 Hz, PhCH-), 4.83 (1H, dd, *J* = 10.9, 8.9 Hz, -COCH-) and 4.75 (1H, dd, *J* = 8.9, 3.0 Hz, -COCH-), 3.21 (1H, ddd, *J* = 10.4, 6.9, 3.5 Hz, -CHH-) and 2.82 (1H, ddd, *J* = 13.4, 8.9, 6.5 Hz, -CHH-), 3.03 (1H, dt, *J* = 13.4, 8.0 Hz, -CHH-) and 2.48 (1H, dt, *J* = 12.9, 8.4 Hz, -CHH-).

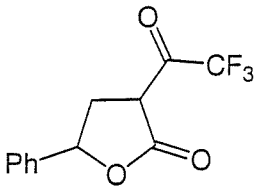
^{13}C NMR (75 MHz) δ 193.0 and 192.9 (CO_{ket}), 172.3 and 172.2 (CO_{lac}), 139.1 and 138.5 (C_{ar}), 136.0 and 135.1 (C_{ar}), 134.4 and 134.2 (CH_{ar}), 129.8

and 129.6 ($\mathbf{C}H_{ar}$), 129.0 and 128.8 ($\mathbf{C}H_{ar}$), 126.1 and 125.6 ($\mathbf{C}H_{ar}$), 81.2 and 80.3 (Ph**C**H-), 49.9 and 49.4 (-CO**C**H-), 35.0 and 34.2 (-$\mathbf{C}H_2$-).

LRMS (AP +ve) *m/z* (relative intensity) 267 (100) $[M+H]^+$.

CHN Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30. Found: C, 76.67; H, 5.29.

5-Phenyl-3-(2,2,2,-trifluoroacetyl)tetrahydro-2-furanone (5.10b)



5.10b

$C_{12}H_9O_3F_3$

m.w. = 258.20 g/mol

White solid

The title compound was prepared according to the general method described by Taber *et al.*[75] Thus, NaH (0.32 g of a 60 % dispersion in mineral oil, 8.0 mmol) was washed with dry hexane (2 x 5 mL) and then suspended in DME (freshly distilled over CaH_2, 6 mL). To this suspension at 0 °C (ice/salt) was added γ-phenyl-γ-butyrolactone (**5.9**) (0.28 mL, 2.0 mmol) in DME (1 mL). After 10 min at 0 °C, 2,2,2-trifluoroethyl trifluoroacetate (0.40 mL, 3.0 mmol) in DME (1 mL) was added dropwise and the mixture was allowed to warm to room temperature and left stirring for 3 h. The reaction mixture was then acidified to pH = 4 with 1N HCl (aq) and diluted with Et_2O (10 mL). The yellow organic layer was separated and the aqueous extracted with Et_2O (3 x 25 mL), dried with $MgSO_4$ and concentrated *in vacuo* to give a yellow oil (1.48 g) that solidified on standing. Purification was accomplished by flash chromatography on silica gel (3 x 7.5) eluting with Et_2O/hexane (3:7) to yield the title compound **5.10b** (0.44 g, 1.7 mmol, 84 %) as a white powdery solid (approx 3:2 mixture of diastereoisomers).

MP 72-75 °C (Et_2O/hexane).

FT-IR (neat) ν_{max} 1737 s, 1193 s, 1141 s cm^{-1}.

Spectroscopic analysis complicated from diastereoisomers – both reported (* major).

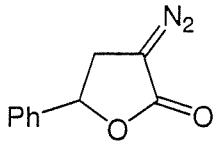
^{1}H NMR (300 MHz) δ 7.48-7.28 (2 x 5H, m, Ph**CH**), 5.78-5.65 (1H, m, -OC**H**-) and 5.44* (1H, dd, *J* = 10.9, 6.0 Hz, -OC**H**-), 3.65-3.51 (2 x 1H, m, -COC**H**-), 3.23 (1H, dd, *J* = 12.4, 8.4 Hz, -C**H**H-), 3.13-2.98 (1H, m, -CH**H**-), 2.87-2.75* (1H, m, -C**H**H-), 2.57* (1H, q, *J* = 11.4 Hz, -CH**H**-).

^{13}C NMR (75 MHz) δ 177.2* and 174.0 ($\mathbf{C}O_{lac}$), 137.5* ($\mathbf{C}_{ar}$), 129.4* ($\mathbf{C}H_{ar}$), 129.2* ($\mathbf{C}H_{ar}$), 129.1 ($\mathbf{C}H_{ar}$), 128.9 ($\mathbf{C}H_{ar}$), 126.2* ($\mathbf{C}H_{ar}$), 125.6 ($\mathbf{C}H_{ar}$),

81.1* and 80.1 (PhCH-), 44.2* and 41.6 (-CH_2-), 33.6* and 32.6 (-COCH-), (no -CF_3 observed).

LRMS (EI) *m/z* (relative intensity) 258 (30) $[M]^{\bullet+}$, 105 (100).

3-Diazo-5-phenyltetrahydro-2-furanone (5.11)



5.11

$C_{10}H_8N_2O_2$

m.w. = 188.19 g/mol

Yellow oil

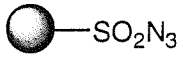
To a solution of trifluoroacetylated lactone **5.10b** (32 mg, 0.12 mmol) in MeCN (1.2 mL) was added di-*iso*-propylethylamine (22 μL, 0.12 mmol) and the mixture stirred at room temperature for 5 min before *p*-nitrobenzenesulfonylazide (33 mg, 0.14 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 18 h, diluted with CH_2Cl_2 (8 mL) and quenched with water (5 mL). The organic phase was separated and the aqueous extracted with CH_2Cl_2 (3 x 8 mL), washed with brine (10 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield a yellow oil. Purification was accomplished by flash chromatography on silica gel (3 x 3) eluting with Et_2O/hexane (3:2) to yield the title compound **5.11** (22 mg, 0.12 mmol, 94 %) as a bright yellow oil.

FT-IR (neat) ν_{max} 2095 s, 1729 s, 1374 m, 1228 m cm^{-1}.

^{1}H NMR (300 MHz) δ 7.46-7.33 (5H, m, Ph**H**), 5.56 (1H, dd, *J* = 8.4, 6.9 Hz, PhC**H**-), 3.75 (1H, dd, *J* = 12.9, 8.9 Hz, -C**H**H-), 3.28 (1H, dd, *J* = 12.9, 6.9 Hz, -CH**H**-).

^{13}C NMR (75 MHz) δ 173.9 (**C**O), 139.4 (**C**$_{ar}$), 129.1 (**C**H$_{ar}$), 129.0 (**C**H$_{ar}$), 125.5 (**C**H$_{ar}$), 78.1 (PhCH-), 31.7 (-**C**H_2-), (no **C**N_2 observed).

Tosyl azide resin (2.32)



2.32

Pale cream resin

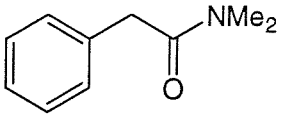
To a suspension of chlorosulfonylated polystyrene (0.8 g, loading 2.56 mmol/g) in 1,4-dioxane (10 mL) and ethanol (0.5 mL) was added a solution of NaN_3 (1.3 g, 20 mmol) in the minimum amount of water. The reaction mixture was agitated under argon at room temperature for 18 h, the resin filtered and washed with water (3 x 20 mL) and CH_2Cl_2 (3 x 30 mL). The resin was then re-subjected to the above reaction conditions for a further 18 h, filtered and washed with water (3 x 30 mL), CH_2Cl_2 (3 x 30 mL), Et_2O (3 x 40 mL)

and dried *in vacuo* to give the title compound (0.79 g) as a pale cream coloured resin (76% conversion from combustion analysis). Spectroscopic details were consistent with those observed in the literature.[88]

FT-IR (resin) ν_{max} 2126 m, 1371 m, 1169 s cm^{-1}.

CHN & S Anal. Found: C, 64.67; H, 5.44; N, 8.62; S, 8.70.

N,N-Dimethyl-2-phenylacetamide (18925-69-4) (5.12)



5.12

$C_{10}H_{13}NO$

m.w. = 163.22 g/mol

White solid

To a solution of phenylacetyl chloride (4.0 mL, 30 mmol) in CH_2Cl_2 (40 mL) at 0 °C (ice/salt bath) was added a solution of dimethylamine hydrochloride (5.87 g, 72 mmol) in NaOH (aq) (3.2 g NaOH in 18 mL of water) by dropwise addition. The reaction mixture was allowed to warm to room temperature and stirred overnight. After dilution with CH_2Cl_2 (40 mL) the reaction mixture was washed sequentially with 2N HCl (aq) (40 mL), sat. $NaHCO_3$ (aq) (40 mL), water (40 mL) and brine (40 mL), dried with $MgSO_4$ and concentrated *in vacuo* to give the title compound **5.12** (4.81 g, 29 mmol, 98 %) as a viscous colourless oil that solidified on standing to a white solid. Spectroscopic details were consistent with those observed in the literature.[175]

MP 37-39 °C (lit.[175] 38-40 °C).

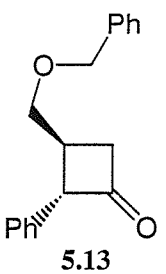
FT-IR (neat) ν_{max} 1628 s, 1496 m, 1394 m, 1117 m cm^{-1}.

^{1}H NMR (300 MHz) δ 7.36-7.22 (5H, m, Ph**H**), 3.73 (2H, s, -C**H**$_2$), 3.00 (3H, s, -C**H**$_3$), 2.98 (3H, s, -C**H**$_3$).

^{13}C NMR (100 MHz) δ 171.4 (**C**O), 135.5 (**C**$_{ar}$), 129.2 (**C**H$_{ar}$), 129.0 (**C**H$_{ar}$), 127.1 (**C**H$_{ar}$), 41.4 (**C**H$_2$), 38.1 (**C**H$_3$), 36.0 (**C**H$_3$).

LRMS (ES +ve) *m/z* (relative intensity) 164 (50) $[M+H]^+$, 186 (15) $[M+Na]^+$, 227 (100) $[M+Na+MeCN]^+$, 349 (25) $[2M+Na]^+$.

(2S*, 3S*)-3-[(Benzyloxy)methyl]-2-phenylcyclobutanone (5.13)



5.13

$C_{18}H_{18}O_2$

m.w. = 266.34 g/mol

Colourless oil

The title compound was prepared according to the method outlined for **5.3**, whereby *N,N*-dimethyl-2-phenylacetamide (**5.12**) (1.63 g, 10.0 mmol) and allylbenzylether[165] (2.3 mL, 15 mmol) were reacted under the conditions described to give the cyclic iminium species; υ_{max} 1734 cm^{-1}. Hydrolysis was effected by treatment with sat. $NaHCO_3$ (aq) at room temperature for 1 h and work-up provided an orange oil (6.2 g). Purification was accomplished by flash chromatography on silica gel (5 x 10) eluting with Et_2O/hexane (1:9 then 1:4) to give the title compound **5.13** (1.73 g, 6.5 mmol, 65 %) as a colourless oil (9:1 mixture of diastereoisomers). NMR data given for the major diastereoisomer.

FT-IR (neat) ν_{max} 3027 w, 2861 m, 1785 s, 1493 m, 1110 s cm^{-1}.

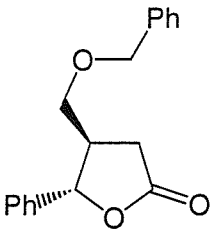
^{1}H NMR (400 MHz) δ 7.48-7.21 (10H, m, PhH), 4.62 (2H, s, $PhCH_2$-), 4.39 (1H, d, J = 7.4 Hz, -CHPh), 3.78 (2H, ABq, J_{A-B} = 5.5 Hz, $-CH_2OBn$), 3.13-3.01 (2H, m, $-COCH_2$-), 2.94-2.81 (1H, m, $-CH_2CH$-).

^{13}C NMR (100 MHz) δ 206.3 (CO), 138.5 (C_{ar}), 136.5 (C_{ar}), 129.1 (CH_{ar}), 128.9 (CH_{ar}), 128.2 (CH_{ar}), 128.1 (CH_{ar}), 127.6 (CH_{ar}), 127.5 (CH_{ar}), 73.7 ($-CH_2OBn$), 72.4 ($-OCH_2Ph$), 66.9 (-CHPh), 47.7 ($-COCH_2$-), 32.8 ($-CH_2CH$-).

LRMS (CI, NH_3) *m/z* (relative intensity) 284 (8) $[M+NH_4]^+$, 91 (100) $[PhCH_2]^+$, 176 (15) $[M+H(-PhCH_2)]^+$.

HRMS (EI) Calcd for $C_{18}H_{18}O_2$ 266.1307, found 266.1303.

(4R*, 5S*)-5-Phenyl-4-[(benzyloxy)methyl]tetrahydro-2-furanone (5.14)



5.14

$C_{18}H_{18}O_3$

m.w. = 282.34 g/mol

Colourless oil

The title compound was prepared according to the method outlined for **5.4**, whereby reaction of cyclobutanone **5.13** (1.20 g, 4.5 mmol) with hydrogen peroxide and work-up under the conditions described gave a crude yellow oil (1.2 g). Purification and separation from the minor diastereoisomer was accomplished by flash chromatography on silica gel (5 x 5) eluting with Et_2O/hexane (3:7) to yield the title compound **5.14** (925 mg, 3.3 mmol, 73 %) as a colourless oil.

FT-IR (neat) ν_{max} 3033 w, 2867 m, 1785 s, 1453 m, 1201 s, 1110 s, 1007 s cm^{-1}.

^{1}H NMR (300 MHz) δ 7.45-7.18 (10H, m, PhH), 5.39 (1H, d, J = 5.5 Hz, PhCH-), 4.60 (1H, d, J = 12 Hz, -CHHPh), 4.54 (1H, d, J = 12 Hz, -CHHPh),

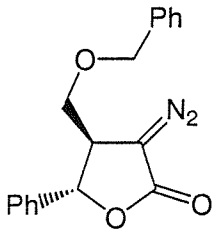
3.61-3.45 (2H, m, -CH_2OBn), 2.78-2.62 (3H, m, -$COCH_2$- and -CH_2CH-).

^{13}C NMR (100 MHz) δ 176.6 (**C**O), 139.3 (**C**$_{ar}$), 137.1 (**C**$_{ar}$), 128.9 (**CH**$_{ar}$), 128.8 (**CH**$_{ar}$), 128.4 (**CH**$_{ar}$), 128.2 (**CH**$_{ar}$), 126.0 (**CH**$_{ar}$), 83.4 (Ph**C**H-), 73.7 (PhCH_2O-), 68.9 (-CH_2OBn), 45.1 (-CH_2CH-), 32.1 (-$COCH_2$-).

LRMS (CI, NH_3) *m/z* (relative intensity) 300 (3) $[M+NH_4]^+$, 91 (100) $[PhCH_2]^+$, 191 (24) $[M-PhCH_2]^+$.

HRMS (EI) Calcd for $C_{18}H_{18}O_3$ 282.1256, found 282.1259.

(4R*, 5S*)-5-Phenyl-3-diazo-4-([benzyloxy]methyl)tetrahydro-2-furanone (5.18)



5.18

$C_{18}H_{16}N_2O_3$

m.w. = 308.34 g/mol

Yellow solid

Method A

To a solution of hexamethyldisilylazane (1.1 mL, 5.02 mmol) in THF (15 mL) at 0 °C (ice/salt bath) was added *n*-BuLi (3.2 mL of a 1.6 M solution in hexanes, 5.16 mmol) dropwise over 5 min. The colourless solution was stirred at 0 °C for 10 min, cooled to –78 °C (CO_2(s)/acetone) and a solution of lactone **5.14** (710 mg, 2.51 mmol) in THF (25 mL) added dropwise over 10 min. The pale yellow reaction mixture was allowed to stir at –78 °C for 45 min before 2,2,2-trifluoroethyl trifluoroacetate (0.37 mL, 2.76 mmol) was added dropwise over 2 min and the reaction warmed to room temperature over 100 min. The reaction mixture was then acidified to pH = 4 with 1N HCl (aq) and diluted with Et_2O (20 mL) before the organic layer was separated and the aqueous extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield **(4R*, 5S*)-5-Phenyl-4-[(benzyloxy)methyl]-3-(trifluoroacetyl)tetrahydro-2-furanone** (**5.17a**) (950 mg, quantitative) as a crude cream solid – this crude material was used directly in the subsequent diazo-transfer reaction: IR ν_{max} (neat) 1784 s, 1747 s cm^{-1}; ^{1}H-NMR (300 MHz) δ 7.45-7.18 (10H, m), 5.38 (1H, d, *J* = 8.4 Hz), 4.66-4.47 (3H, m), 3.67-3.38 (3H, m). Thus, to a solution of crude trifluoroacetylated lactone **5.17a** (2.20 mmol theoretical) in bench grade CH_2Cl_2 (30 mL) at room temperature was added 4-nitrobenzenesulfonyl azide (0.65 g, 2.86 mmol) followed by NEt_3 (0.40 mL, 2.86 mmol) and the yellow reaction mixture was left to stir for 18 h. The mixture was poured onto water (30 mL) and diluted with CH_2Cl_2 (10

mL), the organic layer was separated and the aqueous extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield a crude yellow oil (3.2 g). Purification was accomplished by flash chromatography on silica gel (5.5 x 6) eluting with Et_2O/hexane (2:3) to yield the title compound **5.18** (550 mg, 1.78 mmol, 81 % from lactone **5.14**) as a pale yellow solid.

Method B

To a solution of NaN_3 (364 mg, 5.60 mmol) and tetra-*n*-butylammonium bromide (2 mg, 1 mol %) in 2N NaOH (aq) (12 mL) and hexane (6 mL) at 0 °C (ice/salt bath) was added Tf_2O (0.47 mL, 2.80 mmol) dropwise over 2 min. The clear colourless reaction mixture was to left stir for 10 min before the rapid addition of a solution of lactone **7.47a** (227 mg, 0.70 mmol) in MeCN (6 mL) with vigorous stirring. The resulting bright yellow solution was allowed to stir at 0 °C for a further 30 min before dilution with EtOAc (30 mL) and water (20 mL). The organic layer was separated and the aqueous extracted with EtOAc (3 x 30 mL), the organic extracts combined, washed with brine (30 mL), dried with Na_2SO_4 and concentrated *in vacuo* to yield a yellow foam (380 mg). Purification was accomplished by flash chromatography on silica gel (2.1 x 2.5) eluting with EtOAc/hexane (1:9) to EtOAc/hexane (1:1) in 5 % increment rises (30 mL each) to give the title compound **5.18** (199 mg, 0.65 mmol, 92 %) as a powdery yellow solid.

MP 57-59 °C (Et_2O/hexane).

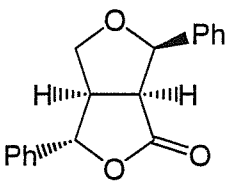
FT-IR (neat) ν_{max} 2106 m, 1722 s, 1093 s, 1080 s, 1029 s cm^{-1}.

^{1}H NMR (400 MHz) δ 7.34-7.17 (10H, m, PhH), 5.18 (1H, d, J = 4.0 Hz, PhCH-), 4.60 (2H, s, $PhCH_2$-), 3.85-3.72 (3H, m, -CH_2OBn and –$CHCN_2$).

^{13}C NMR (100 MHz) δ 169.6 (CO), 139.3 (C_{ar}), 137.6 (C_{ar}), 129.4 (CH_{ar}), 129.3 (CH_{ar}), 129.0 (CH_{ar}), 128.5 (CH_{ar}), 128.1 (CH_{ar}), 125.8 (CH_{ar}), 80.8 (PhCH-), 74.1 ($PhCH_2$-), 71.1 (-CH_2OBn), 53.1 (-CN_2), 45.8 (-CHN_2).

CHN Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.09; H, 5.23. Found: C, 70.01; H, 5.36.

(1S*, 2R*, 5R*, 6S*) 2,6-Diphenyl-3,7-dioxabicyclo[3.3.0]octan-8-one (5.19)



5.19

$C_{18}H_{16}O_3$

m.w. = 280.32 g/mol

White crystalline solid

To a solution of diazo-lactone **5.18** (100 mg, 0.32 mmol) in CH_2Cl_2 (4 mL) at room temperature was added $Rh_2(OAc)_4$ (3 mg, 0.006 mmol) and the resulting pale green, effervescing (N_2) reaction mixture was stirred under nitrogen for 3 h. The mixture was diluted with CH_2Cl_2 (10 mL) and poured onto water (10 mL), the organic layer separated and the aqueous extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with sat. $NaHCO_3$ (aq) (10 mL) and brine (10 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield a white solid (105 mg). Purification was accomplished by flash chromatography on silica gel (1.5 x 7) eluting with Et_2O/hexane (2:3) to yield the title compound **5.19** (80 mg, 0.29 mmol, 89 %) as a white crystalline solid.

MP 121-123 °C (Et_2O/hexane).

FT-IR (neat) ν_{max} 1773 s, 1169 s, 1049 s cm^{-1}.

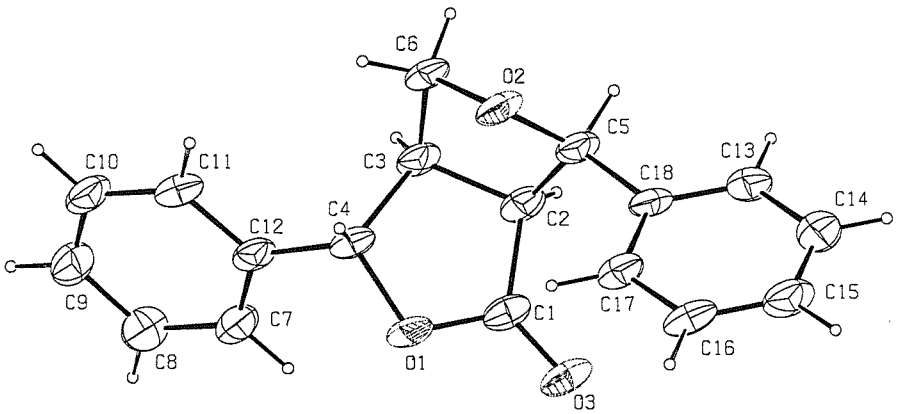
^{1}H NMR (400 MHz) δ 7.45-7.32 (10H, m, Ph**H**), 5.33 (1H, d, *J* = 6.5 Hz, PhC**H**O_2C-), 5.12 (1H, d, *J* = 8.9 Hz, PhC**H**O-), 4.38 (1H, d, *J* = 9.4 Hz, -OC**H**H-), 3.96 (1H, dd, *J* = 9.4, 5.0 Hz, -OCH**H**-), 3.61 (1H, t, *J* = 8.9 Hz, -O_2CC**H**-), 3.27 (1H, ddd, *J* = 9.4, 6.5, 5.0, -OCH_2C**H**-).

^{13}C NMR (100 MHz) δ 174.7 (**C**O), 140.0 (**C**$_{ar}$), 136.5 (**C**$_{ar}$), 129.4 (**C**H$_{ar}$), 129.2 (**C**H$_{ar}$), 129.0 (**C**H$_{ar}$), 126.7 (**C**H$_{ar}$), 125.8 (**C**H$_{ar}$), 85.8 (Ph**C**HO_2C-), 84.4 (Ph**C**HO-), 72.4 (-**C**H_2-), 51.9 (-**C**H-), 51.6 (-**C**H-).

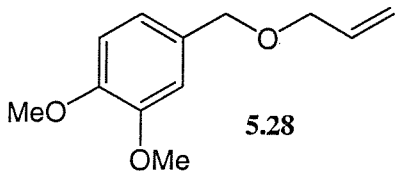
LRMS (CI, NH_3) *m/z* (relative intensity) 281 (65) $[M+H]^+$, 298 (100) $[M+NH_4]^+$, 263 (20) $[M+H(-H_2O)]^+$.

CHN Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.27; H, 5.79.

X-ray structure



4-[(Allyloxy)methyl]-1,2-dimethoxybenzene (5.28)



5.28

$C_{12}H_{16}O_3$

m.w. = 208.26 g/mol

Colourless oil

The title compound was prepared according to the general procedure described by *Reese et al.*[165] Thus, to a solution of NaOH (24 g, 600 mmol) in water (50 mL), at room temperature, was added a solution of 3,4-dimethoxybenzyl alcohol (14.5 g, 86 mmol) in allyl chloride (56mL, 690 mmol) followed by Adogen[464] (2 g, 4 mmol) with vigorous stirring. The reaction mixture was stirred at room temperature for 24 h, the aqueous phase separated and the organic phase diluted with CH_2Cl_2 (100 mL). This organic phase was washed with water (100 mL), 1N HCl (aq) (100 mL), sat. $NaHCO_3$ (100 mL), water (100 mL), brine (100 mL) and dried with $MgSO_4$ and concentrated *in vacuo* to yield an orange oil (30 g). Purification was accomplished by distillation under reduced pressure to give the title compound **5.28** (16.6 g, 80 mmol, 93 %) as a colourless oil. Spectroscopic details were consistent with those observed in the literature.[251]

BP 108-112 °C (0.4 mbar).

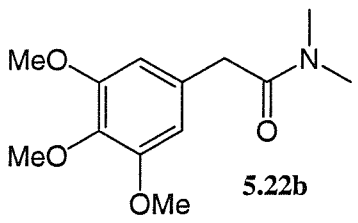
FT-IR (neat) ν_{max} 1593 w, 1515 s, 1264 s, 1237 s, 1157 s, 1138 s, 1029 s cm^{-1}.

^{1}H NMR (300 MHz) δ 6.92-6.82 (3H, m, PhH), 6.03-5.89 (1H, ddt, *J* = 16.9, 10.3, 5.9 Hz, -CH=CH_2), 5.32 (1H, dq, *J* = 16.9, 1.5 Hz, -CH=CHH_{trans}), 5.21 (1H, dq, *J* = 10.3, 1.5 Hz, -CH=CHH_{cis}), 4.47 (2H, s, -CH_2Ar), 4.02 (2H, dt, *J* = 5.9, 1.5 Hz, -CH_2CH=CH_2), 3.90 (3H, s, -OCH_3), 3.88 (3H, s, -OCH_3).

^{13}C NMR (75 MHz) δ 149.1 (C_{ar}), 148.7 (C_{ar}), 135.0 (-CH=CH_2), 130.9 (C_{ar}), 120.5 (CH_{ar}), 117.3 (-CH=CH_2), 111.2 (CH_{ar}), 111.0 (CH_{ar}), 72.2 (-CH_2-), 71.1 (-CH_2-), 56.1 (-OCH_3), 56.0 (-OCH_3).

LRMS (EI) *m/z* (relative intensity) 208 (30) $[M]^{\bullet+}$, 151 (100) $[M\text{-}OCH_2CH{=}CH_2]^{\bullet+}$), 166 (30) $[M\text{-}CH_3CH{=}CH_2]^{\bullet+}$.

***N,N*-Dimethyl-2-(3,4,5-trimethoxyphenyl)acetamide (5.22b)**



5.22b

$C_{13}H_{19}NO_4$

m.w. = 253.30 g/mol

White solid

To a partially suspended mixture of 3,4,5-trimethoxyphenylacetic acid (7.92 g, 35 mmol) in CH_2Cl_2 (35 mL) at room temperature was added oxalyl chloride (3.4 mL, 38.5 mmol) followed by two drops of DMF. The reaction was stirred for 6 h where upon gaseous evolution had ceased and full conversion of acid was observed (monitoring by IR - $C{=}O_{(COOH)}$ 1699 cm^{-1} and $-C{=}O_{(COCl)}$ 1793 cm^{-1}). This crude acid chloride was immediately converted to the amide according to the method outlined for **5.12**. Purification was accomplished by distillation under reduced pressure to give the title compound **5.22b** (8.45 g, 33 mmol, 95 %) as a very viscous colourless oil that solidified on standing to give a white solid.

BP 136-139 °C (0.4 mbar).

MP 53-55 °C.

FT-IR (neat) ν_{max} 1652 s, 1593 m, 1463 m, 1338 m, 1248 m, 1122 s, 1013 m cm^{-1}.

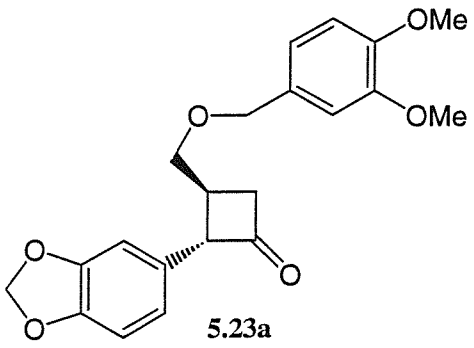
^{1}H NMR (400 MHz) δ 6.46 (2H, s, PhH), 3.82 (6H, s, $-OCH_3$), 3.80 (3H, s, $-OCH_3$), 3.68 (2H, s, $-CH_2-$), 3.00 (3H, s, $-NCH_3$), 3.26 (3H, s, $-NCH_3$).

^{13}C NMR (100 MHz) δ 171.3 (CO), 153.7 (C_{ar}), 137.3 (C_{ar}), 131.1 (C_{ar}), 106.3 (CH_{ar}), 61.2 ($-OCH_3$), 56.5 ($-OCH_3$), 41.5 ($-CH_2-$), 38.1 ($-NCH_3$), 36.1 ($-NCH_3$).

LRMS (ES +ve) *m/z* (relative intensity) 254 (4) $[M+H]^+$, 317 (30) $[M+Na+MeCN]^+$, 529 (100) $[2M+Na]^+$.

CHN Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.58; H, 7.65; N, 5.45.

(2S*, 3S*)-2-(3,4-Methylenedioxy)phenyl-3-{[(3,4-dimethoxybenzyl)oxy]methyl} cyclobutanone (5.23a)



5.23a

$C_{21}H_{22}O_6$

m.w. = 370.40 g/mol

Pale yellow oil

The title compound was prepared according to a modified procedure described by Ghosez *et al.*[166] Thus, to a solution of *N,N*-dimethyl(3,4-methylenedioxy)phenylacetamide (**5.22a**) (207 mg, 1.0 mmol) in CH_2Cl_2 (3.5 mL) at –25 °C (internal, CO_2(s)/acetone) was

added Tf_2O (0.18 mL, 1.05 mmol) at such a rate that the temperature did not rise above –20 °C. The colourless homogeneous reaction mixture was stirred at –25 °C for 2 min before addition of anhydrous potassium carbonate (152 mg, 1.1 mmol) followed by a mixture of 2,6-di-*tert*-butylpyridine (0.25 mL, 1.1 mmol) and 4-[(allyloxy)methyl]-1,2-dimethoxybenzene (**5.28**) (310 mg, 1.5 mmol) in CH_2Cl_2 (0.5 mL) over a period of 2 min. The reaction was then allowed to warm to room temperature and stirred for 18 h (the formation of the cyclic iminium species was monitored by IR; υ_{max} 1733 cm^{-1}). The mixture was diluted with CH_2Cl_2 (10 mL) and treated with sat. $NaHCO_3$ (aq) (10 mL) with vigorous stirring for 1 h. The organic layer was separated, the aqueous extracted with CH_2Cl_2 (3 x 20 mL) and the combined extracts were washed with water (20 mL) and brine (20 mL), dried with $MgSO_4$, and concentrated *in vacuo* to yield a yellow oil (740 mg). Purification was accomplished by flash chromatography on silica gel (3 x 8.5) eluting with EtOAc/hexane (3:7) to give the title compound **5.23a** (158 mg, 0.43 mmol, 43 %) as a colourless oil (12:1 mixture of diastereoisomers). NMR data reported for major diastereoisomer.

FT-IR (neat) ν_{max} 1778 s, 1515 s, 1504 s, 1489 s, 1263 s, 1236 s, 1031 s cm^{-1}.

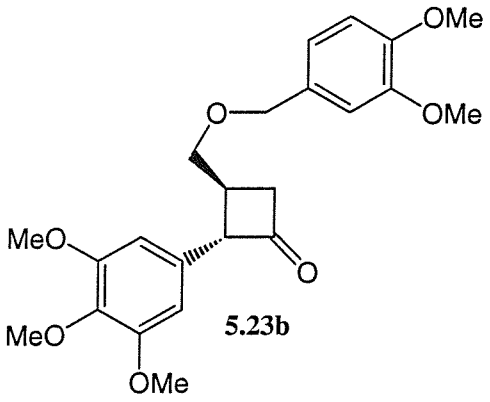
^{1}H NMR (400 MHz) δ 6.87-6.81 (3H, m, PhH), 6.76-6.69 (3H, m, PhH), 5.91 (2H, s, -OC**H**$_2$O-), 4.52 (2H, s, ArC**H**$_2$O-), 4.24 (1H, d, *J* = 8.0 Hz, -COC**H**Ar), 3.87 (3H, s, -OC**H**$_3$), 3.84 (3H, s, -OC**H**$_3$), 3.77-3.69 (2H, m, -C**H**$_2$OCH$_2$Ar), 3.02 (2H, ABq, *J* = 9.0 Hz, -COC**H**$_2$-), 2.79-2.70 (1H, m, -COCH$_2$C**H**-).

^{13}C NMR (100 MHz) δ 206.3 (**C**O), 149.6 (**C**$_{ar}$), 149.2 (**C**$_{ar}$), 148.3 (**C**$_{ar}$), 147.0 (**C**$_{ar}$), 131.0 (**C**$_{ar}$), 130.1 (**C**$_{ar}$), 120.6 (**C**H$_{ar}$), 111.4 (**C**H$_{ar}$), 108.8 (**C**H$_{ar}$), 108.2 (**C**H$_{ar}$), 101.4 (-O**C**H$_2$O-), 73.5 (-O**C**H$_2$Ar), 72.2 (-**C**H$_2$OCH$_2$Ar), 66.8 (-**C**HAr), 56.4 (-O**C**H$_3$), 56.2 (-O**C**H$_3$), 47.5 (-CO**C**H$_2$-), 33.1 (-CH$_2$**C**H-).

LRMS (CI, NH_3) *m/z* (relative intensity) 388 (10) $[M+NH_4]^+$, 151 (100) $[ArCH_2]^+$, 235 (70).

HRMS (EI) Calcd for $C_{21}H_{22}O_6$ 370.1416, found 370.1426.

(2S*, 3S*)-3-{[(3,4-Dimethoxybenzyl)oxy]methyl}-2-(3,4,5-trimethoxyphenyl)cyclobutanone (5.23b)



5.23b

$C_{23}H_{28}O_7$

m.w. = 416.47 g/mol

Pale yellow oil

The title compound was prepared according to the method outlined for **5.23a**, whereby reaction of *N,N*-dimethyl(3,4,5-trimethoxy)phenylacetamide (**5.22b**) (2.78 g, 11.0 mmol) with 4-[(allyloxy)methyl]-1,2-dimethoxybenzene (**5.28**) (3.44 g, 16.5 mmol) and work-up under the conditions described (except reaction quenched at +5 °C after 150 min.) gave a crude yellow oil (7.4 g). Purification was accomplished by flash chromatography on silica gel (5 x 10) eluting with EtOAc/hexane (1:9 then 1:1) to yield the title compound **5.23b** (720 mg, 1.73 mmol, 16 %) as a very pale yellow oil (12:1 mixture of diastereoisomers). NMR data reported for major diastereoisomer.

FT-IR (neat) ν_{max} 1777 m, 1587 m, 1510 m, 1463 m, 1419 m, 1263 m, 1238 m, 1157 1111 s, 1027 m, 1009 m cm^{-1}.

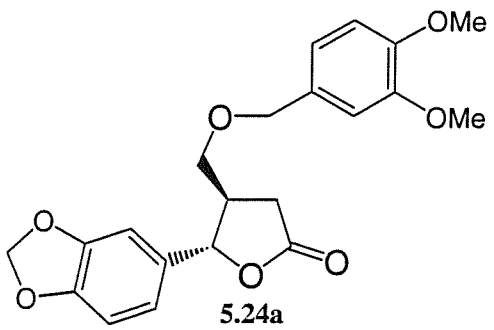
^{1}H NMR (400 MHz) δ 6.89-6.84 (2H, m, PhH), 6.85-6.81 (1H, m, PhH), 6.52 (2H, s, PhH), 4.54 (2H, s, $ArCH_2O$-), 4.28 (1H, d, J = 8.0 Hz, -COCHAr), 3.87 (3H, s, $-OCH_3$), 3.84 (3H, s, $-OCH_3$), 3.80 (3H, s, $-OCH_3$), 3.79 (6H, s, 2 x $-OCH_3$), 3.78-3.71 (2H, m, $-CH_2OCH_2Ar$), 3.05 (1H, dd, J = 5.5, 1.5 Hz, -COCHH-), 3.04 (1H, dd, J = 4.5, 1.5 Hz, -COCHH-), 2.86-2.77 (1H, m, $-COCH_2CH$-).

^{13}C NMR (100 MHz) δ 206.2 (CO), 153.7 (C_{ar}), 149.3 (C_{ar}), 149.2 (C_{ar}), 137.5 (C_{ar}), 132.0 (C_{ar}), 131.0 (C_{ar}), 120.8 (CH_{ar}), 111.6 (CH_{ar}), 111.4 (CH_{ar}), 104.6 (CH_{ar}), 73.6 ($-CH_2Ar$), 72.5 ($-CH_2OCH_2Ar$), 67.3 (-CHAr), 61.2 ($-OCH_3$), 56.5 ($-OCH_3$), 56.4 ($-OCH_3$), 56.3 ($-OCH_3$), 47.4 ($-COCH_2$-), 33.0 ($-CH_2CH$-).

LRMS (CI, NH_3) *m/z* (relative intensity) 434 (4) $[M+NH_4]^+$, 151 (100) $[ArCH_2]^+$.

HRMS (EI) Calcd for $C_{23}H_{28}O_7$ 416.1835, found 416.1837.

(4R,* 5S*)-5-(3,4-Methylenedioxy)phenyl-4-{[(3,4-dimethoxybenzyl)oxy]methyl} tetrahydro-2-furanone (5.24a)



5.24a

$C_{21}H_{22}O_7$

m.w. = 386.40 g/mol

Colourless oil

The title compound was prepared according to the method outlined for **5.4**, whereby reaction of cyclobutanone **5.23a** (1.50 g, 4.05 mmol) with hydrogen peroxide and work-up under the conditions described led to a crude yellow oil (1.9 g). Purification and separation from the minor diastereoisomer was accomplished by flash chromatography on silica gel (5 x 7) eluting with EtOAc/hexane (2:3) to yield the title compound **5.24a** (1.11 g, 2.87 mmol, 71 %) as a colourless oil.

FT-IR (neat) ν_{max} 1777 s, 1515 m, 1251 s, 1157 m, 1139 m, 1030 s cm^{-1}.

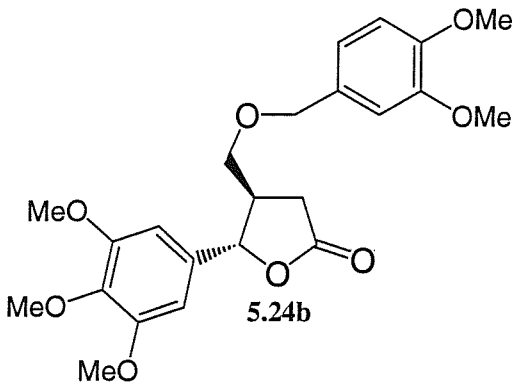
^{1}H NMR (400 MHz) δ 6.84 (3H, s, PhH), 6.77-6.69 (3H, m, PhH), 5.95 (2H, s, -OC**H**$_2$O-), 5.23 (1H, d, *J* = 6.5 Hz, -C**H**Ar), 4.49 (1H, d, *J* = 11.5 Hz, -C**H**HAr), 4.44 (1H, d, *J* = 11.5 Hz, -CH**H**Ar), 3.88 (6H, s, 2 x -OC**H**$_3$), 3.53-3.45 (2H, m, -C**H**$_2$OCH$_2$Ar), 2.75-2.57 (3H, m, -COC**H**$_2$- and -CH$_2$C**H**-).

^{13}C NMR (100 MHz) δ 176.4 (**C**O), 149.6 (**C**$_{ar}$), 149.3 (**C**$_{ar}$), 148.6 (**C**$_{ar}$), 148.3 (**C**$_{ar}$), 132.9 (**C**$_{ar}$), 130.6 (**C**$_{ar}$), 120.8 (**C**H$_{ar}$), 119.9 (**C**H$_{ar}$), 111.5 (**C**H$_{ar}$), 111.4 (**C**H$_{ar}$), 108.7 (**C**H$_{ar}$), 106.6 (**C**H$_{ar}$), 101.7 (-O**C**H$_2$O-), 83.4 (Ar**C**H-), 73.6 (-O**C**H$_2$Ar), 68.6 (-**C**H$_2$OCH$_2$Ar), 56.4 (-O**C**H$_3$), 56.3 (-O**C**H$_3$), 45.0 (-CH$_2$**C**H-), 32.2 (-CO**C**H$_2$-).

LRMS (EI) *m/z* (relative intensity) 386 (30) $[M]^{\bullet+}$, 151 (100) $[ArCH_2]^{\bullet+}$), 235 (70) $[M\text{-}ArCH_2]^{\bullet+}$.

HRMS (EI) Calcd for $C_{21}H_{22}O_7$ 386.1366, found 386.1372.

(4R*, 5S*)-4-{[(3,4-Dimethoxybenzyl)oxy]methyl}-5-(3,4,5-trimethoxyphenyl)-tetrahydro-2-furanone (5.24b)



5.24b

$C_{23}H_{28}O_8$

m.w. = 432.47 g/mol

Colourless oil

The title compound was prepared according to the method outlined for **5.4**, whereby reaction of cyclobutanone **5.23b** (650 mg, 1.56 mmol) with hydrogen peroxide and workup under the conditions described led to a crude yellow oil (3.5 g). Purification and separation from the minor diastereoisomer was accomplished by flash chromatography on silica gel (4 x 8) eluting with EtOAc/hexane (3:2) to yield the title compound **5.24b** (535 mg, 1.24 mmol, 79 %) as a colourless oil.

FT-IR (neat) ν_{max} 1778 s, 1593 m, 1514 s, 1237 s, 1125 s, 1026 s cm^{-1}.

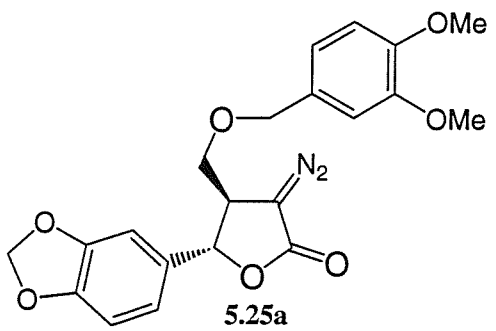
^{1}H NMR (400 MHz) δ 6.87-6.81 (3H, m, PhH), 6.45 (2H, s, PhH), 5.27 (1H, d, *J* = 6.0 Hz, -CHAr), 4.53 (1H, d, *J* = 11.5 Hz, -CHHAr), 4.44 (1H, d, *J* = 11.5 Hz, -CHHAr), 3.87 (3H, s, $-OCH_3$), 3.87 (3H, s, $-OCH_3$), 3.82 (3H, s, $-OCH_3$), 3.79 (6H, s, 2 x $-OCH_3$), 3.52 (2H, d, *J* = 4.5 Hz, $-CH_2OCH_2Ar$), 2.77-2.59 (3H, m, $-COCH_2-$ and $-CH_2CH-$).

^{13}C NMR (100 MHz) δ 176.3 (CO), 153.8 (C_{ar}), 149.4 (C_{ar}), 149.2 (C_{ar}), 138.3 (C_{ar}), 134.8 (C_{ar}), 130.4 (C_{ar}), 120.7 (CH_{ar}), 111.4 (CH_{ar}), 111.2 (CH_{ar}), 102.8 (CH_{ar}), 83.3 (ArCH-), 73.5 ($-CH_2Ar$), 68.6 ($-CH_2OCH_2Ar$), 61.1 ($-OCH_3$), 56.4 ($-OCH_3$), 56.2 ($-OCH_3$), 44.8 ($-CH_2CH-$), 31.9 ($-CH_2CH-$).

LRMS (EI) *m/z* (relative intensity) 432 (30) $[M]^{\bullet+}$, 151 (100) $[ArCH_2]^{\bullet+}$, 281 (30) $[M-ArCH_2]^{\bullet+}$.

HRMS (EI) Calcd for $C_{23}H_{28}O_8$ 432.1784, found 432.1790.

(4R*, 5S*)-5-(3,4-Methylenedioxy)phenyl-3-diazo-4-{[(3,4-dimethoxybenzyl)oxy] methyl}-tetrahydro-2-furanone (5.25a)



5.25a

$C_{21}H_{20}N_2O_7$

m.w. = 412.40 g/mol

Yellow oil

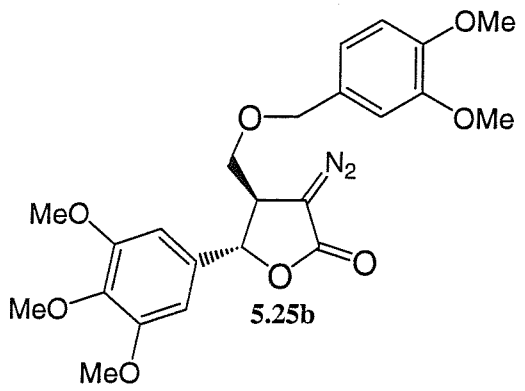
The title compound was prepared according to the method outlined for **5.18** (Method A), whereby reaction of lactone **5.24a** (1.0 g, 2.6 mmol) with LiHMDS and 2,2,2-trifluoroethyltrifluoroacetate (0.38 mL, 2.86 mmol) under the conditions described gave crude **(4R*, 5S*)-5-(3,4-methylenedioxy)phenyl-4-{[(3,4 dimethoxybenzyl)oxy]-methyl}-3-(trifluoroacetyl)-tetrahydro-2-furanone** (1.39 g, quantitative) as a pale orange foam. This crude material was used directly in the subsequent diazo-transfer reaction, which was conducted following the procedure described for **5.18**, whereby reaction of the crude trifluoroacetylated lactone (2.6 mmol theoretical) with 4-nitrobenzenesulfonyl azide (0.77 g, 3.4 mmol) and workup under the conditions described gave a crude yellow oil (3.2 g). Purification was accomplished by flash chromatography on silica gel (5 x 7) eluting with EtOAc/hexane (2:3) to yield the title compound **5.25a** (730 mg, 1.77 mmol, 68 % - from lactone **5.24a**) as a bright yellow oil.

FT-IR (neat) ν_{max} 2101 s, 1733 s, 1516 m, 1504 m, 1253 s, 1103 m, 1029 s cm^{-1}.

^{1}H NMR (400 MHz) δ 6.85-6.80 (3H, m, PhH), 6.79-6.72 (3H, m, PhH), 5.96 (2H, s, -OC**H**$_2$O-), 5.02 (1H, d, J = 5.0 Hz, -C**H**Ar), 4.49 (2H, s, -C**H**$_2$Ar), 3.87 (3H, s, -OC**H**$_3$), 3.87 (3H, s, -OC**H**$_3$), 3.76-3.65 (3H, m, -C**H**$_2$OCH$_2$Ar and -CH$_2$C**H**-).

^{13}C NMR (100 MHz) δ 169.4 (**C**O), 149.6 (**C**$_{ar}$), 149.3 (**C**$_{ar}$), 148.7 (**C**$_{ar}$), 148.5 (**C**$_{ar}$), 132.9 (**C**$_{ar}$), 130.1 (**C**$_{ar}$), 120.8 (**C**H$_{ar}$), 119.8 (**C**H$_{ar}$), 111.4 (**C**H$_{ar}$), 111.4 (**C**H$_{ar}$), 108.8 (**C**H$_{ar}$), 106.3 (**C**H$_{ar}$), 101.8 (-O**C**H$_2$O-), 80.9 (Ar**C**H-), 73.7 (-O**C**H$_2$Ar), 70.7 (-**C**H$_2$OCH$_2$Ar), 56.4 (-O**C**H$_3$), 56.3 (-O**C**H$_3$), 53.2 (-**C**N$_2$), 45.7 (-**C**HCN$_2$).

(4R*, 5S*)-3-Diazo-4-{[(3,4-dimethoxybenzyl)oxy]methyl}-5-(3,4,5-trimethoxyphenyl)tetrahydro-2-furanone (5.25b)



5.25b

$C_{23}H_{26}N_2O_8$

m.w. = 458.47 g/mol

Pale yellow solid

The title compound was prepared according to the method outlined for **5.18**, whereby reaction of lactone **5.24b** (450 mg, 1.04 mmol) with LiHMDS and 2,2,2-trifluoroethyl-trifluoroacetate (0.15 mL, 1.14 mmol) under the conditions described gave crude **(4R*, 5S*)-4-{[(3,4-dimethoxybenzyl)oxy]methyl}-3-(trifluoroacetyl)-5-(3,4,5-trimethoxy-phenyl)tetrahydro-2-furanone** (600 mg, quantitative) as a foam. This crude material was used directly in the subsequent diazo-transfer reaction, which was conducted following the procedure described for **5.18**, whereby reaction of the crude trifluoroacetylated lactone (1.04 mmol theoretical) with 4-nitrobenzenesulfonyl azide (310 mg, 1.35 mmol) and workup under the conditions described gave a crude yellow oil (1.2 g). Trituration with Et_2O/EtOAc and filtration gave the title compound **5.25b** (294 mg, 0.64 mmol, 62 %) as a pale yellow solid. Further purification was accomplished by flash chromatography on silica gel (3 x 7) eluting with EtOAc/hexane (3:2) to yield the title compound **5.25b** (66 mg, 0.14 mmol, 14 %) as a pale yellow powdery solid - overall yield of **5.25b** (360 mg, 0.79 mmol, 76 % - from lactone **5.24b**).

MP 131-132 °C.

FT-IR (neat) ν_{max} 2110 m, 1730 s, 1511 m, 1374 m, 1257 m, 1238 m, 1131 s cm^{-1}.

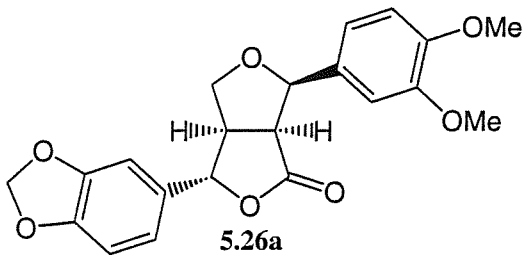
^{1}H NMR (400 MHz) δ 6.84 (3H, s, PhH), 6.49 (2H, s, PhH), 5.09 (1H, d, J = 4.0 Hz, -CHAr), 4.54 (1H, d, J = 11.5 Hz, -CHHAr), 4.51 (1H, d, J = 11.5 Hz, -CHHAr), 3.88 (3H, s, $-OCH_3$), 3.88 (3H, s, $-OCH_3$), 3.83 (3H, s, $-OCH_3$), 3.82 (6H, s, 2 x $-OCH_3$), 3.81-3.71 (3H, m, $-CH_2OCH_2Ar$ and $-CHCN_2$).

^{13}C NMR (100 MHz) δ 169.5 (CO), 154.1 (C_{ar}), 149.7 (C_{ar}), 149.5 (C_{ar}), 138.8 (C_{ar}), 134.8 (C_{ar}), 130.1 (C_{ar}), 120.9 (CH_{ar}), 111.5 (CH_{ar}), 111.4 (CH_{ar}), 102.8 (CH_{ar}), 81.0 (ArCH-), 74.0 ($-CH_2Ar$), 70.7 ($-CH_2OCH_2Ar$),

61.3 (-OCH_3), 56.7 (-OCH_3), 56.4 (-OCH_3), 56.3 (-OCH_3), 53.2 (-CN_2), 45.7 (-$CHCN_2$).

CHN Anal. Calcd for $C_{23}H_{26}N_2O_8$: C, 60.26; H, 5.72; N, 6.11. Found: C, 60.21; H, 5.78; N, 6.21.

(1S*, 2R*, 5R*, 6S*)-2-(3,4-Dimethoxy)phenyl-6-(3,4-methylenedioxy)phenyl-3,7-dioxabicyclo[3.3.0]octan-8-one (5.26a)



5.26a

$C_{21}H_{20}O_7$
m.w. = 384.38 g/mol
White crystalline solid

The title compound was prepared according to the method outlined for **5.19**, whereby reaction of diazo lactone **5.25a** (0.48 g, 1.16 mmol) with dirhodium (II) tetraacetate (10 mg, 0.02 mmol) and workup under the conditions described gave crude furofuranone as a yellow oil (0.48 g). Purification was accomplished by flash chromatography on silica gel (4.5 x 10) eluting with EtOAc/hexane (2:3) to give the title compound **5.26a** (0.36 g, 0.94 mmol, 81 %) as a white crystalline solid.

MP 125-127 °C (EtOAc/hexane).

FT-IR (neat) ν_{max} 1761 s, 1253 s, 1242 s, 1177 s, 1138 s, 1034 s, 1023 s cm^{-1}.

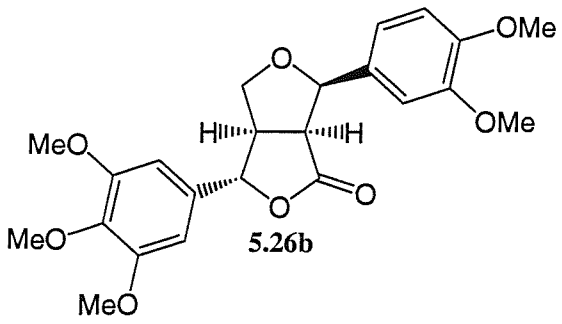
^{1}H NMR (400 MHz) δ 6.95 (1H, dd, *J* = 8.0, 2.0 Hz, PhH), 6.89-6.86 (2H, m, PhH), 6.81 (3H, s, PhH), 5.97 (2H, s, -OCH_2O-), 5.20 (1H, d, *J* = 6.5 Hz, -CO_2CHAr), 5.03 (1H, d, *J* = 8.5 Hz, -OCHAr), 4.29 (1H, d, *J* = 9.5 Hz, -OCHH-), 3.90 (1H, dd, *J* = 10.0, 5.0 Hz, -OCHH-), 3.89 (3H, s, -OCH_3), 3.87 (3H, s, -OCH_3), 3.54 (1H, t, *J* = 8.5 Hz, -COCH-), 3.21 (1H, ddd, *J* = 9.0, 6.5, 4.5 Hz, -OCH_2CH-).

^{13}C NMR (100 MHz) δ 174.7 (CO), 149.5 (C_{ar}), 149.4 (C_{ar}), 148.8 (C_{ar}), 148.5 (C_{ar}), 133.7 (C_{ar}), 128.9 (C_{ar}), 119.8 (CH_{ar}), 119.3 (CH_{ar}), 111.5 (CH_{ar}), 109.9 (CH_{ar}), 108.9 (CH_{ar}), 106.3 (CH_{ar}), 101.8 (-OCH_2O-), 85.9 (-CO_2CHAr), 84.3 (-OCHAr), 72.1 (-CH_2-), 56.3 (-OCH_3), 56.2 (-OCH_3), 51.9 (-COCH-), 51.7 (-CH_2CH-).

LRMS (ES +ve) *m/z* (relative intensity) 791 (70) $[2M+Na]^+$, 448 (100) $[M+Na(+MeCN)]^+$.

CHN Anal. Calcd for $C_{21}H_{20}O_7$: C, 65.62; H, 5.24. Found: C, 65.23; H, 5.02.

(1S*, 2R*, 5R*, 6S*)-2-(3,4-Dimethoxy)phenyl-6-(3,4,5-trimethoxy)phenyl-3,7-dioxabicyclo[3.3.0]octan-8-one (5.26b)



5.26b

$C_{23}H_{26}O_8$
m.w. = 430.45 g/mol
White powdery solid

The title compound was prepared according to the method outlined for **5.19**, whereby reaction of diazo lactone **5.25b** (320 mg, 0.70 mmol) with dirhodium (II) tetraacetate (6 mg, 0.02 mmol) and workup under the conditions described gave crude furofuranone as an off-white powdery solid (285 mg). Purification was accomplished by flash chromatography on silica gel (2.5 x 4) eluting with EtOAc/hexane (3:2) to give the title compound **5.26b** (261 mg, 0.60 mmol, 87 %) as a white crystalline solid.

MP 175-176 °C (EtOAc/hexane).

FT-IR (neat) ν_{max} 1763 s, 1591 m, 1519 m, 1330 m, 1270 m, 1236 s, 1118 s cm^{-1}.

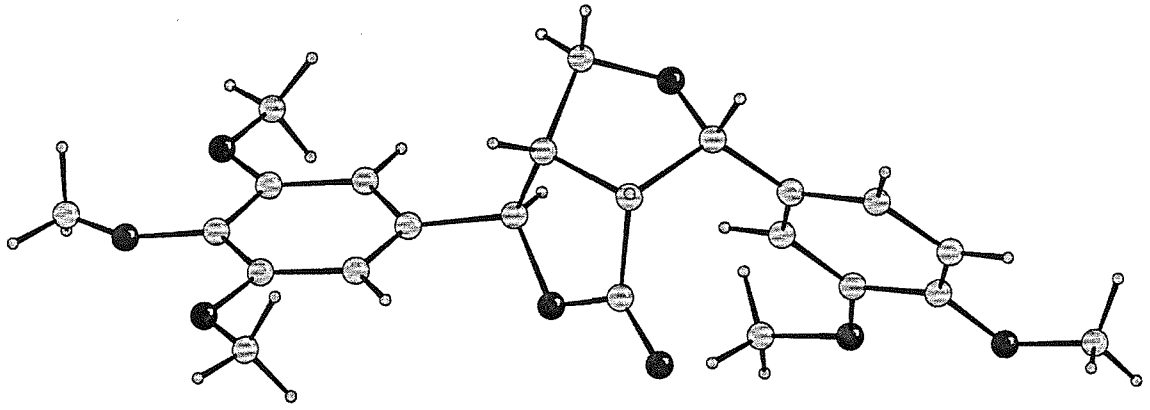
^{1}H NMR (400 MHz) δ 7.00-6.87 (3H, m, PhH), 6.54 (2H, s, PhH), 5.24 (1H, d, *J* = 6.5 Hz, -CO_2CHAr), 5.05 (1H, d, *J* = 8.5 Hz, -OCHAr), 4.34 (1H, d, *J* = 9.5 Hz, -OCHH-), 3.94 (1H, dd, *J* = 9.5, 4.5 Hz, -OCHH-), 3.90 (3H, s, -OCH_3), 3.88 (3H, s, -OCH_3), 3.88 (6H, s, 2 x -OCH_3), 3.85 (3H, s, -OCH_3), 3.55 (1H, t, *J* = 9.0 Hz, -COCH-), 3.24 (1H, ddd, *J* = 9.0, 6.5, 4.5 Hz, -CH_2CH-).

^{13}C NMR (100 MHz) δ 174.8 (CO), 154.2 (C_{ar}), 149.6 (C_{ar}), 149.5 (C_{ar}), 138.8 (C_{ar}), 135.5 (C_{ar}), 128.8 (C_{ar}), 119.3 (CH_{ar}), 111.5 (CH_{ar}), 110.0 (CH_{ar}), 102.8 (CH_{ar}), 85.9 (-CO_2CHAr), 84.3 (-OCHAr), 72.2 (-CH_2-), 56.7 (-OCH_3), 56.3 (-OCH_3), 56.2 (-OCH_3), 51.9 (-COCH-), 51.8 (-CH_2CH-).

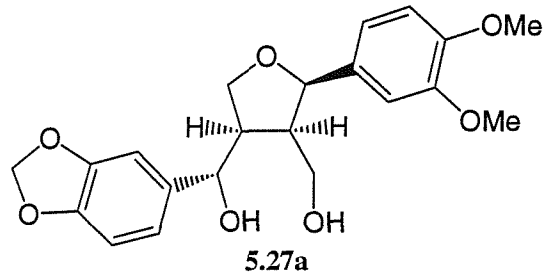
LRMS (ES +ve) *m/z* (relative intensity) 883 (80) $[2M+Na]^+$, 494 (100) $[M+Na(+MeCN)]^+$.

CHN Anal. Calcd for $C_{23}H_{26}O_8$: C, 64.18; H, 6.09. Found: C, 63.87; H, 5.89.

X-ray structure



(2R*, 3R*, 4S*)-2[(3,4-Dimethoxy)phenyl]-3-hydroxymethyl-4-{[(3,4-methylene-dioxy)phenyl]hydroxy}methyltetrahydrofuran (5.27a)



5.27a

$C_{21}H_{24}O_7$

m.w. = 388.42 g/mol

White powdery solid

To a suspension of $LiAlH_4$ (35 mg, 0.93 mmol) in THF (5 mL) at 0 °C (ice/salt bath) was added furofuranone **5.26a** (120 mg, 0.31 mmol) in THF (10 mL) and the grey suspension warmed to room temperature over 20 min. Water (0.04 mL), 15% NaOH (aq) (0.04 mL) and water (0.12 mL) were sequentially added dropwise, producing a pale grey/white granular precipitate that was filtered and washed with THF (5 mL) and EtOAc (10 mL). The filtrate was poured onto brine (15 mL), the organic phase separated and the aqueous extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine (20 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield crude diol as a white solid (125 mg). Purification was accomplished by flash chromatography on silica gel (3 x 2.5) eluting with EtOAc/hexane (1:1) to yield the title compound **5.27a** (118 mg, 0.30 mmol, 98 %) as a white powdery solid.

MP 66-68 °C.

FT-IR (neat) ν_{max} 3376 w br, 1516 s, 1254 s, 1237 s, 1037 s cm^{-1}.

^{1}H NMR (400 MHz) δ 6.93 (1H, d, *J* = 1.5 Hz, PhH), 6.87-6.77 (5H, m, PhH), 5.97 (2H, s, -OCH_2O-), 5.09 (1H, d, *J* = 5.0 Hz, -OCHAr), 4.78 (1H, d, *J* = 10.5 Hz, ArCHOH), 3.88 (3H, s, -OCH_3), 3.88 (3H, s, -OCH_3),

3.70-3.60 (3H, m, -OC**H**$_2$- and -C**H**HOH), 3.49 (1H, br s, -CHO**H**), 3.41 (1H, dd, *J* = 11.0, 2.5 Hz, -CH**H**OH), 3.04 (1H, dq, *J* = 6.0, 9.5 Hz, -OCH$_2$C**H**-), 2.77-2.70 (1H, m, -C**H**CH$_2$OH), 2.30 (1H, br s, -CH$_2$O**H**).

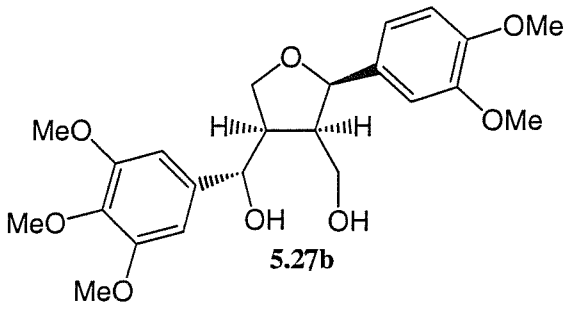
^{13}C NMR (100 MHz) δ 149.4 (**C**$_{ar}$), 148.6 (**C**$_{ar}$), 148.5 (**C**$_{ar}$), 147.8 (**C**$_{ar}$), 137.0 (**C**$_{ar}$), 131.8 (**C**$_{ar}$), 120.2 (**C**H$_{ar}$), 118.2 (**C**H$_{ar}$), 111.6 (**C**H$_{ar}$), 109.2 (**C**H$_{ar}$), 108.7 (**C**H$_{ar}$), 107.0 (**C**H$_{ar}$), 101.5 (-O**C**H$_2$O-), 83.7 (-O**C**HAr), 74.0 (-**C**HOH), 69.2 (-OCH$_2$-), 60.2 (-**C**H$_2$OH), 56.4 (-OCH$_3$), 56.3 (-OCH$_3$), 51.9 (-**C**HCH$_2$OH), 47.8 (-**C**HCHOH).

LRMS (EI) *m/z* (relative intensity) 388 (75) $[M]^{\bullet+}$, 370 (100) $[M\text{-}H_2O]^{\bullet+}$).

HRMS (EI) Calcd for $C_{21}H_{24}O_7$ 388.1522, found 388.1518.

CHN Anal. Calcd for $C_{21}H_{24}O_7$: C, 64.94; H, 6.23. Found: C, 63.44; H, 5.99.

(2R*, 3R*, 4S*)-2[(3,4-Dimethoxy)phenyl]-3-hydroxymethyl-4-{[(3,4,5-trimethoxy) phenyl]hydroxy}methyltetrahydrofuran (5.27b)



5.27b

$C_{23}H_{30}O_8$

m.w. = 434.49 g/mol

White powdery solid

The title compound was prepared according to the method outlined for **5.27a**, whereby reaction of furofuranone **5.26b** (165 mg, 0.38 mmol) with $LiAlH_4$ (43 mg, 1.14 mmol) and workup under the conditions described gave crude diol as a white solid (166 mg). Purification was accomplished by flash chromatography on silica gel (2.3 x 1) eluting with EtOAc/hexane (7:3) to yield the title compound **5.27b** (149 mg, 0.34 mmol, 90 %) as a powdery white solid.

MP 141-143 °C.

FT-IR (neat) ν_{max} 1593 m, 1515 m, 1417 m, 1329 m, 1241 s, 1126 s, 1023 s cm^{-1}.

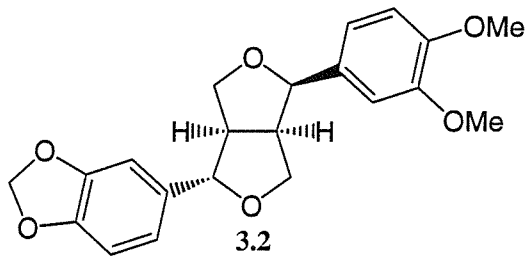
^{1}H NMR (400 MHz) δ 6.86-6.79 (3H, m, Ph**H**), 6.61 (2H, s, Ph**H**), 5.08 (1H, d, *J* = 5.0 Hz, -OC**H**Ar), 4.76 (1H, d, *J* = 10.5 Hz, ArC**H**OH), 3.87 (6H, s, 2 x -OCH$_3$), 3.87 (6H, s, 2 x -OCH$_3$), 3.84 (3H, s, -OCH$_3$), 3.72 (1H, q, *J* = 9.0 Hz, -OCH**H**-), 3.69-3.61 (2H, m, -OCH**H**- and -C**H**HOH), 3.39 (1H, d, *J* = 11.0 Hz, -CH**H**OH), 3.05 (1H, dq, *J* =

6.5, 9.5 Hz, -OCH_2C**H**-), 2.76-2.69 (1H, m, -C**H**CH_2OH), 2.55 (1H, br s, -O**H**).

^{13}C NMR (100 MHz) δ 153.8 (**C**$_{ar}$), 149.4 (**C**$_{ar}$), 148.6 (**C**$_{ar}$), 138.7 (**C**$_{ar}$), 138.1 (**C**$_{ar}$), 131.8 (**C**$_{ar}$), 118.2 (**CH**$_{ar}$), 111.6 (**CH**$_{ar}$), 109.2 (**CH**$_{ar}$), 103.6 (**CH**$_{ar}$), 83.7 (-**O**CHAr), 74.3 (-**C**HOH), 69.2 (-O**C**H_2-), 61.2 (-O**C**H_3), 60.1 (-**C**H_2OH), 56.6 (-O**C**H_3), 56.4 (-O**C**H_3), 56.3 (-O**C**H_3), 51.9 (-**C**HCH_2OH), 47.8 (-**C**HCHOH).

CHN Anal. Calcd for $C_{23}H_{30}O_8$: C, 63.58; H, 6.96. Found: C, 63.31; H, 6.99.

(1R*, 2R*, 5R*, 6S*)-2-(3,4-Dimethoxy)phenyl-6-(3,4-methylenedioxy)phenyl-3,7-dioxabicyclo[3.3.0]octane ((±)-Fargesin) (3.2)



3.2

$C_{21}H_{22}O_6$
m.w. = 370.40 g/mol
White powdery solid

To a solution of diol **5.27a** (40 mg, 0.103 mmol) in CH_2Cl_2 (0.4 mL) and pyridine (0.1 mL) at 0 °C (ice/salt bath) was added MsCl (40 μL, 0.515 mmol) and the reaction warmed to room temperature and stirred for 4 days. The mixture was pipetted onto 1N HCl (aq) (5 mL) and diluted with CH_2Cl_2 (8 mL). The organic layer was separated and the aqueous extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with 1N HCl (aq) (10 mL) and brine (15 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield a crude orange oil (51 mg). Purification was accomplished by flash chromatography on silica gel (2.3 x 2.5) eluting with EtOAc/hexane (2:3) to yield (±)-fargesin (**3.2**) (23 mg, 0.062 mmol, 60 %) as a white solid. Spectroscopic details were consistent with those reported previously.[138,144,252,253]

MP 138-141 °C (lit.[138] 138-141 °C, lit.[144] 135-136 °C, lit.[253] 138-139 °C).

FT-IR (neat) ν_{max} 1516 m, 1504 m, 1444 m, 1239 s, 1077 m, 1033 s cm^{-1}.

^{1}H NMR (400 MHz) δ 6.93 (1H, s, Ph**H**), 6.87-6.76 (5H, m, Ph**H**), 5.95 (2H, s, -O**C**H_2O-), 4.87 (1H, d, J = 5.0 Hz, -C**H**Ar^1), 4.42 (1H, d, J = 7.0 Hz, -C**H**Ar^2), 4.12 (1H, d, J = 9.5 Hz, Ar^{1}CHOC**H**H-), 3.91 (3H, s, -O**C**H_3), 3.88 (3H, s, -O**C**H_3), 3.88-3.81 (2H, m, Ar^{1}CHOCH**H**-

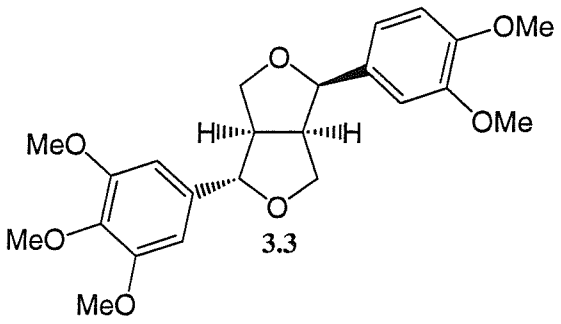
and $Ar^2CHOCHH$-), 3.37-3.28 (2H, m, $Ar^2CHOCHH$- and Ar^1CHCH-), 2.91-2.84 (1H, m, Ar^2CHCH-).

^{13}C NMR (100 MHz) δ 149.3 (C_{ar}), 148.5 (C_{ar}), 148.4 (C_{ar}), 147.6 (C_{ar}), 135.6 (C_{ar}), 131.4 (C_{ar}), 119.9 (CH_{ar}), 118.1 (CH_{ar}), 111.5 (CH_{ar}), 109.4 (CH_{ar}), 108.6 (CH_{ar}), 106.9 (CH_{ar}), 101.4 (-OCH_2O-), 88.1 (Ar^2CH-), 82.4 (Ar^1CH-), 71.4 (Ar^1CHOCH_2-), 70.2 (Ar^2CHOCH_2-), 56.3 (-OCH_3), 56.3 (-OCH_3), 55.0 (Ar^2CHCH-), 50.6 (Ar^1CHCH-).

Where Ar^1 = 3,4 – dimethoxy-, Ar^2 = 3,4-methylenedioxy-.

LRMS (EI) *m/z* (relative intensity) 370 (45) $[M]^{\bullet+}$, 339 (6) $[M\text{-}OMe]^{\bullet+}$, 149 (100), 165 (60) $[Ar^1CO]^{\bullet+}$.

(1R*, 2R*, 5R*, 6S*)-2-(3,4-Dimethoxy)phenyl-6-(3,4,5-trimethoxy)phenyl-3,7-dioxabicyclo[3.3.0]octane ((±)-Epimagnolin A) (3.3)



3.3

$C_{23}H_{28}O_7$

m.w. = 416.47 g/mol

Viscous colourless oil/glassy solid

To a solution of diol **5.27b** (40 mg, 0.092 mmol) in CH_2Cl_2 (1 mL) at 0 °C (ice/salt bath) was added NEt_3 (38 μL, 0.276 mmol) and DMAP (1 mg, cat.) followed by MsCl (9 μL, 0.11 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 6 h before additional MsCl (4 μL, 0.046 mmol) was added and the reaction stirred for a further 12 h. TLC analysis still showed starting diol **5.27b**, so additional NEt_3 (38 μL, 0.276 mmol) and MsCl (18 μL, 0.221 mmol) were added and the reaction stirred for 15 min before pipetting onto water (5 mL) and diluting with CH_2Cl_2 (8 mL). The organic layer was separated and the aqueous extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with 1N HCl (aq) (15 mL) and brine (15 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield an orange oil (58 mg). Purification was accomplished by flash chromatography on silica gel (2.3 x 2) eluting with EtOAc/hexane (3:2) to yield epimagnolin A (**3.3**) (29 mg, 0.070 mmol, 76 %) as a glassy solid/viscous oil. Spectroscopic details were consistent with those previously reported.[127,254]

FT-IR (neat) ν_{max} 1591 m, 1508 m, 1462 m, 1234 s, 1127 s, 1078 m, 1028 m cm^{-1}.

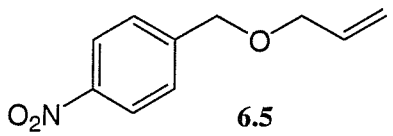
^{1}H NMR (400 MHz) δ 6.95 (1H, s, PhH), 6.87 (2H, s, PhH), 6.60 (2H, s, PhH), 4.89 (1H, d, J = 5.5 Hz, -CHAr^1), 4.45 (1H, d, J = 7.0 Hz, -CHAr^2), 4.17 (1H, d, J = 9.0 Hz, Ar^{1}CHOCHH-), 3.92 (3H, s, -OCH$_3$), 3.89 (3H, s, -OCH$_3$), 3.88 (6H, s, 2 x –OCH$_3$), 3.91-3.86 (2H, m, Ar^{1}CHOCHH- and Ar^{2}CHOCHH-), 3.84 (3H, s, -OCH$_3$), 3.39-3.31 (2H, m, Ar^{2}CHOCHH- and Ar^{1}CHCH-), 2.97-2.90 (1H, m, Ar^{2}CHCH-).

^{13}C NMR (100 MHz) δ 153.8 (C$_{ar}$), 149.3 (C$_{ar}$), 148.5 (C$_{ar}$), 138.0 (C$_{ar}$), 137.3 (C$_{ar}$), 131.3 (C$_{ar}$), 118.1 (CH$_{ar}$), 111.5 (CH$_{ar}$), 109.4 (CH$_{ar}$), 103.4 (CH$_{ar}$), 88.2 (Ar^{2}CH-), 82.4 (Ar^{1}CH-), 71.5 (Ar^{1}CHOCH$_2$-), 70.2 (Ar^{2}CHOCH$_2$-), 61.2 (-OCH$_3$), 56.6 (-OCH$_3$), 56.4 (-OCH$_3$), 56.3 (-OCH$_3$), 55.0 (Ar^{2}CHCH-), 50.5 (Ar^{1}CHCH-).

Where Ar^1 = 3,4-dimethoxy-and Ar^2 = 3,4,5-trimethoxy-.

LRMS (EI) *m/z* (relative intensity) 416 (100) [M]$^{\bullet+}$, 385 (10) [M-OMe]$^{\bullet+}$.

Allyl-(4-nitrobenzyl)-ether (14593-44-3) (6.5)



6.5

C$_{10}$H$_{11}$NO$_3$

m.w. = 193.20 g/mol

Colourless oil

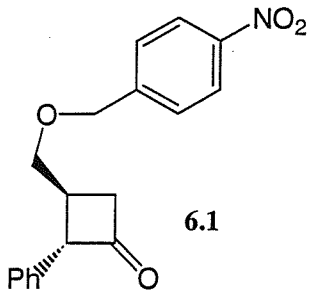
The title compound was prepared according to the method outlined for **5.28**, whereby reaction of 4-nitrobenzyl alcohol (9.2 g, 0.06 mol) with allyl chloride (39 mL, 0.48 mol) and CH_2Cl_2 (50 mL – to aid dissolution) for 48 h (still large presence of starting alcohol) and workup under the conditions described gave a crude yellow solid (9.5 g). Purification was accomplished by flash chromatography on silica gel (5 x 15) eluting with Et_2O/hexane (1:9) to yield the title compound **6.5** (3.4 g, 0.018 mol, 30 %) as a colourless oil. Spectroscopic details were consistent with those observed in the literature.[176]

FT-IR (neat) ν_{max} 1606 w, 1519 s, 1344 s, 1089 m cm^{-1}.

^{1}H NMR (300 MHz) δ 8.20 (2H, d, J = 8.1 Hz, PhH), 7.52 (2H, d, J = 8.1 Hz, PhH), 6.30-5.89 (1H, m, -CH=CH$_2$), 5.38-5.21 (2H, m, -CH=CH$_2$), 4.62 (2H, s, -CH$_2$Ar), 4.09 (2H, dt, J = 5.9, 1.5 Hz, -CH$_2$CH=CH$_2$).

^{13}C NMR (75 MHz) δ 147.5 (C$_{ar}$), 146.2 (C$_{ar}$), 134.3 (-CH=CH$_2$), 127.8 (CH$_{ar}$), 123.7 (CH$_{ar}$), 117.8 (-CH=CH$_2$), 71.9 (-CH$_2$Ar), 70.9 (CH$_2$CH=CH$_2$).

(2S*, 3S*)-3-{[(4-Nitrobenzyl)oxy]methyl}-2-phenylcyclobutanone (6.1)



6.1

$C_{18}H_{17}NO_4$

m.w. = 311.34 g/mol

White crystalline solid

The title compound was prepared according to the method outlined for **5.3** whereby, reaction of *N,N*-dimethyl-2-phenylacetamide (**5.12**) (1.63 g, 10.0 mmol) with allyl-(4-nitrobenzyl)ether (**6.5**) (2.9 g, 15 mmol) and workup under the conditions described gave a crude dark yellow oil (6.75 g). Purification was accomplished by flash chromatography on silica gel (5 x 12) eluting with Et_2O/hexane (1:9 then 2:3) to yield the title compound **6.1** (1.32 g, 4.3 mmol, 43%) as an off-white solid (9:1 mixture of diastereoisomers). Diastereomerically pure product **6.1** was obtained upon recrystallisation from Et_2O/hexane to provide a white crystalline solid.

MP 70-72 °C (Et_2O/hexane).

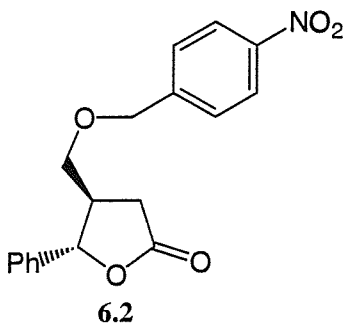
FT-IR (neat) ν_{max} 1778 m, 1511 s, 1350 s, 1126 m, 1113 m, 1101 m cm^{-1}.

^{1}H NMR (400 MHz) δ 8.25 (2H, d, *J* = 9.0 Hz, PhH), 7.54 (2H, d, *J* = 9.0 Hz, PhH), 7.41-7.28 (5H, m, PhH), 4.76 (2H, s, ArCH_2-), 4.45 (1H, d, *J* = 7.5 Hz, -CHPh), 3.96-3.88 (2H, m, -CH_2OCH_2Ar), 3.18-3.14 (2H, m, -COCH_2-), 3.02-2.92 (1H, m, -COCH_2CH-).

^{13}C NMR (100 MHz) δ 205.6 (CO), 147.6 (C_{ar}), 145.8 (C_{ar}), 135.8 (C_{ar}), 128.9 (CH_{ar}), 127.8 (CH_{ar}), 127.4 (CH_{ar}), 127.2 (CH_{ar}), 123.9 (CH_{ar}), 73.0 (-CH_2OCH_2Ar), 72.1 (-CH_2Ar), 66.9 (-CHPh), 47.3 (-CH_2CH-), 32.4 (-CH_2CH-).

CHN Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.39; H, 5.41; N, 4.40.

(4R*, 5S*)-4-{[(4-Nitrobenzyl)oxy]methyl}-5-phenyltetrahydro-2-furanone (6.2)



6.2

$C_{18}H_{17}NO_5$

m.w. = 327.34 g/mol

White powdery solid

The title compound was prepared according to the method outlined for **5.4**, whereby reaction of cyclobutanone **6.1** (300 mg, 0.96 mmol) with hydrogen peroxide and workup under the conditions described gave a pale yellow solid (310 mg). Purification was accomplished by recrystallisation from Et_2O/hexane to yield the title compound **6.2** (262 mg, 0.80 mmol, 83 %) as a pale yellow solid.

MP 74-76 °C (Et_2O/hexane).

FT-IR (neat) ν_{max} 1790 m, 1513 s, 1350 s, 1204 m, 1150 m, 1093 m, 990 s cm^{-1}.

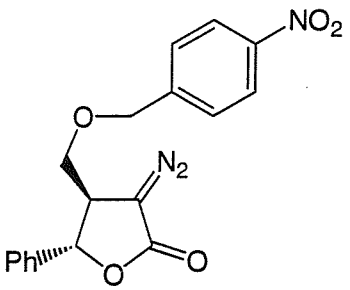
^{1}H NMR (400 MHz) δ 8.26 (2H, d, *J* = 9.0 Hz, PhH), 7.51 (2H, d, *J* = 9.0 Hz, PhH), 7.46-7.33 (5H, m, PhH), 5.43 (1H, d, *J* = 6.5 Hz, PhCH-), 4.70 (2H, s, -CH_2Ar), 3.73-3.66 (2H, m, -CH_2OCH_2Ar), 2.87-2.77 (2H, m, -COCHH- and -CH_2CH-), 2.72-2.63 (1H, m, -COCHH-).

^{13}C NMR (100 MHz) δ 176.2 (CO), 148.0 (C_{ar}), 145.5 (C_{ar}), 139.1 (C_{ar}), 129.3 (CH_{ar}), 129.1 (CH_{ar}), 128.1 (CH_{ar}), 126.0 (CH_{ar}), 124.2 (CH_{ar}), 83.5 (PhCH-), 72.5 (ArCH_2-), 70.3 (-CH_2OCH_2Ar), 44.8 (-CH_2CH-), 32.0 (-COCH_2-).

LRMS (CI, NH_3) *m/z* (relative intensity) 328 (1) $[M+H]^+$, 107 (100).

CHN Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found: C, 65.91; H, 5.16; N, 4.15.

(4R*, 5S*)-3-Diazo-4-{[(4-nitrobenzyl)oxy]methyl}-5-phenyltetrahydro-2-furanone (6.3)



6.3

$C_{18}H_{15}N_3O_5$

m.w. = 353.33 g/mol

Yellow oil

Method A

The title compound was prepared according to the method outlined for **5.18** (Method A), whereby reaction of lactone **6.2** (180 mg, 0.55 mmol) with LiHMDS and 2,2,2-trifluoroethyltrifluoroacetate (82 μL, 0.61 mmol) under the conditions described gave crude **(4R*, 5S*) -4-{[(4-nitrobenzyl)oxy]methyl}-5-phenyl-3-(2,2,2,-trifluoroacetyl) tetrahydro-2-furanone** (215 mg, quantitative) as a yellow oil. This crude material was used directly in the subsequent diazo-transfer reaction, which was conducted following the procedure described for **5.18**, whereby reaction of the crude trifluoroacetylated

lactone (0.55 mmol theoretical) with 4-nitrobenzenesulfonyl azide (140 mg, 0.61 mmol) and workup under the conditions described gave a crude yellow oil (340 mg). Purification was accomplished by flash chromatography on silica gel (2.3 x 6.5) eluting with Et_2O/hexane (4:1) to yield the title compound **6.3** (99 mg, 0.28 mmol, 60 %) as a yellow oil.

Method B

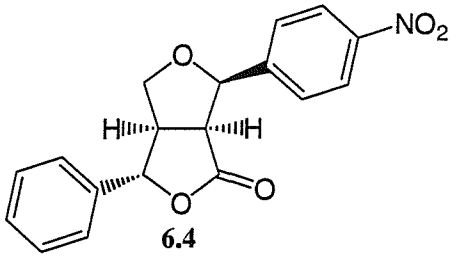
The title compound was prepared according to the method outlined for **5.18** (Method B) whereby lactone **7.47b** (92 mg, 0.25 mmol), Tf_2O (168 μL, 1.00 mmol) and NaN_3 (130 mg, 2.00 mmol) were reacted and worked up under the conditions described to yield a crude yellow foam (101 mg). Purification was accomplished by flash chromatography on silica gel (2.2 x 3.5) eluting with EtOAc/hexane (3:97) to EtOAc/hexane (1:4) in 3 % increment rises (20 mL each) to give the title compound **6.3** (70 mg, 0.20 mmol, 80 %) as a yellow oil.

FT-IR (neat) ν_{max} 2101 s, 1735 s, 1518 s, 1376 m, 1345 s, 1261 m, 1107 s cm^{-1}.

^{1}H NMR (300 MHz) δ 8.24 (2H, d, *J* = 8.8 Hz, PhH), 7.47 (2H, d, *J* = 8.8 Hz, PhH), 7.44-7.32 (5H, m, PhH), 5.20 (1H, d, *J* = 4.4 Hz, PhCH-), 4.71 (2H, s, -OCH$_2$PNP), 3.93-3.78 (3H, m, -CH$_2$OPNB and -CHCH$_2$-).

^{13}C NMR (75 MHz) δ 169.2 (CO), 147.8 (C_{ar}), 144.7 (C_{ar}), 138.8 (C_{ar}), 129.2 (CH_{ar}), 127.8 (CH_{ar}), 125.5 (CH_{ar}), 124.0 (CH_{ar}), 80.5 (PhCH-), 72.5 (PNPCH$_2$O-), 71.8 (-CH$_2$OPNB), 52.8 (-CN$_2$), 45.4 (-CHCH$_2$-).

(1S*, 2R*, 5R*, 6S*)-2-(4-Nitrophenyl)-6-phenyl-3,7-dioxabicyclo[3.3.0]octan-8-one (6.4)



6.4

$C_{18}H_{15}NO_5$

m.w. = 325.32 g/mol

Pale yellow solid

The title compound was prepared according to the method outlined for **5.19**, whereby reaction of diazo lactone **6.3** (65 mg, 0.18 mmol) with dirhodium (II) tetraacetate (2 mg, cat.) and workup under the conditions described gave crude furofuranone as a yellow foam (59 mg). Triturating with Et_2O gave the product as a very pale yellow powdery solid (35 mg, 0.11 mmol, 60 %). Purification of the filtrate was accomplished by flash chromatography on silica gel (2 x 6.5) eluting with Et_2O/hexane (1:1 then 4:1) to yield the

title compound **6.4** (7 mg, 0.02 mmol, 12 %) as a pale yellow solid - overall yield (42 mg, 0.13 mmol, 72 %).

MP 175-177 °C (Et_2O).

FT-IR (neat) ν_{max} 1762 s, 1512 m, 1347 s, 1172 s, 1072 m, 1019 m cm^{-1}.

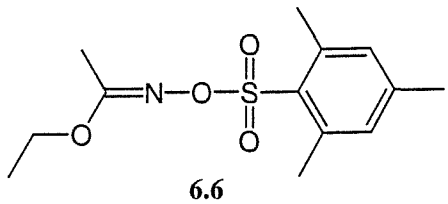
^{1}H NMR (400 MHz) δ 8.25 (2H, d, *J* = 8.5 Hz, PhH), 7.59 (2H, d, *J* = 9.0 Hz, PhH), 7.44-7.35 (3H, m, PhH), 7.34-7.30 (2H, m, PhH), 5.30 (1H, d, *J* = 6.0 Hz, PhCH-), 5.17 (1H, d, *J* = 8.0 Hz, PNPCH-), 4.42 (1H, d, *J* = 9.5 Hz, -CHH-), 4.03 (1H, dd, *J* = 10.0, 5.0 Hz, -CHH-), 3.68 (1H, t, *J* = 8.5 Hz, -COCH-), 3.32 (1H, ddd, *J* = 10.5, 9.5, 5.5, $-CH_2CH-$).

^{13}C NMR (100 MHz) δ 174.1 (CO), 148.3 (C_{ar}), 143.7 (C_{ar}), 139.6 (C_{ar}), 129.5 (CH_{ar}), 129.4 (CH_{ar}), 127.6 (CH_{ar}), 125.7 (CH_{ar}), 124.1 (CH_{ar}), 86.2 (PhCH-) 83.1 (PNPCH-), 73.2 ($-CH_2-$), 51.6 (-COCH-), 51.1 ($-CH_2CH-$).

LRMS (EI) *m/z* (relative intensity) 325 (6) $[M]^{\bullet+}$, 104 (100).

CHN Anal. Calcd for $C_{18}H_{15}NO_5$: C, 66.46; H, 4.65; N, 4.30. Found: C, 66.17; H, 4.66; N, 4.27.

Ethyl *O*-(mesitylenesulfonyl)-acetohydroxamate (38202-27-6) (6.6)



6.6

$C_{13}H_{19}NSO_4$

m.w. = 285.36 g/mol

White solid

The title compound was prepared according to the method described by Tamura *et al.*[178] Thus, to a solution of ethyl *N*-hydroxyacetimidate (4.0 g, 38.8 mmol) and NEt_3 (5.4 mL, 38.8 mmol) in DMF (15 mL) at 0 °C (ice/salt bath) was added 2-mesitylenesulfonyl chloride (8.5 g, 38.8 mmol) portionwise over 15 min. Stirring was continued for a further 25 min at 0 °C and then the reaction mixture was poured onto ice/water (30 mL). The pale yellow precipitated solid was collected, washed with cold water (70 mL), dissolved in Et_2O (50 mL) and dried with Na_2SO_4. Concentration *in vacuo* (below 40 °C) gave a yellow oil which solidified on standing to a yellow solid. This was dissolved in petroleum ether by slight warming, the solution filtered and chilled in a CO_2(s)/acetone bath (-40 °C). The resulting precipitate was collected and dried under vacuum for 1 hour

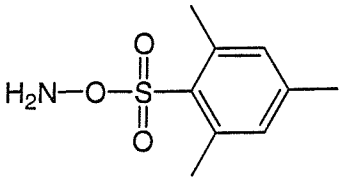
to give the title compound **6.6** (7.6 g, 26.5 mmol, 68 %) as a white solid. Spectroscopic details were consistent with those observed in the literature.[177,178]

MP 56-57 °C (pet. ether) (lit.[178] 54-56 °C, lit.[177] 57-58 °C).

FT-IR (neat) ν_{max} 1634 m, 1363 s, 1317 m, 1199 m, 1178 s cm^{-1}.

^{1}H NMR (300 MHz) δ 6.98 (2H, s, PhH), 3.92 (2H, q, J = 7.0 Hz, CH_3CH_2-), 2.66 (6H, s, 2 x $PhCH_3$), 2.32 (3H, s, $PhCH_3$), 2.05 (3H, s, -$NCCH_3$), 1.20 (3H, t, J = 7.0, CH_3CH_2-).

O-Mesitylenesulfonylhydroxylamine (36016-40-7)



$C_9H_{13}NSO_3$

m.w. = 215.27 g/mol

White solid

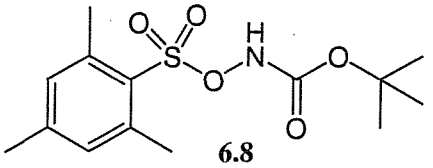
The title compound was prepared according to a modification of the procedure described by Tamura *et al.*[178] Thus, to perchloric acid (1.1 g of a 70 % aqueous solution, 7.7 mmol) at 0 °C (ice bath) was added a solution of ethyl *N*-mesitylenesulfonyl-acetohydroxamate (**6.6**) (2.0 g, 7.0 mmol) in 1,4-dioxane (5 mL) over 10 min. The reaction mixture was stirred for a further 15 min, whereby TLC analysis still showed presence of **6.6**. Perchloric acid (0.5 g of a 70 % aqueous solution) was added dropwise and the reaction stirred at 0 °C for 60 min. The pasty coloured reaction mixture was then poured onto ice/water to give a white solid which was collected, washed with cold water, ice-cold hexane and dried under vacuum to yield the title compound (1.2 g, 5.6 mmol, 80 %) as a white solid. [Note: product should be stored in a freezer/refrigerator following observation of its rapid and explosive decomposition when allowed to stand at room temperature for long periods of time.] Spectroscopic details were consistent with those observed in the literature.[177,178]

MP 94-96 °C (lit.[177,178] 93-94 °C).

FT-IR (neat) ν_{max} 3339 w, 1599 w, 1347 m, 1173 s, 779 s cm^{-1}.

^{1}H NMR (300 MHz) δ 6.99 (2H, s, PhH), 5.57 (2H, s br, -NH_2), 2.64 (6H, s, 2 x -CH_3), 2.32 (3H, s, -CH_3).

***Tert*-butyl-*N*-(mesitylenesulfonyloxy)carbamate (36016-39-4) (6.8)**



6.8

$C_{14}H_{21}NO_5S$

m.w. = 315.28 g/mol

White solid

The title compound was prepared according to the method described by Haga *et al.*[183] Thus, potassium carbonate (2.2 g, 15.8 mmol) was added to a solution of hydroxylamine hydrochloride (1.0 g, 14.4 mmol) in water (4 mL) with stirring at 0 °C (ice bath). To this was added THF (4 mL) followed by a solution of di-*tert*-butyl dicarbonate (3.45 g, 15.8 mmol) in THF (30 mL) at 0 °C dropwise over 1 h. The reaction mixture was then allowed to warm to room temperature and left stirring for 1 h before addition of brine (15 mL). The organic layer was separated and the aqueous extracted with Et_2O (3 x 20 mL). The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo* to give the crude *N*-Boc protected hydroxylamine as a colourless oil (2.0 g). To a solution of this crude material in DMF (10 mL) at 0 °C (ice/salt bath) was added NEt_3 (2.1 mL, 15 mmol) then mesitylenesulfonyl chloride (3.3 g, 15 mmol) portionwise over 20 min. After 1 h at 0 °C the viscous yellow reaction mixture was treated with water (100 mL) before extraction with CH_2Cl_2 (3 x 200 mL). The combined organic phases were washed with water (3 x 200 mL) and brine (100 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield a crude yellow oil (3.9 g). Purification was accomplished by flash chromatography on silica gel (5 x 8) eluting with CH_2Cl_2/hexane (1:1) followed by CH_2Cl_2 to yield the title compound **6.8** (1.4 g, 4.4 mmol, 30 %) as a white crystalline solid.

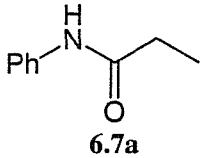
MP 102-105 °C (lit.[182] 104-105.5 °C).

FT-IR (neat) ν_{max} 3284 w, 2983 w, 1762 s, 1357 s, 1248 s, 1152 s cm^{-1}.

^{1}H NMR (300 MHz) δ 7.63 (1H, s, -N**H**), 7.00 (2H, s, Ph**H**), 2.69 (6H, s, 2 x PhC**H**$_3$), 2.33 (3H, s, PhC**H**$_3$), 1.33 (9H, s, -C(C**H**$_3$)$_3$).

^{13}C NMR (75 MHz) δ 173.8 (**C**O), 154.1 (**C**$_{ar}$), 141.9 (**C**$_{ar}$), 131.6 (**C**H$_{ar}$), 128.2 (**C**$_{ar}$), 84.0 (-O**C**(CH$_3$)$_3$), 27.9 (-OC(**C**H$_3$)$_3$), 23.3 (-**C**H$_3$), 21.3(-**C**H$_3$).

***N*-Phenyl propionamide (620-71-3) (6.7a)**



6.7a

$C_9H_{11}NO$

m.w. = 149.19 g/mol

White crystalline solid

To a solution of propiophenone (0.2 mL, 1.5 mmol) in CH_2Cl_2 (5 mL) at 0 °C (ice/salt) was added sulfonyl hydroxamate **6.6** (640 mg, 2.25 mmol) in one portion, followed by perchloric acid (0.15 mL of a 70 % aqueous solution). The reaction mixture was allowed to warm to room temperature and stirred for 1h before concentrating *in vacuo* (1 mL). The resulting suspension was loaded onto an alumina (basic – Brockmann grade I, 10 g) column, eluted with MeOH (30 mL) and the filtrate concentrated *in vacuo*. The resulting residue was dissolved in $CHCl_3$ and the insoluble material removed by filtration before re-concentration to yield a dark yellow oil (530 mg). Purification was accomplished by flash chromatography on silica gel (3 x 10) eluting with Et_2O/hexane (1:1) to yield the title compound **6.7a** (222 mg, 1.49 mmol, 99 %) as a white crystalline solid. Spectroscopic details were consistent with those observed in the literature.[255]

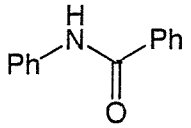
MP 102-105 °C (lit.[256] 102.6-104.5 °C).

FT-IR (neat) ν_{max} 3255 w, 1664 s, 1602 s, 1548 s, 1479 s, 1441 s, 1253 m cm^{-1}.

^{1}H NMR (400 MHz) δ 7.52 (2H, d, J = 7.5 Hz, Ph**H**), 7.46 (1H, s br, -N**H**-), 7.31 (2H, t, J = 8.0 Hz, Ph**H**), 7.09 (1H, t, J = 7.5 Hz, Ph**H**), 2.38 (2H, q, J = 7.5 Hz, -C**H**$_2$CH$_3$), 1.24 (3H, t, J = 7.5 Hz, -CH$_2$C**H**$_3$).

^{13}C NMR (100 MHz) δ 172.6 (**C**O), 138.4 (**C**$_{ar}$), 129.4 (**C**H$_{ar}$), 124.6 (**C**H$_{ar}$), 120.3 (**C**H$_{ar}$), 31.1 (-**C**H$_2$CH$_3$), 10.1 (-CH$_2$**C**H$_3$).

***N*-Phenyl benzamide (93-98-1) (6.7b)**



6.7b

$C_{13}H_{11}NO$

m.w. = 197.24 g/mol

Off-white crystalline solid

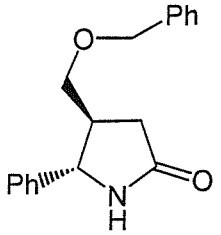
To a solution of benzophenone (273 mg, 1.5 mmol) in CH_2Cl_2 (5 mL) at 0 °C (ice/salt bath) was added sulfonyl hydroxamate **6.6** (45 mg, 0.15 mmol) in one portion, followed by perchloric acid (0.15 mL of a 70 % aqueous solution). The remainder of the hydroxamate **6.6** (600 mg, 2.10 mmol) was added over a period of 20 min at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 h before concentrating *in vacuo* (1 mL). Purification was accomplished by flash chromatography on silica gel (3 x 3) eluting with Et_2O/hexane (1:1), followed by recrystallisation of the resulting crude cream solid from Et_2O to yield the title compound **6.7b** (228 mg, 1.16 mmol, 77 %) as an off-white crystalline solid. Spectroscopic details were consistent with those observed in the literature.[257]

MP 161-164 °C (Et_2O) (lit.[257] 162-163 °C).

FT-IR (neat) ν_{max} 3343 w, 1654 s, 1599 m, 1526 s, 1491 m, 1445 s, 1321 m cm^{-1}.

^{1}H NMR (400 MHz) δ 7.89 (3H, m, Ph**H** and -N**H**), 7.65 (2H, dd, *J* = 7.5, 1.0 Hz, Ph**H**), 7.55 (1H, tt, *J* = 7.5, 2.0 Hz, Ph**H**), 7.51-7.46 (2H, m, Ph**H**), 7.40-7.35 (2H, m, Ph**H**), 7.16 (1H, tt, *J* = 7.5, 1.0 Hz, Ph**H**).

(4R*, 5S*)-5-Phenyl-4-[(benzyloxy)methyl]tetrahydro-2-pyrrolone (6.9)



6.9

$C_{18}H_{19}NO_2$

m.w. = 281.35 g/mol

Colourless oil

Method A

To a solution of *tert*-butyl-*N*-(mesitylenesulfonyloxy)carbamate (**6.8**) (200 mg, 0.63 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C (ice/salt bath) was added TFA (50 μL, 0.63 mmol). The reaction mixture was left stirring at 0 °C for 10 min before adding a solution of cyclobutanaone **5.13** in CH_2Cl_2 (0.5 mL) dropwise over 5 min. The reaction was allowed to warm to room temperature and left stirring for 18 h, diluted with CH_2Cl_2 (5 mL) and quenched with sat. $NaHCO_3$ (aq) (5 mL). The organic layer was separated and the aqueous extracted with CH_2Cl_2 (3 x 5 mL), the combined organic layers were washed with brine (5 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield a crude yellow oil (222 mg). Purification was accomplished by flash chromatography on silica gel (2.3 x 5) eluting with Et_2O/hexane (3:2) followed by CH_2Cl_2/methanol (49:1) to yield the title compound **6.9** (75 mg, 0.27 mmol, 42 %) as a colourless oil.

Method B

To a solution of cyclobutanone **5.13** (155 mg, 0.58 mmol) in CH_2Cl_2 (5 mL) at 0 °C (ice/salt bath) was added *O*-mesitylenesulfonylhydroxylamine (MSH) (187 mg, 0.87 mmol) portionwise over 2 minutes. TLC analysis after 20 min still showed the presence of cyclobutanone **5.13** so further MSH (62 mg, 0.43 mmol) was added, the reaction mixture warmed to room temperature and left stirring for 18 h. The mixture was diluted with CH_2Cl_2 (5 mL) and poured onto water (10 mL), the organic phase separated and the aqueous extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield a crude colourless oil (250 mg). Purification was accomplished by flash chromatography on

silica gel (1.5 x 5) eluting with Et_2O/hexane (1:1) followed by CH_2Cl_2/methanol (49:1) to give the title compound **6.9** (140 mg, 0.50 mmol, 86 %) as a colourless oil.

FT-IR (neat) ν_{max} 3032 br w, 1696 s, 1454 w, 1110 m cm^{-1}.

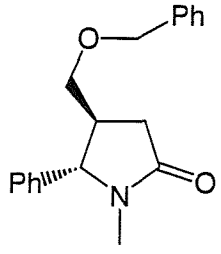
^{1}H NMR (400 MHz) δ 7.41-7.24 (10H, m, PhH), 5.82 (1H, br s, -NH), 4.61 (1H, d, *J* = 5.5 Hz, PhCH-), 4.58 (1H, d, *J* = 12 Hz, PhCHH-), 4.52 (1H, d, *J* = 12 Hz, PhCHH-), 3.58-3.47 (2H, m, -CH_2OBn), 2.64-2.44 (2H, m, -COCHH- and -CH_2CH-), 2.39 (1H, dd, *J* = 14.4, 5.5 Hz, -COCHH-).

^{13}C NMR (100 MHz) δ 177.5 (CO), 142.1 (C_{ar}), 138.3 (C_{ar}), 129.3 (CH_{ar}), 128.9 (CH_{ar}), 128.5 (CH_{ar}), 128.2 (CH_{ar}), 128.1 (CH_{ar}), 126.4 (CH_{ar}), 73.6 (-OCH_2Ph), 70.3 (-CH_2OBn), 60.7 (PhCH-), 45.5 (-CH_2CH-), 33.6 (-COCH_2-).

LRMS (ES +ve) *m/z* (relative intensity) 282 (50) $[M+H]^+$, 304 (30) $[M+Na]^+$.

HRMS (ES +ve) Calcd for $C_{18}H_{19}NO_2Na$ 304.1308, found 304.1303.

(4R*, 5S*)-4-[(Benzyloxy)methyl]-1-methyl-5-phenyltetrahydro-2-pyrrolone (6.10)



6.10

$C_{19}H_{21}NO_2$

m.w. = 295.38 g/mol

Colourless oil

To a solution of lactam **6.9** (130 mg, 0.46 mmol) in THF (3 mL) at room temperature was added potassium-*tert*-butoxide (57 mg, 0.51 mmol) in portionwise over 1 min. The resulting colourless reaction mixture was stirred for 20 min before a solution of MeI (34 μL, 0.55 mmol) in THF (1 mL) was added dropwise over 1 min. The resulting cream coloured suspension was left stirring for 10 h, diluted with Et_2O (10 mL) and quenched with sat. NH_4Cl (aq) (10 mL). The organic layer was separated and the aqueous extracted with Et_2O (3 x 10 mL), the combined organic extracts were washed with brine (20 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield a pale yellow oil (139 mg). Purification was accomplished by flash chromatography on silica (1.5 x 6) eluting with CH_2Cl_2/methanol (49:1) to yield the title compound **6.10** (131 mg, 0.44 mmol, 96 %) as a colourless oil.

FT-IR (neat) ν_{max} 1690 s, 1454 m, 1396 m, 1102 m cm^{-1}.

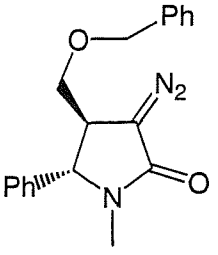
^{1}H NMR (400 MHz) δ 7.39-7.28 (8H, m, PhH), 7.15 (2H, dd, *J* = 7.5, 2.0 Hz, PhH), 4.55 (1H, d, *J* = 12.0 Hz, -CHHPh), 4.50 (1H, d, *J* = 12.0 Hz, -CHHPh), 4.37 (1H, d, *J* = 5.0 Hz, PhCH-), 3.53-3.43 (2H, m, -CH_2OBn), 2.71-2.63 (1H, obsc. dd, *J* = 15.6, 8.5 Hz, -COCHH-) 2.65 (3H, s, -NCH_3), 2.46-2.32 (2H, m, -COCHH- and -CH_2CH-).

^{13}C NMR (100 MHz) δ 174.9 (CO), 140.8 (C_{ar}), 138.4 (C_{ar}), 129.4 (CH_{ar}), 128.9 (CH_{ar}), 128.5 (CH_{ar}), 128.2 (CH_{ar}), 128.1 (CH_{ar}), 127.0 (CH_{ar}), 73.6 (-CH_2Ph), 70.9 (-CH_2OBn), 67.5 (PhCH-), 42.3 (-CH_2CH-), 33.8 (-$COCH_2$-), 28.7 (-NCH_3).

LRMS (CI, NH_3) *m/z* (relative intensity) 296 (18) $[M+H]^+$, 204 (100) $[M-PhCH_2]^+$, 91 (86) $[PhCH_2]^+$.

HRMS (ES +ve) Calcd for $C_{19}H_{21}NO_2Na$ 318.1465, found 318.1465.

(4R*, 5S*)-4-[(Benzyloxy)methyl]-3-diazo-1-methyl-5-phenyltetrahydro-2-pyrrolone (6.11)



6.11

$C_{19}H_{19}N_3O_2$

m.w. = 321.38 g/mol

Yellow oil

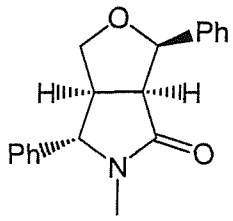
The title compound was prepared according to the method outlined for **5.18**, whereby reaction of lactam **6.10** (115 mg, 0.39 mmol) with LiHMDS and 2,2,2-trifluoroethyl-trifluoroacetate (57 μL, 0.43 mmol) and workup under the conditions described gave **(4R*, 5S*)-4-[(benzyloxy)methyl]-1-methyl-5-phenyl-3-trifluoroacetyl-tetrahydro-2-pyrrolone** (160 mg, quantitative) as a crude yellow oil. To a solution of this crude material in acetonitrile (4 mL), at room temperature, was added Hünig's base (68 μL, 0.39 mmol) and the reaction stirred for 5 min before addition of 4-nitrobenzenesulfonyl azide (**2.31**) (107 mg, 0.47 mmol) in one portion. The mixture was stirred for 44 h before diluting with CH_2Cl_2 (15 mL) and pouring onto water (10 mL). The organic layer was separated and the aqueous extracted with CH_2Cl_2 (3 x 10 mL), washed with brine (15 mL), dried with $MgSO_4$ and concentrated in vacuo to yield a crude yellow oil (230 mg). Purification was accomplished by flash chromatography on silica gel (2.5 x 7) eluting with EtOAc/hexane (1:1) to yield the title compound **6.11** (55 mg, 0.17 mmol, 44 % from lactam **6.10**) as a bright yellow oil.

FT-IR (neat) ν_{max} 2083 s, 1681 s, 1454 m, 1422 m, 1394 m, 1107 m cm^{-1}.

^{1}H NMR (400 MHz) δ 7.42-7.21 (10H, m, PhH), 4.56 (2H, s, -CH_2Ph), 4.14 (1H, d, *J* = 4.5 Hz, PhCH-), 3.74 (1H, dd, *J* = 9.0, 5.5 Hz, -CHHOBn), 3.67 (1H, dd, *J* = 9.0, 7.5 Hz, -CHHOBn), 3.48 (1H, ddd, *J* = 7.5, 5.5, 4.5 Hz, -$CHCH_2$-), 2.67 (3H, s, -NCH_3).

^{13}C NMR (100 MHz) δ 168.0 (CO), 140.1 (C_{ar}), 137.9 (C_{ar}), 129.6 (CH_{ar}), 129.0 (CH_{ar}), 128.9 (CH_{ar}), 128.3 (CH_{ar}), 128.0 (CH_{ar}), 126.9 (CH_{ar}), 73.9 (-CH_2Ph), 71.5 (-CH_2OBn), 65.2 (PhCH-), 54.7 (-CN_2), 43.1 (-$CHCH_2$-), 29.5 (-NCH_3).

(1S*, 2R*, 5R*, 6S*) 2,6-Diphenyl-3-oxa-7-aza(methyl)bicyclo[3.3.0]octan-8-one (6.12)



6.12

$C_{19}H_{19}NO_2$

m.w. = 293.36 g/mol

White crystalline solid

The title compound was prepared according to the method outlined for **5.19**, whereby reaction of diazo lactam **6.11** (50 mg, 0.16 mmol) with dirhodium (II) tetraacetate (0.1 mg, 2 mol %) and workup under the conditions described gave a crude furofuranone as a colourless oil (55 mg). Purification was accomplished on silica gel (2.2 x 8) eluting with EtOAc/hexane (1:1) to yield the title compound **6.12** (42 mg, 0.14 mmol, 90 %) as a white crystalline solid.

MP 146-149 °C.

FT-IR (neat) ν_{max} 1687 s, 1392 m, 1101 m, 1056 s cm^{-1}.

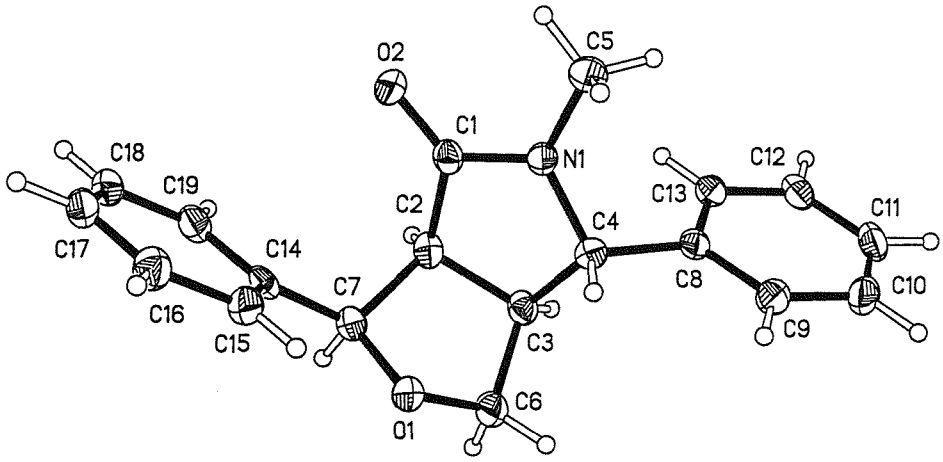
^{1}H NMR (400 MHz) δ 7.44-7.21 (10H, m, PhH), 5.06 (1H, d, *J* = 8.5 Hz, PhCHO-), 4.40 (1H, d, *J* = 5.0 Hz, PhCHN-), 4.29 (1H, d, *J* = 9.5 Hz, -OCHH-), 3.89 (1H, dd, *J* = 9.5, 5.0 Hz, -OCHH-), 3.48 (1H, t, *J* = 8.5 Hz, -NCOCH-), 2.96 (1H, dt, *J* = 9.5, 5.0, -OCH_2CH-), 2.48 (3H, s, -NCH_3).

^{13}C NMR (100 MHz) δ 172.9 (CO), 141.1 (C_{ar}), 137.7 (C_{ar}), 129.7 (CH_{ar}), 128.9 (CH_{ar}), 128.6 (CH_{ar}), 128.5 (CH_{ar}), 127.1 (CH_{ar}), 126.8 (CH_{ar}), 84.5 (PhCHO-), 72.8 (-CH_2-), 70.7 (PhCHN-), 52.7 (-NCOCH-), 49.4 (-OCH_2CH-), 28.4 (-NCH_3).

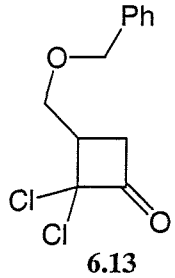
LRMS (EI) *m/z* (relative intensity) 293 (85) $[M]^{\bullet+}$, 91 (100) $[PhCH_2]^{\bullet+}$.

CHN Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.42; H, 6.53; N, 4.67.

X-ray structure



3-(Benzyloxymethyl)-2,2-dichlorocyclobutanone (6.13)



6.13

$C_{12}H_{12}O_2Cl_2$

m.w. = 259.13 g/mol

Colourless oil

Activation of Zinc. This procedure is a slight modification of that described by Hassner *et al.*[184] Thus, a stirred suspension of zinc dust (6.54 g, 0.1 mol) in water (30 mL) was degassed by bubbling argon through for 15 min. Copper (II) sulphate (780 mg, 3.1 mmol) was added in one portion and the resulting black suspension stirred, with argon agitation, for an additional 30 min before filtering under a stream of argon. The resulting black powder was washed with water (100 mL), acetone (100 mL) and dried *in vacuo* for 4 h before being used directly in the subsequent reaction.

The title compound was prepared according to a general procedure described by Oehlschlager *et al.*[185] Thus, to a suspension of zinc-copper couple (6 g, 93 mmol) in dry Et_2O (70 mL) and DME, (10 mL - freshly distilled over $LiAlH_4$) was added allylbenzyl ether (4.6 mL, 30 mmol). To this black suspension was added a solution of

trichloroacetyl chloride (9.0 mL, 81 mmol) in Et_2O/DME (8:1, 45 mL) over 40 min *via* dropping funnel. The reaction mixture was refluxed for 66 h, cooled to room temperature then filtered through Celite and the residual salts washed thoroughly with Et_2O (3 x 40 mL). The filtrate was concentrated *in vacuo* and the resulting residue was dissolved in hexane (150 mL). The insoluble material was removed by filtering through Celite and the filtrate washed with sat. $NaHCO_3$ (aq) (2 x 100 mL) and brine (80 mL), dried with $MgSO_4$, and concentrated *in vacuo* to yield a dark orange oil (15.6 g). This crude oil was quickly passed through silica gel (5.5 x 6), eluting with Et_2O/hexane (1:4) to yield an orange oil (8.5 g). Final purification was accomplished by distillation under reduced pressure to yield the title compound **6.13** (4.89 g, 18.9 mmol, 63 %) as a colourless oil. Spectroscopic details were consistent with those observed in the literature.[165]

BP 108-110 °C (0.4 mbar).

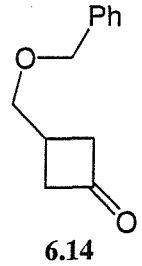
FT-IR (neat) ν_{max} 1810 s, 1100 m, 1077 m, 1028 m cm^{-1}.

^{1}H NMR (400 MHz) δ 7.40-7.30 (5H, m, PhH), 4.59 (2H, s, $PhCH_2$-), 3.89-3.84 (1H, dd, J = 10.0, 6.0 Hz, -CHHOBn), 3.71 (1H, dd, J = 10.0, 5.5 Hz, -CHHOBn), 3.51-3.39 (1H, m, -COCHH-), 3.25-3.11 (2H, m, -COCHH- and $-CHCCl_2$).

^{13}C NMR (100 MHz) δ 192.6 (CO), 137.9 (C_{ar}), 128.9 (CH_{ar}), 128.3 (CH_{ar}), 128.1 (CH_{ar}), 87.9 ($-CCl_2$), 73.9 ($PhCH_2$-), 69.4 ($-CH_2OBn$), 45.9 ($-COCH_2$-), 45.6 ($-CHCCl_2$).

LRMS (CI, NH_3) *m/z* (relative intensity) 208 (4) $[(M+NH_4(-Cl_2)]^+$, 91 (100) $[PhCH_2]^+$.

3-(Benzyloxymethyl)cyclobutanone (6.14)



6.14

$C_{12}H_{14}O_2$

m.w. = 190.24 g/mol

Colourless oil

The title compound was prepared according to the general procedure described by Oehlschlager *et al.*[185] Thus, to a solution of dichlorocyclobutanone **6.13** (3.89 g, 15 mmol) in MeOH (60 mL), saturated with NH_4Cl, was added zinc powder (6 g) and the reaction stirred at room temperature for 90 min. The mixture was filtered through Celite and washed with Et_2O and the filtrate concentrated *in vacuo*. The resulting pale cream

residue was partitioned between Et_2O (200 mL) and water (100 mL), the aqueous layer separated and the organic washed further with water (150 mL), dried with $MgSO_4$, and concentrated *in vacuo* to yield a pale yellow oil (2.7 g). Purification was accomplished by bulb-to-bulb distillation under reduced pressure to yield the title compound **6.14** (2.56 g, 13.5 mmol, 90 %) as a colourless oil. Spectroscopic details were consistent with those observed in the literature.[165]

BP 102-104 °C (0.4 mbar).

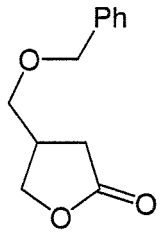
FT-IR (neat) ν_{max} 1782 s, 1454 w, 1383 m, 1365 m, 1093 s cm^{-1}.

^{1}H NMR (300 MHz) δ 7.42-7.29 (5H, m, Ph**H**), 4.58 (2H, s, -C**H**$_2$Ph), 3.61 (2H, d, J = 5.9 Hz, -C**H**$_2$OBn), 3.21-3.08 (2H, m, -COC**H**$_2$-), 2.95-2.85 (2H, m, -COC**H**$_2$-), 2.78-2.66 (1H, m, -CHCH$_2$-).

^{13}C NMR (75 MHz) δ 207.6 (**C**O), 138.1 (**C**$_{ar}$), 128.5 (**C**H$_{ar}$), 127.8 (**C**H$_{ar}$), 127.7 (**C**H$_{ar}$), 73.4 (-**C**H$_2$-), 73.1 (-**C**H$_2$-), 50.2 (-CO**C**H$_2$-), 23.7 (-**C**HCH$_2$-).

LRMS (CI, NH_3) *m/z* (relative intensity) 208 (15) $[M+NH_4]^+$, 91 (100) $[PhCH_2]^+$.

4-(Benzyloxymethyl)tetrahydro-2-furanone (6.15)



6.15

$C_{12}H_{14}O_3$

m.w. = 206.24 g/mol

Colourless oil

The title compound was prepared according to the method outlined for **5.4**, whereby reaction of cyclobutanone **6.14** (0.57 g, 3.0 mmol) with hydrogen peroxide (1.0 mL of a 30 % aqueous solution, 9.0 mmol) for 36 hours and workup under the conditions described gave a colourless oil (580 mg). Purification was accomplished by flash chromatography on silica gel (3.5 x 7) eluting with Et_2O/hexane (1:1) to yield the title compound **6.15** (495 mg, 2.4 mmol, 80 %) as a colourless oil. Spectroscopic details were consistent with those observed in the literature.[258]

FT-IR (neat) ν_{max} 1774 s, 1366 w, 1172 m, 1102 m, 1022 m cm^{-1}.

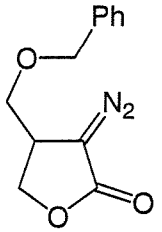
^{1}H NMR (400 MHz) δ 7.40-7.29 (5H, m, Ph**H**), 4.54 (2H, s, -C**H**$_2$Ph), 4.41 (1H, dd, J = 9.0, 7.5 Hz, -CO$_2$CH**H**-), 4.19 (1H, dd, J = 9.0, 5.5 Hz, -CO$_2$CH**H**-), 3.53-3.44 (2H, m, -C**H**$_2$OBn), 2.90-2.79 (1H, m,

-CHCH$_2$-), 2.61 (1H, dd, J = 17.6, 9.0 Hz, -COCHH-), 2.38 (1H, dd, J = 17.6, 6.5 Hz, -COCHH-).

^{13}C NMR (100 MHz) δ 177.2 (CO), 138.1 (C_{ar}), 128.9 (CH_{ar}), 128.3 (CH_{ar}), 128.1 (CH_{ar}), 73.8 (-CH_2-), 71.2 (-CH_2-), 70.8 (-CH_2-), 35.9 (-CHCH$_2$-), 31.6 (-COCH$_2$-).

LRMS (CI, NH_3) *m/z* (relative intensity) 207 (24) $[M+H]^+$, 224 (35) $[M+NH_4]^+$, 91 (100) $[PhCH_2]^+$.

4-(Benzyloxymethyl)-3-diazotetrahydro-2-furanone (6.16)



6.16

$C_{12}H_{12}N_2O_3$

m.w. = 232.24 g/mol

Yellow powdery solid

The title compound was prepared according to the method outlined for **5.18**, whereby reaction of lactone **6.15** (247 mg, 1.2 mmol) with LiHMDS and 2,2,2-trifluoroethyl-trifluoroacetate (0.18 mL, 1.32 mmol) and workup under the conditions described gave **4-(benzyloxymethyl)-3-(trifluoroacetyl)tetrahydro-2-furanone** (440 mg, quantitative) as a crude yellow solid. This crude material was used directly in the subsequent diazo-transfer reaction, which was conducted following the procedure described for **6.11**, whereby reaction of the crude trifluoroacetylated lactone (1.2 mmol theoretical) with 4-nitrobenzenesulfonylazide (329 mg, 1.44 mmol) and workup under the conditions described gave a crude orange oil (795 mg). Purification was accomplished by flash chromatography on silica gel (3 x 7.5) eluting with Et_2O/hexane (1:1) to yield the title compound **6.16** (237 mg, 1.0 mmol, 85 %) as a powdery yellow solid.

MP 68-70 °C (Et_2O/hexane).

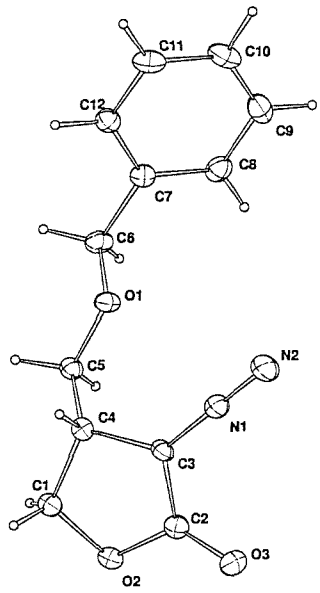
FT-IR (neat) ν_{max} 2109 m, 1724 s, 1394 m, 1093 m, 1079 m, 1030 m cm^{-1}.

^{1}H NMR (400 MHz) δ 7.40-7.28 (5H, m, PhH), 4.58 (1H, d, J = 11.5 Hz, -CHHPh), 4.55 (1H, d, J = 11.5 Hz, -CHHPh), 4.40 (1H, t, J = 9.0 Hz, -CO_2CHH-), 4.02 (1H, dd, J = 9.0, 4.5 Hz, -CO_2CHH-) 3.88 (1H, m, -CHCN$_2$), 3.69 (1H, dd, J = 8.5, 5.5 Hz, -CHHOBn), 3.62 (1H, t, J = 8.5 Hz, -CHHOBn).

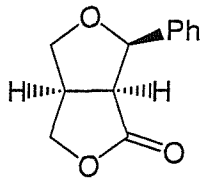
^{13}C NMR (100 MHz) δ 170.3 (CO), 137.6 (C_{ar}), 129.0 (CH_{ar}), 128.5 (CH_{ar}), 128.1 (CH_{ar}), 74.0 (-CH_2Ph), 71.7 (-CH_2OBn), 67.9 (-CO_2CH_2-), 53.3 (-CN_2), 37.2 (-CHCH$_2$-).

CHN Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.83; H, 5.26; N, 11.77.

X-ray structure



(1S*, 2R*, 5R*)-2-Phenyl-3,7-dioxabicyclo[3.3.0]octan-8-one (6.17)



6.17

$C_{12}H_{12}O_3$

m.w. = 204.23 g/mol

White crystalline solid

The title compound was prepared according to the method outlined for **5.19**, whereby reaction of diazo lactone **6.16** (100 mg, 0.43 mmol) with dirhodium (II) tetraacetate (0.4 mg, 2 mol %) and workup under the conditions described gave crude furofuranone as a colourless oil (104 mg). Purification was accomplished on silica gel (2.2 x 7.5) eluting with EtOAc/hexane (2:3) to yield the title compound **6.17** (74 mg, 0.36 mmol, 84 %) as a white crystalline solid.

MP 75-77 °C.

FT-IR (neat) ν_{max} 1773 s, 1169 s, 1049 s, 1037 s cm^{-1}.

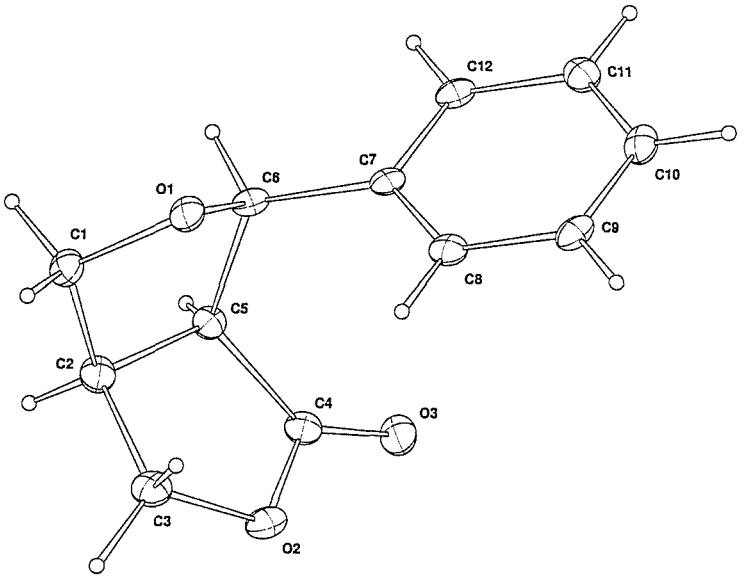
^{1}H NMR (400 MHz) δ 7.41-7.30 (5H, m, PhH), 5.07-5.01 (1H, m, PhCH-), 4.58-4.50 (1H, m, -CHHO$_2$C-), 4.17-4.11 (2H, m, -CHHO$_2$C- and -CHHO-), 3.95-3.90 (1H, m, -CHHO-), 3.42-3.34 (2H, m, -OCH$_2$CH- and PhCHCH-).

^{13}C NMR (100 MHz) δ 175.5 (**C**O), 136.4 ($\mathbf{C}_{ar}$), 128.8 ($\mathbf{C}H_{ar}$), 126.6 ($\mathbf{C}H_{ar}$), 84.3 (-**C**HPh), 73.4 (PhCHO$\mathbf{C}H_2$-), 72.9 (-$CO_2\mathbf{C}H_2$-), 50.4 (-$O_2\mathbf{C}$CH-), 41.7 (-$CO_2CH_2\mathbf{C}$H-).

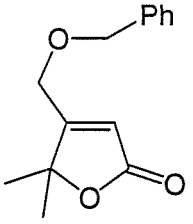
LRMS (EI) *m/z* (relative intensity) 204 (78) $[M]^{\bullet+}$, 105 (100).

CHN Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92. Found: C, 70.61; H, 6.03.

X-ray structure



4-[(Benzyloxy)methyl]-5,5-dimethyl-2(5H)-furanone (6.19)



6.19

$C_{14}H_{16}O_3$

m.w. = 232.28 g/mol

Pale yellow oil

The title compound was prepared using the method outlined for the preparation of **5.18**, whereby reaction of lactone **5.4** (750 mg, 3.20 mmol) with LiHMDS and 2,2,2-trifluoro-ethyltrifluoroacetate (0.47 mL, 3.52 mmol) under the conditions described gave crude **4-[(benzyloxy)methyl]-5,5-dimethyl-3-(trifluoroacetyl)dihydro-2-furanone** (1.19 g, quantitative) as a crude orange oil. This crude material was used directly in the subsequent diazo-transfer reaction, which was conducted following the procedure described for **5.18** (Method A), whereby reaction of the crude trifluoroacetylated lactone (3.20 mmol theoretical) with 4-nitrobenzenesulfonylazide (950 mg, 4.2 mmol) and workup under the conditions described (with addition of a quick 1N HCl (aq) wash) gave a crude yellow oil (3.2 g). TLC and IR analysis showed diazo decomposition had taken place. Purification was accomplished on silica gel (5 x 10) eluting with Et_2O/hexane

(1:1) to yield the title compound **6.19** as a pale yellow oil (280 mg, 1.2 mmol, 38 % from lactone **5.4**). Note: compound **6.19** has only been isolated in ~90 % purity but gives spectroscopic data as follows.

FT-IR (neat) ν_{max} 1749 s, 1250 m, 1109 m, 939 m cm^{-1}.

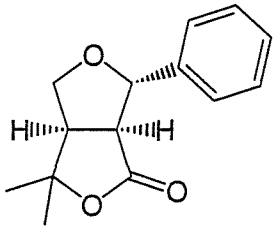
^{1}H NMR (300 MHz) δ 7.43-7.20 (5H, m, Ph**H**), 5.97 (1H, t, *J* = 2.0 Hz, -C**H**=C-), 4.61 (2H, s, -CH_2Ph), 4.29 (2H, d, *J* = 2.0 Hz, -CH_2OBn), 1.47 (6H, s, 2 x -CH_3).

^{13}C NMR (75 MHz) δ 172.9 (**C**O), 171.3 (-**C**=CH-), 136.9 (**C**$_{ar}$), 128.5 (**C**H$_{ar}$), 128.4 (**C**H$_{ar}$), 128.0 (**C**H$_{ar}$), 127.6 (**C**H$_{ar}$), 127.5 (**C**H$_{ar}$), 115.2 (-C=**C**H-), 85.8 (-**C**Me$_2$), 73.2 (-**C**H$_2$Ph), 64.7 (-**C**H$_2$OBn), 25.2 (2 x -**C**H$_3$).

LRMS (CI, NH_3) 233 (100) $[M+H]^+$, 250 (45) $[M+NH_4]^+$, 91 (30) $[PhCH_2]^+$.

HRMS (ES +ve) Calcd for $C_{28}H_{32}O_6Na$ (dimer) 487.2091, found 487.2103.

(1S*, 2S*, 5R*)-2-Phenyl-6,6-dimethyl-3,7-dioxabicyclo[3.3.0]octan-8-one (6.20)



6.20

$C_{14}H_{16}O_3$

m.w. = 232.28 g/mol

Colourless oil

The title compound was prepared using the method outlined for the preparation of **5.18**, whereby reaction of lactone **5.4** (750 mg, 3.20 mmol) with LiHMDS and 2,2,2-trifluoro-ethyltrifluoroacetate (0.47 mL, 3.52 mmol) under the conditions described gave crude **4-[(benzyloxy)methyl]-5,5-dimethyl-3-(trifluoroacetyl)dihydro-2-furanone** (1.13 g, quantitative) as a crude orange oil. This crude material was used directly in the subsequent diazo-transfer reaction, which was conducted following the procedure described for **5.18**, whereby reaction of the crude trifluoroacetylated lactone (3.20 mmol theoretical) with 4-nitrobenzenesulfonylazide (950 mg, 4.2 mmol) and workup under the conditions described gave a crude yellow oil (3.1 g). This crude material was used directly in the subsequent C-H insertion reaction, which was conducted following the procedure described for **5.19**, whereby reaction of the crude diazo lactone (3.20 mmol theoretical) with dirhodium tetraacetate (28 mg, 0.06 mmol) and workup under the conditions described gave a crude yellow oil (2.6 g). Purification was accomplished by flash chromatography on silica gel (4 x 15) eluting with Et_2O/hexane (1:1) to yield the title compound **6.20** (146 mg, 0.63 mmol, 20 % from lactone **5.4**) as a colourless oil.

FT-IR (neat) ν_{max} 1759 s, 1375 m, 1274 s, 1167 m, 1131 s, 1091 m cm^{-1}.

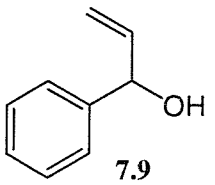
^{1}H NMR (300 MHz) δ 7.43-7.19 (5H, m, Ph**H**), 5.30 (1H, d, *J* = 3.5 Hz, -C**H**Ph), 4.20 (1H, dd, *J* = 9.4, 7.5 Hz, -OC**H**H-), 3.92 (1H, dd, *J* = 9.4, 7.9 Hz, -OCH**H**-), 3.46 (1H, dd, *J* = 8.9, 3.5 Hz, -O_2CC**H**-), 2.96 (1H, q, *J* = 9.9 Hz, -C(CH_3)$_2$C**H**-), 1.48 (3H, s, -CH_3), 1.46 (3H, s, -CH_3).

^{13}C NMR (75 MHz) δ 177.1 (**C**O), 141.4 (C_{ar}), 129.1 (CH_{ar}), 128.3 (CH_{ar}), 125.8 (CH_{ar}), 84.3 (-**C**Me$_2$), 83.7 (-**C**HPh), 69.4 (-CH_2-), 55.9 (-O_2**C**CH-), 50.9 (-C(CH_3)$_2$**C**H-), 30.6 (-CH_3), 23.9 (-CH_3).

LRMS (CI, NH_3) 233 (30) $[M+H]^+$, 250 (100) $[M+NH_4]^+$, 215 (8) $[M+H(-H_2O)]^+$.

CHN Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.02; H, 6.85.

1-Phenyl-2-propen-1-ol (4393-06-0) (7.9)



7.9

$C_9H_{10}O$

m.w. = 134.18 g/mol

Colourless oil

To a solution of vinylmagnesium bromide (52.0 mL of a 1M sol in THF, 52 mmol) in THF (12 mL) at -10 °C (CO_2(s)/acetone) was added benzaldehyde (**7.8**) (4.8 mL, 47 mmol) dropwise over 10 min. The yellow homogeneous solution was allowed to warm to room temperature and stirred for a further 15 min. The mixture was cooled to 0 °C (ice bath) and stirred vigorously as $NH_4^+Cl^-$ (aq) (6.25 g in 30 mL) was added dropwise, the organic layer was then separated and the aqueous extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield a yellow oil (6.35 g). Purification was accomplished by flash chromatography on silica gel (5.5 x 6) eluting with Et_2O/hexane (1:4) to yield the title compound **7.9** (5.82 g, 43.4 mmol, 92 %) as a colourless oil. Spectroscopic details were consistent with those observed in the literature.[259]

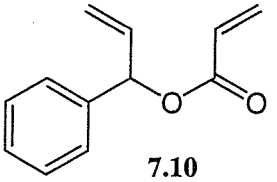
FT-IR (neat) ν_{max} 3382 br s, 3033 m, 1499 m, 1459 m, 1030 s cm^{-1}.

^{1}H NMR (300 MHz) δ 7.25-7.43 (5H, m, Ph**H**), 6.07 (1H, ddd, *J* = 17.3, 10.4, 5.9 Hz, -C**H**=CH_2), 5.36 (1H, d, *J* = 17.3 Hz, -CH=C**H**H), 5.18-5.25 (2H, m, PhC**H**- and -CH=CH**H**), 2.46 (1H, br s, -O**H**).

^{13}C NMR (75 MHz) δ 142.8 (C_{ar}), 140.4 (-**C**H=CH_2), 128.7 (CH_{ar}), 127.9 (CH_{ar}), 126.5 (CH_{ar}), 115.3 (-CH=**C**H_2), 75.5 (-**C**H-).

LRMS (CI, NH_3) 152 (2) $[M+NH_4]^+$, 117 (100) $[M+H(-H_2O)]^+$.

1-Phenylallyl acrylate (145655-36-3) (7.10)



7.10

$C_{12}H_{12}O_2$

m.w. = 188.23 g/mol

Colourless oil

To a solution of alcohol **7.9** (6.0 g, 45 mmol) in CH_2Cl_2 (120 mL) at 0 °C (ice/salt bath) was added Et_3N (12.5 mL, 90 mmol) dropwise over 10 min and a solution of DMAP (270 mg, 2 mmol) in CH_2Cl_2 (0.5 mL). Acryloyl chloride (4.4 mL, 54 mmol) was then added dropwise and the orange coloured solution was allowed to warm to room temperature and left to stir for 18 h. The mixture was stirred vigorously and quenched with water (70 mL), the organic layer separated and the aqueous extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were washed with 2N HCl (aq) (100 mL), sat. $NaHCO_3$ (aq) (100 mL) and brine (100 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield a crude yellow oil. Purification was accomplished by flash chromatography on silica gel (5.5 x 5.5) eluting with Et_2O/cyclohexane (1:49) to give the title compound **7.10** (7.6 g, 40 mmol, 90 %) as a colourless oil. Spectroscopic details were consistent with those observed in the literature.[260]

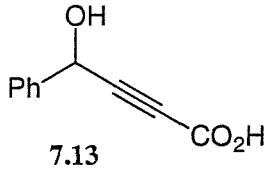
FT-IR (neat) ν_{max} 1728 s, 1642 m, 1413 s, 1299 m, 1264 s, 1196 s cm^{-1}.

^{1}H NMR (300 MHz) δ 7.26-7.41 (5H, m, Ph**H**), 6.48 (1H, dd, *J* = 17.4, 2.0 Hz, -COCH=C**H**H), 6.36 (1H, dt, *J* = 6.0, 1.5 Hz, PhC**H**-), 6.20 (1H, dd, *J* = 17.4, 10.4 Hz, -COC**H**=CHH), 6.06 (1H, ddd, *J* = 17.4, 10.4, 6.0 Hz, PhCHC**H**=CH_2), 5.87 (1H, dd, *J* = 10.4, 2.0 Hz, -COCH=CH**H**), 5.25-5.38 (2H, m, PhCHCH=C**H**$_2$).

^{13}C NMR (75 MHz) δ 165.3 (**C**O), 138.9 (**C**$_{ar}$), 136.3 (PhCH**C**H=CH_2), 131.3 (-COCH=**C**H_2), 128.7 (-**C**H-), 128.6 (-**C**H-), 128.4 (-**C**H-), 127.3 (-**C**H-), 117.2 (PhCHCH=**C**H_2), 76.5 (Ph**C**H-).

LRMS (CI, NH_3) 117 (85) $[M+H(-CH_2=CHCO_2H)]^+$, 55 (100) $[COCH=CH_2]^+$.

4-Hydroxy-4-phenylbut-2-ynoic acid (80663-17-8) (7.13)



7.13

$C_{10}H_8O_3$

m.w. = 176.17 g/mol

White solid

To a solution of propiolic acid (**7.12**) (4.4 mL, 71 mmol) in THF (120 mL) at 0 °C (ice/salt bath) was added methylmagnesium chloride (47 mL of a 3M sol in THF, 142 mmol) dropwise over 15 min. Addition of the second equivalent of Grignard resulted in a yellow coloured solution which was stirred for 90 min at 0 °C before benzaldehyde (7.6 mL, 75 mmol) was added in one portion. The reaction mixture was stirred for 1h and then allowed to warm to room temperature. The red/orange reaction mixture was diluted with Et_2O (100 mL), cooled to 0 °C and acidified to pH=1 with 2N H_2SO_4 (aq). The organic phase was extracted with sat. $NaHCO_3$ (aq) (3 x 300 mL) and the combined aqueous layers were re-acidified to pH=1 with 2N H_2SO_4 (aq) before extraction with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield a crude brown oil which solidified on standing. Recrystallisation from $CHCl_3$ afforded the title compound **7.13** (3.25 g, 18 mmol, 26 %) as an off-white solid. Further recrystallisation of the filtrate from CH_2Cl_2 provided the title compound **7.13** (3.96 g, 22 mmol, 32 %) as a white solid – overall yield (7.21 g, 41 mmol, 58 %). Spectroscopic details were consistent with those observed in the literature.[196]

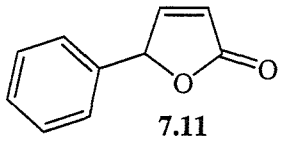
MP 90-91 °C CH_2Cl_2 (lit.[196] 88-90 °C).

FT-IR (neat) ν_{max} 2240 m, 1659 s, 1459 m, 1399 m, 1279 s, 1188 m cm^{-1}.

^{1}H NMR (300 MHz) δ 13.7 (1H, br s, -CO_2**H**), 7.52-7.28 (5H, m, Ph**H**), 6.44 (1H br s, -**OH**), 5.59 (1H, s, PhC**H**-).

^{13}C NMR (75 MHz) δ 151.1 (-**C**O_2H), 140.6 (**C**$_{ar}$), 128.6 (**CH**$_{ar}$), 128.1 (**CH**$_{ar}$), 126.5 (**CH**$_{ar}$), 87.5 (-**C**≡CCO$_2$H), 77.5 (-C≡**C**CO$_2$H), 62.3 (Ph**C**-).

5-Phenyl-5H-furan-2-one (70404-21-6) (7.11)



7.11

$C_{10}H_8O_2$

m.w. = 160.17 g/mol

Pale yellow oil

To a solution of acetylenic acid **7.13** (400 mg, 2.3 mmol) in EtOAc (4 mL) was added Lindlar catalyst ([palladium 5 % wt. on calcium carbonate poisoned with lead] 25 mg, cat.) and the stirred mixture was thoroughly purged with N_2. The N_2 was then replaced by H_2 (*via* balloon) and the reaction mixture stirred under a slight positive pressure of H_2 at room temperature for 135 min. The reaction mixture was then filtered through Celite, washed with EtOAc and concentrated *in vacuo* to afford a yellow oil. This crude oil was

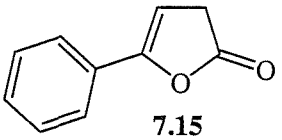
redissolved in $CHCl_3$ (2 mL) and left stirring at room temperature for 18 h. The reaction mixture was then concentrated *in vacuo* to yield the title compound **7.11** (320 mg, 2.0 mmol, 88 % crude) as a pale yellow oil. Spectroscopic details were consistent with those observed in the literature.[193]

FT-IR (neat) ν_{max} 1797 s, 1762 s, 1499 m, 1459 m, 1304 m, 1161 m, 1093 m cm^{-1}.

^{1}H NMR (300 MHz) δ 7.54 (1H, dd, *J* = 5.5, 1.5 Hz, -C**H**=CHCO-), 7.44-7.25 (5H, m, Ph**H**), 6.24 (1H, dd, *J* = 6.0, 2.0 Hz, PhC**H**-), 6.02 (1H, t, *J* = 2.0 Hz, -CH=C**H**CO-).

^{13}C NMR (75 MHz) δ 173.3 (**C**O), 156.1 (-**C**H=CHCO-), 134.3 ($\mathbf{C}_{ar}$), 129.5 ($\mathbf{C}H_{ar}$), 129.2 ($\mathbf{C}H_{ar}$), 126.7 ($\mathbf{C}H_{ar}$), 121.1 (-CH=**C**HCO-), 84.6 (Ph**C**-).

5-Phenyl-2,3-dihydro-2-furanone (1955-39-1) (7.15)



7.15

$C_{10}H_8O_2$

m.w. = 160.17 g/mol

Orange crystalline solid

Furanone **7.15** was afforded following rearrangement of **7.11** on silica gel treated with 1 % triethylamine. Spectroscopic details were consistent with those observed in the literature.[261]

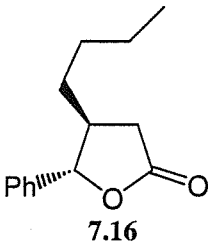
MP 89-91°C Et_2O/hexane (lit.[262] 89-90 °C).

FT-IR (neat) ν_{max} 1774 s, 1654 m, 1494 m, 1379 m, 1289 s, 1258 s, 1073 s cm^{-1}.

^{1}H NMR (300 MHz) δ 7.64-7.58 (2H, m, Ph**H**), 7.46-7.38 (3H, m, Ph**H**), 5.80 (1H, t, *J* = 2.5 Hz, -C=C**H**-), 3.43 (2H, d, *J* = 2.5 Hz, -C$\mathbf{H}_2$-).

^{13}C NMR (75 MHz) δ 176.1 (**C**O), 154.1 (-**C**=CH-), 129.8 ($\mathbf{C}H_{ar}$), 128.8 ($\mathbf{C}H_{ar}$), 128.5 ($\mathbf{C}_{ar}$), 124.9 ($\mathbf{C}H_{ar}$), 97.8 (-C=**C**H), 34.8 (-**C**H_2-).

(4S*, 5S*)-4-Butyl-5-phenyltetrahydro-2-furanone (7.16)



7.16

$C_{14}H_{18}O_2$

m.w. = 218.30 g/mol

Pale orange oil

To a suspension of copper (I) iodide (190 mg, 1.00 mmol) in THF (2 mL) at –78 °C (CO_2(s)/acetone) was added *n*-butyl lithium (1.27 mL of a 1.57M sol. in hexanes, 1.99

mmol) dropwise over 5 min. The mixture was allowed to warm to 0 °C (ice/salt bath) to aid dissolution providing a colourless solution (although some black residue remained) before re-cooling the reaction to –78 °C. Boron trifluoride etherate (0.26 mL, 2.02 mmol) was then added dropwise followed by a solution of crude butenolide **7.11** (80 mg, 0.50 mmol) in THF (0.5 mL) dropwise over 2 min and the mixture stirred for 2 h at –78 °C. The reaction mixture was allowed to warm to room temperature and treated with sat. $NH_4^+Cl^-$ (aq) (5 mL), diluted with Et_2O (15 mL) and $NH_4^+OH^-$ (aq) (15 mL of a 25 % sol) added before extraction with Et_2O (3 x 20 mL). The combined organic extracts were washed with $NH_4^+OH^-$ (aq) (20 mL of a 25 % sol) and brine (20 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield a crude red/brown oil. Purification was accomplished by flash chromatography on silica gel (2.3 x 10) eluting with EtOAc/hexane (1:4) to give the title compound **7.16** (22 mg, 0.01 mmol, 20 %) as an orange oil.

FT-IR (neat) ν_{max} 2964 m, 2930 m, 1785 s, 1459 m, 1230 m, 1150 m, 1001 m cm^{-1}.

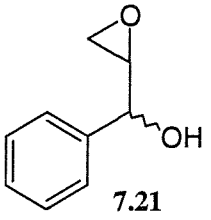
^{1}H NMR (300 MHz) δ 7.44-7.30 (5H, m, Ph**H**), 5.02 (1H, d, *J* = 7.9 Hz, PhC**H**-), 2.80 (1H, dd, *J* = 15.9, 6.5 Hz, PhCHC**H**-), 2.48-2.29 (2H, m, -CO**CH$_2$**-), 1.70-1.15 (6H, m, 6 x -(**CH$_2$**)$_3$-), 0.87 (3H, t, *J* = 9.6 Hz, -**CH$_3$**).

^{13}C NMR (75 MHz) δ 176.5 (**C**O), 138.6 (**C$_{ar}$**), 128.9 (**CH$_{ar}$**), 126.2 (**CH$_{ar}$**), 87.0 (Ph**C**H-), 45.1 (PhCH**C**H-), 35.5 (-CO**CH$_2$**-), 31.9 (-**CH**CH$_2$CH$_2$-), 29.9 (-CH$_2$**CH$_2$**CH$_2$-), 22.7 (-**CH$_2$**CH$_3$), 14.0 (-**CH$_3$**).

LRMS (CI, NH_3) 236 (5) $[M+NH_4]^+$, 201 (20) $[M+H(-H_2O)]^+$, 218 (60), 107 (100).

HRMS (EI) Calcd for $C_{14}H_{18}O_2$ 218.1307, found 218.1309.

1-Phenyl-2,3-epoxy-1-propanol (3314-44-1) (7.21)



7.21

$C_9H_{10}O_2$

m.w. = 150.18 g/mol

Colourless oil

To a solution of phenylallyl alcohol **7.9** (4.0 g, 29.8 mmol) in $CHCl_3$ (130 mL) at 0 °C (ice/salt bath) was added *m*-CPBA (20.6 g, 50%, 59.6 mmol) portionwise over 30 min. The resulting mixture was left to warm slowly to room temperature and left stirring overnight. After dilution with $CHCl_3$ (100 mL), the reaction mixture was washed sequentially with a 10% aqueous sodium sulfite solution (3 x 100 mL), sat. $NaHCO_3$ (aq) (3 x 100 mL) and brine (1 x 100 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield a colourless oil (4.42 g). Purification was accomplished by distillation under

reduced pressure to give the title compound **7.21** (3.81 g, 25.4 mmol, 85 %) as a colourless oil (1:1 mixture of diastereoisomers). Spectroscopic details were consistent with those observed in the literature.[208,263]

BP 140-142 °C (0.5 mbar).

FT-IR ν_{max} (neat) 3420 br w, 1451 m, 1251 s, 1041 s cm^{-1}.

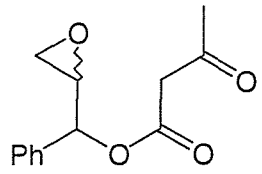
Both diastereoisomers reported for NMR analysis.

^{1}H NMR (400 MHz) δ 7.50-7.31 (2 x 5H, m, Ph**H**), 4.92 (1H, s, -C**H**OH *anti*), 4.46 (1H, t, *J* = 4.8 Hz, -C**H**OH *syn*), 3.24-3.21 (2 x 1H, m, -C**H**CH_2), 2.96 (1H, ddd, *J* = 5.0, 2.8, 0.8 Hz, -CH**H** *anti*), 2.87-2.81 (2H, m, -CH_2 *syn*), 2.76 (1H, dd, *J* = 5.0, 4.0 Hz, -C**H**H *anti*), 2.65 (1H, br d, *J* = 4.8 Hz, -O**H**), 2.40 (1H, br d, *J* = 1.8 Hz, -O**H**).

^{13}C NMR (100 MHz) *anti* isomer δ 139.9 (**C**$_{ar}$), 129.1 (**CH**$_{ar}$), 128.7 (**CH**$_{ar}$), 126.9 (**CH**$_{ar}$), 71.2 (Ph**C**H-), 55.5 (-O**C**H-), 44.0 (-**C**H_2-); *syn* isomer δ 140.6 (**C**$_{ar}$), 129.1 (**CH**$_{ar}$), 128.7 (**CH**$_{ar}$), 126.7 (**CH**$_{ar}$), 75.0 (Ph**C**H-), 56.4 (-O**C**H-), 45.9 (-**C**H_2-).

LRMS (CI, NH_3) *m/z* (relative intensity) 150 (12) $[M]^+$, 133 (40) $[M+H(-H_2O)]^+$, 91 (100) $[PhCH_2]^+$.

1-Phenyl-2,3-epoxy-1-propyl acetoacetate (7.22)



7.22

$C_{13}H_{14}O_4$

m.w. = 234.25 g/mol

Colourless oil

The title compound was prepared according to the general procedure described by Clemens *et al.*[200] Thus, to solution of alcohol **7.21** (1.00 g, 6.7 mmol) in xylenes (1 mL) was added 2,2,6-trimethyl-4H-1,3-dioxin-4-one (0.91 mL, 7.0 mmol) in an Erlenmeyer flask. The resulting mixture was placed directly into a preheated oil bath at 150 °C and the solution stirred vigorously. The evolution of acetone became apparent within several minutes and heating was continued for a total of 40 min. The reaction was cooled and concentrated *in vacuo* to remove excess xylenes. Purification was accomplished by distillation under reduced pressure to give the title compound **7.22** (1.43 g, 6.1 mmol, 92 %) as a colourless oil (1:1 mixture of diastereoisomers).

BP 137-138 °C (0.5 mbar).

FT-IR ν_{max} (neat) 1748 s, 1719 s, 1360 m, 1266 m, 1150 s cm^{-1}.

Both diastereoisomers reported for NMR analysis (keto/enol ratio 11:1).

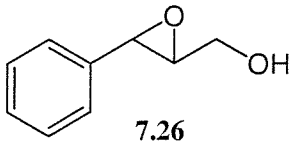
^{1}H NMR (300 MHz) δ 7.42-7.32 (2 x 5H, m, Ph**H**), 5.92 (1H, d, *J* = 7.0 Hz, -C**H**Ph) and 5.58 (1H, d, *J* = 4.0 Hz, -C**H**Ph), 3.55 (2H, s, -C**H**$_2$CO-) and 3.51 (2H, s, -C**H**$_2$CO-), 3.35 (1H, ddd, *J* = 4.0, 4.0, 2.5 Hz –C**H**OCH$_2$-) and 3.30 (1H, ddd, *J* = 6.5, 4.0, 2.5 Hz, -C**H**OCH$_2$-), 2.86 (1H, dd, *J* = 5.0, 4.0 Hz, -CH**H**-) and 2.81 (1H, dd, *J* = 5.0, 4.5 Hz, -CH**H**-), 2.77 (1H, dd, *J* = 5.0, 2.5 Hz, -C**H**H-) and 2.69 (1H, dd, *J* = 5.0, 2.5 Hz, -C**H**H-), 2.26 (2 x 3H, s, -COC**H**$_3$); enolic acetoacetyl resonances were observed at δ 10.57, 5.19-5.09, 1.97.

^{13}C NMR (75 MHz) δ 200.4 (**C**O$_{ket}$), 166.2 (**C**O$_{est}$), 136.2 (**C**$_{ar}$) and 135.5 (**C**$_{ar}$), 129.1 (**C**H$_{ar}$) and 128.8 (**C**H$_{ar}$), 127.5 (**C**H$_{ar}$) and 127.1 (**C**H$_{ar}$), 77.7 (-**C**HPh) and 75.0 (-**C**HPh), 53.7 (-CH$_2$O**C**H-) and 52.8 (-CH$_2$O**C**H-), 50.2 (-**C**H$_2$CO-) and 50.2 (-**C**H$_2$CO-), 45.3 (-O**C**H$_2$-), 44.9 (-O**C**H$_2$-) and only 1 resonance at 30.3 (-**C**H$_3$).

LRMS (CI, NH$_3$) *m/z* (relative intensity) 150 (14) [M+H(-COCH$_2$COCH$_3$)]$^+$, 133 (43) [M+H(-HOCOCH$_2$COCH$_3$)]$^+$, 91 (100) [PhCH$_2$]$^+$.

HRMS (ES +ve) Calcd for $C_{13}H_{14}O_4Na$ 257.0784, found 257.0782.

3-Phenyl-2,3-epoxy-1-propanol (21915-53-7) (7.26)



7.26

$C_9H_{10}O_2$

m.w. = 150.18 g/mol

Colourless oil

The title compound was prepared according to the method outlined for **7.21** whereby cinnamyl alcohol (2.01 g, 15.0 mmol) and *m*-CPBA (10.4 g, 30.0 mmol) were reacted together and worked up under the conditions described to yield a colourless oil. Purification was accomplished by distillation under reduced pressure to give the title compound **7.26** (1.7 g, 11.4 mmol, 76 %) as a colourless oil. Spectroscopic details were consisitent with those observed in the literature.[264]

BP 129-132 °C (0.5 mbar).

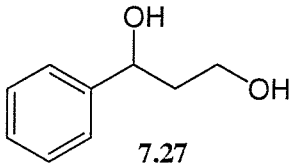
FT-IR ν_{max} (neat) 3417 br w, 1496 w, 1451 m, 1070 s, 1028 s cm^{-1}.

^{1}H NMR (300 MHz) δ 7.43-7.25 (5H, m, Ph**H**), 4.07 (1H, br d, *J* = 12.9 Hz, -CH**H**OH), 3.95 (1H, d, *J* = 1.8 Hz, -C**H**Ph), 3.81 (1H, br d, *J* = 12.5 Hz,

-CHHOH), 3.25 (1H, dt, J = 4.1, 2.2 Hz, -CHCH$_2$-), 2.41 (1H, br s, -OH).

^{13}C NMR (75 MHz) δ 137.0 (C$_{ar}$), 128.9 (CH$_{ar}$), 128.7 (CH$_{ar}$), 126.1 (CH$_{ar}$), 62.9 (-CHPh), 61.6 (-CH$_2$OH), 56.0 (-CHCH$_2$OH).

1-Phenyl-propane-1,3-diol (4850-49-1) (7.27)



7.27

$C_9H_{12}O_2$

m.w. = 152.19 g/mol

White solid

The title compound was prepared according to the general procedure described by Soai *et al.*[209] Thus, to a solution of ethyl benzylacetate (6.9 mL, 40.0 mmol) in THF (80 mL) was added sodium borohydride (3.8 g, 100 mmol) portionwise over 10 min. The resulting suspension was heated to reflux and methanol (32 mL) was added dropwise over a period of 40 min. The yellow mixture was allowed to cool to room temperature, diluted with EtOAc (100 mL) and acidified with 2N HCl (aq) (200 mL). The organic layer was separated and the aqueous extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (200 mL), dried with $MgSO_4$ and concentrated *in vacuo* to give a viscous yellow oil (9.4 g). Purification was accomplished by distillation under reduced pressure to give the title compound **7.27** (4.3 g, 28.2 mmol, 71 %) as a colourless oil that solidified on standing. Spectroscopic details were consistent with those observed in the literature.[265]

BP 137-138 °C (0.5 mbar).

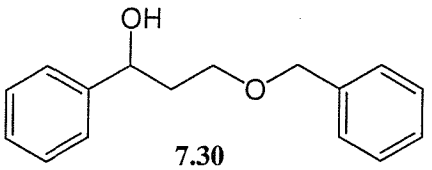
MP 71-73 °C.

FT-IR ν_{max} (neat) 3384 br m, 1480 m, 1404 s, 1334 s, 1286 s, 1128 s, 1095 s cm^{-1}.

^{1}H NMR (300 MHz) δ 7.58-7.35 (5H, m, PhH), 5.20 (1H, dd, J = 9.4, 3.0 Hz, -CHPh), 4.11 (1H, dt, J = 3.2, 10.9 Hz, -CHHOH), 3.97 (1H, dt, J = 10.7, 4.0 Hz, -CHHOH), 2.21 (1H, dq, J = 14.1, 3.2 Hz, -CHHCH$_2$OH), 1.96-1.81 (1H, m, -CHHCH$_2$OH).

^{13}C NMR (75 MHz) δ 142.7 (C$_{ar}$), 128.6 (CH$_{ar}$), 127.7 (CH$_{ar}$), 125.5 (CH$_{ar}$), 74.0 (-CHPh), 61.8 (-CH$_2$OH), 35.3 (-CH$_2$CH$_2$OH).

3-Benzyloxy-1-phenyl-propan-1-ol (7.30)



7.30

$C_{16}H_{18}O_2$

m.w. = 242.32 g/mol

Colourless oil

The title compound was prepared according to the general procedure described by David *et al.*[210,211] Thus, to a solution of 1,3-diol **7.27** (1.30 g, 8.5 mmol) in benzene (40 mL) was added dibutyltin oxide (2.34 g, 9.4 mmol) and the mixture refluxed for 24 h with azeotropic removal of water by a Dean-Stark condenser. The crude stannylene derivative was then benzylated directly by the addition of benzyl bromide (1.2 mL, 10.3 mmol) and tetra-*n*-butylammonium bromide (2.75 g, 8.5 mmol) to the reaction mixture. Reflux for a further 36 h and concentration *in vacuo* provided a crude slurry that was purified by flash chromatography on silica gel (5 x 12) eluting with EtOAc/hexane (1:4) to give the title compound **7.30** (0.87 g, 3.6 mmol, 42 %) as a colourless oil.

FT-IR ν_{max} (neat) 3420 br w, 1492 w, 1452 m, 1374 m, 1210 m, 1096 s cm^{-1}.

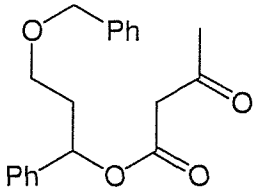
^{1}H NMR (400 MHz) δ 7.45-7.30 (10H, m, Ph**H**), 4.99 (1H, ddd, *J* = 11.5, 7.5, 3.5 Hz, -C**H**OH), 4.60 (2H, s, -C**H**$_2$Ph), 3.79-3.68 (2H, m, -C**H**$_2$OBn), 3.36 (1H, d, *J* = 3.0 Hz, -O**H**), 2.19-2.03 (2H, m, -OCH$_2$C**H**$_2$-).

^{13}C NMR (100 MHz) δ 144.8 (**C**$_{ar}$), 138.3 (**C**$_{ar}$), 128.9 (**CH**$_{ar}$), 128.8 (**CH**$_{ar}$), 128.2 (**CH**$_{ar}$), 128.2 (**CH**$_{ar}$), 127.7 (**CH**$_{ar}$), 126.1 (**CH**$_{ar}$), 73.8 (-**C**HOH), 73.5 (-**C**H$_2$Ph), 69.1 (-**C**H$_2$OBn), 39.1 (-**C**H$_2$CH$_2$O-).

LRMS (CI, NH_3) *m/z* (relative intensity) 225 (100) $[M+H(-H_2O)]^+$, 91 (65) $[PhCH_2]^+$.

HRMS (ES +ve) Calcd for $C_{16}H_{18}O_2Na$ 265.1199, found 265.1198.

3-Benzyloxy-1-phenyl-propyl acetoacetate (7.31)



7.31

$C_{20}H_{22}O_4$

m.w. = 326.39 g/mol

Colourless oil

The title compound was prepared according to the method outlined for **7.22** whereby alcohol **7.30** (540 mg, 2.23 mmol) and 2,2,6-trimethyl-4H-1,3-dioxin-4-one (0.31 mL, 2.34 mmol) were reacted under the conditions described (except reaction for 30 min). Purification was accomplished by flash chromatography on silica gel (3.2 x 11) eluting

with EtOAc/hexane (1:4) to give the title compound **7.31** (640 mg, 1.96 mmol, 88 %) as a colourless oil.

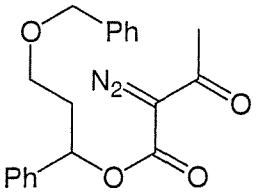
FT-IR ν_{max} (neat) 1743 s, 1716 s, 1361 m, 1268 m, 1150 s, 1098 s cm^{-1}.

^{1}H NMR (400 MHz) δ 7.39-7.27 (10H, m, Ph**H**), 6.01 (1H, dd, *J* = 5.5, 8.5 Hz, PhC**H**O-), 4.49 (2H, s, -OC**H**$_2$Ph), 3.58-3.51 (1H, m, -CH**H**OBn), 3.43 (1H, dt, *J* = 9.5, 5.5 Hz, -C**H**HOBn), 3.41 (2H, s, -COC**H**$_2$CO-), 2.32-2.21 (1H, m, -OCH$_2$CH**H**-), 2.19 (3H, s, -C**H**$_3$), 2.13-2.02 (1H, m, -OCH$_2$C**H**H-); keto/enol ratio 15:1 - enolic acetoacetyl resonances were observed at δ 12.01, 5.03, 1.94.

^{13}C NMR (100 MHz) δ 200.8 (**C**O$_{ket}$), 166.6 (**C**O$_{est}$), 140.2 (**C**$_{ar}$), 138.7 (**C**$_{ar}$), 129.0 (**C**H$_{ar}$), 128.8 (**C**H$_{ar}$), 128.6 (**C**H$_{ar}$), 128.3 (**C**H$_{ar}$), 128.1 (**C**H$_{ar}$), 128.1 (**C**H$_{ar}$), 127.0 (**C**H$_{ar}$), 75.0 (-O**C**HPh), 73.5 (-**C**H$_2$Ph), 66.5 (-**C**H$_2$OBn), 50.7 (-CO**C**H$_2$CO-), 36.8 (-**C**H$_2$CH$_2$O-), 30.5 (-**C**H$_3$); enolic acetoacetyl resonances were observed at δ 176.1, 172.3, 90.3, 73.3, 37.1, 21.6.

LRMS (CI, NH_3) *m/z* (relative intensity) 241 (7) [M+H(-HOCCH$_2$COCH$_3$)]$^+$, 225 (100) [M+H(-HO$_2$CCH$_2$COCH$_3$)]$^+$, 91 (56) [PhCH$_2$]$^+$.

3-Benzyloxy-1-phenyl-propyl diazoacetoacetate (7.32)



7.32

$C_{20}H_{20}N_2O_4$

m.w. = 352.51 g/mol

Pale yellow oil

To a solution of β-keto-ester **7.31** (98 mg, 0.30 mmol) in MeCN (3 mL) at room temperature was added di-*iso*-propylethylamine (120 μL, 0.69 mmol) and the mixture stirred for 5 min. *p*-Carboxybenzenesulfonyl azide (89 mg, 0.39 mmol) was added in one portion and the solution stirred for 18 h. The resulting white precipitate was filtered and washed with Et_2O (25 mL). The filtrate was poured onto water (15 mL), the organic layer separated and the aqueous extracted with Et_2O (2 x 15 mL) and the combined extracts were washed with sat. $NaHCO_3$ (aq) (2 x 15 mL) and brine (15 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield a white emulsion (142 mg). Purification was accomplished by flash chromatography on pre-packed silica (2.2 x 3) eluting with

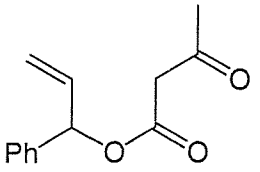
Et_2O/petrol (1:19 then 1:9 then 1:4) to give the title compound **7.32** (97 mg, 0.28 mmol, 92 %) as a very pale yellow oil.

FT-IR ν_{max} (neat) 2140 m, 1716 s, 1658 m, 1364 s, 1322 s, 1305 s, 1063 s cm^{-1}.

^{1}H NMR (400 MHz) δ 7.39-7.26 (10H, m, PhH), 6.06 (1H, dd, *J* = 5.6, 8.0 Hz, PhCHO-), 4.50 (1H, d, *J* = 12.0 Hz, -OCHHPh), 4.45 (1H, d, *J* = 12.0 Hz, -OCHHPh), 3.56-3.48 (1H, m, -CHHOBn), 3.45-3.39 (1H, m, -CHHOBn), 2.42 (3H, s, $-CH_3$), 2.33-2.23 (1H, m, $-OCH_2CHH-$), 2.15-2.06 (1H, m, $-OCH_2CHH-$).

^{13}C NMR (100 MHz) δ 190.4 (CO_{ket}), 161.0 (CO_{est}), 140.1 (C_{ar}), 138.5 (C_{ar}), 129.1 (CH_{ar}), 128.8 (CH_{ar}), 128.2 (CH_{ar}), 128.2 (CH_{ar}), 126.8 (CH_{ar}), 75.2 (-OCHPh), 73.5 ($-CH_2Ph$), 66.3 ($-CH_2OBn$), 36.9 ($-CH_2CH_2O-$), 28.6 ($-CH_3$), (no $C{=}N_2$ observed).

1-Phenyl-allyl acetoacetate (7.34)



7.34

$C_{13}H_{14}O_3$

m.w. = 218.25 g/mol

Colourless oil

The title compound was prepared according to the method outlined for **7.22** whereby phenylallyl alcohol **7.9** (705 mg, 5.25 mmol) and 2,2,6-trimethyl-4H-1,3-dioxin-4-one (0.70 mL, 5.36 mmol) were reacted under the conditions described (except reaction for 8 min). Purification was accomplished by flash chromatography on pre-packed silica gel (4 x 7) eluting with petrol (200 mL), followed by Et_2O/hexane (1:1) to give the title compound **7.34** (1075 mg, 4.93 mmol, 94 %) as a colourless oil.

FT-IR ν_{max} (neat) 1746 s, 1720 s, 1368 m, 1262 m, 1153 m cm^{-1}.

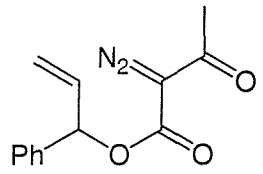
^{1}H NMR (250 MHz) δ 7.41-7.27 (5H, m, PhH), 6.31 (1H, dt, *J* = 6.0, 1.3 Hz, PhCHO-), 6.02 (1H, ddd, *J* = 16.4, 10.4, 6.0 Hz, $-CH{=}CH_2$), 5.37-5.26 (2H, m, $-CH{=}CH_2$), 3.50 (2H, s, $-CH_2CO-$), 2.23 (3H, s, $-CH_3$); (keto/enol ratio 10:1 - enolic acetoacetyl resonances were observed at δ 11.95, 5.09, 1.95).

^{13}C NMR (63 MHz) δ 200.6 (CO_{ket}), 166.5 (CO_{est}), 138.6 (C_{ar}), 136.0 ($-CH{=}CH_2$), 129.0 (CH_{ar}), 129.0 (CH_{ar}), 127.6 (CH_{ar}), 118.0 ($-CH{=}CH_2$), 77.7 (-CHPh), 50.7 ($-CH_2CO-$), 30.5 ($-CH_3$); enolic resonances were observed at δ 176.4, 136.7, 117.3, 90.2, 76.1, 21.6.

LRMS (CI, NH_3) *m/z* (relative intensity) 133 (20) $[M\text{-}COCH_2COCH_3]^+$, 117 (100) $[PhCH{=}CHCH_2]^+$, 91 (8) $[PhCH_2]^+$.

HRMS (ES +ve) Calcd for $C_{13}H_{14}O_3Na$ 241.0835, found 241.0833.

1-Phenyl-allyl diazoacetoacetate (7.37)



7.37

$C_{13}H_{12}N_2O_3$

m.w. = 244.25 g/mol

Pale yellow oil

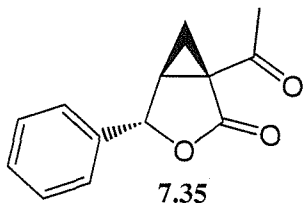
The title compound was prepared according to the method outlined for **7.32** whereby β-ketoester **7.34** (502 mg, 2.30 mmol), Hünigs' base (0.84 mL, 4.80 mmol) and *p*-carboxybenzenesulfonyl azide (680 mg, 3.0 mmol) were reacted and worked-up under the conditions described (except extraction with EtOAc) to afford a crude yellow oil (550 mg). Purification was accomplished by flash chromatography on pre-packed silica (4 x 7) eluting with EtOAc/petrol (3:97) to EtOAc/petrol (3:7) in 3% increment rises (100 mL each) to give the title compound **7.37** (524 mg, 2.15 mmol, 93 %) as a very pale yellow oil.

FT-IR ν_{max} (neat) 2141 m, 1721 s, 1662 m, 1366 s, 1338 m, 1153 m, 1062 m cm^{-1}.

^{1}H NMR (250 MHz) δ 7.36-7.21 (5H, m, Ph**H**), 6.31 (1H, dt, *J* = 6.0, 1.2 Hz, PhC**H**O-), 5.98 (1H, ddd, *J* = 16.2, 10.3, 6.0 Hz, -C**H**=CH_2), 5.29 (2H, m, -CH=C**H**$_2$), 2.39 (3H, s, -C**H**$_3$).

^{13}C NMR (63 MHz) δ 190.4 (**C**O_{ket}), 160.9 (**C**O_{est}), 138.5 (**C**$_{ar}$), 136.0 (-**C**H=CH_2), 129.2 (**C**H_{ar}), 129.0 (**C**H_{ar}), 127.5 (**C**H_{ar}), 118.2 (-CH=**C**H_2), 77.7 (-**C**HPh), 28.7 (-**C**H_3), (**C**=N_2 not observed).

(1R*, 4S*, 5S*)-1-Acetyl-4-phenyl-3-oxa-bicyclo[3.1.0]hexan-2-one (7.35)



7.35

$C_{13}H_{12}O_3$

m.w. = 216.24 g/mol

Off white solid

Method A

To a slurry of copper (II) sulphate (350 mg, 2.20 mmol) and copper (II) acetylacetonate (13 mg, 0.05 mmol) in dry toluene (7 mL) at reflux was added a solution of diazo ketoester **7.37** (122 mg, 0.50 mmol) in toluene (3 mL) dropwise over 10 min. The mixture was left at reflux for 2 h, cooled to room temperature and filtered through Celite before concentration *in vacuo*. The resulting green residue was suspended in Et_2O, re-filtered through Celite and concentrated *in vacuo* to yield a green oil (108 mg). Purification was accomplished by flash chromatography on pre-packed silica gel (2.7 x 5) eluting with Et_2O/petrol (1:19) to Et_2O/petrol (1:1) in 5 % increment rises (20 mL each) to provide the title compound **7.35** (45 mg, 0.21 mmol, 42 %) as a pale yellow oil (3:7 mixture of *cis*:*trans* diastereoisomers respectively).

Method B

To a suspension of manganese (III) acetate dihydrate (72.4 g, 270 mmol), copper (II) acetate (24.5 g, 135 mmol) and potassium acetate (22.1g, 225 mmol) in AcOH (500 mL) at 70 °C (internal) was added β-ketoester **7.34** (19.6 g, 90 mmol) in AcOH (50 mL) in one portion. The reaction was maintained at 70 °C for 15 min whereby the original brown slurry turned to a blue turquoise suspension. The mixture was allowed to cool to room temperature and concentrated *in vacuo* to remove AcOH. The resulting residue was partitioned between EtOAc (600 mL) and water (500 mL) and the particulate matter removed by filtration through Celite. The organic layer was separated and the aqueous extracted with EtOAc (3 x 500 mL), the combined extracts were washed with water (2 x 500 mL), 10 % (w/v) $NaHCO_3$ (aq) (2 x 500 mL) and brine (500 mL), dried with $MgSO_4$ and concentrated *in vacuo* to give a yellow oil (23.1 g). Purification was accomplished by flash chromatography on silica gel (10 x 12) eluting with EtOAc/hexane (1:1) to give the title compound **7.35** (14.5 g, 67 mmol, 74 %) as a pale yellow oil (22:1 mixture of diastereoisomers). A series of triturations with ice-cold Et_2O provided the *trans*-isomer **7.35** (12.1 g, 56 mmol, 62 %) as an off-white solid.

MP 78-80 °C.

FT-IR ν_{max} (neat) 1774 s, 1692 s, 1383 m, 1319 m, 1254 m, 1083 s, 981 s cm^{-1}.

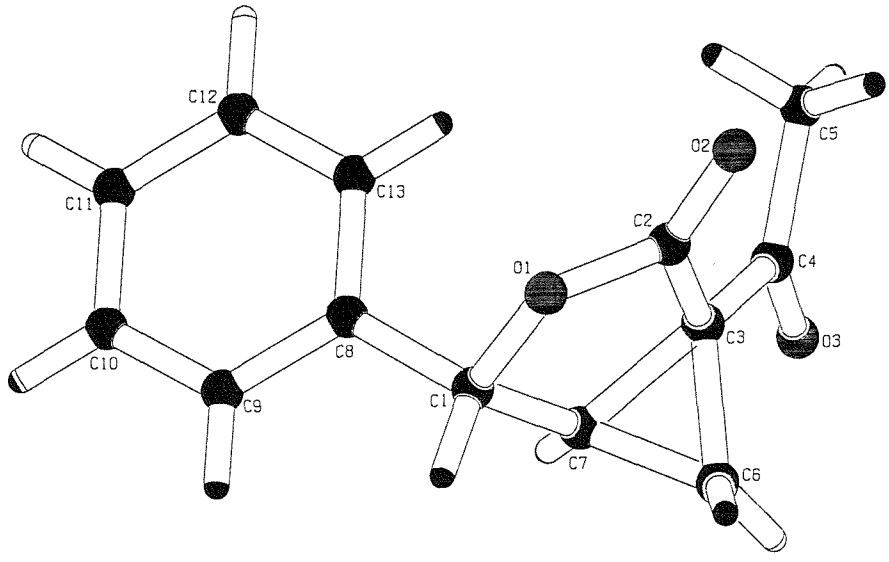
^{1}H NMR (400 MHz) δ 7.44-7.36 (3H, m, Ph**H**), 7.31-7.27 (2H, m, Ph**H**), 5.31 (1H, s, -C**H**Ph), 2.80 (1H, dd, *J* = 8.0, 5.5 Hz, -C**H**CH_2-), 2.60 (3H, s, -CH_3), 2.15 (1H, dd, *J* = 8.0, 4.3 Hz, -C**H**H-), 1.59 (1H, dd, *J* = 5.3, 4.3 Hz, -CH**H**-).

^{13}C NMR (100 MHz) δ 200.5 (**C**O$_{ket}$), 172.8 (**C**O$_{est}$), 139.0 (**C**$_{ar}$), 129.6 (**C**H$_{ar}$), 129.6 (**C**H$_{ar}$), 125.7 (**C**H$_{ar}$), 79.8 (-**C**HPh), 37.4 (-**C**COCH$_3$), 37.1 (-**C**HCH$_2$-), 29.7 (-**C**H$_3$), 24.6 (-**C**H$_2$-).

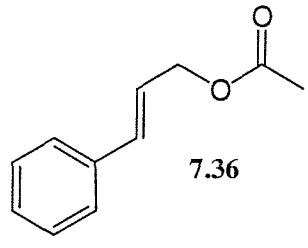
LRMS (CI, NH$_3$) *m/z* (relative intensity) 217 (100) $[M+H]^+$, 234 (65) $[M+NH_4]^+$.

CHN Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.21; H, 5.60.

X-ray structure



3-Phenyl-allyl acetate (21040-45-9) (7.36)



7.36

$C_{11}H_{12}O_2$

m.w. = 176.21 g/mol

Colourless oil

Spectroscopic details were consistent with those observed in the literature.[266]

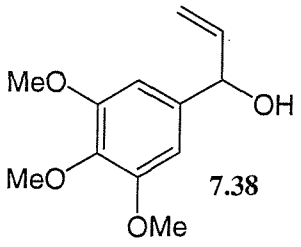
FT-IR ν_{max} (neat) 1738 s, 1380 m, 1382 m, 1229 s, 1025 m cm^{-1}.

^{1}H NMR (250 MHz) δ 7.42-7.21 (5H, m, Ph**H**), 6.65 (1H, dt, *J* = 15.9, 1.2 Hz, PhC**H**=CH-), 6.29 (1H, dt, *J* = 15.9, 6.4 Hz, -C**H**CH$_2$-), 4.73 (2H, dd, *J* = 6.4, 1.2 Hz, -OC**H**$_2$-), 2.10 (3H, s, -C**H**$_3$).

^{13}C NMR (63 MHz) δ 171.2 (**C**O), 136.6 (**C**$_{ar}$), 134.6 (Ph**C**H), 129.0 (**C**H$_{ar}$), 128.5 (**C**H$_{ar}$), 127.0 (**C**H$_{ar}$), 123.6 (-**C**HCH$_2$-), 65.5 (-**C**H$_2$-), 21.4 (-**C**H$_3$).

LRMS (CI, NH$_3$) *m/z* (relative intensity) 176 (3) $[M]^+$, 117 (100) $[PhCH=CHCH_2]^+$, 134 (15) $[PhCH=CHCH_2OH]^+$, 91 (6) $[PhCH_2]^+$.

1-(3,4,5-Trimethoxyphenyl)-prop-2-en-1-ol (7.38)



7.38

$C_{12}H_{16}O_4$

m.w. = 224.26 g/mol

Colourless oil

The title compound was prepared according to the method outlined for **7.9** whereby 3,4,5-trimethoxybenzaldehyde (1.96 g, 10 mmol) and vinylmagnesium bromide (11.0 mL of a 1M sol, 11 mmol) were reacted together and worked up under the conditions described to yield a crude yellow oil (2.28 g). Purification was accomplished by flash chromatography on silica gel (3.3 x 10) eluting with EtOAc/hexane (1:1) to give the title compound **7.38** (2.10 g, 9.36 mmol, 94 %) as a colourless oil.

FT-IR ν_{max} (neat) 3425 br w, 1590 m, 1455 m, 1415 m, 1325 m, 1228 m, 1116 s cm^{-1}.

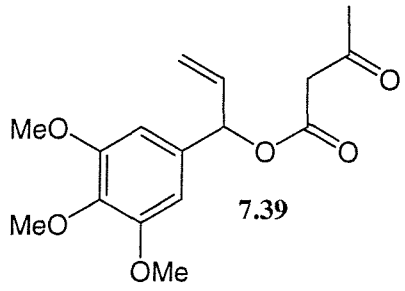
^{1}H NMR (400 MHz) δ 6.58 (2H, s, PhH), 6.01 (1H, ddd, *J* = 17.1, 10.3, 6.0 Hz, -CH=CH_2), 5.34 (1H, dt, *J* = 17.1, 1.3 Hz, -CH=CHH), 5.19 (1H, dt, *J* = 10.3, 1.3 Hz, -CH=CHH), 5.10 (1H, d, *J* = 6.0 Hz, -CHAr), 3.84 (6H, s, 2 x -OCH_3), 3.81 (3H, s, -OCH_3), 2.23 (1H, br s, -OH).

^{13}C NMR (100 MHz) δ 153.7 (C_{ar}), 140.5 (-CH=CH_2), 138.8 (C_{ar}), 137.8 (C_{ar}), 115.6 (-CH=CH_2), 103.7 (CH_{ar}), 75.8 (-CHAr), 61.2 (-OCH_3), 56.5 (-OCH_3).

LRMS (CI, NH_3) *m/z* (relative intensity) 225 (14) $[M+H]^+$, 209 (100), 207 (42) $[M+H(-H_2O)]^+$, 91 (6) $[PhCH_2]^+$.

HRMS (ES +ve) Calcd for $C_{24}H_{32}O_8Na$ (dimer) 471.1989, found 471.1984.

1-(3,4,5-Trimethoxyphenyl)-allyl acetoacetate (7.39)



7.39

$C_{16}H_{20}O_6$

m.w. = 308.33 g/mol

Colourless oil

The title compound was prepared according to the method outlined for **7.22** whereby 1-(3,4,5-trimethoxyphenyl)-prop-2-en-1-ol (**7.38**) (1.76 g, 7.85 mmol) and 2,2,6-trimethyl-4H-1,3-dioxin-4-one (1.05 mL, 8.00 mmol) were reacted under the conditions described

(except reaction for 8 min). Purification was accomplished by flash chromatography on pre-packed silica gel (3.3 x 11) eluting with petrol (200 mL), followed by EtOAc/hexane (2:3) to give the title compound **7.39** (2.18 g, 7.08 mmol, 90 %) as a colourless oil.

FT-IR ν_{max} (neat) 1722 m, 1590 m, 1493 s, 1286 m, 1246 s, 1028 m cm^{-1}.

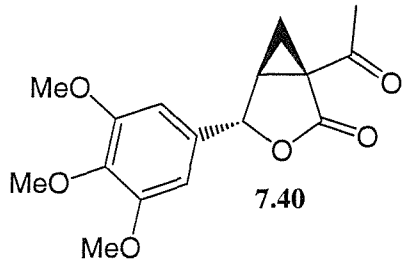
^{1}H NMR (400 MHz) δ 6.57 (2H, s, PhH), 6.23 (1H, dt, *J* = 6.0, 1.3 Hz, PhCHO-), 5.98 (1H, ddd, *J* = 16.6, 10.5, 5.8 Hz, -CH=CH_2), 5.34 (1H, dt, *J* = 17.1, 1.3 Hz, -CH=CHH), 5.28 (1H, dt, *J* = 10.5, 1.3 Hz, -CH=CHH), 3.85 (6H, s, 2 x -OCH_3), 3.82 (3H, s, -OCH_3), 3.51 (2H, s, -CH_2CO-), 2.24 (3H, s, -CH_3); keto/enol ratio 20:1 - enolic acetoacetyl resonances were observed at δ 11.95, 5.09, 1.95.

^{13}C NMR (100 MHz) δ 200.6 (CO_{ket}), 166.4 (CO_{est}), 153.8 (C_{ar}), 138.4 (C_{ar}), 135.8 (-CH=CH_2), 134.2 (C_{ar}), 118.0 (-CH=CH_2), 104.7 (CH_{ar}), 77.6 (-OCHPh), 61.2 (-OCH_3), 56.6 (2 x -OCH_3), 50.7 (-CH_2CO-), 30.6 (-CH_3); enolic acetoacetyl resonances were observed at δ 176.6, 136.5, 135.4, 134.8, 117.3, 104.3, 90.1, 76.0, 21.7.

LRMS (CI, NH_3) *m/z* (relative intensity) 225 (20) $[M+H(-COCH_2COCH_3)]^+$, 207 (50) $[ArCH=CHCH_2]^+$, 209 (100).

HRMS (ES +ve) Calcd for $C_{32}H_{40}O_{12}Na$ (dimer) 639.2412, found 639.2412.

(1R*, 4S*, 5S*)-1-Acetyl-4-(3,4,5-trimethoxyphenyl)-3-oxa-bicyclo[3.1.0]hexan-2-one



7.40

$C_{16}H_{18}O_6$

m.w. = 306.31 g/mol

Pale yellow solid

Method A

The title compound was prepared according to the method outlined for **7.35** (Method B) whereby β-ketoester **7.39** (154 mg, 0.50 mmol), manganese (III) acetate dihydrate (402 mg, 1.50 mmol), copper (II) acetate (136 mg, 0.75 mmol) and potassium acetate (123 mg, 1.25 mmol) were reacted and worked-up under the conditions described to yield a crude yellow oil (146 mg). Purification was accomplished by flash chromatography on silica gel (2.2 x 10) eluting with EtOAc/hexane (1:2). The title compound **7.40** (20 mg, 6.53 mmol, 13 %) was isolated as a yellow oil (25:1 mixture of diastereoisomers) along with alkene by-product **7.41** (31 mg, 0.12 mmol, 23 %) as a colourless oil.

Method B

To a partial solution of manganese (III) acetate dihydrate (402 mg, 1.50 mmol) and copper (II) acetate (136 mg, 0.75 mmol) in dry DMSO (3.5 mL), preheated to 70 °C, was added a solution of β-ketoester **7.39** (154 mg, 0.50 mmol) in DMSO (0.5 mL) in one portion. The reaction mixture was stirred for 90 min at 70 °C and the resulting turquoise solution allowed to cool to room temperature before dilution with EtOAc (40 mL) and water (50 mL). The particulates were filtered off through Celite, the organic layer separated and the aqueous extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with sat. $NaHCO_3$ (aq) (40 mL), water (40 mL) and brine (40 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield a crude yellow oil (120 mg). Purification was accomplished by flash chromatography on silica gel (2.2 x 5) eluting with EtOAc/hexane (1:1) to give the title compound **7.40** (79 mg, 0.26 mmol, 52 %) as a pale yellow solid (25:1 mixture of diastereoisomers), which was recrystallised from EtOAc/hexane to provide *trans*-cyclopropane **7.40** as a pale yellow solid.

MP 107-109 °C (EtOAc/hexane).

FT-IR ν_{max} (neat) 1767 s, 1699 m, 1592 m, 1462 m, 1335 m, 1238 m, 1126 s cm^{-1}.

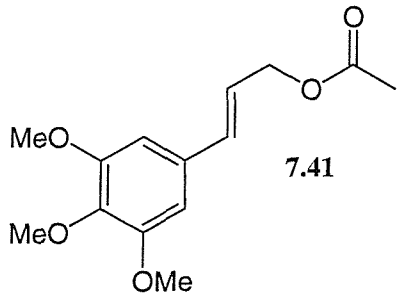
^{1}H NMR (400 MHz) δ 6.50 (2H, s, PhH**I**), 5.26 (1H, s, PhC**H**O-), 3.87 (6H, s, 2 x -OC**H**$_3$), 3.85 (3H, s, -OC**H**$_3$), 2.83 (1H, dd, *J* = 8.0, 5.5 Hz, -C**H**CH$_2$-), 2.61 (3H, s, -C**H**$_3$), 2.17 (1H, dd, *J* = 7.8, 4.3, -CH**H**-), 1.59 (1H, dd, *J* = 5.3, 4.3 Hz, -CH**H**-).

^{13}C NMR (100 MHz) δ 200.3 (**C**O$_{ket}$), 172.7 (**C**O$_{est}$), 154.2 (**C**$_{ar}$), 139.0 (**C**$_{ar}$), 134.6 (**C**$_{ar}$), 102.6 (**C**H$_{ar}$), 79.7 (-**C**HPh), 61.3 (-O**C**H$_3$), 56.6 (2 x -O**C**H$_3$), 37.3 (-**C**COCH$_3$), 37.1 (-**C**HCH$_2$-), 29.6 (-**C**H$_3$), 24.5 (-**C**H$_2$-).

LRMS (CI, NH_3) *m/z* (relative intensity) 307 (100) $[M+H]^+$, 265 (27).

CHN Anal. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.78; H, 5.99.

3-(3,4,5-Trimethoxy)phenyl-allyl acetate (7.41)



7.41

$C_{14}H_{18}O_5$

m.w. = 266.29 g/mol

Colourless oil

Compound **7.41** has not been isolated in pure form (contaminated with approx. 10 % 3,4,5-trimethoxybenzaldehyde) but gives spectroscopic data as follows.

FT-IR ν_{max} (neat) 1735 m, 1582 m, 1505 m, 1419 m, 1331 m, 1230 s, 1124 s cm^{-1}.

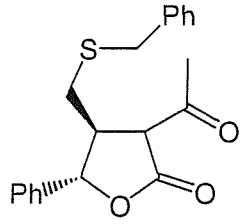
^{1}H NMR (400 MHz) δ 6.61 (2H, s, PhH), 6.58 (1H, d, *J* = 15.8 Hz, PhCH=CH-), 6.20 (1H, dt, *J* = 15.8, 6.5 Hz, -CHCH$_2$-), 4.71 (2H, d, *J* = 6.5 Hz, -CH$_2$-), 3.87 (6H, s, 2 x -OCH$_3$), 3.84 (3H, s, -OCH$_3$), 2.10 (3H, s, -CH$_3$).

^{13}C NMR (100 MHz) δ 171.2 (CO), 153.7 (C$_{ar}$), 138.7 (C$_{ar}$), 134.7 (PhCH=CH-), 132.3 (C$_{ar}$), 123.1 (-CHCH$_2$-), 104.2 (CH$_{ar}$), 65.4 (-CH$_2$-), 61.3 (-OCH$_3$), 56.5 (2 x -OCH$_3$), 21.4 (-CH$_3$).

LRMS (CI, NH_3) *m/z* (relative intensity) 266 (14) $[M]^+$, 209 (100), 207 (90) $[ArCH=CHCH_2]^+$.

HRMS (ES +ve) Calcd for $C_{28}H_{36}O_{10}Na$ (dimer) 555.2201, found 555.2194.

(4S*, 5S*)-3-Acetyl-4S-benzylsulfanylmethyl-5-phenyl-dihydro-furan-2-one (7.42a)



7.42a

$C_{20}H_{20}SO_3$

m.w. = 340.44 g/mol

Colourless oil

To a solution of cyclopropane **7.35** (432 mg, 2.00 mmol) in dry DMSO (5 mL) was added benzyl mercaptan (209 μL, 2.04 mmol) followed by $NaHCO_3$ (184 mg, 2.20 mmol) in one portion. The reaction was stirred at 100 °C for 45 min, cooled to room temperature, diluted with EtOAc (30 mL) and treated with 1N HCl (aq) (30 mL). The organic layer was separated and the aqueous extracted with EtOAc (4 x 30 mL). The combined organic layers were washed with water (4 x 30 mL) and brine (2 x 30 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield a crude yellow oil (830 mg). Purification was accomplished by flash chromatography on silica gel (3.2 x 9) eluting with EtOAc/hexane (1:4) to give the title compound **7.42a** (634 mg, 1.86 mmol, 93 %) as a colourless oil.

FT-IR ν_{max} (neat) 1762 s, 1714 s, 1453 m, 1356 m, 1226 m, 1144 s, 990 s cm^{-1}.

^{1}H NMR (400 MHz) δ 7.44-7.15 (10H, m, PhH), 5.07 (1H, d, *J* = 9.0 Hz, -CHPh), 3.83 (1H, d, *J* = 10.3 Hz, -CHCO-), 3.64 (1H, d, *J* = 13.6 Hz, -CHHPh), 3.60 (1H, d, *J* = 13.6 Hz, -CHHPh), 3.35 (1H, dddd, *J* = 10.3, 9.3, 8.0, 4.5 Hz, -CHCH$_2$-), 2.63 (1H, dd, *J* = 13.6, 4.5 Hz, -CHCHH-),

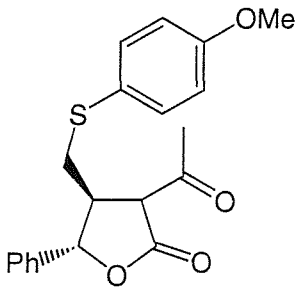
2.53 (3H, s, -C**H**$_3$), 2.50 (1H, dd, *J* = 13.8, 8.0 Hz, -CHC**H**H-); keto/enol ratio 10:1 - enolic resonances were observed at δ 11.27 (1H, s), 5.30 (1H, d, *J* = 1.3 Hz), 3.80 (1H, d, *J* = 4.0 Hz), 1.84 (3H, s).

^{13}C NMR (100 MHz) δ 200.4 (**C**O$_{ket}$), 171.3 (**C**O$_{est}$), 137.6 (**C**$_{ar}$), 137.4 (**C**$_{ar}$), 129.6 (**C**H$_{ar}$), 129.3 (**C**H$_{ar}$), 129.2 (**C**H$_{ar}$), 129.0 (**C**H$_{ar}$), 127.7 (**C**H$_{ar}$), 126.7 (**C**H$_{ar}$), 83.9 (-**C**HPh), 58.8 (-**C**HCO-), 45.7 (-**C**HCH$_2$-), 36.3 (-**C**H$_2$Ar), 31.1 (-CH**C**H$_2$S-), 30.9 (-CO**C**H$_3$); enolic resonances were observed at δ 170.6, 125.7, 125.5, 98.8, 79.9, 37.1, 36.7, 19.2.

LRMS (ES +ve) *m/z* (relative intensity) 703 (100) $[2M+Na]^+$.

HRMS (ES +ve) Calcd for $C_{40}H_{40}S_2O_6Na$ (dimer) 703.2159, found 703.2193.

(4S*, 5S*)-3-Acetyl-4-(4-methoxy-phenylsulfanylmethyl)-5-phenyl-dihydro-furan-2-one (7.42b)



7.42b

$C_{20}H_{20}SO_4$

m.w. = 356.38 g/mol

Colourless oil

The title compound was prepared according to the method outlined for **7.42a**, whereby reaction of cyclopropane **7.35** (88 mg, 0.40 mmol) with 4-methoxybenzenethiol (59 μL, 0.48 mmol) and workup under the conditions described gave a crude yellow (148 mg). Purification was accomplished by flash chromatography on silica gel (2.2 x 11) eluting with EtOAc/hexane (2:3) to give the title compound **7.42b** (129 mg, 0.36 mmol, 90 %) as a colourless oil.

FT-IR ν_{max} (neat) 1765 s, 1717 s, 1591 m, 1493 s, 1285 m, 1244 s, 1173 s cm^{-1}.

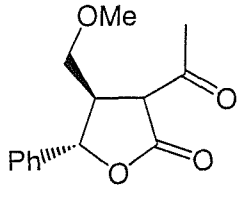
^{1}H NMR (400 MHz) δ 7.40-7.19 (7H, m, Ph**H**), 6.86-6.81 (2H, m, Ph**H**), 5.20 (1H, d, *J* = 9.3 Hz, -C**H**Ph), 3.98 (1H, d, *J* = 10.8 Hz, -C**H**CO-), 3.79 (3H, s, -OC**H**$_3$), 3.35-3.26 (1H, m, -C**H**CH$_2$-), 3.10 (1H, dd, *J* = 14.3, 4.8 Hz, -SC**H**H-), 2.93 (1H, dd, *J* = 14.3, 5.5 Hz, -SCH**H**-), 2.37 (3H, s, -C**H**$_3$); keto/enol ratio 11:2 - enolic resonances were observed at δ 11.16 (1H, s), 5.38 (1H, d, *J* = 10.0 Hz), 3.78 (3H, s), 1.81 (3H, s).

^{13}C NMR (100 MHz) δ 200.4 (CO_{ket}), 171.2 (CO_{est}), 159.9 (C_{ar}), 137.0 (C_{ar}), 133.6 (CH_{ar}), 129.6 (CH_{ar}), 129.2 (CH_{ar}), 127.1 (CH_{ar}), 115.3 (CH_{ar}), 83.2 (-CHPh), 57.9 (-CHCO-), 55.8 ($-OCH_3$), 46.2 ($-CHCH_2-$), 35.6 ($-CH_2S-$), 30.6 ($-COCH_3$); enolic resonances were observed at δ 170.5, 140.7, 134.3, 129.2, 125.6, 115.2, 84.1, 77.7, 45.8, 41.6, 19.2.

LRMS (CI, NH_3) *m/z* (relative intensity) 357 (50) $[M+H]^+$, 374 (6) $[M+NH_4]^+$, 108 (100) $[C_6H_5OCH_3]^+$, 217 (42) $[M+H(-ArSH)]^+$.

HRMS (ES +ve) Calcd for $C_{40}H_{40}S_2O_8Na$ (dimer) 735.2057, found 735.2040.

(4R*, 5S*)-3-Acetyl-4-methoxymethyl-5-phenyl-dihydro-furan-2-one (7.43)



7.43

$C_{14}H_{16}O_4$
m.w. = 248.28 g/mol
Colourless oil

To a solution of cyclopropane **7.35** (108 mg, 0.50 mmol) in dry MeOH (2 mL) was added $Zn(OTf)_2$ (218 mg, 0.60 mmol) and the mixture microwaved at 120 °C for 30 min (pressure 5 bar) before concentrated *in vacuo*. Purification was accomplished by flash chromatography on silica gel (2.3 x 14) eluting with EtOAc/hexane (1:9) to EtOAc/hexane (2:3) in 10 % increment rises (50 mL each). The title compound **7.43** (55 mg, 0.22 mmol, 44 %) was isolated as a colourless oil along with methyl enol ether **7.44** (45 mg, 0.17 mmol, 34 %) as a colourless oil. Data for title compound **7.43**.

FT-IR ν_{max} (neat) 1770 s, 1720 s, 1217 m, 1165 s, 1000 s cm^{-1}.

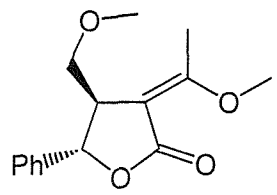
^{1}H NMR (400 MHz) δ 7.42-7.27 (5H, m, PhH), 5.28 (1H, d, *J* = 9.3 Hz, -CHPh), 3.97 (1H, d, *J* = 10.5 Hz, -CHCO-), 3.44-3.37 (2H, m, $-CHCH_2-$), 3.35 (3H, s, $-OCH_3$), 3.12 (1H, ddt, *J* = 10.5, 9.5, 3.5 Hz $-CHCH_2-$), 2.51 (3H, s, $-COCH_3$); keto/enol ratio 8:1 - enolic resonances were observed at δ 11.28 (1H, s), 5.47 (1H, d, *J* = 2.3 Hz), 1.98 (3H, s).

^{13}C NMR (100 MHz) δ 200.8 (CO_{ket}), 171.7 (CO_{est}), 137.8 (C_{ar}), 129.4 (CH_{ar}), 129.2 (CH_{ar}), 126.8 (CH_{ar}), 81.4 (-CHPh), 68.8 ($-CH_2-$), 59.5 (-CHCO-), 56.1 ($-OCH_3$), 46.5 ($-CHCH_2-$), 30.5 ($-COCH_3$); enolic resonances were observed at δ 170.8, 140.9, 125.4, 115.2, 82.8, 70.4, 46.7.

LRMS (CI, NH_3) *m/z* (relative intensity) 249 (100) $[M+H]^+$, 266 (32) $[M+NH_4]^+$.

HRMS (EI) Calcd for $C_{14}H_{16}O_4$ 248.1049, found 248.1054.

(4R*, 5S*)-3-(1-Methoxy-ethylidene)-4-methoxymethyl-5-phenyl-dihydro-furan-2-one (7.44)



7.44

$C_{15}H_{18}O_4$

m.w. = 262.30 g/mol

Colourless oil

FT-IR ν_{max} (neat) 1701 s, 1644 s, 1437 m, 1382 m, 1217 s, 1117 s, 1090 s cm^{-1}.

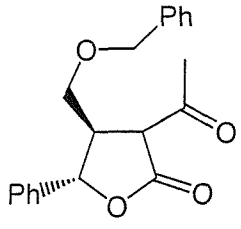
^{1}H NMR (400 MHz) δ 7.38-7.28 (5H, m, Ph**H**), 5.53 (1H, d, *J* = 4.5 Hz, -C**H**Ph), 3.70 (3H, s, -C=CO**CH$_3$**), 3.70 (1H, obsc dd, *J* = 9.0, 3.5 Hz, -CHCH**H**-), 3.49 (1H, t, *J* = 9.0 Hz, -CHC**H**H-), 3.40 (3H, s, -CH$_2$OC**H$_3$**), 3.42-3.34 (1H, m, -C**H**CH$_2$-), 2.33 (3H, s, -CC**H$_3$**).

^{13}C NMR (100 MHz) δ 170.1 (**CO$_{est}$**), 166.5 (-C=**C**O-), 142.0 (**C$_{ar}$**), 129.0 (**CH$_{ar}$**), 128.3 (**CH$_{ar}$**), 125.6 (**CH$_{ar}$**), 102.0 (-**C**=CO-), 86.9 (-**C**HPh), 74.2 (-**CH$_2$**-), 59.3 (-**C**HCH$_2$-), 51.9 (-O**CH$_3$**), 51.2 (-O**CH$_3$**), 14.9 (-C**CH$_3$**).

LRMS (CI, NH_3) *m/z* (relative intensity) 263 (100) $[M+H]^+$, 231 (64) [M+H (-MeOH)]$^+$.

HRMS (ES +ve) Calcd for $C_{15}H_{18}O_4Na$ 285.1097, found 285.1095.

(4R*, 5S*)-3-Acetyl-4-benzyloxymethyl-5-phenyl-dihydro-furan-2-one (7.45)



7.45

$C_{20}H_{20}O_4$

m.w. = 324.38 g/mol

Colourless oil

To a solution of cyclopropane **7.35** (216 mg, 1.0 mmol) in dry benzyl alcohol (0.31 mL, 3.0 mmol) was added magnesium perchlorate (22 mg, 0.1 mmol) before heating the mixture to 120 °C for 90 min. The reaction was cooled to room temperature before partitioning between CH_2Cl_2 (30 mL) and water (30 mL), the organic layer separated and the aqueous extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with sat. $NH_4^+Cl^-$ (aq) (20 mL) and brine (20 mL), dried with $MgSO_4$ and concentrated *in vacuo* to give a pale yellow oil (611 mg). The excess benzyl alcohol was removed by distillation under reduced pressure (b.p. ~ 120 °C, 0.5 mbar) and the residue purified by flash chromatography on silica gel (2.3 x 8) eluting with EtOAc/hexane (1:9)

to EtOAc/hexane (2:3) in 10 % increment rises (40 mL each). The title compound **7.45** (295 mg, 0.80 mmol, 80 %) was isolated as a colourless oil along with benzyl enol ether **7.46** (9 mg, 0.02 mmol, 2 %) isolated as a colourless oil. Data for title compound **7.45**.

FT-IR ν_{max} (neat) 1780 s, 1767 s, 1720 s, 1454 m, 1359 m, 1169 s cm^{-1}.

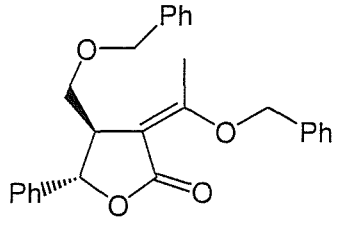
^{1}H NMR (400 MHz) δ 7.43-7.20 (10H, m, Ph**H**), 5.31 (1H, d, *J* = 9.5 Hz, -C**H**Ph), 4.56 (1H, d, *J* = 12.0 Hz, -OC**H**HPh), 4.48 (1H, d, *J* = 12.0 Hz, -OCH**H**Ph), 4.02 (1H, d, *J* = 10.5 Hz, -C**H**CO-), 3.50 (2H, ABq, *J* = 3.5, 2.5 Hz, -CHC**H**$_2$-), 3.12 (1H, ddt, *J* = 10.5, 9.5, 3.5 Hz -C**H**CH$_2$-), 2.49 (3H, s, -COC**H**$_3$); keto/enol ratio 7:1 - enolic resonances were observed at δ 11.28 (1H, s), 5.50 (1H, d, *J* = 2.5 Hz), 1.94 (3H, s).

^{13}C NMR (100 MHz) δ 200.8 (**C**O$_{ket}$), 171.7 (**C**O$_{est}$), 137.9 (**C**$_{ar}$), 137.7 (**C**$_{ar}$), 129.4 (**C**H$_{ar}$), 129.2 (**C**H$_{ar}$), 129.0 (**C**H$_{ar}$), 128.5 (**C**H$_{ar}$), 128.4 (**C**H$_{ar}$), 126.7 (**C**H$_{ar}$), 81.4 (-O**C**HPh), 73.7 (-O**C**H$_2$Ph), 65.7 (-**C**H$_2$OBn), 56.0 (-**C**HCOCH$_3$), 46.7 (-**C**HCH$_2$-), 30.5 (-CO**C**H$_3$); enolic resonances were observed at δ 170.8, 141.0, 128.6, 125.4, 82.8, 72.1, 46.9, 19.5.

LRMS (CI, NH_3) *m/z* (relative intensity) 325 (14) $[M+H]^+$, 342 (5) $[M+NH_4]^+$, 106 (100) $[PhCHO]^+$, 91 (82) $[PhCH_2]^+$.

HRMS (ES +ve) Calcd for $C_{20}H_{20}O_4Na$ 347.1254, found 347.1250.

(4R*, 5S*)-3-(1-Benzyloxy-ethylidene)-4-benzyloxymethyl-5-phenyl-dihydro-furan-2-one (7.46)



7.46

$C_{27}H_{26}O_4$
m.w. = 414.50 g/mol
Colourless oil

FT-IR ν_{max} (neat) 1702 s, 1693 s, 1642 s, 1495 m, 1454 m, 1214 s, 1075 s cm^{-1}.

^{1}H NMR (400 MHz) δ 7.40-7.20 (15H, m, Ph**H**), 5.57 (1H, d, *J* = 5.0 Hz, -OC**H**Ph), 5.17 (1H, d, *J* = 12.7 Hz, -C=COC**H**HPh), 5.10 (1H, d, *J* = 12.7 Hz, -C=COCH**H**Ph), 4.57 (1H, d, *J* = 12.1 Hz, -CH$_2$OC**H**HPh), 4.51 (1H, d, *J* = 12.1 Hz, -CH$_2$OCH**H**Ph), 3.82 (1H, dd, *J* = 9.3, 3.5

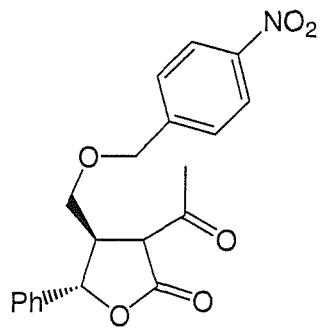
Hz, -CHCHH-), 3.58 (1H, t, J = 8.5 Hz, -CHCHH-), 3.48-3.42 (1H, m, -CHCH$_2$-), 2.34 (3H, s, -CCH$_3$).

^{13}C NMR (100 MHz) δ 170.6 (CO), 165.9 (-C=CO-), 142.0 (C_{ar}), 138.9 (C_{ar}), 137.0 (C_{ar}), 129.1 (CH_{ar}), 129.0 (CH_{ar}), 128.9 (CH_{ar}), 128.5 (CH_{ar}), 128.5 (CH_{ar}), 128.4 (CH_{ar}), 128.1 (CH_{ar}), 125.7 (CH_{ar}), 102.0 (-C=CO-), 87.1 (-OCHPh), 73.4 (-CH$_2$Ph), 71.6 (-CH$_2$Ph), 65.8 (-CH$_2$OBn), 52.1 (-CHCH$_2$-), 15.0 (-CCH$_3$).

LRMS (CI, NH_3) *m/z* (relative intensity) 415 (10) $[M+H]^+$, 307 (18) [M+H(-BnOH)]$^+$, 106 (70) $[PhCHO]^+$, 91 (100) $[PhCH_2]^+$.

HRMS (EI) Calcd for $C_{27}H_{26}O_4$ 414.1831, found 414.1826.

(4R*,5S*)-3-Acetyl-4-(4-nitrobenzyloxy)methyl-5-phenyl-dihydrofuran-2-one (7.47b)



7.47b

$C_{20}H_{19}NO_6$
m.w. = 369.37 g/mol
White powdery solid

The title compound was prepared according to the method outlined for **7.45**, whereby reaction of cyclopropane **7.35** (216 mg, 1.0 mmol) with 4-nitrobenzylalcohol (459 mg, 3.0 mmol) and workup under the conditions described gave a crude viscous yellow oil (970 mg). The excess benzyl alcohol was removed by distillation under reduced pressure (b.p. ~ 200 °C, 0.5 mbar) and the residue purified by flash chromatography on silica gel (2.3 x 8) eluting with EtOAc/hexane (1:9) to EtOAc/hexane (1:1) in 10 % increment rises (40 mL each) to yield the title compound **7.47b** (326 mg, 0.88 mmol, 88 %) as a viscous colourless oil that solidified on standing to provide a white powdery solid.

MP 79-81 °C (EtOAc/hexane).

FT-IR ν_{max} (neat) 1768 s, 1718 s, 1512 s, 1344 s, 1156 s, 1123 s, 1088 s cm^{-1}.

^{1}H NMR (400 MHz) δ 8.20 (2H, d, J = 8.5 Hz, ArH), 7.43 (2H, d, J = 8.5 Hz, ArH), 7.43-7.28 (5H, m, PhH), 5.30 (1H, d, J = 9.3 Hz, -CHPh), 4.62 (1H, d, J = 13.1 Hz, -OCHHAr), 4.57 (1H, d, J = 12.8 Hz, -OCHHAr), 3.97 (1H, d, J = 10.5 Hz, -CHCO-), 3.61 (1H, dd, J = 10.0, 4.0 Hz, -CHCHH-), 3.57 (1H, dd, J = 10.0, 4.0 Hz,

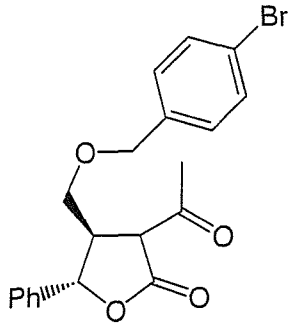
-CHCHH-), 3.23 (1H, ddt, J = 10.3, 9.3, 4.0 Hz -CHCH$_2$-), 2.51 (3H, s, -COCH$_3$); keto/enol ratio 18:1 - enolic resonances were observed at δ 1.89 (3H, s).

^{13}C NMR (100 MHz) δ 200.5 (CO$_{ket}$), 171.4 (CO$_{est}$), 148.0 (C$_{ar}$), 145.3 (C$_{ar}$), 137.5 (C$_{ar}$), 129.6 (CH$_{ar}$), 129.3 (CH$_{ar}$), 128.1 (CH$_{ar}$), 126.8 (CH$_{ar}$), 124.2 (CH$_{ar}$), 87.2 (-CHPh), 72.4 (-CH$_2$Ar), 67.6 (-CHCH$_2$O-), 56.3 (-CHCO-), 46.3 (-CHCH$_2$-), 30.4 (-COCH$_3$); enolic resonances were observed at δ 87.2, 62.5, 59.1, 51.0, 21.1.

LRMS (ES +ve) *m/z* (relative intensity) 761 (100) $[2M+Na]^+$, 1130 (50) $[3M+Na]^+$.

CHN Anal. Calcd for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79. Found: C, 65.22; H, 5.21; N, 3.77.

(4R*, 5S*)-3-Acetyl-4-(4-bromobenzyloxy)methyl-5-phenyl-dihydrofuran-2-one (7.47c)



7.47c

$C_{20}H_{19}O_4Br$

m.w. = 403.27 g/mol

White powdery solid

The title compound was prepared according to the method outlined for **7.45**, whereby reaction of cyclopropane **7.35** (432 mg, 2.0 mmol) with 4-bromobenzylalcohol (1.12 g, 6.0 mmol) and workup under the conditions described gave a crude viscous yellow oil (1.62 g). The excess benzyl alcohol was removed by distillation under reduced pressure (b.p. ~ 170 °C, 0.5 mbar) and the residue purified by flash chromatography on silica gel (2.7 x 8) eluting with EtOAc/hexane (1:9) to EtOAc/hexane (3:7) in 10 % increment rises (100 mL each) to yield the title compound **7.47c** (732 mg, 1.82 mmol, 91 %) as a viscous colourless oil that solidified on standing to provide a white powdery solid.

MP 56-58 °C (EtOAc/hexane).

FT-IR ν_{max} (neat) 1766 s, 1719 s, 1485 m, 1351 m, 1304 m, 1157 s, 1125 s cm^{-1}.

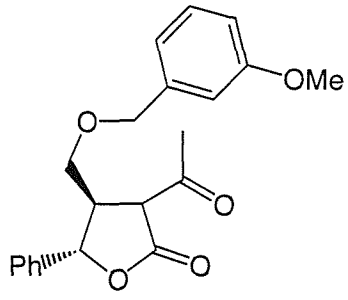
^{1}H NMR (400 MHz) δ 7.50 (2H, d, J = 8.3 Hz, ArH), 7.38-7.21 (5H, m, PhH), 7.16 (2H, d, J = 8.3 Hz, ArH), 5.27 (1H, d, J = 9.5 Hz, -CHPh), 4.49 (1H, d, J = 12.1 Hz, -OCHHAr), 4.40 (1H, d, J = 12.1 Hz, -OCHHAr), 3.97 (1H, d, J = 10.6 Hz, -CHCO-), 3.50 (1H, dd, J = 10.0, 3.5 Hz,

-CHCHH-), 3.47 (1H, dd, J = 10.0, 3.5 Hz, -CHCHH-), 3.14 (1H, ddt, J = 10.5, 9.5, 3.5 Hz -CHCH$_2$-), 2.50 (3H, s, -COCH$_3$); keto/enol ratio 10:1 - enolic resonances were observed at δ 11.28 (1H, s), 5.48 (1H, d, J = 2.3 Hz), 4.55 (1H, d, J = 7.5 Hz), 1.94 (3H, s).

^{13}C NMR (100 MHz) δ 200.7 (CO$_{ket}$), 171.5 (CO$_{est}$), 137.6 (C$_{ar}$), 136.8 (C$_{ar}$), 132.1 (CH$_{ar}$), 129.9 (CH$_{ar}$), 129.5 (CH$_{ar}$), 129.3 (CH$_{ar}$), 126.7 (CH$_{ar}$), 122.4 (C$_{ar}$), 81.5 (-CHPh), 72.9 (-CH$_2$Ar), 66.1 (-CHCH$_2$O-), 56.1 (-CHCO-), 46.5 (-CHCH$_2$-), 30.5 (-COCH$_3$); enolic resonances were observed at δ 128.7, 125.3, 82.8, 72.3, 46.8, 19.6.

CHN Anal. Calcd for $C_{20}H_{19}O_4Br$: C, 59.57; H, 4.75. Found: C, 59.54; H, 4.76.

(4R*, 5S*)-3-Acetyl-4-(3-methoxybenzyloxy)methyl-5-phenyl-dihydro-furan-2-one (7.47d)



7.47d

$C_{21}H_{22}O_5$
m.w. = 354.40 g/mol
Colourless oil

The title compound was prepared according to the method outlined for **7.45**, whereby reaction of cyclopropane **7.35** (216 mg, 1.0 mmol) with 3-methoxybenzylalcohol (0.37 mL, 3.0 mmol) and workup under the conditions described gave a crude viscous yellow oil (705 mg). The excess benzyl alcohol was removed by distillation under reduced pressure (b.p. ~ 130 °C, 0.5 mbar) and the residue purified by flash chromatography on silica gel (2.2 x 7) eluting with EtOAc/hexane (1:9) to EtOAc/hexane (3:7) in 10 % increment rises (50 mL each) to yield the title compound **7.47d** (297 mg, 0.84 mmol, 84 %) as a viscous colourless oil.

FT-IR ν_{max} (neat) 1762 s, 1715 s, 1584 m, 1454 m, 1358 m, 1263 s, 1153 s cm^{-1}.

^{1}H NMR (400 MHz) δ 7.36-7.21 (6H, m, PhH), 6.89-6.83 (3H, m, PhH), 5.29 (1H, d, J = 9.3 Hz, -CHPh), 4.51 (1H, d, J = 12.0 Hz, -OCHHAr), 4.43 (1H, d, J = 12.0 Hz, -OCHHAr), 4.00 (1H, d, J = 10.8 Hz, -CHCO-), 3.81 (3H, s, -OCH$_3$), 3.48 (1H, dd, J = 10.3, 3.5 Hz, -CHCHH-),

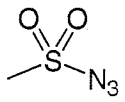
3.46 (1H, dd, J = 10.3, 3.5 Hz, -CHCH**H**-), 3.10 (1H, ddt, J = 10.5, 9.5, 3.5 Hz -C**H**CH_2-), 2.47 (3H, s, -COC**H**$_3$); keto/enol ratio 10:1 - enolic resonances were observed at δ 11.27 (1H, s), 5.49 (1H, d, J = 2.0 Hz), 4.56 (1H, d, J = 12.8 Hz), 1.92 (3H, s).

^{13}C NMR (100 MHz) δ 200.8 (**C**O$_{ket}$), 171.7 (**C**O$_{est}$), 160.3 (**C**$_{ar}$), 139.5 (**C**$_{ar}$), 137.7 (**C**$_{ar}$), 130.1 (**C**H$_{ar}$), 129.4 (**C**H$_{ar}$), 129.2 (**C**H$_{ar}$), 126.8 (**C**H$_{ar}$), 120.5 (**C**H$_{ar}$), 114.0 (**C**H$_{ar}$), 113.7 (**C**H$_{ar}$), 81.4 (-**C**HPh), 73.5 (-**C**H$_2$Ar), 65.7 (-CH**C**H$_2$O-), 56.0 (-**C**HCO-), 55.7 (-O**C**H$_3$), 46.7 (-**C**HCH$_2$-), 30.6 (-CO**C**H$_3$); enolic resonances were observed at δ 128.6, 125.4, 120.2, 113.9, 113.4, 82.9, 72.1, 46.9, 19.5.

LRMS (ES +ve) *m/z* (relative intensity) 377 (60) $[M+Na]^+$, 731 (100) $[2M+Na]^+$.

HRMS (ES +ve) Calcd for $C_{42}H_{44}O_{10}Na$ (dimer) 731.2827, found 731.2856.

Methanesulfonyl azide (1516-70-7)



$CH_3SO_2N_3$

m.w. = 121.12 g/mol

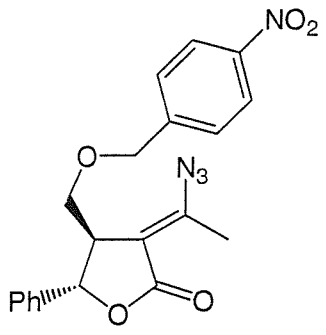
Colourless oil

The title compound was prepared according to a modified procedure described by Nickon *et al.*[223] Thus, to a solution of methanesulfonyl chloride (0.39 mL, 5.0 mmol) in MeOH (5 mL) at 0 °C (ice/salt bath) was added a saturated aqueous solution of NaN_3 (423 mg, 6.5 mmol) dropwise over 20 min. The reaction was allowed to warm to room temperature and left stirring for 90 min before dilution with Et_2O (20 mL) and water (20 mL). The organic layer was separated and the aqueous extracted with Et_2O (3 x 20 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated *in vacuo* to give methanesulfonyl azide (562 mg, 4.6 mmol, 93 %) as a clear colourless oil which was used for diazo transfer reactions without further purification. The reagent was stored at 0 °C (freezing point ~ 10 °C) for several months without detectable deterioration. Spectroscopic details were consistent with those observed in the literature.[223]

FT-IR ν_{max} (neat) 2134 s, 1347 s, 1194 m, 1143 s cm^{-1}.

^{1}H NMR (300 MHz) δ 3.28 (3H, s, -CH_3).

(4R*, 5S*)-3-(1-Azidoethylidene)-4-benzyloxymethyl-5-phenyl-dihydrofuran-2-one (7.49a)



7.49a

$C_{20}H_{18}O_5N_4$

m.w. = 394.39 g/mol

Pale yellow oil

To a solution of lactone **7.47b** (60 mg, 0.16 mmol) in MeCN (1 mL) at room temperature was added DBU (24 μL, 0.16 mmol). After 5 min a solution of methanesulfonyl azide (58 mg, 0.48 mmol) in MeCN (0.6 mL) was added and the reaction stirred at room temperature for 18 h. The mixture was then diluted with CH_2Cl_2 (20 mL) and water (20 mL), the organic layer separated and the aqueous extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield a yellow oil (132 mg). Purification was accomplished by flash chromatography on silica gel (2.2 x 7) eluting with EtOAc/hexane (1:1) to give the title compound **7.49a** (46 mg, 0.12 mmol, 73 %) as a pale yellow oil.

FT-IR ν_{max} (neat) 2110 s, 1765 m, 1737 s, 1643 s, 1516 s, 1342 s, 1145 s cm^{-1}.

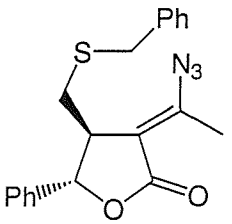
^{1}H NMR (400 MHz) δ 8.23 (2H, dt, *J* = 8.8, 1.8 Hz, Ph**H**), 7.51 (2H, d, *J* = 8.8 Hz, Ph**H**), 7.39-7.24 (5H, m, Ph**H**), 5.51 (1H, d, *J* = 2.3 Hz, -OC**H**Ph), 4.72 (1H, d, *J* = 13.1 Hz, -C**H**HPh), 4.68 (1H, d, *J* = 13.1 Hz, -CH**H**Ph), 3.82 (1H, dd, *J* = 9.0, 4.0 Hz, -CHC**H**H-), 3.62 (1H, t, *J* = 8.8 Hz, -CHCH**H**-), 3.41-3.37 (1H, m, -C**H**CH_2-), 2.57 (3H, s, -CC**H**$_3$).

^{13}C NMR (100 MHz) δ 170.3 (**C**O), 149.4 (-C=**C**N_3), 147.9 (**C**$_{ar}$), 145.8 (**C**$_{ar}$), 141.0 (**C**$_{ar}$), 129.2 (**C**H$_{ar}$), 128.6 (**C**H$_{ar}$), 128.0 (**C**H$_{ar}$), 125.4 (**C**H$_{ar}$), 124.1 (**C**H$_{ar}$), 110.2 (-**C**=CN_3), 80.5 (-O**C**HPh), 72.4 (-**C**H_2Ph), 71.2 (-**C**H_2OBn), 48.5 (-**C**HCH_2-), 14.5 (-C**C**H_3).

LRMS (ES +ve) *m/z* (relative intensity) 811 (100) $[2M+Na]^+$.

HRMS (ES +ve) Calcd for $C_{40}H_{36}O_{10}N_8Na$ (dimer) 811.2447, found 811.2472.

(4R*, 5S*)-3-(1-Azidoethylidene)-4-benzylsulfanylmethyl-5-phenyl-dihydrofuran-2-one (7.49b)



7.49b

$C_{20}H_{19}SO_2N_3$

m.w. = 365.46 g/mol

Yellow solid

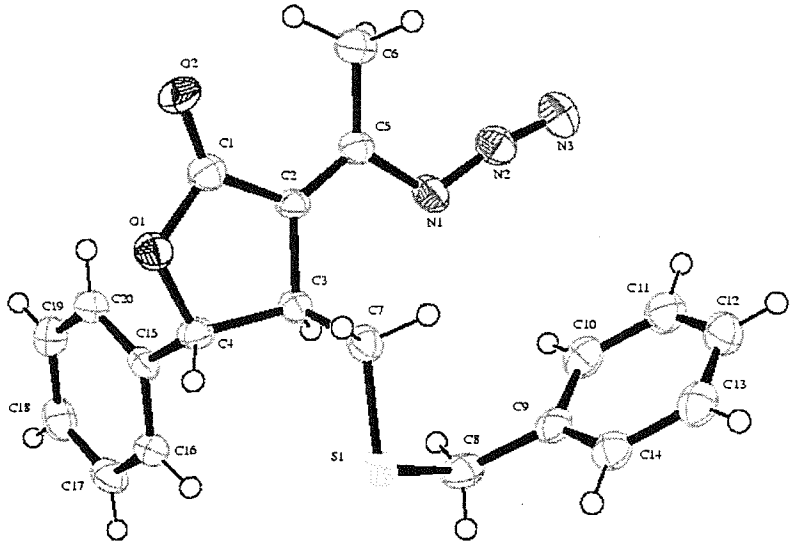
The title compound was prepared according to the method outlined for **7.49a**, whereby reaction of lactone **7.42a** (82 mg, 0.24 mmol) with MsN_3 (87 mg, 0.72 mmol) and workup under the conditions described gave a crude yellow oil (211 mg). Purification was accomplished by flash chromatography on silica gel (2.2 x 7) eluting with EtOAc/hexane (1:4) to yield the title compound **7.49b** (61 mg, 0.17 mmol, 70 %) as a yellow oil which solidified on standing to provide a crystalline yellow solid.

FT-IR ν_{max} (neat) 2110 s, 1731 s, 1637 s, 1283 s, 1254 s, 1140 s, 1027 s cm^{-1}.

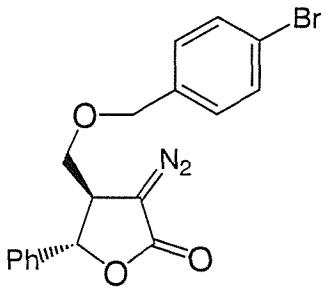
^{1}H NMR (400 MHz) δ 7.39-7.23 (10H, m, Ph**H**), 5.41 (1H, s, -C**H**Ph), 3.77 (2H, s, -C**H**$_2$Ph), 3.19-3.14 (1H, m, -C**H**CH$_2$-), 2.86 (1H, dd, *J* = 13.3, 3.3 Hz, -CHC**H**H-), 2.56-2.47 (1H, obsc m, -CHCH**H**-), 2.52 (3H, s, -CH$_3$).

^{13}C NMR (100 MHz) δ 170.4 (**C**O), 149.1 (-C=**C**N$_3$), 141.2 (**C**$_{ar}$), 138.3 (**C**$_{ar}$), 129.6 (**C**H$_{ar}$), 129.2 (**C**H$_{ar}$), 129.0 (**C**H$_{ar}$), 128.5 (**C**H$_{ar}$), 127.8 (**C**H$_{ar}$), 125.4 (**C**H$_{ar}$), 112.9 (-**C**=CN$_3$), 81.5 (-**C**HPh), 47.5 (-**C**HCH$_2$-), 36.5 (-**C**H$_2$Ph), 34.6 (-**C**H$_2$SBn), 14.5 (-C**C**H$_3$).

X-Ray Structure



(4R*, 5S*)-3-Diazo-4-{[(4-bromobenzyl)oxy]methyl}-5-phenyltetrahydro-2-furanone (7.57c)



7.57c

$C_{18}H_{15}N_2O_3Br$

m.w. = 387.23 g/mol

Yellow oil

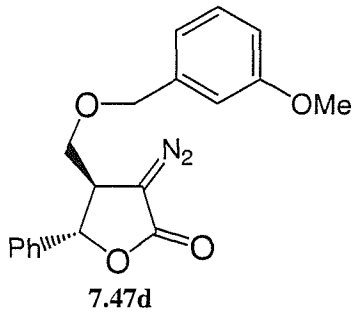
The title compound was prepared according to the method outlined for **5.18** (method B), whereby reaction of lactone **7.47c** (500 mg, 1.24 mmol) with Tf_2O (0.83 mL, 4.96 mmol) and NaN_3 (645 mg, 9.92 mmol) and workup under the conditions described gave a crude yellow foam (750 mg). Purification was accomplished by flash chromatography on silica gel (2.8 x 3.5) eluting with EtOAc/hexane (1:20) to EtOAc/hexane (1:4) in 5 % increment rises (50 mL each) to yield the title compound **7.57c** (399 mg, 1.03 mmol, 83 %) as a bright yellow oil.

FT-IR (neat) ν_{max} 2100 s, 1711 s, 1485 m, 1369 s, 1263 s, 1208 s, 1108, 1007 s cm^{-1}.

^{1}H NMR (300 MHz) δ 7.50 (2H, d, *J* = 8.5 Hz, Ar**H**), 7.45-7.23 (5H, m, Ph**H**), 7.18 (2H, d, *J* = 8.2 Hz, Ar**H**), 5.16 (1H, d, *J* = 4.0 Hz, PhC**H**-), 4.54 (2H, s, -OC**H**$_2$Ar), 3.80 (1H, dd, *J* = 12.0, 2.6 Hz, -CHC**H**HO-), 3.77-3.70 (2H, m, -CHCH**H**O- and -C**H**CH$_2$-).

^{13}C NMR (75 MHz) δ 169.5 (**C**O), 139.2 (**C**$_{ar}$), 136.6 (**C**$_{ar}$), 132.2 (**C**H$_{ar}$), 129.7 (**C**H$_{ar}$), 129.4 (**C**H$_{ar}$), 125.8 (**C**H$_{ar}$), 122.4 (**C**$_{ar}$), 80.8 (Ph**C**H-), 73.3 (Ar**C**H$_2$O-), 71.3 (-**C**H$_2$OBn), 53.1 (-**C**N$_2$), 45.7 (-**C**HCH$_2$-).

(4R*, 5S*)-3-Diazo-4-{[(3-methoxybenzyl)oxy]methyl}-5-phenyltetrahydro-2-furanone (7.57d)



7.47d

$C_{19}H_{18}N_2O_4$

m.w. = 338.36 g/mol

Yellow oil

The title compound was prepared according to the method outlined for **5.18** (method B), whereby reaction of lactone **7.47d** (248 mg, 0.70 mmol) with Tf_2O (0.47 mL, 2.80 mmol)

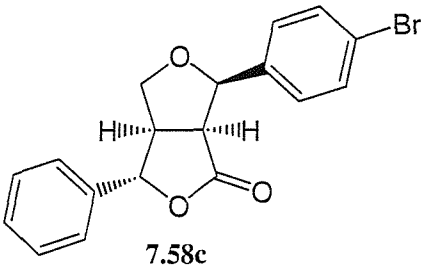
and NaN_3 (364 mg, 5.60 mmol) and workup under the conditions described gave a crude yellow foam (573 mg). Purification was accomplished by flash chromatography on silica gel (2.2 x 3) eluting with EtOAc/hexane (1:20) to EtOAc/hexane (1:4) in 5 % increment rises (30 mL each) to yield the title compound **7.47d** (198 mg, 0.59 mmol, 84 %) as a bright yellow oil.

FT-IR (neat) ν_{max} 2094 s, 1728 s, 1453 m, 1371 m, 1258 s, 1103 s, 1012 s cm^{-1}.

^{1}H NMR (300 MHz) δ 7.48-7.31 (6H, m, PhH), 6.95-6.90 (3H, m, PhH), 5.21 (1H, d, *J* = 4.3 Hz, PhCH-), 4.62 (2H, s, -OCH_2Ar), 3.88 (3H, s, -OCH_3), 3.89-3.77 (3H, m, -$CHCH_2$- and -$CHCH_2$-).

^{13}C NMR (75 MHz) δ 169.6 (CO), 160.3 (C_{ar}), 139.3 (C_{ar}), 139.2 (C_{ar}), 130.1 (CH_{ar}), 129.4 (CH_{ar}), 129.3 (CH_{ar}), 125.8 (CH_{ar}), 120.3 (CH_{ar}), 114.1 (CH_{ar}), 113.4 (CH_{ar}), 80.8 (PhCH-), 73.9 (ArCH_2O-), 71.1 (-CH_2OBn), 55.7 (-OCH_3), 53.2 (-CN_2), 45.8 (-$CHCH_2$-).

(1S*, 2R*, 5R*, 6S*)-2-(4-Bromophenyl)-6-phenyl-3,7-dioxabicyclo[3.3.0]octan-8-one (7.58c)



7.58c

$C_{18}H_{15}O_3Br$

m.w. = 359.22 g/mol

White crystalline solid

The title compound was prepared according to the method outlined for **5.19**, whereby reaction of diazo lactone **7.57c** (333 mg, 0.86 mmol) with dirhodium (II) tetraacetate (7 mg, cat.) and workup under the conditions described gave crude furofuranone as a pale yellow oil (318 mg). Purification was accomplished by flash chromatography on silica gel (3.2 x 10) eluting with EtOAc/hexane (1:9) to EtOAc/heaxane (1:1) in 5 % increment rises (50 mL each) to yield the title compound **7.58c** (234 mg, 0.65 mmol, 76 %) as a white crystalline solid.

MP 135-137 °C (EtOAc/hexane).

FT-IR (neat) ν_{max} 1761 s, 1490 w, 1331 w, 1255 m, 1168 s, 1061 s, 1010 s cm^{-1}.

^{1}H NMR (400 MHz) δ7.52 (2H, d, *J* = 8.5 Hz, PhH), 7.44-7.28 (7H, m, PhH), 5.28 (1H, d, *J* = 6.5 Hz, PhCH-), 5.05 (1H, d, *J* = 8.5 Hz, ArCH-), 4.36 (1H, d, *J* = 9.5 Hz, -CHH-), 3.95 (1H, dd, *J* = 9.5, 4.8 Hz, -CHH-), 3.59

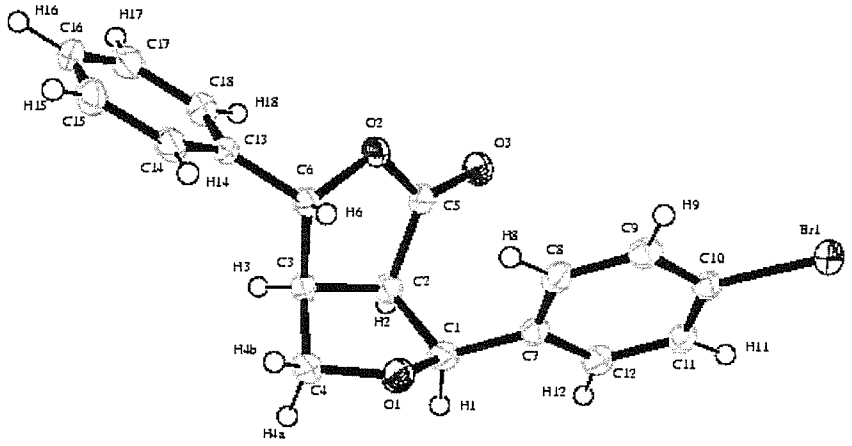
(1H, t, J = 9.0 Hz, -COC**H**-), 3.26 (1H, ddd, J = 9.0, 6.5, 4.8 -CH_2C**H**-).

^{13}C NMR (100 MHz) δ 174.5 (**C**O), 139.9 (**C**$_{ar}$), 135.5 (**C**$_{ar}$), 132.1 (**C**H$_{ar}$), 129.4 (**C**H$_{ar}$), 129.3 (**C**H$_{ar}$), 128.4 (**C**H$_{ar}$), 125.8 (**C**H$_{ar}$), 122.8 (**C**$_{ar}$), 86.0 (Ph**C**H-), 83.6 (Ar**C**H-), 72.6 (-**C**H_2-), 51.7 (-CO**C**H-), 51.4 (-CH_2**C**H-).

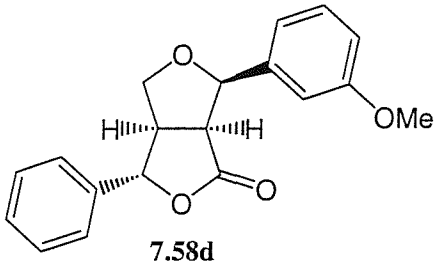
LRMS (ES +ve) *m/z* (relative intensity) 741 (100) $[2M+Na]^+$.

CHN Anal. Calcd for $C_{18}H_{15}O_3Br$: C, 60.19; H, 4.21. Found: C, 60.29; H, 4.27.

X-Ray structure



(1S*, 2R*, 5R*, 6S*)-2-(3-Methoxyphenyl)-6-phenyl-3,7-dioxabicyclo[3.3.0]octan-8-one (7.58d)



7.58d

$C_{19}H_{18}O_4$

m.w. = 310.35 g/mol

White powdery solid

The title compound was prepared according to the method outlined for **5.19**, whereby reaction of diazo lactone **7.57d** (160 mg, 0.47 mmol) with dirhodium (II) tetraacetate (4 mg, cat.) and workup under the conditions described gave crude furofuranone as a colourless oil (155 mg). Purification was accomplished by flash chromatography on silica gel (2.2 x 2.8) eluting with EtOAc/hexane (1:9) to EtOAc/heaxane (1:1) in 5 %

increment rises (25 mL each) to yield the title compound **7.58d** (118 mg, 0.38 mmol, 82 %) as a white powdery solid.

MP 121-122 °C (EtOAc/hexane).

FT-IR (neat) ν_{max} 1770 s, 1603 m, 1493 m, 1322 m, 1275 m, 1166 s, 1031 s cm^{-1}.

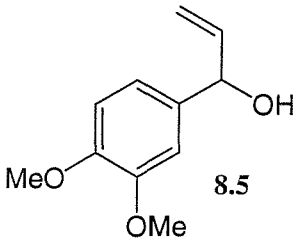
^{1}H NMR (400 MHz) δ 7.43-7.29 (6H, m, PhH), 7.01-6.96 (2H, m, PhH), 6.87 (1H, ddd, *J* = 8.3, 2.5, 0.8 Hz, PhH), 5.30 (1H, d, *J* = 6.5 Hz, PhCH-), 5.07 (1H, d, *J* = 8.5 Hz, ArCH-), 4.36 (1H, d, *J* = 9.8 Hz, -CHH-), 3.94 (1H, dd, *J* = 9.8, 4.8 Hz, -CHH-), 3.82 (3H, s, $-OCH_3$), 3.58 (1H, t, *J* = 8.8 Hz, -COCH-), 3.24 (1H, ddd, *J* = 9.0, 6.5, 4.8, $-CH_2CH-$).

^{13}C NMR (100 MHz) δ 174.6 (CO), 160.2 (C_{ar}), 140.0 (C_{ar}), 138.1 (C_{ar}), 130.0 (CH_{ar}), 129.4 (CH_{ar}), 129.2 (CH_{ar}), 125.8 (CH_{ar}), 119.1 (CH_{ar}), 114.2 (CH_{ar}), 112.4 (CH_{ar}), 85.8 (PhCH-) 84.2 (ArCH-), 72.3 ($-CH_2-$), 55.6 ($-OCH_3$), 51.9 (-COCH-), 51.6 ($-CH_2CH-$).

LRMS (ES +ve) *m/z* (relative intensity) 643 (100) $[2M+Na]^+$.

CHN Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.40; H, 5.92.

1-(3,4-Dimethoxy)phenyl-prop-2-en-1-ol (31706-95-3) (8.5)



8.5

$C_{11}H_{14}O_3$

m.w. = 194.23 g/mol

Pale yellow solid

The title compound was prepared according to the method outline for **7.9**, whereby reaction of 3,4-dimethoxybenzaldehyde (49.85 g, 0.30 mol) with vinyl magnesium bromide (345 mL of a 1M sol in THF, 0.345 mol) and workup under the conditions described gave a crude yellow oil (68.2 g). Purification was accomplished by flash chromatography on silica gel (8.5 x 8) eluting with EtOAc/hexane (1:1) to yield the title compound **8.5** (56.82, 0.29 mol, 98 %) as a very viscous yellow oil that crystallised on standing to provide a pale yellow, low-melting, solid. Spectroscopic details were consistent with those observed in the literature.[267]

MP 31-33 °C. Previously reported as an oil.[267]

FT-IR (neat) ν_{max} 3501 s, 1593 m, 1514 s, 1462 s, 1255 s, 1223 s, 1137 s cm^{-1}.

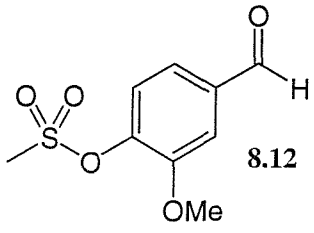
^{1}H NMR (400 MHz) δ 6.92-6.87 (2H, m, PhH), 6.83 (1H, d, *J* = 8.3 Hz, PhH), 6.04 (1H, ddd, *J* = 17.1, 10.3, 6.0 Hz, $-CH=CH_2$), 5.34 (1H, dt, *J* = 17.1, 1.3

Hz, -CH=CHH), 5.19 (1H, dt, J = 10.3, 1.3 Hz, -CH=CHH), 5.14 (1H, br d, J = 5.5 Hz, ArCH-), 3.87 (3H, s, $-OCH_3$), 3.86 (3H, s, $-OCH_3$).

^{13}C NMR (100 MHz) δ 149.5 (C_{ar}), 149.0 (C_{ar}), 140.7 (-CH=CH_2), 135.7 (C_{ar}), 119.1 (CH_{ar}), 115.3 (-CH=CH_2), 111.5 (CH_{ar}), 110.0 (CH_{ar}), 75.5 (-CHAr), 56.4 ($-OCH_3$), 56.3 ($-OCH_3$).

LRMS (CI, NH_3) *m/z* (relative intensity) 176 (100) $[M(-H_2O)]^+$.

4-Methanesulfonyloxy-3-methoxybenzaldehyde (52200-05-2) (8.12)



8.12

$C_9H_{10}SO_5$

m.w. = 230.24 g/mol

White crystalline solid

To a solution of vanillin (22.8 g, 0.150 mol) in CH_2Cl_2 (750 mL) at -30 °C (internal, CO_2(s)/acetone) was added NEt_3 (41.8 mL, 0.300 mol) dropwise over 10 min and the reaction mixture was stirred at –30 °C for 5 min. Mesyl chloride (17.4 mL, 0.225 mol) was then added dropwise over 15 min and the mixture maintained at –30 °C for 30 min. The reaction was allowed to warm to –10 °C over 30 min then quenched with sat. $NaHCO_3$ (aq) (300 mL). The organic layer was separated and the aqueous extracted with CH_2Cl_2 (3 x 300 mL). The combined organic layers were washed with brine (400 mL), dried with Na_2SO_4, and concentrated *in vacuo* to yield a crude off-white solid (37.2 g). Purification was accomplished by flash chromatography on silica gel (9 x 7) eluting with EtOAc/hexane (1:1) to give the title compound **8.12** (34.2 g, 0.149 mol, 99 %) as a white powdery solid. Spectroscopic details were consistent with those previously reported.[268]

MP 90-91 °C (EtOAc/hexane) (lit.[268] 93-94 °C).

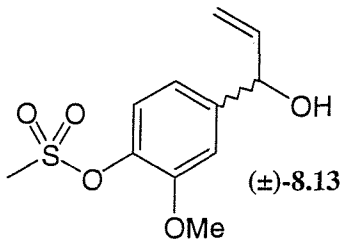
FT-IR (neat) ν_{max} 1694 s, 1587 m, 1352 s, 1286 s, 1148 s, 1101 s, 1021 s cm^{-1}.

^{1}H NMR (400 MHz) δ 9.96 (1H, s, -CHO), 7.53 (1H, d, J = 1.3 Hz, PhH), 7.51-7.46 (2H, m, PhH), 3.97 (3H, s, $-OCH_3$), 3.24 (3H, s, $-SO_2CH_3$).

^{13}C NMR (100 MHz) δ 191.2 (CO), 152.8 (C_{ar}), 143.3 (C_{ar}), 136.5 (C_{ar}), 125.5 (CH_{ar}), 125.2 (CH_{ar}), 111.8 (CH_{ar}), 56.8 ($-OCH_3$), 39.3 ($-SO_2CH_3$).

CHN Anal. Calcd for $C_9H_{10}SO_5$: C, 46.95; H, 4.38. Found: C, 47.00; H, 4.40.

1-(4-Methanesulfonyloxy-3-methoxyphenyl)-prop-2-en-1-ol ((±)-8.13)



(±)-**8.13**

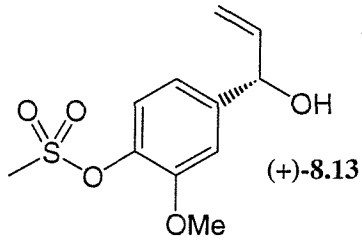
$C_{11}H_{14}SO_5$

m.w. = 258.29 g/mol

Pale yellow oil

To a partial solution of aldehyde **8.12** (23.02 g, 0.100 mol) in THF (200 mL) at –60 °C (internal, CO_2(s)/acetone) was added vinylmagnesium bromide (105 mL of a 1M solution in THF, 0.105 mol) *via* dropping funnel at such a rate that the temperature did not rise above –55 °C (90 min). The resulting yellow homogeneous solution was warmed to –10 °C diluted with EtOAc (200 mL) and treated with saturated NH_4Cl (aq) (300 mL) with vigorous stirring. The organic layer was separated and the aqueous extracted with EtOAc (3 x 300 mL). The combined organic layers were washed with brine (400 mL), dried with Na_2SO_4, and concentrated *in vacuo* to yield the title compound (±)-**8.13** (27.1 g, quantitative) as a pale yellow oil – this crude material was used directly in the subsequent enzymatic resolution. See compound (+)-**8.13** for spectroscopic data.

(1S)-(4-Methanesulfonyloxy-3-methoxyphenyl)-prop-2-en-1-ol ((+)-8.13)



(+)-**8.13**

$C_{11}H_{14}SO_5$

m.w. = 258.29 g/mol

Pale yellow oil

To a solution of crude alcohol (+)-**8.13** (0.100 mol, theoretical) in isopropenyl acetate (110 mL, 1.000 mol) was added Novozym 435 (12.90 g, 50 wt.%), the mixture gently stirred and warmed to 40 °C for 17 h (reaction monitored by chiral HPLC, column: Chiracel OD-H, until 50 % completion). The enzyme was filtered, washed with EtOAc (200 mL) and the filtrate concentrated *in vacuo* to yield a crude yellow oil (33.1 g). Purification was accomplished by flash chromatography on silica gel (9 x 30) eluting with EtOAc/hexane (3:7 then 2:3 then 1:1). The title compound (+)-**8.13** (10.11 g, 0.039 mol, 39 %) was isolated as a pale yellow oil along with acetate (*R*)-**8.14** (11.08 g, 0.037 mol, 37 %), which was also isolated as a pale yellow oil and acetate by-product **8.15** (0.75 g, 0.003 mol, 3 %) isolated as a white powdery solid following titration with Et_2O/hexane. Data for (*S*)-**8.13**.

$[\alpha]_D$ + 16.7 (c. 0.50, $CHCl_3$).

FT-IR (neat) ν_{max} 3521 br w, 1600 m, 1502 m, 1355 s, 1267 m, 1108 s cm^{-1}.

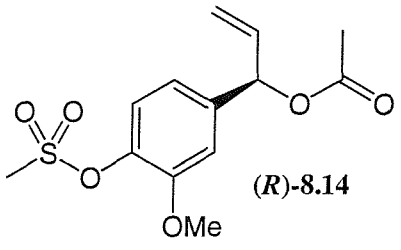
^{1}H NMR (400 MHz) δ 7.25 (1H, d, *J* = 8.3 Hz, PhH), 7.06 (1H, d, *J* = 1.8 Hz, PhH), 6.93 (1H, dd, *J* = 8.3, 1.8 Hz, PhH), 6.00 (1H, ddd, *J* = 17.1, 10.3, 6.3 Hz, -CH=CH_2), 5.36 (1H, dt, *J* = 17.1, 1.3 Hz, -CH=CHH), 5.22 (1H, dt, *J* = 10.3, 1.3 Hz, -CH=CHH), 5.18 (1H, br d, *J* = 6.0 Hz, ArCH-), 3.89 (3H, s, -OCH_3), 3.16 (3H, s, -SO_2CH_3).

^{13}C NMR (100 MHz) δ 151.9 (C_{ar}), 143.5 (C_{ar}), 140.2 (-CH=CH_2), 138.0 (C_{ar}), 124.8 (CH_{ar}), 119.3 (CH_{ar}), 116.3 (-CH=CH_2), 111.2 (CH_{ar}), 75.2 (-CHAr), 56.5 (-OCH_3), 38.7 (-SO_2CH_3).

LRMS (CI, NH_3) *m/z* (relative intensity) 276 (15) $[M+NH_4]^+$, 241 (40) $[M+H(-H_2O)]^+$, 79 (100) $[CH_3SO_2]^+$.

HRMS (ES +ve) Calcd for $C_{22}H_{28}S_2O_{10}Na$ (dimer) 539.1016, found 539.1034.

(1R)-(4-Methanesulfonyloxy-3-methoxyphenyl)-allyl acetate ((*R*)-8.14)



(*R*)-8.14

$C_{13}H_{16}SO_6$

m.w. = 300.33 g/mol

Pale yellow oil

$[\alpha]_D$ + 38.6 (c. 0.47, $CHCl_3$).

FT-IR (neat) ν_{max} 1736 m, 1504 m, 1362 s, 1227 s, 1149 m, 1113 s, 1026 m cm^{-1}.

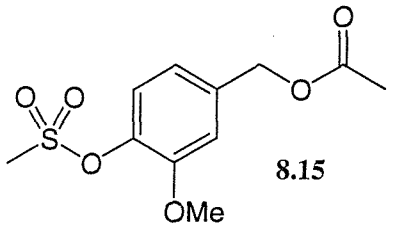
^{1}H NMR (400 MHz) δ 7.27 (1H, d, *J* = 8.5 Hz, PhH), 6.99-6.94 (2H, m, PhH), 6.23 (1H, d, *J* = 6.0 Hz, ArCH-), 5.97 (1H, ddd, *J* = 17.1, 10.3, 5.8 Hz, -CH=CH_2), 5.31 (1H, dt, *J* = 17.1, 1.3 Hz, -CH=CHH), 5.27 (1H, dt, *J* = 10.3, 1.3 Hz, -CH=CHH), 3.89 (3H, s, -OCH_3), 3.17 (3H, s, -SO_2CH_3), 2.12 (3H, s, -$COCH_3$).

^{13}C NMR (100 MHz) δ 170.3 (CO), 151.9 (C_{ar}), 139.8 (C_{ar}), 138.5 (C_{ar}), 136.1 (-CH=CH_2), 125.0 (CH_{ar}), 120.3 (CH_{ar}), 117.9 (-CH=CH_2), 112.4 (CH_{ar}), 76.0 (-CHAr), 56.5 (-OCH_3), 38.8 (-SO_2CH_3), 21.6 (-$COCH_3$).

LRMS (CI, NH_3) *m/z* (relative intensity) 241 (60) $[M+H(-CH_3CO_2H)]^+$, 260 (100).

HRMS (ES +ve) Calcd for $C_{13}H_{16}SO_6Na$ 323.0560, found 323.0564.

4-Methanesulfonyloxy-3-methoxybenzyl acetate (8.15)



8.15

$C_{11}H_{14}SO_6$

m.w. = 274.29 g/mol

White powdery solid

MP 83-84 °C (EtOAc/hexane).

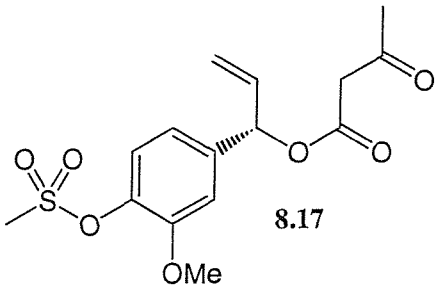
FT-IR (neat) ν_{max} 1735 s, 1354 s, 1241 s, 1147 s, 1176 s, 1116 s, 1027 s cm^{-1}.

^{1}H NMR (400 MHz) δ 7.28 (1H, d, *J* = 8.0 Hz, PhH), 7.00 (1H, d, *J* = 1.8 Hz, PhH), 6.96 (1H, dd, *J* = 8.3, 1.8 Hz, PhH), 5.07 (2H, s, ArC**H**$_2$-), 3.90 (3H, s, -OC**H**$_3$), 3.17 (3H, s, -SO$_2$C**H**$_3$), 2.11 (3H, s, -COC**H**$_3$).

^{13}C NMR (100 MHz) δ 171.2 (**C**O), 151.9 (**C**$_{ar}$), 138.6 (**C**$_{ar}$), 136.9 (**C**$_{ar}$), 125.0 (**C**H$_{ar}$), 121.4 (**C**H$_{ar}$), 113.3 (**C**H$_{ar}$), 66.1 (-**C**H$_2$Ar), 56.5 (-O**C**H$_3$), 38.8 (-SO$_2$**C**H$_3$), 21.4 (-CO**C**H$_3$).

CHN Anal. Calcd for $C_{11}H_{14}SO_6$: C, 48.17; H, 5.14. Found: C, 48.53; H, 5.28.

(1S)-(4-Methanesulfonyloxy-3-methoxyphenyl)-allyl acetoacetate (8.17)



8.17

$C_{15}H_{18}SO_7$

m.w. = 342.37 g/mol

Pale yellow oil

The title compound was prepared according to the method outlined for **7.22** whereby (1S)-(4-methanesulfonyloxy-3-methoxy-phenyl)-prop-2-en-1-ol (**8.13**) (5.94 g, 23 mmol) and 2,2,6-trimethyl-4H-1,3-dioxin-4-one (3.0 mL, 23.2 mmol) were reacted under the conditions described (except reaction for 15 min). Purification was accomplished by flash chromatography on silica gel (8 x 7) eluting with petrol (800 mL), followed by EtOAc/hexane (1:1) to give the title compound **8.17** (7.25 g, 21.2 mmol, 92 %) as a pale yellow oil.

$[\alpha]_D$ - 38.2 (c. 0.34, $CHCl_3$).

FT-IR ν_{max} (neat) 1737 s, 1714 s, 1504 m, 1358 s, 1255 s, 1146 s, 1112 s cm^{-1}.

^{1}H NMR (400 MHz) δ 7.28 (1H, d, *J* = 8.3 Hz, PhH), 7.02 (1H, d, *J* = 2.0 Hz, PhH), 6.95 (1H, ddd, *J* = 8.3, 2.0, 0.5 Hz, PhH), 6.28 (1H, d, *J* = 6.0 Hz,

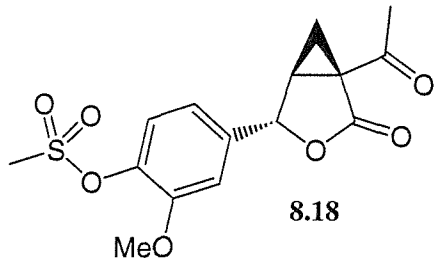
ArC**H**-), 5.97 (1H, ddd, *J* = 17.1, 10.5, 6.0 Hz, -C**H**=CH$_2$), 5.36 (1H, dt, *J* = 17.3, 1.3 Hz, -CH=CH**H**), 5.31 (1H, dt, *J* = 10.3, 1.3 Hz, -CH=CH**H**), 3.91 (3H, s, -OC**H**$_3$), 3.53 (2H, s, -C**H**$_2$CO-), 3.17 (3H, s, -SO$_2$C**H**$_3$), 2.25 (3H, s, -C**H**$_3$); keto/enol ratio 6:1 - enolic acetoacetyl resonances were observed at δ 11.90 (1H, d, *J* = 0.8 Hz), 5.08 (1H, d, *J* = 0.8 Hz), 3.89 (3H, s), 1.97 (3H, s).

^{13}C NMR (100 MHz) δ 200.6 (**C**O$_{ket}$), 166.4 (**C**O$_{est}$), 152.0 (**C**$_{ar}$), 139.2 (**C**$_{ar}$), 138.5 (**C**$_{ar}$), 135.5 (-**C**H=CH$_2$), 125.0 (**C**H$_{ar}$), 120.1 (**C**H$_{ar}$), 118.7 (-CH=**C**H$_2$), 112.2 (**C**H$_{ar}$), 77.0 (-**C**HAr), 56.6 (-O**C**H$_3$), 50.6 (-**C**H$_2$CO-), 38.8 (-SO$_2$**C**H$_3$), 30.7 (-CO**C**H$_3$); enolic acetoacetyl resonances were observed at δ 177.0, 139.8, 136.2, 117.9, 112.1, 90.0, 75.4, 21.7.

LRMS (ES +ve) *m/z* (relative intensity) 365 (100) [M+Na]$^+$, 707 (30) [2M+Na]$^+$.

HRMS (ES +ve) Calcd for $C_{15}H_{18}SO_7Na$ 365.0665, found 365.0675.

(1R, 4S, 5S)-1-Acetyl-4-(4-methanesulfonyloxy-3-methoxyphenyl)-3-oxa-bicyclo[3.1.0]hexan-2-one (8.18)



8.18

$C_{15}H_{16}SO_7$

m.w. = 340.35 g/mol

Cream powdery solid

The title compound was prepared according to the method outlined for **7.35** (Method B), whereby β-ketoester **8.17** (6.85 g, 20.0 mmol), manganese (III) acetate dihydrate (16.1 g, 60.0 mmol), copper (II) acetate (5.45 g, 30.0 mmol) and potassium acetate (22.1g, 225 mmol) were reacted and worked-up under the conditions described to yield a crude yellow oil (7.38 g). Purification was accomplished by flash chromatography on silica gel (5 x 12) eluting with EtOAc/hexane (2:3) to give the title compound **8.18** (4.59 g, 13.5 mmol, 67 %) as a pale yellow oil (25:1 mixture of diastereoisomers). A series of triturations with ice-cold Et$_2$O/hexane provided the *trans*-isomer as an off-white solid.

MP 113-115 °C (EtOAc/hexane).

[α]$_D$ + 96.6 (c. 0.38, $CHCl_3$).

FT-IR ν_{max} (neat) 1770 s, 1695 s, 1599 w, 1513 m, 1346 s, 1318 s, 1151 s, 1116 s, 1087 s, 1011 s cm^{-1}.

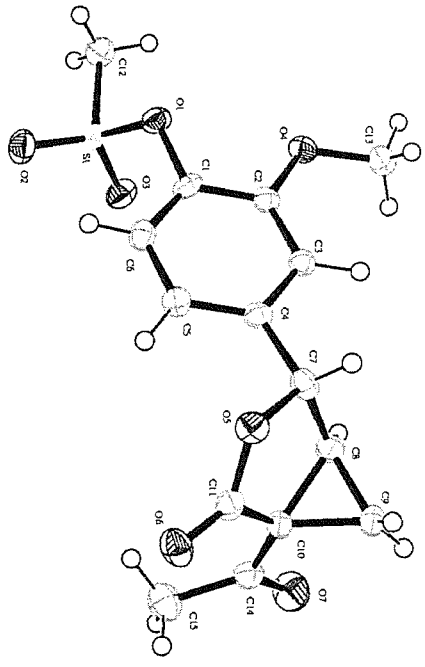
^{1}H NMR (400 MHz) δ 7.33 (1H d, *J* = 8.8 Hz, Ph**H**), 6.93-6.89 (2H, m, Ph**H**), 5.30 (1H, s, ArC**H**-), 3.90 (3H, s, -OC**H**$_3$), 3.19 (3H, s, -SO_2C**H**$_3$), 2.82 (1H, dd, *J* = 8.0, 6.0 Hz, -C**H**C**H**$_2$-), 2.58 (3H, s, -COC**H**$_3$), 2.15 (1H, dd, *J* = 8.0, 4.3, -C**H**H-), 1.61 (1H, m, -CH**H**-).

^{13}C NMR (100 MHz) δ 200.1 (**C**O$_{ket}$), 172.5 (**C**O$_{est}$), 152.5 (**C**$_{ar}$), 139.4 (**C**$_{ar}$), 139.1 (**C**$_{ar}$), 125.7 (**C**H$_{ar}$), 118.0 (**C**H$_{ar}$), 110.3 (**C**H$_{ar}$), 78.9 (-**C**HAr), 56.6 (-O**C**H$_3$), 39.0 (-SO_2**C**H$_3$), 37.2 (-**C**COCH$_3$), 36.7 (-**C**HCH$_2$-), 29.7 (-COCH$_3$), 24.7 (-**C**H$_2$-).

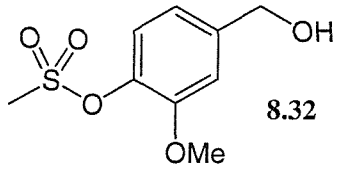
LRMS (ES +ve) *m/z* (relative intensity) 703 (100) $[2M+Na]^+$.

CHN Anal. Calcd for $C_{15}H_{16}SO_7$: C, 52.94; H, 4.74. Found: C, 52.93; H, 4.78.

X-ray structure



4-Methanesulfonyloxy-3-methoxybenzyl alcohol (8.32)



8.32

$C_9H_{12}SO_5$

m.w. = 232.26 g/mol

White powdery solid

To a partial solution of aldehyde **8.12** (3.45 g, 15.0 mmol) in MeOH (35 mL) at 0 °C (ice bath) was added $NaBH_4$ portionwise (624 mg, 16.5 mmol) over 1 min. The colourless homogeneous reaction mixture was allowed to warm to room temperature and left stirring for 30 min. The mixture was then concentrated *in vacuo* and the resulting residue partitioned between EtOAc (40 mL) and 1N HCl (aq) (40 mL), the organic layer separated and the aqueous extracted with EtOAc (3 x 40 mL). The combined organic

layers were washed with brine (40 mL), dried with Na_2SO_4 and concentrated *in vacuo* to yield a crude colourless oil (3.85 g). Purification was accomplished by flash chromatography on silica gel (5 x 5) eluting with EtOAc/hexane (1:1) to give the title compound **8.32** (3.15 g, 13.6 mmol, 90 %) as a white powdery solid following trituration with Et_2O/hexane.

MP 66-67 °C.

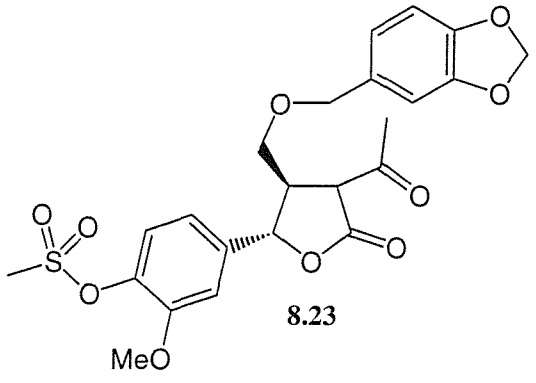
FT-IR (neat) ν_{max} 3548 m, 1604 m, 1502 m, 1346 s, 1166 s, 1141 s, 1107 s cm^{-1}.

^{1}H NMR (400 MHz) δ 7.24 (1H, d, *J* = 8.3 Hz, PhH), 7.05 (1H, d, *J* = 1.8 Hz, PhH), 6.91 (1H, dd, *J* = 8.3, 1.8 Hz, PhH), 4.66 (2H, s, ArC**H**$_2$-), 3.89 (3H, s, -OC**H**$_3$), 3.16 (3H, s, -SO_2C**H**$_3$).

^{13}C NMR (100 MHz) δ 151.9 (**C**$_{ar}$), 142.0 (**C**$_{ar}$), 137.9 (**C**$_{ar}$), 124.8 (**C**H$_{ar}$), 119.5 (**C**H$_{ar}$), 111.8 (**C**H$_{ar}$), 65.0 (-**C**H$_2$Ar), 56.5 (-O**C**H$_3$), 38.7 (-SO_2**C**H$_3$).

CHN Anal. Calcd for $C_9H_{12}SO_5$: C, 46.54; H, 5.21. Found: C, 46.74; H, 5.24.

(4R, 5S)-5-(4-Methanesulfonyloxy-3-methoxy)phenyl-4-{[(3,4-methylenedioxybenzyl) oxy]methyl}-3-acetyl-tetrahydro-2-furanone (8.23)



8.23

$C_{23}H_{24}SO_{10}$

m.w. = 492.50 g/mol

Viscous colourless oil

To a mixture of cyclopropane **8.18** (1.70 g, 5.0 mmol), 3,4-methylenedioxybenzyl alcohol (3.80 g, 25.0 mmol) and 2,6-di-*tert*-butylpyridine (1.12 mL, 5.0 mmol) was added magnesium perchlorate (223 mg, 1.0 mmol) and the mixture heated to 120 °C for 2 h. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc (80 mL) and treated with sat. NH_4Cl (aq) (80 mL). The organic layer was separated and the aqueous extracted with EtOAc (3 x 80 mL). The combined organic layers were washed with brine (1 x 80 mL), dried with Na_2SO_4 and concentrated *in vacuo* to yield a crude yellow oil (6.18 g). Purification was accomplished by flash chromatography on silica gel (4 x 20) eluting with EtOAc/hexane (1:4 then 1:3, 1:2 and 1:1) to give the title compound **8.23** (1.33 g, 2.7 mmol, 54 %) as a viscous colourless oil, along with recovered

cyclopropane **8.18** (0.58 g, 1.7 mmol, 34 %) as an off-white powdery solid. Data for **8.23**.

$[\alpha]_D$ + 33.6 (c. 0.67, $CHCl_3$).

FT-IR ν_{max} (neat) 1768 s, 1711 s, 1503 s, 1359 s, 1240 s, 1152 s, 1114 s, 1032 s cm^{-1}.

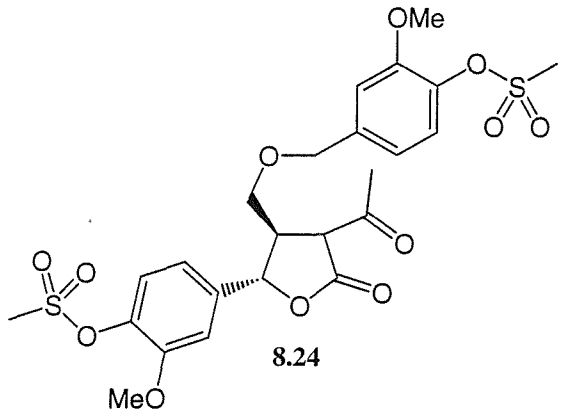
^{1}H NMR (400 MHz) δ 7.27 (1H, d, *J* = 8.3 Hz, PhH), 6.92 (1H, d, *J* = 1.8 Hz, PhH), 6.81-6.73 (4H, m, PhH), 5.98 (2H s, -OC**H**$_2$O-), 5.27 (1H, d, *J* = 9.3 Hz, -C**H**Ar), 4.47 (1H, d, *J* = 11.8 Hz, -OC**H**HAr), 4.36 (1H, d, *J* = 11.8 Hz, -OCH**H**Ar), 3.99 (1H, d, *J* = 10.5 Hz, -C**H**CO-), 3.87 (3H, s, -OC**H**$_3$), 3.48 (1H, dd, *J* = 8.3, 3.5 Hz, -CHC**H**H-), 3.45 (1H, dd, *J* = 8.3, 3.5 Hz, -CHCH**H**-), 3.19 (3H, s, -SO_2C**H**$_3$), 3.07 (1H, ddt, *J* = 10.5, 9.3, 3.5 Hz -C**H**CH$_2$-), 2.50 (3H, s, -COC**H**$_3$); keto/enol ratio 10:1 - enolic resonances were observed at δ 11.24 (1H, s), 5.48 (1H, d, *J* = 2.5 Hz), 4.53 (1H, d, *J* = 11.5 Hz), 1.97 (3H, s).

^{13}C NMR (100 MHz) δ 200.6 (**C**O$_{ket}$), 171.4 (**C**O$_{est}$), 152.3 (**C**$_{ar}$), 148.4 (**C**$_{ar}$), 148.0 (**C**$_{ar}$), 139.0 (**C**$_{ar}$), 138.4 (**C**$_{ar}$), 131.6 (**C**$_{ar}$), 125.1 (**C**H$_{ar}$), 122.1 (**C**H$_{ar}$), 119.4 (**C**H$_{ar}$), 110.8 (**C**H$_{ar}$), 108.9 (**C**H$_{ar}$), 108.7 (**C**H$_{ar}$), 101.6 (-O**C**H$_2$O-), 80.7 (-**C**HAr), 73.6 (-**C**H$_2$Ar), 65.5 (-CH**C**H$_2$O-), 56.5 (-O**C**H$_3$), 55.9 (-**C**HCO-), 46.5 (-**C**HCH$_2$-), 38.8 (-SO_2**C**H$_3$), 30.6 (-CO**C**H$_3$); enolic resonances were observed at δ 125.2, 121.8, 117.6, 108.8, 108.6, 82.2, 73.7, 71.8, 46.9, 19.6.

LRMS (ES +ve) *m/z* (relative intensity) 515 (90) $[M+Na]^+$, 1007 (100) $[2M+Na]^+$.

HRMS (ES +ve) Calcd for $C_{23}H_{24}SO_{10}Na$ 515.0982, found 515.0985.

(4R, 5S)-5-(4-Methanesulfonyloxy-3-methoxy)phenyl-4-{[(4-methanesulfonyloxy-3-methoxybenzyl)oxy]methyl}-3-acetyl-tetrahydro-2-furanone (8.24)



8.24

$C_{24}H_{28}S_2O_{12}$

m.w. = 572.61 g/mol

White foam

To a mixture of cyclopropane **8.18** (204 mg, 0.60 mmol), 4-methanesulfonyloxy-3-methoxy-benzyl alcohol (**8.32**) (418 mg, 1.80 mmol) and 2,6-di-*tert*-butylpyridine (13 μL, 0.06 mmol) was added magnesium perchlorate (13 mg, 0.06 mmol) and the mixture heated to 120 °C for 2.5 h. The reaction mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 (30 mL) and treated with sat. NH_4Cl (aq) (25 mL). The organic layer was separated and the aqueous extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried with Na_2SO_4 and concentrated *in vacuo* to yield a crude yellow oil (730 mg). To a solution of this crude material in isopropenyl acetate (3 mL) was added Novozym 435 (140 mg, 50 wt.% based on 1.2 mmol of excess benzyl alcohol **8.32** remaining) and the gently stirred mixture warmed to 40 °C for 12 h. The enzyme was then filtered, washed with EtOAc (30 mL) and the filtrate concentrated *in vacuo* to yield a colourless oil (790 mg). Purification was accomplished by flash chromatography on silica gel (3.2 x 14) eluting with EtOAc/hexane (1:1 then 2:1 then 3:1) to give the title compound **8.24** (247 mg, 0.43 mmol, 72 %) as a white foamy solid.

MP 57-59 °C.

$[\alpha]_D$ + 31.2 (c. 0.38, $CHCl_3$).

FT-IR ν_{max} (neat) 1771 m, 1718 m, 1505 m, 1360 s, 1272 s, 1151 s, 1114 s cm^{-1}.

^{1}H NMR (400 MHz) δ 7.30-7.25 (2H, m, Ph**H**), 6.94-6.91 (2H, m, Ph**H**), 6.89 (1H, dd, *J* = 8.3, 1.8 Hz, Ph**H**), 6.76 (1H, dd, *J* = 8.3, 1.8 Hz, Ph**H**), 5.26 (1H, d, *J* = 9.0 Hz, -C**H**Ar), 4.53 (1H, d, *J* = 12.3 Hz, -OC**H**HAr), 4.44 (1H, d, *J* = 12.3 Hz, -OCH**H**Ar), 3.96 (1H, d, *J* = 10.0 Hz, -C**H**CO-), 3.89 (3H, s, -OC**H**$_3$), 3.85 (3H, s, -OC**H**$_3$), 3.55 (2H, d, *J* = 3.8 Hz, -CHC**H**$_2$-), 3.20 (3H, s, -SO_2C**H**$_3$), 3.18 (3H, s, -SO_2C**H**$_3$), 3.13 (1H, ddt, *J* = 10.0, 9.0, 3.8 Hz -C**H**CH$_2$-), 2.50 (3H, s, -COC**H**$_3$); keto/enol ratio 12:1 - enolic resonances were observed at δ 11.24 (1H, s), 5.49 (1H, d, *J* = 2.5 Hz), 4.58 (1H, d, *J* = 10.0 Hz), 1.96 (3H, s).

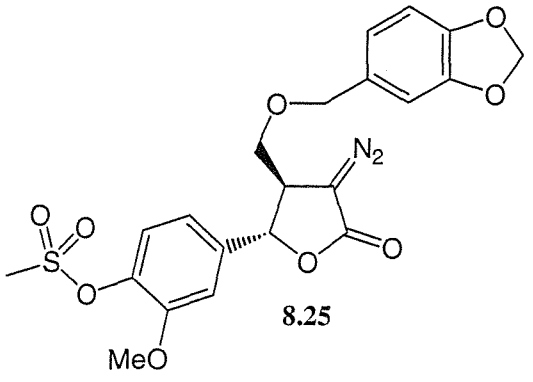
^{13}C NMR (100 MHz) δ 200.4 (**C**O$_{ket}$), 171.3 (**C**O$_{est}$), 152.5 (**C**$_{ar}$), 152.1 (**C**$_{ar}$), 139.1 (**C**$_{ar}$), 138.3 (**C**$_{ar}$), 138.3 (**C**$_{ar}$), 125.2 (**C**H$_{ar}$), 125.1 (**C**H$_{ar}$), 120.6 (**C**H$_{ar}$), 119.4 (**C**H$_{ar}$), 112.7 (**C**H$_{ar}$), 110.7 (**C**H$_{ar}$), 81.0 (-**C**HAr), 73.2 (-**C**H$_2$Ar), 67.0 (-CH**C**H$_2$O-), 56.7 (-O**C**H$_3$), 56.6 (-O**C**H$_3$), 56.3 (-**C**HCO-), 46.3 (-**C**HCH$_2$-), 39.0 (-SO_2**C**H$_3$), 38.9 (-SO_2**C**H$_3$),

30.5 (-$COCH_3$); enolic resonances were observed at δ 141.4, 117.8, 19.8.

LRMS (ES +ve) *m/z* (relative intensity) 595 (100) $[M+Na]^+$.

CHN Anal. Calcd for $C_{24}H_{28}S_2O_{12}$: C, 50.34; H, 4.93. Found: C, 50.19; H, 5.01.

(4R, 5S)-5-(4-Methanesulfonyloxy-3-methoxy)phenyl-3-diazo-4-{[(3,4-methylene-dioxybenzyl)oxy]methyl}tetrahydro-2-furanone (8.25)



8.25

$C_{21}H_{20}N_2SO_9$

m.w. = 476.46 g/mol

Bright yellow oil/foam

The title compound was prepared according to the method outlined for **5.18** (method B), whereby reaction of lactone **8.23** (1.00 g, 2.03 mmol) with Tf_2O (1.37 mL, 8.12 mmol) and NaN_3 (1.06 g, 16.24 mmol) and workup under the conditions described gave a crude yellow oil (1.12 g). Purification was accomplished by flash chromatography on silica gel (4 x 6) eluting with EtOAc/hexane (1:1) to give the title compound **8.25** (848 mg, 1.78 mmol, 88 %) as a viscous bright yellow oil/foam.

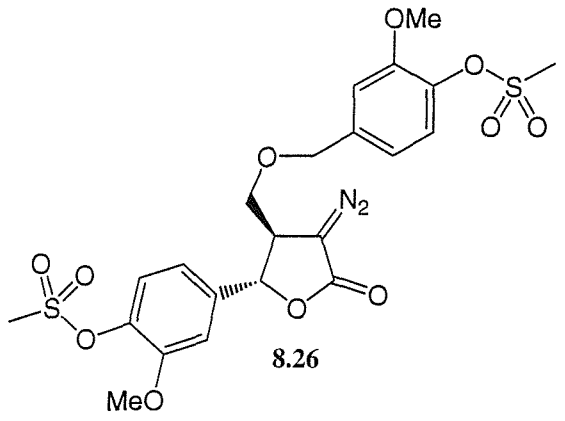
$[\alpha]_D$ + 44.7 (c. 0.28, $CHCl_3$).

FT-IR ν_{max} (neat) 2103 s, 1736 s, 1504 m, 1365 s, 1256 m, 1116 m, 1035 m cm^{-1}.

^{1}H NMR (400 MHz) δ 7.29 (1H, d, *J* = 8.3 Hz, PhH), 6.96 (1H, d, *J* = 2.0 Hz, PhH), 6.87 (1H, dd, *J* = 8.3, 2.0 Hz, PhH), 6.80-6.73 (3H, m, PhH), 5.96 (2H s, -OCH_2O-), 5.17 (1H, d, *J* = 4.8 Hz, -CHAr), 4.48 (2H, s, -OCH_2Ar), 3.86 (3H, s, -OCH_3), 3.78-3.65 (3H, m, -$CHCH_2$- and -$CHCH_2$-), 3.18 (3H, s, -SO_2CH_3).

^{13}C NMR (100 MHz) δ 169.3 (CO), 152.4 (C_{ar}), 148.5 (C_{ar}), 148.0 (C_{ar}), 139.9 (C_{ar}), 138.8 (C_{ar}), 131.3 (C_{ar}), 125.4 (CH_{ar}), 122.0 (CH_{ar}), 118.2 (CH_{ar}), 110.2 (CH_{ar}), 108.8 (CH_{ar}), 108.7 (CH_{ar}), 101.6 (-OCH_2O-), 80.2 (-CHAr), 74.0 (-CH_2Ar), 70.6 (-$CHCH_2O$-), 56.6 (-OCH_3), 52.9 (CN_2), 45.6 (-$CHCH_2$-), 38.9 (-SO_2CH_3).

(4R, 5S)-5-(4-Methanesulfonyloxy-3-methoxy)phenyl-3-diazo-4-{[(4-methanesulfonyl oxy-3-methoxybenzyl)oxy]methyl}tetrahydro-2-furanone (8.26)



8.26

$C_{22}H_{24}N_2S_2O_{11}$

m.w. = 556.57 g/mol

Bright yellow foam

The title compound was prepared according to the method outlined for **5.18** (method B), whereby reaction of lactone **8.24** (160 mg, 0.28 mmol) with Tf_2O (0.19 mL, 1.12 mmol) and NaN_3 (146 mg, 2.24 mmol) and workup under the conditions described gave a crude yellow oil (226 mg). Purification was accomplished by flash chromatography on silica gel (2.2 x 9) eluting with EtOAc/hexane (3:1) to give the title compound **8.26** (150 mg, 0.27 mmol, 96 %) as a viscous bright yellow foam.

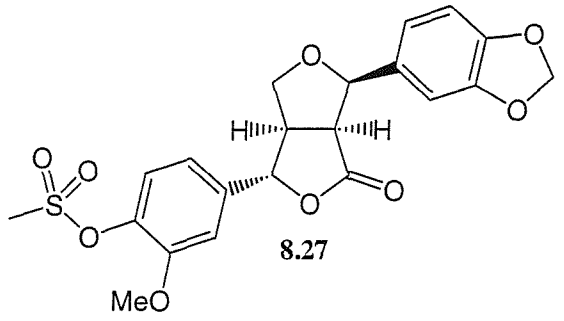
$[\alpha]_D$ + 42.3 (c. 0.41, $CHCl_3$).

FT-IR ν_{max} (neat) 2101 m, 1731 m, 1603 w, 1505 m, 1359 s, 1113 s, 1028 m, cm^{-1}.

^{1}H NMR (400 MHz) δ 7.30 (1H, d, *J* = 8.3 Hz, PhH), 7.27 (1H, d, *J* = 8.3 Hz, PhH), 6.97 (1H, d, *J* = 2.0 Hz, PhH), 6.96 (1H, d, *J* = 2.0 Hz, PhH), 6.89 (1H, d, *J* = 1.8 Hz, PhH), 6.87 (1H, d, *J* = 1.8 Hz, PhH), 5.18 (1H, d, *J* = 4.8 Hz, -CHAr), 4.58 (2H, s, $-OCH_2Ar$), 3.88 (3H, s, $-OCH_3$), 3.87 (3H, s, $-OCH_3$), 3.85-3.71 (3H, m, $-CHCH_2-$ and $-CHCH_2-$), 3.19 (3H, s, $-SO_2CH_3$), 3.19 (3H, s, $-SO_2CH_3$).

^{13}C NMR (100 MHz) δ 169.2 (CO), 152.5 (C_{ar}), 152.2 (C_{ar}), 139.7 (C_{ar}), 138.9 (C_{ar}), 138.4 (C_{ar}), 138.1 (C_{ar}), 125.5 (CH_{ar}), 125.0 (CH_{ar}), 120.4 (CH_{ar}), 118.2 (CH_{ar}), 112.3 (CH_{ar}), 110.2 (CH_{ar}), 80.1 (-CHAr), 73.5 ($-CH_2Ar$), 71.3 ($-CHCH_2O-$), 56.7 ($-OCH_3$), 56.5 ($-OCH_3$), 53.0 (CN_2), 45.7 ($-CHCH_2-$), 39.0 ($-SO_2CH_3$), 38.9 ($-SO_2CH_3$).

(1S, 2R, 5R, 6S)-2-(3,4-Methylenedioxy)phenyl-6-(4-methanesulfonyloxy-3-methoxy) phenyl-3,7-dioxabicyclo[3.3.0]octan-8-one (8.27)



8.27

$C_{21}H_{20}SO_9$

m.w. = 448.45 g/mol

White powdery solid

The title compound was prepared according to the method outlined for **5.19**, whereby reaction of diazo lactone **8.25** (800 mg, 1.62 mmol) with dirhodium (II) tetraacetate (14 mg, 0.03 mmol) and workup under the conditions described gave crude furofuranone as a white foam (740 mg). Purification was accomplished by flash chromatography on silica gel (4 x 8) eluting with EtOAc/hexane (1:1 then 2:1) to give the title compound **8.27** (601 mg, 1.34 mmol, 83 %) as a white powdery solid:

MP 124-126 °C (EtOAc/hexane).

$[\alpha]_D$ + 89.0 (c. 0.46, $CHCl_3$).

FT-IR (neat) ν_{max} 1771 s, 1605 w, 1504 m, 1363 s, 1252 m, 1170 s, 1035 s cm^{-1}.

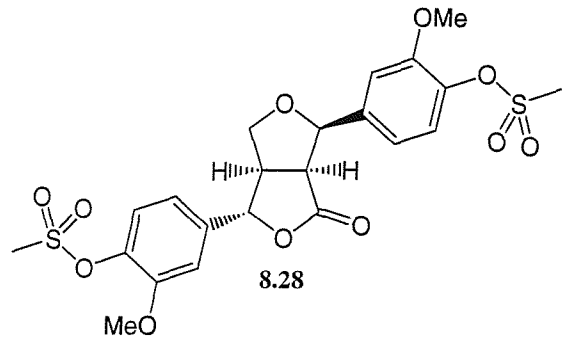
^{1}H NMR (400 MHz) δ 7.31 (1H, d, *J* = 8.3 Hz, PhH), 6.98 (1H, d, *J* = 1.8 Hz, PhH), 6.91 (1H, dd, *J* = 8.3, 1.8 Hz, PhH), 6.88-6.78 (3H, m, PhH), 5.95 (2H, s, -OC**H**$_2$O-), 5.26 (1H, d, *J* = 6.8 Hz, -CO$_2$C**H**Ar), 5.02 (1H, d, *J* = 8.5 Hz, -OC**H**Ar), 4.31 (1H, d, *J* = 9.8 Hz, -OC**H**H-), 3.91 (1H, obsc dd, *J* = 10.0, 4.8 Hz, -OCH**H**-), 3.89 (3H, s, -OC**H**$_3$), 3.53 (1H, t, *J* = 8.8 Hz, -COC**H**-), 3.22 (1H, obsc ddd, *J* = 8.8, 6.5, 4.8 Hz, -OCH$_2$C**H**-), 3.19 (3H, s, -SO$_2$C**H**$_3$).

^{13}C NMR (100 MHz) δ 174.6 (**C**O), 152.4 (**C**$_{ar}$), 148.4 (**C**$_{ar}$), 148.2 (**C**$_{ar}$), 140.4 (**C**$_{ar}$), 138.8 (**C**$_{ar}$), 130.2 (**C**$_{ar}$), 125.4 (**C**H$_{ar}$), 120.4 (**C**H$_{ar}$), 118.2 (**C**H$_{ar}$), 110.3 (**C**H$_{ar}$), 108.8 (**C**H$_{ar}$), 107.1 (**C**H$_{ar}$), 101.6 (-O**C**H$_2$O-), 85.0 (-CO$_2$**C**HAr), 84.2 (-O**C**HAr), 72.1 (-**C**H$_2$-), 56.7 (-O**C**H$_3$), 51.9 (-COCH-), 51.6 (-CH$_2$**C**H-), 38.9 (-SO$_2$**C**H$_3$).

LRMS (ES +ve) *m/z* (relative intensity) 919 (100) $[2M+Na]^+$.

CHN Anal. Calcd for $C_{21}H_{20}SO_9$: C, 56.25; H, 4.50. Found: C, 55.98; H, 4.50.

(1S, 2R, 5R, 6S)-2-(4-Methanesulfonyloxy-3-methoxy)phenyl-6-(4-methanesulfonyl oxy-3-methoxy)phenyl-3,7-dioxabicyclo[3.3.0]octan-8-one (8.28)



8.28

$C_{22}H_{24}S_2O_{11}$

m.w. = 528.56 g/mol

White powdery solid

The title compound was prepared according to the method outlined for **5.19**, whereby reaction of diazo lactone **8.26** (128 mg, 0.23 mmol) with dirhodium (II) tetraacetate (2 mg, cat.) and workup under the conditions described gave crude furofuranone as a white foam (118 mg). Purification was accomplished by flash chromatography on silica gel (2.2 x 7) eluting with EtOAc/hexane (4:1) then EtOAc to give the title compound **8.28** (97 mg, 0.18 mmol, 80 %) as a white powdery solid.

MP 135-137 °C (EtOAc/hexane).

$[\alpha]_D$ + 81.8 (c. 0.38, $CHCl_3$).

FT-IR (neat) ν_{max} 1779 m, 1602 w, 1502 m, 1360 s, 1283 m, 1156 s, 1116 s cm^{-1}.

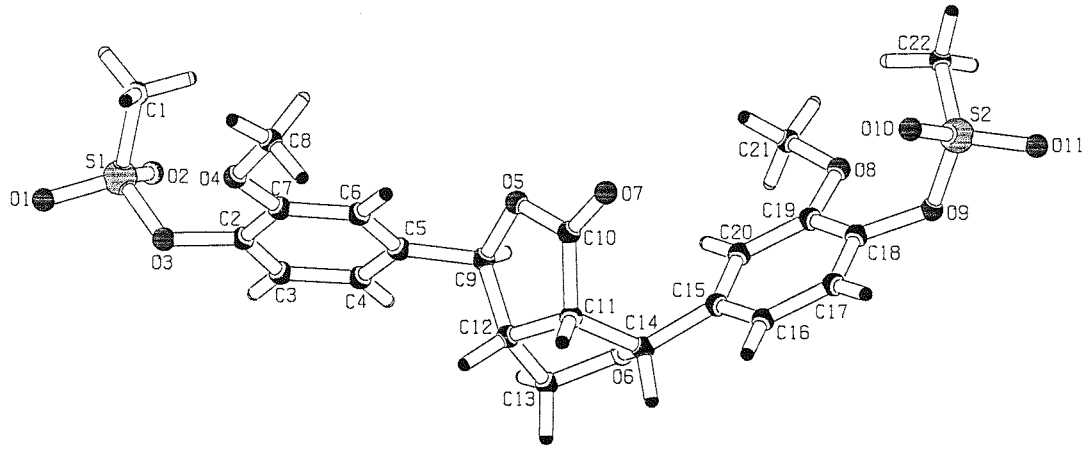
^{1}H NMR (400 MHz) δ 7.32 (2H, d, *J* = 8.3 Hz, Ph**H**), 7.04 (1H, d, *J* = 1.2 Hz, Ph**H**), 7.01 (1H, dd, *J* = 8.3, 1.5 Hz, Ph**H**), 6.97 (1H, d, *J* = 1.2 Hz, Ph**H**), 6.91 (1H, dd, *J* = 8.3, 1.5 Hz, Ph**H**), 5.27 (1H, d, *J* = 6.3 Hz, -CO_2**C**H**H**Ar), 5.08 (1H, d, *J* = 8.3 Hz, -OC**H**HAr), 4.37 (1H, d, *J* = 9.8 Hz, -OC**H**H-), 3.98 (1H, dd, *J* = 9.8, 4.8 Hz, -OCH**H**-), 3.90 (3H, s, -OC**H**$_3$), 3.90 (3H, s, -OC**H**$_3$), 3.60 (1H, t, *J* = 8.8 Hz, -COC**H**-), 3.26 (1H, ddd, *J* = 8.8, 6.3, 4.8 Hz, -OCH_2C**H**-), 3.20 (3H, s, -SO_2C**H**$_3$), 3.14 (3H, s, -SO_2C**H**$_3$).

^{13}C NMR (100 MHz) δ 174.2 (**C**O), 152.5 (**C**$_{ar}$), 152.0 (**C**$_{ar}$), 140.4 (**C**$_{ar}$), 138.8 (**C**$_{ar}$), 138.7 (**C**$_{ar}$), 136.8 (**C**$_{ar}$), 125.5 (**CH**$_{ar}$), 124.9 (**CH**$_{ar}$), 119.5 (**CH**$_{ar}$), 118.1 (**CH**$_{ar}$), 111.4 (**CH**$_{ar}$), 110.2 (**CH**$_{ar}$), 85.0 (-CO_2**C**HAr), 83.6 (-O**C**HAr), 72.7 (-**C**H_2-), 56.7 (-O**C**H_3), 56.6 (-O**C**H_3), 51.6 (-COCH-), 51.3 (-CH_2**C**H-), 39.0 (-SO_2**C**H_3), 38.5 (-SO_2**C**H_3).

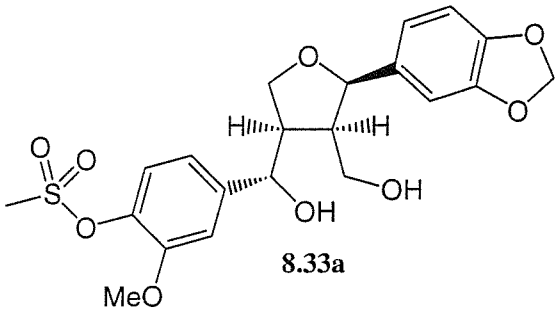
LRMS (ES +ve) *m/z* (relative intensity) 1079 (100) $[2M+Na]^+$.

CHN Anal. Calcd for $C_{22}H_{24}S_2O_{11}$: C, 49.99; H, 4.58. Found:C, 49.81; H, 4.59.

X-Ray Structure



(2R, 3R, 4S)-2[(3,4-Methylenedioxy)phenyl]-3-hydroxymethyl-4-{[(4-methane-sulfonyloxy-3-methoxy)phenyl]hydroxy}methyltetrahydrofuran (8.33a)



8.33a

$C_{21}H_{24}SO_9$

m.w. = 452.48 g/mol

White powdery solid

To a suspension of $LiAlH_4$ (122 mg, 3.21 mmol) in THF (17 mL) at 0 °C (ice bath) was added a solution of furofuranone **8.27** (480 mg, 1.07 mmol) in THF (35 mL) dropwise over 10 min and the grey suspension stirred for a further 10 min. Water (0.12 mL), 15 % NaOH (aq) (0.12 mL) and water (0.36 mL) were sequentially added dropwise to the reaction mixture at 0 °C, producing a pale grey/white granular precipitate that was filtered through Celite and washed with THF (20 mL) and EtOAc (30 mL). The filtrate was poured onto brine (60 mL), the organic phase separated and the aqueous extracted with EtOAc (2 x 60 mL). The combined organic layers were washed with brine (60 mL), dried with Na_2SO_4 and concentrated *in vacuo* to yield a crude colourless oil (506 mg). Purification was accomplished by flash chromatography on silica gel (3 x 9) eluting with EtOAc/hexane (1:1 then 2:1) to give the title compound **8.33a** (359 mg, 0.79 mmol, 74 %) as a white powdery solid along with lactol **8.34a** (63 mg, 0.14 mmol, 13 %) as a white foam. Data for **8.33a**.

MP 158-160 °C.

$[\alpha]_D$ + 86.5 (c. 0.13, $CHCl_3$).

FT-IR (neat) ν_{max} 3375 br w, 1603 w, 1502 m, 1490 m, 1361 s, 1112 m, 1033 s cm^{-1}.

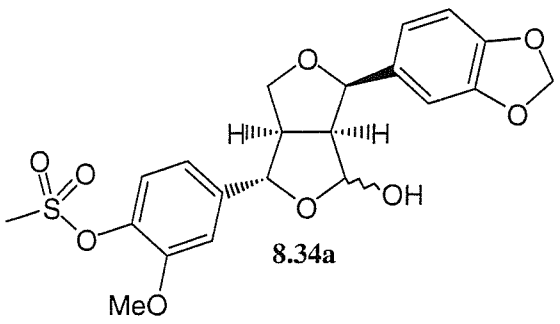
^{1}H NMR (400 MHz) δ 7.27 (1H, d, *J* = 8.3 Hz, PhH), 7.09 (1H, d, *J* = 1.8 Hz, PhH), 6.92 (1H, dd, *J* = 8.3, 1.8 Hz, PhH), 6.80-6.71 (3H, m, PhH), 5.95 (2H, s, -OC**H**$_2$O-), 5.04 (1H, d, *J* = 5.3 Hz, -OC**H**Ar), 4.80 (1H, d, *J* = 10.3 Hz, ArC**H**OH), 3.92 (3H, s, -OC**H**$_3$), 3.74-3.58 (3H, m, -OC**H**$_2$- and -C**H**HOH), 3.39 (1H, dd, *J* = 10.8, 1.8 Hz, -CH**H**OH), 3.18 (3H, s, -SO_2C**H**$_3$), 3.04 (1H, dq, *J* = 6.0, 9.8 Hz, -OCH_2C**H**-), 2.74-2.68 (1H, m, -C**H**CH_2OH), 2.50 (1H, br s, -O**H**).

^{13}C NMR (100 MHz) δ 152.2 (C$_{ar}$), 148.3 (C$_{ar}$), 147.3 (C$_{ar}$), 143.7 (C$_{ar}$), 138.3 (C$_{ar}$), 133.1 (C$_{ar}$), 125.0 (CH$_{ar}$), 119.3 (CH$_{ar}$), 119.2 (CH$_{ar}$), 111.1 (CH$_{ar}$), 108.7 (CH$_{ar}$), 106.7 (CH$_{ar}$), 101.5 (-O**C**H$_2$O-), 83.7 (-O**C**HAr), 73.6 (-**C**HOH), 69.0 (-O**C**H$_2$-), 60.2 (-**C**H$_2$OH), 56.6 (-O**C**H$_3$), 52.2 (-**C**HCH$_2$OH), 47.8 (-**C**HCHOH), 38.8 (-SO_2**C**H$_3$).

LRMS (ES +ve) *m/z* (relative intensity) 927 (100) $[2M+Na]^+$.

CHN Anal. Calcd for $C_{21}H_{24}SO_9$: C, 55.74; H, 5.35. Found: C, 55.77; H, 5.38.

(1S, 2R, 5R, 6S)-2-(3,4-Methylenedioxy)phenyl-6-(4-methanesulfonyloxy-3-methoxy) phenyl-3,7-dioxabicyclo[3.3.0]octan-8-ol (8.34a)



8.34a

$C_{21}H_{22}SO_9$

m.w. = 450.46 g/mol

White foam

$[\alpha]_D$ + 84.2 (c. 0.38, $CHCl_3$).

FT-IR (neat) ν_{max} 3448 br w, 1502 m, 1362 s, 1114 m cm^{-1}.

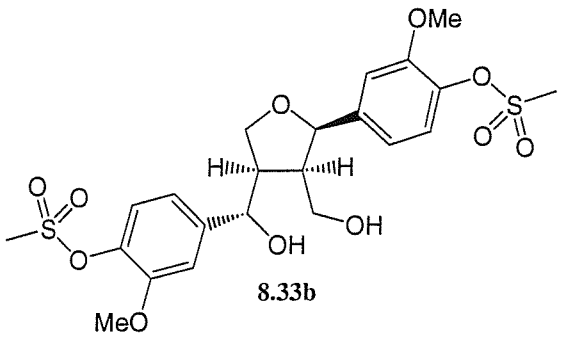
^{1}H NMR (400 MHz) δ 7.27 (1H, d, *J* = 8.3 Hz, PhH), 7.19 (1H, d, *J* = 1.8 Hz, PhH), 7.00 (1H, dd, *J* = 8.3, 1.8 Hz, PhH), 6.94-6.79 (3H, m, PhH), 5.97 (2H, s, -OC**H**$_2$O-), 4.96 (1H, br s, -OC**H**OH), 4.91 (1H, d, *J* = 6.8 Hz, -C**H**Ar), 4.83 (1H, d, *J* = 4.8 Hz, ArC**H**-), 4.14 (1H, d, *J* = 9.5 Hz, -OC**H**H-), 3.90 (3H, s, -OC**H**$_3$), 3.85 (1H, dd, *J* = 9.3, 4.5 Hz, -OCH**H**-), 3.18 (3H, s, -SO_2C**H**$_3$), 3.15-3.08 (2H, m, -C**H**CHOH and -OCH_2C**H**-), 2.74 (1H, br s, -O**H**).

^{13}C NMR (100 MHz) δ 152.0 (C_{ar}), 148.3 (C_{ar}), 147.5 (C_{ar}), 143.4 (C_{ar}), 138.2 (C_{ar}), 132.2 (C_{ar}), 124.9 (CH_{ar}), 120.0 (CH_{ar}), 119.2 (CH_{ar}), 111.4 (CH_{ar}), 108.7 (CH_{ar}), 107.4 (CH_{ar}), 101.6 (-CHOH), 101.6 (-OCH_2O-), 87.7 (-CHAr), 82.5 (-CHAr), 72.1 (-OCH_2-), 57.6 (-CHCHOH), 56.6 (-OCH_3), 53.5 (-$CHCH_2$-), 38.8 (-SO_2CH_3).

LRMS (ES +ve) *m/z* (relative intensity) 923 (100) $[2M+Na]^+$.

HRMS (ES +ve) Calcd for $C_{42}H_{44}S_2O_{18}Na$ (dimer) 923.1861, found 923.1862.

(2R, 3R, 4S)-2[(4-Methanesulfonyloxy-3-methoxy)phenyl]-3-hydroxymethyl-4-{[(4-methanesulfonyloxy-3-methoxy)phenyl]hydroxy}methyltetrahydrofuran (8.33b)



8.33b

$C_{22}H_{28}S_2O_{11}$

m.w. = 532.59 g/mol

White powdery solid

The title compound was prepared according to the method outlined for **8.33a**, whereby reaction of furofuranone **8.28** (390 mg, 0.74 mmol) with $LiAlH_4$ (84 mg, 2.21 mmol) and workup under the conditions described gave crude diol as an off-white foam (385 mg). Purification was accomplished by flash chromatography on silica gel (3.2 x 9) eluting with EtOAc/hexane (4:1) to give the title compound **8.33b** (295 mg, 0.55 mmol, 75 %) as a white powdery solid along with lactol **8.34b** (55 mg, 0.10 mmol, 14 %) as a white foam. Data for **8.33b**.

MP 162-164 °C.

$[\alpha]_D$ + 77.3 (c. 0.43, $CHCl_3$).

FT-IR (neat) ν_{max} 3384 br w, 1602 w, 1503 m, 1359 s, 1276 m, 1172 s, 1150 s cm^{-1}.

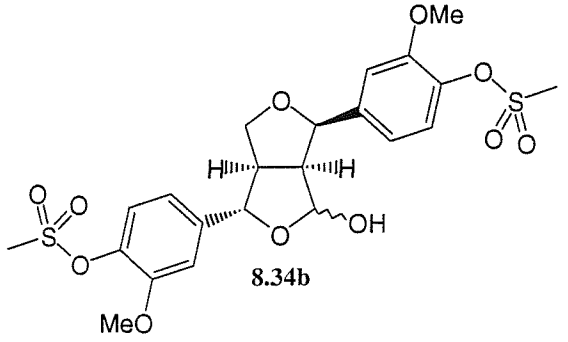
^{1}H NMR (400 MHz) δ 7.26 (1H, d, *J* = 3.5 Hz, PhH), 7.24 (1H, d, *J* = 3.5 Hz, PhH), 7.08 (1H, s, PhH), 6.95 (1H, s, PhH), 6.90 (1H, d, *J* = 8.3 Hz, PhH), 6.83 (1H, d, *J* = 8.3 Hz, PhH), 5.07 (1H, d, *J* = 4.8 Hz, -OCHAr), 4.77 (1H, d, *J* = 10.0 Hz, ArCHOH), 3.90 (3H, s, -OCH_3), 3.87 (3H, s, -OCH_3), 3.74 (1H, t, *J* = 9.3 Hz, -OCHH-), 3.65-3.56 (2H, m, -OCHH- and -CHHOH), 3.27 (1H, d, *J* = 9.5 Hz, -CHHOH), 3.18 (3H, s, -SO_2CH_3), 3.17 (3H, s, -SO_2CH_3), 3.06-2.96 (1H, m, -OCH_2CH-), 2.80-2.71 (1H, m, -$CHCH_2OH$).

^{13}C NMR (100 MHz) δ 152.2 (C_{ar}), 151.9 (C_{ar}), 143.5 (C_{ar}), 139.9 (C_{ar}), 138.3 (C_{ar}), 137.6 (C_{ar}), 124.9 (CH_{ar}), 124.8 (CH_{ar}), 119.2 (CH_{ar}), 118.6 (CH_{ar}), 111.1 (CH_{ar}), 110.6 (CH_{ar}), 83.2 (-OCHAr), 73.5 (CHOH), 69.0 ($-OCH_2-$), 59.7 ($-CH_2OH$), 56.5 (2 x $-OCH_3$), 52.3 ($CHCH_2OH$), 47.5 (-CHCHOH), 38.8 ($-SO_2CH_3$), 38.8 ($-SO_2CH_3$).

LRMS (ES +ve) *m/z* (relative intensity) 555 (100) $[M+Na]^+$, 1065 (30) $[2M+H]^+$, 1087 (35) $[2M+Na]^+$.

CHN Anal. Calcd for $C_{22}H_{28}S_2O_{11}$: C, 49.62; H, 5.30. Found: C, 49.90; H, 5.40.

(1S, 2R, 5R, 6S)-2-(4-Methanesulfonyloxy-3-methoxy)phenyl-6-(4-methanesulfonyl-oxy-3-methoxy)phenyl-3,7-dioxabicyclo[3.3.0]octan-8-ol (8.34b)



8.34b

$C_{22}H_{26}S_2O_{11}$

m.w. = 530.57 g/mol

White foam

$[\alpha]_D$ + 74.3 (c. 0.38, $CHCl_3$).

FT-IR (neat) ν_{max} 3488 br w, 1737 w, 1504 m, 1360 s, 1173 m, 1150 m, 1114 m cm^{-1}.

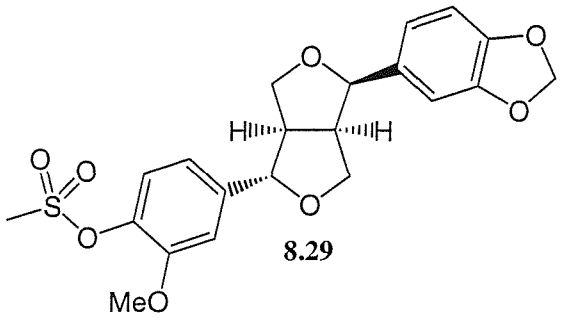
^{1}H NMR (400 MHz) δ 7.26 (2H, t, *J* = 8.5 Hz, PhH), 7.19 (1H, s, PhH), 7.09 (1H, s, PhH), 6.97 (2 x 1H, t, *J* = 8.3 Hz, PhH), 4.95 (1H, d, *J* = 7.0 Hz, -CHAr), 4.87 (1H, br s, -OCHOH), 4.79 (1H, d, *J* = 5.8 Hz, ArCH-), 4.15 (1H, d, *J* = 9.3 Hz, -OCHH-), 3.90 (3H, s, $-OCH_3$), 3.88 (3H, s, $-OCH_3$), 3.90-3.85 (1H, obsc m, -OCHH-), 3.18 (3H, s, $-SO_2CH_3$), 3.17 (3H, s, $-SO_2CH_3$), 3.17-3.08 (2H, m, -CHCHOH and $-OCH_2CH-$).

^{13}C NMR (100 MHz) δ 152.0 (C_{ar}), 151.8 (C_{ar}), 143.2 (C_{ar}), 138.9 (C_{ar}), 138.1 (C_{ar}), 137.8 (C_{ar}), 124.8 (CH_{ar}), 124.7 (CH_{ar}), 119.2 (CH_{ar}), 119.0 (CH_{ar}), 111.3 (CH_{ar}), 111.3 (CH_{ar}), 101.3 (-CHOH), 87.2 (-CHAr), 81.9 (-CHAr), 72.2 ($-OCH_2-$), 57.2 (-CHCHOH), 56.5 ($-OCH_3$), 56.5 ($-OCH_3$), 53.5 ($-CHCH_2-$), 38.8 ($-SO_2CH_3$), 38.7 ($-SO_2CH_3$).

LRMS (ES +ve) *m/z* (relative intensity) 553 (50) $[M+Na]^+$, 594 (95) $[M+Na+MeCN]^+$, 1083 (100) $[2M+Na]^+$.

HRMS (ES +ve) Calcd for $C_{44}H_{52}S_4O_{22}Na$ (dimer) 1083.1725, found 1083.1756.

(1R, 2R, 5R, 6S)-2-(3,4-Methylenedioxy)phenyl-6-(4-methanesulfonyloxy-3-methoxy) phenyl-3,7-dioxabicyclo[3.3.0]octane (8.29)



8.29

$C_{21}H_{22}SO_8$
m.w. = 434.47 g/mol
White powdery solid

To a solution of diol **8.33a** (320 mg, 0.71 mmol) in CH_2Cl_2 (25 mL) at 0 °C (ice/salt bath) was added NEt_3 (0.12 mL, 0.85 mmol) followed by DMAP (2 mg, cat.) and the reaction stirred for 5 min. A solution of Ms_2O (185 mg, 1.06 mmol) in CH_2Cl_2 (5 mL) was added dropwise and the reaction allowed to warm to room temperature and stirred for 8 h before additional NEt_3 (0.08 mL, 0.56 mmol) and Ms_2O (123 mg, 0.71 mmol) was added and stirred for a further 12 h. TLC analysis still showed starting diol **8.33a** so DMAP (7 mg, cat.) and Ms_2O (123 mg, 0.71 mmol) were again added and the mixture stirred for 20 h. The reaction was then cooled to 0°C (ice bath), diluted with CH_2Cl_2 (10 mL) and treated with 1N HCl (aq) (40 mL). The mixture was allowed to warm to room temperature, the organic phase separated and the aqueous extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were washed with brine (40 mL), dried with Na_2SO_4 and concentrated *in vacuo* to yield a pale orange oil (475 mg). Purification was accomplished by flash chromatography on silica gel (3.2 x 6) eluting with EtOAc/hexane (1:3 then 1:2) to give the title compound **8.29** (233 mg, 0.54 mmol, 76 %) as a white powdery solid.

MP 130-131 °C (EtOAc/hexane).

$[\alpha]_D$ + 125.2 (c. 0.38, $CHCl_3$).

FT-IR (neat) ν_{max} 2870 w, 1599 m, 1501 m, 1369 s, 1238 s, 1111 s, 1026 s cm^{-1}.

^{1}H NMR (400 MHz) δ 7.27 (1H, d, *J* = 8.3 Hz, PhH), 7.04 (1H, d, *J* = 1.5 Hz, PhH), 6.92 (1H, dd, *J* = 8.3, 1.8 Hz, PhH), 6.87 (1H, s, PhH), 6.84-6.77 (2H, m, PhH), 5.96 (2H, s, -OCH$_2$O-), 4.84 (1H, d, *J* = 5.3 Hz, -CHAr^1), 4.48 (1H, d, *J* = 7.0 Hz, -CHAr^2), 4.14 (1H, d, *J* = 9.5 Hz, Ar^{1}CHOCHH-), 3.90 (3H, s, -OCH$_3$), 3.90-3.82 (2H, m, Ar^{1}CHOCHH- and Ar^{2}CHOCHH-), 3.37-3.26 (2H, m,

$Ar^2CHOCHH$- and Ar^1CHCH-), 3.17 (3H, s, $-SO_2CH_3$), 2.91-2.85 (1H, m, Ar^2CHCH-).

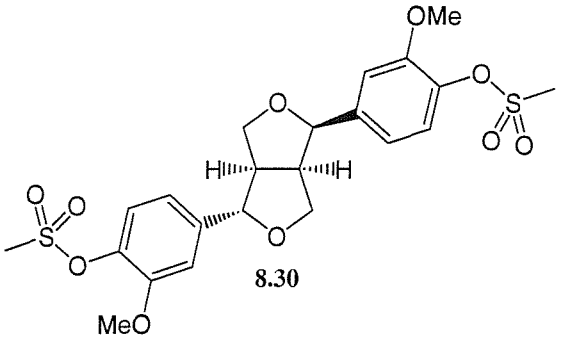
^{13}C NMR (100 MHz) δ 152.1 (C_{ar}), 148.2 (C_{ar}), 147.1 (C_{ar}), 142.4 (C_{ar}), 138.2 (C_{ar}), 132.6 (C_{ar}), 125.0 (CH_{ar}), 119.2 (CH_{ar}), 118.9 (CH_{ar}), 110.8 (CH_{ar}), 108.7 (CH_{ar}), 106.9 (CH_{ar}), 101.4 ($-OCH_2O-$), 87.5 (Ar^2CH-), 82.5 (Ar^1CH-), 71.4 (Ar^1CHOCH_2-), 70.3 (Ar^2CHOCH_2-), 56.6 ($-OCH_3$), 55.2 (Ar^2CHCH-), 50.6 (Ar^1CHCH-), 38.7 ($-SO_2CH_3$).

Where Ar^1 = 3,4-methylenedioxy-, Ar^2 = 4-methanesulfonyloxy-3-methoxy-

LRMS (ES +ve) *m/z* (relative intensity) 891 (100) $[2M+Na]^+$.

CHN Anal. Calcd for $C_{21}H_{22}SO_8$: C, 58.06; H, 5.10. Found: C, 58.17; H, 5.14.

(1R, 2R, 5R, 6S)-2-(4-Methanesulfonyloxy-3-methoxy)phenyl-6-(4-methanesulfonyl-oxy-3-methoxy)phenyl-3,7-dioxabicyclo[3.3.0]octane (8.30)



8.30

$C_{22}H_{26}S_2O_{10}$

m.w. = 514.57 g/mol

White powdery solid

The title compound was prepared according to the method outlined for **8.29**, whereby reaction of diol **8.33b** (122 mg, 0.23 mmol) with Ms_2O (60 mg + 40 mg + 40 mg, 0.35 mmol + 0.23 mmol + 0.23 mmol) addition over 48 h and workup under the conditions described gave crude furofuran as a pale orange oil (204 mg). Purification was accomplished by flash chromatography on silica gel (2.2 x 8) eluting with EtOAc/hexane (2:1) to give the title compound **8.30** (93 mg, 0.18 mmol, 78 %) as a white powdery solid.

MP 137-139 °C (EtOAc/hexane).

$[\alpha]_D$ + 114.0 (c. 0.40, $CHCl_3$).

FT-IR (neat) ν_{max} 1602 w, 1504 m, 1362 s, 1174 m, 1151 m, 1114 m cm^{-1}.

^{1}H NMR (400 MHz) δ 7.29 (1H, d, *J* = 8.3 Hz, Ph**H**), 7.28 (1H, d, *J* = 8.3 Hz, Ph**H**), 7.12 (1H, d, *J* = 1.8 Hz, Ph**H**), 7.05 (1H, d, *J* = 1.8 Hz, Ph**H**), 6.92 (1H, dd, *J* = 8.3, 2.0 Hz, Ph**H**), 6.88 (1H, dd, *J* = 8.3, 1.8 Hz, Ph**H**), 4.90 (1H, d, *J* = 5.8 Hz, -C**H**Ar^1), 4.51 (1H, d, *J* = 6.9 Hz, -C**H**Ar^2), 4.18 (1H, d, *J* = 9.5 Hz, $Ar^1CHOCHH$-), 3.93 (3H, s,

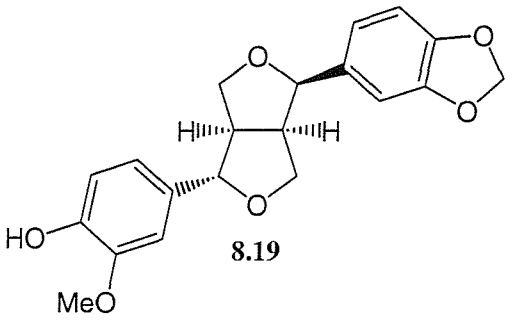
-OCH_3), 3.91 (3H, s, -OCH_3), 3.93-3.85 (2H, obsc m, $Ar^1CHOCHH$- and $Ar^2CHOCHH$-), 3.43-3.34 (1H, m, Ar^1CHCH-), 3.28 (1H, t, J = 8.3 Hz, $Ar^2CHOCHH$-), 3.19 (3H, s, -SO_2CH_3), 3.18 (3H, s, -SO_2CH_3), 2.96-2.89 (1H, m, Ar^2CHCH-).

^{13}C NMR (100 MHz) δ 152.1 (C_{ar}), 151.9 (C_{ar}), 142.2 (C_{ar}), 139.4 (C_{ar}), 138.2 (C_{ar}), 137.7 (C_{ar}), 125.0 (CH_{ar}), 124.9 (CH_{ar}), 118.9 (CH_{ar}), 118.6 (CH_{ar}), 110.9 (CH_{ar}), 110.8 (CH_{ar}), 87.5 (Ar^2CH-), 82.1 (Ar^1CH-), 71.6 (Ar^1CHOCH_2-), 70.3 (Ar^2CHOCH_2-), 56.6 (-OCH_3), 56.6 (-OCH_3), 55.1 (Ar^2CHCH-), 50.4 (Ar^1CHCH-), 38.8 (2x-SO_2CH_3).

Where Ar^1 = *endo*-4-methanesulfonyloxy-3-methoxy-, Ar^2 = *exo*-4-methanesulfonyloxy-3-methoxy-

CHN Anal. Calcd for $C_{22}H_{26}S_2O_{10}$: C, 51.35; H, 5.09. Found: C, 51.50; H, 5.16.

(1R, 2R, 5R, 6S)-2-(3,4-Methylenedioxy)phenyl-6-(4-hydroxy-3-methoxy)phenyl-3,7-dioxabicyclo[3.3.0]octane (+)-Xanthoxylol (8.19)



8.19

$C_{20}H_{20}O_6$

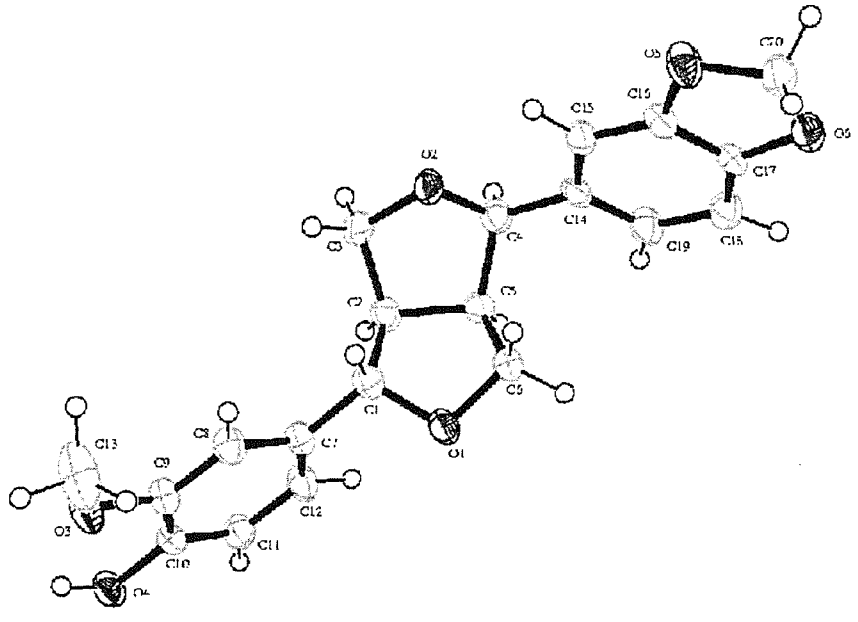
m.w. = 356.37 g/mol

White powdery solid

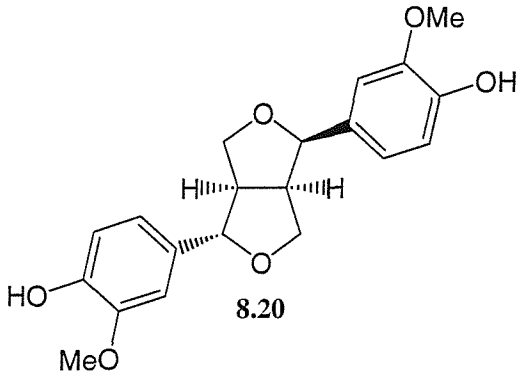
The title compound was prepared according to a modified procedure described by Kawada *et al.*[234] Thus, to a solution of furofuran **8.29** (130 mg, 0.30 mmol) in dioxane/methanol (8 mL, 1:1) was added 3N KOH (aq) (8 mL). The cloudy mixture was stirred at 50 °C for 40 h and the resulting clear yellow solution diluted with EtOAc (30 mL) and acidified with 2N HCl (aq) (30 mL). The organic layer was separated, the aqueous extracted with EtOAc (3 x 30 mL) and the combined extracts were washed with brine (30 mL), dried with Na_2SO_4 and concentrated *in vacuo* to yield an off-white solid (113 mg). Purification was accomplished by flash chromatography on silica gel (2.2 x 8) eluting with EtOAc/hexane (1:1) to give the title compound **8.19** (96 mg, 0.27 mmol, 90 %) as a white powdery solid. Spectroscopic details were consistent with those previously reported.[269-272]

MP 136-138 °C (lit.[270] 138-140 °C, lit.[269,271] 140-142 °C).

$[\alpha]_D$	+ 126.1 (c. 0.38, $CHCl_3$) (lit.[270] + 126 - $CHCl_3$, lit.[271] + 122 - $CHCl_3$).
FT-IR (neat) ν_{max}	3433 br w, 1603 w, 1492 m, 1438 m, 1226 m, 1073 m, 1029 s cm^{-1}.
^{1}H NMR (400 MHz)	δ 6.91-6.78 (6H, m, Ph**H**), 5.96 (2H, s, -OC**H**$_2$O-), 5.62 (1H, s, -O**H**), 4.83 (1H, d, *J* = 5.5 Hz, -C**H**Ar^1), 4.41 (1H, d, *J* = 7.0 Hz, -C**H**Ar^2), 4.11 (1H, d, *J* = 9.5 Hz, Ar^{1}CHOC**H**H-), 3.90 (3H, s, -OC**H**$_3$), 3.89-3.80 (2H, m, Ar^{1}CHOCH**H**- and Ar^{2}CHOC**H**H-), 3.36-3.26 (2H, m, Ar^{2}CHOCH**H**- and Ar^{1}CHC**H**-), 2.93-2.85 (1H, m, Ar^{2}CHC**H**-).
^{13}C NMR (100 MHz)	δ 148.1 (**C**$_{ar}$), 147.2 (**C**$_{ar}$), 147.0 (**C**$_{ar}$), 145.8 (**C**$_{ar}$), 133.5 (**C**$_{ar}$), 132.8 (**C**$_{ar}$), 119.7 (**C**H$_{ar}$), 119.2 (**C**H$_{ar}$), 114.7 (**C**H$_{ar}$), 109.1 (**C**H$_{ar}$), 108.6 (**C**H$_{ar}$), 106.9 (**C**H$_{ar}$), 101.4 (-O**C**H$_2$O-), 88.2 (Ar^2**C**H-), 82.5 (Ar^1**C**H-), 71.4 (Ar^{1}CHO**C**H$_2$-), 70.1 (Ar^{2}CHO**C**H$_2$-), 56.4 (-O**C**H$_3$), 55.0 (Ar^{2}CH**C**H-), 50.6 (Ar^{1}CH**C**H-). Where Ar^1 = 3,4-methylenedioxy-, Ar^2 = 4-hydroxy-3-methoxy-.
LRMS (ES +ve)	*m/z* (relative intensity) 713 (100) $[2M+H]^+$, 735 (60) $[2M+Na]^+$.
CHN Anal.	Calcd for $C_{20}H_{20}O_6$: C, 67.41; H, 5.66. Found: C, 67.47; H, 5.65.
X-ray structure	



(1R, 2R, 5R, 6S)-2-(4-Hydroxy-3-methoxy)phenyl-6-(4-hydroxy-3-methoxy)phenyl-3,7-dioxabicyclo[3.3.0]octane (+)-Epipinoresinol (8.20)



8.20

$C_{20}H_{22}O_6$

m.w. = 358.39 g/mol

White powdery solid

The title compound was prepared according to the method outlined for **8.19**, whereby hydrolysis of furofuran **8.30** (80 mg, 0.16 mmol) in KOH and workup under the conditions described gave a yellow oil (68 mg). Purification was accomplished by flash chromatography on silica gel (3.2 x 4) eluting with EtOAc/hexane (2:3) to give the title compound **8.20** (56 mg, 0.16 mmol, 98 %) as a white powdery solid. Spectroscopic details were consistent with those previously reported.[273,274]

MP 135-137 °C (lit.[275] 137-138 °C, lit.[274] 138-139 °C).

$[\alpha]_D$ + 115.7 (c. 0.38, $CHCl_3$) (lit.[273] + 118.4 - $CHCl_3$, lit.[274] + 110 - MeOH, lit.[275] + 130.4 - Me_2CO).

FT-IR (neat) ν_{max} 3474 br w, 1628 s, 1494 m, 1452 m, 1395 m, 1130 m cm^{-1}.

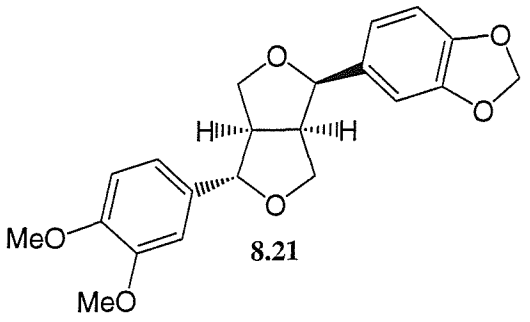
^{1}H NMR (400 MHz) δ 6.97-6.76 (6H, m, PhH), 5.65 (1H, s, -OH), 5.63 (1H, s, -OH), 4.86 (1H, d, *J* = 5.0 Hz, -CHAr^1), 4.44 (1H, d, *J* = 7.0 Hz, -CHAr^2), 4.12 (1H, d, *J* = 9.3 Hz, Ar^{1}CHOCHH-), 3.91 (3H, s, -OCH$_3$), 3.89 (3H, s, -OCH$_3$), 3.89-3.80 (2H, m, Ar^{1}CHOCHH- and Ar^{2}CHOCHH-), 3.37-3.28 (2H, m, Ar^{2}CHOCHH- and Ar^{1}CHCH-), 2.94-2.87 (1H, m, Ar^{2}CHCH-).

^{13}C NMR (100 MHz) δ 147.2 (C_{ar}), 146.9 (C_{ar}), 145.8 (C_{ar}), 145.1 (C_{ar}), 133.5 (C_{ar}), 130.8 (C_{ar}), 119.6 (CH_{ar}), 118.9 (CH_{ar}), 114.7 (CH_{ar}), 109.0 (CH_{ar}), 108.9 (CH_{ar}), 88.2 (Ar^{2}CH-), 82.6 (Ar^{1}CH-), 71.5 (Ar^{1}CHOCH$_2$-), 70.2 (Ar^{2}CHOCH$_2$-), 56.5 (-OCH$_3$), 56.4 (-OCH$_3$), 55.0 (Ar^{2}CHCH-), 50.6 (Ar^{1}CHCH-).

Where Ar^1 = *endo*-4-hydroxy-3-methoxy-, Ar^2 = *exo*-4-hydroxy-3-methoxy-.

LRMS (ES +ve) *m/z* (relative intensity) 717 (100) $[2M+H]^+$.

(1R, 2R, 5R, 6S)-2-(3,4-Methylenedioxy)phenyl-6-(3,4-dimethoxy)phenyl-3,7-dioxabicyclo[3.3.0]octane (+)-Methyl xanthoxylol (8.21)



8.21

$C_{21}H_{22}O_6$
m.w. = 370.40 g/mol
White powdery solid

To a solution of furofuran **8.19** (50 mg, 0.14 mmol) in AnalaR acetone (10 mL) was added cesium carbonate (69 mg, 2.10 mmol) followed by methyl iodide (87 μL, 1.40 mmol) in one portion. The cloudy mixture was stirred at reflux for 18 h and the resulting clear colourless solution diluted with EtOAc (20 mL) and 1N HCl (aq) (15 mL). The organic layer, separated and the aqueous extracted with EtOAc (3 x 20 mL) and the combined extracts washed with brine (20 mL), dried with Na_2SO_4 and concentrated *in vacuo* to yield an off-white solid (67 mg). Purification was accomplished by flash chromatography on silica gel (2.2 x 5) eluting with EtOAc/hexane (1:1) to give the title compound **8.21** (49 mg, 0.13 mmol, 94 %) as a white powdery solid. Spectroscopic details were consistent with those previously reported.

MP 120-121 °C (lit.[144] 115-116 °C, lit.[276] 124-125 °C).

$[\alpha]_D$ + 123.3 (c. 0.21, $CHCl_3$) (lit.[277] + 119 $CHCl_3$, lit.[276] + 112 $CHCl_3$).

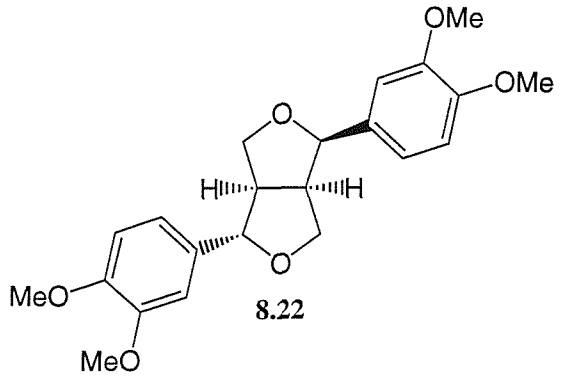
FT-IR (neat) ν_{max} 1517 m, 1441 m, 1364 m, 1233 m, 1135 m, 1076 m, 1024 s cm^{-1}.

^{1}H NMR (400 MHz) δ 6.93-6.87 (6H, m, PhH), 5.96 (2H, s, -OC**H**$_2$O-), 4.84 (1H, d, *J* = 5.0 Hz, -C**H**Ar^1), 4.42 (1H, d, *J* = 7.3 Hz, -C**H**Ar^2), 4.11 (1H, d, *J* = 9.3 Hz, Ar^{1}CHOC**H**H-), 3.90 (3H, s, -OC**H**$_3$), 3.87 (3H, s, -OC**H**$_3$), 3.89-3.80 (2H, m, Ar^{1}CHOCH**H**- and Ar^{2}CHOC**H**H-), 3.38-3.28 (2H, m, Ar^{2}CHOCH**H**- and Ar^{1}CHC**H**-), 2.94-2.86 (1H, m, Ar^{2}CHC**H**-).

^{13}C NMR (100 MHz) δ 149.7 (**C**$_{ar}$), 149.2 (**C**$_{ar}$), 148.1 (**C**$_{ar}$), 147.1 (**C**$_{ar}$), 134.1 (**C**$_{ar}$), 132.8 (**C**$_{ar}$), 119.2 (**C**H$_{ar}$), 119.0 (**C**H$_{ar}$), 111.6 (**C**H$_{ar}$), 109.7 (**C**H$_{ar}$), 108.6 (**C**H$_{ar}$), 106.9 (**C**H$_{ar}$), 101.4 (-O**C**H$_2$O-), 88.1 (Ar^2**C**H-), 82.5 (Ar^1**C**H-), 71.4 (Ar^{1}CHO**C**H$_2$-), 70.1 (Ar^{2}CHO**C**H$_2$-), 56.4 (-O**C**H$_3$), 56.4 (-O**C**H$_3$), 55.0 (Ar^2**C**HCH-), 50.6 (Ar^1**C**HCH-).

Where Ar^1 = 3,4-methylenedioxy-, Ar^2 = 3,4-dimethoxy-.

(1R, 2R, 5R, 6S)-2-(3,4-Dimethoxy)phenyl-6-(3,4-dimethoxy)phenyl-3,7-dioxabicyclo[3.3.0]octane (+)-Epieudesmin (8.22)



8.22

$C_{22}H_{26}O_6$

m.w. = 386.44 g/mol

White powdery solid

The title compound was prepared according to the method outlined for **8.21**, whereby reaction of furofuran **8.20** (26 mg, 0.073 mmol) with MeI (45 μL, 0.73 mmol) and workup under the conditions described gave a yellow oil (35 mg). Purification was accomplished by flash chromatography on silica gel (2.2 x 3) eluting with EtOAc/hexane (2:3) to give the title compound **8.22** (26 mg, 0.068 mmol, 93 %) as a white powdery solid. Spectroscopic details were consistent with those previously reported.[163,278]

MP 126-127 °C (lit.[163] 124-125 °C, lit.[278] 122-125 °C).

$[\alpha]_D$ + 118.2 (c. 0.17, $CHCl_3$) (lit.[278] + 113.3 - $CHCl_3$).

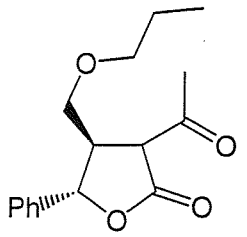
FT-IR (neat) ν_{max} 2841 w, 1513 s, 1446 m, 1265 s, 1235 s, 1141 s, 1019 s cm^{-1}.

^{1}H NMR (400 MHz) δ 6.95-6.82 (6H, m, PhH), 4.88 (1H, d, *J* = 5.3 Hz, -CHAr^1), 4.45 (1H, d, *J* = 7.0 Hz, -CHAr^2), 4.14 (1H, d, *J* = 9.5 Hz, Ar^{1}CHOCHH-), 3.91 (3H, s, -OCH$_3$), 3.90 (3H, s, -OCH$_3$), 3.89 (3H, s, -OCH$_3$), 3.88 (3H, s, -OCH$_3$), 3.90-3.83 (2H, m, Ar^{1}CHOCHH- and Ar^{2}CHOCHH-), 3.40-3.29 (2H, m, Ar^{2}CHOCHH- and Ar^{1}CHCH-), 2.95-2.89 (1H, m, Ar^{2}CHCH-).

^{13}C NMR (100 MHz) δ 149.8 (C_{ar}), 149.4 (C_{ar}), 149.2 (C_{ar}), 148.5 (C_{ar}), 134.2 (C_{ar}), 131.5 (C_{ar}), 119.0 (CH_{ar}), 118.2 (CH_{ar}), 111.6 (CH_{ar}), 111.6 (CH_{ar}), 109.7 (CH_{ar}), 109.5 (CH_{ar}), 88.1 (Ar^{2}CH-), 82.6 (Ar^{1}CH-), 71.5 (Ar^{1}CHOCH$_2$-), 70.2 (Ar^{2}CHOCH$_2$-), 56.5 (-OCH$_3$), 56.4 (-OCH$_3$), 56.4 (-OCH$_3$), 55.0 (Ar^{2}CHCH-), 50.7 (Ar^{1}CHCH-).

Where Ar^1 = *endo*-3,4-dimethoxy-, Ar^2 = *exo*-3,4-dimethoxy-.

(4R*, 5S*)-3-Acetyl-4-propoxymethyl-5-phenyl-dihydrofuran-2-one (9.1)



9.1

$C_{16}H_{20}O_4$

m.w. = 276.33 g/mol

Colourless oil

To a solution of cyclopropane **7.35** (216 mg, 1.00 mmol) in propan-1-ol (0.6 mL, 8.00 mmol) was added $Mg(ClO_4)_2$ (22 mg, 0.10 mmol) and the mixture heated to reflux for 3 h, cooled to room temperature then diluted with EtOAc (20 mL) and water (20 mL). The organic layer was separated and the aqueous extracted with EtOAc (3 x 20 mL). The combined extracts were washed with brine (20 mL), dried with $MgSO_4$ and concentrated *in vacuo* to give a crude colourless oil (279 mg). Purification was accomplished by flash chromatography on silica gel (3.4 x 9) eluting with EtOAc/hexane (1:9) to give the title compound **9.1** (155 mg, 0.56 mmol, 56 %) as a colourless oil along with propyl enol ether **9.2** (78 mg, 0.25 mmol, 25 %) as a colourless oil. Data for title compound **9.1**.

FT-IR ν_{max} (neat) 1764 s, 1716 s, 1360 m, 1154 s, 1118 s cm^{-1}.

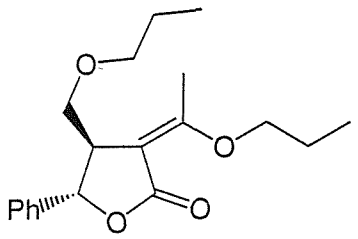
^{1}H NMR (400 MHz) δ 7.45-7.27 (5H, m, Ph**H**), 5.30 (1H, d, *J* = 9.3 Hz, -C**H**Ph), 4.00 (1H, d, *J* = 10.5 Hz, -C**H**CO-), 3.44 (2H, dd, *J* = 5.3, 3.8 Hz, -CHC**H**$_2$-), 3.38 (2H, t, *J* = 6.8 Hz, -OC**H**$_2$CH$_2$-), 3.12 (1H, ddt, *J* = 10.5, 9.5, 3.8 Hz -C**H**CH$_2$-), 2.51 (3H, s, -COC**H**$_3$), 1.67-1.53 (2H, m, -OCH$_2$C**H**$_2$-), 0.92 (3H, t, *J* = 7.3 Hz, -CH$_2$C**H**$_3$); keto/enol ratio 8:1 - enolic resonances were observed at δ 11.28 (1H, s), 5.48 (1H, d, *J* = 2.3 Hz), 1.99 (3H, s).

^{13}C NMR (100 MHz) δ 201.0 (**C**O$_{ket}$), 171.9 (**C**O$_{est}$), 138.0 (**C**$_{ar}$), 129.5 (**C**H$_{ar}$), 129.3 (**C**H$_{ar}$), 126.8 (**C**H$_{ar}$), 81.6 (-**C**HPh), 73.5 (-O**C**H$_2$-), 66.8 (-O**C**H$_2$-), 56.2 (-**C**HCO-), 46.8 (-**C**HCH$_2$-), 30.6 (-CO**C**H$_3$), 23.2 (-OCH$_2$**C**H$_2$), 11.1 (-CH$_2$**C**H$_3$); enolic resonances were observed at δ 170.8, 141.1, 125.4, 82.9, 19.6.

LRMS (CI, NH_3) *m/z* (relative intensity) 277 (37) $[M+H]^+$, 294 (30) $[M+NH_4]^+$, 43 (100) $[CH_3CH_2CH_2]^+$.

HRMS (ES +ve) Calcd for $C_{32}H_{40}O_8Na$ (dimer) 575.2615, found 575.2628.

(4R*, 5S*)-3-(1-propoxyethylidene)-4-propoxymethyl-5-phenyl-dihydrofuran-2-one (9.2)



9.2

$C_{19}H_{26}O_4$

m.w. = 318.41 g/mol

Colourless oil

FT-IR ν_{max} (neat) 1691 s, 1640 s, 1379 m, 1330 m, 1213 s, 1195 s, 1081 s cm^{-1}.

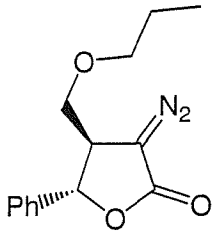
^{1}H NMR (400 MHz) δ 7.39-7.26 (5H, m, Ph**H**), 5.56 (1H, d, *J* = 4.8 Hz, -C**H**Ph), 4.10 (1H, dt, *J* = 10.5, 6.5 Hz, -C=COC**H**H), 4.03 (1H, dt, *J* = 10.5, 6.5 Hz, -C=COCH**H**), 3.80 (1H, dd, *J* = 9.3, 3.5 Hz, -CHC**H**HO-), 3.51-3.45 (2H, m, -CHCH**H**O- and -OC**H**HCH$_2$-), 3.42-3.35 (2H, m, -OCH**H**CH$_2$- and -C**H**CH$_2$-), 2.34 (3H, d, *J* = 1.3 Hz, -CC**H**$_3$), 1.71-1.57 (4H, m, 2 x -OCH$_2$C**H**$_2$-), 0.96 (3H, t, *J* = 7.3 Hz, -CH$_2$C**H**$_3$), 0.94 (3H, t, *J* = 7.5 Hz, -CH$_2$C**H**$_3$).

^{13}C NMR (100 MHz) δ 169.8 (**C**O), 166.3 (-C=**C**O-), 142.3 (**C**$_{ar}$), 129.0 (**C**H$_{ar}$), 128.2 (**C**H$_{ar}$), 125.6 (**C**H$_{ar}$), 102.3 (-**C**=CO-), 87.1 (-**C**HPh), 73.2 (-O**C**H$_2$-), 72.5 (-O**C**H$_2$-), 65.7 (-O**C**H$_2$-), 52.2 (-**C**HCH$_2$-), 23.4 (-OCH$_2$**C**H$_2$), 22.6 (-OCH$_2$**C**H$_2$), 14.9 (-C**C**H$_3$), 11.1 (2x-CH$_2$**C**H$_3$).

LRMS (CI, NH_3) *m/z* (relative intensity) 319 (100) $[M+H]^+$, 259 (60) [M+H (-PrOH)]$^+$.

HRMS (ES +ve) Calcd for $C_{19}H_{26}O_4Na$ 341.1723, found 341.1727.

(4R*, 5S*)-4-Propoxymethyl-3-diazo-5-phenyl-dihydrofuran-2-one (9.3)



9.3

$C_{14}H_{16}N_2O_3$

m.w. = 260.29 g/mol

Yellow oil

The title compound was prepared according to the method outlined for **5.18** (method B), whereby reaction of lactone **9.1** (124 mg, 0.45 mmol) with Tf_2O (0.30 mL, 1.80 mmol) and NaN_3 (234 mg, 3.60 mmol) and workup under the conditions described gave a crude yellow foam (182 mg). Purification was accomplished by flash chromatography on silica

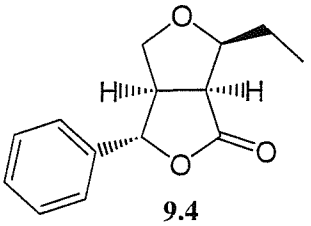
gel (2.2 x 7) eluting with EtOAc/hexane (1:4) to give the title compound **9.3** (108 mg, 0.41 mmol, 92 %) as a bright yellow oil.

FT-IR ν_{max} (neat) 2093 s, 1728 s, 1454 w, 1371 s, 1256 s, 1102 s cm^{-1}.

^{1}H NMR (400 MHz) δ 7.43-7.32 (5H, m, Ph**H**), 5.15 (1H, m, -C**H**Ph), 3.82-3.67 (3H, m, -C**H**C**H**$_2$O-), 3.46 (2H, t, *J* = 6.5 Hz, -OC**H**$_2$C**H**$_2$-), 1.59 (2H, tq, *J* = 6.5, 7.5 Hz, -C**H**$_2$CH$_3$), 0.92 (3H, t, *J* = 7.0 Hz, -C**H**$_3$).

^{13}C NMR (100 MHz) δ 169.7 (**C**O), 139.4 (**C**$_{ar}$), 129.4 (**C**H$_{ar}$), 129.3 (**C**H$_{ar}$), 125.8 (**C**H$_{ar}$), 80.8 (-**C**HPh), 74.0 (-O**C**H$_2$-), 72.1 (-O**C**H$_2$-), 53.3 (**C**N$_2$), 45.8 (-**C**HCH$_2$-), 23.2 (-OCH$_2$**C**H$_2$), 10.9 (-CH$_2$**C**H$_3$).

(1S*, 2R*, 5R*, 6S*)-2-Ethyl-6-phenyl-3,7-dioxabicyclo[3.3.0]octan-8-one (9.4)



9.4

$C_{14}H_{16}O_3$

m.w. = 232.28 g/mol

Colourless oil

The title compound was prepared according to the method outlined for **5.19**, whereby reaction of diazo lactone **9.3** (82 mg, 0.32 mmol) with dirhodium (II) tetraacetate (3 mg, cat.) and workup under the conditions described gave crude furofuranone as a yellow oil (80 mg). Purification was accomplished by flash chromatography on silica gel (2.2 x 11) eluting with EtOAc/hexane (3:7) to give the title compound **9.4** (64 mg, 0.28 mmol, 86 %) as a colourless oil.

FT-IR (neat) ν_{max} 1768 s, 1456 w, 1365 w, 1175 m, 1114 w, 1063 w cm^{-1}.

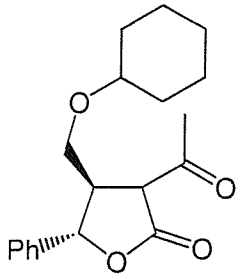
^{1}H NMR (400 MHz) δ 7.42-7.28 (5H, m, Ph**H**), 5.15 (1H, d, *J* = 6.0 Hz, -C**H**Ph), 4.14 (1H, d, *J* = 9.8 Hz, -OC**H**H-), 3.84 (1H, td, *J* = 8.3, 8.3, 4.8 Hz, -OC**H**Et), 3.75 (1H, dd, *J* = 9.8, 5.5 Hz, -OCH**H**-), 3.31 (1H, t, *J* = 9.0 Hz, -O$_2$CC**H**-), 3.17-3.11 (1H, m, -OCH$_2$C**H**), 2.02-1.90 (1H, m, CH$_3$C**H**H-), 1.74-1.62 (1H, m, CH$_3$CH**H**-), 1.12 (3H, t, *J* = 7.5 Hz, -CH$_2$C**H**$_3$).

^{13}C NMR (100 MHz) δ 176.0 (**C**O), 140.3 (**C**$_{ar}$), 129.4 (**C**H$_{ar}$), 129.1 (**C**H$_{ar}$), 125.8 (**C**H$_{ar}$), 86.3 (-**C**HPh), 84.0 (-O**C**HEt), 72.3 (-O**C**H$_2$-), 51.4 (PhC**H**C**H**-), 49.2 (-CO$_2$**C**H-), 25.2 (-**C**H$_2$CH$_3$), 11.7 (-CH$_2$**C**H$_3$).

LRMS (CI, NH_3) *m/z* (relative intensity) 233 (50) $[M+H]^+$, 250 (96) $[M+NH_4]^+$, 91 (100) $[PhCH_2]^+$.

HRMS (ES +ve) Calcd for $C_{28}H_{32}O_6Na$ (dimer) 487.2091, found 487.2109.

(4R*, 5S*)-3-Acetyl-4-cyclohexyloxymethyl-5-phenyl-dihydrofuran-2-one (9.5)



9.5

$C_{19}H_{24}O_4$

m.w. = 316.40 g/mol

Colourless oil

The title compound was prepared according to the method outlined for **7.45**, whereby reaction of cyclopropane **7.35** (216 mg, 1.0 mmol) with cyclohexanol (0.32 mL, 3.0 mmol) and workup under the conditions described gave a crude viscous yellow oil (423 mg). The excess alcohol was removed by gentle heating on the Hi-Vac and the residue was purified by flash chromatography on silica gel (2 x 4.5) eluting with EtOAc/hexane (3:97) to EtOAc/hexane (1:4) in 3 % increment rises (20 mL each) to yield the title compound **9.5** (285 mg, 0.90 mmol, 90 %) as a colourless oil.

FT-IR ν_{max} (neat) 2928 m, 2853 m, 1765 s, 1717 s, 1360 m, 1155 s, 1090 s cm^{-1}.

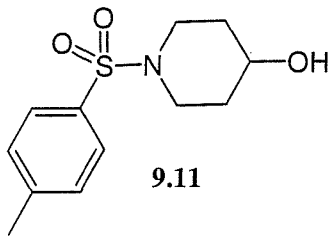
^{1}H NMR (400 MHz) δ 7.42-7.29 (5H, m, Ph**H**), 5.30 (1H, d, *J* = 9.5 Hz, -C**H**Ph), 4.01 (1H, d, *J* = 10.5 Hz, -C**H**CO-), 3.46 (2H, d, *J* = 3.5 Hz, -CHC**H**$_2$-), 3.27-3.20 (1H, m, -OC**H**^{c}hex-), 3.12 (1H, ddt, *J* = 10.5, 9.3, 3.5 Hz -C**H**CH$_2$-), 2.50 (3H, s, -COC**H**$_3$), 1.95-1.60 (4H, m, -C**H**^{c}hex), 1.56-1.47 (1H, m, -C**H**^{c}hex), 1.43-1.20 (5H, m, -C**H**^{c}hex); keto/enol ratio 8:1 - enolic resonances were observed at δ 11.28 (1H, s), 5.48 (1H, d, *J* = 2.3 Hz), 1.98 (3H, s).

^{13}C NMR (100 MHz) δ 201.0 (**C**O$_{ket}$), 172.0 (**C**O$_{est}$), 138.0 (**C**$_{ar}$), 129.2 (**C**H$_{ar}$), 129.1 (**C**H$_{ar}$), 126.8 (**C**H$_{ar}$), 81.6 (-**C**HPh), 78.1 (-O**C**H^{c}hex-), 63.6 (-O**C**H$_2$-), 56.1 (-**C**HCO-), 47.0 (-**C**HCH$_2$-), 32.3 (-**C**H$_2$^{c}hex), 32.3 (-**C**H$_2$^{c}hex), 30.6 (-CO**C**H$_3$), 26.1 (-**C**H$_2$^{c}hex), 24.2 (-**C**H$_2$^{c}hex); enolic resonances were observed at δ 170.7, 125.3, 83.0, 70.1, 47.2, 19.6.

LRMS (ES +ve) *m/z* (relative intensity) 317 (15) $[M+H]^+$, 380 (100) $[M+Na+MeCN]^+$, 655 (60) $[2M+Na]^+$.

HRMS (ES +ve) Calcd for $C_{38}H_{48}O_8Na$ (dimer) 655.3241, found 655.3259.

1-(Toluene-4-sulfonyl)-piperidin-4-ol (80213-12-3) (9.11)



9.11

$C_{12}H_{17}NSO_3$

m.w. = 255.34 g/mol

White powdery solid

The title compound was prepared according to the method outlined for **8.32**, whereby reaction of 1-(toluene-4-sulfonyl)-piperidin-4-one (1.01 g, 4.0 mmol) with sodium borohydride (166 mg, 4.1 mmol) and workup under the conditions described gave a crude colourless oil (1.10 g). Purification was accomplished by trituration with ice-cold Et_2O/hexane (3:1) to give the title compound **9.11** (0.97 g, 3.80 mmol, 95 %) as a white powdery solid.

MP 127-128 °C (lit.[279] 131-132 °C).

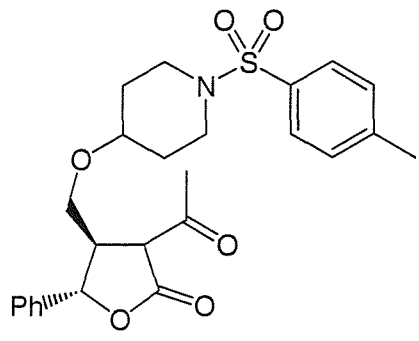
FT-IR (neat) ν_{max} 3521 m, 1596 w, 1322 s, 1270 m, 1158 s, 1092 s, 1030 s cm^{-1}.

^{1}H NMR (400 MHz) δ 7.63 (2H, d, *J* = 8.2 Hz, Ph**H**), 7.32 (2H, d, *J* = 8.2 Hz, Ph**H**), 3.74 (1H, tt, *J* = 7.7, 3.7 Hz, -C**H**OH), 3.30 (2H, ddd, *J* = 11.4, 7.3, 4.1 Hz, 2 x -NC**H**H-), 2.82 (2H, ddd, *J* = 11.8, 8.2, 3.6 Hz, 2 x -NCH**H**-), 2.43 (3H, s, -C**H**$_3$), 1.91 (2H, dddd, *J* = 13.7, 10.0, 6.4, 2.7 Hz, 2 x -NCH$_2$C**H**H-), 1.70-1.58 (2H, m, 2 x -NCH$_2$CH**H**-).

^{13}C NMR (100 MHz) δ 144.0 (**C**$_{ar}$), 133.7 (**C**$_{ar}$), 130.1 (**CH**$_{ar}$), 128.1 (**CH**$_{ar}$), 66.0 (-**C**HOH), 43.3 (2 x -N**C**H$_2$-), 33.3 (2 x -NCH$_2$**C**H$_2$-), 21.6 (-**C**H$_3$).

LRMS (ES +ve) *m/z* (relative intensity) 256 (100) $[M+H]^+$.

(4R*, 5S*)-3-Acetyl-5-phenyl-4-[1-(toluene-4-sulfonyl)-piperidin-4-yloxymethyl]-dihydro-furan-2-one (9.6)



9.6

$C_{25}H_{29}NSO_6$

m.w. = 471.57 g/mol

White powdery solid

To a mixture of cyclopropane **7.35** (216 mg, 1.0 mmol) and 1-(toluene-4-sulfonyl)-piperidin-4-ol (**9.11**) (511 mg, 2.0 mmol) was added magnesium perchlorate (22 mg, 0.1 mmol) and the mixture heated to 140 °C for 120 min. The reaction was cooled to room

temperature before partitioning between EtOAc (30 mL) and sat. NH_4Cl (aq) (30 mL), the organic layer separated and the aqueous extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried with $MgSO_4$ and concentrated *in vacuo* to give a colourless oil (840 mg). Purification was accomplished by flash chromatography on silica gel (3 x 10) eluting with EtOAc/hexane (1:1) to yield the title compound **9.6** (412 mg, 0.87 mmol, 87 %) as a powdery white solid.

MP 57-60 °C.

FT-IR ν_{max} (neat) 1766 m, 1718 m, 1345 m, 1329 m, 1162 s, 1090 m cm^{-1}.

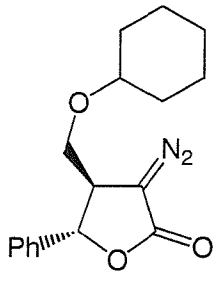
^{1}H NMR (400 MHz) δ 7.64 (2H, d, *J* = 8.0 Hz, Ph**H**), 7.38-7.13 (7H, m, Ph**H**), 5.11 (1H, d, *J* = 9.3 Hz, -C**H**Ph), 3.79 (1H, d, *J* = 10.5 Hz, -C**H**CO-), 3.44-3.32 (3H, m, -OC**H**$_2$- and -OC**H**-), 3.14-3.03 (3H, m, 2 x -NC**H**H- and -OCH$_2$C**H**-), 2.97-2.89 (2H, m, 2 x -NCH**H**-), 2.41 (6H, s, 2 x -C**H**$_3$), 1.91-1.81 (2H, m, 2 x -NCH$_2$C**H**H-), 1.74-1.63 (2H, m, 2 x -NCH$_2$CH**H**-); keto/enol ratio 8:1 - enolic resonances were observed at δ 11.21 (1H, s), 5.25 (1H, d, *J* = 1.5 Hz), 1.89 (3H, s).

^{13}C NMR (100 MHz) δ 200.6 (**C**O$_{ket}$), 171.5 (**C**O$_{est}$), 144.2 (**C**$_{ar}$), 137.6 (**C**$_{ar}$), 133.5 (**C**$_{ar}$), 130.1 (**C**H$_{ar}$), 129.6 (**C**H$_{ar}$), 129.3 (**C**H$_{ar}$), 128.2 (**C**H$_{ar}$), 126.8 (**C**H$_{ar}$), 81.6 (-**C**HPh), 73.6 (-O**C**H-), 64.3 (-O**C**H$_2$-), 56.1 (-**C**HCO-), 46.6 (-**C**HCH$_2$-), 43.4 (-N**C**H$_2$-), 43.4 (-N**C**H$_2$-), 30.5 (-NCH$_2$**C**H$_2$-), 30.4 (-NCH$_2$**C**H$_2$-), 30.3 (-CO**C**H$_3$), 22.0 (-**C**H$_3$); enolic resonances were observed at δ 129.2, 128.6, 125.2, 82.8, 60.8, 46.6, 19.6.

LRMS (ES +ve) *m/z* (relative intensity) 472 (90) $[M+H]^+$, 494 (85) $[M+Na]^+$, 965 (100) $[2M+Na]^+$.

CHN Anal. Calcd for $C_{25}H_{29}NSO_6$: C, 63.68; H, 6.20; N, 2.97. Found: C, 63.51; H, 6.28; N, 2.91.

(4R*, 5S*)-4-Propoxymethyl-3-diazo-5-phenyl-dihydrofuran-2-one (9.7)



9.7

$C_{17}H_{20}N_2O_3$

m.w. = 300.36 g/mol

Yellow oil

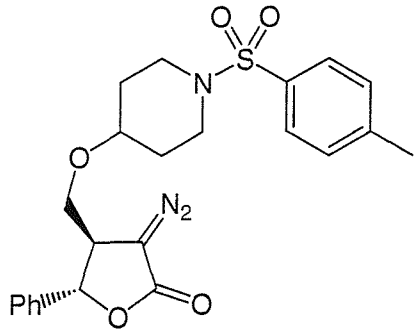
The title compound was prepared according to the method outlined for **5.18** (method B), whereby reaction of lactone **9.5** (222 mg, 0.70 mmol) with Tf_2O (0.47 mL, 2.80 mmol) and NaN_3 (364 mg, 5.60 mmol) and workup under the conditions described gave a crude yellow foam (245 mg). Purification was accomplished by flash chromatography on silica gel (2.3 x 3.5) eluting with EtOAc/hexane (1:4) to give the title compound **9.7** (173 mg, 0.58 mmol, 82 %) as a bright yellow oil.

FT-IR ν_{max} (neat) 2928 m, 2853 m, 2096 s, 1732 s, 1372 m, 1257 m, 1090 s cm^{-1}.

^{1}H NMR (400 MHz) δ 7.43-7.27 (5H, m, PhH), 5.14 (1H, d, *J* = 4.3 Hz, -CHPh), 3.85-3.65 (3H, m, -CHC**H**$_2$- and -C**H**CH$_2$-), 3.38-3.28 (1H, m, -OC**H**^{c}hex-), 1.92-1.62 (4H, m, -C**H**^{c}hex), 1.43-1.56 (1H, m, -C**H**^{c}hex), 1.42-1.18 (5H, m, -C**H**^{c}hex).

^{13}C NMR (100 MHz) δ 169.9 (CO), 139.6 (C$_{ar}$), 129.4 (CH$_{ar}$), 129.3 (CH$_{ar}$), 125.8 (CH$_{ar}$), 80.9 (-CHPh), 78.7 (-OCH^{c}hex-), 69.4 (-OCH$_2$-), 53.4 (CN$_2$), 46.1 (-CHCH$_2$-), 32.3 (-CH$_2{}^c$hex), 32.2 (-CH$_2{}^c$hex), 26.1 (-CH$_2{}^c$hex), 24.1 (-CH$_2{}^c$hex).

3-Diazo-(5S*)-phenyl-(4R*)-[1-(toluene-4-sulfonyl)-piperidin-4-yloxymethyl]-dihydro-furan-2-one (9.8)



9.8

$C_{23}H_{25}SN_3O_5$

m.w. = 455.53 g/mol

Yellow oil

The title compound was prepared according to the method outlined for **5.18** (method B), whereby reaction of lactone **9.6** (380 mg, 0.81 mmol) with Tf_2O (0.55 mL, 3.24 mmol) and NaN_3 (421 mg, 6.48 mmol) and workup under the conditions described gave a crude yellow foam (650 mg). Purification was accomplished by flash chromatography on silica gel (3 x 6) eluting with EtOAc/hexane (1:1) to give the title compound **9.8** (315 mg, 0.69 mmol, 85 %) as a bright yellow oil.

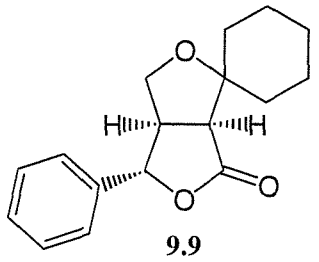
FT-IR ν_{max} (neat) 2099 s, 1734 s, 1373 m, 1345 m, 1261 m, 1164 s, 1091 s cm^{-1}.

^{1}H NMR (400 MHz) δ 7.62 (2H, d, *J* = 8.3 Hz, PhH), 7.40-7.33 (3H, m, PhH), 7.31 (2H, d, *J* = 8.3 Hz, PhH), 7.27-7.22 (2H, m, PhH), 5.02 (1H, d, *J* = 4.5

Hz, -CHPh), 3.75-3.69 (1H, m, -CHCN$_2$), 3.66-3.59 (2H, m, -OCH$_2$-), 3.48 (1H, tt, J = 6.5, 3.3 Hz, -OCH-), 3.06-2.97 (4H, m, 2 x -NCH$_2$-), 2.41 (3H, s, -CH$_3$), 1.91-1.83 (2H, m, 2 x -NCH$_2$CHH-), 1.79-1.66 (2H, m, 2 x -NCH$_2$CHH-).

^{13}C NMR (100 MHz) δ 169.4 (CO), 144.1 (C$_{ar}$), 139.2 (C$_{ar}$), 133.5 (C$_{ar}$), 130.1 (CH$_{ar}$), 129.4 (CH$_{ar}$), 128.0 (CH$_{ar}$), 125.6 (CH$_{ar}$), 80.6 (-CHPh), 73.9 (-OCH-), 69.7 (-OCH$_2$-), 53.2 (CN$_2$), 45.8 (-CHCN$_2$), 43.0 (2 x -NCH$_2$-), 30.4 (-NCH$_2$CH$_2$-), 30.1 (-NCH$_2$CH$_2$-), 21.9 (-CH$_3$).

(9R*, 10S*, 13S*)-10-Phenyl-7,11-dioxaspiro[5.2.0.3]-octan-12-one (9.9)



9.9

$C_{17}H_{20}O_3$

m.w. = 272.34 g/mol

White powdery solid

The title compound was prepared according to the method outlined for **5.19**, whereby reaction of diazo lactone **9.7** (90 mg, 0.30 mmol) with dirhodium (II) tetraacetate (3 mg, cat.) and workup under the conditions described gave crude furofuranone as a colourless oil (93 mg). Purification was accomplished by flash chromatography on silica gel (2.2 x 3.5) eluting with EtOAc/hexane (1:19) to EtOAc/hexane (1:4) in 5 % increment rises (20 mL each) to give the title compound **9.9** (71 mg, 0.26 mmol, 87 %) as a white powdery solid.

MP 66-67 °C (EtOAc/hexane).

FT-IR (neat) ν_{max} 2932 m, 2852 w, 1768 s, 1752 s, 1444 w, 1177 s, 1022 s cm^{-1}.

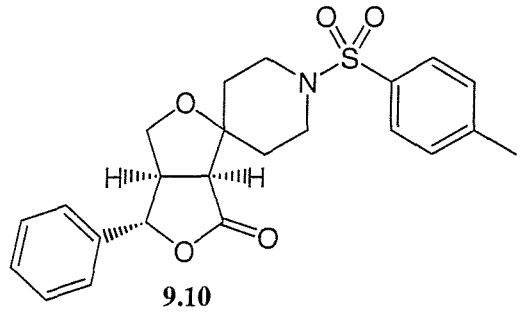
^{1}H NMR (400 MHz) δ 7.42-7.28 (5H, m, PhH), 5.18 (1H, d, J = 6.8 Hz, -CHPh), 4.02 (1H, d, J = 10.0 Hz, -OCHH-), 3.93 (1H, dd, J = 10.0, 5.0 Hz, -OCHH), 3.18-3.11 (1H, m, -OCH$_2$CH-), 2.97 (1H, d, J = 9.0 Hz, -O$_2$CCH-), 1.91-1.82 (1H, m, -CH^{c}hex), 1.80-1.57 (6H, m, -CH^{c}hex), 1.55-1.41 (2H, m, -CH^{c}hex), 1.38-1.26 (1H, m, -CH^{c}hex).

^{13}C NMR (100 MHz) δ 176.1 (CO), 140.0 (C$_{ar}$), 129.3 (CH$_{ar}$), 129.1 (CH$_{ar}$), 125.9 (CH$_{ar}$), 85.7 (-CHPh), 85.4 (-OC^{c}hex), 69.1 (-OCH$_2$-), 55.9 (-CH-), 52.2 (-CH-), 36.4 (-CH$_2{}^c$hex), 34.8 (-CH$_2{}^c$hex), 25.5 (-CH$_2{}^c$hex), 23.2 (-CH$_2{}^c$hex), 23.1 (-CH$_2{}^c$hex).

LRMS (CI, NH_3) *m/z* (relative intensity) 273 (74) $[M+H]^+$, 290 (100) $[M+NH_4]^+$.

CHN Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.97; H, 7.43.

(9R*, 10S*, 13S*)-10-Phenyl-3-(toluene-4-sulfonyl)-3-aza-7,11-dioxaspiro[5.2.0.3]-octan-12-one (9.10)



9.10

$C_{23}H_{25}SNO_5$

m.w. = 427.52 g/mol

White powdery solid

The title compound was prepared according to the method outlined for **5.19**, whereby reaction of diazo lactone **9.8** (290 mg, 0.64 mmol) with dirhodium (II) tetraacetate (5.5 mg, 0.012 mmol) and workup under the conditions described gave crude furofuranone as a colourless oil (280 mg). Purification was accomplished by flash chromatography on silica gel (3 x 8) eluting with EtOAc/hexane (1:1) to give the title compound **9.10** (244 mg, 0.57 mmol, 89 %) as a white powdery solid.

MP 90-92 °C.

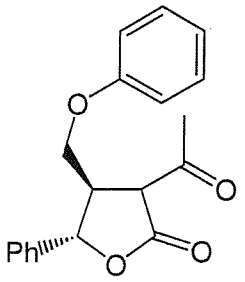
FT-IR (neat) ν_{max} 1764 m, 1351 m, 1329 m, 1162 s, 1049 m, 1019 m cm^{-1}.

^{1}H NMR (400 MHz) δ 7.64 (2H, d, *J* = 8.3 Hz, Ph**H**), 7.40-7.33 (3H, m, Ph**H**), 7.31 (2H, d, *J* = 8.3 Hz, Ph**H**), 7.27-7.23 (2H, m, Ph**H**), 5.11 (1H, d, *J* = 6.3 Hz, -C**H**Ph), 3.95 (1H, d, *J* = 10.0 Hz, -OC**H**H-), 3.86 (1H, dd, *J* = 10.0, 5.3 Hz, -OCH**H**-), 3.72-3.64 (1H, m, -NC**H**H-), 3.56-3.48 (1H, m, -NCH**H**-), 3.18-3.11 (1H, m, -OCH_2C**H**-), 2.98 (1H, d, *J* = 9.0 Hz, -O_2CC**H**-), 2.70 (2H, ddd, *J* = 14.8, 11.8, 2.8 Hz, 2 x -NCH**H**-), 2.43 (3H, s, -CH_3), 2.23 (1H, ddd, *J* =13.8, 12.8, 4.8 Hz, -NCH_2C**H**H-), 1.85-1.66 (3H, m, -NCH_2C**H**H- and 2 x -NCH_2CH**H**-).

^{13}C NMR (100 MHz) δ 175.0 (**C**O), 144.0 (C_{ar}), 139.5 (C_{ar}), 133.8 (C_{ar}), 130.1 (CH_{ar}), 129.4 (CH_{ar}), 129.3 (CH_{ar}), 128.1 (CH_{ar}), 125.7 (CH_{ar}), 85.7 (-**C**HPh), 82.3 (-O**C**-), 69.6 (-OCH_2-), 54.9 (-**C**H-), 51.4 (-**C**H-), 43.5 (-NCH_2-), 43.0 (-NCH_2-), 34.9 (-NCH_2CH_2-), 33.7 (-NCH_2CH_2-), 21.9 (-CH_3).

CHN Anal. Calcd for $C_{23}H_{25}SNO_5$: C, 64.62; H, 5.89; N, 3.27. Found: C, 64.41; H, 5.96; N, 3.25.

(4R*, 5S*)-3-Acetyl-4-phenoxymethyl-5-phenyl-dihydrofuran-2-one (9.12)



9.12

$C_{19}H_{18}O_4$

m.w. = 310.35 g/mol

Off-white solid

To a solution of cyclopropane **7.35** (216 mg, 1.0 mmol) and phenol (470 mg, 5.0 mmol) in DMSO (5 mL) was added cesium carbonate (652 mg, 2.0 mmol) and the mixture heated to 90 °C for 120 min. The reaction was cooled to room temperature before diluting with EtOAc (50 mL) and water (50 mL), the organic layer separated and the aqueous extracted with EtOAc (3 x 60 mL). The combined organic extracts were washed with water (4 x 60 mL), brine (2 x 60 mL), dried with Na_2SO_4 and concentrated *in vacuo* to give a yellow oil (806 mg). The excess phenol was removed by distillation under reduced pressure (b.p. ~ 130 °C, 0.5 mbar) and the residue purified by flash chromatography on silica gel (2.2 x 9) eluting with EtOAc/hexane (1:3) to yield the title compound **9.12** (274 mg, 0.88 mmol, 88 %) as a viscous colourless oil that solidified on standing.

MP 76-78 °C.

FT-IR ν_{max} (neat) 1764 s, 1715 s, 1597 m, 1495 m, 1237 s, 1163 s cm^{-1}.

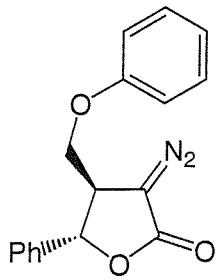
^{1}H NMR (400 MHz) δ 7.30-7.12 (7H, m, Ph**H**), 6.88 (1H, t, *J* = 7.3 Hz, Ph**H**), 6.76 (2H, d, *J* = 8.3 Hz, Ph**H**), 5.32 (1H, d, *J* = 9.5 Hz, -C**H**Ph), 4.00 (1H, d, *J* = 10.8 Hz, -C**H**CO-), 3.92 (1H, dd, *J* = 10.0, 3.5 Hz, -OC**H**H), 3.85 (1H, dd, *J* = 10.0, 3.0 Hz, -OCH**H**-), 3.23 (1H, tt, *J* = 10.0, 3.3 Hz, -OCH_2C**H**-), 2.42 (3H, s, -CH_3); no enolic resonances were observed.

^{13}C NMR (100 MHz) δ 200.5 (**C**O_{ket}), 171.3 (**C**O_{est}), 158.5 (**C**$_{ar}$), 137.4 (**C**$_{ar}$), 130.1 (**C**H$_{ar}$), 129.6 (**C**H$_{ar}$), 129.4 (**C**H$_{ar}$), 126.9 (**C**H$_{ar}$), 122.1 (**C**H$_{ar}$), 114.8 (**C**H$_{ar}$), 81.2 (-**C**HPh), 63.8 (-O**C**H$_2$-), 55.9 (-**C**HCO-), 46.1 (-**C**HCH$_2$-), 30.5 (-**C**H$_3$); no enolic resonances were observed.

LRMS (ES +ve) *m/z* (relative intensity) 311 (95) $[M+H]^+$, 643 (100) $[2M+Na]^+$.

CHN Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.31; H, 5.79.

(4R*, 5S*)-3-Diazo-4-phenoxymethyl-5-phenyl-dihydrofuran-2-one (9.13)



9.13

$C_{17}H_{14}N_2O_3$

m.w. = 294.31 g/mol

Yellow oil

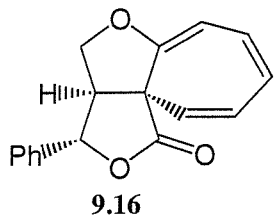
The title compound was prepared according to the method outlined for **5.18** (method B), whereby reaction of lactone **9.12** (230 mg, 0.74 mmol) with Tf_2O (0.50 mL, 2.96 mmol) and NaN_3 (385 mg, 5.92 mmol) and workup under the conditions described gave a crude yellow foam (472 mg). Purification was accomplished by flash chromatography on silica gel (3 x 8) eluting with EtOAc/hexane (1:4) to give the title compound **9.13** (201 mg, 0.68 mmol, 92 %) as a bright yellow oil.

FT-IR ν_{max} (neat) 2094 s, 1726 s, 1598 m, 1495 m, 1371 m, 1239 s, 1077 m cm^{-1}.

^{1}H NMR (400 MHz) δ 7.46-7.36 (5H, m, Ph**H**), 7.35-7.28 (2H, m, Ph**H**), 7.02 (1H, dt, *J* = 1.0, 7.3 Hz, Ph**H**), 6.91 (2H, dd, *J* = 8.3, 1.0 Hz, Ph**H**), 5.30 (1H, d, *J* = 4.8 Hz, -C**H**Ph), 4.34 (1H, dd, *J* = 9.0, 5.5 Hz, -OC**H**H), 4.24 (1H, dd, *J* = 9.0, 7.8 Hz, -OCH**H**-), 3.95 (1H, ddd, *J* = 7.5, 5.5, 5.0 Hz, -C**H**CN_2).

^{13}C NMR (100 MHz) δ 169.3 (**C**O), 158.3 (C_{ar}), 139.1 (C_{ar}), 130.2 (CH_{ar}), 129.5 (CH_{ar}), 125.8 (CH_{ar}), 122.3 (CH_{ar}), 114.8 (CH_{ar}), 80.6 (-**C**HPh), 69.0 (-OCH_2-), 53.0 (CN_2), 45.5 (-$CHCN_2$).

(3S*, 4R*)-3-Phenyl-3a,4-dihydro-3H-2,5-dioxa-cyclopenta[*c*]azulene (9.16)



9.16

$C_{17}H_{14}O_3$

m.w. = 266.30 g/mol

Pale yellow oil

The title compound was prepared according to the method outlined for **5.19**, whereby reaction of diazo lactone **9.13** (170 mg, 0.58 mmol) with dirhodium (II) tetraacetate (5 mg, 0.011 mmol) and workup under the conditions described gave a crude yellow oil (150 mg). Purification was accomplished by flash chromatography on silica gel (3 x 5) eluting

with EtOAc/hexane (1:2) to give the title compound **9.16** (138 mg, 0.52 mmol, 89 %) as a pale yellow oil.

FT-IR (neat) ν_{max} 1771 s, 1643 m, 1275 m, 1152 s, 1012 m cm^{-1}.

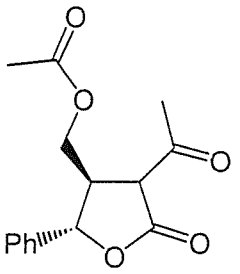
^{1}H NMR (400 MHz) δ 7.46-7.33 (5H, m, Ph**H**), 6.44-6.32 (3H, m, -CH–C**H**=C**H**–C**H**-), 6.00 (1H, d, *J* = 6.0 Hz, -OC=C**H**-), 5.27 (1H, d, *J* = 5.5 Hz, -C**H**Ph), 5.04 (1H, d, *J* = 9.0 Hz, -O_2CCC**H**=CH-), 4.38 (1H, dd, *J* = 9.5, 3.5 Hz, -OC**H**H-), 4.20 (1H, dd, *J* = 9.5, 5.5 Hz, -OCH**H**-), 3.22 (1H, dt, *J* = 3.5, 5.5 Hz, -OCH_2C**H**-).

^{13}C NMR (100 MHz) δ 172.3 (**C**O), 148.2 (-O**C**-), 139.1 (**C**$_{ar}$), 131.4 (-**C**H=CH-), 129.6 (**C**H$_{ar}$), 129.4 (**C**H$_{ar}$), 126.9 (-**C**H=CH-), 126.0 (-**C**H=CH-), 125.9 (**C**H$_{ar}$), 117.3 (-O_2**C**CCH=CH-), 100.4 (-OC=**C**H-), 81.5 (-**C**HPh), 73.1 (-O**C**H_2-), 57.8 (PhCH**C**H-), 57.8 (-O_2**C**C-).

LRMS (CI, NH_3) *m/z* (relative intensity) 267 (40) $[M+H]^+$, 284 (45) $[M+NH_4]^+$, 131 (100).

HRMS (ES +ve) Calcd for $C_{34}H_{28}O_6Na$ (dimer) 555.1778, found 555.1784.

(4R*, 5S*)-3-Acetyl-4-acetoxymethyl-5-phenyl-dihydrofuran-2-one (9.17)



9.17

$C_{15}H_{16}O_5$

m.w. = 276.29 g/mol

Colourless oil

To a solution of cyclopropane **7.35** (432 mg, 2.0 mmol) in dry DMSO (10 mL) was added potassium acetate (982 mg, 10 mmol) followed by acetic acid (0.69 mL, 12.0 mmol) and the mixture heated to 90 °C for 4 h. The mixture was then diluted with EtOAc (50 mL) and poured onto water (50 mL). The organic layer was separated and the aqueous extracted with EtOAc (3 x 50 mL), the combined extracts were washed with water (3 x 60 mL) and brine (2 x 60 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield a crude brown oil (720 mg). Purification was accomplished by flash chromatography on silica gel (4 x 9) eluting with petrol (200 mL), followed by EtOAc/hexane (1:1) to give the title compound **9.17** (496 mg, 1.80 mmol, 90 %) as a colourless oil.

FT-IR ν_{max} (neat) 1765 s, 1738 s, 1717 s, 1363 m, 1222 s, 1158 s, 1041 m cm^{-1}.

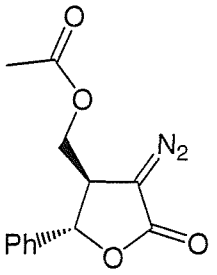
^{1}H NMR (250 MHz) δ 7.47-7.24 (5H, m, Ph**H**), 5.16 (1H, d, *J* = 9.5 Hz, -C**H**Ph), 4.17 (2H, d, *J* = 4.4 Hz, -C**H**$_2$-), 3.83 (1H, d, *J* = 10.7 Hz, -C**H**COCH$_3$), 3.30 (1H, ddt, *J* = 10.7, 9.5, 4.4 Hz, -C**H**CH$_2$-), 2.52 (3H, s, -COC**H**$_3$), 2.05 (3H, s, -OCOC**H**$_3$); keto/enol ratio, 4:1 - enolic resonances were observed at δ 11.31 (1H, s), 5.43 (1H, d, *J* = 2.4 Hz), 4.33 (1H, dd, *J* = 11.2, 4.5 Hz), 4.10 (1H, dd, *J* = 11.2, 8.8 Hz), 2.12 (3H, s), 2.03 (3H, s).

^{13}C NMR (62 MHz) δ 199.9 (**C**O$_{ket}$), 171.0 (**C**O$_{est}$), 170.9 (**C**O$_{est}$), 137.0 (**C**$_{ar}$), 129.8 (**C**H$_{ar}$), 129.4 (**C**H$_{ar}$), 126.8 (**C**H$_{ar}$), 81.5 (-**C**HPh), 61.4 (-**C**H$_2$-), 56.6 (-**C**HCO-), 45.3 (-**C**HCH$_2$-), 30.4 (-CO**C**H$_3$), 21.1 (-OCO**C**H$_3$); enolic resonances were observed at δ 175.7, 171.7, 171.1, 140.3, 128.9, 125.3, 95.3, 82.6, 65.7, 45.7, 21.2, 19.6.

LRMS (CI, NH$_3$) *m/z* (relative intensity) 277 (3) $[M+H]^+$, 294 (4) $[M+NH_4]^+$, 217 (100) $[M+H(-AcOH)]^+$, 234 (47) $[M+NH_4(-AcOH)]^+$.

HRMS (ES +ve) Calcd for $C_{15}H_{16}O_5Na$ 299.0890, found 299.0888.

(4R*, 5S*)-4-Acetoxymethyl-3-diazo-5-phenyl-dihydrofuran-2-one (9.18)



9.18

$C_{13}H_{12}N_2O_4$

m.w. = 260.25 g/mol

Yellow oil

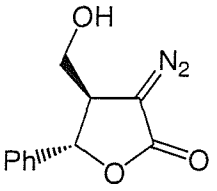
The title compound was prepared according to the method outlined for **5.18** (method B), whereby reaction of lactone **9.17** (160 mg, 0.58 mmol) with Tf_2O (0.39 mL, 2.32 mmol) and NaN_3 (302 mg, 4.64 mmol) and workup under the conditions described gave a crude yellow foam (225 mg). Purification was accomplished by flash chromatography on silica gel (2.2 x 8) eluting with EtOAc/hexane (1:2) to give the title compound **9.18** (124 mg, 0.48 mmol, 82 %) as a bright yellow oil.

FT-IR ν_{max} (neat) 2104 s, 1740 s, 1457 w, 1375 s, 1229 s cm^{-1}.

^{1}H NMR (400 MHz) δ 7.43-7.29 (5H, m, Ph**H**), 5.20 (1H, d, *J* = 5.3 Hz, -C**H**Ph), 4.47 (1H, dd, *J* = 11.0, 5.3 Hz, -OC**H**H-), 4.30 (1H, dd, *J* = 11.3, 6.8 Hz, -OCH**H**-), 3.77 (1H, dt, *J* = 6.8, 5.3 Hz, -C**H**CH$_2$-), 2.08 (3H, s, -C**H**$_3$).

^{13}C NMR (100 MHz) δ 170.8 (CO), 169.1 (CO), 138.8 (C_{ar}), 129.6 (CH_{ar}), 129.5 (CH_{ar}), 125.8 (CH_{ar}), 80.8 (-CHPh), 70.0 (-CH_2-), 52.5 (-CN_2), 44.9 (-$CHCH_2$-), 20.9 (-CH_3).

(4R*, 5S*)-3-Diazo-4-hydroxymethyl-5-phenyl-dihydrofuran-2-one (9.19)



9.19

$C_{11}H_{10}N_2O_3$

m.w. = 218.21 g/mol

Yellow oil

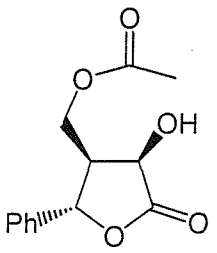
To a solution of NaN_3 (302 mg, 4.64 mmol) and tetra-*n*-butylammonium bromide (2 mg, 1 mol %) in 2N NaOH (aq) (12 mL) and hexane (6 mL) at 0 °C (ice/salt bath) was added Tf_2O (0.39 mL, 2.32 mmol) dropwise over 2 min. The clear colourless reaction mixture was to left stir for 10 min before the rapid addition of a solution of lactone **9.17** (160 mg, 0.58 mmol) in MeCN (6 mL) with vigorous stirring. The resulting bright yellow solution was allowed to stir at 0 °C for a further 30 min before dilution with EtOAc (30 mL) and water (20 mL). This mixture was left unstirred for 18 h, the organic layer separated and the aqueous extracted with EtOAc (3 x 30 mL), the organic extracts combined, washed with brine (30 mL), dried with Na_2SO_4 and concentrated *in vacuo* to yield a yellow foam (151 mg). Purification was accomplished by flash chromatography on silica gel (3.2 x 6) eluting with EtOAc/hexane (1:2 then 1:1) to give the title compound **9.19** (28 mg, 0.13 mmol, 22 %) as a bright yellow oil along with diazo-acetate **9.18** (69 mg, 0.27 mmol, 46 %) as a bright yellow oil. Data for **9.19**.

FT-IR ν_{max} (neat) 3432 br w, 2103 s, 1716 s, 1456 w, 1375 m, 1265 m, 1109 w cm^{-1}.

^{1}H NMR (400 MHz) δ 7.43-7.29 (5H, m, Ph**H**), 5.23 (1H, d, J = 4.8 Hz, -C**H**Ph), 4.01 (1H, dd, J = 10.5, 5.3 Hz, -OC**H**H-), 3.93 (1H, dd, J = 10.5, 6.8 Hz, -OCH**H**-), 3.65 (1H, dt, J = 6.8, 5.3 Hz, -C**H**CH_2-), 2.59 (1H, br s, -O**H**).

^{13}C NMR (100 MHz) δ 170.3 (**C**O), 139.4 (C_{ar}), 129.5 (CH_{ar}), 129.4 (CH_{ar}), 125.8 (CH_{ar}), 80.9 (-CHPh), 63.8 (-CH_2-), 47.7 (-$CHCH_2$-) (no **C**=N_2 observed).

(3R*, 4S*, 5S*)-4-Acetoxymethyl-3-hydroxy-5-phenyl-dihydrofuran-2-one (9.22)



9.22

$C_{13}H_{14}O_5$

m.w. = 250.25 g/mol

Colourless oil

To a solution of diazolactone **9.18** (60 mg, 0.23 mmol) in CH_2Cl_2 (3 mL) at room temperature was added dirhodium tetraacetate (2 mg, 0.005 mmol) and the mixture stirred for 3 h before addition of a second portion of dirhodium tetraacetate (3 mg, 0.007 mmol). The reaction was left stirring for a further 60 min then diluted with CH_2Cl_2 (15 mL) and water (15 mL). The organic layer was separated and the aqueous extracted with CH_2Cl_2 (3 x 15 mL), the organic extracts combined and washed with brine (20 mL), dried with Na_2SO_4 and concentrated *in vacuo* to give a crude yellow oil (78 mg). Purification was accomplished by flash chromatography on silica gel (2.2 x 8) eluting with EtOAc/hexane (1:2 then 1:1) to give the title compound **9.22** (27 mg, 0.11 mmol, 47 %) as a colourless oil.

FT-IR ν_{max} (neat) 3452 br w, 1778 s, 1738 s, 1231 s, 1132 s, 1043 s cm^{-1}.

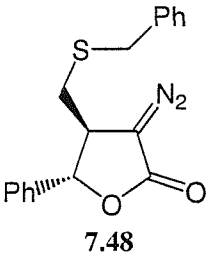
^{1}H NMR (400 MHz) δ 7.44-7.33 (5H, m, Ph**H**), 5.15 (1H, d, *J* = 10.0 Hz, -C**H**Ph), 4.58 (1H, d, *J* = 10.8 Hz, -C**H**OH), 4.36 (1H, dd, *J* = 12.0, 4.5 Hz, -OC**H**H), 4.25 (1H, dd, *J* = 12.1, 3.8 Hz, -OCH**H**), 3.79 (1H, br s, -O**H**), 3.30 (1H, dddd, *J* = 10.8, 10.0, 4.5, 3.8 -C**H**CH_2-), 2.01 (3H, s, -CH_3).

^{13}C NMR (100 MHz) δ 176.4 (**C**O), 171.2 (**C**O), 136.6 (C_{ar}), 129.9 (CH_{ar}), 129.3 (CH_{ar}), 127.1 (CH_{ar}), 79.3 (-**C**HPh), 70.2 (-**C**HOH), 60.1 (-CH_2-), 51.9 (-**C**HCH_2-), 21.0 (-CH_3).

LRMS (ES +ve) *m/z* (relative intensity) 523 (100) $[2M+Na]^+$, 773 (15) $[3M+Na]^+$.

HRMS (ES +ve) Calcd for $C_{26}H_{28}O_{10}Na$ (dimer) 523.1575, found 523.1582.

(4S*, 5S*)-4-Benzylsulfanylmethyl-3-diazo-5-phenyl-dihydrofuran-2-one (7.48)



7.48

$C_{18}H_{16}N_2SO_2$

m.w. = 324.40 g/mol

Yellow oil

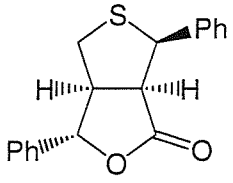
The title compound was prepared according to the method outlined for **5.18** (method B), whereby reaction of lactone **7.42a** (102 mg, 0.30 mmol) with Tf_2O (0.20 mL, 1.20 mmol) and NaN_3 (156 mg, 2.40 mmol) and workup under the conditions described gave a crude yellow foam (100 mg). Purification was accomplished by flash chromatography on silica gel (3.2 x 6) eluting with EtOAc/hexane (1:3) to give the title compound **7.48** (84 mg, 0.26 mmol, 86 %) as a bright yellow oil.

FT-IR ν_{max} (neat) 2092 s, 1728 s, 1493 w, 1453 w, 1368 m, 1254 m, 1103 m cm^{-1}.

^{1}H NMR (400 MHz) δ 7.42-7.36 (3H, m, Ph**H**), 7.31-7.19 (7H, m, Ph**H**), 5.12 (1H, d, *J* = 4.5 Hz, -C**H**Ph), 3.73 (2H, s, -C**H**$_2$Ph-), 3.35 (1H, ddd, *J* = 7.3, 6.8, 4.5 Hz, -C**H**CN$_2$), 2.85 (1H, dd, *J* = 13.3, 6.5 Hz, -CHC**H**H-), 2.79 (1H, dd, *J* = 13.3, 7.3 Hz, -CHCH**H**-).

^{13}C NMR (100 MHz) δ 169.4 (**C**O), 139.2 (**C**$_{ar}$), 137.6 (**C**$_{ar}$), 129.3 (**C**H$_{ar}$), 129.3 (**C**H$_{ar}$), 129.2 (**C**H$_{ar}$), 128.0 (**C**H$_{ar}$), 125.7 (**C**H$_{ar}$), 83.3 (-**C**HPh), 54.2 (-**C**N$_2$), 45.3 (-**C**HCH$_2$-), 36.9 (-**C**H$_2$Ph), 35.2 (-CH**C**H$_2$S-).

(1R*, 2R*, 5S*, 6S*) 2,6-Diphenyl-3-thio-7-oxabicyclo[3.3.0]octan-8-one (9.23)



9.23

$C_{18}H_{16}SO_2$

m.w. = 296.39 g/mol

White crystalline solid

The title compound was prepared according to the method outlined for **5.19**, whereby reaction of diazo lactone **7.48** (64 mg, 0.20 mmol) with dirhodium (II) tetraacetate (2 mg, 0.004 mmol) and workup under the conditions described gave crude thiofuranone as a yellow oil (65 mg). Purification was accomplished by flash chromatography on silica gel (2 x 4) eluting with EtOAc/hexane (1:2) to give the title compound **9.23** (44 mg, 0.15 mmol, 74 %) as a white crystalline solid.

MP 137-139 °C (Et_2O/hexane).

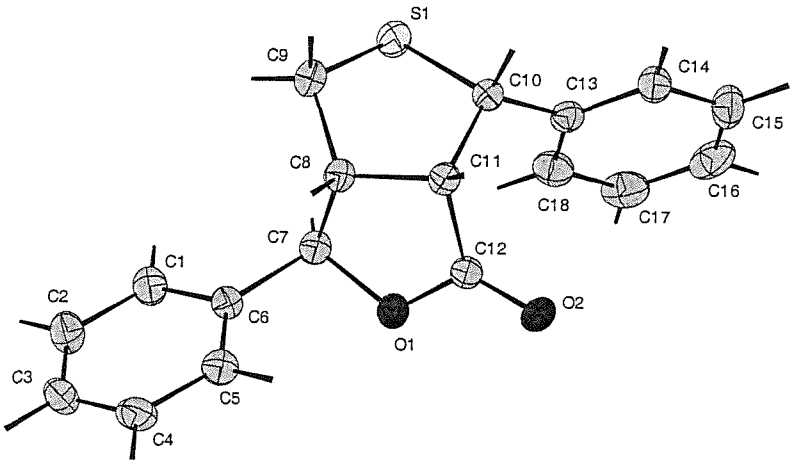
FT-IR (neat) ν_{max} 1758 s, 1492 w, 1453 w, 1250 m, 1168 m, 1149 m, 996 s cm^{-1}.

^{1}H NMR (400 MHz) δ 7.50-7.30 (10H, m, Ph**H**), 5.43 (1H, d, *J* = 7.1 Hz, PhC**H**O-), 4.87 (1H, d, *J* = 9.2 Hz, PhC**H**S-), 3.58 (1H, t, *J* = 8.9 Hz, -O$_2$CC**H**-), 3.41 (1H, dddd, *J* = 8.2, 7.1, 5.9, 0.8, -SCH$_2$C**H**-), 3.27 (1H, dd, *J* = 12.4, 5.6 Hz, -SC**H**H-), 3.08 (1H, d, *J* = 12.4 Hz, -SCH**H**-).

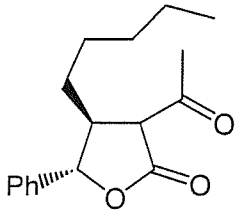
^{13}C NMR (100 MHz) δ 174.8 (**C**O), 139.8 (**C**$_{ar}$), 135.6 (**C**$_{ar}$), 129.4 (**C**H$_{ar}$), 129.2 (**C**H$_{ar}$), 129.1 (**C**H$_{ar}$), 128.9 (**C**H$_{ar}$), 128.8 (**C**H$_{ar}$), 126.1 (**C**H$_{ar}$), 85.4 (Ph**C**HO-), 57.0 (Ph**C**HS-), 54.9 (-S**C**H$_2$CH-), 54.1 (-O$_2$**C**CH-), 37.3 (-**C**H$_2$-).

CHN Anal. Calcd for $C_{18}H_{16}SO_2$: C, 72.95; H, 5.44. Found: C, 72.75; H, 5.54.

X-ray structure



(4S*, 5S*)-3-Acetyl-4-pentyl-5-phenyl-dihydrofuran-2-one (9.24)



9.24

$C_{17}H_{22}O_3$

m.w. = 274.36 g/mol

Colourless oil

To a suspension of copper iodide (190 mg, 1.00 mmol) in THF (1.5 mL) at –20 °C (CO_2(s)/acetone) was added *n*-butyl lithium (0.86 mL of a 2.33 M sol. in hexanes, 2.00 mmol) and the resulting black solution was stirred at –20 °C for 20 min. A solution of cyclopropane **7.35** (108 mg, 0.50 mmol) in THF (1.5 mL) was then added dropwise over 10 min and the reaction left stirring at –20 °C for a further 45 min before warming to room temperature. The mixture was partitioned between Et_2O (20 mL) and sat. NH_4Cl (aq) (20 mL), the organic layer separated and the aqueous extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield a crude colourless oil (155 mg). Purification was accomplished by flash chromatography on silica gel (2.2 x 11) eluting with

EtOAc/hexane (1:4) to give the title compound **9.24** (125 mg, 0.46 mmol, 91 %) as a colourless oil.

FT-IR ν_{max} (neat) 2927 m, 1761 s, 1716 s, 1456 m, 1358 m, 1226 m, 1158 s cm^{-1}.

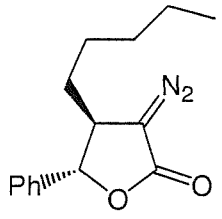
^{1}H NMR (300 MHz) δ 7.46-7.33 (5H, m, Ph**H**), 4.97 (1H, d, *J* = 9.2 Hz, -C**H**Ph), 3.60 (1H, d, *J* = 10.3 Hz, -C**H**CO-), 3.14-3.02 (1H, m, -C**H**C_5H_{11}), 2.51 (3H, s, -COC**H**$_3$), 1.63-1.52 (1H, m, -C**H**HC_4H_9), 1.51-1.33 (1H, m, -CH**H**C_4H_9), 1.29-1.02 (6H, m, 3 x -C**H**$_2$-), 0.82 (3H, t, *J* = 6.6 Hz, -CH_2C**H**$_3$); keto/enol ratio, 16:1 - enolic resonances were observed at δ 11.22 (1H, s), 5.25 (1H, d, *J* = 2.2 Hz), 1.97 (3H, s).

^{13}C NMR (75 MHz) δ 200.7 (**C**O_{ket}), 171.8 (**C**O_{est}), 137.7 (**C**$_{ar}$), 129.3 (**C**H_{ar}), 128.9 (**C**H_{ar}), 126.9 (**C**H_{ar}), 85.8 (-**C**HPh), 60.3 (-**C**HCO-), 45.6 (-**C**HC_5H_{11}), 31.8 (-CH**C**$H_2C_4H_9$), 30.6 (-CO**C**H_3), 27.2 (-**C**H_2-), 22.5 (-**C**H_2-), 14.1 (-**C**H_3).

LRMS (CI, NH_3) *m/z* (relative intensity) 275 (100) $[M+H]^+$, 292 (39) $[M+NH_4]^+$.

HRMS (EI) Calcd for $C_{17}H_{22}O_3$ 274.1569, found 274.1564.

(4S*, 5S*)-3-Diazo-4-pentyl-5-phenyl-dihydrofuran-2-one (9.25)



9.25

$C_{15}H_{18}N_2O_2$

m.w. = 258.32 g/mol

Yellow oil

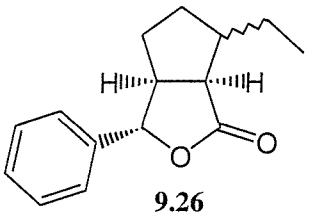
The title compound was prepared according to the method outlined for **5.18** (method B), whereby reaction of lactone **9.24** (95 mg, 0.34 mmol) with Tf_2O (0.23 mL, 1.39 mmol) and NaN_3 (177 mg, 2.72 mmol) and workup under the conditions described gave a crude yellow foam (141 mg). Purification was accomplished by flash chromatography on silica gel (2.2 x 9) eluting with EtOAc/hexane (1:2) to give the title compound **9.25** (72 mg, 0.28 mmol, 82 %) as a bright yellow oil.

FT-IR ν_{max} (neat) 2931 m, 2093 s, 1740 s, 1375 m, 1257 m, 1110 m cm^{-1}.

^{1}H NMR (400 MHz) δ 7.43-7.27 (5H, m, Ph**H**), 5.09 (1H, d, *J* = 5.3 Hz, -C**H**Ph), 3.14-3.02 (1H, dt, *J* = 5.3, 6.5 Hz, -C**H**C_5H_{11}), 1.87-1.79 (2H, m, -$CH_2C_4H_9$), 1.48-1.10 (6H, m, 3 x -C**H**$_2$-), 0.88 (3H, t, *J* = 7.0 Hz, -CH_2C**H**$_3$).

^{13}C NMR (100 MHz) δ 170.0 (**C**O), 139.6 (**C**$_{ar}$), 129.4 (**C**H$_{ar}$), 129.4 (**C**H$_{ar}$), 126.1 (**C**H$_{ar}$), 84.6 (-**C**HPh), 45.6 (-**C**HC$_5$H$_{11}$), 34.3 (-**C**H$_2$-), 32.0 (-**C**H$_2$-), 26.5 (-**C**H$_2$-), 22.8 (-**C**H$_2$-), 14.3 (-**C**H$_3$).

(1S*, 5R*, 6S*)-2-Ethyl-6-phenyl-7-oxabicyclo[3.3.0]octan-8-one (9.26)



9.26

$C_{15}H_{18}O_2$

m.w. = 230.31 g/mol

Colourless oil

The title compound was prepared according to the method outlined for **5.19**, whereby reaction of diazo lactone **9.25** (45 mg, 0.174 mmol) with dirhodium (II) tetraacetate (1.5 mg, 0.003 mmol) and workup under the conditions described gave a crude colourless oil (52 mg). Purification was accomplished by flash chromatography on silica gel (2.2 x 7) eluting with Et_2O/hexane (3:7) to give the title compound **9.26** (27 mg, 0.117 mmol, 67 %) as a colourless oil (3:1 mixture of *endo,exo*/*exo,exo*-diastereoisomers, respectively) and butenolide **9.27** (6 mg, 0.026 mmol, 15 %). Data for **9.26**.

FT-IR (neat) ν_{max} 2955 m, 1759 s, 1454 m, 1167 m cm^{-1}.

NMR data reported for both diastereoisomers (* major *endo,exo*- isomer).

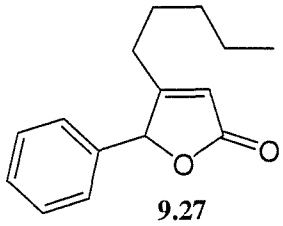
^{1}H NMR (400 MHz) δ 7.41-7.25 (2 x 5H, m, Ph**H**), 5.19 (1H, d, *J* = 3.3 Hz, -C**H**Ph), 4.99* (1H, d, *J* = 5.3 Hz, -C**H**Ph), 3.13* (1H, t, *J* = 9.0 Hz, -O$_2$CC**H**-), 2.97-2.90* (1H, m, -OCHC**H**), 2.90-2.83 (1H, m, -OCHC**H**), 2.76 (1H, dd, *J* = 9.3, 4.5 Hz, -O$_2$CC**H**-), 2.30-1.20 (2 x 7H, m, CH$_3$CH$_2$C**H**- and 3 x -C**H**$_2$-), 1.04* (3H, t, *J* = 7.5 Hz, -C**H**$_3$), 0.98 (3H, t, *J* = 7.3 Hz, -C**H**$_3$).

^{13}C NMR (100 MHz) δ 180.5 (**C**O), 178.0* (**C**O), 141.5* (**C**$_{ar}$), 141.2 (**C**$_{ar}$), 129.3 (**C**H$_{ar}$), 129.2* (**C**H$_{ar}$), 128.7* (**C**H$_{ar}$), 128.6 (**C**H$_{ar}$), 125.5* (**C**H$_{ar}$), 125.4 (**C**H$_{ar}$), 87.0* (-**C**HPh), 86.3 (-**C**HPh), 50.6 (-**C**H-), 49.6* (-**C**H-), 49.2 (-**C**H-), 47.7* (-**C**H-), 46.7* (-**C**H-), 46.5 (-**C**H-), 32.4* (-**C**H$_2$-), 32.4 (-**C**H$_2$-), 31.6* (-**C**H$_2$-), 28.7 (-**C**H$_2$-), 24.4* (-**C**H$_2$-), 14.0* (-**C**H$_3$), 12.9 (-**C**H$_3$).

LRMS (CI, NH_3) *m/z* (relative intensity) 231 (100) $[M+H]^+$, 248 (70) $[M+NH_4]^+$.

HRMS (ES +ve) Calcd for $C_{30}H_{36}O_4Na$ (dimer) 483.2506, found 483.2513.

4-Pentyl-5-phenyl-2(5H)-furanone (9.27)



9.27

$C_{15}H_{18}O_2$

m.w. = 230.31 g/mol

Colourless oil

Compound **9.27** has only been isolated in ~95 % purity but gives spectroscopic data as follows:

FT-IR (neat) ν_{max} 2928 w, 1754 s, 1637 w, 1455 w, 1167 w, 1006 w cm^{-1}.

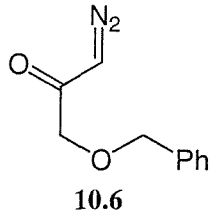
^{1}H NMR (300 MHz) δ 7.41-7.37 (3H, m, Ph**H**), 7.23-7.20 (2H, m, Ph**H**), 5.92 (1H, dt, *J* = 1.5, 1.8 Hz, -C**H**=C-), 5.73 (1H, d, *J* = 1.5 Hz, -C**H**Ph), 2.12 (2H, dt, *J* = 1.0, 7.5 Hz, -CC**H**$_2$-), 1.60-1.44 (2H m, -CCH$_2$C**H**$_2$-), 1.31-1.10 (4H, m, 2 x -C**H**$_2$-), 0.86 (3H, t, *J* = 7.3 Hz, -C**H**$_3$).

^{13}C NMR (75 MHz) δ 173.9 (**C**O or -**C**=CH-), 173.7 (-**C**=CH- or **C**O), 135.0 (**C**$_{ar}$), 129.9 (**C**H$_{ar}$), 129.5 (**C**H$_{ar}$), 127.4 (**C**H$_{ar}$), 115.5 (-C=**C**H-), 86.4 (-**C**HPh), 31.7 (-**C**H$_2$-), 28.7 (-**C**H$_2$-), 27.1 (-**C**H$_2$-), 22.7 (-**C**H$_2$-), 14.3 (-**C**H$_3$).

LRMS (CI, NH_3) 231 (100) $[M+H]^+$, 248 (50) $[M+NH_4]^+$.

HRMS (ES +ve) Calcd for $C_{30}H_{36}O_4Na$ (dimer) 483.2506, found 483.2515.

1-Benzyloxy-3-diazo-propan-2-one (10.6)



10.6

$C_{10}H_{10}N_2O_2$

m.w. = 190.20 g/mol

Yellow oil

To a solution of benzyloxyacetic acid (**10.5**) (2.15 mL, 15.0 mmol) in CH_2Cl_2 (150 mL) at 0 °C (ice/salt bath) was added oxalyl chloride (9.0 mL of a 2M sol, 18.0 mmol) over 2 min followed by DMF (0.11, 1.5 mmol). The solution was gradually warmed to room temperature and left stirring overnight before concentrating *in vacuo* (azeotroping with toluene 2 x 10 mL) to give benzyloxyacetyl chloride as a pale yellow oil (2.78 g, quantitative) – this crude material was used directly in the subsequent reaction. Thus, to a solution of trimethylsilyl-diazomethane (9.0 mL of a 2M sol, 18.0 mmol) in THF/acetonitrile (1:1, 150 mL) at 0 °C (ice/salt bath) was added a solution of crude acid chloride (15 mmol theoretical) in THF (8 mL) dropwise over 5 min. The mixture was

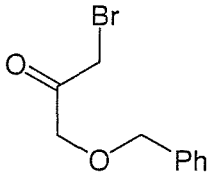
allowed to warm slowly to room temperature over 4 h and concentrated *in vacuo* to give a yellow oil (3.3 g). Purification was accomplished by flash chromatography on pre-packed silica gel (4 x 12) eluting with Et_2O/petrol (1:19) to Et_2O/petrol (1:1) in 5 % increment rises (100 mL each) to give the title compound **10.6** (2.18 g, 11.5 mmol, 77 % from acid **10.5**) as a bright yellow oil. Spectroscopic details were consistent with those observed in the literature.[280]

IR ν_{max} (neat) 2105 s, 1646 s, 1352 s cm^{-1}.

^{1}H NMR (400 MHz) δ 7.41-7.27 (5H, m, Ph**H**), 5.78 (1H, br s, -C**H**N_2), 4.57 (2H, s, PhCH_2-), 4.04 (2H, s, -COCH_2-).

^{13}C NMR (100 MHz) δ 193.9 (**C**O), 137.4 (**C**$_{ar}$), 129.0 (**C**H$_{ar}$), 128.6 (**C**H$_{ar}$), 128.2 (**C**H$_{ar}$), 74.2 (-**C**H_2-), 74.0 (-**C**H_2-), 53.6 (-**C**HN_2).

1-Benzyloxy-3-bromo-propan-2-one (10.7)



10.7

$C_{10}H_{11}O_2Br$

m.w. = 243.10 g/mol

Pale yellow oil

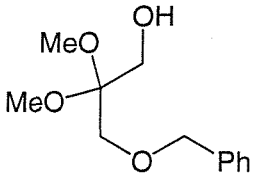
To a solution of diazoketone **10.6** (1.17 g, 6.2 mmol) in Et_2O (60 mL) at 0 °C (ice/salt bath) was added hydrobromic acid (0.84 mL of a 48 % wt. sol in H_2O, 7.4 mmol) dropwise over 1 min. The reaction mixture was stirred at 0 °C for 20 min before diluting with Et_2O (40 mL) and treating with sat. $NaHCO_3$ (aq) (80 mL). The organic layer was separated and the aqueous extracted with Et_2O (3 x 100 mL), the organic extracts combined and washed with brine (100 mL), dried with $MgSO_4$ and concentrated *in vacuo* to give the title compound **10.7** (1.45 g, 5.96 mmol, 96 %) as a pale yellow oil - this material was used crude in subsequent reactions. Spectroscopic details were consistent with those observed in the literature.[281]

IR ν_{max} (neat) 1734 s, 1725 s cm^{-1}.

^{1}H NMR (250 MHz) δ 7.41-7.27 (5H, m, Ph**H**), 4.61 (2H, s, PhCH_2-), 4.27 (2H, s, -C**H**$_2$Br), 4.05 (2H, s, -COCH_2-).

^{13}C NMR (63 MHz) δ 200.4 (**C**O), 137.1 (**C**$_{ar}$), 129.0 (**C**H$_{ar}$), 128.7 (**C**H$_{ar}$), 128.4 (**C**H$_{ar}$), 74.1 (-CO**C**H_2- or -**C**H_2Ph), 73.5 (-CO**C**H_2- or -**C**H_2Ph), 32.0 (-**C**H_2Br).

1-Benzyloxy-2,2-dimethoxypropan-3-ol (10.10)



10.10

$C_{12}H_{18}O_4$

m.w. = 226.27 g/mol

Colourless oil

To a solution of bromoketone **10.7** (100 mg, 0.41 mmol) in methanol (5 mL) at room temperature was added potassium carbonate (57 mg, 0.41 mmol) in one portion and the mixture stirred for 30 min and concentrated *in vacuo*. Purification was accomplished by flash chromatography on pre-packed silica gel (2.7 x 5) eluting with EtOAc/petrol (1:19) to EtOAc/petrol (2:3) in 5 % increment rises (20 mL each) to give the title compound **10.10** (58 mg, 0.26 mmol, 63 %) as a colourless oil along with methoxyketone **10.9** (11 mg, 0.06 mmol, 14 %) as a colourless oil. Data for **10.10** - spectroscopic details were consistent with those observed in the literature.[282]

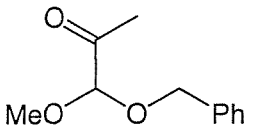
FT-IR ν_{max} (neat) 3445 br w, 2942 w, 1453 w, 1074 s cm^{-1}.

^{1}H NMR (250 MHz) δ 7.37-7.28 (5H, m, Ph**H**), 4.57 (2H, s, PhC**H**$_2$-), 3.69 (2H, br d, *J* = 5.1 Hz, -C**H**$_2$OH), 3.53 (2H, s, -CC**H**$_2$O-), 3.26 (6H, s, 2 x -OC**H**$_3$), 2.14 (1H, br t, *J* = 5.1 Hz, -O**H**).

^{13}C NMR (63 MHz) δ 138.0 (**C**$_{ar}$), 128.9 (**C**H$_{ar}$), 128.3 (**C**H$_{ar}$), 128.3 (**C**H$_{ar}$), 100.4 (-**C**CH$_2$-), 74.0 (-**C**H$_2$Ph), 68.9 (-CO**C**H$_2$-), 62.0 (-**C**H$_2$OH), 49.0 (-O**C**H$_3$).

LRMS (CI, NH_3) *m/z* (relative intensity) 195 (34) $[M+H(-MeOH)]^+$, 212 (24) $[M+NH_4(-MeOH)]^+$, 91 (100) $[PhCH_2]^+$.

1-Benzyloxy-1-methoxy-propan-2-one (10.9)



10.9

$C_{11}H_{14}O_3$

m.w. = 194.23 g/mol

Colourless oil

FT-IR ν_{max} (neat) 1727 s, 1453 w, 1351 w, 1203 w, 1109 s, 1062 s, 1043 s cm^{-1}.

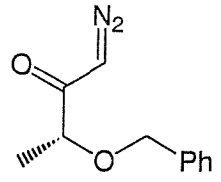
^{1}H NMR (250 MHz) δ 7.37-7.28 (5H, m, Ph**H**), 4.70 (1H, d, *J* = 11.8 Hz, -CH**H**Ph), 4.60 (1H, d, *J* = 11.8 Hz, -CH**H**Ph), 4.59 (1H, s, -C**H**OCH$_3$), 3.42 (3H, s, -OC**H**$_3$), 2.22 (3H, s, -C**H**$_3$).

^{13}C NMR (63 MHz) δ 204.2 (**C**O), 137.3 (**C**$_{ar}$), 128.9 (**C**H$_{ar}$), 128.5 (**C**H$_{ar}$), 128.4 (**C**H$_{ar}$), 102.9 (-**C**HOCH$_3$), 69.6 (-**C**H$_2$Ph), 55.1 (-O**C**H$_3$), 25.4 (-**C**H$_3$).

LRMS (CI, NH_3) *m/z* (relative intensity) 212 (63) $[M+NH_4]^+$, 91 (100) $[PhCH_2]^+$.

HRMS (ES +ve) Calcd for $C_{11}H_{14}O_3Na$ 217.0835, found 217.0834.

(3R)-3-Benzyloxy-1-diazo-butan-2-one (10.12)



10.12

$C_{11}H_{12}N_2O_2$

m.w. = 204.23 g/mol

Yellow oil

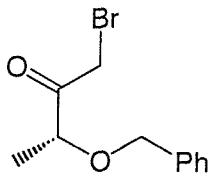
The title compound was prepared according to the method outlined for **10.6**, whereby (R)-(+)-2-benzyloxypropionic acid (**10.11**) (4.50 g, 25.0 mmol) and oxalyl chloride (13.8 mL of a 2M sol, 27.5 mmol) were reacted together under the described conditions to provide the crude acid chloride (6.5 g). This was subsequently reacted with trimethylsilyl-diazomethane (15 mL, 30 mmol) to afford a crude yellow oil (6.12 g). Purification was accomplished by flash chromatography on silica gel (8 x 12) eluting with Et_2O/petrol (1:19) to Et_2O/petrol (1:1) in 5 % increment rises (100 mL each) to give the title compound **10.12** (4.55 g, 22.3 mmol, 89 % from acid **10.11**) as a bright yellow oil.

FT-IR ν_{max} (neat) 2099 s, 1632 s, 1453 w, 1342 s, 1093 s, 1041 m cm^{-1}.

^{1}H NMR (250 MHz) δ 7.41-7.26 (5H, m, Ph**H**), 5.79 (1H, br s, -C**H**N$_2$), 4.59 (1H, d, *J* = 11.7 Hz, PhC**H**H-), 4.51 (1H, d, *J* = 11.7 Hz, PhCH**H**-), 3.97 (1H, q, *J* = 6.8 Hz, -C**H**CH$_3$), 1.38 (3H, d, *J* = 6.8 Hz, -C**H**$_3$).

^{13}C NMR (63 MHz) δ 198.0 (**C**O), 137.8 (**C**$_{ar}$), 129.0 (**C**H$_{ar}$), 128.4 (**C**H$_{ar}$), 128.1 (**C**H$_{ar}$), 80.3 (-O**C**HCH$_3$), 72.4 (-**C**H$_2$Ph), 52.5 (-**C**HN$_2$), 19.1 (-**C**H$_3$).

(3R)-3-Benzyloxy-1-bromo-butan-2-one (10.13)



10.13

$C_{11}H_{13}O_2Br$

m.w. = 257.13 g/mol

Pale yellow oil

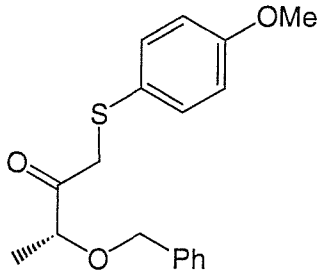
The title compound was prepared according to the method outlined for **10.7**, whereby diazoketone **10.12** (2.65 g, 13.0 mmol) and hydrobromic acid (1.77 mL of a 48 % wt. sol in H_2O, 15.6 mmol) were reacted together and worked up under the conditions described to give the title compound **10.13** (3.22 g, 12.5 mmol, 96 %) as a pale yellow oil - this material was used crude in subsequent reactions.

FT-IR ν_{max} (neat) 1733 s, 1723 s, 1453 m, 1389 m, 1370 m, 1103 s, 1026 s cm^{-1}.

^{1}H NMR (250 MHz) δ 7.41-7.27 (5H, m, PhH), 4.61 (1H, d, *J* = 11.6 Hz, PhCHH-), 4.55 (1H, d, *J* = 11.6 Hz, PhCHH-), 4.22 (1H, d, *J* = 14.3 Hz, -CHHBr), 4.19 (1H, q, *J* = 6.8 Hz, -CHCH$_3$), 4.16 (1H, d, *J* = 14.3 Hz, -CHHBr), 1.41 (3H, d, *J* = 6.8 Hz, -CHCH$_3$).

^{13}C NMR (63 MHz) δ 203.6 (CO), 137.5 (C_{ar}), 129.0 (CH_{ar}), 128.6 (CH_{ar}), 128.3 (CH_{ar}), 79.4 (-OCHCH$_3$), 72.6 (-CH$_2$Ph), 32.3 (-CH$_2$Br), 17.6 (-CH$_3$).

(3R)-3-Benzyloxy-1-(4-methoxyphenylsulfanyl)-butan-2-one (10.14)



10.14

$C_{18}H_{20}SO_3$

m.w. = 316.42 g/mol

Pale yellow oil

To a solution of bromoketone **10.13** (2.80 g, 10.9 mmol) in dry MeOH (110 mL) was added 4-methoxybenzenethiol (1.34 mL, 10.9 mmol) followed by K_2CO_3 (96 mg, 1.14 mmol) in one portion. The mixture was stirred at room temperature for 30 min, concentrated *in vacuo* and partitioned between EtOAc (100 mL) and water (80 mL). The organic layer was separated and the aqueous extracted with EtOAc (3 x 100 mL), the combined extracts washed with brine (100 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield a crude yellow oil (3.49 g). Purification was accomplished by flash chromatography on pre-packed silica gel (4 x 8) eluting with Et_2O/petrol (1:1) to give the title compound **10.14** (3.37 g, 10.7 mmol, 98 %) as a pale yellow oil.

FT-IR ν_{max} (neat) 1717 m, 1591 m, 1493 s, 1246 s, 1105 m, 1028 m cm^{-1}.

^{1}H NMR (400 MHz) δ 7.41-7.27 (7H, m, PhH), 6.82 (2H, d, *J* = 8.8 Hz, PhH), 4.54 (1H, d, *J* = 11.8 Hz, PhCHH-), 4.50 (1H, d, *J* = 11.8 Hz, PhCHH-), 4.15 (1H, q, *J* = 6.8 Hz, -CHCH$_3$), 3.81 (1H, d, *J* = 15.1 Hz, -CHHS-),

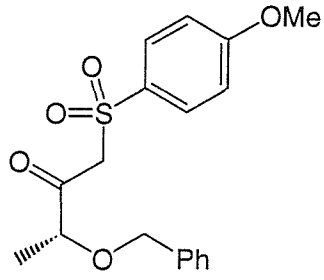
3.78 (3H, s, -OC**H**$_3$), 3.74 (1H, d, J = 15.1 Hz, -CH**H**S-), 1.34 (3H, d, J = 6.8 Hz, -CHC**H**$_3$).

^{13}C NMR (100 MHz) δ 206.8 (**C**O), 160.0 (**C**$_{ar}$), 137.9 (**C**$_{ar}$), 134.4 (**C**H$_{ar}$), 128.9 (**C**H$_{ar}$), 128.4 (**C**H$_{ar}$), 128.2 (**C**H$_{ar}$), 125.4 (**C**$_{ar}$), 115.2 (**C**H$_{ar}$), 79.6 (-O**C**HCH$_3$), 72.4 (-**C**H$_2$Ph), 55.7 (-OC**H**$_3$), 42.2 (-**C**H$_2$S-), 17.6 (-**C**H$_3$).

LRMS (CI, NH_3) *m/z* (relative intensity) 317 (13) $[M+H]^+$, 91 (100) $[PhCH_2]^+$.

HRMS (ES +ve) Calcd for $C_{18}H_{20}SO_3Na$ 339.1025, found 339.1025.

(3R)-3-Benzyloxy-1-(4-methoxyphenylsulfonyl)-butan-2-one (10.15)



10.15

$C_{18}H_{20}SO_5$

m.w. = 348.36 g/mol

Colourless oil

To a solution of sulfide **10.14** (3.42 g, 10.8 mmol) in CH_2Cl_2 (110 mL) at 0 °C (ice/salt bath) was added *m*-chloroperoxybenzoic acid (6.66 g, 70 %, 27.0 mmol) portionwise over 10 min. The mixture was stirred at 0 °C for 30 min, warmed to room temperature then treated with Na_2SO_3/$NaHCO_3$ (aq) (10 g Na_2SO_3 in 500 mL sat. $NaHCO_3$ (aq), 25 mL). The organic layer was separated and the aqueous extracted with CH_2Cl_2 (3 x 50 mL), the combined extracts washed with sat. $NaHCO_3$ (aq) (50 mL) and brine (50 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield a crude yellow oil (4.10 g). Purification was accomplished by flash chromatography on silica gel (6 x 10) eluting with EtOAc/petrol (1:9) to EtOAc/petrol (1:1) in 10 % increment rises (200 mL each) to give the title compound **10.15** (3.18 g, 9.1 mmol, 85 %) as a colourless oil.

FT-IR ν_{max} (neat) 1729 m, 1595 m, 1497 m, 1322 m, 1263 s, 1148 s cm^{-1}.

^{1}H NMR (400 MHz) δ 7.82 (2H, d, J = 8.9 Hz, Ph**H**), 7.43-7.30 (5H, m, Ph**H**), 7.00 (2H, d, J = 8.9 Hz, Ph**H**), 4.56 (2H, s, -C**H**$_2$Ph), 4.47 (1H, d, J = 14.4 Hz, -C**H**HSO$_2$-), 4.29 (1H, d, J = 14.4 Hz, -CH**H**SO$_2$-), 4.11 (1H, q, J = 6.7 Hz, -C**H**CH$_3$), 3.89 (3H, s, -OC**H**$_3$), 1.31 (3H, d, J = 7.0 Hz, -CHC**H**$_3$).

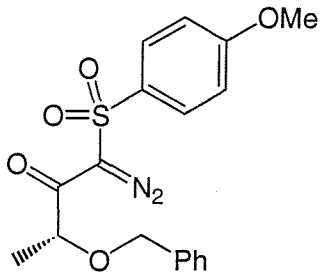
^{13}C NMR (100 MHz) δ 200.6 (**C**O), 164.5 (**C**$_{ar}$), 137.5 (**C**$_{ar}$), 131.2 (**C**$_{ar}$), 131.1 (**C**H$_{ar}$), 129.0 (**C**H$_{ar}$), 128.6 (**C**H$_{ar}$), 128.4 (**C**H$_{ar}$), 114.8 (**C**H$_{ar}$), 80.7

(-O**C**HCH$_3$), 72.6 (-**C**H$_2$Ph), 62.3 (-**C**H$_2$SO$_2$-), 56.1 (-O**C**H$_3$), 16.5 (-**C**H$_3$).

LRMS (CI, NH_3) *m/z* (relative intensity) 366 (8) $[M+NH_4]^+$, 91 (100) $[PhCH_2]^+$.

HRMS (ES +ve) Calcd for $C_{18}H_{20}SO_5Na$ 371.0924, found 371.0926.

(3R)-3-Benzyloxy-1-diazo-1-(4-methoxyphenylsulfonyl)-butan-2-one (10.16)



10.16

$C_{18}H_{18}N_2SO_5$

m.w. = 374.42 g/mol

Yellow solid

To a solution of sulfone **10.15** (1.99 g, 5.70 mmol) in acetonitrile (60 mL) at room temperature was added di-*iso*-propylethyl amine (2.1 mL, 11.97 mmol) and the mixture stirred for 5 min before adding 4-carboxybenzenesulfonyl azide (1.55 g, 6.84 mmol) in one portion. The mixture was left stirring at room temperature for 18 h, the precipitate filtered and the filtrate diluted with EtOAc (50 mL) then poured onto water (50 mL). The organic layer was separated and the aqueous extracted with EtOAc (3 x 50 mL), the combined organic extracts washed with sat. $NaHCO_3$ (aq) (2 x 50 mL) and brine (50 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield a crude yellow oil (2.05 g). Purification was accomplished by flash chromatography on silica gel (5 x 10) eluting with EtOAc/petrol (1:9) to EtOAc/petrol (1:1) in 10 % increment rises (200 mL each) to give the title compound **10.16** (1.77 g, 4.73 mmol, 83 %) as a powdery yellow solid.

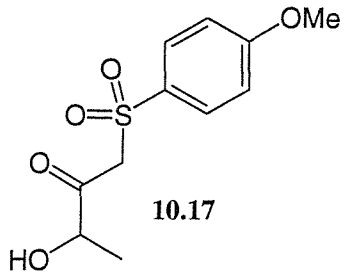
MP 87-89 °C.

IR ν_{max} (neat) 2116 s, 1662 s, 1594 s, 1496 s, 1338 s, 1265 s, 1150 s cm^{-1}.

^{1}H NMR (250 MHz) δ 7.96 (2H, d, *J* = 8.9 Hz, Ph**H**), 7.39-7.21 (5H, m, Ph**H**), 6.99 (2H, d, *J* = 8.9 Hz, Ph**H**), 4.47 (2H, s, -**C**H$_2$Ph), 4.13 (1H, q, *J* = 6.8 Hz, -**C**HCH$_3$), 3.88 (3H, s, -OC**H**$_3$), 1.34 (3H, d, *J* = 6.8 Hz, -CHC**H**$_3$).

^{13}C NMR (63 MHz) δ 190.3 (**C**O), 164.4 (**C**$_{ar}$), 136.7 (**C**$_{ar}$), 133.5 (**C**$_{ar}$), 130.8 (**C**H$_{ar}$), 129.0 (**C**H$_{ar}$), 128.7 (**C**H$_{ar}$), 128.4 (**C**H$_{ar}$), 114.6 (**C**H$_{ar}$), 81.2 (-O**C**HCH$_3$), 72.6 (-**C**H$_2$Ph), 56.1 (-O**C**H$_3$), 17.8 (-**C**H$_3$), (no **C**=N$_2$ observed).

3-Hydroxy-1-(4-methyl-benzenesulfonyl)-butan-2-one (10.17)



10.17

$C_{11}H_{14}SO_5$

m.w. = 258.24 g/mol

Colourless oil

To a solution of diazo sulfone **10.16** (112 mg, 0.30 mmol) in dry CH_2Cl_2 (6 mL) at room temperature was added dirhodium (II) tetraacetate (3 mg, 0.007 mmol) in one portion and the reaction stirred for 24 h. The mixture was diluted with CH_2Cl_2 (20 mL) and poured onto water (20 mL). The organic layer was separated and the aqueous extracted with CH_2Cl_2 (3 x 25 mL), the extracts combined, washed with brine (25 mL), dried with $MgSO_4$ and concentration *in vacuo* to yield a yellow oil (104 mg). Purification was accomplished by flash chromatography on pre-packed silica gel (2.7 x 7) eluting with EtOAc/petrol (1:19) increasing to EtOAc/petrol (1:1) in 5 % increment rises (20 mL each) to give the title compound **10.17** (35 mg, 0.14 mmol, 45 %) as a colourless oil.

IR ν_{max} (neat) 1724 s, 1595 s, 1497 s, 1321 s, 1298 s, 1261 s, 1145 s cm^{-1}.

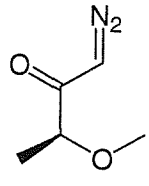
^{1}H NMR (250 MHz) δ 7.82 (2H, d, *J* = 8.9 Hz, PhH), 7.03 (2H, d, *J* = 8.9 Hz, PhH), 4.45 (1H, d, *J* = 13.2 Hz, -CHHSO$_2$-), 4.35 (1H, d, *J* = 13.2 Hz, -CHHSO$_2$-), 4.46-4.33 (1H, obsc m, -CHCH$_3$), 3.90 (3H, s, -OCH$_3$), 3.49 (1H, br s, -OH), 1.39 (3H, d, *J* = 7.1 Hz, -CHCH$_3$).

^{13}C NMR (63 MHz) δ 202.3 (CO), 164.8 (C$_{ar}$), 131.0 (CH$_{ar}$), 130.3 (C$_{ar}$), 115.0 (CH$_{ar}$), 74.1 (-OCHCH$_3$), 63.3 (-CH$_2$SO$_2$-), 56.2 (-OCH$_3$), 19.5 (-CH$_3$).

LRMS (ES +ve) *m/z* (relative intensity) 539 (100) $[2M+Na]^+$.

HRMS (ES +ve) Calcd for $C_{11}H_{14}SO_5Na$ 281.0454, found 281.0450.

(3S)-1-Diazo-3-methoxy-butan-2-one (10.19)



10.19

$C_5H_8N_2O_2$

m.w. = 128.13 g/mol

Yellow oil

The title compound was prepared according to the method outlined for **10.6**, whereby reaction of (S)-(-)-2-methoxypropionic acid (**10.18**) (1.87 g, 18.0 mmol) and oxalyl chloride (9.9 mL of a 2M sol, 19.8 mmol) under the described conditions provided the

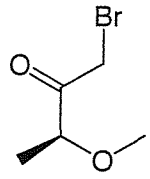
crude acid chloride (due to volatility problems the mixture was concentrated to approx. 5 mL). This was subsequently reacted with trimethylsilyl-diazomethane (10.8 mL, 21.6 mmol) to afford a crude yellow oil (3.1 g). Purification was accomplished by flash chromatography on pre-packed silica gel (4 x 12) eluting with Et_2O/petrol (1:19) to Et_2O/petrol (1:1) in 5 % increment rises (100 mL each) to give the title compound **10.19** (1.73 g, 13.5 mmol, 75 % from acid **10.18**) as a bright yellow oil.

FT-IR ν_{max} (neat) 2101 s, 1631 s, 1335 s, 1093 s cm^{-1}.

^{1}H NMR (250 MHz) δ 5.73 (1H, br s, -C**H**N_2) 3.75 (1H, q, *J* = 6.6 Hz, -C**H**CH_3), 3.39 (3H, s, -OC**H**$_3$), 1.33 (3H, d, *J* = 6.8 Hz, -CHC**H**$_3$).

^{13}C NMR (63 MHz) δ 198.0 (**C**O), 82.5 (-O**C**HCH_3), 58.1 (-O**C**H_3), 52.2 (-**C**HN_2), 18.7 (-**C**H_3).

(3S)-1-Bromo-3-methoxy-butan-2-one (10.20)



10.20

$C_5H_9O_2Br$

m.w. = 181.03 g/mol

Pale yellow oil

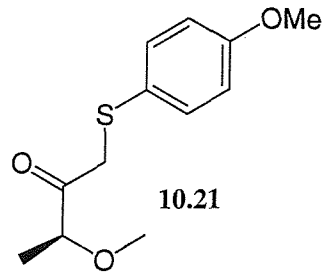
The title compound was prepared according to the method outlined for **10.7**, whereby diazoketone **10.19** (1.0 g, 7.8 mmol) and hydrobromic acid (1.1 mL of a 48 % wt. sol in H_2O, 9.4 mmol) were reacted together under the described conditions to give the title compound **10.20** (810 mg, 4.5 mmol, 57 %) as a pale yellow oil (volatility problems lowered yield) - this material was used crude in subsequent reactions.

FT-IR ν_{max} (neat) 2927 m, 1737 m, 1727 m, 1456 m, 1374 m, 1199 m, 1108 s cm^{-1}.

^{1}H NMR (250 MHz) δ 4.21 (1H, d, *J* = 13.7 Hz, -CH**H**Br), 4.15 (1H, d, *J* = 13.7 Hz, -CH**H**Br), 4.02 (1H, q, *J* = 6.8 Hz, -C**H**CH_3), 3.41 (3H, s, -OC**H**$_3$), 1.37 (3H, d, *J* = 6.8 Hz, -CHC**H**$_3$).

^{13}C NMR (63 MHz) δ 203.7 (**C**O), 81.6 (-O**C**HCH_3), 58.1 (-O**C**H_3), 32.1 (-**C**H_2Br), 17.2 (-CH**C**H_3).

(3S)-3-Methoxy-1-(4-methoxyphenylsulfanyl)-butan-2-one (10.21)



10.21

$C_{12}H_{16}SO_3$

m.w. = 240.32 g/mol

Pale yellow oil

The title compound was prepared according to the method outlined for **10.14**, whereby reaction of bromoketone **10.20** (721 mg, 4.0 mmol) and 4-methoxybenzenethiol (0.49 mL, 4.0 mmol) and work-up under the conditions described gave a crude yellow oil (919 mg). Purification was accomplished by flash chromatography on pre-packed silica gel (3 x 7) eluting with EtOAc/petrol (1:1) to yield the title compound **10.21** (888 mg, 3.7 mmol, 93 %) as a pale yellow oil.

FT-IR ν_{max} (neat) 1717 m, 1592 m, 1494 s, 1286 m, 1246 s, 1109 m, 1031 m cm^{-1}.

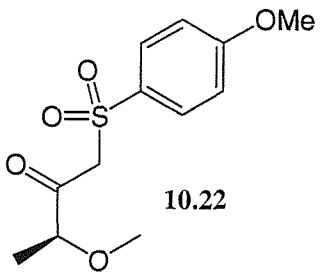
^{1}H NMR (400 MHz) δ 7.37 (2H, d, *J* = 8.8 Hz, Ph**H**), 6.83 (2H, d, *J* = 8.8 Hz, Ph**H**), 3.93 (1H, q, *J* = 6.8 Hz, -C**H**CH_3), 3.78 (1H, obsc d, *J* = 14.8 Hz, -C**H**HS-), 3.78 (3H, s, -OC**H**$_3$), 3.72 (1H, d, *J* = 14.8 Hz, -CH**H**S-), 3.32 (3H, s, -CHOC**H**$_3$), 1.28 (3H, d, *J* = 7.0 Hz, -CHC**H**$_3$).

^{13}C NMR (100 MHz) δ 206.9 (**C**O), 160.0 (**C**$_{ar}$), 134.4 (**C**H$_{ar}$), 125.4 (**C**$_{ar}$), 115.2 (**C**H$_{ar}$), 81.7 (-O**C**HCH$_3$), 58.0 (-CHO**C**H$_3$), 55.7 (-O**C**H$_3$), 42.1 (-**C**H$_2$S-), 17.1 (-CH**C**H$_3$).

LRMS (CI, NH_3) *m/z* (relative intensity) 241 (26) $[M+H]^+$, 258 (6) $[M+NH_4]^+$, 209 (16) $[M+H(-MeOH)]^+$, 59 (100) $[CH_3CHOCH_3]^+$.

HRMS (ES +ve) Calcd for $C_{12}H_{16}SO_3Na$ 263.0712, found 263.0711.

(3S)-3-Methoxy-1-(4-methoxyphenylsulfonyl)-butan-2-one (10.22)



10.22

$C_{12}H_{16}SO_5$

m.w. = 272.32 g/mol

Colourless oil

The title compound was prepared according to the method outlined for **10.15**, whereby reaction of sulfide **10.21** (850 mg, 3.54 mmol) and *m*-chloroperoxybenzoic acid (2.18 g, 70%, 8.84 mmol) and work-up under the conditions described gave a crude yellow oil

(1.01 g). Purification was accomplished by flash chromatography on pre-packed silica gel (4 x 8) eluting with EtOAc/petrol (1:9) to EtOAc/petrol (1:1) in 10 % increment rises (100 mL each) to yield the title compound **10.22** (823 mg, 3.02 mmol, 85 %) as a colourless oil.

FT-IR ν_{max} (neat) 1726 m, 1594 m, 1498 m, 1323 m, 1261 m, 1147 s, 1023 m cm^{-1}.

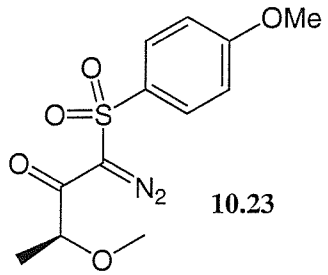
^{1}H NMR (400 MHz) δ 7.84 (2H, d, *J* = 8.9 Hz, PhH), 7.02 (2H, d, *J* = 8.9 Hz, PhH), 4.47 (1H, d, *J* = 14.2 Hz, -CHHSO$_2$-), 4.27 (1H, d, *J* = 14.2 Hz, -CHHSO$_2$-), 3.89 (1H, obsc q, *J* = 6.7 Hz, -CHCH$_3$), 3.88 (3H, s, -OCH$_3$), 3.36 (3H, s, -CHOCH$_3$), 1.26 (3H, d, *J* = 6.7 Hz, -CHCH$_3$).

^{13}C NMR (100 MHz) δ 200.7 (CO), 164.5 (C$_{ar}$), 131.1 (CH$_{ar}$), 114.8 (CH$_{ar}$), 82.6 (-OCHCH$_3$), 62.2 (-CH$_2$SO$_2$-), 58.0 (-CHOCH$_3$), 56.1 (-OCH$_3$), 15.9 (-CHCH$_3$).

LRMS (CI, NH_3) *m/z* (relative intensity) 273 (6) $[M+H]^+$, 290 (27) $[M+NH_4]^+$, 59 (100) $[CH_3CHOCH_3]^+$.

HRMS (ES +ve) Calcd for $C_{12}H_{16}SO_5Na$ 295.0611, found 295.0610.

(3S)-1-Diazo-3-methoxy-1-(4-methoxyphenylsulfonyl)-butan-2-one (10.23)



10.23

$C_{12}H_{14}N_2SO_5$
m.w. = 298.32 g/mol
Yellow solid

The title compound was prepared according to the method outlined for **10.16**, whereby reaction of sulphone **10.22** (750 mg, 2.75 mmol) and 4-carboxybenzenesulfonyl azide (751 mg, 3.30 mmol) and work-up under the conditions described gave a crude yellow oil (1.01 g). Purification was accomplished by flash chromatography on pre-packed silica gel (2.7 x 7) eluting with EtOAc/petrol (1:1) to give the title compound **10.23** (785 mg, 2.63 mmol, 96 %) as a powdery yellow solid.

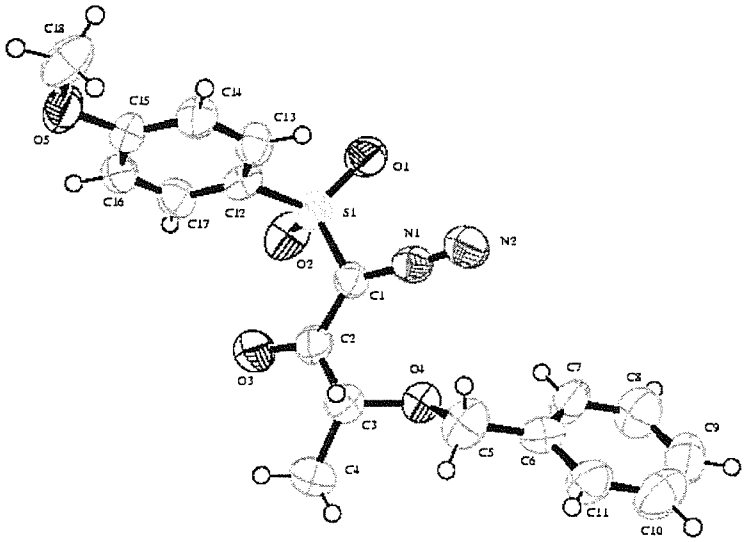
MP 48-50 °C.

FT-IR ν_{max} (neat) 2118 s, 1650 s, 1591 s, 1495 m, 1308 s, 1258 s, 1142 s cm^{-1}.

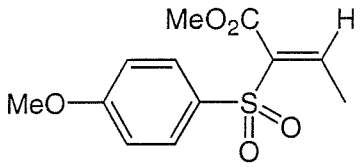
^{1}H NMR (250 MHz) δ 7.98 (2H, d, *J* = 8.9 Hz, PhH); 7.00 (2H, d, *J* = 8.9 Hz, PhH), 3.93 (1H, q, *J* = 6.8 Hz, -CHCH$_3$), 3.88 (3H, s, -OCH$_3$), 3.31 (3H, s, -CHOCH$_3$), 1.29 (3H, d, *J* = 6.8 Hz, -CHCH$_3$).

^{13}C NMR (63 MHz) δ 190.4 (**C**O), 164.4 (**C**$_{ar}$), 133.5 (**C**$_{ar}$), 130.8 (**C**H$_{ar}$), 114.6 (**C**H$_{ar}$), 83.2 (-O**C**HCH$_3$), 57.6 (-CHO**C**H$_3$), 56.1 (-O**C**H$_3$), 17.2 (-CH**C**H$_3$), (no **C**=N$_2$ observed).

X-ray structure



2-(4-Methoxybenzenesulfonyl)-but-2-enoic acid methyl ester (10.25)



10.25

$C_{12}H_{14}SO_5$

m.w. = 270.25 g/mol

Colourless oil

A solution of diazo sulfone **10.23** (30 mg, 0.10 mmol) in toluene (1 mL) was heated to reflux for 60 min, cooled and concentrated *in vacuo*. Purification was accomplished by flash chromatography on pre-packed silica gel (2.7 x 3) eluting with EtOAc/petrol (1:19) increasing to EtOAc/petrol (1:1) in 5 % increment rises (10 mL each) to give the title compound **10.25** (23 mg, 0.08 mmol, 84 %) as a colourless oil (~18:1 mixture of *Z*/*E* isomers, respectively).

FT-IR ν_{max} (neat) 1721 s, 1592 s, 1297 s, 1257 s, 1227 s, 1146 s, 1125 s cm^{-1}.

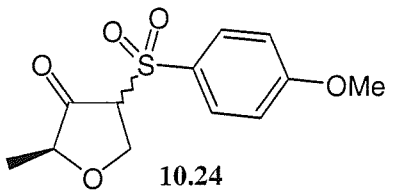
^{1}H NMR (250 MHz) δ 7.82 (2H, d, *J* = 9.0 Hz, Ph**H**), 7.65 (1H, q, *J* = 7.3 Hz, -C=C**H**), 6.99 (2H, d, *J* = 9.0 Hz, Ph**H**), 3.89 (3H, s, -OC**H**$_3$), 3.74 (3H, s, -CO$_2$C**H**$_3$), 2.20 (3H, d, *J* = 7.3 Hz, -CC**H**$_3$).

^{13}C NMR (63 MHz) δ 164.0 (**C**$_{ar}$), 162.5 (**C**O), 151.0 (-C=**C**H), 137.6 (-**C**=CH), 131.9 (**C**$_{ar}$), 131.3 (**C**H$_{ar}$), 114.4 (**C**H$_{ar}$), 56.0 (-O**C**H$_3$), 52.6 (-CO$_2$**C**H$_3$), 16.6 (-**C**H$_3$).

LRMS (CI, NH_3) *m/z* (relative intensity) 271 (100) $[M+H]^+$, 288 (77) $[M+NH_4]^+$.

HRMS (ES +ve) Calcd for $C_{12}H_{14}SO_5Na$ 293.0454, found 293.0452.

(2S)-4-(4-Methoxybenzenesulfonyl)-2-methyl-dihydrofuran-3-one (10.24)



10.24

$C_{12}H_{14}SO_5$

m.w. = 270.25 g/mol

Colourless oil

To a solution of diazo sulphone **10.23** (149 mg, 0.50 mmol) in CH_2Cl_2 (5 mL) at room temperature was added dirhodium tetraacetate (33 mg, 0.075 mmol) and the reaction stirred for 3 days. The mixture was diluted with CH_2Cl_2 (20 mL) and poured onto water (20 mL). The organic layer was separated and the aqueous extracted with CH_2Cl_2 (3 x 25 mL), the organic extracts combined, washed with brine (25 mL), dried with $MgSO_4$ and concentration *in vacuo* to yield a brown oil (131 mg). Purification was accomplished by flash chromatography on pre-packed silica gel (2.7 x 5) eluting with EtOAc/petrol (1:19) increasing to EtOAc/petrol (1:1) in 5 % increment rises (20 mL each) to give the title compound **10.24** (61 mg, 0.23 mmol, 45 %) as a colourless oil (~1:1 mixture of diastereoisomers), along with alcohol **10.17** (16 mg, 0.06 mmol, 12 %) and alkene **10.25** (8 mg, 0.03 mmol, 6 %). Data for **10.24** (both isomers reported together).

FT-IR ν_{max} (neat) 1763 m, 1594 m, 1497 m, 1322 m, 1264 m, 1144 s cm^{-1}.

^{1}H NMR (400 MHz) δ 7.85-7.78 (2 x 2H, m, PhH), 7.06-7.01 (2 x 2H, m, PhH), 4.88 (1H, dd, *J* = 11.6, 3.5 Hz), 4.60-4.52 (2H, m), 4.34 (1H, dd, *J* = 11.5, 7.3 Hz), 4.06 (1H, t, *J* = 8.3 Hz), 3.97 (1H, dd, *J* = 7.3, 3.3 Hz), 3.91 and 3.90 (2 x 3H, s, -OC**H**$_3$), 3.86 (2 x 1H, obsc q, *J* = 6.8 Hz, -C**H**CH$_3$), 1.25 (3H, d, *J* = 6.8 Hz, -CHC**H**$_3$), and 1.13 (3H, d, *J* = 7.0 Hz, -CHC**H**$_3$).

^{13}C NMR (100 MHz) δ 205.3 and 204.3 (CO), 164.9 (**C**$_{ar}$), 132.0 and 131.9 (**C**H$_{ar}$), 129.5 and 129.3 (**C**$_{ar}$), 114.9 (**C**H$_{ar}$), 78.0 and 77.4 (-O**C**HCH$_3$), 69.3 and 68.2 (-**C**HSO$_2$-), 65.9 and 64.7 (-**C**H$_2$-), 56.2 (-O**C**H$_3$), 15.4 and 15.3 (-**C**H$_3$).

LRMS (CI, NH_3) *m/z* (relative intensity) 271 (3) $[M+H]^+$, 288 (33) $[M+NH_4]^+$, 99 (100).

HRMS (ES +ve) Calcd for $C_{12}H_{14}SO_5Na$ 293.0454, found 293.0453.

Chapter 13

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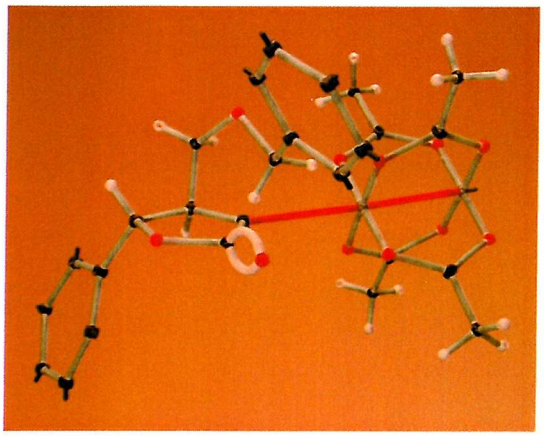
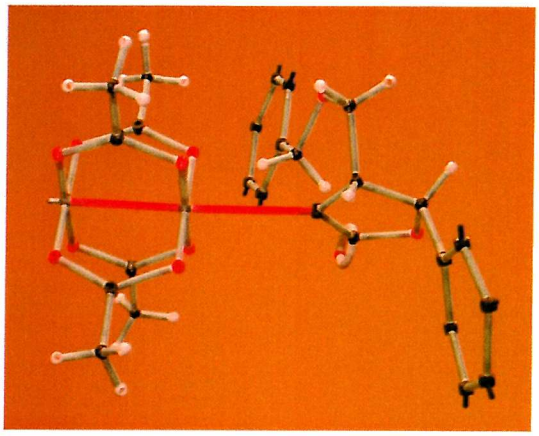
Appendix 1

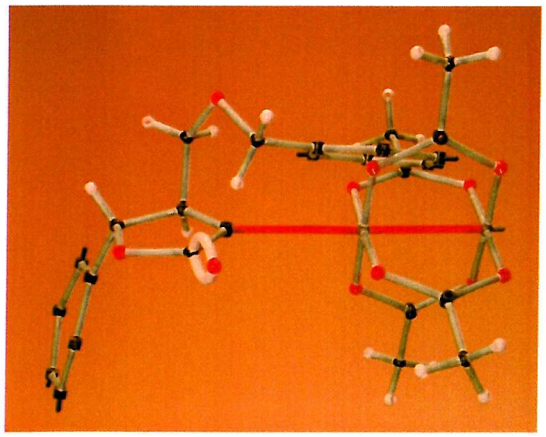
Two pseudo-transition states for the dirhodium (II) tetraacetate catalysed C-H insertion reaction of diazo-lactone **5.18**.

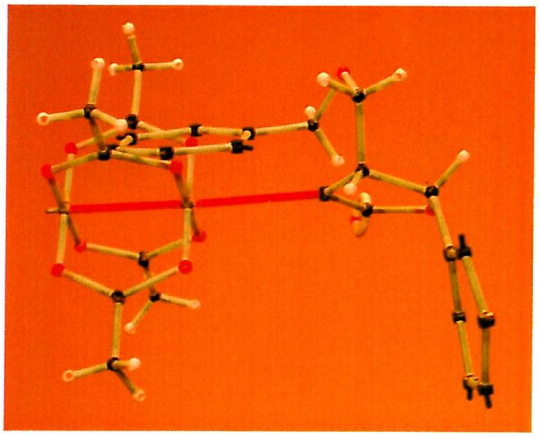
Endo- selectivity:





Exo- selectivity:





Appendix 2

Unpublished X-Ray Crystallographic Data

X-Ray Data for **6.12**

Table 1. Crystal data and structure refinement.

Identification code	**01sot063**	
Empirical formula	$C_{19}H_{19}NO_2$	
Formula weight	293.35	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 10.3182(3) Å	α = 90°
	b = 21.7444(7) Å	β = 96.89(2)°
	c = 6.7000(2) Å	γ = 90°
Volume	1492.36(8) Å^3	
Z	4	
Density (calculated)	1.306 Mg / m^3	
Absorption coefficient	0.084 mm^{-1}	
F(000)	624	
Crystal	Plate; colourless	
Crystal size	0.40 × 0.40 × 0.20 mm^3	
θ range for data collection	3.20 – 25.99°	
Index ranges	$-12 \le h \le 12$, $-26 \le k \le 26$, $-8 \le l \le 8$	
Reflections collected	7863	
Independent reflections	2882 [R_{int} = 0.0487]	
Completeness to θ = 25.99°	98.3 %	
Max. and min. transmission	0.9833 and 0.9670	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2882 / 0 / 200	
Goodness-of-fit on F^2	0.977	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0445, $wR2$ = 0.1084	
R indices (all data)	$R1$ = 0.0697, $wR2$ = 0.1182	
Extinction coefficient	0.016(3)	
Largest diff. peak and hole	0.235 and –0.306 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**: *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:

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 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	3829(1)	5736(1)	9113(2)	25(1)	1
O2	1180(1)	5332(1)	4117(2)	26(1)	1
N1	1993(1)	4557(1)	6228(2)	21(1)	1
C1	1580(1)	5141(1)	5804(2)	20(1)	1
C2	1663(1)	5497(1)	7757(2)	22(1)	1
C3	2156(1)	5035(1)	9428(2)	22(1)	1
C4	2563(1)	4458(1)	8301(2)	20(1)	1
C5	2036(2)	4097(1)	4687(2)	29(1)	1
C6	3308(2)	5362(1)	10601(2)	27(1)	1
C7	2709(1)	6017(1)	8033(2)	22(1)	1
C8	2145(1)	3862(1)	9201(2)	20(1)	1

C9	3081(2)	3474(1)	10181(2)	25(1)	1
C10	2715(2)	2951(1)	11178(2)	31(1)	1
C11	1409(2)	2815(1)	11184(2)	31(1)	1
C12	471(2)	3197(1)	10191(2)	27(1)	1
C13	828(2)	3716(1)	9185(2)	23(1)	1
C14	3048(1)	6340(1)	6180(2)	22(1)	1
C15	4288(2)	6303(1)	5569(2)	25(1)	1
C16	4589(2)	6634(1)	3915(2)	28(1)	1
C17	3662(2)	7005(1)	2852(2)	29(1)	1
C18	2424(2)	7037(1)	3439(2)	27(1)	1
C19	2116(2)	6706(1)	5073(2)	25(1)	1

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

O1–C7	1.4259(17)
O1–C6	1.4387(18)
O2–C1	1.2291(17)
N1–C1	1.3585(19)
N1–C5	1.4413(19)
N1–C4	1.4571(18)
C1–C2	1.515(2)
C2–C3	1.545(2)
C2–C7	1.559(2)
C2–H2	1.0000
C3–C6	1.521(2)
C3–C4	1.548(2)
C3–H3	1.0000
C4–C8	1.514(2)
C4–H4	1.0000
C5–H5A	0.9800
C5–H5B	0.9800
C5–H5C	0.9800
C6–H6A	0.9900
C6–H6B	0.9900
C7–C14	1.503(2)
C7–H7	1.0000
C8–C9	1.387(2)
C8–C13	1.393(2)
C9–C10	1.393(2)
C9–H9	0.9500
C10–C11	1.380(2)
C10–H10	0.9500
C11–C12	1.383(2)
C11–H11	0.9500
C12–C13	1.388(2)
C12–H12	0.9500
C13–H13	0.9500
C14–C19	1.392(2)
C14–C15	1.392(2)
C15–C16	1.388(2)
C15–H15	0.9500
C16–C17	1.382(2)
C16–H16	0.9500
C17–C18	1.383(2)
C17–H17	0.9500
C18–C19	1.379(2)
C18–H18	0.9500
C19–H19	0.9500
C7–O1–C6	104.28(11)
C1–N1–C5	122.28(12)
C1–N1–C4	114.68(12)
C5–N1–C4	122.46(12)
O2–C1–N1	124.87(14)
O2–C1–C2	126.78(14)
N1–C1–C2	108.33(12)
C1–C2–C3	105.77(12)
C1–C2–C7	116.15(13)
C3–C2–C7	102.91(11)
C1–C2–H2	110.5
C3–C2–H2	110.5
C7–C2–H2	110.5
C6–C3–C2	103.79(12)
C6–C3–C4	113.00(13)
C2–C3–C4	105.02(11)
C6–C3–H3	111.5
C2–C3–H3	111.5
C4–C3–H3	111.5
N1–C4–C8	113.87(12)
N1–C4–C3	104.08(11)
C8–C4–C3	113.11(12)
N1–C4–H4	108.5
C8–C4–H4	108.5
C3–C4–H4	108.5
N1–C5–H5A	109.5
N1–C5–H5B	109.5
H5A–C5–H5B	109.5
N1–C5–H5C	109.5
H5A–C5–H5C	109.5
H5B–C5–H5C	109.5
O1–C6–C3	103.88(11)
O1–C6–H6A	111.0
C3–C6–H6A	111.0
O1–C6–H6B	111.0
C3–C6–H6B	111.0
H6A–C6–H6B	109.0
O1–C7–C14	111.43(12)
O1–C7–C2	104.82(11)
C14–C7–C2	117.83(11)
O1–C7–H7	107.4
C14–C7–H7	107.4
C2–C7–H7	107.4
C9–C8–C13	119.21(15)
C9–C8–C4	119.60(13)
C13–C8–C4	121.04(13)
C8–C9–C10	120.65(15)
C8–C9–H9	119.7
C10–C9–H9	119.7
C11–C10–C9	119.84(15)
C11–C10–H10	120.1
C9–C10–H10	120.1
C10–C11–C12	119.78(16)
C10–C11–H11	120.1
C12–C11–H11	120.1
C11–C12–C13	120.73(15)
C11–C12–H12	119.6
C13–C12–H12	119.6

C12–C13–C8	119.78(14)	C18–C17–H17	120.4
C12–C13–H13	120.1	C19–C18–C17	120.52(15)
C8–C13–H13	120.1	C19–C18–H18	119.7
C19–C14–C15	118.50(15)	C17–C18–H18	119.7
C19–C14–C7	119.52(14)	C18–C19–C14	120.78(15)
C15–C14–C7	121.94(13)	C18–C19–H19	119.6
C16–C15–C14	120.42(14)	C14–C19–H19	119.6
C16–C15–H15	119.8		
C14–C15–H15	119.8	Symmetry transformations used to generate equivalent atoms:	
C17–C16–C15	120.51(15)		
C17–C16–H16	119.7		
C15–C16–H16	119.7		
C16–C17–C18	119.25(15)		
C16–C17–H17	120.4		

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H2	786	5661	7976	26	1
H3	1463	4937	10301	26	1
H4	3535	4456	8346	24	1
H5A	1569	4248	3422	43	1
H5B	1622	3719	5089	43	1
H5C	2947	4012	4503	43	1
H6A	3019	5620	11682	32	1
H6B	3965	5063	11204	32	1
H7	2388	6336	8930	27	1
H9	3980	3565	10172	30	1
H10	3362	2690	11853	37	1
H11	1155	2460	11867	38	1
H12	−427	3102	10198	32	1
H13	177	3972	8487	27	1
H15	4933	6049	6288	30	1
H16	5439	6606	3512	34	1
H17	3874	7236	1731	35	1
H18	1780	7290	2711	33	1
H19	1258	6727	5446	30	1

X-Ray Data for **6.16**

Table 1. Crystal data and structure refinement.

Identification code	**01SOT064**	
Empirical formula	$C_{12}H_{12}N_2O_3$	
Formula weight	232.24	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 10.5205(2) Å	
	b = 8.96580(10) Å	β = 90.572(3)°
	c = 11.9767(2) Å	
Volume	1129.64(3) $Å^3$	
Z	4	
Density (calculated)	1.366 Mg / m^3	
Absorption coefficient	0.100 mm^{-1}	
F(000)	488	
Crystal	Yellow plate	
Crystal size	0.10 × 0.08 × 0.04 mm^3	
θ range for data collection	2.99 – 25.02°	
Index ranges	$-12 \le h \le 12$, $-10 \le k \le 10$, $-14 \le l \le 14$	
Reflections collected	8132	

Independent reflections	1979 [R_{int} = 0.0902]
Completeness to θ = 25.02°	99.0 %
Max. and min. transmission	0.9960 and 0.9901
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1979 / 0 / 203
Goodness-of-fit on F^2	0.995
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0427, $wR2$ = 0.0875
R indices (all data)	$R1$ = 0.0884, $wR2$ = 0.1048
Extinction coefficient	0.015(3)
Largest diff. peak and hole	0.196 and −0.208 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* 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: All hydrogen atoms were located from the difference map and fully refined.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 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.*
N1	4161(2)	2519(2)	538(2)	32(1)	1
N2	3243(2)	2501(2)	33(2)	49(1)	1
O1	4239(1)	5555(2)	1482(1)	27(1)	1
O2	6810(1)	1523(2)	2147(1)	31(1)	1
O3	5391(1)	−114(2)	1458(1)	36(1)	1
C1	7061(2)	3121(3)	2114(2)	32(1)	1
C2	5744(2)	1167(3)	1551(2)	27(1)	1
C3	5221(2)	2527(2)	1125(2)	26(1)	1
C4	5978(2)	3877(2)	1435(2)	26(1)	1
C5	5272(2)	4998(3)	2133(2)	27(1)	1
C6	3520(2)	6627(3)	2095(2)	30(1)	1
C7	2402(2)	7090(2)	1388(2)	26(1)	1
C8	1303(2)	6239(3)	1355(2)	33(1)	1
C9	282(2)	6650(3)	684(2)	39(1)	1
C10	363(2)	7912(3)	30(2)	39(1)	1
C11	1445(2)	8767(3)	57(2)	35(1)	1
C12	2460(2)	8371(3)	738(2)	29(1)	1

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

N1–N2	1.134(2)
N1–C3	1.312(2)
O1–C5	1.422(2)
O1–C6	1.430(2)
O2–C2	1.362(2)
O2–C1	1.458(3)
O3–C2	1.212(2)
C1–C4	1.549(3)
C2–C3	1.430(3)
C3–C4	1.494(3)
C4–C5	1.508(3)
C6–C7	1.501(3)
C7–C8	1.386(3)
C7–C12	1.388(3)
C8–C9	1.385(3)
C9–C10	1.379(4)
C10–C11	1.372(3)
C11–C12	1.384(3)
N2–N1–C3	179.5(2)
C5–O1–C6	111.05(15)
C2–O2–C1	111.39(15)
O2–C1–C4	108.16(16)
O3–C2–O2	121.36(18)
O3–C2–C3	131.22(19)
O2–C2–C3	107.42(18)
N1–C3–C2	120.53(18)
N1–C3–C4	125.87(18)
C2–C3–C4	113.59(17)
C3–C4–C5	114.42(17)
C3–C4–C1	99.41(17)
C5–C4–C1	111.40(17)
O1–C5–C4	107.95(16)
O1–C6–C7	108.16(16)
C8–C7–C12	118.7(2)
C8–C7–C6	120.9(2)
C12–C7–C6	120.43(19)
C9–C8–C7	120.8(2)

C10–C9–C8	119.7(2)	C11–C12–C7	120.4(2)
C11–C10–C9	120.1(2)		
C10–C11–C12	120.3(2)		

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}
N1	33(1)	26(1)	37(1)	−4(1)	−5(1)	2(1)
N2	41(1)	41(1)	63(2)	−9(1)	−25(1)	5(1)
O1	29(1)	27(1)	25(1)	−2(1)	−5(1)	8(1)
O2	26(1)	30(1)	36(1)	2(1)	−5(1)	5(1)
O3	36(1)	28(1)	44(1)	0(1)	1(1)	2(1)
C1	26(1)	30(1)	39(1)	−4(1)	−5(1)	3(1)
C2	27(1)	30(1)	25(1)	−1(1)	4(1)	3(1)
C3	21(1)	28(1)	27(1)	0(1)	−5(1)	3(1)
C4	23(1)	27(1)	28(1)	0(1)	−1(1)	0(1)
C5	26(1)	28(1)	27(1)	−1(1)	−6(1)	3(1)
C6	35(1)	30(1)	26(1)	−4(1)	−2(1)	9(1)
C7	29(1)	27(1)	21(1)	−3(1)	2(1)	4(1)
C8	36(1)	27(1)	36(1)	−3(1)	7(1)	2(1)
C9	26(1)	45(2)	45(1)	−21(1)	−1(1)	1(1)
C10	34(1)	54(2)	30(1)	−12(1)	−8(1)	18(1)
C11	41(1)	39(2)	26(1)	2(1)	2(1)	14(1)
C12	28(1)	31(1)	28(1)	−4(1)	2(1)	3(1)

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

Atom	x	y	z	U_{eq}	*S.o.f.*
H1A	7880(20)	3240(20)	1753(17)	34(6)	1
H1B	7090(20)	3420(30)	2910(20)	42(6)	1
H4	6320(20)	4380(20)	773(19)	38(6)	1
H5A	5865(19)	5840(20)	2390(17)	30(6)	1
H5B	4938(19)	4430(20)	2831(19)	35(6)	1
H6A	3227(19)	6140(20)	2799(19)	35(6)	1
H6B	4093(19)	7540(20)	2250(17)	35(6)	1
H8	1260(20)	5340(30)	1786(18)	39(6)	1
H9	−470(20)	6060(30)	680(20)	50(7)	1
H10	−360(20)	8230(30)	−470(20)	53(7)	1
H11	1510(20)	9660(30)	−390(20)	49(7)	1
H12	3204(19)	8970(20)	808(16)	22(5)	1

X-Ray Data for **6.17**

Table 1. Crystal data and structure refinement.

Identification code	**01SOT062**	
Empirical formula	$C_{12}H_{12}O_3$	
Formula weight	204.22	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 15.1406(3) Å	
	b = 6.0060(2) Å	β = 111.100(3)°
	c = 11.2672(2) Å	
Volume	955.88(4) $Å^3$	
Z	4	
Density (calculated)	1.419 Mg / m^3	
Absorption coefficient	0.102 mm^{-1}	

F(000)	432
Crystal	Colourless block
Crystal size	$0.10 \times 0.10 \times 0.10$ mm^3
θ range for data collection	3.62 – 25.02°
Index ranges	$-17 \le h \le 18$, $-7 \le k \le 7$, $-13 \le l \le 12$
Reflections collected	5946
Independent reflections	1677 [$R_{int} = 0.1001$]
Completeness to $\theta = 25.02°$	99.6 %
Max. and min. transmission	0.9899 and 0.9899
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1677 / 0 / 185
Goodness-of-fit on F^2	0.964
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0483$, $wR2 = 0.1043$
R indices (all data)	$R1 = 0.0851$, $wR2 = 0.1209$
Extinction coefficient	0.011(3)
Largest diff. peak and hole	0.228 and –0.305 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* 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: All hydrogen atoms were located from the difference map and fully refined.

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	2965(2)	6804(4)	6532(2)	24(1)	1
C2	3829(2)	6167(4)	6206(2)	23(1)	1
C3	3992(2)	7793(4)	5259(2)	25(1)	1
C4	3799(2)	4354(4)	4282(2)	22(1)	1
C5	3519(2)	4031(4)	5429(2)	19(1)	1
C6	2421(2)	3928(4)	5132(2)	20(1)	1
C7	1795(2)	3327(4)	3806(2)	19(1)	1
C8	1586(2)	4901(4)	2837(2)	21(1)	1
C9	1009(2)	4375(4)	1606(2)	23(1)	1
C10	619(2)	2265(4)	1333(2)	24(1)	1
C11	811(2)	687(4)	2284(2)	23(1)	1
C12	1400(2)	1204(4)	3517(2)	22(1)	1
O1	2185(1)	6116(2)	5432(1)	23(1)	1
O2	4102(1)	6463(3)	4243(2)	25(1)	1
O3	3795(1)	3010(3)	3485(2)	30(1)	1

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

C1–O1	1.431(3)	C8–C9	1.384(3)
C1–C2	1.529(3)	C9–C10	1.385(3)
C2–C5	1.529(3)	C10–C11	1.381(3)
C2–C3	1.530(3)	C11–C12	1.389(3)
C3–O2	1.454(3)	O1–C1–C2	103.31(18)
C4–O3	1.205(3)	C1–C2–C5	103.55(19)
C4–O2	1.353(3)	C1–C2–C3	112.0(2)
C4–C5	1.511(3)	C5–C2–C3	103.26(19)
C5–C6	1.574(3)	O2–C3–C2	106.93(19)
C6–O1	1.434(3)	O3–C4–O2	121.0(2)
C6–C7	1.497(3)	O3–C4–C5	128.5(2)
C7–C8	1.392(3)	O2–C4–C5	110.5(2)
C7–C12	1.396(3)	C4–C5–C2	105.02(19)
		C4–C5–C6	115.10(19)
		C2–C5–C6	103.77(18)
		O1–C6–C7	109.50(18)

O1–C6–C5	104.33(17)	C11–C10–C9	120.1(2)
C7–C6–C5	117.53(19)	C10–C11–C12	120.2(2)
C8–C7–C12	118.6(2)	C11–C12–C7	120.3(2)
C8–C7–C6	120.2(2)	C1–O1–C6	105.71(17)
C12–C7–C6	121.1(2)	C4–O2–C3	110.66(18)
C9–C8–C7	121.0(2)		
C8–C9–C10	119.7(2)		

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

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	22(1)	31(1)	22(1)	−5(1)	11(1)	1(1)
C2	18(1)	28(1)	22(1)	−2(1)	7(1)	2(1)
C3	19(1)	27(1)	31(2)	−2(1)	12(1)	2(1)
C4	10(1)	31(1)	25(1)	−1(1)	7(1)	3(1)
C5	15(1)	21(1)	19(1)	1(1)	5(1)	2(1)
C6	19(1)	23(1)	23(1)	2(1)	13(1)	0(1)
C7	13(1)	25(1)	23(1)	−3(1)	13(1)	1(1)
C8	16(1)	25(1)	27(1)	−1(1)	12(1)	2(1)
C9	22(1)	29(1)	22(1)	5(1)	12(1)	6(1)
C10	20(1)	31(1)	21(1)	−4(1)	9(1)	5(1)
C11	19(1)	25(1)	28(1)	−6(1)	12(1)	−1(1)
C12	19(1)	25(1)	26(1)	3(1)	15(1)	3(1)
O1	19(1)	30(1)	23(1)	−4(1)	11(1)	2(1)
O2	22(1)	30(1)	28(1)	2(1)	15(1)	0(1)
O3	19(1)	45(1)	30(1)	−13(1)	13(1)	0(1)

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

Atom	x	y	z	U_{eq}	*S.o.f.*
H1A	2896(16)	8460(40)	6660(20)	18(6)	1
H1B	2958(16)	5940(40)	7320(20)	21(6)	1
H2	4415(18)	6010(40)	6920(20)	28(7)	1
H3A	4572(19)	8740(40)	5610(20)	34(7)	1
H3B	3413(17)	8800(30)	4864(19)	17(6)	1
H5	3848(15)	2730(30)	5900(20)	13(6)	1
H6	2354(16)	2900(30)	5770(20)	15(6)	1
H8	1845(16)	6440(40)	3020(20)	19(6)	1
H9	893(18)	5450(40)	940(20)	34(7)	1
H10	232(18)	1860(40)	480(20)	29(7)	1
H11	539(16)	−830(40)	2080(20)	19(6)	1
H12	1535(16)	50(30)	4190(20)	19(6)	1

X-Ray Data for **7.35**

Table 1. Crystal data and structure refinement.

Identification code	**01sot184**	
Empirical formula	$C_{13}H_{12}O_3$	
Formula weight	216.23	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 12.7786(2) Å	α = 90°
	b = 6.4780(2) Å	β = 109.2450(10)°
	c = 13.6922(3) Å	γ = 90°
Volume	1070.10(4) $Å^3$	
Z	4	

Density (calculated)	1.342 Mg / m^3
Absorption coefficient	0.095 mm^{-1}
F(000)	456
Crystal	Block; colourless
Crystal size	0.45 × 0.45 × 0.30 mm^3
θ range for data collection	3.05 – 27.48°
Index ranges	$-16 \le h \le 14$, $-8 \le k \le 8$, $-16 \le l \le 17$
Reflections collected	10973
Independent reflections	2327 [R_{int} = 0.0524]
Completeness to θ = 27.48°	94.6 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9720 and 0.9584
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2327 / 0 / 147
Goodness-of-fit on F^2	1.034
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0407, *wR2* = 0.1035
R indices (all data)	*R1* = 0.0505, *wR2* = 0.1100
Extinction coefficient	0.074(6)
Largest diff. peak and hole	0.233 and –0.191 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**: *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:

Chirality: C1 = R, C3 = S, C7 = R.

Table 2. Atomic coordinates [× 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.*
C6	8770(1)	–2980(2)	3845(1)	27(1)	1
C1	7926(1)	175(2)	4427(1)	23(1)	1
C2	9135(1)	674(2)	3494(1)	28(1)	1
C3	8514(1)	–1228(2)	3055(1)	24(1)	1
C4	8089(1)	–1718(2)	1928(1)	34(1)	1
C5	8231(2)	–143(3)	1199(1)	55(1)	1
C7	7791(1)	–1670(2)	3720(1)	23(1)	1
C8	6915(1)	1540(2)	4128(1)	22(1)	1
C9	6207(1)	1487(2)	4705(1)	24(1)	1
C10	5256(1)	2691(2)	4429(1)	27(1)	1
C11	5012(1)	3966(2)	3568(1)	29(1)	1
C12	5710(1)	4023(2)	2986(1)	28(1)	1
C13	6661(1)	2818(2)	3261(1)	24(1)	1
O1	8870(1)	1300(1)	4331(1)	27(1)	1
O2	9798(1)	1614(2)	3223(1)	45(1)	1
O3	7608(1)	–3344(2)	1650(1)	49(1)	1

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

C6–C7	1.4740(18)
C6–C3	1.5267(18)
C6–H6A	0.9900
C6–H6B	0.9900
C1–O1	1.4520(15)
C1–C8	1.5066(17)
C1–C7	1.5114(17)
C1–H1	1.0000
C2–O2	1.1967(17)
C2–O1	1.3599(17)
C2–C3	1.4816(18)
C3–C4	1.4917(18)
C3–C7	1.5223(18)
C4–O3	1.216(2)
C4–C5	1.480(2)
C5–H5A	0.9800
C5–H5B	0.9800
C5–H5C	0.9800
C7–H7	1.0000
C8–C9	1.3838(19)
C8–C13	1.3949(18)
C9–C10	1.3869(19)
C9–H9	0.9500
C10–C11	1.388(2)
C10–H10	0.9500

C11–C12	1.379(2)	H5A–C5–H5C	109.5
C11–H11	0.9500	H5B–C5–H5C	109.5
C12–C13	1.3881(19)	C6–C7–C1	117.87(11)
C12–H12	0.9500	C6–C7–C3	61.24(9)
C13–H13	0.9500	C1–C7–C3	105.69(10)
C7–C6–C3	60.94(8)	C6–C7–H7	119.1
C7–C6–H6A	117.7	C1–C7–H7	119.1
C3–C6–H6A	117.7	C3–C7–H7	119.1
C7–C6–H6B	117.7	C9–C8–C13	119.18(12)
C3–C6–H6B	117.7	C9–C8–C1	119.62(11)
H6A–C6–H6B	114.8	C13–C8–C1	121.17(12)
O1–C1–C8	110.14(10)	C8–C9–C10	120.64(12)
O1–C1–C7	105.20(10)	C8–C9–H9	119.7
C8–C1–C7	112.55(10)	C10–C9–H9	119.7
O1–C1–H1	109.6	C9–C10–C11	119.88(13)
C8–C1–H1	109.6	C9–C10–H10	120.1
C7–C1–H1	109.6	C11–C10–H10	120.1
O2–C2–O1	120.50(13)	C12–C11–C10	119.91(12)
O2–C2–C3	129.57(14)	C12–C11–H11	120.0
O1–C2–C3	109.92(11)	C10–C11–H11	120.0
C2–C3–C4	124.05(12)	C11–C12–C13	120.28(12)
C2–C3–C7	105.29(10)	C11–C12–H12	119.9
C4–C3–C7	119.55(11)	C13–C12–H12	119.9
C2–C3–C6	111.73(11)	C12–C13–C8	120.12(13)
C4–C3–C6	119.63(12)	C12–C13–H13	119.9
C7–C3–C6	57.82(8)	C8–C13–H13	119.9
O3–C4–C5	123.19(14)	C2–O1–C1	111.79(10)
O3–C4–C3	118.87(14)		
C5–C4–C3	117.87(14)	Symmetry transformations used to generate equivalent atoms:	
C4–C5–H5A	109.5		
C4–C5–H5B	109.5		
H5A–C5–H5B	109.5		
C4–C5–H5C	109.5		

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}
C6	24(1)	22(1)	30(1)	−2(1)	2(1)	0(1)
C1	22(1)	22(1)	22(1)	−1(1)	5(1)	−2(1)
C2	19(1)	28(1)	35(1)	3(1)	4(1)	0(1)
C3	18(1)	30(1)	22(1)	−2(1)	4(1)	0(1)
C4	21(1)	53(1)	26(1)	−8(1)	5(1)	11(1)
C5	74(1)	62(1)	29(1)	12(1)	18(1)	40(1)
C7	20(1)	21(1)	25(1)	−2(1)	6(1)	−3(1)
C8	22(1)	18(1)	22(1)	−4(1)	2(1)	−2(1)
C9	26(1)	22(1)	22(1)	−2(1)	5(1)	−2(1)
C10	26(1)	26(1)	30(1)	−6(1)	10(1)	−2(1)
C11	24(1)	22(1)	35(1)	−4(1)	3(1)	1(1)
C12	30(1)	20(1)	27(1)	1(1)	1(1)	−1(1)
C13	25(1)	22(1)	24(1)	−2(1)	6(1)	−4(1)
O1	20(1)	25(1)	33(1)	−7(1)	2(1)	−5(1)
O2	31(1)	42(1)	67(1)	7(1)	22(1)	−9(1)
O3	30(1)	78(1)	38(1)	−32(1)	8(1)	−10(1)

X-Ray Data for **7.49b**

Table 1. Crystal data and structure refinement.

Identification code	**02sot012**	
Empirical formula	$C_{20}H_{19}N_3O_2S$	
Formula weight	365.44	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 11.4941(9) Å	α = 90°
	b = 10.8158(7) Å	β = 98.028(4)°
	c = 14.7814(12) Å	γ = 90°
Volume	1819.6(2) Å^3	
Z	4	
Density (calculated)	1.334 Mg / m^3	
Absorption coefficient	0.197 mm^{-1}	
F(000)	768	
Crystal	Plate; Colourless	
Crystal size	0.25 × 0.20 × 0.03 mm^3	
θ range for data collection	3.06 – 25.02°	
Index ranges	$-13 \le h \le 13$, $-12 \le k \le 12$, $-17 \le l \le 17$	
Reflections collected	12831	
Independent reflections	3195 [R_{int} = 0.0881]	
Completeness to θ = 25.02°	99.4 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9941 and 0.9523	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3195 / 0 / 311	
Goodness-of-fit on F^2	0.960	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0488, $wR2$ = 0.0939	
R indices (all data)	$R1$ = 0.1069, $wR2$ = 0.1109	
Largest diff. peak and hole	0.265 and –0.238 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 [× 10^4], equivalent isotropic displacement parameters [Å^2 × 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	9576(1)	1432(1)	4019(1)	34(1)	1
N2	10127(2)	4494(2)	7080(2)	36(1)	1
O1	6317(2)	1501(2)	5366(1)	32(1)	1
O2	6287(2)	1801(2)	6853(1)	39(1)	1
N1	9428(2)	3990(2)	6457(2)	34(1)	1
C5	8423(2)	3415(2)	6732(2)	28(1)	1
C15	6166(2)	2827(2)	4018(2)	26(1)	1
C20	5235(2)	3465(3)	4294(2)	31(1)	1
N3	10849(2)	4982(2)	7540(2)	47(1)	1
C3	8076(2)	2526(3)	5123(2)	25(1)	1
C10	11772(3)	3720(3)	5361(2)	37(1)	1
C2	7798(2)	2747(2)	6072(2)	25(1)	1
C4	6928(2)	1950(3)	4637(2)	27(1)	1
C6	8180(3)	3590(3)	7686(2)	37(1)	1

C16	6421(3)	3000(3)	3136(2)	30(1)	1
C17	5763(3)	3799(3)	2541(2)	35(1)	1
C8	10537(3)	2763(3)	4011(2)	36(1)	1
C9	11567(2)	2749(3)	4751(2)	31(1)	1
C19	4567(3)	4259(3)	3695(2)	36(1)	1
C18	4828(3)	4421(3)	2819(2)	38(1)	1
C11	12705(3)	3707(3)	6063(2)	42(1)	1
C7	9119(2)	1650(3)	5130(2)	29(1)	1
C14	12345(2)	1746(3)	4864(2)	32(1)	1
C13	13269(3)	1730(3)	5564(2)	38(1)	1
C1	6747(2)	2015(3)	6186(2)	31(1)	1
C12	13444(3)	2705(3)	6167(2)	42(1)	1

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

S1–C7	1.808(3)
S1–C8	1.815(3)
N2–N3	1.129(3)
N2–N1	1.258(3)
O1–C1	1.362(3)
O1–C4	1.449(3)
O2–C1	1.205(3)
N1–C5	1.420(3)
C5–C2	1.339(4)
C5–C6	1.488(4)
C15–C20	1.381(4)
C15–C16	1.388(4)
C15–C4	1.510(4)
C20–C19	1.386(4)
C20–H20	0.90(2)
C3–C2	1.501(4)
C3–C7	1.527(4)
C3–C4	1.543(4)
C3–H3	0.94(2)
C10–C9	1.382(4)
C10–C11	1.384(4)
C10–H10	0.95(3)
C2–C1	1.473(4)
C4–H4	0.93(2)
C6–H6C	1.01(3)
C6–H6B	1.04(3)
C6–H6A	1.09(4)
C16–C17	1.381(4)
C16–H16	0.93(3)
C17–C18	1.378(4)
C17–H17	0.92(3)
C8–C9	1.496(4)
C8–H8A	1.00(3)
C8–H8B	0.89(3)
C9–C14	1.400(4)
C19–C18	1.381(4)
C19–H19	0.90(3)
C18–H18	0.95(3)
C11–C12	1.373(4)
C11–H11	1.00(3)
C7–H7B	0.99(2)
C7–H7A	0.94(3)
C14–C13	1.375(4)
C14–H14	0.96(3)
C13–C12	1.377(4)
C13–H13	0.89(3)
C12–H12	0.88(3)
C7–S1–C8	99.01(15)
N3–N2–N1	169.9(3)
C1–O1–C4	111.7(2)
N2–N1–C5	116.3(2)
C2–C5–N1	113.8(2)
C2–C5–C6	127.3(3)
N1–C5–C6	118.9(2)
C20–C15–C16	118.9(3)
C20–C15–C4	122.9(2)
C16–C15–C4	118.2(2)
C15–C20–C19	120.3(3)
C15–C20–H20	118.3(16)
C19–C20–H20	121.5(16)
C2–C3–C7	111.2(2)
C2–C3–C4	102.7(2)
C7–C3–C4	111.9(2)
C2–C3–H3	112.6(13)
C7–C3–H3	109.4(13)
C4–C3–H3	108.8(13)
C9–C10–C11	121.6(3)
C9–C10–H10	118.9(17)
C11–C10–H10	119.5(16)
C5–C2–C1	124.9(2)
C5–C2–C3	127.2(2)
C1–C2–C3	107.8(2)
O1–C4–C15	111.1(2)
O1–C4–C3	105.1(2)
C15–C4–C3	114.5(2)
O1–C4–H4	106.8(15)
C15–C4–H4	108.9(14)
C3–C4–H4	110.1(14)
C5–C6–H6C	109.3(18)
C5–C6–H6B	105.1(18)
H6C–C6–H6B	104(3)
C5–C6–H6A	112.9(18)
H6C–C6–H6A	113(3)
H6B–C6–H6A	112(2)
C17–C16–C15	120.9(3)
C17–C16–H16	121.1(16)
C15–C16–H16	117.9(16)
C18–C17–C16	119.7(3)
C18–C17–H17	120.6(18)
C16–C17–H17	119.7(18)
C9–C8–S1	114.0(2)
C9–C8–H8A	108.2(15)
S1–C8–H8A	111.1(16)
C9–C8–H8B	115.0(19)
S1–C8–H8B	103.7(19)
H8A–C8–H8B	104(2)
C10–C9–C14	117.6(3)
C10–C9–C8	121.0(3)
C14–C9–C8	121.5(3)
C18–C19–C20	120.2(3)
C18–C19–H19	118.6(17)

C20–C19–H19	121.2(17)	C14–C13–C12	120.3(3)
C17–C18–C19	119.9(3)	C14–C13–H13	120.3(18)
C17–C18–H18	119.4(17)	C12–C13–H13	119.3(18)
C19–C18–H18	120.7(17)	O2–C1–O1	120.2(2)
C12–C11–C10	119.7(3)	O2–C1–C2	131.1(2)
C12–C11–H11	119.9(16)	O1–C1–C2	108.7(2)
C10–C11–H11	120.4(16)	C11–C12–C13	119.9(3)
C3–C7–S1	113.73(19)	C11–C12–H12	118(2)
C3–C7–H7B	111.1(14)	C13–C12–H12	122(2)
S1–C7–H7B	107.9(14)		
C3–C7–H7A	106.4(16)		
S1–C7–H7A	107.9(16)	Symmetry transformations used to generate equivalent atoms:	
H7B–C7–H7A	110(2)		
C13–C14–C9	120.8(3)		
C13–C14–H14	120.9(15)		
C9–C14–H14	118.2(16)		

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)	39(1)	27(1)	−7(1)	3(1)	4(1)
N2	41(2)	34(2)	33(1)	2(1)	2(1)	2(1)
O1	34(1)	36(1)	26(1)	6(1)	2(1)	−5(1)
O2	34(1)	56(1)	29(1)	9(1)	10(1)	−3(1)
N1	35(2)	38(2)	28(1)	−3(1)	−3(1)	−7(1)
C5	29(2)	30(2)	24(2)	4(1)	2(1)	6(1)
C15	28(2)	27(2)	21(2)	0(1)	−2(1)	−5(1)
C20	31(2)	37(2)	26(2)	0(2)	5(1)	−4(1)
N3	46(2)	48(2)	44(2)	−6(1)	−5(1)	−6(1)
C3	27(2)	25(2)	23(2)	4(1)	2(1)	−3(1)
C10	36(2)	32(2)	44(2)	2(2)	13(2)	−2(2)
C2	27(2)	30(2)	18(1)	5(1)	5(1)	3(1)
C4	31(2)	28(2)	23(2)	0(1)	7(1)	−3(1)
C6	44(2)	42(2)	27(2)	1(2)	6(2)	4(2)
C16	30(2)	35(2)	26(2)	−3(1)	3(1)	0(1)
C17	42(2)	41(2)	22(2)	4(2)	−2(2)	−7(2)
C8	41(2)	40(2)	29(2)	8(2)	12(2)	6(2)
C9	28(2)	36(2)	31(2)	6(1)	12(1)	−4(1)
C19	31(2)	35(2)	41(2)	0(2)	4(2)	0(1)
C18	34(2)	37(2)	39(2)	8(2)	−7(2)	0(2)
C11	36(2)	47(2)	45(2)	−10(2)	9(2)	−8(2)
C7	28(2)	31(2)	27(2)	3(1)	2(1)	−4(1)
C14	33(2)	33(2)	33(2)	3(2)	9(1)	−3(1)
C13	32(2)	40(2)	42(2)	12(2)	10(2)	0(2)
C1	31(2)	34(2)	27(2)	6(1)	4(1)	5(1)
C12	32(2)	57(2)	38(2)	3(2)	4(2)	−12(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.*
H7B	9800(20)	1950(20)	5550(16)	24(7)	1
H20	5080(20)	3350(20)	4868(18)	24(7)	1
H3	8226(18)	3260(20)	4822(14)	11(6)	1
H19	3960(20)	4670(20)	3864(18)	34(8)	1
H13	13770(20)	1090(30)	5628(18)	38(9)	1
H7A	8880(20)	880(30)	5329(17)	35(8)	1
H16	7070(20)	2600(20)	2972(17)	32(8)	1
H4	7100(20)	1260(20)	4299(16)	22(7)	1
H8A	10100(20)	3550(30)	4061(17)	39(8)	1
H6C	8880(30)	3300(30)	8120(20)	67(10)	1
H17	5960(20)	3920(30)	1970(20)	44(9)	1
H6B	8170(30)	4540(30)	7780(20)	70(11)	1

H6A	7360(30)	3170(30)	7810(20)	73(10)	1
H18	4380(20)	4960(30)	2407(18)	43(8)	1
H8B	10720(30)	2770(30)	3440(20)	49(10)	1
H14	12230(20)	1080(30)	4431(18)	33(8)	1
H11	12810(20)	4400(30)	6513(19)	45(8)	1
H10	11270(20)	4420(30)	5287(18)	41(8)	1
H12	14030(30)	2720(30)	6620(20)	49(10)	1

X-Ray Data for **7.58c**

Table 1. Crystal data and structure refinement.

Identification code	**02sot099**	
Empirical formula	$C_{18}H_{15}BrO_3$	
Formula weight	359.21	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 10.3321(2) Å	α = 90°
	b = 13.4800(3) Å	β = 107.376(2)°
	c = 11.4618(2) Å	γ = 90°
Volume	1523.51(5) Å^3	
Z	4	
Density (calculated)	1.566 Mg / m^3	
Absorption coefficient	2.708 mm^{-1}	
F(000)	728	
Crystal	Block; Colourless	
Crystal size	0.40 × 0.30 × 0.20 mm^3	
θ range for data collection	3.02 – 27.48°	
Index ranges	$-13 \le h \le 12$, $-17 \le k \le 16$, $-14 \le l \le 14$	
Reflections collected	15966	
Independent reflections	3473 [R_{int} = 0.0466]	
Completeness to θ = 27.48°	99.5 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.6135 and 0.4105	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3473 / 0 / 260	
Goodness-of-fit on F^2	1.028	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0289, $wR2$ = 0.0638	
R indices (all data)	$R1$ = 0.0387, $wR2$ = 0.0676	
Extinction coefficient	0.0054(5)	
Largest diff. peak and hole	0.444 and –0.396 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 [× 10^4], equivalent isotropic displacement parameters [Å^2 × 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.*
Br1	10896(1)	–880(1)	13757(1)	28(1)	1
O1	6921(2)	2579(1)	10107(1)	30(1)	1
O2	6693(2)	664(1)	7840(1)	24(1)	1
O3	6270(2)	–474(1)	9075(1)	28(1)	1
C1	6334(2)	1696(2)	10421(2)	25(1)	1

C2	5501(2)	1230(2)	9166(2)	23(1)	1
C3	5453(2)	2065(2)	8235(2)	24(1)	1
C4	5947(3)	2971(2)	9037(2)	31(1)	1
C5	6181(2)	376(2)	8736(2)	22(1)	1
C6	6474(2)	1724(1)	7576(2)	23(1)	1
C7	7452(2)	1060(1)	11224(2)	23(1)	1
C8	8687(2)	960(2)	10982(2)	24(1)	1
C9	9710(2)	369(2)	11719(2)	24(1)	1
C10	9471(2)	−124(1)	12701(2)	22(1)	1
C11	8245(2)	−44(2)	12951(2)	24(1)	1
C12	7240(2)	555(2)	12210(2)	25(1)	1
C13	6026(2)	1878(1)	6211(2)	24(1)	1
C14	6618(2)	2622(2)	5710(2)	29(1)	1
C15	6229(3)	2779(2)	4460(2)	40(1)	1
C16	5235(3)	2177(2)	3699(2)	44(1)	1
C17	4633(3)	1436(2)	4193(2)	39(1)	1
C18	5023(2)	1288(2)	5449(2)	30(1)	1

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

O1–C1	1.430(2)
O1–C4	1.434(3)
O2–C5	1.345(2)
O2–C6	1.464(2)
O3–C5	1.205(2)
C1–C7	1.510(3)
C1–C2	1.570(3)
C1–H1	0.98(2)
C2–C5	1.506(3)
C2–C3	1.543(3)
C2–H2	0.96(2)
C3–C4	1.522(3)
C3–C6	1.540(3)
C3–H3	0.95(2)
C4–H4A	0.95(3)
C4–H4B	1.01(3)
C6–C13	1.507(3)
C6–H6	0.99(2)
C7–C12	1.391(3)
C7–C8	1.392(3)
C8–C9	1.390(3)
C8–H8	0.98(2)
C9–C10	1.391(3)
C9–H9	0.93(2)
C10–C11	1.385(3)
C11–C12	1.387(3)
C11–H11	0.94(3)
C12–H12	0.96(3)
C13–C14	1.386(3)
C13–C18	1.389(3)
C14–C15	1.384(3)
C14–H14	0.97(3)
C15–C16	1.392(4)
C15–H15	0.95(3)
C16–C17	1.384(4)
C16–H16	0.96(3)
C17–C18	1.389(3)
C17–H17	0.94(3)
C18–H18	0.96(3)
C1–O1–C4	106.26(16)
C5–O2–C6	111.63(15)
O1–C1–C7	108.79(17)
O1–C1–C2	105.10(15)
C7–C1–C2	116.20(16)
O1–C1–H1	109.0(13)
C7–C1–H1	112.1(13)
C2–C1–H1	105.2(13)
C5–C2–C3	104.61(15)
C5–C2–C1	115.06(16)
C3–C2–C1	103.70(16)
C5–C2–H2	109.3(12)
C3–C2–H2	116.8(13)
C1–C2–H2	107.5(13)
C4–C3–C6	112.37(18)
C4–C3–C2	103.39(16)
C6–C3–C2	103.72(15)
C4–C3–H3	114.1(14)
C6–C3–H3	111.2(14)
C2–C3–H3	111.3(14)
O1–C4–C3	104.17(16)
O1–C4–H4A	111.6(14)
C3–C4–H4A	110.9(15)
O1–C4–H4B	105.5(14)
C3–C4–H4B	112.7(13)
H4A–C4–H4B	112(2)
O3–C5–O2	120.78(18)
O3–C5–C2	128.22(18)
O2–C5–C2	110.97(16)
O2–C6–C13	109.27(15)
O2–C6–C3	105.98(15)
C13–C6–C3	115.14(17)
O2–C6–H6	105.9(12)
C13–C6–H6	110.6(12)
C3–C6–H6	109.5(12)
C12–C7–C8	119.38(19)
C12–C7–C1	119.73(19)
C8–C7–C1	120.88(18)
C9–C8–C7	120.69(18)
C9–C8–H8	120.2(14)
C7–C8–H8	119.1(14)
C8–C9–C10	118.64(19)
C8–C9–H9	122.4(13)
C10–C9–H9	119.0(13)
C11–C10–C9	121.66(19)
C11–C10–Br1	119.53(15)
C9–C10–Br1	118.76(15)
C10–C11–C12	118.83(19)
C10–C11–H11	117.4(16)
C12–C11–H11	123.8(16)
C11–C12–C7	120.8(2)
C11–C12–H12	119.3(14)
C7–C12–H12	119.9(14)

C14–C13–C18	119.50(19)	C16–C17–C18	120.1(2)
C14–C13–C6	119.56(19)	C16–C17–H17	122.7(16)
C18–C13–C6	120.94(19)	C18–C17–H17	117.2(17)
C15–C14–C13	120.8(2)	C13–C18–C17	120.1(2)
C15–C14–H14	119.6(15)	C13–C18–H18	120.0(15)
C13–C14–H14	119.6(15)	C17–C18–H18	119.9(15)
C14–C15–C16	119.5(2)		
C14–C15–H15	119.1(17)	Symmetry transformations used to generate equivalent atoms:	
C16–C15–H15	121.3(17)		
C17–C16–C15	120.1(2)		
C17–C16–H16	121(2)		
C15–C16–H16	119(2)		

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}
Br1	27(1)	30(1)	23(1)	2(1)	4(1)	4(1)
O1	43(1)	21(1)	24(1)	1(1)	8(1)	0(1)
O2	31(1)	21(1)	23(1)	6(1)	12(1)	7(1)
O3	33(1)	22(1)	28(1)	4(1)	9(1)	1(1)
C1	32(1)	23(1)	22(1)	1(1)	11(1)	1(1)
C2	23(1)	24(1)	22(1)	3(1)	9(1)	3(1)
C3	27(1)	25(1)	21(1)	4(1)	9(1)	8(1)
C4	43(1)	25(1)	26(1)	4(1)	12(1)	9(1)
C5	21(1)	24(1)	19(1)	2(1)	3(1)	1(1)
C6	27(1)	19(1)	23(1)	3(1)	9(1)	3(1)
C7	27(1)	22(1)	19(1)	−5(1)	4(1)	−2(1)
C8	30(1)	25(1)	18(1)	1(1)	7(1)	−3(1)
C9	23(1)	27(1)	23(1)	−4(1)	9(1)	−4(1)
C10	25(1)	20(1)	19(1)	−3(1)	2(1)	−1(1)
C11	28(1)	25(1)	19(1)	0(1)	7(1)	−1(1)
C12	25(1)	28(1)	22(1)	−2(1)	9(1)	−1(1)
C13	30(1)	20(1)	23(1)	2(1)	11(1)	7(1)
C14	35(1)	24(1)	32(1)	7(1)	15(1)	7(1)
C15	54(2)	38(1)	38(1)	19(1)	28(1)	21(1)
C16	65(2)	48(2)	21(1)	10(1)	16(1)	33(1)
C17	45(2)	35(1)	29(1)	−5(1)	0(1)	16(1)
C18	37(1)	25(1)	28(1)	2(1)	8(1)	5(1)

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

Atom	x	y	z	U_{eq}	$S.o.f.$
H1	5660(20)	1879(16)	10830(20)	26(6)	1
H2	4650(20)	1012(15)	9249(19)	19(5)	1
H3	4570(20)	2135(17)	7680(20)	27(6)	1
H4A	5210(30)	3290(18)	9230(20)	31(6)	1
H4B	6470(30)	3451(18)	8670(20)	34(6)	1
H6	7360(20)	2047(15)	7954(19)	18(5)	1
H8	8840(20)	1333(17)	10310(20)	30(6)	1
H9	10550(20)	295(16)	11581(19)	21(5)	1
H11	8140(30)	−411(19)	13610(20)	37(7)	1
H12	6400(30)	630(17)	12390(20)	31(6)	1
H14	7340(30)	3018(18)	6240(20)	35(7)	1
H15	6680(30)	3270(20)	4140(20)	46(8)	1
H16	4970(30)	2280(20)	2830(30)	66(9)	1
H17	3960(30)	1010(20)	3710(20)	42(7)	1
H18	4610(30)	769(18)	5790(20)	35(7)	1

X-Ray Data for **8.18**

Table 1. Crystal data and structure refinement.

Identification code	**02sot123**	
Empirical formula	$C_{15}H_{16}O_7S$	
Formula weight	340.34	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 6.98690(10) Å	α = 90°
	b = 10.6937(2) Å	β = 90°
	c = 20.5161(5) Å	γ = 90°
Volume	1532.88(5) Å^3	
Z	4	
Density (calculated)	1.475 Mg / m^3	
Absorption coefficient	0.246 mm^{-1}	
F(000)	712	
Crystal	Plate; Colourless	
Crystal size	0.34 × 0.12 × 0.02 mm^3	
θ range for data collection	3.08 – 27.49°	
Index ranges	$-9 \le h \le 8$, $-13 \le k \le 11$, $-26 \le l \le 26$	
Reflections collected	16449	
Independent reflections	3501 [R_{int} = 0.0696]	
Completeness to θ = 27.49°	99.7 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9951 and 0.9211	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3501 / 0 / 272	
Goodness-of-fit on F^2	1.076	
Final R indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0415, *wR2* = 0.0792	
R indices (all data)	*R1* = 0.0653, *wR2* = 0.0862	
Absolute structure parameter	–0.01(8)	
Largest diff. peak and hole	0.199 and –0.399 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:

The absolute structure is most likely correct, but the absolute structure parameter is at the limit for an accurate determination.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 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	7923(1)	3603(1)	4975(1)	22(1)	1
O1	6048(2)	4458(1)	4917(1)	26(1)	1
O2	7726(3)	2816(2)	5532(1)	34(1)	1
O3	9571(2)	4394(1)	4945(1)	30(1)	1
O4	6029(2)	6660(2)	4316(1)	26(1)	1
O5	4897(2)	8659(2)	7070(1)	26(1)	1
O6	6305(2)	8745(2)	8042(1)	32(1)	1
O7	10839(3)	10625(2)	7023(1)	44(1)	1
C1	5996(3)	5548(2)	5304(1)	22(1)	1
C2	5944(3)	6697(2)	4981(1)	21(1)	1

C3	5767(3)	7780(2)	5348(1)	21(1)	1
C4	5661(3)	7707(2)	6029(1)	21(1)	1
C5	5753(3)	6567(2)	6340(1)	23(1)	1
C6	5917(3)	5479(2)	5972(1)	24(1)	1
C7	5339(3)	8925(2)	6391(1)	24(1)	1
C8	7041(4)	9803(2)	6405(1)	25(1)	1
C9	6784(4)	10960(2)	6787(1)	29(1)	1
C10	7727(3)	9825(2)	7118(1)	23(1)	1
C11	6321(3)	9039(2)	7477(1)	24(1)	1
C12	7653(4)	2755(3)	4256(1)	28(1)	1
C13	5868(4)	7831(3)	3980(1)	28(1)	1
C14	9793(4)	9889(2)	7299(1)	28(1)	1
C15	10515(4)	9025(3)	7820(2)	37(1)	1

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

S1–O2	1.4249(17)
S1–O3	1.4300(16)
S1–O1	1.6023(15)
S1–C12	1.742(3)
O1–C1	1.412(3)
O4–C2	1.364(3)
O4–C13	1.435(3)
O5–C11	1.361(3)
O5–C7	1.455(3)
O6–C11	1.200(3)
O7–C14	1.214(3)
C1–C6	1.373(3)
C1–C2	1.397(3)
C2–C3	1.387(3)
C3–C4	1.401(3)
C3–H3	1.00(3)
C4–C5	1.379(3)
C4–C7	1.516(3)
C5–C6	1.392(3)
C5–H5	1.00(2)
C6–H6	0.92(3)
C7–C8	1.516(3)
C7–H7	0.95(2)
C8–C9	1.476(3)
C8–C10	1.539(3)
C8–H8	0.97(3)
C9–C10	1.538(3)
C9–H9A	1.00(2)
C9–H9B	0.93(3)
C10–C11	1.489(3)
C10–C14	1.492(4)
C12–H12A	0.95(3)
C12–H12B	0.88(4)
C12–H12C	0.93(3)
C13–H13A	0.91(3)
C13–H13B	0.94(3)
C13–H13C	0.99(3)
C14–C15	1.500(4)
C15–H15A	1.02(4)
C15–H15B	0.96(3)
C15–H15C	0.99(3)
O2–S1–O3	117.51(11)
O2–S1–O1	108.52(10)
O3–S1–O1	108.49(8)
O2–S1–C12	111.15(12)
O3–S1–C12	111.03(12)
O1–S1–C12	98.34(12)
C1–O1–S1	116.75(13)
C2–O4–C13	116.86(18)
C11–O5–C7	111.97(18)
C6–C1–C2	121.4(2)
C6–C1–O1	121.2(2)
C2–C1–O1	117.32(19)
O4–C2–C3	124.8(2)
O4–C2–C1	116.64(19)
C3–C2–C1	118.6(2)
C2–C3–C4	120.0(2)
C2–C3–H3	119.2(13)
C4–C3–H3	120.8(13)
C5–C4–C3	120.6(2)
C5–C4–C7	122.6(2)
C3–C4–C7	116.7(2)
C4–C5–C6	119.5(2)
C4–C5–H5	118.9(14)
C6–C5–H5	121.6(14)
C1–C6–C5	119.9(2)
C1–C6–H6	118.8(15)
C5–C6–H6	121.2(15)
O5–C7–C8	105.68(18)
O5–C7–C4	109.47(19)
C8–C7–C4	115.11(19)
O5–C7–H7	106.4(13)
C8–C7–H7	111.0(13)
C4–C7–H7	108.8(13)
C9–C8–C7	115.7(2)
C9–C8–C10	61.28(16)
C7–C8–C10	105.73(19)
C9–C8–H8	120.1(15)
C7–C8–H8	119.5(15)
C10–C8–H8	120.0(15)
C8–C9–C10	61.38(16)
C8–C9–H9A	119.2(14)
C10–C9–H9A	115.5(14)
C8–C9–H9B	117.1(15)
C10–C9–H9B	117.5(16)
H9A–C9–H9B	115(2)
C11–C10–C14	122.7(2)
C11–C10–C9	112.4(2)
C14–C10–C9	119.2(2)
C11–C10–C8	104.9(2)
C14–C10–C8	122.6(2)
C9–C10–C8	57.34(15)
O6–C11–O5	120.5(2)
O6–C11–C10	129.2(2)
O5–C11–C10	110.29(19)
S1–C12–H12A	105.6(15)
S1–C12–H12B	104(2)
H12A–C12–H12B	114(3)
S1–C12–H12C	108.7(19)
H12A–C12–H12C	111(2)

H12B–C12–H12C	113(3)	C10–C14–C15	118.3(2)
O4–C13–H13A	110.0(16)	C14–C15–H15A	105.2(18)
O4–C13–H13B	111.2(15)	C14–C15–H15B	105.1(18)
H13A–C13–H13B	110(2)	H15A–C15–H15B	109(2)
O4–C13–H13C	108.6(16)	C14–C15–H15C	109.0(17)
H13A–C13–H13C	110(2)	H15A–C15–H15C	121(2)
H13B–C13–H13C	106(2)	H15B–C15–H15C	107(2)
O7–C14–C10	119.7(2)		
O7–C14–C15	121.9(2)		

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	25(1)	18(1)	23(1)	0(1)	1(1)	1(1)
O1	25(1)	20(1)	33(1)	−7(1)	−4(1)	2(1)
O2	52(1)	24(1)	25(1)	4(1)	4(1)	2(1)
O3	25(1)	24(1)	41(1)	−2(1)	1(1)	−2(1)
O4	30(1)	27(1)	20(1)	−2(1)	−2(1)	1(1)
O5	27(1)	28(1)	21(1)	−2(1)	7(1)	0(1)
O6	36(1)	38(1)	21(1)	4(1)	5(1)	7(1)
O7	41(1)	46(1)	46(1)	12(1)	−1(1)	−14(1)
C1	19(1)	17(1)	30(1)	−6(1)	0(1)	−1(1)
C2	17(1)	24(1)	23(1)	−2(1)	−1(1)	1(1)
C3	18(1)	23(1)	23(1)	0(1)	−2(1)	1(1)
C4	16(1)	22(1)	25(1)	−4(1)	−1(1)	−1(1)
C5	24(1)	24(1)	21(1)	−1(1)	2(1)	2(1)
C6	21(1)	22(1)	28(1)	3(1)	2(1)	0(1)
C7	26(1)	28(1)	19(1)	2(1)	1(1)	6(1)
C8	34(1)	22(1)	18(1)	−1(1)	2(1)	0(1)
C9	43(2)	20(1)	24(1)	2(1)	−3(1)	4(1)
C10	32(1)	20(1)	19(1)	0(1)	0(1)	3(1)
C11	29(1)	22(1)	22(1)	−3(1)	3(1)	8(1)
C12	30(2)	26(1)	28(1)	−3(1)	3(1)	2(1)
C13	28(1)	31(2)	25(1)	2(1)	−2(1)	4(1)
C14	34(1)	26(1)	24(1)	−4(1)	−1(1)	−1(1)
C15	28(2)	45(2)	37(2)	7(1)	−3(1)	1(1)

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

Atom	x	y	z	U_{eq}	*S.o.f.*
H3	5660(30)	8610(20)	5119(11)	22(6)	1
H5	5670(30)	6540(20)	6825(12)	19(6)	1
H6	5940(30)	4700(20)	6168(12)	22(6)	1
H7	4240(30)	9330(20)	6215(10)	11(5)	1
H8	7970(40)	9780(20)	6054(12)	28(6)	1
H9A	5480(30)	11180(20)	6950(11)	21(6)	1
H9B	7570(40)	11640(30)	6682(12)	29(7)	1
H12A	6540(40)	2250(20)	4318(11)	24(6)	1
H12B	8720(50)	2320(30)	4226(14)	55(9)	1
H12C	7480(50)	3310(30)	3913(15)	56(10)	1
H13A	6810(40)	8360(20)	4112(12)	27(7)	1
H13B	4670(40)	8190(20)	4048(11)	23(7)	1
H13C	5970(40)	7670(30)	3508(15)	38(7)	1
H15A	11970(50)	9100(30)	7802(15)	61(9)	1
H15B	10060(40)	9380(30)	8223(16)	44(8)	1
H15C	9880(40)	8200(30)	7772(14)	42(8)	1

X-Ray Data for **8.28**

Table 1. Crystal data and structure refinement.

Identification code	**02sot124**	
Empirical formula	$C_{22}H_{24}O_{11}S_2$	
Formula weight	528.53	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 5.9032(4) Å	α = 90°
	b = 15.6841(12) Å	β = 100.906(3)°
	c = 12.9404(10) Å	γ = 90°
Volume	1176.47(15) Å^3	
Z	2	
Density (calculated)	1.492 Mg / m^3	
Absorption coefficient	0.287 mm^{-1}	
F(000)	552	
Crystal	Block; colourless	
Crystal size	0.14 × 0.12 × 0.08 mm^3	
θ range for data collection	3.05 – 27.49°	
Index ranges	$-7 \le h \le 6$, $-20 \le k \le 19$, $-16 \le l \le 16$	
Reflections collected	11339	
Independent reflections	5114 [R_{int} = 0.0329]	
Completeness to θ = 27.49°	98.6 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9774 and 0.9609	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5114 / 1 / 321	
Goodness-of-fit on F^2	0.963	
Final R indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0409, *wR2* = 0.0932	
R indices (all data)	*R1* = 0.0528, *wR2* = 0.1002	
Absolute structure parameter	0.00(6)	
Extinction coefficient	0.0111(16)	
Largest diff. peak and hole	0.392 and –0.339 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:

Absolute structure correctly determined. Chirality; C9 & C11 = S, C12 & C14 = R.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 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.*
O7	3063(3)	4090(1)	3990(2)	42(1)	1
C1	9527(4)	8727(2)	1832(2)	36(1)	1
C2	4464(4)	7905(2)	1421(2)	22(1)	1
C3	3239(4)	7480(2)	561(2)	24(1)	1
C4	2550(4)	6646(2)	687(2)	23(1)	1
C5	3050(4)	6255(2)	1666(2)	23(1)	1
C6	4288(4)	6694(2)	2534(2)	25(1)	1

C7	5008(4)	7530(2)	2411(2)	23(1)	1
C8	6924(7)	7652(2)	4213(2)	56(1)	1
C9	2152(4)	5370(2)	1784(2)	23(1)	1
C10	2199(4)	4522(2)	3254(2)	29(1)	1
C11	−330(4)	4690(2)	2847(2)	25(1)	1
C12	−380(4)	5342(2)	1956(2)	24(1)	1
C13	−1973(4)	4934(2)	1016(2)	27(1)	1
C14	−1720(4)	3922(2)	2290(2)	26(1)	1
C15	−941(4)	3034(2)	2631(2)	24(1)	1
C16	−1794(4)	2659(2)	3455(2)	28(1)	1
C17	−1244(4)	1818(2)	3732(2)	28(1)	1
C18	126(4)	1359(2)	3183(2)	25(1)	1
C19	1035(4)	1730(2)	2364(2)	25(1)	1
C20	492(4)	2574(2)	2097(2)	25(1)	1
C21	3654(5)	1614(2)	1176(2)	32(1)	1
C22	4767(4)	0(2)	3701(2)	35(1)	1
O1	7098(3)	9939(1)	806(2)	33(1)	1
O2	7230(3)	8554(1)	−67(2)	37(1)	1
O3	5005(3)	8780(1)	1339(1)	22(1)	1
O4	6193(3)	8030(1)	3191(1)	32(1)	1
O5	3532(3)	4952(1)	2684(1)	28(1)	1
O6	−1630(3)	4038(1)	1200(1)	28(1)	1
O8	2384(3)	1215(1)	1887(1)	31(1)	1
O9	393(3)	474(1)	3355(1)	27(1)	1
O10	2758(4)	692(1)	5123(2)	43(1)	1
O11	1461(4)	−728(1)	4452(2)	41(1)	1
S1	7219(1)	9034(1)	860(1)	25(1)	1
S2	2329(1)	92(1)	4280(1)	29(1)	1

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

O7–C10	1.201(3)
C1–S1	1.738(3)
C1–H1A	0.9800
C1–H1B	0.9800
C1–H1C	0.9800
C2–C3	1.379(3)
C2–C7	1.391(3)
C2–O3	1.417(3)
C3–C4	1.388(3)
C3–H3	0.9500
C4–C5	1.388(3)
C4–H4	0.9500
C5–C6	1.400(3)
C5–C9	1.504(3)
C6–C7	1.396(3)
C6–H6	0.9500
C7–O4	1.362(3)
C8–O4	1.439(3)
C8–H8A	0.9800
C8–H8B	0.9800
C8–H8C	0.9800
C9–O5	1.445(3)
C9–C12	1.552(3)
C9–H9	1.0000
C10–O5	1.356(3)
C10–C11	1.510(4)
C11–C12	1.538(4)
C11–C14	1.555(3)
C11–H11	1.0000
C12–C13	1.530(3)
C12–H12	1.0000
C13–O6	1.433(3)
C13–H13A	0.9900
C13–H13B	0.9900
C14–O6	1.434(3)
C14–C15	1.507(3)
C14–H14	1.0000
C15–C20	1.391(3)
C15–C16	1.393(4)
C16–C17	1.390(4)
C16–H16	0.9500
C17–C18	1.377(3)
C17–H17	0.9500
C18–C19	1.401(3)
C18–O9	1.410(3)
C19–O8	1.360(3)
C19–C20	1.391(3)
C20–H20	0.9500
C21–O8	1.436(3)
C21–H21A	0.9800
C21–H21B	0.9800
C21–H21C	0.9800
C22–S2	1.750(3)
C22–H22A	0.9800
C22–H22B	0.9800
C22–H22C	0.9800
O1–S1	1.423(2)
O2–S1	1.4171(19)
O3–S1	1.5987(16)
O9–S2	1.6062(18)
O10–S2	1.426(2)
O11–S2	1.418(2)
S1–C1–H1A	109.5
S1–C1–H1B	109.5
H1A–C1–H1B	109.5
S1–C1–H1C	109.5

H1A–C1–H1C	109.5
H1B–C1–H1C	109.5
C3–C2–C7	122.2(2)
C3–C2–O3	119.9(2)
C7–C2–O3	117.5(2)
C2–C3–C4	118.8(2)
C2–C3–H3	120.6
C4–C3–H3	120.6
C5–C4–C3	120.4(2)
C5–C4–H4	119.8
C3–C4–H4	119.8
C4–C5–C6	120.2(2)
C4–C5–C9	118.9(2)
C6–C5–C9	120.8(2)
C7–C6–C5	119.6(2)
C7–C6–H6	120.2
C5–C6–H6	120.2
O4–C7–C2	115.8(2)
O4–C7–C6	125.5(2)
C2–C7–C6	118.7(2)
O4–C8–H8A	109.5
O4–C8–H8B	109.5
H8A–C8–H8B	109.5
O4–C8–H8C	109.5
H8A–C8–H8C	109.5
H8B–C8–H8C	109.5
O5–C9–C5	110.15(19)
O5–C9–C12	106.49(19)
C5–C9–C12	114.08(19)
O5–C9–H9	108.7
C5–C9–H9	108.7
C12–C9–H9	108.7
O7–C10–O5	120.6(2)
O7–C10–C11	128.2(2)
O5–C10–C11	111.1(2)
C10–C11–C12	104.77(19)
C10–C11–C14	115.3(2)
C12–C11–C14	103.6(2)
C10–C11–H11	110.9
C12–C11–H11	110.9
C14–C11–H11	110.9
C13–C12–C11	103.82(19)
C13–C12–C9	111.2(2)
C11–C12–C9	104.09(19)
C13–C12–H12	112.4
C11–C12–H12	112.4
C9–C12–H12	112.4
O6–C13–C12	103.45(19)
O6–C13–H13A	111.1
C12–C13–H13A	111.1
O6–C13–H13B	111.1
C12–C13–H13B	111.1
H13A–C13–H13B	109.0
O6–C14–C15	109.8(2)
O6–C14–C11	104.08(19)
C15–C14–C11	118.4(2)
O6–C14–H14	108.1
C15–C14–H14	108.1
C11–C14–H14	108.1
C20–C15–C16	120.2(2)
C20–C15–C14	121.0(2)
C16–C15–C14	118.6(2)
C17–C16–C15	119.8(2)
C17–C16–H16	120.1
C15–C16–H16	120.1
C18–C17–C16	119.6(2)
C18–C17–H17	120.2
C16–C17–H17	120.2
C17–C18–C19	121.4(2)
C17–C18–O9	119.4(2)
C19–C18–O9	118.7(2)
O8–C19–C20	125.4(2)
O8–C19–C18	116.0(2)
C20–C19–C18	118.6(2)
C15–C20–C19	120.3(2)
C15–C20–H20	119.9
C19–C20–H20	119.9
O8–C21–H21A	109.5
O8–C21–H21B	109.5
H21A–C21–H21B	109.5
O8–C21–H21C	109.5
H21A–C21–H21C	109.5
H21B–C21–H21C	109.5
S2–C22–H22A	109.5
S2–C22–H22B	109.5
H22A–C22–H22B	109.5
S2–C22–H22C	109.5
H22A–C22–H22C	109.5
H22B–C22–H22C	109.5
C2–O3–S1	118.85(15)
C7–O4–C8	117.8(2)
C10–O5–C9	111.54(18)
C13–O6–C14	104.90(18)
C19–O8–C21	117.0(2)
C18–O9–S2	121.83(15)
O2–S1–O1	119.75(12)
O2–S1–O3	109.32(10)
O1–S1–O3	103.32(10)
O2–S1–C1	109.73(14)
O1–S1–C1	109.66(13)
O3–S1–C1	103.72(12)
O11–S2–O10	119.72(13)
O11–S2–O9	103.16(11)
O10–S2–O9	108.80(11)
O11–S2–C22	110.04(14)
O10–S2–C22	109.94(14)
O9–S2–C22	103.82(11)

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}
O7	51(1)	36(1)	33(1)	10(1)	−8(1)	−10(1)
C1	24(1)	39(2)	43(2)	0(1)	2(1)	3(1)
C2	24(1)	19(1)	23(1)	−2(1)	8(1)	0(1)
C3	27(1)	26(1)	20(1)	2(1)	6(1)	−1(1)
C4	23(1)	24(1)	22(1)	−2(1)	2(1)	−1(1)
C5	23(1)	23(1)	24(1)	2(1)	9(1)	2(1)
C6	34(1)	21(1)	21(1)	1(1)	7(1)	2(1)
C7	28(1)	22(1)	21(1)	−4(1)	6(1)	−1(1)
C8	99(3)	37(2)	22(2)	3(1)	−12(2)	−16(2)
C9	23(1)	21(1)	25(1)	2(1)	6(1)	3(1)
C10	38(1)	24(1)	23(1)	−2(1)	2(1)	−5(1)
C11	31(1)	19(1)	30(1)	−4(1)	17(1)	0(1)
C12	27(1)	20(1)	28(1)	−1(1)	8(1)	2(1)
C13	24(1)	23(1)	33(1)	1(1)	1(1)	2(1)
C14	24(1)	23(1)	33(1)	−1(1)	10(1)	1(1)
C15	23(1)	20(1)	28(1)	−5(1)	5(1)	−3(1)
C16	31(1)	25(1)	31(1)	−4(1)	10(1)	−1(1)
C17	31(1)	27(1)	28(1)	−1(1)	12(1)	−3(1)
C18	31(1)	18(1)	27(1)	0(1)	7(1)	−4(1)
C19	26(1)	22(1)	26(1)	−3(1)	6(1)	0(1)
C20	26(1)	24(1)	26(1)	2(1)	7(1)	−2(1)
C21	36(2)	31(2)	34(2)	3(1)	19(1)	2(1)
C22	30(1)	40(2)	34(1)	2(1)	4(1)	1(1)
O1	36(1)	20(1)	45(1)	5(1)	11(1)	−1(1)
O2	45(1)	40(1)	30(1)	−10(1)	20(1)	−10(1)
O3	25(1)	18(1)	23(1)	2(1)	8(1)	1(1)
O4	53(1)	22(1)	20(1)	0(1)	0(1)	−6(1)
O5	24(1)	24(1)	33(1)	5(1)	2(1)	0(1)
O6	30(1)	21(1)	30(1)	0(1)	2(1)	1(1)
O8	39(1)	24(1)	34(1)	4(1)	17(1)	6(1)
O9	34(1)	18(1)	29(1)	4(1)	5(1)	−1(1)
O10	63(1)	35(1)	28(1)	−8(1)	−1(1)	9(1)
O11	49(1)	28(1)	44(1)	14(1)	7(1)	−5(1)
S1	26(1)	22(1)	27(1)	0(1)	10(1)	−1(1)
S2	39(1)	23(1)	24(1)	2(1)	7(1)	0(1)

X-Ray Data for **8.19**

Table 1. Crystal data and structure refinement.

Identification code	**02sot122**	
Empirical formula	$C_{20}H_{20}O_6$	
Formula weight	356.36	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	$a = 5.7909(3)$ Å	$\alpha = 90°$
	$b = 9.3699(4)$ Å	$\beta = 95.641(2)°$
	$c = 15.5907(8)$ Å	$\gamma = 90°$
Volume	841.86(7) $Å^3$	
Z	2	
Density (calculated)	1.406 Mg / m^3	
Absorption coefficient	0.104 mm^{-1}	
F(000)	376	
Crystal	Plate; Colourless	
Crystal size	$0.12 \times 0.06 \times 0.02$ mm^3	
θ range for data collection	3.41 – 27.45°	

Index ranges	$-7 \le h \le 7, -11 \le k \le 12, -20 \le l \le 18$
Reflections collected	9896
Independent reflections	3722 [R_{int} = 0.0767]
Completeness to θ = 27.45°	99.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9979 and 0.9876
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3722 / 1 / 316
Goodness-of-fit on F^2	0.994
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0550, $wR2$ = 0.0933
R indices (all data)	$R1$ = 0.1129, $wR2$ = 0.1094
Absolute structure parameter	-0.9(12)
Extinction coefficient	0.036(3)
Largest diff. peak and hole	0.188 and -0.189 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:

Unable to accurately determine stereochemistry so used predicted enantiomer.

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

Atom	x	y	z	U_{eq}	$S.o.f.$
C1	7624(6)	5283(3)	11668(2)	32(1)	1
C2	6954(5)	3818(4)	11258(2)	30(1)	1
C3	4380(5)	3626(4)	10982(2)	36(1)	1
C4	6074(5)	3480(3)	9720(2)	32(1)	1
C5	8090(5)	3831(3)	10397(2)	28(1)	1
C6	9051(6)	5350(3)	10361(2)	30(1)	1
C7	8210(5)	5279(3)	12628(2)	29(1)	1
C8	6882(6)	6092(3)	13150(2)	34(1)	1
C9	7350(5)	6067(3)	14038(2)	30(1)	1
C10	9168(5)	5244(3)	14420(2)	30(1)	1
C11	10492(6)	4440(4)	13916(2)	35(1)	1
C12	10010(6)	4459(4)	13021(2)	37(1)	1
C13	4540(10)	7858(5)	14247(3)	63(1)	1
C14	6204(5)	4126(3)	8837(2)	28(1)	1
C15	4371(6)	4939(3)	8448(2)	31(1)	1
C16	4673(5)	5541(3)	7662(2)	29(1)	1
C17	6679(5)	5387(3)	7278(2)	28(1)	1
C18	8463(6)	4566(4)	7627(2)	37(1)	1
C19	8199(6)	3921(4)	8425(2)	36(1)	1
C20	4305(6)	6830(4)	6442(2)	39(1)	1
O1	9585(4)	5747(2)	11248(1)	33(1)	1
O2	4070(3)	4011(2)	10086(1)	35(1)	1
O3	6129(4)	6803(2)	14613(1)	42(1)	1
O4	9683(4)	5223(2)	15302(1)	36(1)	1
O5	3101(4)	6354(3)	7153(1)	41(1)	1
O6	6516(3)	6125(2)	6499(1)	35(1)	1

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

C1–O1	1.433(4)	C2–C5	1.552(4)
C1–C7	1.502(4)	C2–H2	0.96(3)
C1–C2	1.547(4)	C3–O2	1.437(4)
C1–H1	1.04(3)	C3–H3A	1.07(3)
C2–C3	1.521(4)	C3–H3B	0.95(4)
		C4–O2	1.432(3)
		C4–C14	1.512(4)

C4–C5	1.531(4)
C4–H4	0.99(4)
C5–C6	1.531(4)
C5–H5	0.93(3)
C6–O1	1.436(3)
C6–H6A	0.98(3)
C6–H6B	1.05(3)
C7–C12	1.388(4)
C7–C8	1.398(4)
C8–C9	1.385(4)
C8–H8	1.02(3)
C9–O3	1.380(3)
C9–C10	1.391(4)
C10–C11	1.376(4)
C10–O4	1.378(3)
C11–C12	1.396(4)
C11–H11	1.03(3)
C12–H12	1.09(4)
C13–O3	1.431(4)
C13–H13A	0.95(4)
C13–H13B	1.06(5)
C13–H13C	1.00(4)
C14–C19	1.389(4)
C14–C15	1.395(4)
C15–C16	1.376(4)
C15–H15	0.98(3)
C16–C17	1.366(4)
C16–O5	1.377(3)
C17–C18	1.358(4)
C17–O6	1.394(3)
C18–C19	1.404(4)
C18–H18	1.02(3)
C19–H19	0.94(3)
C20–O6	1.436(4)
C20–O5	1.436(4)
C20–H20A	1.01(4)
C20–H20B	0.99(3)
O4–H4O	0.96(4)
O1–C1–C7	110.1(2)
O1–C1–C2	105.0(2)
C7–C1–C2	115.6(3)
O1–C1–H1	109.4(16)
C7–C1–H1	107.5(15)
C2–C1–H1	109.1(17)
C3–C2–C1	114.9(3)
C3–C2–C5	104.1(2)
C1–C2–C5	103.9(2)
C3–C2–H2	112.7(17)
C1–C2–H2	108.8(16)
C5–C2–H2	112.2(16)
O2–C3–C2	105.7(2)
O2–C3–H3A	106.1(13)
C2–C3–H3A	113.3(14)
O2–C3–H3B	105(2)
C2–C3–H3B	114(2)
H3A–C3–H3B	111(2)
O2–C4–C14	109.8(2)
O2–C4–C5	104.1(2)
C14–C4–C5	116.0(3)
O2–C4–H4	109.7(18)
C14–C4–H4	110.2(17)
C5–C4–H4	106.7(19)
C6–C5–C4	115.4(3)
C6–C5–C2	103.0(2)
C4–C5–C2	103.6(2)
C6–C5–H5	111(2)
C4–C5–H5	111(2)
C2–C5–H5	112.6(19)
O1–C6–C5	104.5(2)
O1–C6–H6A	110.9(17)
C5–C6–H6A	108.4(19)
O1–C6–H6B	108.7(15)
C5–C6–H6B	112.2(15)
H6A–C6–H6B	112(2)
C12–C7–C8	118.5(3)
C12–C7–C1	121.8(3)
C8–C7–C1	119.7(3)
C9–C8–C7	120.5(3)
C9–C8–H8	122.0(16)
C7–C8–H8	117.5(16)
O3–C9–C8	125.4(3)
O3–C9–C10	114.4(2)
C8–C9–C10	120.2(3)
C11–C10–O4	119.0(3)
C11–C10–C9	120.0(3)
O4–C10–C9	121.0(2)
C10–C11–C12	119.7(3)
C10–C11–H11	117.1(18)
C12–C11–H11	123.1(18)
C7–C12–C11	121.1(3)
C7–C12–H12	121.6(18)
C11–C12–H12	117.3(18)
O3–C13–H13A	108(2)
O3–C13–H13B	110(3)
H13A–C13–H13B	118(3)
O3–C13–H13C	105(2)
H13A–C13–H13C	110(3)
H13B–C13–H13C	106(3)
C19–C14–C15	120.4(3)
C19–C14–C4	118.9(3)
C15–C14–C4	120.7(3)
C16–C15–C14	116.9(3)
C16–C15–H15	118.5(17)
C14–C15–H15	124.5(17)
C17–C16–C15	122.3(3)
C17–C16–O5	110.4(2)
C15–C16–O5	127.3(3)
C18–C17–C16	122.0(3)
C18–C17–O6	127.9(3)
C16–C17–O6	110.0(3)
C17–C18–C19	117.0(3)
C17–C18–H18	119.3(16)
C19–C18–H18	123.6(16)
C14–C19–C18	121.2(3)
C14–C19–H19	117.0(16)
C18–C19–H19	121.8(16)
O6–C20–O5	107.9(2)
O6–C20–H20A	111(2)
O5–C20–H20A	108(2)
O6–C20–H20B	110.6(18)
O5–C20–H20B	109.5(18)
H20A–C20–H20B	110(3)
C1–O1–C6	104.8(2)
C4–O2–C3	105.8(2)
C9–O3–C13	115.9(2)
C10–O4–H4O	110(2)
C16–O5–C20	105.9(2)
C17–O6–C20	105.4(2)

Symmetry transformations used to generate equivalent atoms:

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

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	37(2)	32(2)	27(2)	2(2)	4(1)	0(2)
C2	34(2)	32(2)	24(2)	6(1)	3(1)	2(2)
C3	32(2)	48(2)	28(2)	7(2)	3(1)	−5(2)
C4	33(2)	35(2)	27(2)	3(1)	3(1)	3(2)
C5	25(2)	32(2)	26(2)	−1(1)	2(1)	1(2)
C6	33(2)	34(2)	24(2)	−1(1)	5(1)	−1(2)
C7	34(2)	28(2)	24(2)	0(1)	4(1)	0(2)
C8	36(2)	35(2)	31(2)	2(2)	5(2)	5(2)
C9	36(2)	31(2)	24(2)	2(1)	6(1)	5(2)
C10	31(2)	38(2)	22(2)	−2(1)	2(1)	−6(2)
C11	28(2)	47(2)	31(2)	−1(2)	3(2)	7(2)
C12	38(2)	45(2)	28(2)	−4(2)	7(2)	7(2)
C13	88(4)	62(3)	40(2)	10(2)	16(3)	51(3)
C14	31(2)	32(2)	21(2)	−6(1)	−1(1)	−1(2)
C15	31(2)	38(2)	25(2)	−1(1)	5(1)	2(2)
C16	32(2)	32(2)	23(2)	−3(1)	0(1)	6(1)
C17	32(2)	34(2)	17(1)	−3(1)	0(1)	−2(2)
C18	32(2)	48(2)	33(2)	−1(2)	8(2)	4(2)
C19	34(2)	45(2)	29(2)	7(2)	0(2)	9(2)
C20	39(2)	47(2)	31(2)	7(2)	5(2)	1(2)
O1	42(1)	36(1)	22(1)	−2(1)	5(1)	−5(1)
O2	27(1)	53(1)	24(1)	8(1)	4(1)	4(1)
O3	58(2)	43(1)	26(1)	5(1)	9(1)	20(1)
O4	37(1)	47(1)	23(1)	−1(1)	0(1)	5(1)
O5	44(1)	53(1)	28(1)	11(1)	4(1)	16(1)
O6	37(1)	41(1)	26(1)	5(1)	5(1)	1(1)

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

Atom	x	y	z	U_{eq}	*S.o.f.*
H1	6260(50)	5990(30)	11530(17)	36(8)	1
H2	7570(50)	3080(30)	11641(18)	23(8)	1
H3A	3300(40)	4340(30)	11304(16)	14(7)	1
H3B	3850(60)	2670(40)	11000(20)	44(10)	1
H4	5990(50)	2430(40)	9678(18)	36(8)	1
H4O	8550(60)	5750(40)	15580(20)	59(12)	1
H5	9280(60)	3160(40)	10387(19)	41(10)	1
H6A	7840(50)	5960(40)	10080(18)	38(9)	1
H6B	10590(50)	5390(30)	10051(17)	24(7)	1
H8	5590(60)	6710(40)	12850(18)	35(8)	1
H11	11800(50)	3830(40)	14230(20)	48(10)	1
H12	11080(60)	3790(40)	12650(20)	53(10)	1
H13A	5380(60)	8490(40)	13920(30)	59(12)	1
H13B	3050(90)	7350(50)	13930(30)	91(17)	1
H13C	4010(60)	8380(40)	14750(20)	65(11)	1
H15	2900(50)	5100(30)	8693(18)	29(8)	1
H18	9860(50)	4410(30)	7292(18)	27(7)	1
H19	9370(50)	3350(30)	8711(17)	18(7)	1
H20A	4510(70)	7890(40)	6490(20)	61(11)	1
H20B	3380(50)	6590(30)	5893(19)	39(9)	1

X-Ray Data for **9.23**

Table 1. Crystal data and structure refinement.

Identification code	**02SOT113**
Empirical formula	$C_{18}H_{16}O_2S$
Formula weight	296.37
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monolcinic
Space group	$P2_1/n$
Unit cell dimensions	a = 9.7350(4) Å
	b = 15.1464(7) Å
	c = 10.6719(6) Å
Volume	1510.49(13) Å^3
Z	4
Density (calculated)	1.303 Mg / m^3
Absorption coefficient	0.216 mm^{-1}
F(000)	624
Crystal	Colourless Plate
Crystal size	0.25 × 0.10 × 0.02 mm^3
θ range for data collection	3.34 – 25.03°
Index ranges	$-11 \le h \le 11$, $-18 \le k \le 17$, $-12 \le l \le 12$
Reflections collected	4967
Independent reflections	2665 [R_{int} = 0.0406]
Completeness to θ = 25.03°	99.6 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9957 and 0.9481
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2665 / 0 / 191
Goodness-of-fit on F^2	0.960
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0494, $wR2$ = 0.1189
R indices (all data)	$R1$ = 0.0830, $wR2$ = 0.1372
Extinction coefficient	0.011(3)
Largest diff. peak and hole	0.289 and –0.198 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: All hydrogen atoms were placed in idealised positions and refined using a riding model.
Relative Chirality: C(7) = S, C(8) = S, C(10) = R, C(11) = R

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

Atom	x	y	z	U_{eq}	*S.o.f.*
C1	8379(3)	2647(2)	9274(3)	61(1)	1
C2	8755(3)	2888(2)	10572(3)	72(1)	1
C3	9679(3)	2372(2)	11473(3)	73(1)	1
C4	10226(3)	1614(2)	11087(3)	72(1)	1
C5	9857(3)	1376(2)	9782(3)	63(1)	1
C6	8924(3)	1898(2)	8864(2)	50(1)	1
C7	8541(2)	1678(2)	7432(2)	50(1)	1
C8	9740(3)	1797(2)	6765(2)	50(1)	1
C9	9654(3)	2665(2)	6043(3)	66(1)	1
C10	8709(2)	1388(2)	4367(2)	45(1)	1
C11	9483(2)	1039(2)	5778(2)	45(1)	1
C12	8645(2)	379(2)	6319(2)	46(1)	1

C13	7437(2)	870(2)	3574(2)	47(1)	1
C14	7527(3)	424(2)	2474(3)	59(1)	1
C15	6362(4)	−83(2)	1758(3)	77(1)	1
C16	5127(3)	−126(2)	2148(3)	82(1)	1
C17	5034(3)	329(2)	3224(3)	74(1)	1
C18	6170(3)	826(2)	3929(3)	61(1)	1
O1	8160(2)	743(1)	7262(2)	55(1)	1
O2	8417(2)	−384(1)	6028(2)	56(1)	1
S1	8216(1)	2530(1)	4565(1)	67(1)	1

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

C1–C6	1.376(4)	C1–C6–C5	118.8(2)
C1–C2	1.380(4)	C1–C6–C7	119.8(2)
C2–C3	1.364(4)	C5–C6–C7	121.3(2)
C3–C4	1.376(4)	O1–C7–C6	108.78(19)
C4–C5	1.384(4)	O1–C7–C8	104.78(18)
C5–C6	1.382(4)	C6–C7–C8	116.09(19)
C6–C7	1.505(3)	C9–C8–C11	109.0(2)
C7–O1	1.462(3)	C9–C8–C7	113.3(2)
C7–C8	1.539(3)	C11–C8–C7	103.36(18)
C8–C9	1.514(4)	C8–C9–S1	105.40(18)
C8–C11	1.531(3)	C13–C10–C11	117.30(18)
C9–S1	1.803(3)	C13–C10–S1	110.90(16)
C10–C13	1.510(3)	C11–C10–S1	106.24(15)
C10–C11	1.574(3)	C12–C11–C8	103.66(19)
C10–S1	1.823(2)	C12–C11–C10	115.17(18)
C11–C12	1.504(3)	C8–C11–C10	110.34(19)
C12–O2	1.201(3)	O2–C12–O1	120.8(2)
C12–O1	1.344(3)	O2–C12–C11	128.3(2)
C13–C14	1.378(3)	O1–C12–C11	110.9(2)
C13–C18	1.390(3)	C14–C13–C18	118.8(2)
C14–C15	1.405(4)	C14–C13–C10	119.7(2)
C15–C16	1.379(5)	C18–C13–C10	121.6(2)
C16–C17	1.364(5)	C13–C14–C15	119.8(3)
C17–C18	1.374(4)	C16–C15–C14	120.0(3)
C6–C1–C2	121.3(3)	C17–C16–C15	120.0(3)
C3–C2–C1	119.6(3)	C16–C17–C18	120.3(3)
C2–C3–C4	120.1(3)	C17–C18–C13	121.1(3)
C3–C4–C5	120.4(3)	C12–O1–C7	111.14(18)
C6–C5–C4	119.8(3)	C9–S1–C10	92.51(12)

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

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	68(2)	57(2)	55(2)	−6(1)	15(1)	0(1)
C2	85(2)	70(2)	66(2)	−15(2)	30(2)	−8(2)
C3	95(2)	81(2)	48(2)	−11(2)	27(2)	−30(2)
C4	83(2)	77(2)	50(2)	13(2)	8(1)	−17(2)
C5	76(2)	54(2)	56(2)	4(1)	14(1)	−2(1)
C6	58(1)	47(2)	45(1)	−3(1)	15(1)	−7(1)
C7	53(1)	45(2)	51(2)	−2(1)	13(1)	−2(1)
C8	53(1)	46(2)	48(1)	−3(1)	9(1)	−9(1)
C9	89(2)	49(2)	63(2)	−9(1)	24(2)	−17(1)
C10	54(1)	39(1)	45(1)	0(1)	15(1)	1(1)
C11	42(1)	42(1)	48(1)	0(1)	10(1)	0(1)
C12	47(1)	43(2)	45(1)	2(1)	7(1)	2(1)
C13	51(1)	39(1)	47(1)	7(1)	8(1)	2(1)
C14	72(2)	49(2)	53(2)	−1(1)	11(1)	3(1)
C15	102(2)	53(2)	61(2)	−12(2)	−2(2)	−1(2)
C16	74(2)	62(2)	88(2)	18(2)	−11(2)	−22(2)
C17	56(2)	84(2)	73(2)	23(2)	2(1)	−9(2)

C18	54(2)	68(2)	57(2)	11(1)	10(1)	3(1)
O1	61(1)	51(1)	55(1)	−9(1)	22(1)	−15(1)
O2	67(1)	38(1)	63(1)	1(1)	18(1)	−1(1)
S1	98(1)	40(1)	58(1)	4(1)	15(1)	11(1)

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1	7730	3007	8650	73	1
H2	8373	3410	10838	86	1
H3	9946	2535	12368	88	1
H4	10861	1252	11718	87	1
H5	10243	855	9519	75	1
H7	7696	2041	6960	60	1
H8	10698	1733	7418	60	1
H9A	10566	2790	5839	80	1
H9B	9446	3157	6574	80	1
H10	9435	1397	3864	55	1
H11	10423	773	5779	54	1
H14	8374	458	2202	71	1
H15	6424	−396	1005	93	1
H16	4342	−472	1667	98	1
H17	4181	303	3487	89	1
H18	6087	1144	4671	73	1

X-Ray Data for **10.23**

Table 1. Crystal data and structure refinement.

Identification code	**02sot115**	
Empirical formula	$C_{18}H_{18}N_2O_5S$	
Formula weight	374.40	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 5.5642(7) Å	α = 90°
	b = 19.724(3) Å	β = 91.795(12)°
	c = 8.2790(13) Å	γ = 90°
Volume	908.2(2) $Å^3$	
Z	2	
Density (calculated)	1.369 Mg / m^3	
Absorption coefficient	0.210 mm^{-1}	
F(000)	392	
Crystal	Plate; Colourless	
Crystal size	0.34 × 0.24 × 0.03 mm^3	
θ range for data collection	3.66 – 27.54°	
Index ranges	$-7 \le h \le 7$, $-16 \le k \le 25$, $-10 \le l \le 10$	
Reflections collected	2581	
Independent reflections	1965 [R_{int} = 0.0403]	
Completeness to θ = 27.54°	72.5 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9937 and 0.9321	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1965 / 1 / 238	
Goodness-of-fit on F^2	0.938	
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0475, *wR2* = 0.0815	
R indices (all data)	*R1* = 0.1219, *wR2* = 0.1020	
Absolute structure parameter	−0.09(13)	
Extinction coefficient	0.016(3)	
Largest diff. peak and hole	0.153 and −0.172 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:

All hydrogen atoms are fixed.
Please note that the sample was collected at room temperature.

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	7352(3)	1656(1)	3615(2)	59(1)	1
O1	7236(8)	1379(2)	5228(5)	74(1)	1
O2	9617(7)	1652(3)	2818(5)	76(1)	1
O3	5932(9)	1761(3)	85(5)	87(2)	1
O4	2507(8)	296(2)	488(4)	59(1)	1
O5	3761(8)	4450(2)	3657(5)	70(1)	1
N1	3937(10)	782(3)	3297(7)	54(2)	1
N2	2861(12)	446(3)	4112(8)	79(2)	1
C1	5250(11)	1184(3)	2439(7)	49(2)	1
C2	4685(12)	1328(4)	765(8)	61(2)	1
C3	2682(12)	974(3)	−145(7)	63(2)	1
C4	2978(15)	972(4)	−1951(7)	91(2)	1
C5	127(13)	38(4)	494(9)	74(2)	1
C6	108(12)	−700(3)	874(7)	57(2)	1
C7	1899(13)	−1024(4)	1719(8)	71(2)	1
C8	1775(14)	−1700(5)	2054(9)	82(2)	1
C9	−146(18)	−2086(4)	1519(10)	85(2)	1
C10	−1955(15)	−1769(5)	675(11)	92(3)	1
C11	−1841(13)	−1090(5)	364(8)	73(2)	1
C12	6242(10)	2494(3)	3613(7)	47(2)	1
C13	4276(11)	2639(4)	4505(7)	58(2)	1
C14	3371(11)	3293(4)	4564(8)	58(2)	1
C15	4469(12)	3787(3)	3687(8)	55(2)	1
C16	6435(12)	3627(4)	2761(7)	60(2)	1
C17	7299(12)	2981(4)	2705(8)	58(2)	1
C18	1816(13)	4639(4)	4621(10)	81(2)	1

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

S1–O2	1.441(4)	C4–H4C	0.9600
S1–O1	1.446(5)	C5–C6	1.490(9)
S1–C1	1.763(6)	C5–H5A	0.9700
S1–C12	1.765(6)	C5–H5B	0.9700
O3–C2	1.246(7)	C6–C7	1.358(8)
O4–C5	1.419(7)	C6–C11	1.384(9)
O4–C3	1.441(7)	C7–C8	1.364(10)
O5–C15	1.365(7)	C7–H7	0.9300
O5–C18	1.415(8)	C8–C9	1.375(11)
N1–N2	1.131(7)	C8–H8	0.9300
N1–C1	1.304(8)	C9–C10	1.360(11)
C1–C2	1.439(8)	C9–H9	0.9300
C2–C3	1.498(8)	C10–C11	1.366(10)
C3–C4	1.509(8)	C10–H10	0.9300
C3–H3	0.9800	C11–H11	0.9300
C4–H4A	0.9600	C12–C17	1.365(8)
C4–H4B	0.9600	C12–C13	1.370(7)
		C13–C14	1.386(9)
		C13–H13	0.9300

C14–C15	1.370(8)	C6–C7–C8	121.5(7)
C14–H14	0.9300	C6–C7–H7	119.2
C15–C16	1.392(8)	C8–C7–H7	119.2
C16–C17	1.362(9)	C7–C8–C9	121.3(7)
C16–H16	0.9300	C7–C8–H8	119.3
C17–H17	0.9300	C9–C8–H8	119.3
C18–H18A	0.9600	C10–C9–C8	117.7(8)
C18–H18B	0.9600	C10–C9–H9	121.1
C18–H18C	0.9600	C8–C9–H9	121.1
O2–S1–O1	119.1(3)	C9–C10–C11	120.7(8)
O2–S1–C1	108.6(3)	C9–C10–H10	119.7
O1–S1–C1	105.3(3)	C11–C10–H10	119.7
O2–S1–C12	108.4(3)	C10–C11–C6	121.8(7)
O1–S1–C12	109.2(3)	C10–C11–H11	119.1
C1–S1–C12	105.5(3)	C6–C11–H11	119.1
C5–O4–C3	114.0(5)	C17–C12–C13	121.0(6)
C15–O5–C18	117.9(5)	C17–C12–S1	120.3(5)
N2–N1–C1	176.4(6)	C13–C12–S1	118.7(5)
N1–C1–C2	122.4(5)	C12–C13–C14	120.7(6)
N1–C1–S1	113.1(4)	C12–C13–H13	119.6
C2–C1–S1	123.3(5)	C14–C13–H13	119.6
O3–C2–C1	117.5(6)	C15–C14–C13	118.3(6)
O3–C2–C3	120.6(6)	C15–C14–H14	120.8
C1–C2–C3	121.9(6)	C13–C14–H14	120.8
O4–C3–C2	107.9(5)	O5–C15–C14	123.8(6)
O4–C3–C4	111.6(5)	O5–C15–C16	116.0(6)
C2–C3–C4	113.4(6)	C14–C15–C16	120.2(6)
O4–C3–H3	107.9	C17–C16–C15	121.0(6)
C2–C3–H3	107.9	C17–C16–H16	119.5
C4–C3–H3	107.9	C15–C16–H16	119.5
C3–C4–H4A	109.5	C16–C17–C12	118.8(6)
C3–C4–H4B	109.5	C16–C17–H17	120.6
H4A–C4–H4B	109.5	C12–C17–H17	120.6
C3–C4–H4C	109.5	O5–C18–H18A	109.5
H4A–C4–H4C	109.5	O5–C18–H18B	109.5
H4B–C4–H4C	109.5	H18A–C18–H18B	109.5
O4–C5–C6	111.3(5)	O5–C18–H18C	109.5
O4–C5–H5A	109.4	H18A–C18–H18C	109.5
C6–C5–H5A	109.4	H18B–C18–H18C	109.5
O4–C5–H5B	109.4		
C6–C5–H5B	109.4		
H5A–C5–H5B	108.0		
C7–C6–C11	116.9(7)		
C7–C6–C5	123.9(6)		
C11–C6–C5	119.2(6)		

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	51(1)	55(1)	72(1)	−10(1)	−3(1)	6(1)
O1	94(3)	62(3)	64(3)	0(2)	−20(2)	7(2)
O2	45(3)	69(3)	114(3)	−14(3)	9(2)	6(3)
O3	115(4)	84(4)	62(3)	4(3)	11(3)	−33(3)
O4	63(3)	55(3)	60(3)	−1(2)	1(2)	−5(2)
O5	83(3)	43(3)	84(3)	−1(2)	4(3)	0(3)
N1	55(4)	56(4)	52(4)	−6(3)	4(3)	8(3)
N2	88(5)	88(5)	61(4)	3(4)	−2(3)	−16(4)
C1	51(4)	48(4)	48(4)	0(3)	11(3)	−1(3)
C2	79(5)	50(4)	56(5)	−6(3)	18(4)	−4(4)
C3	78(5)	52(5)	57(4)	−2(3)	−5(3)	1(4)
C4	140(7)	85(6)	48(4)	−4(4)	10(4)	−14(5)
C5	61(5)	62(5)	97(5)	−8(4)	0(4)	8(4)

C6	49(4)	68(5)	53(4)	−14(4)	0(3)	3(4)
C7	74(5)	51(5)	86(5)	−5(4)	−14(4)	−13(4)
C8	75(6)	71(6)	99(6)	2(5)	−5(4)	9(5)
C9	103(7)	59(5)	94(6)	−2(5)	31(5)	−7(5)
C10	78(6)	90(8)	108(7)	−25(5)	5(5)	−26(6)
C11	68(5)	73(6)	76(5)	−8(4)	−10(4)	−10(4)
C12	34(4)	50(4)	57(4)	−13(3)	−1(3)	5(3)
C13	52(4)	53(5)	67(5)	4(3)	11(4)	−4(4)
C14	57(4)	54(5)	63(5)	−5(4)	13(3)	7(4)
C15	62(5)	42(5)	59(4)	−1(3)	2(4)	−5(4)
C16	70(5)	57(5)	54(4)	4(3)	10(4)	−15(4)
C17	56(4)	63(5)	57(4)	5(4)	15(3)	−6(4)
C18	75(5)	59(5)	111(6)	−27(4)	7(5)	16(4)

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.*
H3	1181	1212	77	75	1
H4A	3146	1429	−2327	136	1
H4B	1589	768	−2470	136	1
H4C	4385	716	−2204	136	1
H5A	−649	113	−556	88	1
H5B	−780	281	1292	88	1
H7	3240	−778	2076	85	1
H8	3015	−1903	2657	99	1
H9	−206	−2549	1727	102	1
H10	−3285	−2016	306	110	1
H11	−3107	−883	−207	87	1
H13	3539	2295	5078	69	1
H14	2052	3394	5184	69	1
H16	7171	3966	2172	72	1
H17	8584	2875	2060	70	1
H18A	419	4379	4309	122	1
H18B	1481	5113	4472	122	1
H18C	2228	4554	5738	122	1