Transition Metal Catalysis: Application to the Synthesis of Novel Heterocycles

by

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Abstract

Methods for the preparation of medium ring ethers are reviewed.

A new method of preparing oxonanes is described, which involves the oxidative cleavage of a 1,3,4,5,6,7-hexahydrobenzo[c]furan. This method has been applied to the synthesis of obtusan, the saturated oxonane containing the carbon skeleton of the marine natural product obtusenyne. This methodology has been further extended to include the preparation of azonanes.

The preparation and rhodium(II) catalysed decomposition of diazoamides has been studied. It has been shown that diazoanilides give rise to oxindole products when treated with catalytic amounts of either rhodium(II) trifluoroacetamide or rhodium(II) perfluorobutyramide. Rhodium(II) acetate has been shown to favour the formation of cyclopropanes and β-lactams

Model studies towards the synthesis of the cytotoxic marine natural product diazonamide A were carried out as follows. 7-Bromo-3-phenylbenzofuran-2-one was prepared by rhodium(II) catalysed decomposition of a diazoester, and by a simple acid catalysed condensation of 2-bromophenol with mandelic acid. Attempts to introduce an aryl group at the 7-position by a palladium catalysed cross coupling reaction were unsuccessful. 7-Bromo-3-phenylbenzo[b]furan was prepared using standard chemistry. The boronic acid derived from this compound was coupled with a 4-bromoindole derivative to give a 4-(benzo[b]furan-7-yl)indole related to the biaryl portion of diazonamide A

Acknowledgements

This thesis and the work described herein would not have been possible without a great deal of help from a large number of people. First of all I would like to thank my supervisor, Christopher J. Moody, for much help and encouragement over the last three years. I would also like to thank Timothy J. Mowlem for his enthusiastic participation in this project, especially during the three months I spent working in the laboratories of Shell Research, Sittingbourne. I am grateful to Albert Padwa and Joe Marino for their collaboration on the work described in Chapter 3. In addition, Harry Heaney, Brian Marples, Russ Bowman, Jon Williams and Mike Shipman have all offered useful advice and help during the course of this work.

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Finally, I would like to thank my parents for their support in everything I do, and my wife Sylvie for her unshakeable love and faith in me. Without this support I would not have made it this far.

Mark C. Elliott
September 1994

To Sylvie

What a catalyst you turned out to be...

The Jam, Eton Rifles

Contents

Abbreviations

Ac	acetyl
Bu	butyl
Bn	benzyl
Bz	benzoyl
CSA	camphorsulfonic acid
DBU	diazabicycloundecane
dec.	decomposed
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
Et	ethyl
HMPA	hexamethylphosphoramide
KHMDS	potassium hexamethyldisilazide
LiHMDS	lithium hexamethyldisilazide
mCPBA	*meta*-chloroperbenzoic acid
Me	methyl
MOM	methoxymethyl
Ms	methanesulfonyl
NMMO	*N*-methylmorpholine-*N*-oxide
PDC	pyridinium dichromate
Ph	phenyl
i-Pr	isopropyl
Pv	pivaloyl
py	pyridine
rt	room temperature
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*t*-butyldiphenylsilyl
TBS	*t*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
2-Th	2-thienyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TPS	triisopropylsilyl
TPP	tetraphenylporphine
Ts	4-toluenesulfonyl

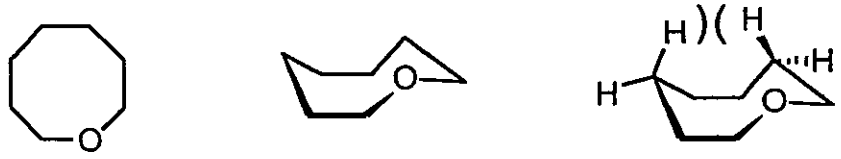
Chapter 1

Recent developments in the synthesis of medium ring ethers

Recent developments in the synthesis of medium ring ethers

1.1. Introduction

Medium sized rings, both carbocyclic and heterocyclic, are widely recognised as being difficult to prepare.[1] The reasons for this difficulty are both entropic and thermodynamic. For a cyclisation reaction to occur, the two ends of an acyclic precursor must come into close proximity. As the chain length increases the likelihood of this happening is reduced. This is reflected in the decreasing entropy of reaction as the ring size increases. We might therefore expect the ease of cyclisation to decrease indefinitely with increasing ring size. However, once the ring size increases above 10-membered the cyclisation reaction becomes more facile. The reason for this effect is the stability of the ring itself, and is illustrated by a recent study of the conformations of the parent saturated eight membered oxygen heterocycle, oxocane (**1**). Meyer *et al.* have shown,[2] by molecular mechanics calculations and NMR studies, that the lowest energy conformation of oxocane is **2**.



1 **2** **3**

Figure 1

Even in this preferred conformation there is a significant amount of steric crowding, or transannular strain (see **3**). When the hydrogen atoms are replaced by bulkier substituents one can expect this strain to increase, making cyclisation even more difficult.

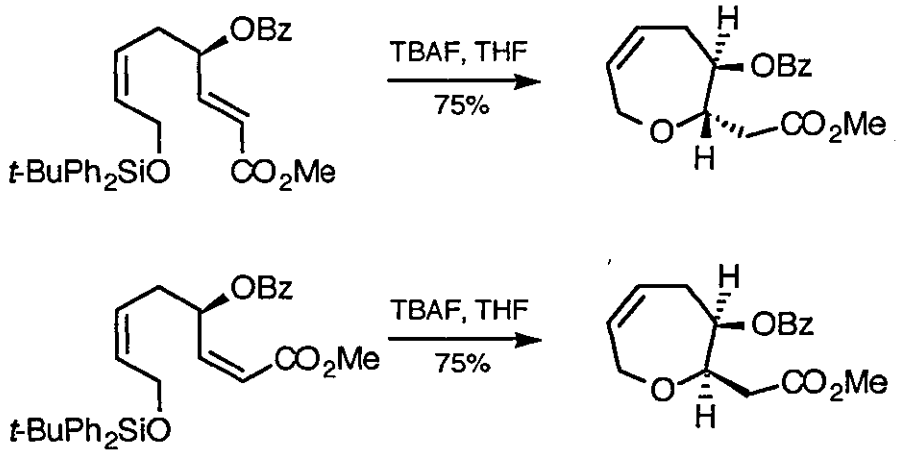
Many syntheses of 7 - 9 membered cyclic ethers have been reported since this subject was last reviewed.[3] Much of the impetus behind this work has been influenced by the structures of the monocyclic (*Laurencia* derived,[4] *etc.*) and polycyclic (brevetoxin,[5] ciguatoxin) natural products containing these functionalities. This review covers the literature on medium ring ether synthesis from 1 October 1990 to 30 June 1994, with emphasis on methods

specifically designed for the synthesis of such compounds rather than extensions of tetrahydropyran synthesis to larger ring sizes. Examples of 6-membered ring formation have, however, been included in some cases in order to explain mechanistic points.

The reactions have been classified into those involving C-O bond formation, C-C bond formation, rearrangement and ring expansion as the cyclic ether forming step. Also a number of groups have developed general methods for the conversion of lactones into cyclic ethers, and a section on these reactions has been included. However, in cases where the lactone has been formed using novel chemistry these reactions have been included elsewhere in the appropriate section.

1.2. Cyclisation by C-O bond formation

V. S. Martin *et al.* have shown[6] that oxepanes can be formed in good yield by an intramolecular hetero-Michael reaction (**Scheme 1**), although the *cis*-double bond in the substrate proved necessary for cyclisation to occur.

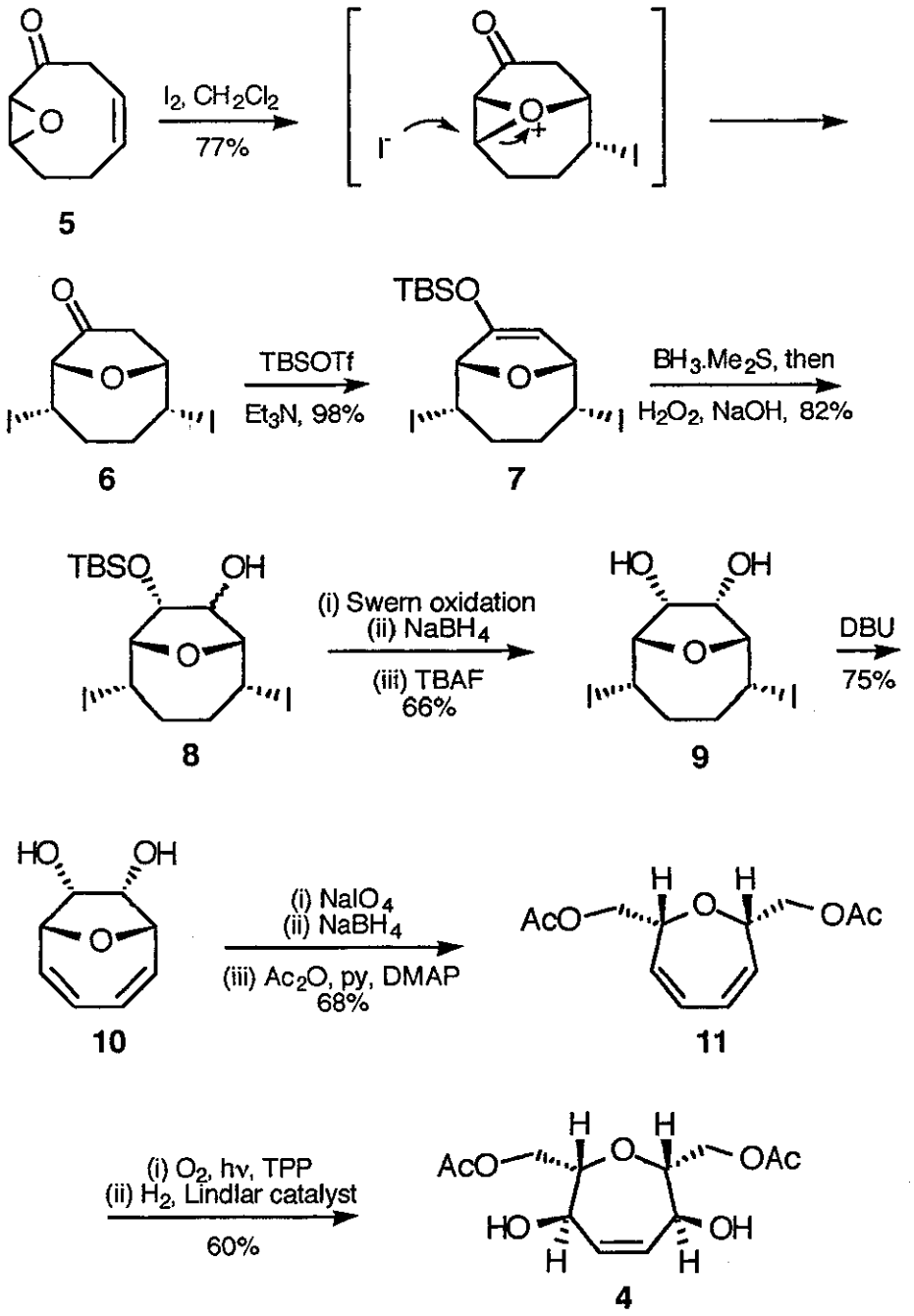


Scheme 1

Nevertheless since oxepane rings in natural products are often unsaturated, any methodology which permits the inclusion of a double bond is valuable. The stereochemistry of the cyclisation can be controlled by the double bond geometry of the Michael acceptor, and therefore either diastereomer of the oxepane can be readily accessed.

This methodology is versatile, and has also been applied to the preparation of tetrahydropyrans and tetrahydrofurans. As expected, in these cases no *cis*-double bond was required for cyclisation to occur.[7,8]

J. D. Martin and colleagues have embarked upon an ambitious program towards the development of methodology for the synthesis of polycyclic medium ring ethers.[9] The symmetrical unsaturated oxepane **4** has been prepared by the route shown in **Scheme 2**.[10]

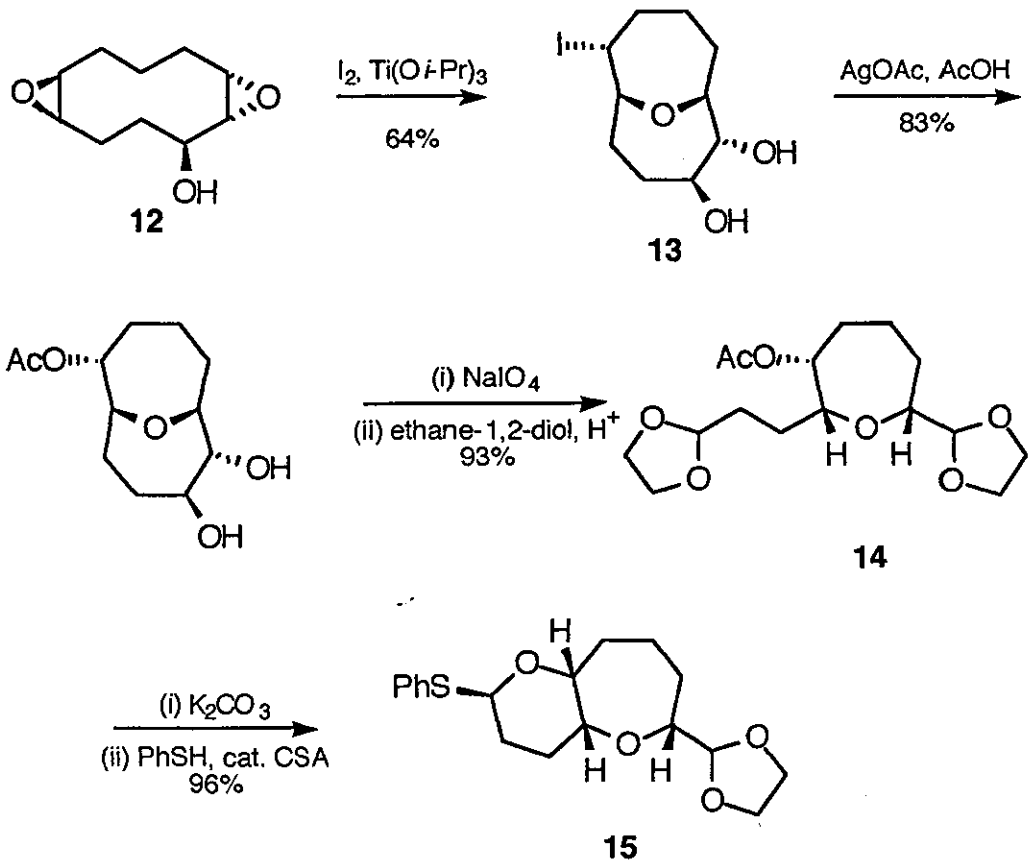


Scheme 2

The bicyclic ketone **6** was prepared[11] by iodination of the cyclooct-3-enone-7,8-epoxide **5**. Its silyl enol ether **7** was hydroborated and oxidised to give **8**. Further oxidation followed by a diastereocontrolled

reduction and deprotection gave the *cis*-diol **9**. Treatment with DBU led to the formation of diene **10**, the diol moiety of which was cleaved with periodate to give, after reduction and protection, the oxepane **11**. Reaction with singlet oxygen followed by reduction gave the desired oxepane **4**, containing the functionality and stereochemistry of the oxepane rings found in polycyclic natural products such as ciguatoxin and the brevetoxins.

A similar transannular iodine mediated epoxide opening of the diepoxide **12** provided the oxacycle **13**. Acetolysis was followed by oxidative cleavage of the diol as above to give, after aldehyde protection, the oxepane **14**. Further manipulation provided the 6-7 fused system **15** as a single stereoisomer (**Scheme 3**).[12]

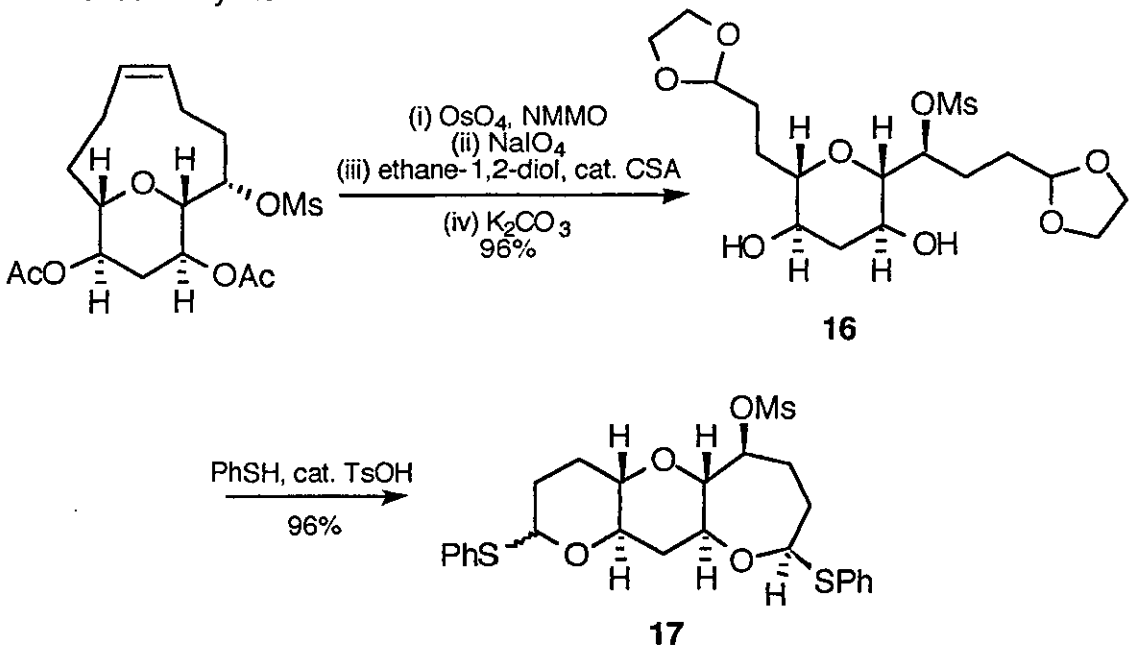


12 **13** **14** **15**

Scheme 3

This method, involving acid catalysed treatment of a hydroxy-acetal in the presence of thiophenol, can also be used to prepare 7-membered rings (**Scheme 4**).[13] The tetrahydropyran precursor **16** was prepared in a similar manner to the above oxepane. Treatment with thiophenol in the presence of

catalytic *p*-toluenesulfonic acid led to the formation of the 6-6-7 fused system **17** in excellent yield.



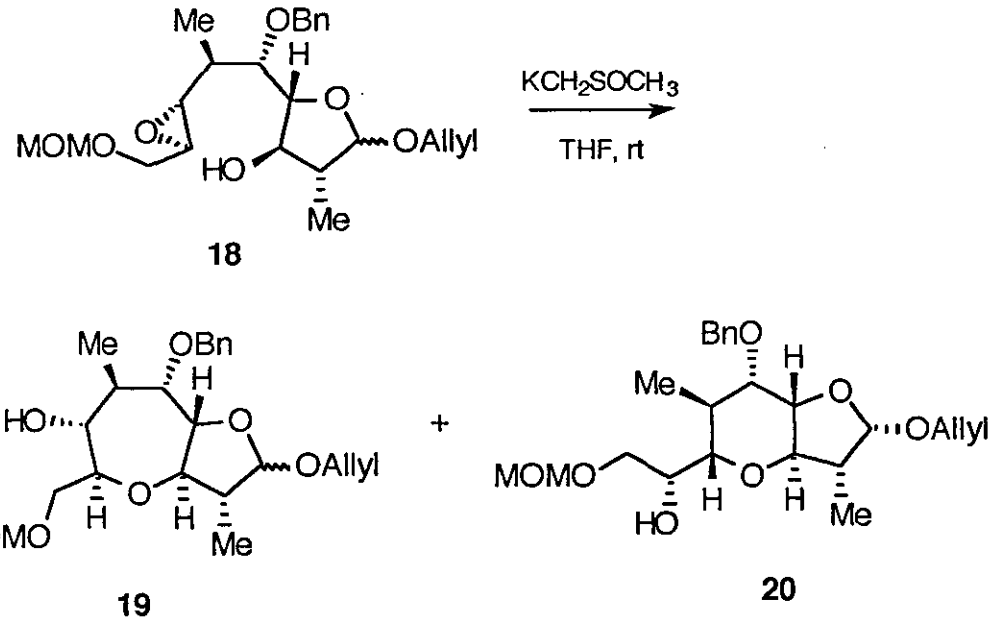
16

17

Scheme 4

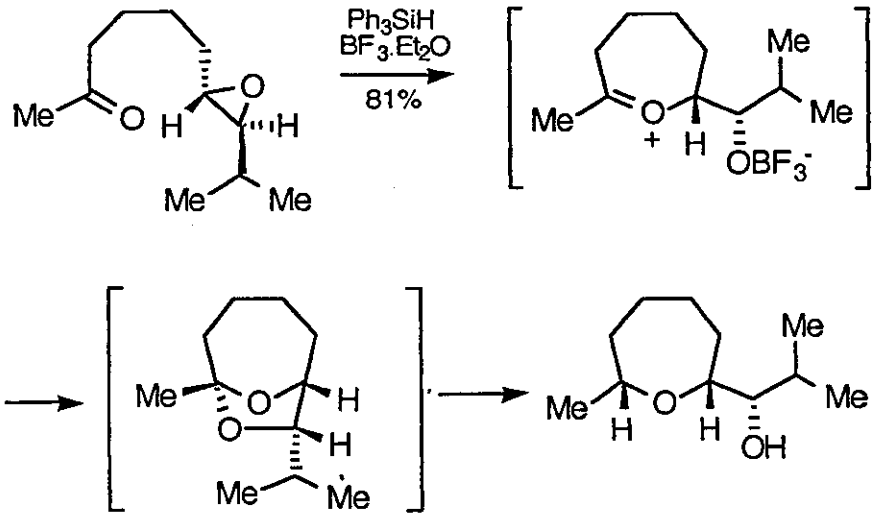
Oxidation of the thioacetal to the sulfone would presumably allow further carbon-carbon bond formation, a process which Martin has described in similar systems.[14]

Recent studies towards ciguatoxin have shown that treatment of a 3:2 anomeric mixture of epoxy alcohols **18** with base produces a mixture of oxepane **19** and tetrahydropyran **20**. It was further shown that the β-anomer produced only the oxepane whereas the α-anomer produced a 1.7:1 mixture of oxepane and tetrahydropyran (**Scheme 5**).[15]



Scheme 5

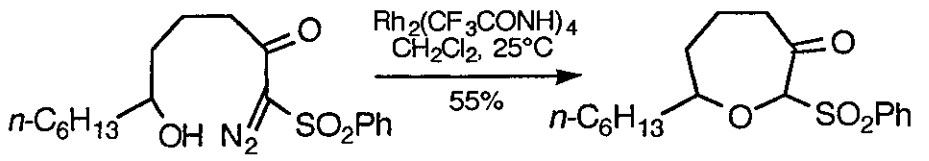
Kotsuki has previously described the use of bicyclic ketals in medium ring ether synthesis.[16] Fotsch and Chamberlin[17] have described a novel variant of this method which involves the intramolecular opening of an epoxide by a carbonyl oxygen (**Scheme 6**).



Scheme 6

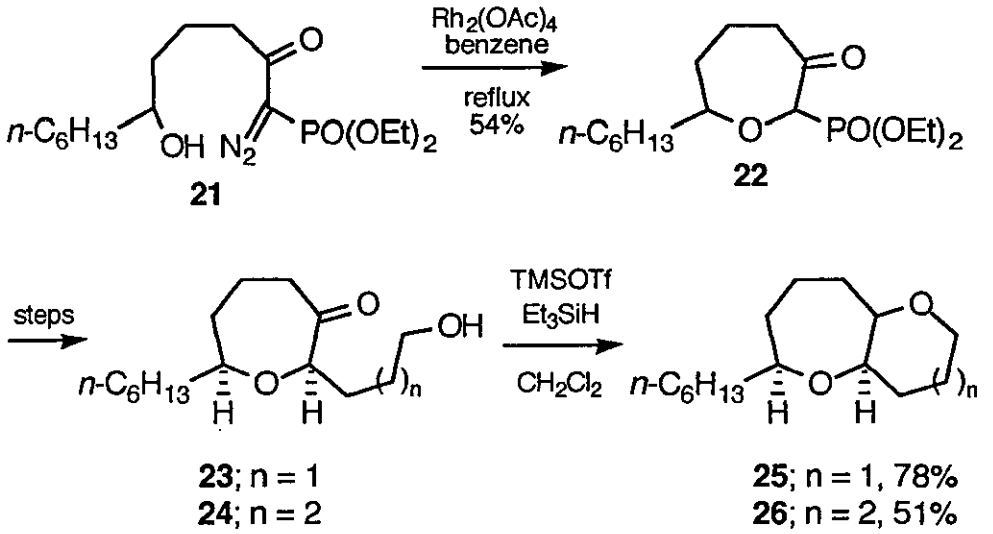
Moody *et al.* have shown that some of the earlier described rhodium(II) acetate catalysed cyclisations leading to oxepanes can be carried out under milder conditions using the more active catalyst rhodium(II) trifluoroacetamide.[18] The reaction shown (**Scheme 7**) can be carried out at

room temperature in dichloromethane, whereas using rhodium(II) acetate as catalyst, heating under reflux in benzene was required to effect conversion.[19]



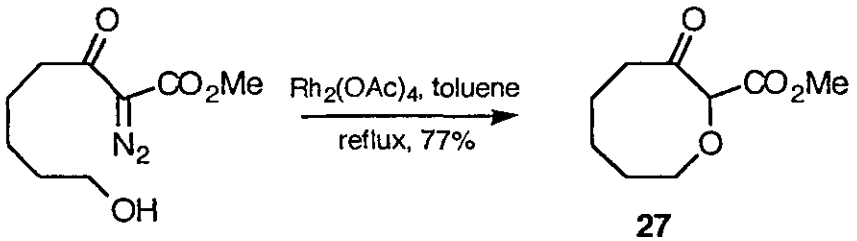
Scheme 7

In related work,[20] the cyclisation of the diazophosphonate **21** resulted in the formation of the corresponding oxepane-2-phosphonate **22**, which was transformed into the *cis*-2,7-disubstituted oxepanes **23** and **24** using standard chemistry. Cyclisation to the 7-6 and 7-7 bicyclic systems **25** and **26** was effected by treatment with TMSOTf and triethylsilane, conditions originally developed by Olah[21] and used to great effect by Nicolaou (see later). Although the reaction predominantly gave the *trans*-ring fused ethers, the stereoselectivity was at best 3:1 (**Scheme 8**).



Scheme 8

The rhodium carbenoid cyclisation can also be used for the formation of 8-membered rings. Meier *et al.* have improved on the earlier reported yield[22] for the synthesis of the oxocane **27** by the use of high dilution techniques and slow addition.[23] A fivefold increase in dilution led to an increase in yield from 31% to 77%.



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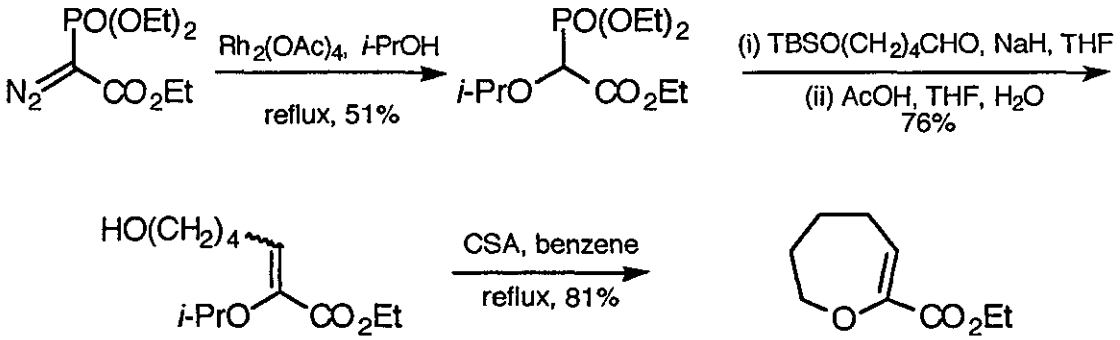
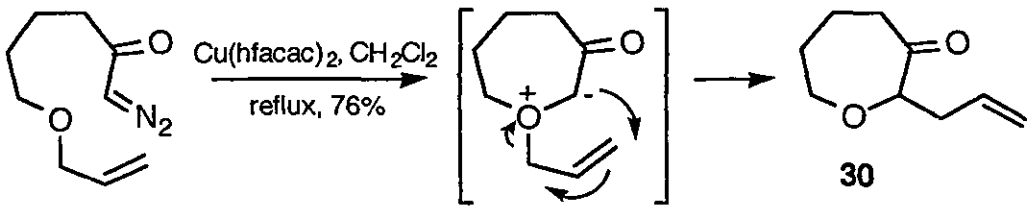
Scheme 9

In an alternative procedure intermolecular rhodium(II) catalysed O-H insertion reactions were used; these were followed by a Wadsworth-Emmons reaction and simple acid catalysed cyclisation (**Scheme 10**).[24]

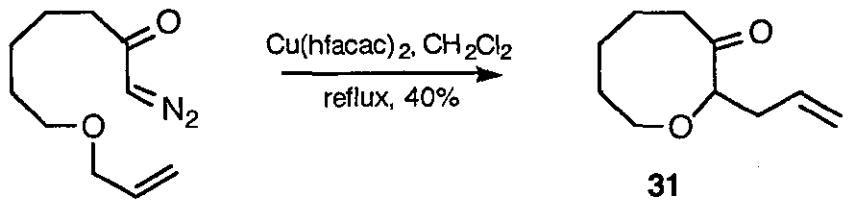


Scheme 10

A further carbenoid based approach to medium ring ether synthesis has been described by Clark and co-workers (**Scheme 11**).[25] The oxonium ylide **29** formed by transition metal catalysed decomposition of the diazo compound **28** rearranges by a [2,3]-sigmatropic shift to give the oxepane **30**. This process also gives, albeit in lower yield, the oxocane **31**.



28 **29** **30**



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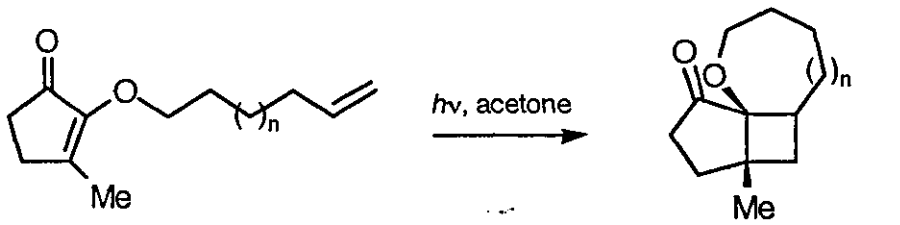
Scheme 11

Copper(II) hexafluoroacetylacetonate is the catalyst of choice, rhodium(II) acetate, the more commonly used catalyst for such reactions, being less selective in that C-H insertion products are also obtained, resulting in a lower yield of the desired cyclic ethers.

Pirrung has described a sequence of photochemical reactions which involve medium ring ethers at two stages.[26] Irradiation of cyclopentanone enol ethers **32** and **33** gave the fused cyclobutanes **34** and **35** containing oxepane and oxocane rings respectively (**Scheme 12**).

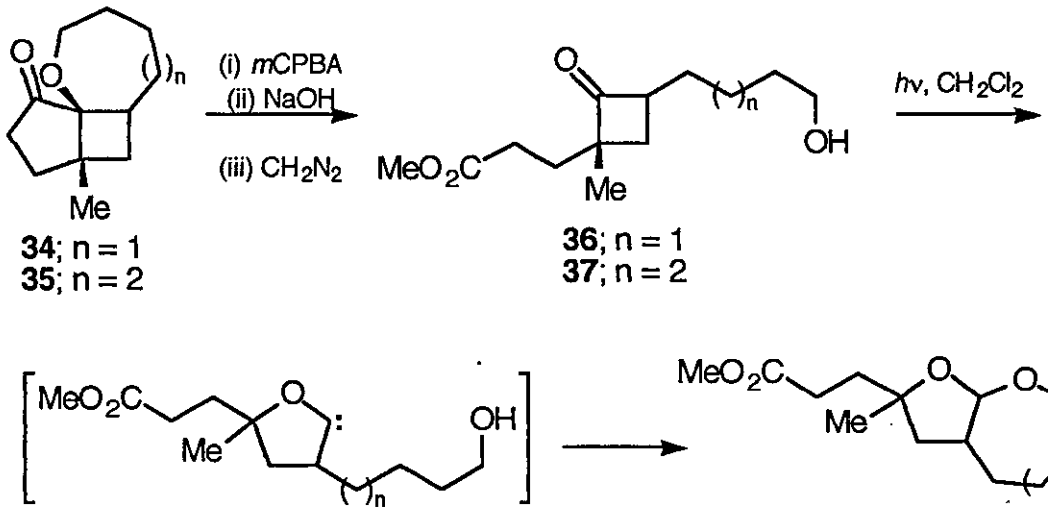


32; n = 1
33; n = 2

34; n = 1, 73%
35; n = 2, 30 - 40%

Scheme 12

Baeyer-Villiger oxidation of **34** and **35** followed by hydrolysis and esterification gave the cyclobutanones **36** and **37** respectively. Photolysis of cyclobutanones is believed to proceed via a 2-tetrahydrofuranylidene, *e.g.* **38** and **39**. This oxacarbene then inserts into O-H bonds to give moderate yields of the oxepane **40** and oxocane **41** acetals as shown in **Scheme 13**.



34; n = 1
35; n = 2

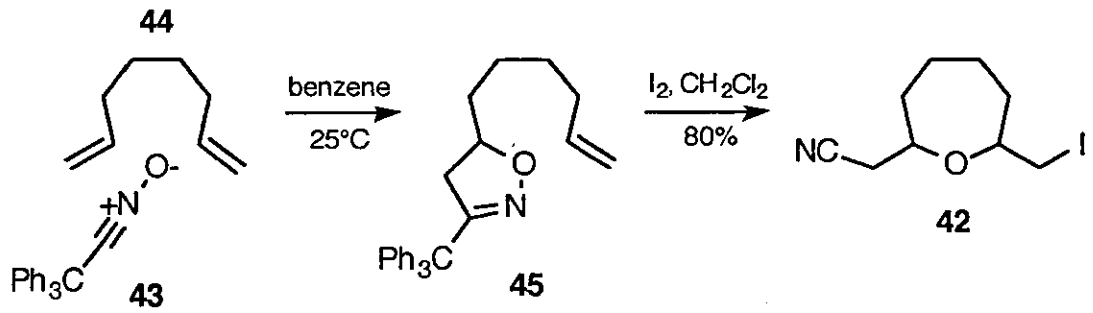
36; n = 1
37; n = 2

38; n = 1
39; n = 2

40; n = 1, 53%
41; n = 2, 49%

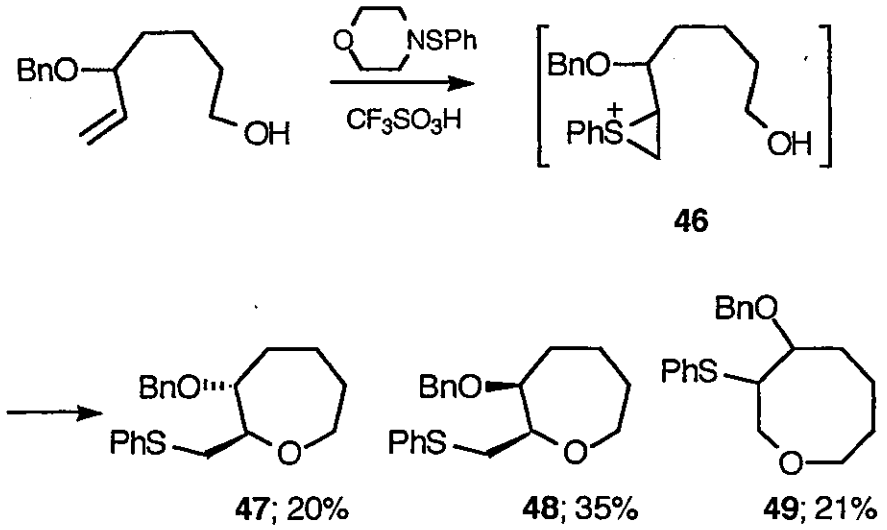
Scheme 13

A simple two step procedure has been used to prepare the functionalised oxepane **42** from 1,7-octadiene.[27] Cycloaddition of triphenylacetonitrile oxide (**43**) with 1,7-octadiene (**44**) gave the isoxazoline **45** in almost quantitative yield. Treatment with iodine then gave the oxepane **42** in 80% overall yield (**Scheme 14**). However following the same protocol using 1,8-nonadiene resulted in none of the corresponding oxocane.



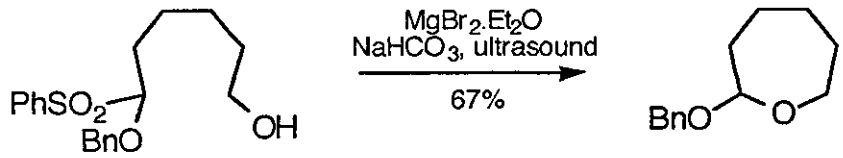
Scheme 14

Intramolecular 7-*exo* cyclisation of an alcohol onto an thiiranium ion **46** gave a mixture of diastereomeric oxepanes **47** and **48** along with a single isomer of the oxocane **49**. As expected oxepane formation was the predominant process (**Scheme 15**).[28]



Scheme 15

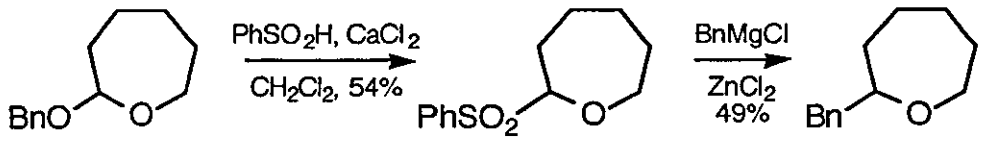
5- to 8-membered ring lactol ethers, *e.g.* **51**, are formed in good yield by the intramolecular cyclisation of ω-hydroxy-α-sulfonylmethanoethers **50**.[29]



50 **51**

Scheme 16

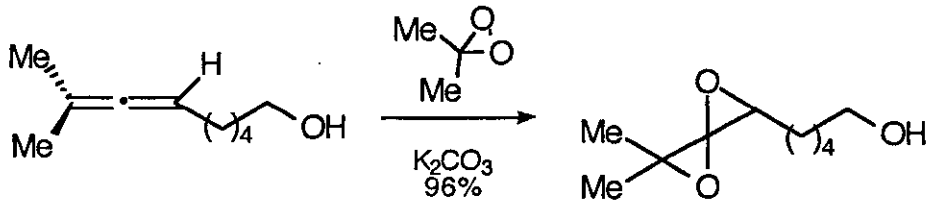
Exchange with benzenesulfinic acid gave the 2-phenylsulfonyloxepane **52** which was allowed to react with benzylmagnesium chloride to give 2-benzyloxepane (**53**).[29]



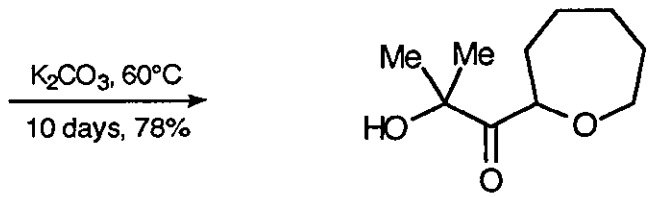
51 **52** **53**

Scheme 17

Dimethyldioxirane oxidation of the ω-hydroxyallene **54** gave the isolable bis-epoxide **55**. Simply heating this compound at 60°C for 10 days in the presence of potassium carbonate gave a 78% yield of the oxepane **56**.[30]



54 **55**

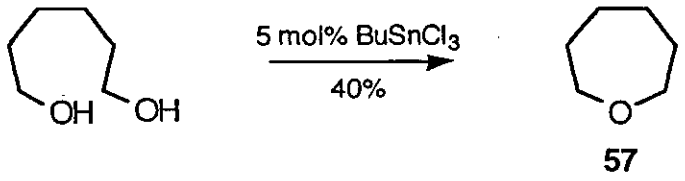


56

Scheme 18

Although direct cyclisation of 1,6-diols is not generally an efficient method for the production of oxepanes, Tagliavini *et al.* have shown[31] that a catalytic amount of butyltin trichloride promotes this cyclisation by way of an organotin

alkoxide. Water and the product oxepane **57** are co-distilled out of the reaction (**Scheme 19**).



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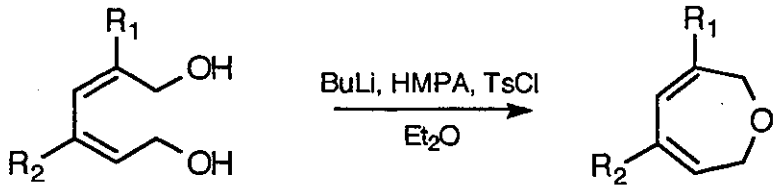
Scheme 19

Cyclisation of diols can, however, be efficient if the conformational mobility of the substrate is reduced. The presence of two *cis*-alkene moieties in the diols **58** facilitates the cyclisation to the dihydrooxepins **59**.[32]

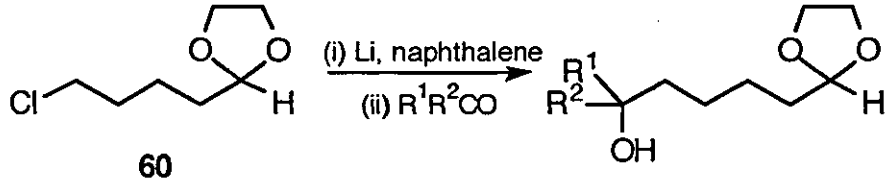


58 **59**

R^1 = *t*-Bu, R^2 = H 85%
R^1 = H, R^2 = *t*-Bu 87%

Scheme 20

The hydroxyaldehydes **61**, prepared as shown in **Scheme 21**, cyclise efficiently to the oxepanes **62** upon treatment with trimethylsilyl cyanide. The yields shown are for the three step process from **60**.[33]



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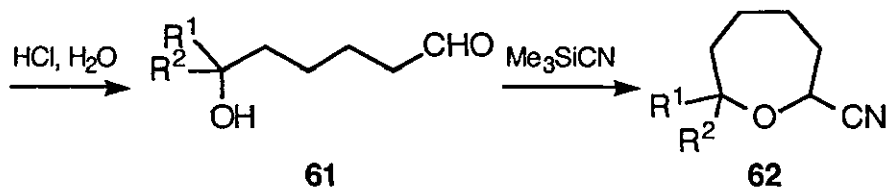
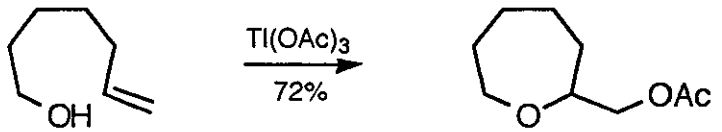


61 **62**

R^1 = H, R^2 = Ph (36%)
R^1 = R^2 = Me (22%)
R^1 = R^2 = Et (39%)
R^1R^2 = -$(CH_2)_5$- (34%)

Scheme 21

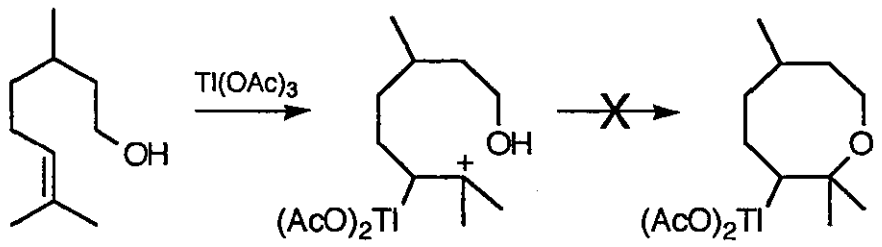
Thallium(III) acetate has been found to promote the intramolecular cyclisation of hydroxyalkenes **63**. This reaction works best for the formation of tetrahydropyrans, but is still efficient for the preparation of tetrahydrofurans and oxepanes, *e.g.* **64**.[34]



63 **64**

Scheme 22

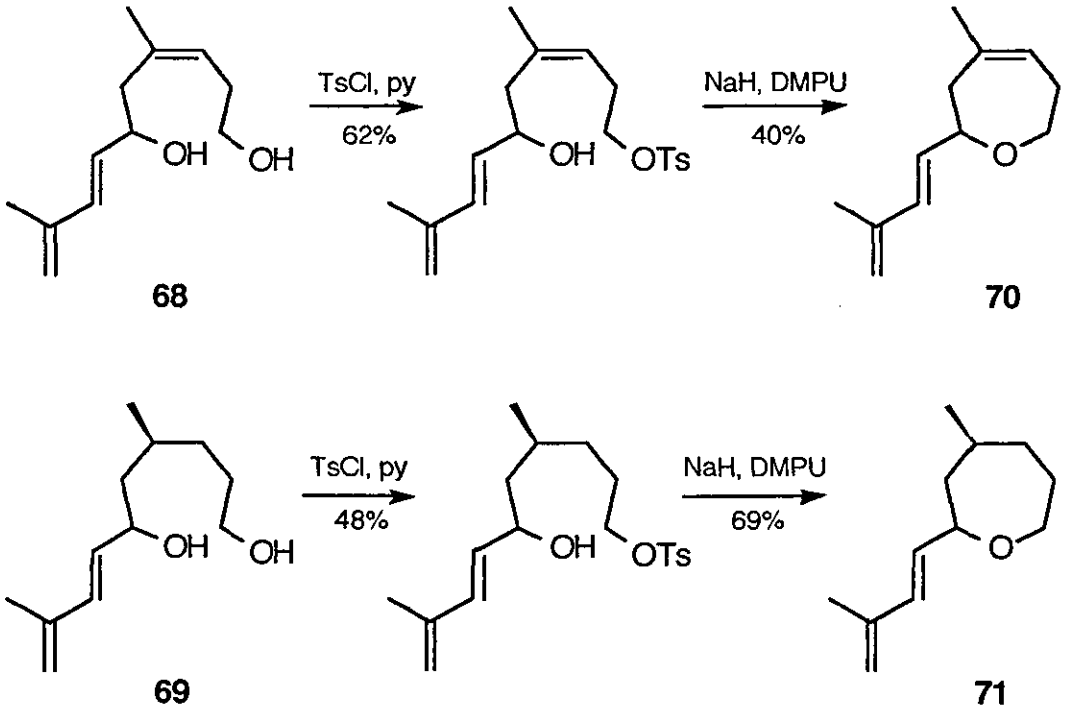
However oxocane formation is unsuccessful, as is oxepane formation from citronellol (**65**). These observations suggest that the reaction proceeds *via* Markovnikov addition of thallium(III) acetate to give the more stable carbenium ion **66**. Thus, in the case of citronellol, cyclisation would give the oxocane **67**, which is presumably disfavoured on entropic grounds (**Scheme 23**).



65 **66** **67**

Scheme 23

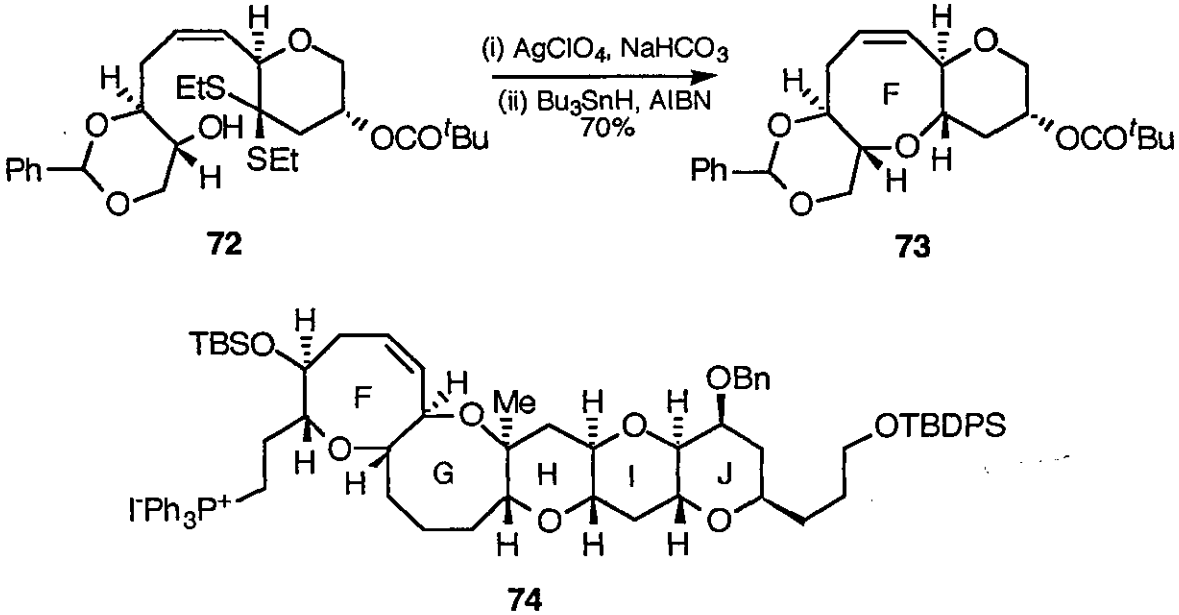
Terpenoid oxepanes **70** and **71**, isolated from quince fruit, have been synthesised from the corresponding diols **68** and **69**. The primary alcohol was selectively tosylated and cyclisation was effected using sodium hydride in DMPU (**Scheme 24**).[35]



Scheme 24

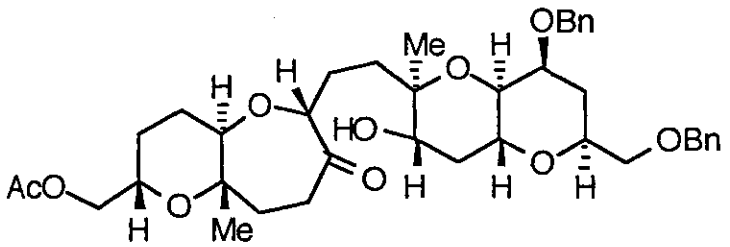
Surprisingly, in this case the inclusion of a double bond in the acyclic precursor **68** actually resulted in a lower yield of the cyclised product **70**.

The 8-8-6-6-6 fused system **74** which corresponds to the FGHI and J rings of brevetoxin A has been synthesised by the Nicolaou group. Both oxocanes were formed by cyclisation of an alcohol onto a dithioketal. One of the cyclisations (**72** to **73**) is shown in **Scheme 25**.[36]

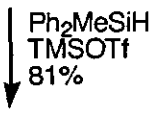


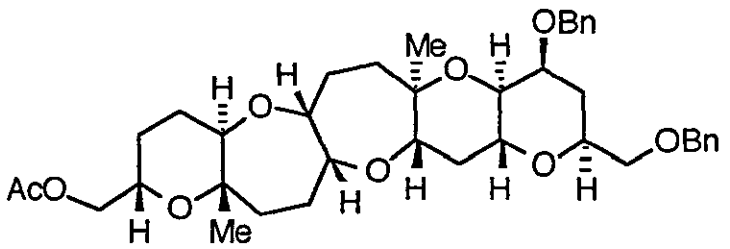
Scheme 25

The same workers have prepared hemibrevetoxin B (see later) and its epimer, (7aα)-*epi*-hemibrevetoxin B using a range of cyclisation chemistry developed for this purpose. The C-ring was prepared using the simple but effective reductive cyclisation of a hydroxyketone (**75** to **76**) as shown in **Scheme 26**.[37]



75



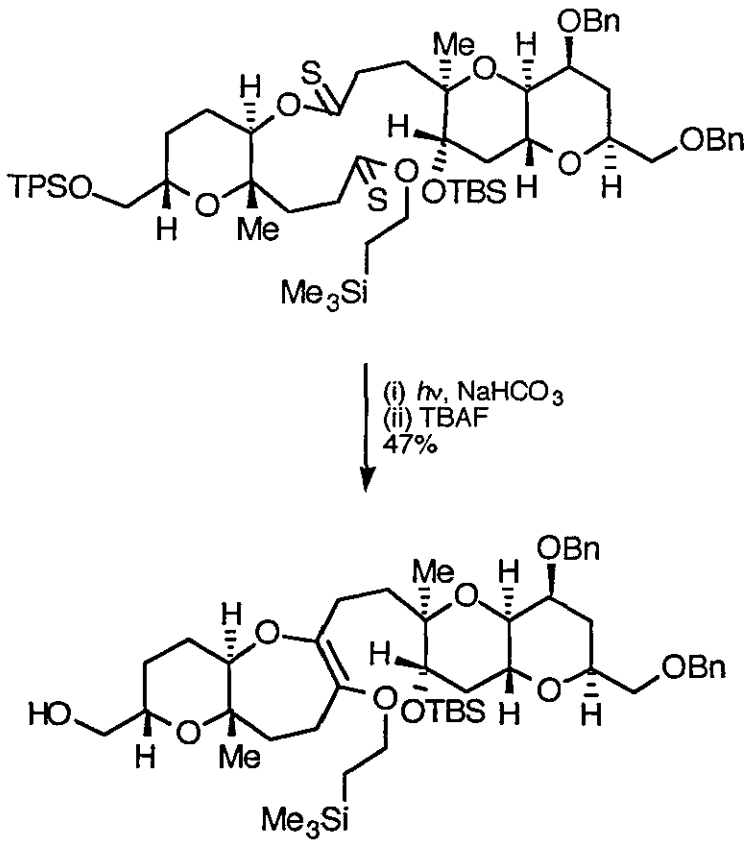


76

Scheme 26

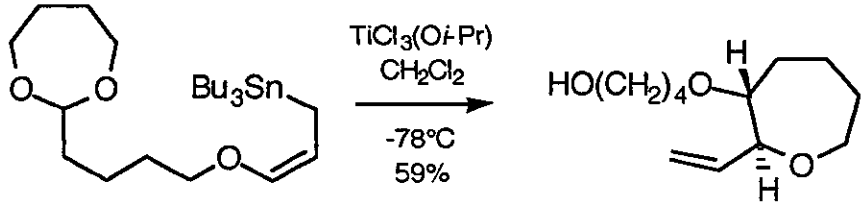
1.3. Cyclisation by C-C bond formation

The B-ring of (7aα)-*epi*-hemibrevetoxin B was prepared using the photochemical cyclisation of a bis-thioester (**Scheme 27**).[37]



Scheme 27

Yamamoto's group have developed an efficient route to β-alkoxy substituted cyclic ethers related to the brevetoxin natural products. Lewis acid treatment of the stannane **77** gave a 59% yield of **78** as a single *trans*-diastereoisomer (**Scheme 28**).[38]

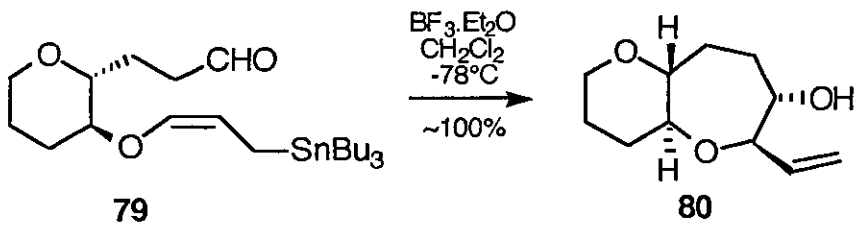


77 **78**

Scheme 28

A similar cyclisation was used to prepare the AB-ring fragment of gambiertoxin 4B. Treatment of chiral non-racemic **79** with boron trifluoride etherate gave an essentially quantitative yield of the fused oxepane **80**.[39] An earlier report[38] suggested that the fusion of a cyclohexyl ring makes cyclisation more favourable by reducing the conformational mobility of the

acyclic precursor. Presumably the tetrahydropyran ring exerts the same effect in this case (**Scheme 29**).

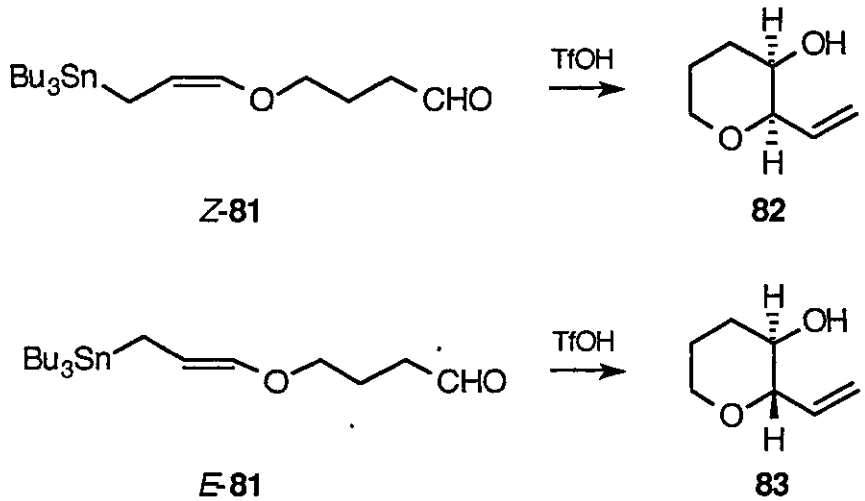


79 **80**

Scheme 29

The cyclisation onto aldehydes is generally accompanied by higher stereocontrol than the acetal cyclisations. In cases where diastereoselectivity is low, the use of titanium(IV) chloride in conjunction with triphenylphosphine can be advantageous.[40] The aldehyde cyclisations have been used to prepare 6-7-7-6 and 7-7-6-6 fused systems related to brevetoxin B and hemibrevetoxin respectively.[41,42]

This methodology is equally applicable to the synthesis of tetrahydropyrans. In this case the reaction has been studied under a wide range of conditions.[43] It has been found that if a protic acid is used, the sense of diastereocontrol is determined by the double bond geometry (**Scheme 30**). However Lewis acid promoted cyclisation of *E* or *Z* **81** produced the same *trans*-isomer **83**.



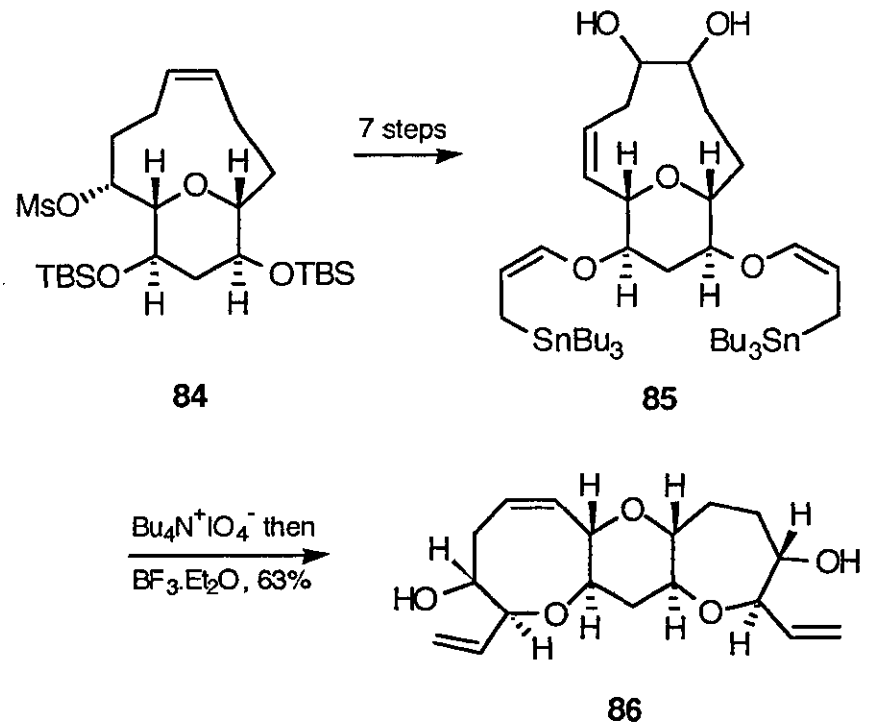
Z-**81** **82**

E-**81** **83**

Scheme 30

Martin has shown that this type of cyclisation can be applied to the preparation of the heavily functionalised 8-6-7 fused system **86**. The protected diol **84** (the diacetate analogue of which was earlier used in the preparation of the 6-6-7 fused system **17**, see **Scheme 4**) was converted into the

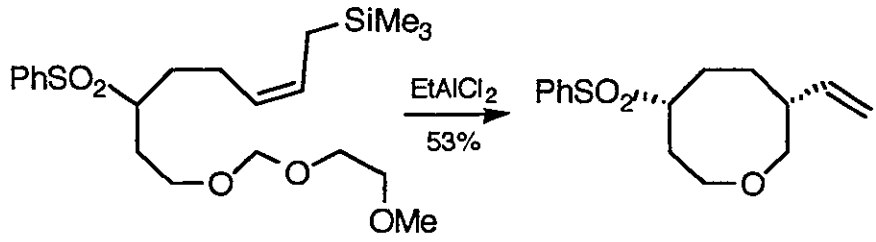
bis-stannane **85**. This was then oxidised and cyclised to **86** in a one-pot process (**Scheme 31**).[44]



84 **85** **86**

Scheme 31

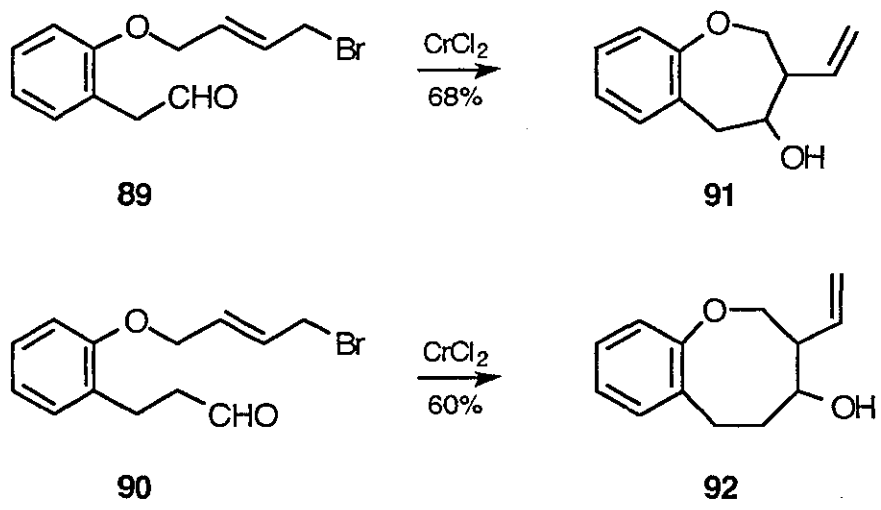
Cyclisation of allylsilanes onto acetals proceeds similarly to the analogous allylstannane cyclisations (**Scheme 32**).[45] In this case an acyclic acetal **87** was used, such that one of the acetal oxygen atoms is retained in the oxacyclic ring **88**. This is therefore an *endo* cyclisation rather than an *exo* acetal cyclisation as described by Yamamoto.



87 **88**

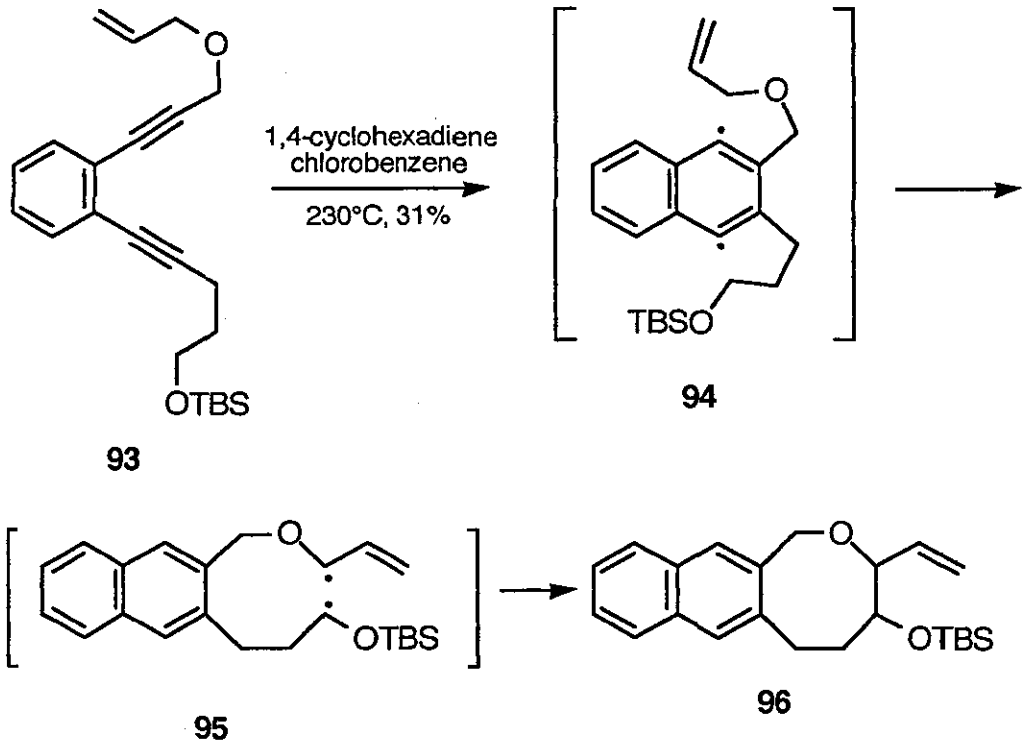
Scheme 32

A further similar example is provided by the chromium mediated cyclisation of bromo aldehydes **89** and **90** to give fused oxepanes **91** and oxocanes **92** (**Scheme 33**).[46] Attempted production of a benzopyran by this method failed, elimination to give the phenol (salicylaldehyde) predominating.



Scheme 33

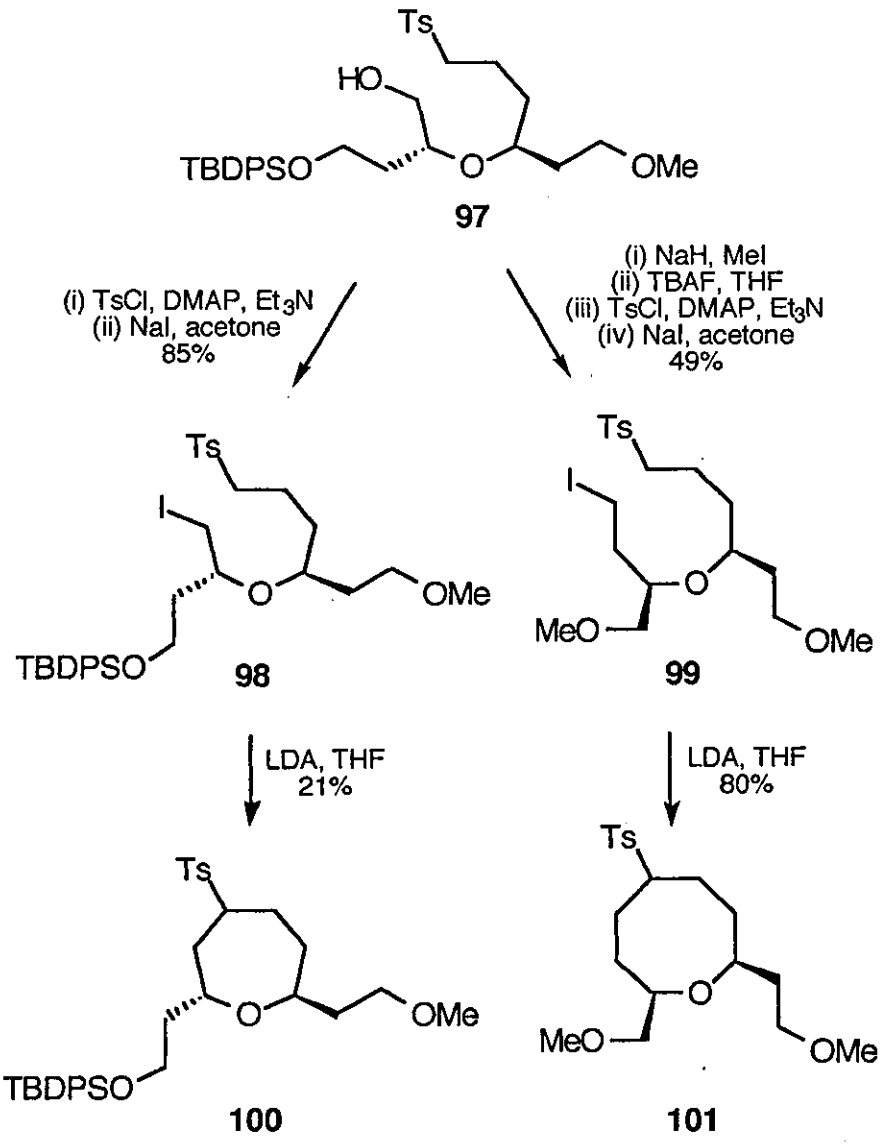
A similar oxocane **96** is formed, albeit in low yield, by the process shown in **Scheme 34**.[47] Bergman cyclisation of the enediyne **93** gives the diradical **94** which rearranges by two [1,5] shifts to the diradical **95**. Recombination then gives the oxocane **96**.



Scheme 34

An elegant approach to oxepanes and oxocanes from a common precursor has recently been reported by Mujica *et al.*[48] whereby the alcohol

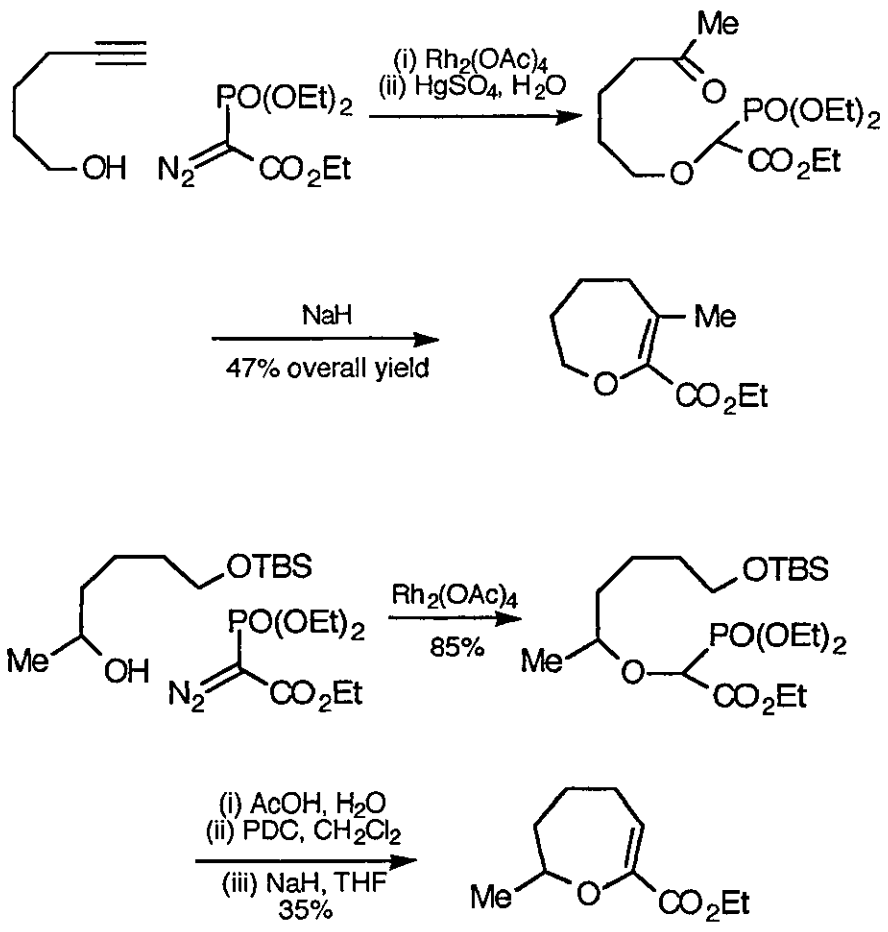
97 was transformed to the halides **98** and **99**. These were then cyclised to the oxepane **100** and oxocane **101** in 21% and 80% yields respectively (**Scheme 35**). The lower yield in the oxepane cyclisation was rationalised in terms of the known difficulty in displacing halides with β-alkoxy substituents.



Scheme 35

In connection with the rhodium(II) acetate catalysed cyclisations of diazo alcohols, it has been shown that it is also possible to use an intermolecular O-H insertion of a rhodium carbenoid, followed by an intramolecular Wadsworth-Emmons reaction as the cyclisation step.[24,49] The reaction is quite general, and works with both aldehydes and ketones as the carbonyl component, and for phosphonyl-ketones, -sulfones, bis-phosphonates as well as phosphonoacetates as shown in **Scheme 36**. Rhodium(II) acetate

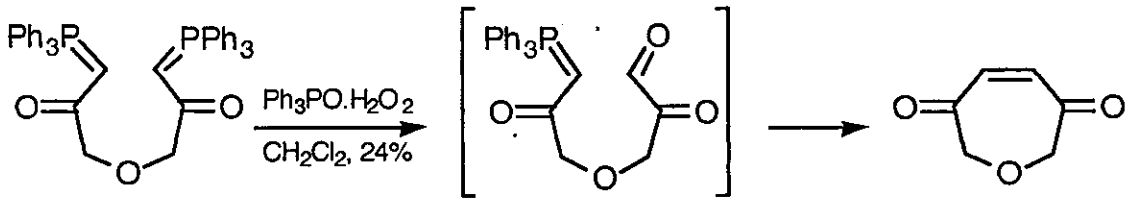
catalysed insertion into a secondary alcohol led to the 2,7-disubstituted oxepane **102**.



102

Scheme 36

A similar intramolecular Wittig reaction has been used by Bestmann *et al.* to prepare the oxepane **105**. Oxidation of the bis-phosphonium ylide **103** gave a 24% yield of the oxepane **105**, presumably *via* the aldehyde **104**.[50]

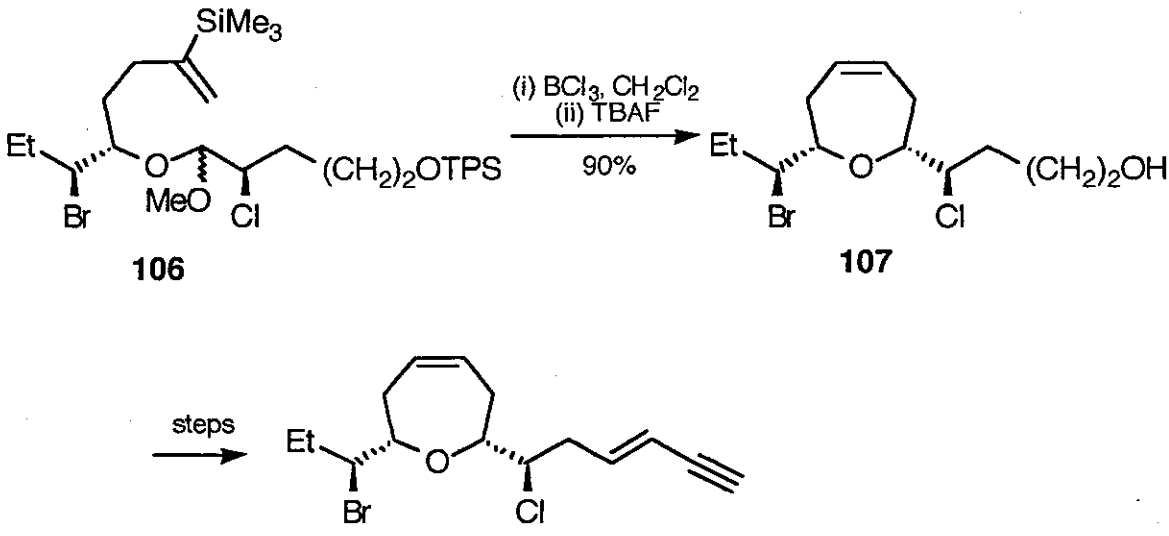


103 **104** **105**

Scheme 37

Overman *et al.* have demonstrated the power of their acetal-alkene cyclisations[51] with an elegant first total synthesis of the marine natural

product isolaurepinnacin. The precursor **106**, with most of the functionality of isolaurepinnacin in place, was cyclised to the oxepane **107** in 90% yield (**Scheme 38**). This intermediate was converted into the natural product **108** in five simple steps.[52]

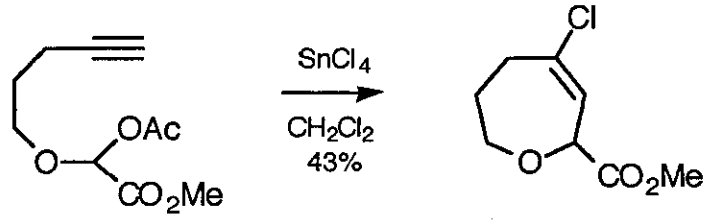


106 **107**

108, isolaurepinnacin

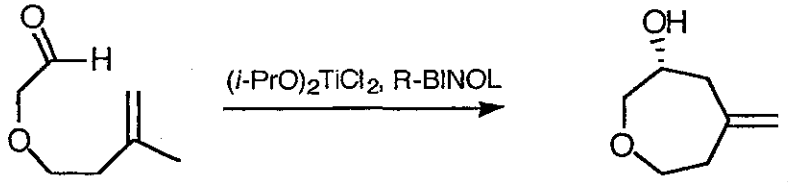
Scheme 38

An acetal-alkyne cyclisation has recently been used by Speckamp and co-workers[53] to provide the unsaturated oxepane shown in **Scheme 39**.



Scheme 39

The Lewis acid catalysed carbonyl-ene reaction has been shown to provide oxepanes **109** in moderate yields (**Scheme 40**). Use of a chiral titanium BINOL complex led to high levels of asymmetric induction.[54]

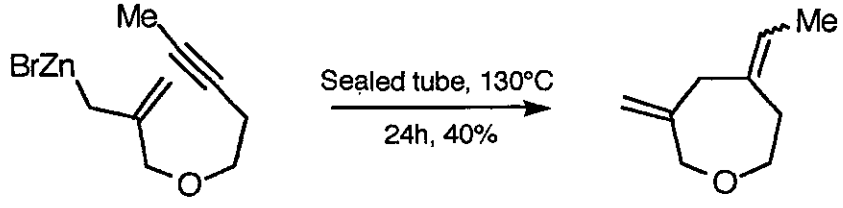


109; n = 1, 64% (88% e.e.)
110; n = 2, 12% (34% e.e.)

Scheme 40

Oxocanes **110** can also be formed by this process although the yields are lower reflecting the greater difficulty of eight membered ring formation. Addition of silver perchlorate led to a slight increase in enantioselectivity, although the yields were again decreased.

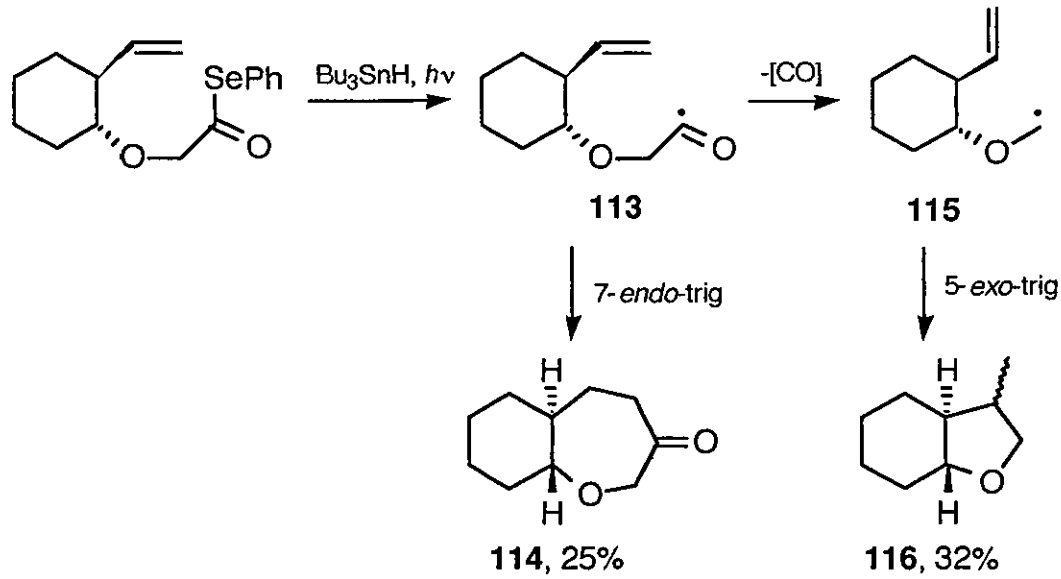
When the organozinc compound **111** is heated under forcing conditions a similar intramolecular ene reaction takes place to give the oxepane **112** as a mixture of geometrical isomers (**Scheme 41**).[55] A small amount of an oxocane, produced by *endo* cyclisation, was also obtained.



111 **112**

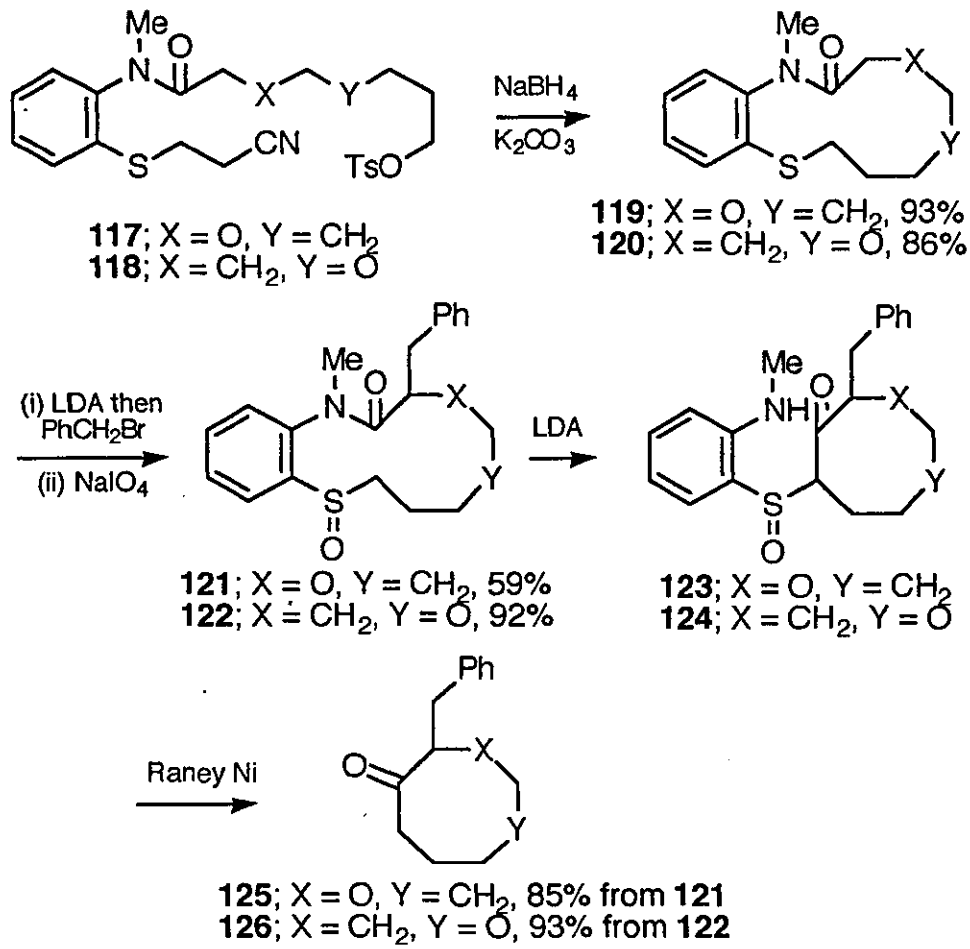
Scheme 41

Radical reactions to form medium sized rings are often accompanied by hydrogen abstraction processes which lead to overall reduction of the radical. Crich has shown that in the case of the cyclisation of the acyl radical **113**, the favoured process is a 7-*endo* cyclisation to give the fused oxepane **114**. The yield is low due to the rapidity of decarbonylation of **113** to give the stabilised radical **115** which cyclises to the tetrahydrofuran **116**. Although a tetrahydropyran would be produced by *exo* cyclisation of the acyl radical **113**, this was not observed.[56]



Scheme 42

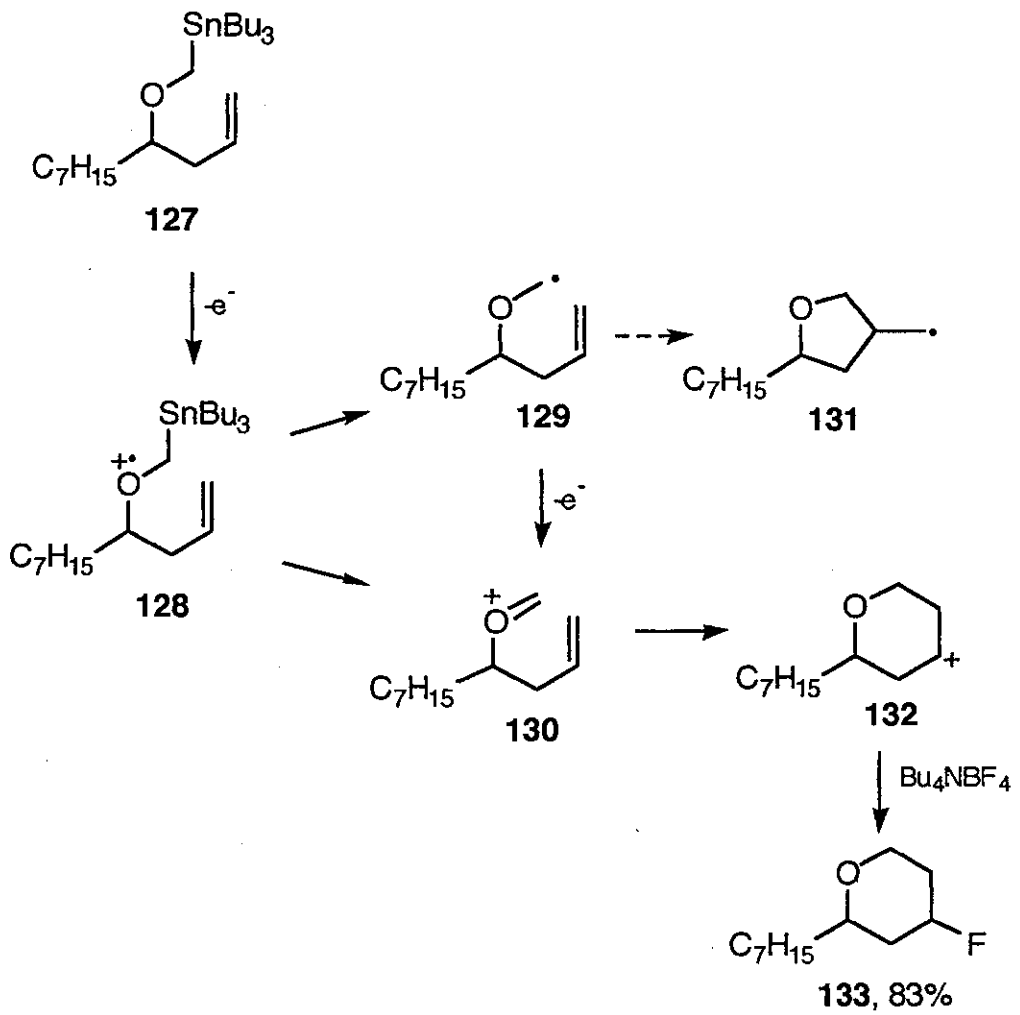
Cyclisations to give rings larger than 10-membered become easier because of the lack of transannular strain present in these molecules.



Scheme 43

Ohtsuka *et al.* have used this to good effect in their preparation of oxocanes (**Scheme 43**) and azocanes. Macrocyclisation of **117** and **118** gave the 12-membered ring amides **119** and **120** in good yields. This functionality then 'holds' the reacting sites together so that the actual cyclisation steps (**121** to **123**, **122** to **124**) proceeded in almost quantitative yield. Having served its purpose, the temporary connection was then reductively removed to give the oxocanes **125** and **126**.[57]

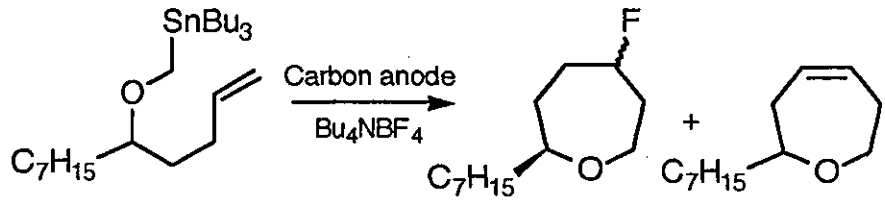
Electrochemical synthesis has recently been enjoying increased popularity.[58] Anodic oxidation of α-stannylethers has been demonstrated to be effective in the synthesis of tetrahydropyrans and oxepanes. The proposed mechanism is illustrated for the formation of a tetrahydropyran **133** (**Scheme 44**).



Scheme 44

Single electron oxidation of the substrate **127** leads to the formation of the radical cation **128**. Loss of the tin can be heterolytic, leading to the oxygen stabilised radical **129**, or homolytic leading to the oxonium ion **130**. Since the radical **129** would be expected to cyclise onto the double bond in a 5-*exo*-trig manner to give a tetrahydrofuran **131**, then it is proposed that if this intermediate is formed, it must be rapidly oxidised to the oxonium ion **130**, which undergoes a 6-*endo*-trig cyclisation to give the more stable (as opposed to the primary carbenium ion which would be formed by 5-*exo* cyclisation) carbenium ion **132** which is quenched by the tetra-*n*-butylammonium tetrafluoroborate present in the reaction mixture.[59]

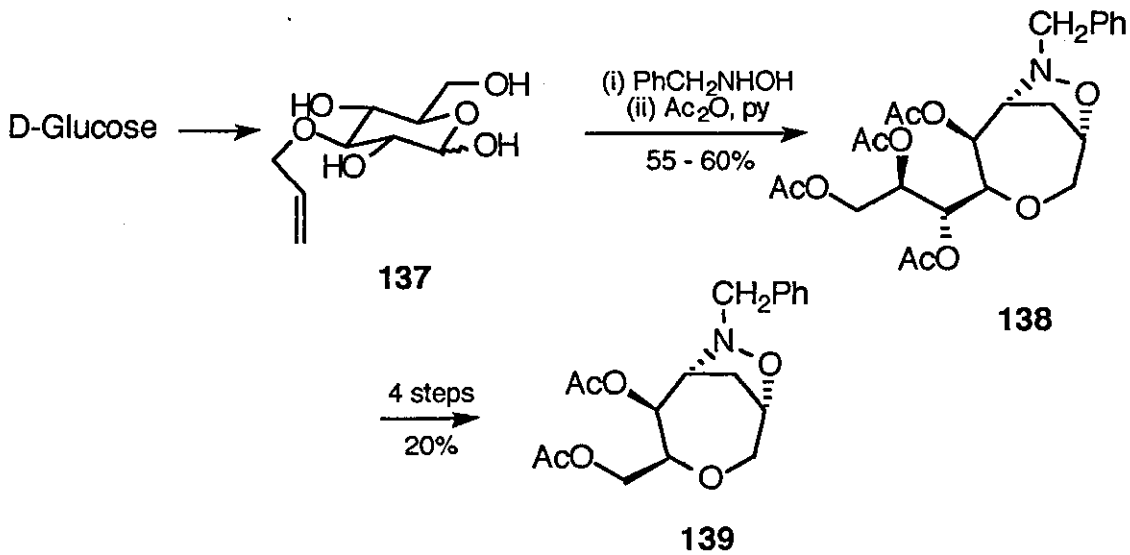
The carbenium ion **132** can also lose a proton to give an alkene. Thus in the case of **134**, the fluorinated oxepane **135** and the tetrahydrooxepin **136** were obtained in a combined yield of 89% (**Scheme 45**).



134 **135**, 61% **136**, 28%

Scheme 45

A nitrone cycloaddition of a glucose derivative provides access to either enantiomer of the chiral oxepane derivative **139** (**Scheme 46**).[60,61]

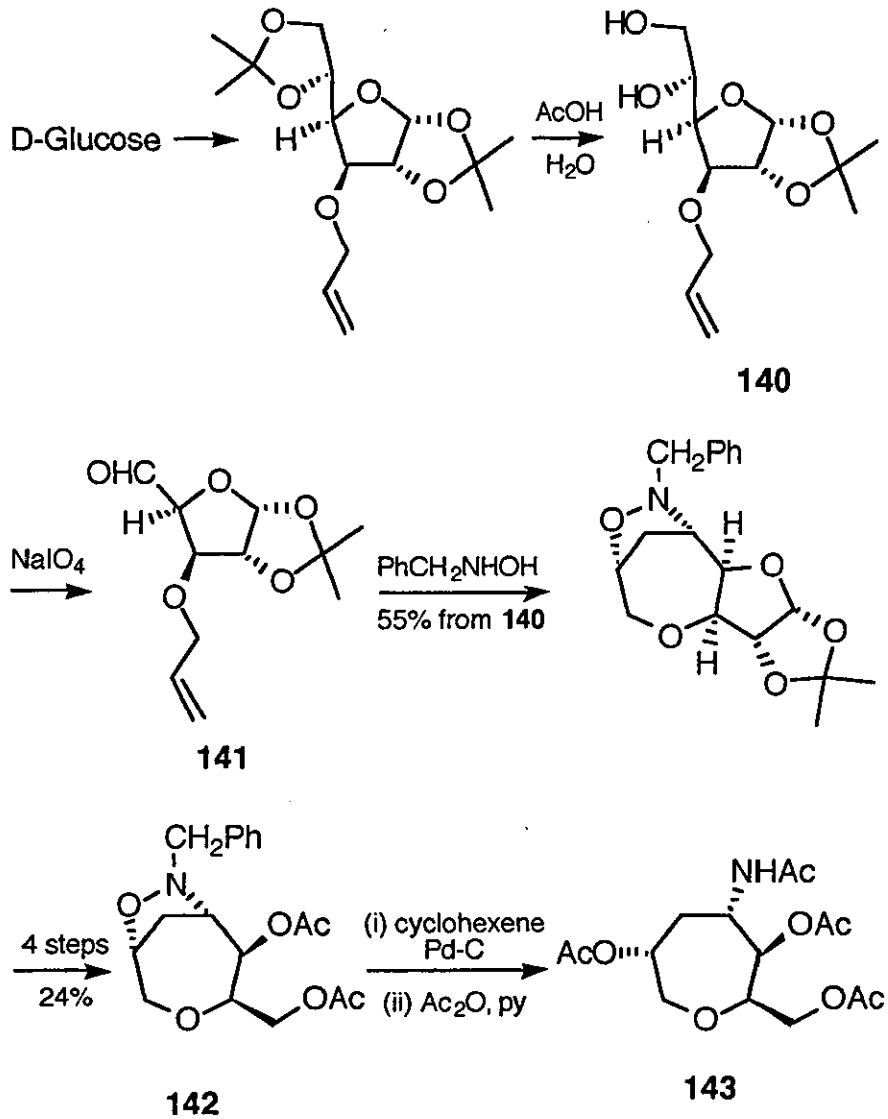


137 **138** **139**

Scheme 46

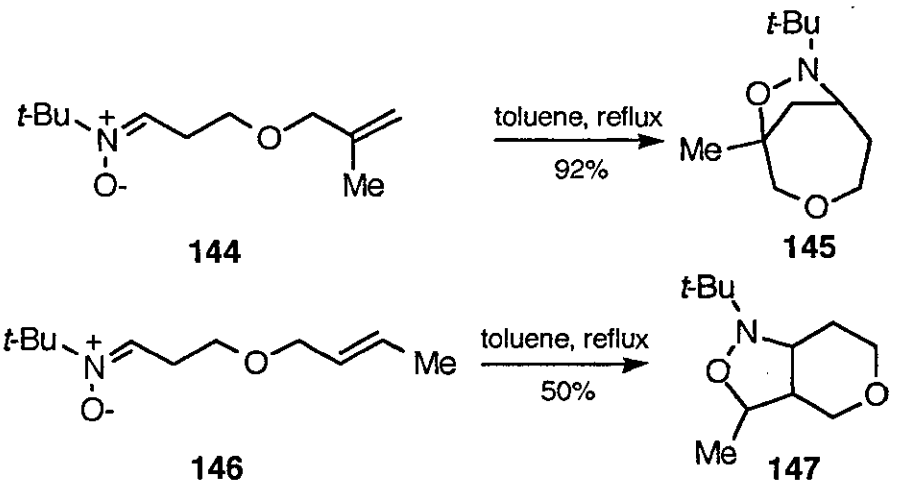
Treatment of 3-*O*-allyl-D-(+)-glucose **137** with *N*-benzylhydroxylamine, followed by acetylation gave a 55 - 60% yield of oxepane **138**, oxidative cleavage of the side chain of which gave **139** which contains two of the original chiral centres of the glucose.

Alternatively[61] a one-carbon degradation of glucose provided the aldehyde **141** in which the two chiral centres to be retained have the opposite stereochemistry to those in the original glucose derivative **137**. Thus formation of the nitrone followed by cycloaddition and modification gave the oxepane **142**, the enantiomer of **139**. Finally, the isoxazolidine ring was reductively cleaved to give the chiral oxepane **143**.



Scheme 47

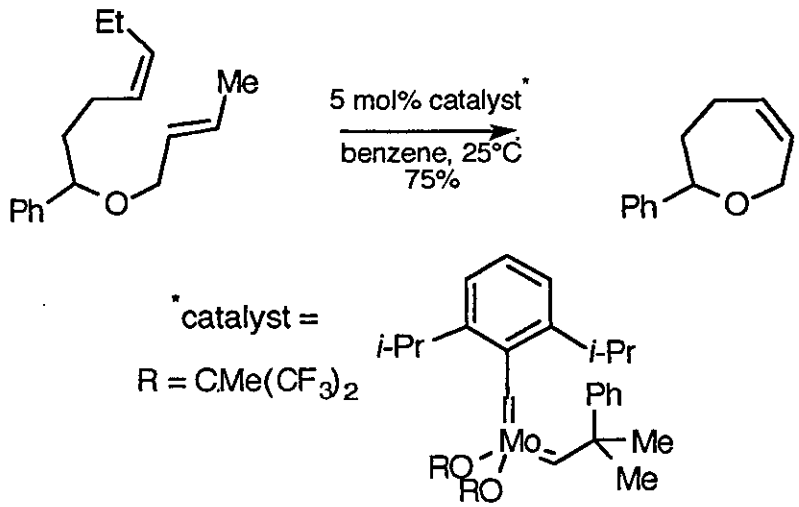
A further example of a nitrone cycloaddition to give oxepanes has been reported by Aurich and co-workers (**Scheme 48**).[62]



Scheme 48

This reaction is extremely substrate dependent. Nitrone **144** gives only the oxepane **145** (92% yield) while the isomeric nitrone **146** gives the tetrahydropyran **147** exclusively. This is in agreement with the observations of Shing *et al.* who have noted[63] that for systems related to **141** minor structural modifications can lead to the formation of tetrahydropyrans at the expense of oxepanes.

Olefin metathesis has received little attention from synthetic organic chemists. The metathetic ring closure of 1,6- 1,7- and 1,8-dienes has been recently investigated and found to be efficient and mild. Oxepane formation by this method is shown in **Scheme 49**.[64]

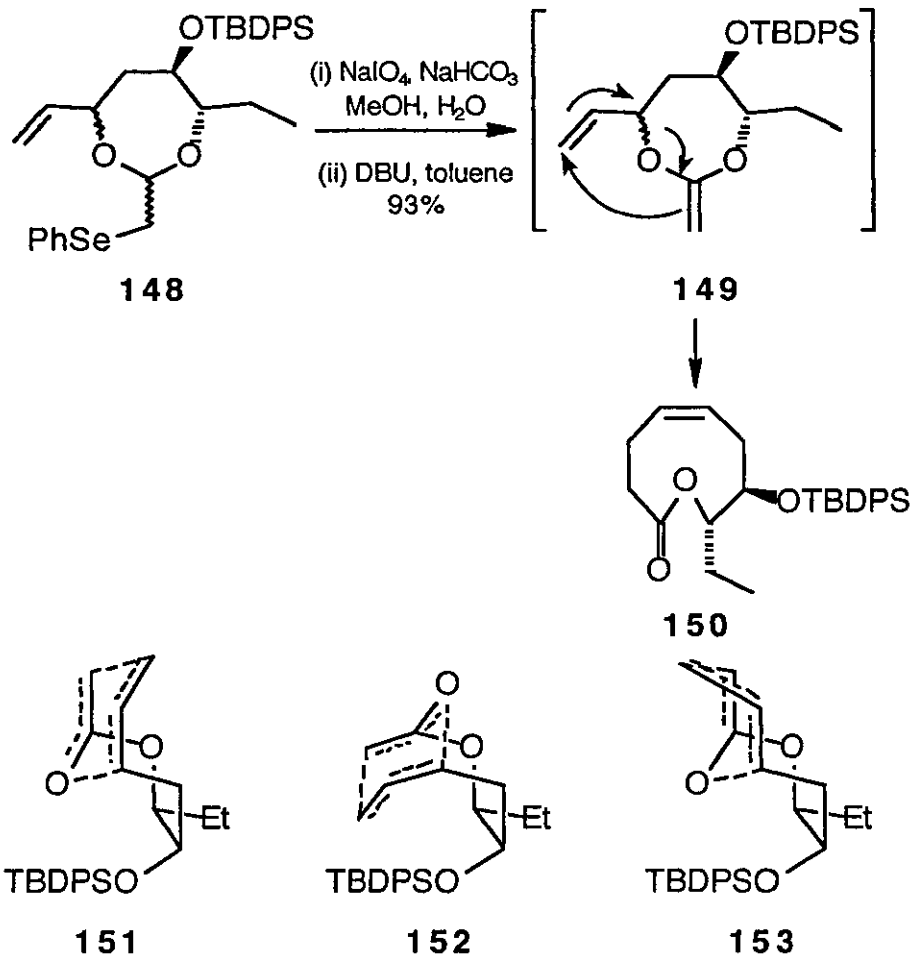


Scheme 49

The same authors have more recently reported[65] a ruthenium based catalyst which gives comparable yields, with the advantage of being less air sensitive.

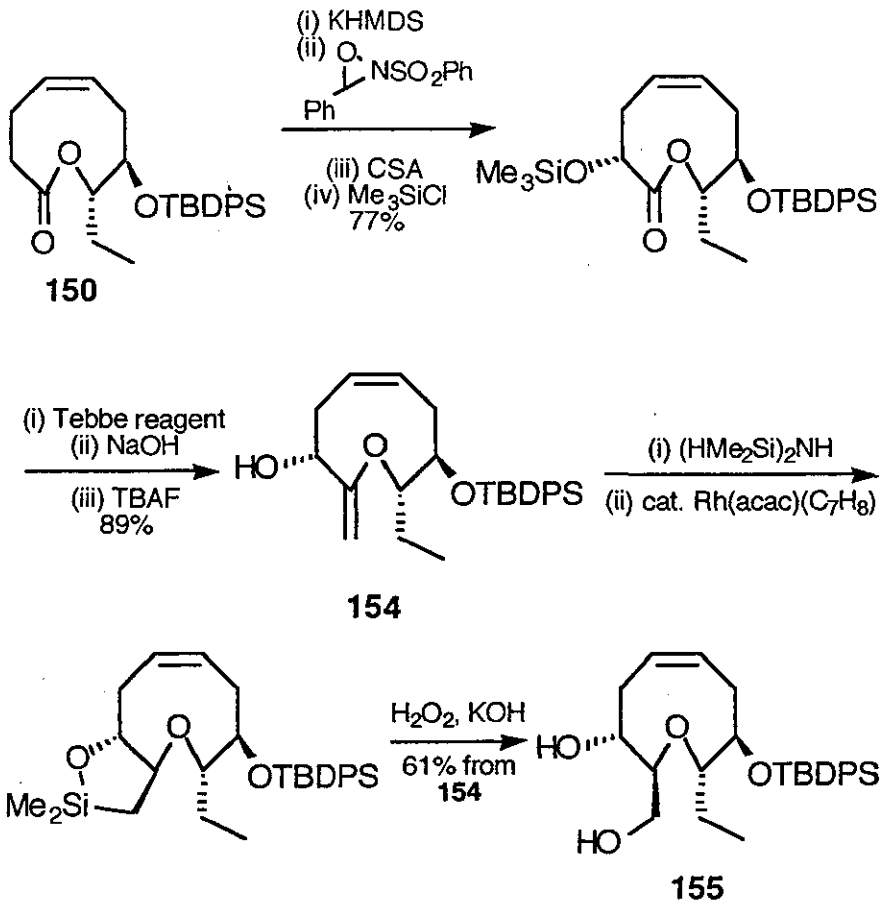
1.4. Rearrangement reactions

Holmes has shown that his earlier described (see ref. 3) Claisen rearrangement of ketene acetals can be readily extended to the synthesis of 9-membered lactones. The easily prepared (79% over 6 steps) selenyl ether **148** was isolated as a mixture of 3 diastereoisomers. These were oxidised to the selenoxide and immediately heated to give the ketene acetal **149** which underwent Claisen rearrangement to the lactone **150**. The ketene acetal is presumably a mixture of diastereoisomers. However both isomers react to give the same lactone *via* chair transition states **151** and **152**. Reaction through a boat transition state **153** would give rise to a product containing a *trans*-double bond, and was not observed (**Scheme 50**).[66]



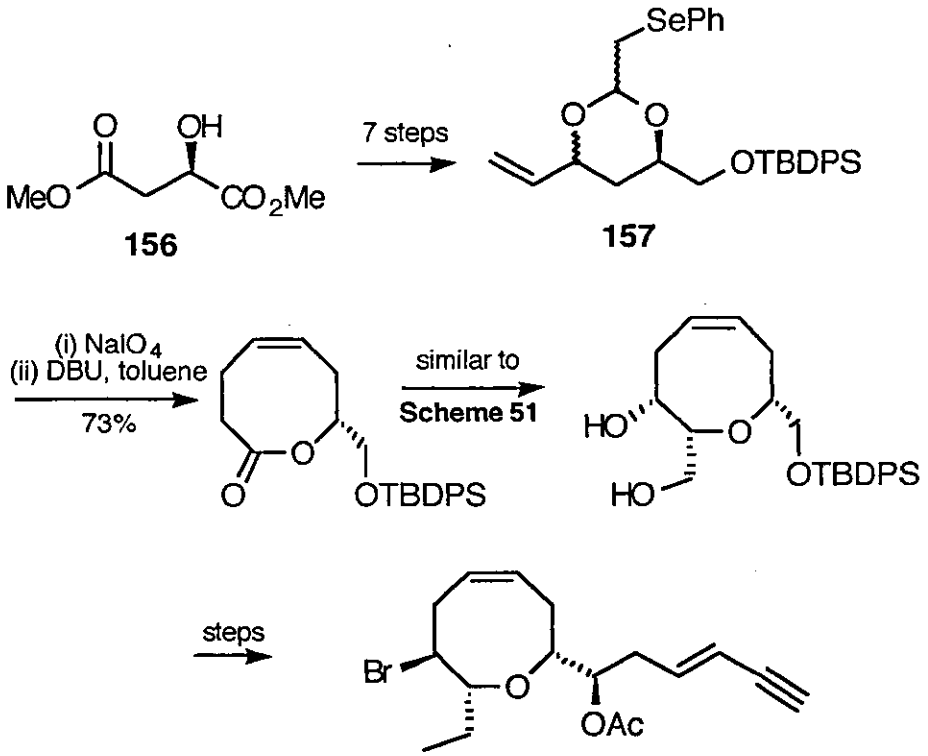
Scheme 50

This lactone has been converted into an advanced intermediate for the synthesis of obtusenyne (**Scheme 51**).[67,68] A highly diastereoselective oxidation of the enolate of **150** followed by Tebbe methylenation gave **154**. This was then subjected to intramolecular hydrosilylation followed by oxidation to give **155**.



Scheme 51

A similar sequence of reactions starting from dimethyl (R)-malate (**156**) *via* a six membered cyclic acetal **157** has yielded an elegant total synthesis of (+)-laurencin **158**, another of the many *Laurencia* metabolites (**Scheme 52**).[69]

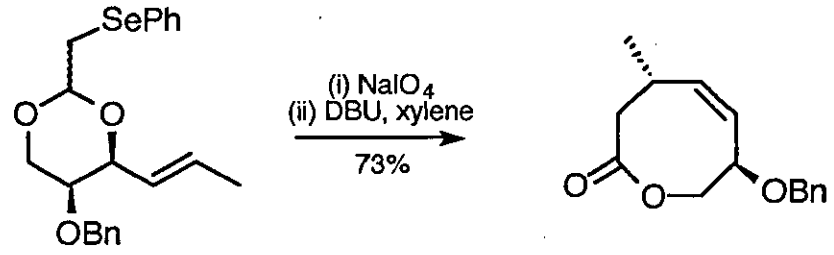


156 **157**

158, (+)-Laurencin

Scheme 52

Incorporation of substituents onto the double bond of the selenyl ether precursor can result in a diastereoselective Claisen rearrangement (*e.g.* **159** to **160**).[70]

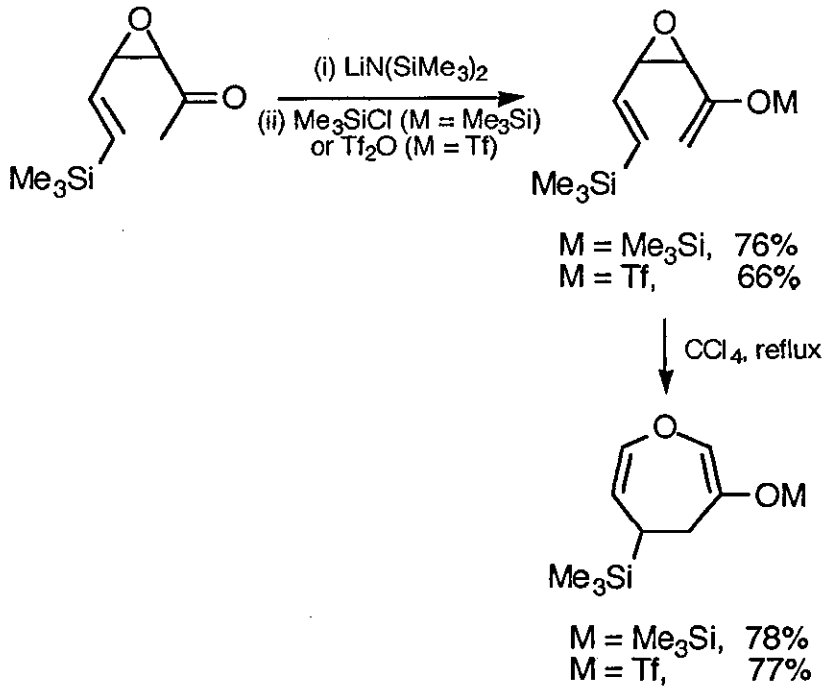


159 **160**

Scheme 53

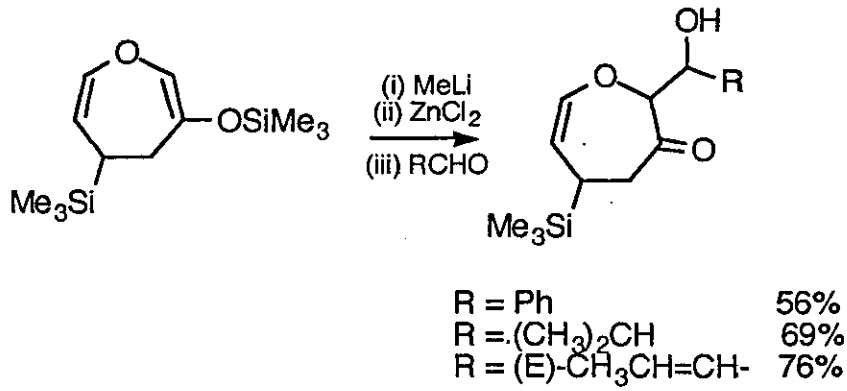
This methodology has also been applied to the synthesis of the proposed 9-membered lactone structure of ascidiatrienolide A, leading to a revision of the structure of this natural product.[71]

Cope rearrangement of *cis*-divinylepoxides gives rise to dihydrooxepins in synthetically useful yields (**Scheme 54**).[72]



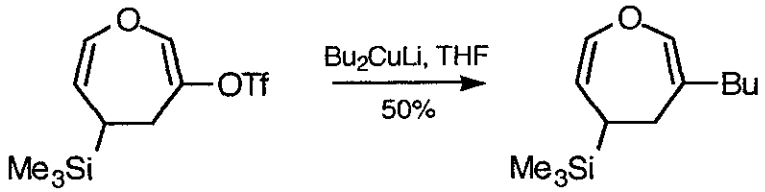
Scheme 54

Since one of the double bonds forms part of a silyl enol ether or an enol triflate, the dihydrooxepins formed are amenable to further modification. The silyl enol ether can be converted into the lithium enolate, which then undergoes aldol reactions with aliphatic, aromatic and α,β-unsaturated aldehydes (**Scheme 55**).[72]



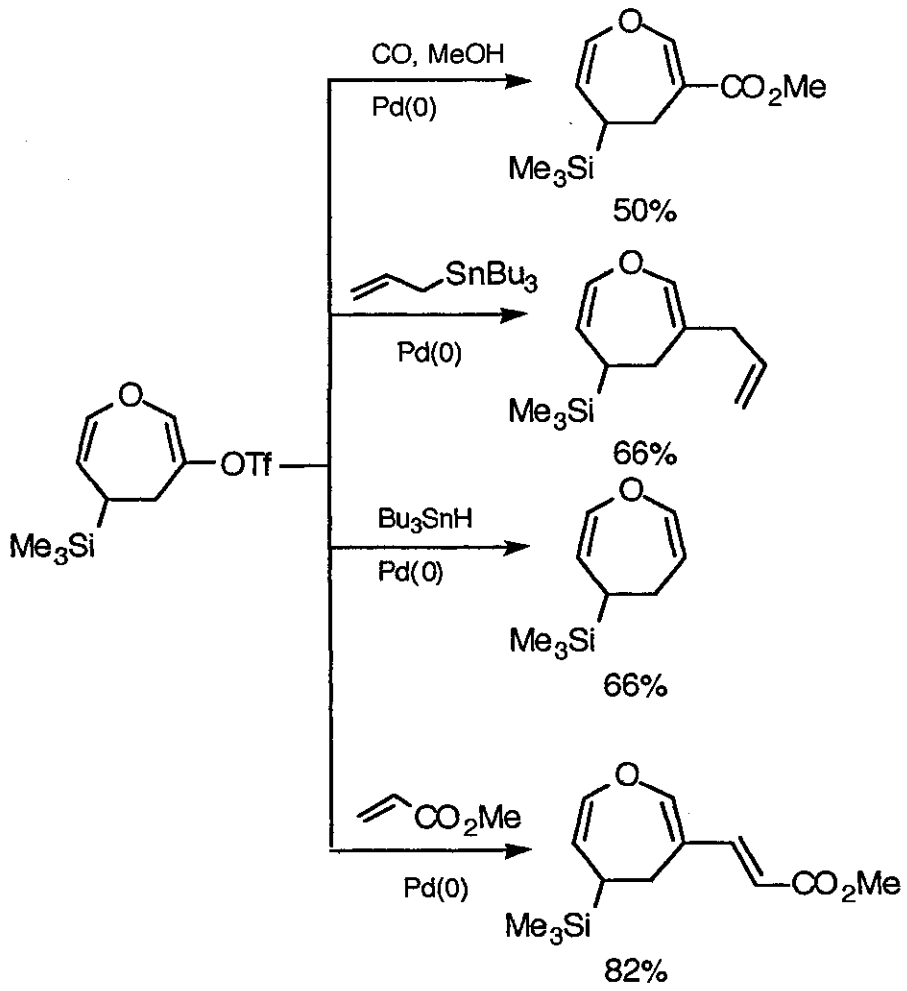
Scheme 55

The triflate group can be replaced by an alkyl group *via* a cuprate displacement (**Scheme 56**).[72]



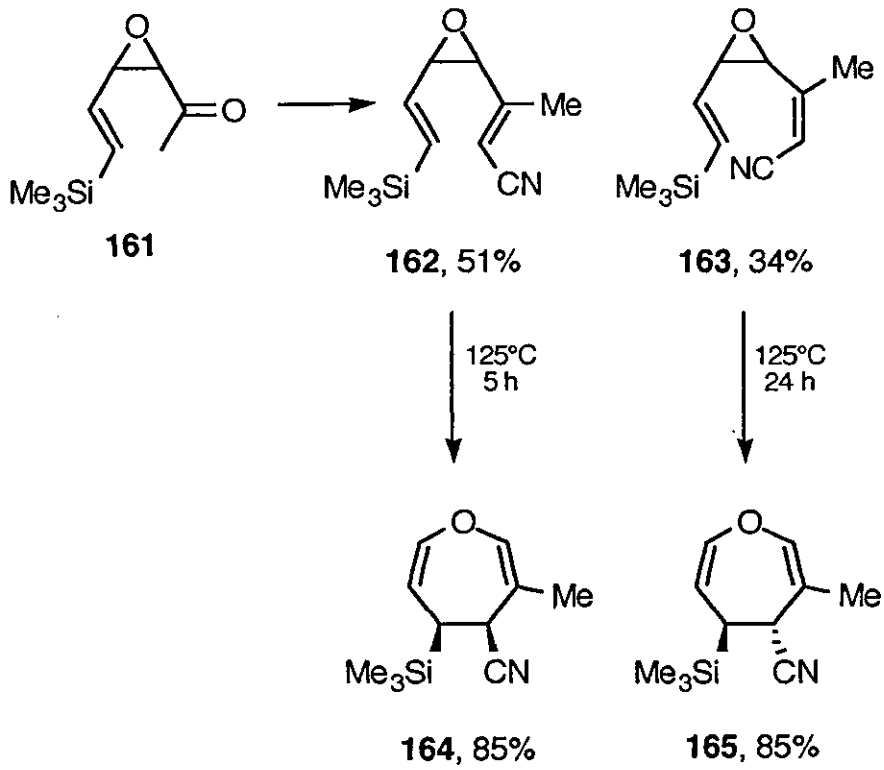
Scheme 56

Palladium catalysed Stille and Heck type couplings can also be carried out on the triflate (**Scheme 57**).[72]



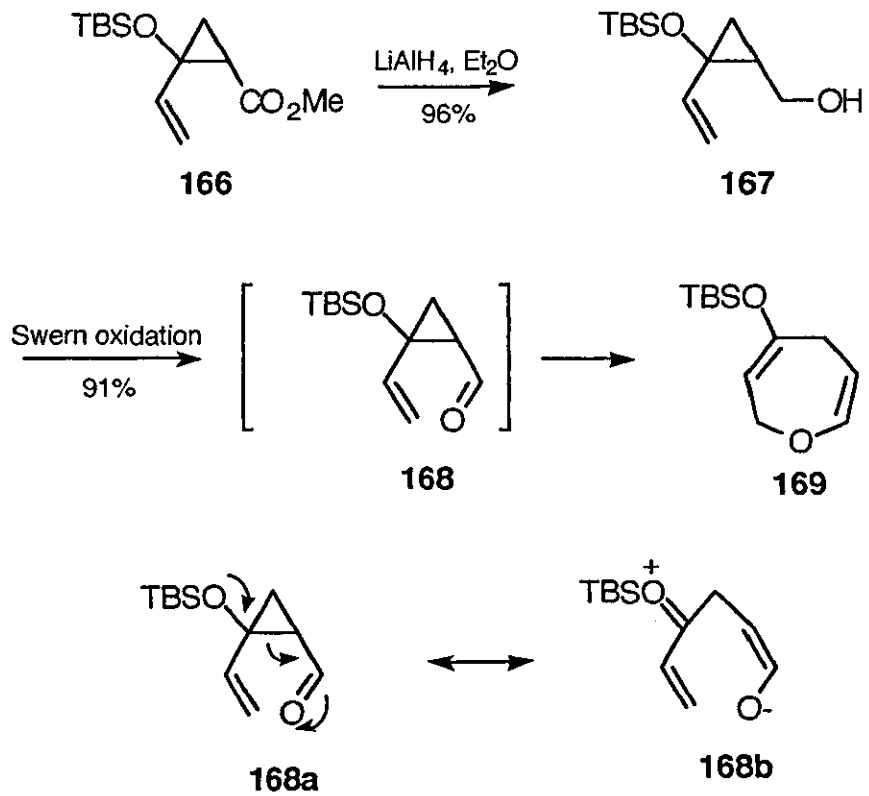
Scheme 57

Wadsworth-Emmons olefination of the 2,3-epoxyketone **161** gave a mixture of *cis*- and *trans*-divinylepoxides **162** and **163** which were readily separated and subjected to Cope rearrangement (**Scheme 58**). Assuming a boat-like transition state (steric constraints due to the epoxide preclude the normally favoured chair transition state), the *E*-isomer **162** rearranges smoothly to give the 4,5-*cis*-dihydrooxepin **164**, whereas the *Z* isomer **163** requires a longer reaction time, giving only the 4,5-*trans*-dihydrooxepin **165**.[73]



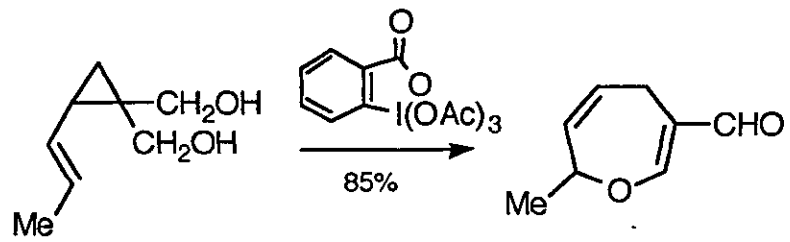
Scheme 58

A similar [3,3]-sigmatropic shift has been used by Hofmann and Reissig[74] and by Boeckman *et al.*[75] to prepare 2,5-dihydrooxepins. Since the product is an allyl vinyl ether, this reaction has been called a retro-Claisen rearrangement. The cyclopropane ester **166** (prepared by a selective metal catalysed cyclopropanation of a 2-siloxy diene with methyl diazoacetate) was reduced to the alcohol **167** in high yield. Partial oxidation under Swern conditions gave only the dihydrooxepin **169**. Since the cyclopropane ring in **168** is substituted by both an electron donor and an electron acceptor, one would expect the central C-C bond to be weakened (see resonance structures **168a** and **168b**), thereby favouring dihydrooxepin formation (**Scheme 59**).[74]



Scheme 59

A similar oxidation of cyclopropane derivative **170** gave the 2,5-dihydrooxepin-6-aldehyde **171**. As expected, if the cyclopropane is enantiomerically enriched, then the dihydrooxepin is formed with no loss of stereochemical integrity.[75]



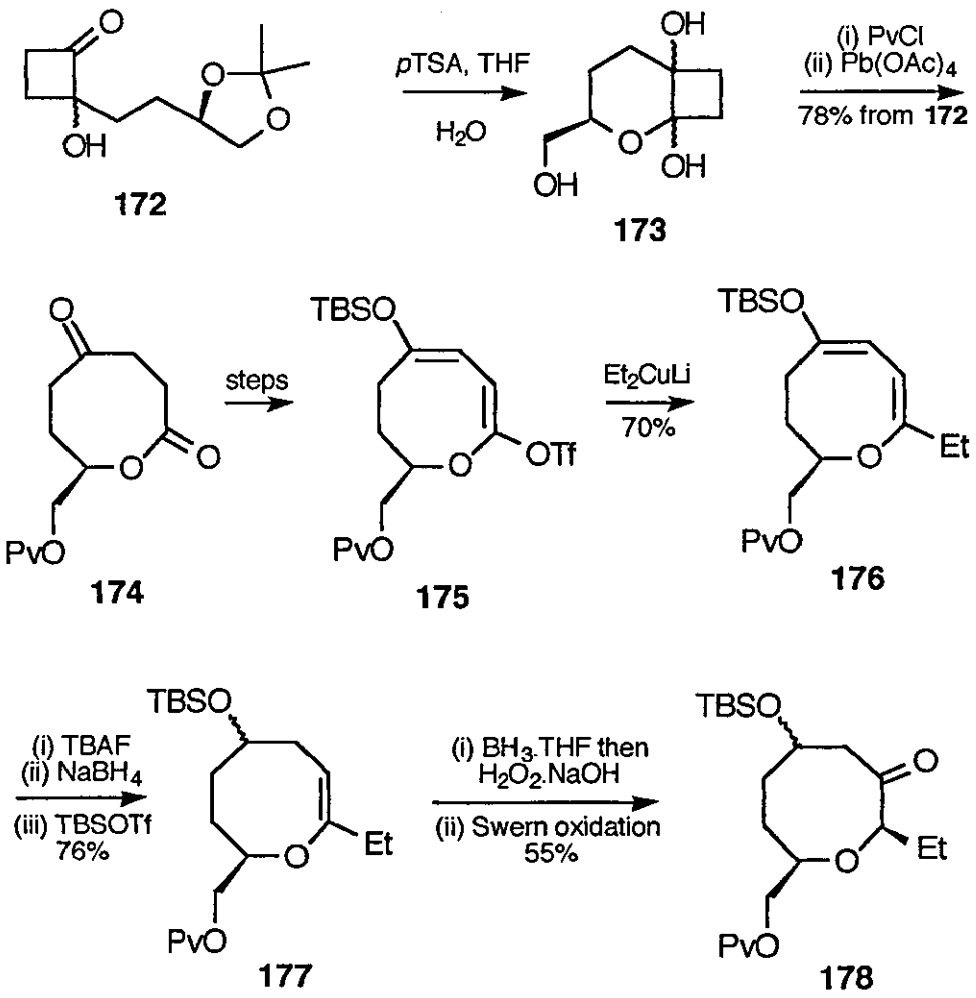
170 **171**

Scheme 60

1.5. Ring expansions

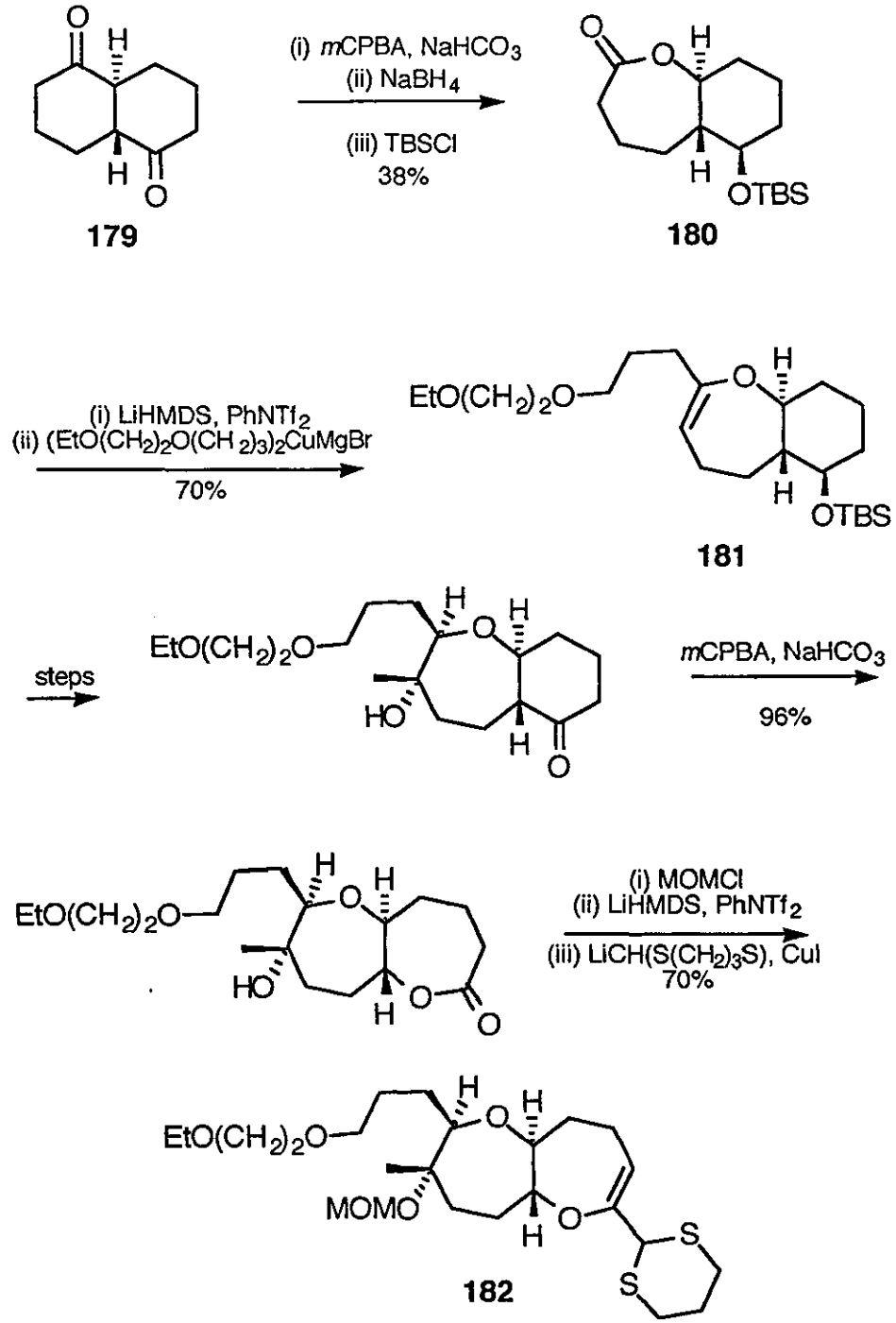
Another total synthesis of (+)-laurencin (**158**) shows an interesting approach to oxocane synthesis (**Scheme 61**). Treatment of the cyclobutanone **172** with acid led to the hemi-ketal **173**. Selective protection of the primary alcohol was followed by oxidative cleavage of the diol to give the keto-lactone **174** in high yield. Conversion to the diene-triflate **175** was

followed by cuprate displacement to give **176**. Finally the silyl enol ether **176** was converted into the silyl ether **177** which was hydroborated and oxidised to give the oxocane ketone **178**, obtained as the 2,8-*cis*-isomer after epimerisation with triethylamine. Conversion into (+)-laurencin was accomplished in a further 11 steps.[76]



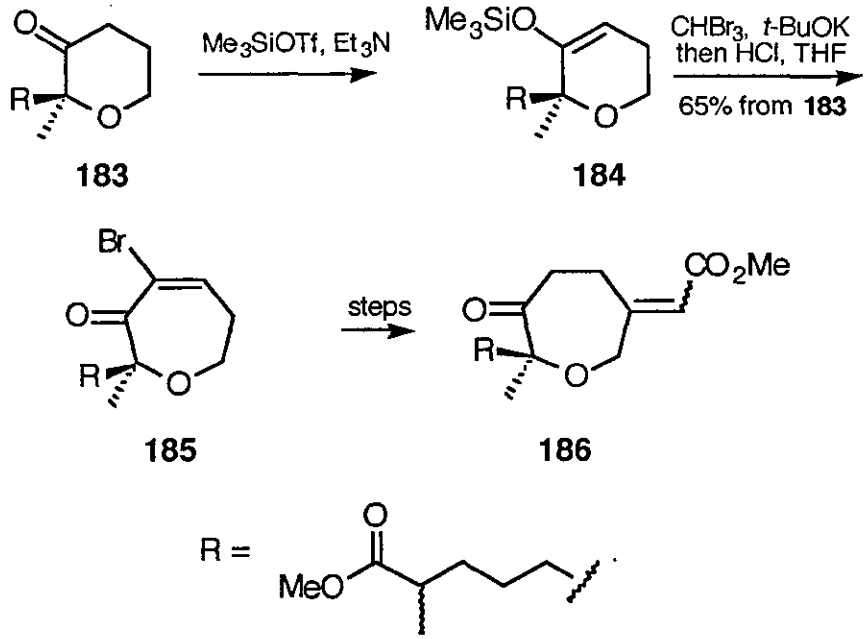
Scheme 61

Feng and Murai have also developed a novel approach to the C- and D-rings of hemibrevetoxin B based on a double Baeyer-Villiger oxidation of the decalin-dione **179**. Oxidation of **179** gave the lactone **180** which was converted into the oxepane **181** using a cuprate displacement of a triflate in a similar manner to the above. Almost identical modification of the other ring gave the fused bis-oxepane system **182**.[77]



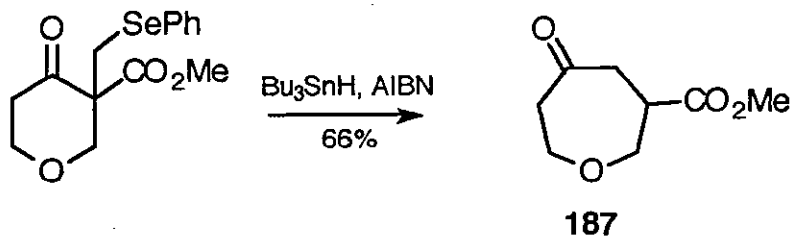
Scheme 62

A recent approach to the anti-fertility agent zoapatanol uses a cyclopropanation-ring expansion strategy to provide the key oxepane ring. Thus the silyl enol ether **184** of the ketone **183** was cyclopropanated using bromoform in the presence of base. Acidic treatment led to the oxepane **185** (65% overall yield) which was further elaborated to provide the advanced intermediate **186**.[78]



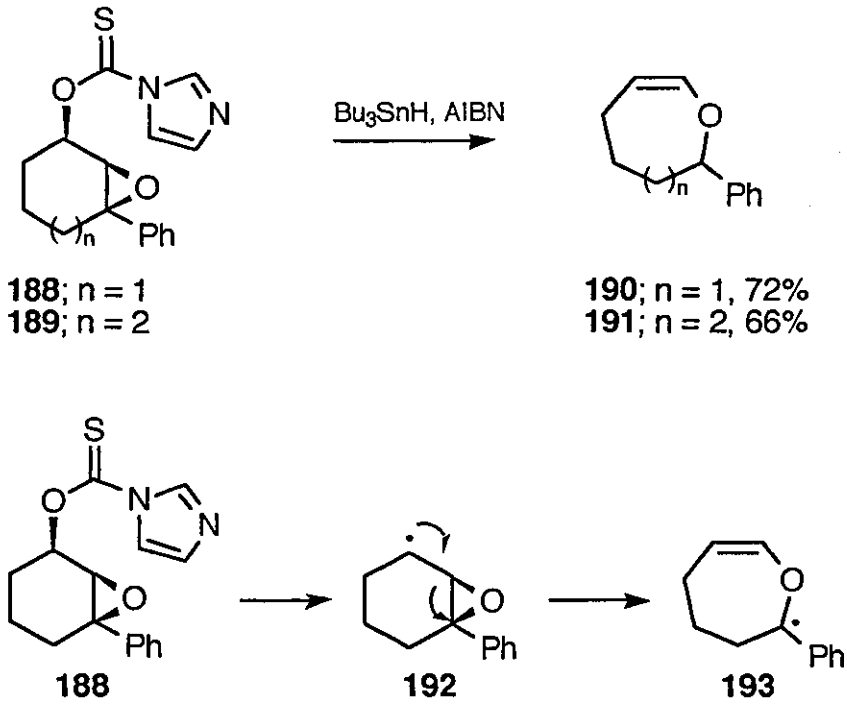
Scheme 63

Free radical ring expansions are much more efficient than direct free radical cyclisations where medium sized rings are desired. Dowd and Choi have used a one-carbon ring expansion to prepare the oxepane **187** in 66% yield. Slow addition of the substrate to tributyltin hydride was required (**Scheme 64**).[79]



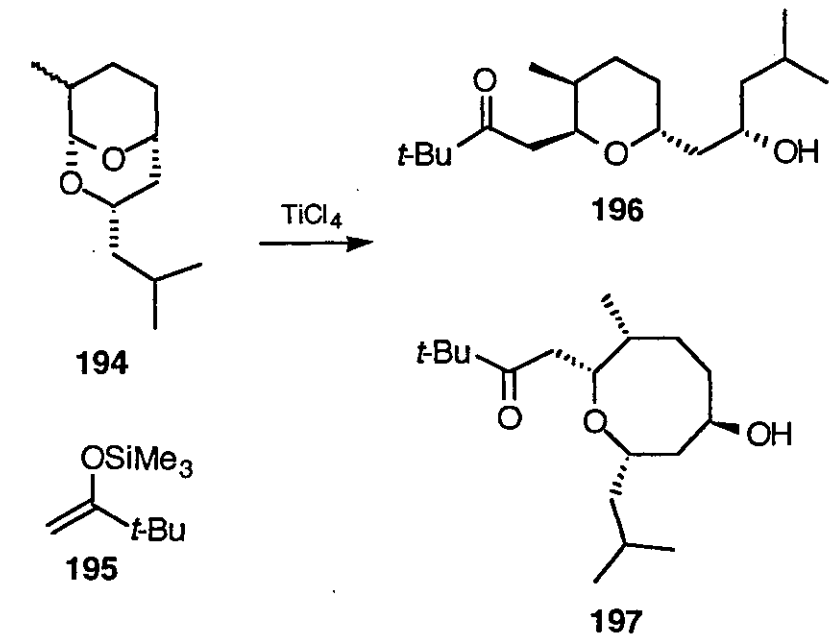
Scheme 64

Directed cleavage of oxiranylcarbinyl radicals, *e.g.* **192**, derived from thiocarbamates **188** and **189** leads to the formation of oxepane **190** and oxocane **191**, both in good yield. The phenyl group is required to stabilise the radical **193**, and so favour C-C bond cleavage over C-O bond cleavage (**Scheme 65**).[80]



Scheme 65

During the course of studies towards nigericin, Holmes and Bartlett discovered that the reaction of silyl enol ether **195** with the cyclic acetal **194** is strongly dependent on the stereochemistry of the substrate (**Scheme 66**).[81]

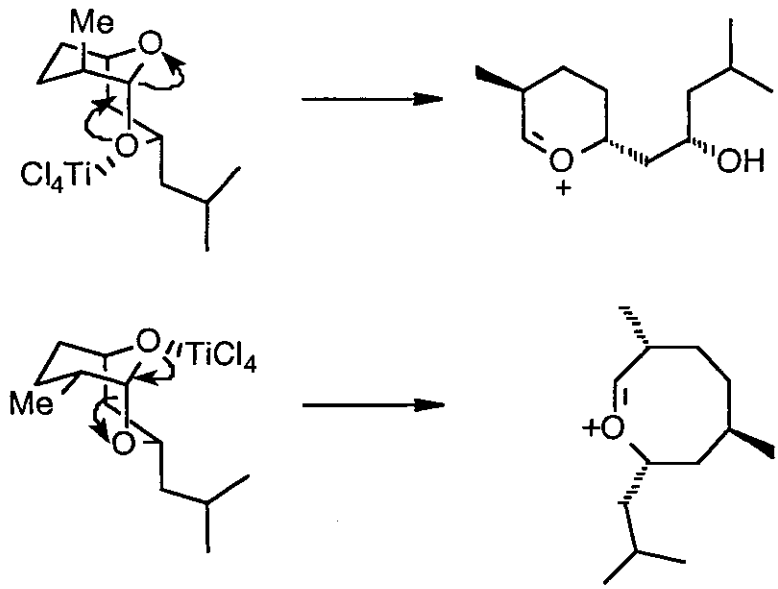


Scheme 66

Thus a 78:22 α:β mixture of **194** gave a 23:77 mixture of tetrahydropyran **196** and oxocane **197** (78% total yield), whereas pure (>95%) α-acetal gave

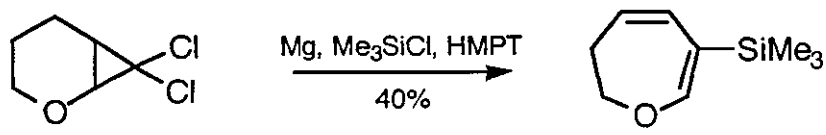
mainly the oxocane **197**, with less than 5% of the tetrahydropyran being formed. Both products were formed as single stereoisomers, suggesting that each isomer of acetal is giving rise to the formation of a single product.[81]

It has been suggested that the methyl group directs approach of the titanium tetrachloride to the least hindered acetal oxygen. This dictates the direction of acetal opening and hence the product formed (**Scheme 67**).[81]



Scheme 67

Finally, thermolysis of the cyclopropanated tetrahydropyran **198** in the presence of magnesium and chlorotrimethylsilane led to a one carbon ring expansion, giving the oxepane **199** in 40% yield.[82]

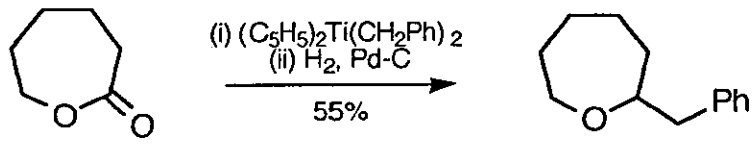


198 **199**

Scheme 68

1.6. Modification of lactones

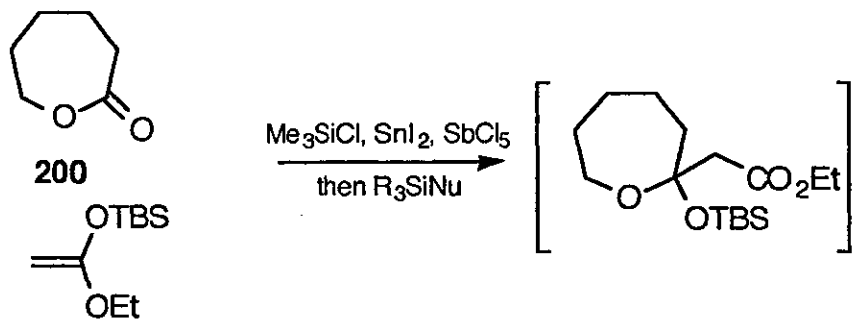
Petasis and Bzowej have reported[83] that dibenzyltitanocene reacts with ketones, esters and amides in the same way as the Tebbe reagent to give the corresponding benzylidene compounds. In the case of the lactone **200** this was immediately followed by hydrogenation to give the oxepane **201**.

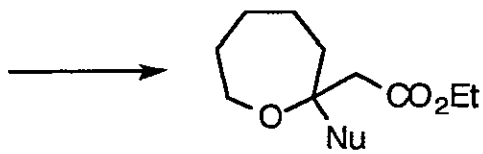


200 **201**

Scheme 69

Mukaiyama has described a Lewis acid mediated reaction of lactones with silyl ketene acetals. ε-Caprolactone **200** has been converted in this way to **202**, **203** and **204** in good yields.[84]



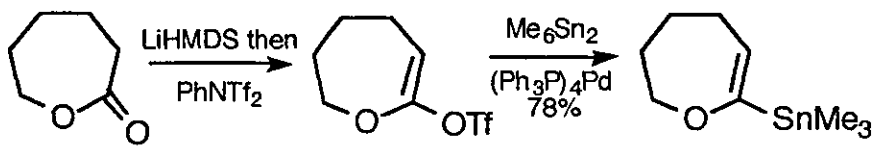


200

202; R = Et, Nu = H, 90%
203; R = Me, Nu = allyl, 67%
204; R = Me, Nu = CN, 62%

Scheme 70

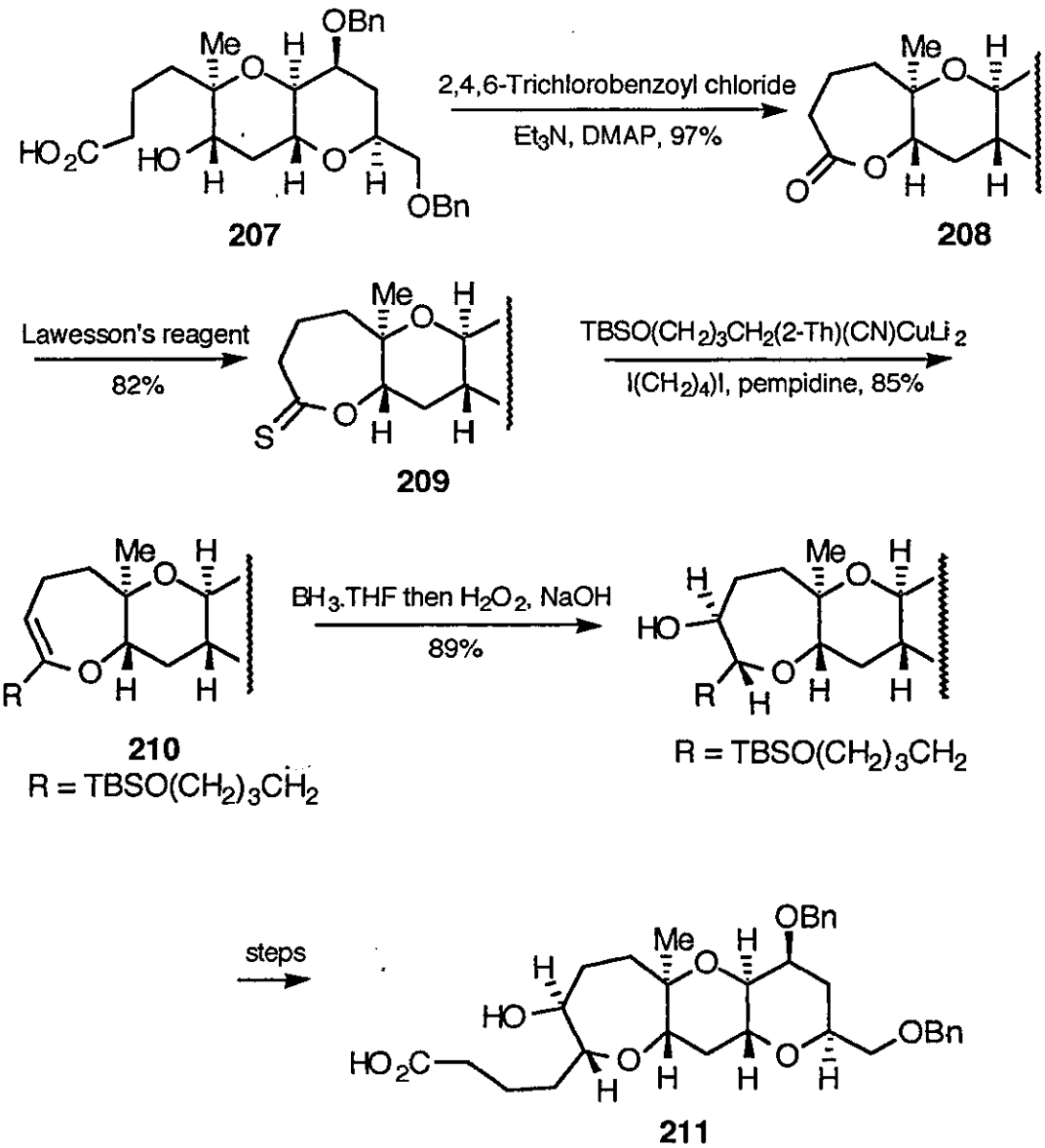
Lactones can also be converted into 6- and 7-membered cyclic enol ethers. Palladium(0) catalysed cross coupling of the triflate **205**, derived from ε-caprolactone, with hexamethylditin gave the oxepane **206** in 78% overall yield.[85]



205 **206**

Scheme 71

The final, and most spectacular, example of lactone modification is provided by Nicolaou's synthesis of hemibrevetoxin B. Cyclisation of the hydroxy-acid **207** provided the lactone **208** which was first converted into the thiolactone **209**. Cuprate alkylation gave the cyclic enol ether **210**. The required oxygen atom was introduced *via* a hydroboration/oxidation sequence followed by standard chemistry to give the hydroxy-acid **211**. This was then elaborated in a similar manner to provide the tetracyclic 7-7-6-6 ring system of brevetoxin.[37,86]



Scheme 72

1.7. Conclusions

The last four years have seen a wide range of new methods for the synthesis of oxepanes, oxocanes and oxonanes. These methods are generally mild and tolerant of other functionality in the molecule, as required by the complex natural products which often contain these moieties. A number of total syntheses have been reported, and no doubt more will be achieved in the near future.

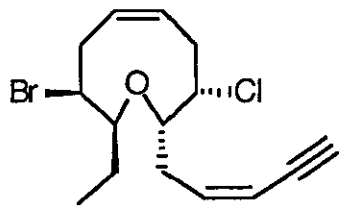
Chapter 2

Synthesis of functionalised oxonanes and azonanes by oxidative ring expansion: preparation of obtusan

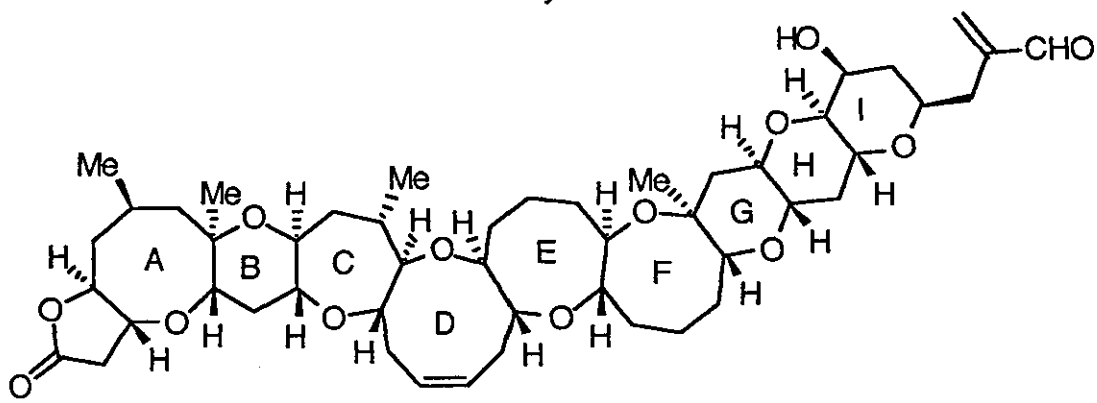
Synthesis of functionalised oxonanes and azonanes by oxidative ring expansion: preparation of obtusan

2.1 Introduction

As Chapter 1 has shown, whilst there are many reported methods for the synthesis of oxepanes and oxocanes, the last four years have seen only three publications,[67,68,87] all from Holmes *et al.*, concerning the synthesis of oxonanes. This is despite the fact that a number of natural products, *e.g.* obtusenyne[88] and brevetoxin A (**Figure 2**), contain this ring system, and is almost certainly related to the known difficulty in the preparation of 9-membered rings compared to their smaller-ring counterparts.



Obtusenyne

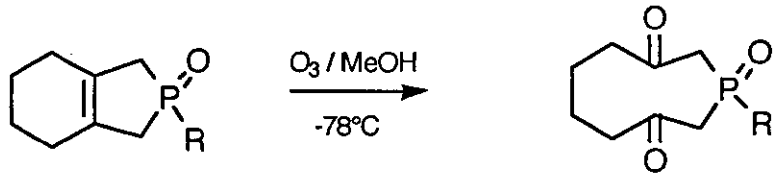


Brevetoxin A

Figure 2

The rhodium(II) catalysed cyclisation of diazo-alcohols to give oxepanes and oxocanes has been the subject of much work within the Moody group[89] (see Chapter 1 for selected examples). However this reaction fails when applied to the synthesis of 9-membered rings, and we therefore sought alternative methodology for the preparation of these systems.

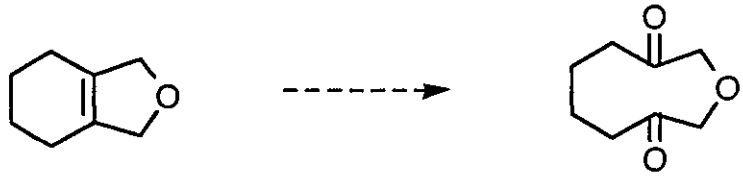
The oxidative cleavage of the zero-ene bridge of bicyclic systems[90] has been used to great effect in the synthesis of medium ring containing compounds. Quin's work on the preparation of nine-membered sulfur[91] and phosphorus[92] heterocycles (**Scheme 73**) is of particular note, and with this work in mind we chose to use a similar route[93] as our entry into the oxonane ring systems of the above mentioned natural products.



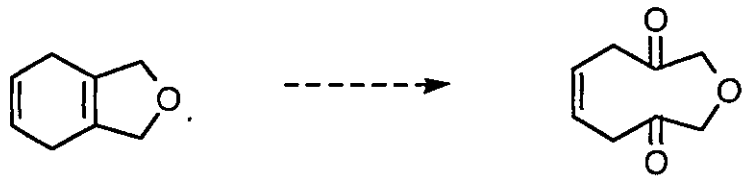
R = Me, 94%
R = Ph, 85%
R = OH, 84%

Scheme 73

It was envisaged that the oxidative cleavage of 1,3,4,5,6,7-hexahydrobenzo[c]furan (**213**) would lead to the desired compound (**214**), and that a selective cleavage of the more nucleophilic double bond of 1,3,4,7-tetrahydrobenzo[c]furan (**212**) might also be possible leading to an unsaturated oxonane (**215**) (**Scheme 74**).



213 **214**



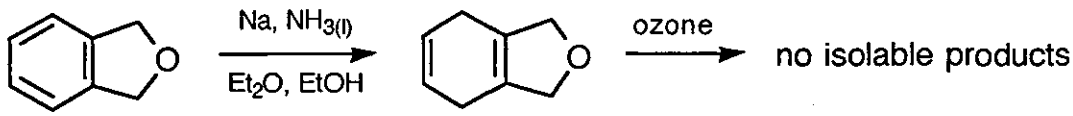
212 **215**

Scheme 74

2.2 Synthesis of oxonane-3,8-dione

The parent compound, 1,3,4,7-tetrahydrobenzo[c]furan (**212**), was readily prepared in high yield by the Birch reduction[94] of commercially

available phthalan (**Scheme 75**). A selective ozonolysis of this compound was attempted. However none of the desired compound **215** was obtained despite careful monitoring of the reaction by TLC, or by calibration of the ozoniser.

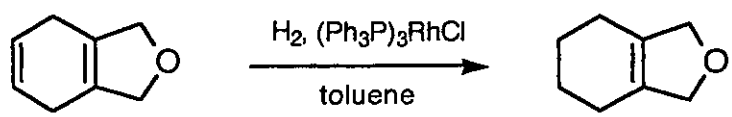


phthalan **212** 85%

Scheme 75

We were unable to obtain any identifiable products from this reaction, and so turned our attention to the presumably simpler case of the hexahydrobenzo[c]furan **213**. The preparation of this compound by selective hydrogenation of the less hindered double bond of tetrahydrobenzo[c]furan **212** in the presence of a platinum catalyst has been reported previously.[95] However in our hands this approach led to inseparable mixtures containing the desired compound along with the fully saturated analogue and phthalan (presumably by disproportionation of the starting diene). The use of palladium-on-carbon as catalyst also gave the same result. However Wilkinson's catalyst (tris(triphenylphosphine)rhodium(I) chloride) is known to efficiently reduce the less hindered double bond of polyunsaturated compounds. Tetrasubstituted double bonds are rarely reduced, if at all.[96]

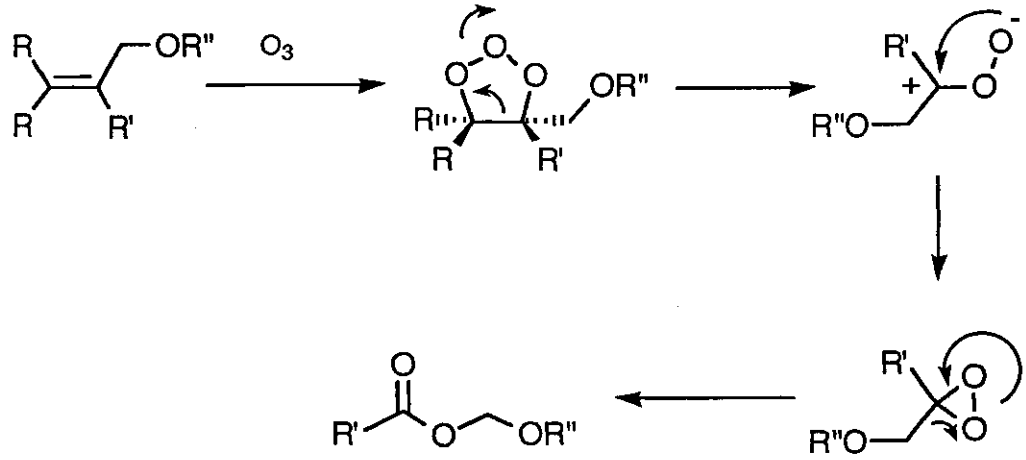
Atmospheric pressure hydrogenation of **212** in the presence of Wilkinson's catalyst gave the desired selectivity, although the reaction times were greatly increased (48 - 72 h compared to 1 - 2 h for heterogeneous catalysts) and in most cases up to 5% of the starting material remained unreacted, and could not be removed by flash column chromatography or distillation. It was observed that use of more catalyst only led to a reduction in yields, the optimum substrate:catalyst ratio being about 250:1 (**Scheme 76**).



212 **213** 73%

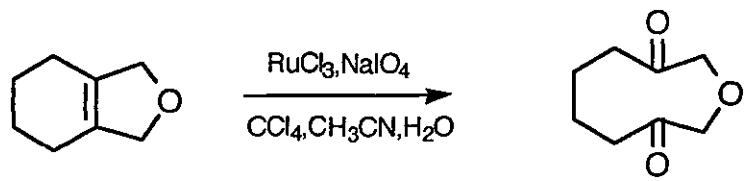
Scheme 76

Oxidative cleavage of this compound by ozonolysis was found to be extremely capricious - out of six experiments the desired compound was obtained only once, and then in only 29% yield. This result is not entirely surprising as allylic ethers have long been known to give rise to abnormal ozonolysis products,[97] presumably *via* the mechanism shown in **Scheme 77** (however we are aware of at least one report of the ozonolysis of allylic ethers in high yield).[98]



Scheme 77

The Sharpless modification[99] of the ruthenium catalysed oxidation of alkenes[100] was found not to suffer from this problem, resulting in the preparation of oxonane-3,8-dione (**214**) reproducibly in 58% yield (36% yield over 3 steps from commercially available starting materials) (**Scheme 78**).

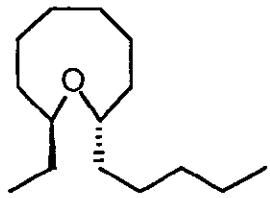


213 **214**

58%

Scheme 78

We therefore had a route to oxonanes with functionality at the 3- and 8-positions. Brevetoxin A and obtusenyne both contain substituents in the 2- and 9-positions of the oxonane ring. We therefore attempted to extend this methodology to incorporate substituents at these positions with the intention of later preparing obtusan[87] (**216**, **Figure 3**), the saturated oxonane containing the carbon skeleton of obtusenyne[88] (see **Figure 2**, page 46).

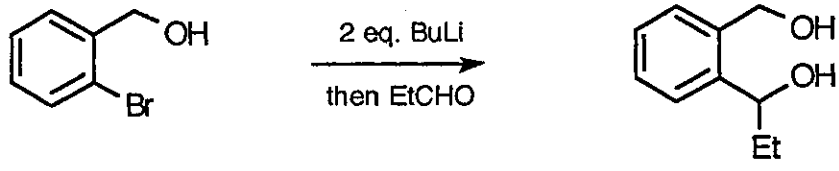


216, obtusan

Figure 3

2.3 Synthesis of substituted oxonanes

Our required starting materials were therefore 1,3-disubstituted phthalans (obtusan requiring 1-ethyl-3-*n*-pentylphthalan). We also chose to investigate the incorporation of a single substituent, for which we required a 1-substituted phthalan. It has been reported that these compounds can be prepared in high yield by the cyclodehydration of the corresponding diols,[101] themselves prepared by reaction of the dianion from 2-bromobenzyl alcohol with aliphatic aldehydes. To realise this, 2-bromobenzyl alcohol (**217**) was treated with two equivalents of butyllithium in THF to give a white suspension of the dianion (**Scheme 79**). Quenching with propionaldehyde gave an essentially quantitative yield of the diol **218** which decomposed on attempted purification (flash chromatography or vacuum distillation).

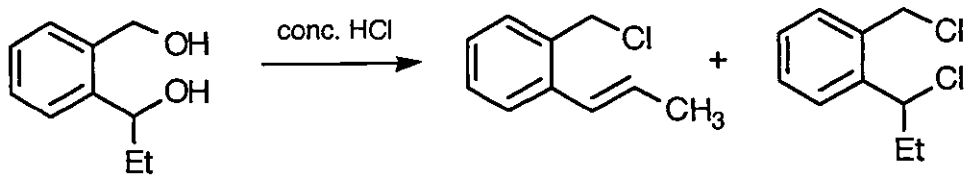


217 **218**

~100%

Scheme 79

However the diol was almost pure by ^{1}H NMR, so the cyclodehydration was attempted on the crude diol as reported. Treatment of the diol **218** with concentrated hydrochloric acid under literature conditions[101(a)] gave a viscous black oil from which only an inseparable mixture of the chlorination-elimination product **219** and the double chlorination product **220** could be obtained, and this in poor yield (**Scheme 80**). The cyclisation was also attempted using formic acid,[101(b),101(c)] phosphoric acid, sulfuric acid, *p*-toluenesulfonyl chloride/sodium hydride and under Mitsunobu conditions. None of these reagents led to any of the desired product,[102] so this approach to substituted phthalans was abandoned.

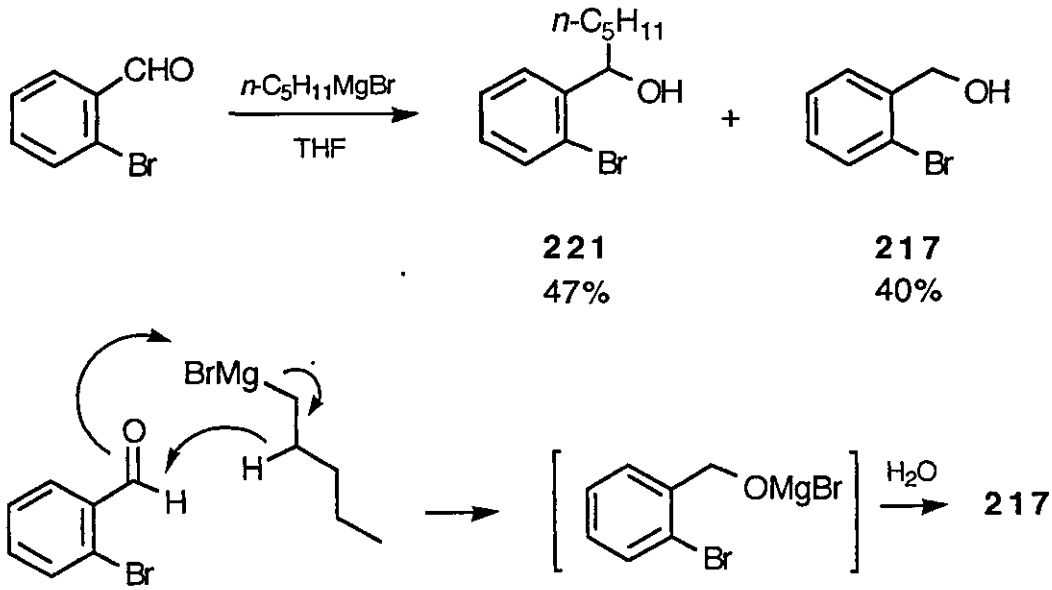


218 **219** **220**

1:2 mixture, 12% combined yield

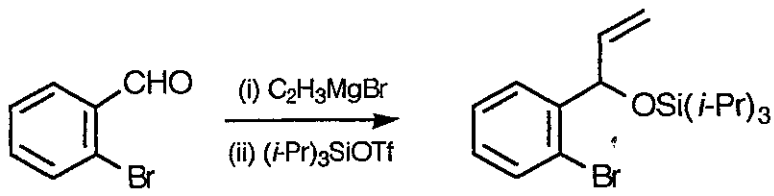
Scheme 80

We also briefly investigated the preparation of a disubstituted phthalan by this method. For this, a secondary 2-bromobenzyl alcohol, *e.g.* **221**, was required. Alkylation of 2-bromobenzaldehyde with *n*-pentylmagnesium bromide led to an approximately equal mixture of the desired product **221** and 2-bromobenzyl alcohol **217**.[103] Unfortunately, although not surprisingly, the secondary benzylic alcohol was extremely prone to eliminate water, and so could not be obtained in pure form. We reasoned that the reduction was the result of β-hydride transfer from the Grignard reagent (**Scheme 81**), and that it might be suppressed by the use of a Grignard reagent which was unable to transfer a β-hydrogen. Reaction of 2-bromobenzaldehyde with vinylmagnesium bromide proceeded smoothly to give, after silylation, the alkylated product **222** (**Scheme 82**). No evidence of reduction was observed in this reaction. However, in view of our lack of success with the cyclodehydration of **218**, this route was abandoned.



221 **217**
47% 40%

Scheme 81

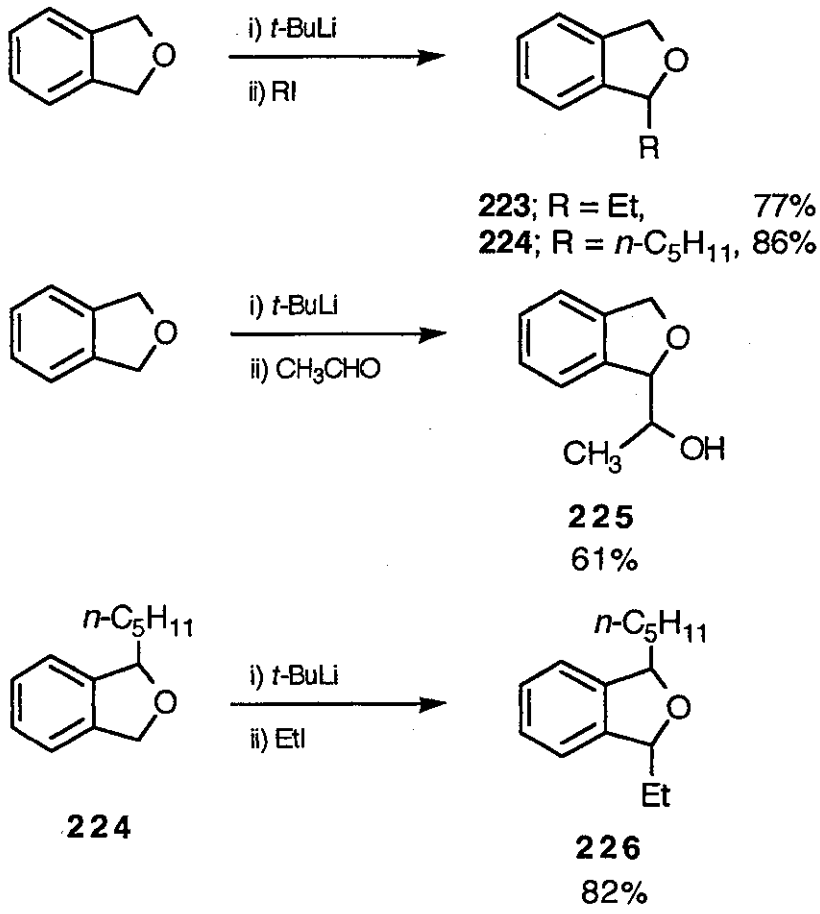


222

62%

Scheme 82

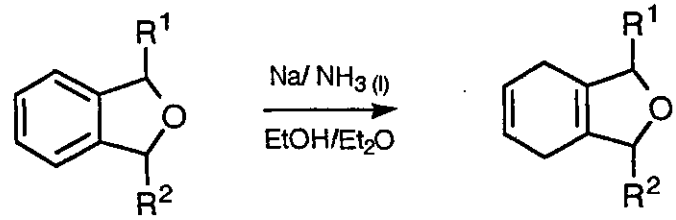
Davies has reported[104] that substituted phthalans can be prepared by the direct alkylation of phthalan. To this end phthalan was deprotonated at the benzylic position with *tert*-butyllithium in THF. The anion was quenched with ethyl iodide, 1-iodopentane and acetaldehyde to afford substituted phthalans **223**, **224** and **225** in good yield, **225** being obtained as an approximately 1:1 mixture of diastereoisomers. A second alkylation of 1-pentylphthalan (**224**) gave a diastereomeric mixture (1.4:1) of 1-ethyl-3-pentylphthalans **226** (**Scheme 83**).



Scheme 83

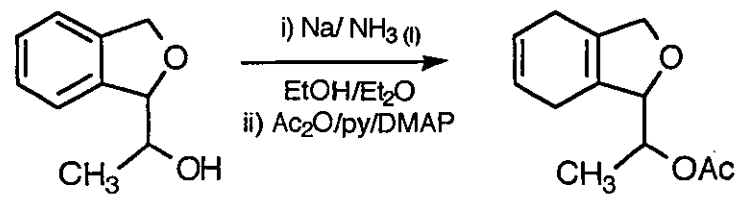
Davies further noted[104] that *cis*-dialkyl phthalans can be prepared selectively by double alkylation of the chromium tricarbonyl complex of phthalan. However since obtusenyne has *trans* stereochemistry between the 2- and 9-alkyl groups we were forced to prepare a mixture of diastereoisomers. These were separated by preparative HPLC to give the pure *cis* and *trans*-dialkyl phthalans **226cis** and **226trans**. At this stage the stereochemistry of the isomers could not be assigned. However since obtusan, the saturated oxonane containing the carbon skeleton of obtusenyne, has been prepared,[87] and ^{13}C data recorded for a number of oxonanes suggesting that the 2- and 9- carbons of 2,9-disubstituted oxonanes resonate at lower field for the *cis* isomers than for the *trans*,[105] (this data is summarised in **Appendix A**) we were confident that conversion of the two separated diastereoisomers into *cis*- and *trans*-obtusan would allow the assignment of their relative stereochemistry. Initially the sequence of reactions described below was carried out on the diastereomeric mixture.

The substituted phthalans **223**, **224**, and **226** were subjected to Birch reduction (**Scheme 84**) to give the tetrahydrobenzo[c]furans **227**, **228** and **229** in good yields. In the case of the 1-(1-hydroxyethyl)phthalan **225** the product diene was acetylated immediately to give **230**.



223; R^1 = Et, R^2 = H
224; R^1 = *n*-C_5H_{11}, R^2 = H
226; R^1 = *n*-C_5H_{11}, R^2 = Et

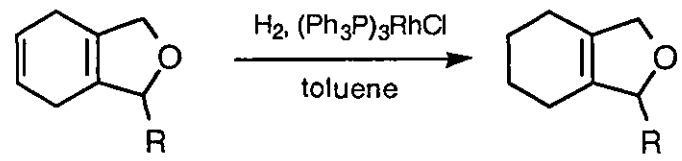
227; R^1 = Et, R^2 = H, 87%
228; R^1 = *n*-C_5H_{11}, R^2 = H, 84%
229; R^1 = *n*-C_5H_{11}, R^2 = Et, 95%



225 **230**
70%

Scheme 84

The selective reduction of the less hindered double bond was attempted as above. For the monosubstituted tetrahydrobenzo[c]furans **227** and **228** this method was effective, giving **231** and **232** in good yields (**Scheme 85**). However the acetoxyethyl compound **230** could not be reduced by this method, the starting material disproportionating to give an inseparable mixture of the desired alkene and the corresponding aromatic compound in low yield. This compound was not pursued further.

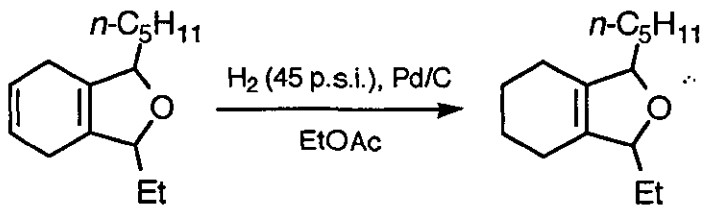


227; R = Et
228; R = *n*-C_5H_{11}

231; R = Et, 90%
232; R = *n*-C_5H_{11}, 62%

Scheme 85

In the case of the dialkyl tetrahydrobenzo[c]furan **229**, the selective reduction using Wilkinson's catalyst proved troublesome. Even in the best case approximately 10% of the product was the phthalan **226** produced by disproportionation, and the reaction was clearly not reliable; in most cases no reduction was observed. Since we would later need to carry out this reaction on the single diastereoisomers of **229**, and the separation of its precursor **226** is a laborious process, we could not afford to use an unreliable reaction. In this case the use of palladium on carbon catalyst under a hydrogen pressure of 45 p.s.i. was found to give essentially quantitative yields of a product which was shown by NMR to consist mostly of the desired compound **233** with less than 10% of the dialkyl phthalan **226**. Since this selectivity matches that of Wilkinson's catalyst in this case, and the yield was high and reproducible on scales ranging from 200 mg to 6 g, we decided to proceed with the oxidative ring expansion.

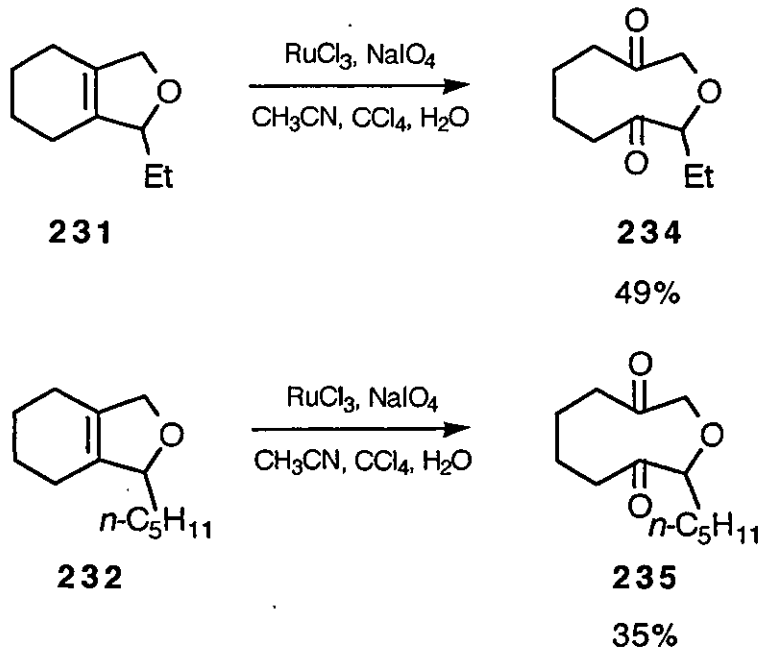


229

233
97% (ca. 90% pure)

Scheme 86

The monoalkyl-hexahydrobenzo[c]furans **231** and **232** were oxidised as before to give substituted oxonanes **234** and **235** in modest yields (**Scheme 87**).

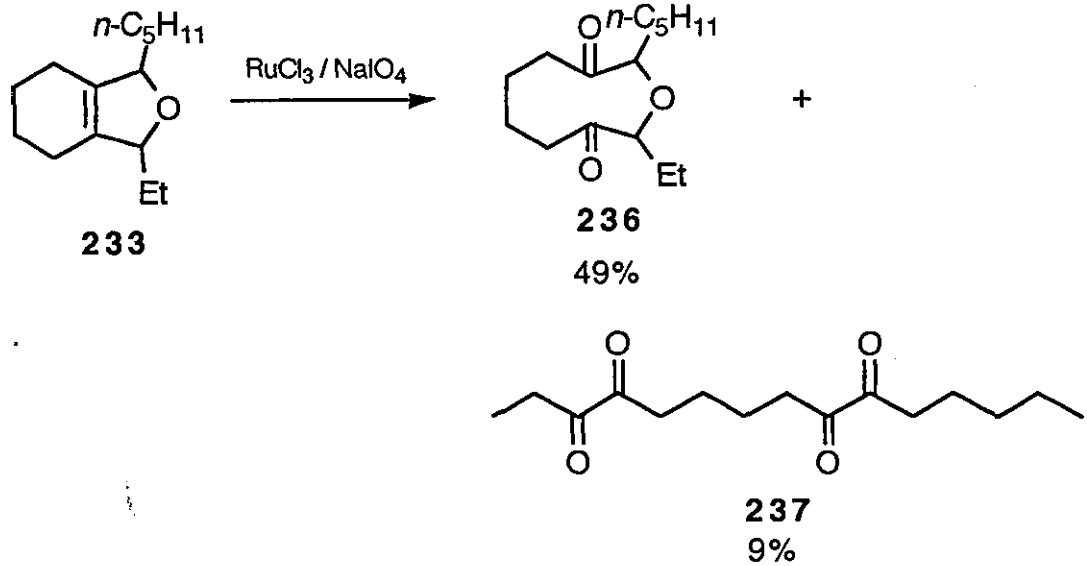


231 **234** 49%

232 **235** 35%

Scheme 87

Oxidation of **233** proceeded similarly to give **236**. In this case a second product was obtained which proved to be the tetraketone **237** (**Scheme 88**).



233

236 49%

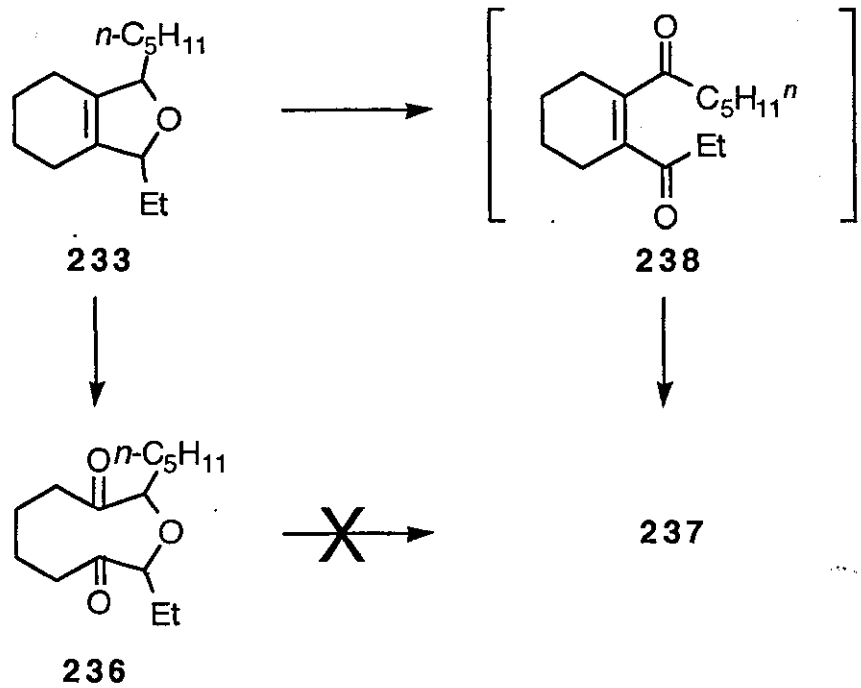
237 9%

Scheme 88

The disubstituted oxonane **236** was found to be unstable to chromatography (either on silica gel or on neutral alumina) so that rapid flash

chromatography on silica gel was the only practical method of purification. The oxonane thus obtained was found to be slightly impure. However, repeated chromatography gave no improvement in purity with a significant loss in yield. Similarly, distillation led to some decomposition with no increase in purity, so that this compound could not be obtained analytically pure.

The cleavage of cyclic ethers by ruthenium tetroxide has been described previously.[100] If **236** were oxidised under the reaction conditions this would lead to a reduced yield which could possibly be improved by shortening the reaction time. However an attempted oxidation of the dialkyl oxonane **236** under the Sharpless conditions[99] for 3 days produced none of the tetraketone **237**. This suggests that the tetraketone is formed by initial oxidation to the unsaturated dione **238** followed by cleavage of the double bond (**Scheme 89**).

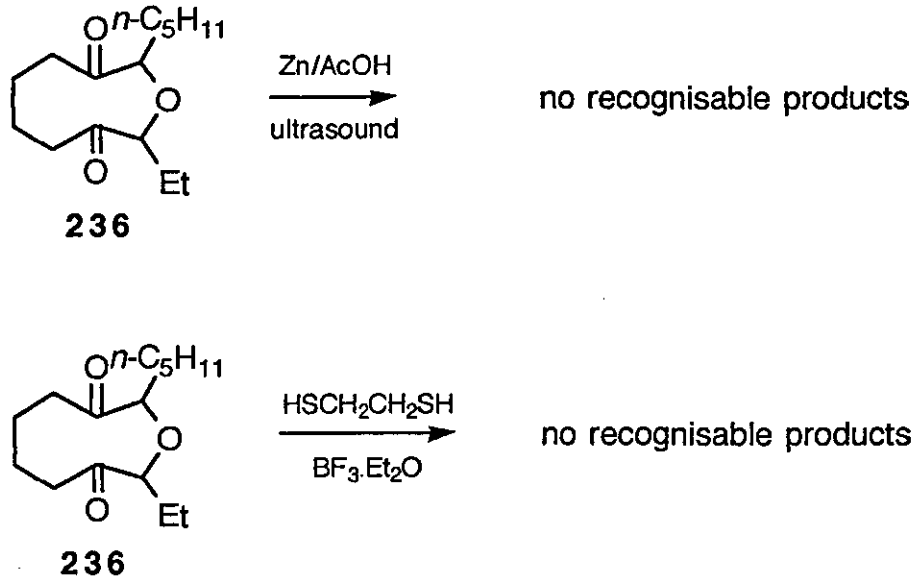


Scheme 89

2.4. Deoxygenation of 2-ethyl-9-pentyloxonane-3,8-dione: Synthesis of obtusan

Conversion of the oxonane-dione **236** into obtusan (**216**) required removal of the two ketonic oxygens. Also since *trans*-obtusan had been prepared previously,[87] conversion of the separated isomers of the dialkyl phthalan **226** into *cis*- and *trans*-obtusan would allow assignment of the relative stereochemistry of these isomers.

A number of direct methods for the deoxygenation of **236** were considered.[106] Most methods suffer from acidic or basic conditions which might epimerise the diketones to a thermodynamic mixture. Nonetheless we tried a direct reduction by zinc/acetic acid promoted by ultrasound.[107] This gave no recognisable products. Formation of the bis-dithiolane also failed (**Scheme 90**).



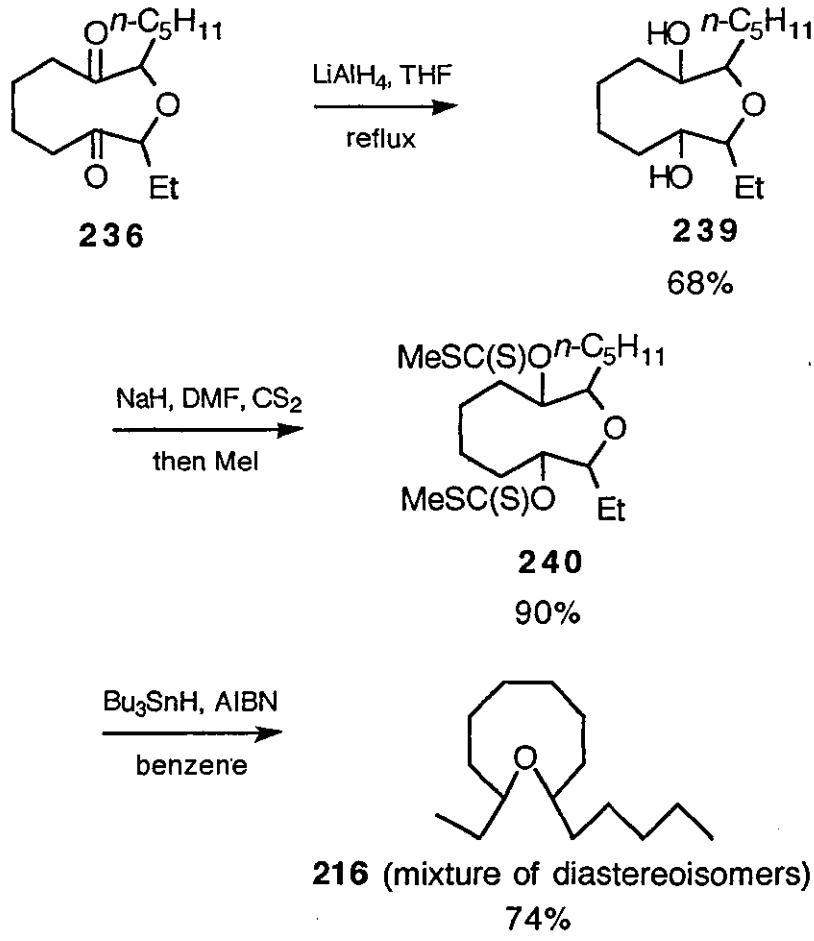
236

236

Scheme 90

Therefore we chose to attempt a radical deoxygenation of the bis-xanthate of the corresponding diol. This process is particularly attractive, since a similar reduction has been reported by Paquette and Sweeney,[108] and such a reduction is known not to compromise the stereochemistry of the α-centre. Lithium aluminium hydride reduction of the diketone **236** gave a complex mixture of diastereomeric diols **239**. Xanthate formation as reported by Paquette and Sweeney (CS_2 as solvent) was inefficient. This was attributed to the low solubility of the disodium salt of **239** in carbon disulfide.

However use of DMF as co-solvent led to the formation of the xanthate **240** in 90% yield. Deoxygenation using tri-*n*-butyltin hydride gave obtusan (**216**) as a mixture of diastereoisomers which could be separated by flash column chromatography (**Scheme 91**).



236

239

68%

240

90%

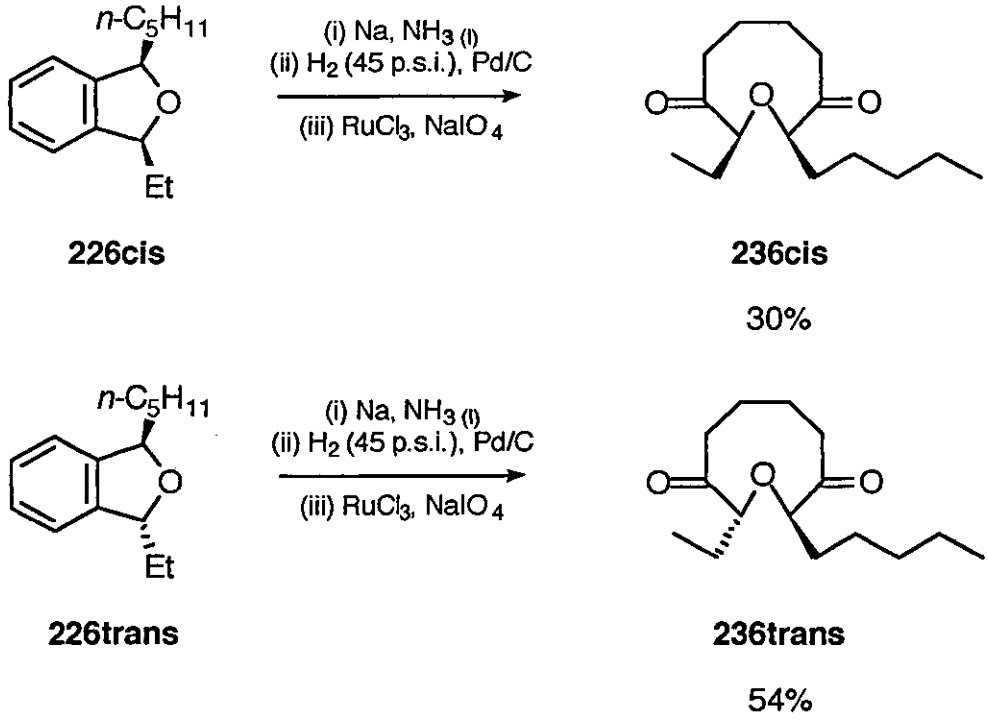
216 (mixture of diastereoisomers)

74%

Scheme 91

At this point it became evident that the ratio of isomers of obtusan (**216**) was 2.5:1 *cis*:*trans*, and not 1.4:1 as in the disubstituted phthalan starting material **226**. NMR evidence suggested that the oxonane-diketone **236** was still a 1.4:1 mixture of isomers (although without spectra of the separated isomers we could not be absolutely certain) so we felt that the epimerisation was occurring during the deoxygenation process. Clearly the nature of the epimerisation is of interest, especially since Paquette and Sweeney[108] reported no such loss of stereochemistry in their related deoxygenation (**Scheme 95**, page 62). The NMR spectra of the diol **239** and the xanthate **240** were complex due to the presence of two extra chiral centres, such that it was not possible to determine the ratios of *cis* and *trans* isomers for these compounds.

Therefore, as intended, we carried the single separated isomers of the phthalan **226** through an identical sequence of reactions as shown in **Scheme 92**. The relative stereochemistry of the isomers of **226** were determined as described below. The *cis* isomer was found to be the major isomer.[109] The correct stereochemistry will be used from this point on, although it should be noted that these are all retrospective assignments.



226cis **236cis**

30%

226trans **236trans**

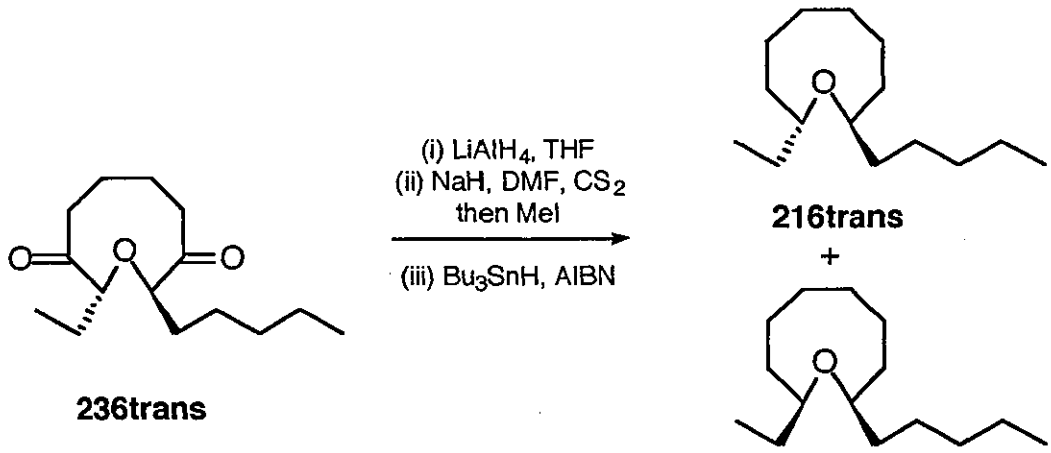
54%

Scheme 92

At this point we were able to confirm that oxonane-diketones **236cis** and **236trans** produced from the chromatographically separated phthalans were single isomers, and furthermore that the ratio of the mixture of oxonane-diones produced from the mixture of phthalans **226** was still 1.4:1 at this stage. As mentioned earlier, the ^{13}C resonances of the 2- and 9-carbon atoms occur at lower field for the *cis* isomers than for the *trans*. On the assumption that this is also true for the oxonane-diones **236cis** and **236trans**, at this point we tentatively assigned the isomer produced from the major phthalan as the *cis* isomer.

Further elaboration of the single isomers (**Scheme 93**) showed that only the *trans*-obtusan was partially epimerised (to a 1.5:1 mixture of *trans* and *cis* obtusan) during the deoxygenation procedure. The *cis* isomer (assigned by ^{13}C NMR following the work of Holmes *et al.*)[87] was obtained isomerically pure from **226cis**, and thus allowed the stereochemistry of the

phthalans **226cis** and **226trans** to be assigned unequivocally. The fact that only **236trans** underwent epimerisation presumably relates to the fact that 2,9-disubstituted oxonanes are more stable in the *cis*-arrangement than in the *trans* since both substituents can occupy pseudo-equatorial positions. Likewise 2,7-disubstituted oxepanes and 2,8-disubstituted oxocanes are also more stable in the *cis*-arrangement.[89(e)]



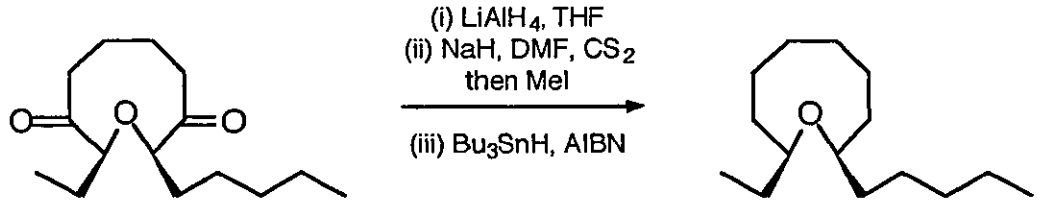
236trans

216trans

+

216cis

1.5:1 *trans*:*cis*
31% combined yield



236cis

216cis

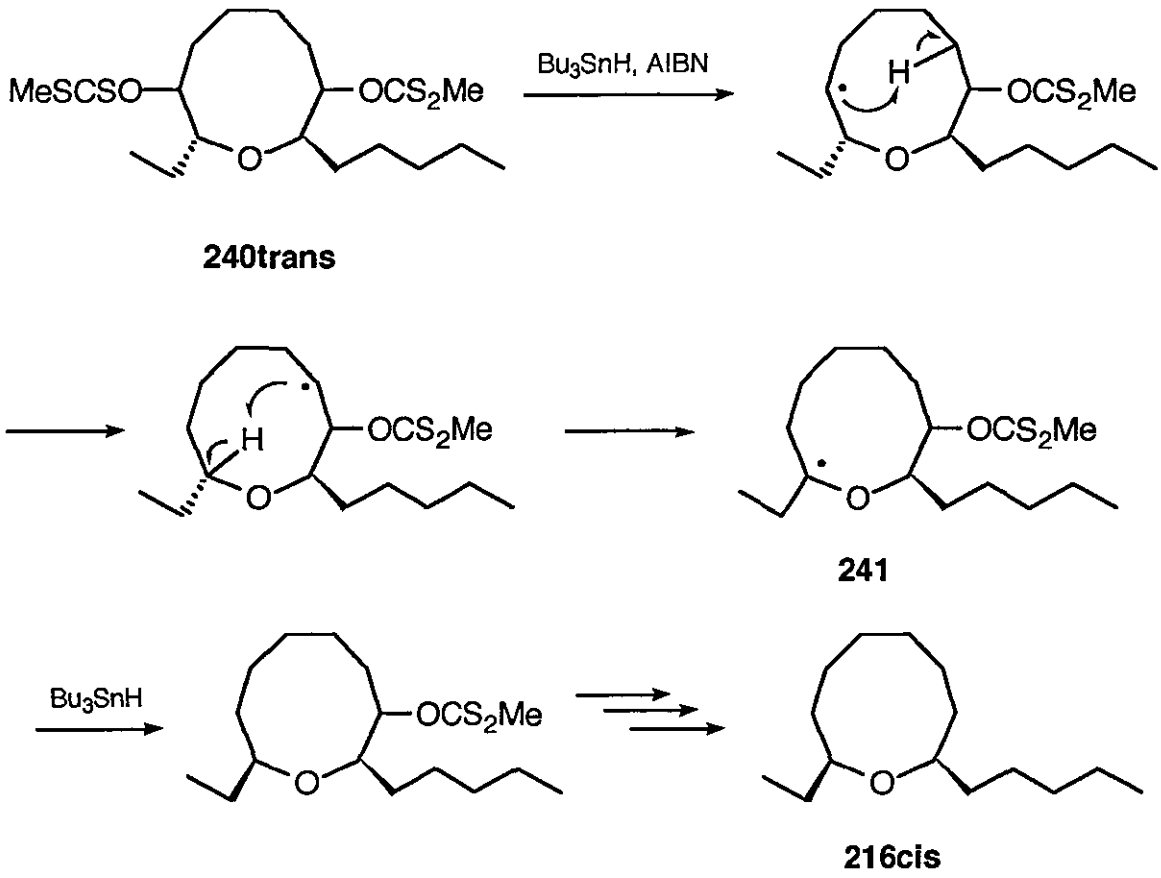
39%

Scheme 93

As mentioned earlier, the NMR spectra of the diols and xanthates were complex due to their extra asymmetric centres, and so the isomer ratios could not be reliably determined. However we could see no mechanism for epimerisation during the formation of these compounds. This left the last step, the radical deoxygenation. An epimerisation during this step can be rationalised in terms two sequential intramolecular S_H2 hydrogen abstractions (**Scheme 94**). This would give an oxygen stabilised radical **241**, with loss of stereochemical integrity, which could then abstract hydrogen from tri-*n*-butyltin

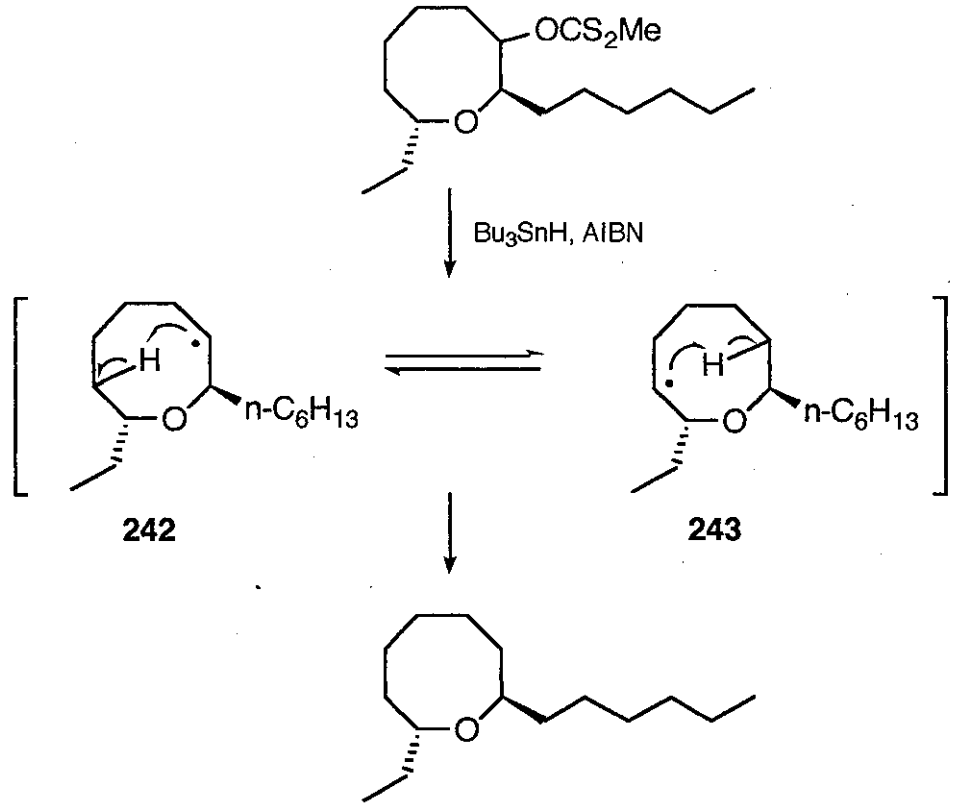
hydride to give (after a second such xanthate removal) the thermodynamically more stable *cis*-obtusan. (For a single hydrogen abstraction to epimerise this centre, a five membered transition state would need to be postulated. Since the S_H2 reaction requires the C-H-C bond angle to be 180° this is unlikely).[110]

One way to confirm or refute this mechanism would be to carry out the deoxygenation in the presence of tri-*n*-butyltin deuteride. Since the 2- and 9-carbons are well separated in the ^{13}C NMR, deuterium incorporation at these positions at the levels required to produce the observed epimerisation should be obvious and conclusive. Unfortunately we did not have time to carry out this experiment.



Scheme 94

The synthesis of lauthisan described by Paquette[108] does not suffer from this problem. In that system, any number of 1,5-hydrogen abstractions (**242** ↔ **243**) can take place without loss of stereochemistry (**Scheme 95**). Also in our case the removal of two xanthate groups is required, so that each molecule of **240trans** has two opportunities to epimerise.

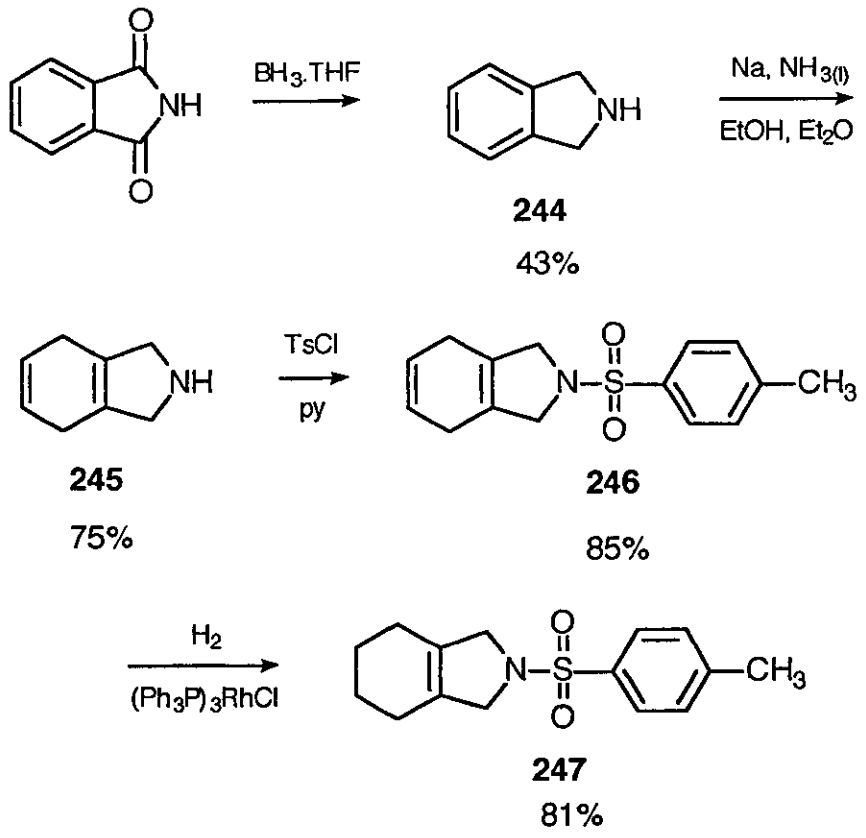


Scheme 95

2.5. Synthesis and chemistry of 1-(4-toluenesulfonyl)azonane-3,8-dione

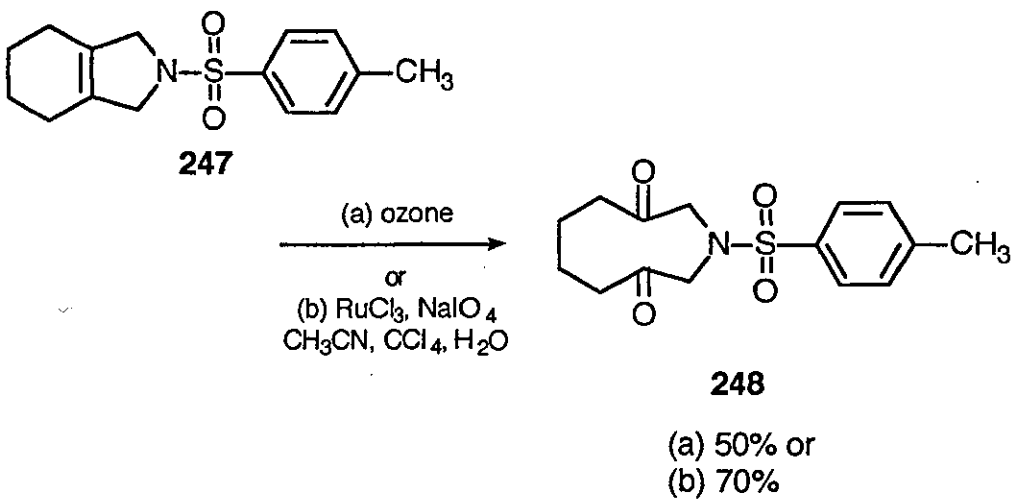
Medium sized rings containing nitrogen atoms are uncommon but not unknown in Nature; like the corresponding oxygen heterocycles, methods for their preparation are sparse.[111] The methodology just described seemed equally applicable to azonane synthesis, so the preparation of azonanes by this route was investigated in parallel with the work on oxonanes.

The nitrogen analogue of phthalan, isoindoline (**244**), can be readily prepared[112] by the reduction of phthalimide with borane in THF. This compound was found to be unstable at room temperature, but could be stored at -15°C for several months without significant decomposition. Birch reduction of **244** gave the unstable diene **245** which was immediately protected as its sulfonamide to give the tetrahydrobenzo[c]pyrrole **246** as a crystalline solid. This compound proved much easier to work with than the corresponding oxygen compounds. Selective hydrogenation of **246** in the presence of Wilkinson's catalyst gave **247** in good yield (**Scheme 96**).



Scheme 96

In this case cleavage of the double bond using ozone proceeded satisfactorily to give the azonane-dione **248** in 50% yield, although once again use of ruthenium(III) chloride/sodium metaperiodate under the conditions described by Sharpless and co-workers[99] gave better results (**Scheme 97**).



Scheme 97

Recrystallisation of **248** from ethanol provided crystals suitable for X-ray crystallographic analysis. The solid state structure, in which the two carbonyl groups are approximately parallel, is shown in **Figure 4** (hydrogen atoms omitted for clarity). Full X-ray structure data is given in **Appendix B**.

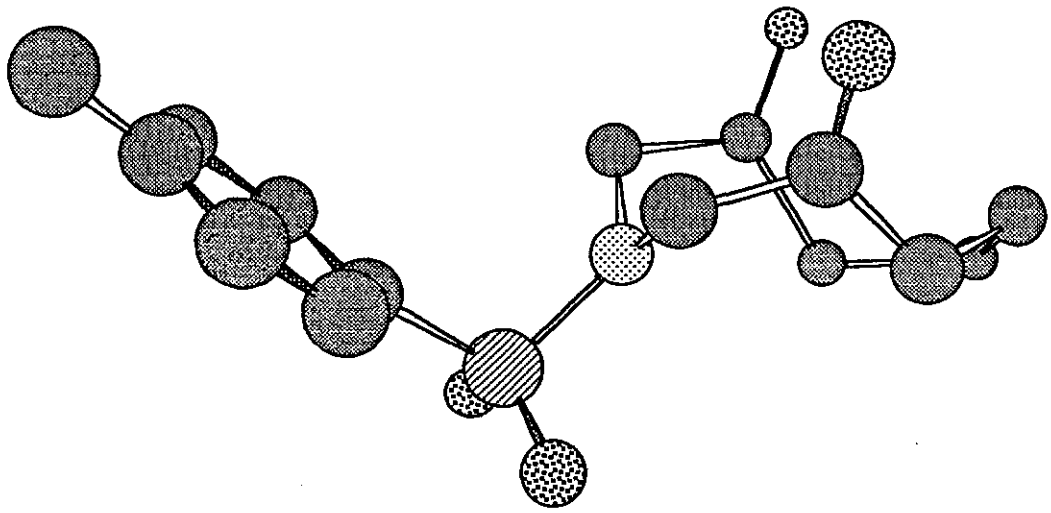
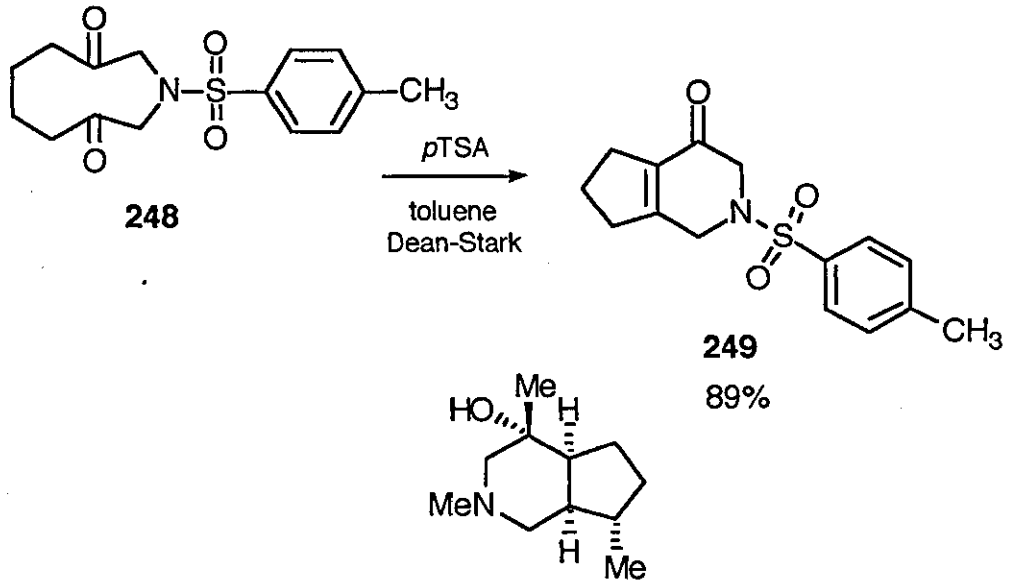


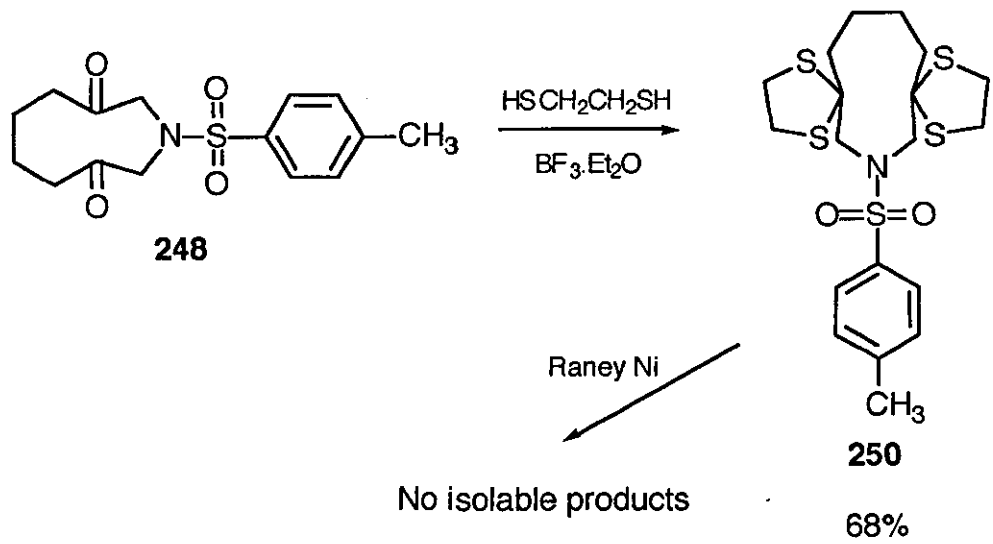
Figure 4

During the course of their work on 9-membered phosphorus heterocycles, Quin and Middlemas[113] reported that a phosphonane-3,8-dione analogous to **248** underwent an intramolecular aldol reaction on treatment with acid. The azonane-dione **248** also undergoes this reaction to give **249** in high yield (**Scheme 98**).The ring system of **249** can be found in Nature in the Skytanthine alkaloids, *e.g.* hydroxyskytanthine I.[114]



Scheme 98

As mentioned on page 57, attempted preparation of the bis-dithiolane of **236** failed. The azonane **248** is a particularly robust compound, and its bis-dithiolane **250** was prepared without problems. Unfortunately reaction of **250** with Raney Nickel led to extensive decomposition, and no products could be obtained (**Scheme 99**).



248 **250**

Scheme 99

2.6. Conclusions

The oxidative cleavage of bicyclic systems has been successfully applied to the synthesis of oxonanes and an azonane. The isomers of oxonane **236** were deoxygenated to give *cis*-obtusan and a mixture of *cis*- and *trans*-obtusans, presumably *via* a tandem radical reaction, although this was not fully investigated. Azonane **248** has been further elaborated to give **249** containing the ring system of the skytanthine alkaloids.

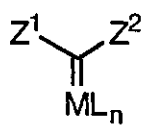
Chapter 3

Synthesis and rhodium(II) catalysed reactions of diazoamides

Synthesis and rhodium(II) catalysed reactions of diazoamides

3.1. Introduction

The catalytic decomposition of diazo compounds by transition metal salts, to give a species which reacts like a carbene, has been widely studied.[115] Most of the work within our group has centred on the synthesis of medium ring ethers,[89] and more recently on diastereoselective O-H insertions.[116] The 'metallocarbene' intermediate is often formulated as **251** (resembling a 'Fischer carbene'),[117] although the exact nature of the species is unknown. There have been some reports on the spectroscopic observation of intermediates in the reaction,[118-120] although in most cases these do not involve the catalysts which are commonly used for these reactions, and hence one must be careful when extrapolating the results to other systems.



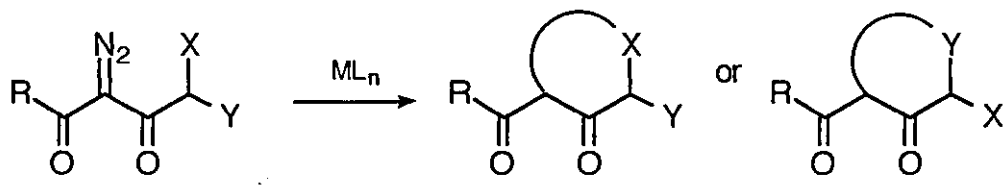
251

Z^1, Z^2 = electron withdrawing groups or H
M = metal (usually rhodium)
L = ligand

Figure 5

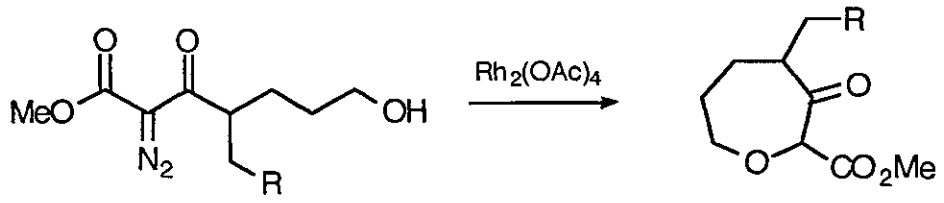
Catalyst effects are of particular interest.[121] Recent work in our laboratories has shown that, at least for O-H insertion, the rate of reaction is dependent on the catalyst used. For instance rhodium(II) trifluoroacetamide is a much more active catalyst than the more commonly used rhodium(II) acetate, and leads to rapid reactions at lower temperatures (**Scheme 7**, Chapter 1).[18]

One way to gain information about the course of the reaction is to investigate the decomposition of a substrate which could undergo more than one reaction (shown schematically in **Scheme 100**).[121(b),122]



Scheme 100

Study of the reaction under a range of conditions might give information about the nature of the intermediates involved. Previous work has shown that insertion into the O-H bond of a hydroxy group is favoured over cyclopropanation, cyclopropenation and C-H insertion (**Scheme 101**), although selectivity between other processes was less sharply defined.[122]



R = Ph, 53%
R = CH=CH$_2$, 35%
R = C≡CH, 37%

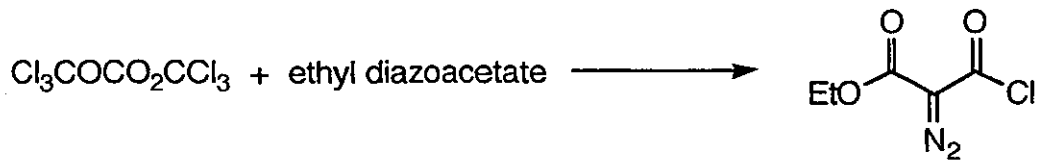
Scheme 101

The work described in this Chapter forms part of an ongoing collaboration between our group and that of Professor A. Padwa. We chose to investigate the catalytic decomposition of diazoamides, where each of the two groups attached to the nitrogen atom contain functionality which can react with the 'metallocarbene'. Such functionality includes hydroxy groups, carbonyl groups, carbon-carbon double and triple bonds, and C-H bonds in both aliphatic and aromatic systems.

3.2. Preparation and reactions of diazoamides

We required an easy route to diazoamides, and therefore chose the coupling of secondary amines with the known acid chloride, ethyl 2-diazomalonyl chloride **252**.[123] This highly convergent approach allows the one-step preparation of diazoamides from the corresponding amines.

Ethyl 2-diazomalonyl chloride can be prepared by the action of ethyl diazoacetate on phosgene. More recently, Padwa has shown[124] that phosgene can be replaced in this reaction by the crystalline substitute, triphosgene.[125] In this way we have prepared ethyl 2-diazomalonyl chloride **252** in moderate yield on scales of up to 40g (**Scheme 102**).

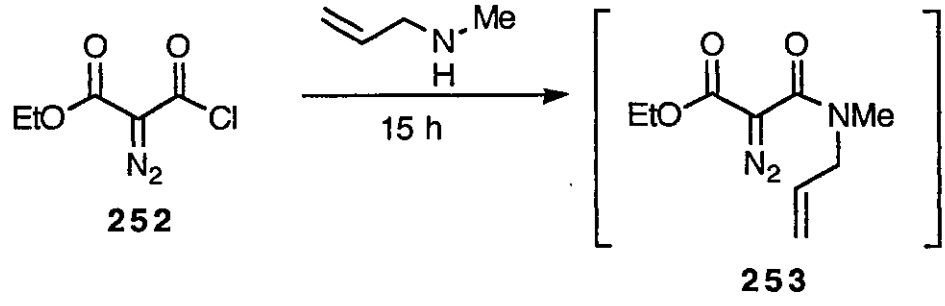


252

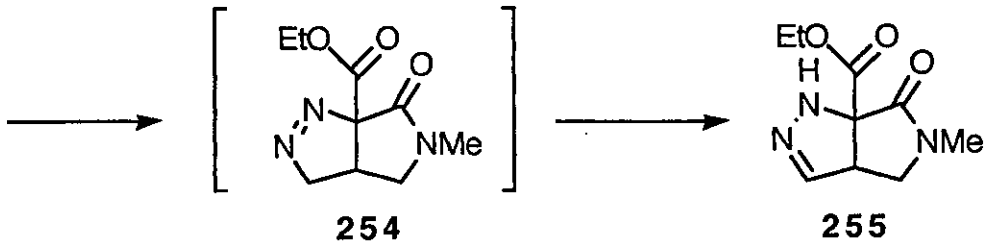
53%

Scheme 102

This proved to be a versatile, stable intermediate which reacted rapidly and in high yield with amines. Reaction with *N*-methylallylamine in dichloromethane in the presence of triethylamine did not, however, lead to the isolation of the desired diazoamide. Instead the intermediate diazoamide **253** underwent a [3+2] cycloaddition to **254** followed by a hydrogen migration to give the pyrrolopyrazole **255** in good yield as shown in **Scheme 103**.



252 **253**



254 **255**

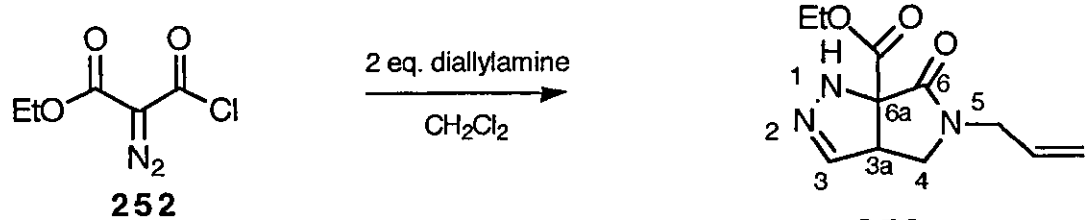
93%

Scheme 103

On examination of the literature it was found that this process is known.[126] The cycloaddition is rapid, so that when the reaction was quenched after 5 minutes, the product obtained was the initial cycloadduct **254**. Hydrogen migration to **255** occurred slowly in the absence of acid or base, but occurred to the extent of ca. 25% upon flash chromatography so that full characterisation of **254** was not possible. The rapidity of this cycloaddition meant that the rhodium(II) catalysed decomposition of diazoamide **253** could not be studied. However the rate of this cycloaddition

could be influenced by both steric and electronic factors. Thus before dismissing these compounds we felt that a few more analogues should be prepared.

When ethyl 2-diazomalonyl chloride (**252**) was allowed to react with diallylamine, the intramolecular [3+2] cycloaddition was again rapid. In this case flash column chromatography on silica gel was sufficient to ensure complete tautomerisation so that the only product obtained was the 1,3a,4,5,6,6a-hexahydropyrrolo[3,4-c]pyrazole **256** (**Scheme 104**).

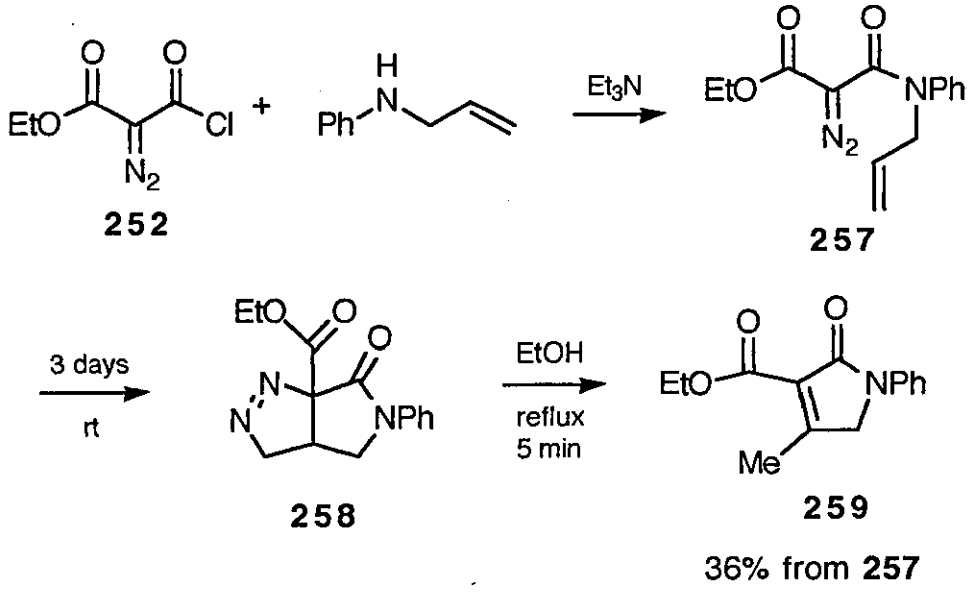


252 **256**

72%

Scheme 104

Reaction of *N*-allylaniline with ethyl 2-diazomalonyl chloride **252** led to the diazo compound **257**. This underwent cycloaddition at a much lower rate (days as opposed to minutes) than the previous two examples (**Scheme 105**). The cycloadduct formed, **258**, is relatively stable, but attempted recrystallisation from ethanol led to a thermal extrusion of nitrogen giving **259**.



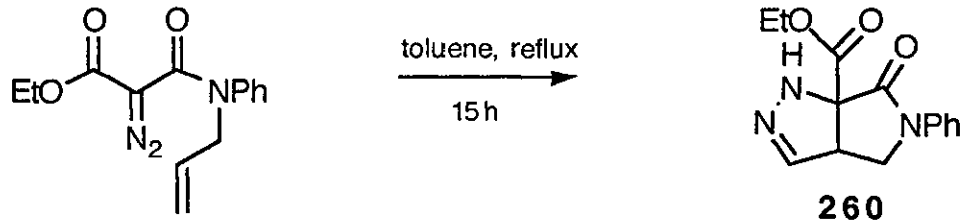
252 **257**

258 **259**

36% from **257**

Scheme 105

However when the crude diazoamide was heated, the cycloaddition was followed by hydrogen migration to give the pyrrolopyrazole **260** as the only isolated product (66% yield). This difference in reactivity was attributed to the presence of excess base (triethylamine) in the reaction mixture (**Scheme 106**).



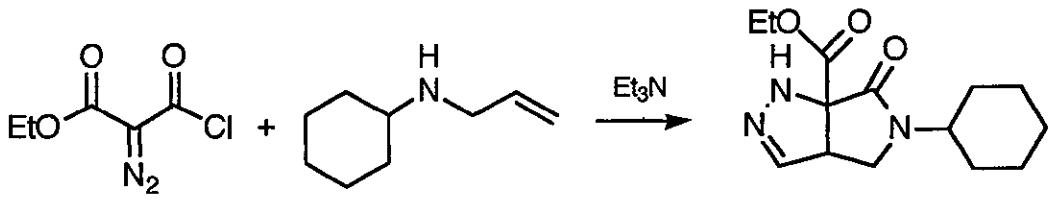
CRUDE **257**

260

60% from **252**

Scheme 106

In order to determine whether the decreased rate of cycloaddition was an electronic effect, or a steric effect as a result of a preferred conformation about the amide bond, ethyl 2-diazomalonyl chloride (**252**) was allowed to react with *N*-allylcyclohexylamine (**Scheme 107**). Cycloaddition was rapid, followed by hydrogen migration upon flash column chromatography to give the pyrrolopyrazole **261**, supporting an explanation based upon electronic effects.



252

261

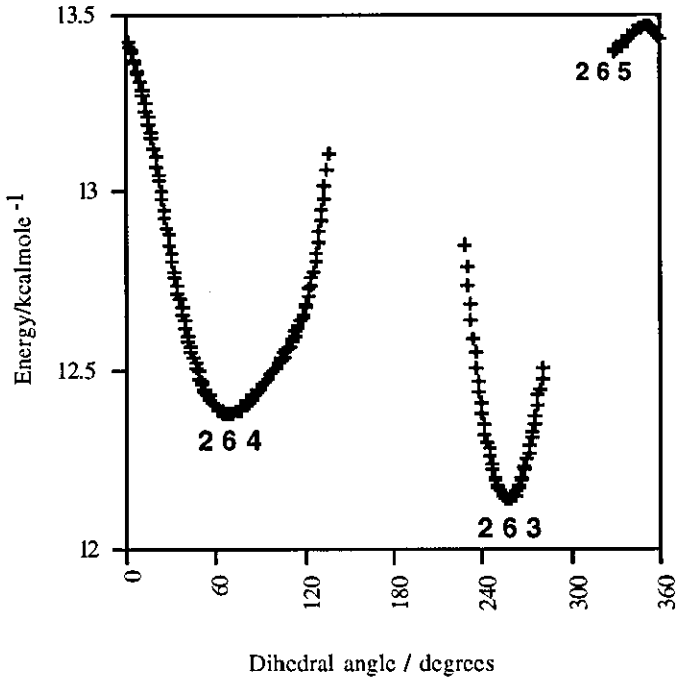
82%

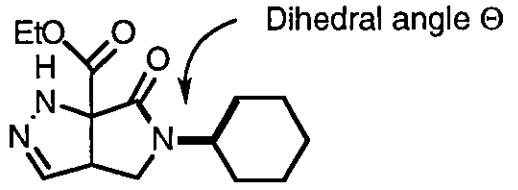
Scheme 107

This cyclohexyl compound is interesting in its own right, since the ^{13}C NMR spectrum showed all six carbons of the cyclohexyl ring, not four as would be expected if free rotation were allowed about the bond between the nitrogen of the pyrrolopyrazole and the carbon of the cyclohexyl ring. Conformational analysis was carried out on the energy minimised structure (see **Appendix C** for details) of **261**. **Graph 1** shows how the energy of the molecule varies as the dihedral angle C-C-N-C (Θ in structure **262**).

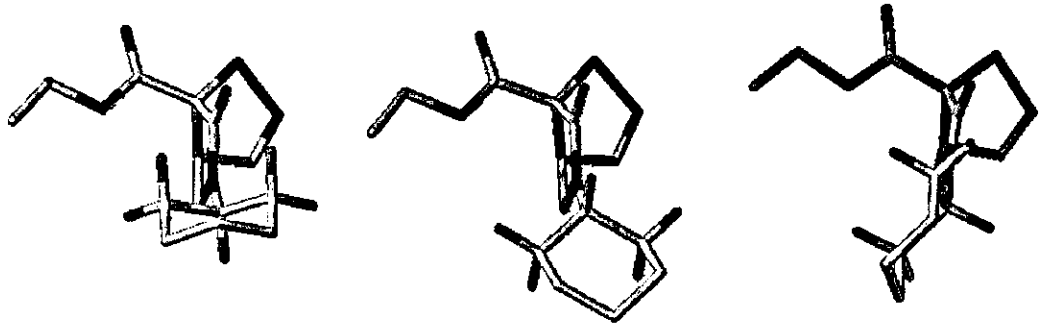
Graph 1

Conformational analysis of **261**





262

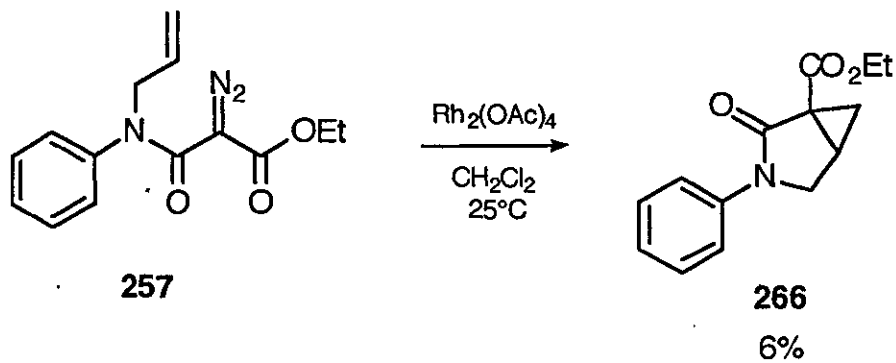


263 **264** **265**

(for clarity, only the hydrogen atoms on the cyclohexyl C-1, C-2 and C-6 carbons are shown)

These calculations show that the interaction of the amide oxygen atom with the axial hydrogens on the C-2 and C-6 carbons prohibits free rotation. The global minimum **263** corresponds to a situation where the amide carbonyl is flanked by these axial hydrogens. Rotation past these hydrogens is energetically unfavourable. In the local minimum conformation **264** the amide carbonyl and the axial hydrogen on the cyclohexyl C-1 are almost parallel. Rotation from conformer **264** to conformer **265** brings the amide oxygen closer to the axial hydrogen on C-2. In conformer **265** the distance between the amide oxygen and the axial hydrogen is 2.796Å, significantly more than the combined Van der Waals radii of these atoms, although the close distance between the carbonyl oxygen and the equatorial hydrogen on C-2 presumably still exerts an effect. These calculations therefore support the NMR data, in that rotation about the N-cyclohexyl bond is not free, and the asymmetry present in the molecule means that the six cyclohexyl carbon atoms are all in magnetically non-equivalent environments. Since the cycloaddition was rapid, chemistry on the intermediate diazo compound was impossible.

Treatment of the freshly prepared diazoanilide **257** with rhodium(II) acetate at room temperature furnished the cyclopropane **266** as the only isolated product, albeit in low yield (6%) (**Scheme 108**). However upon addition of catalyst the reaction mixture turned brown after a few minutes. This is unusual, and may indicate poisoning of the catalyst. Dauben and co-workers have demonstrated poisoning of copper-based catalysts by pyrazoles similar in structure to **258** in related cyclopropanations.[127] The same cyclopropane (**266**) was formed (23% yield) by photolysis of **258**.[126]



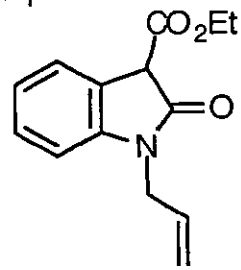
257 **266**

6%

Scheme 108

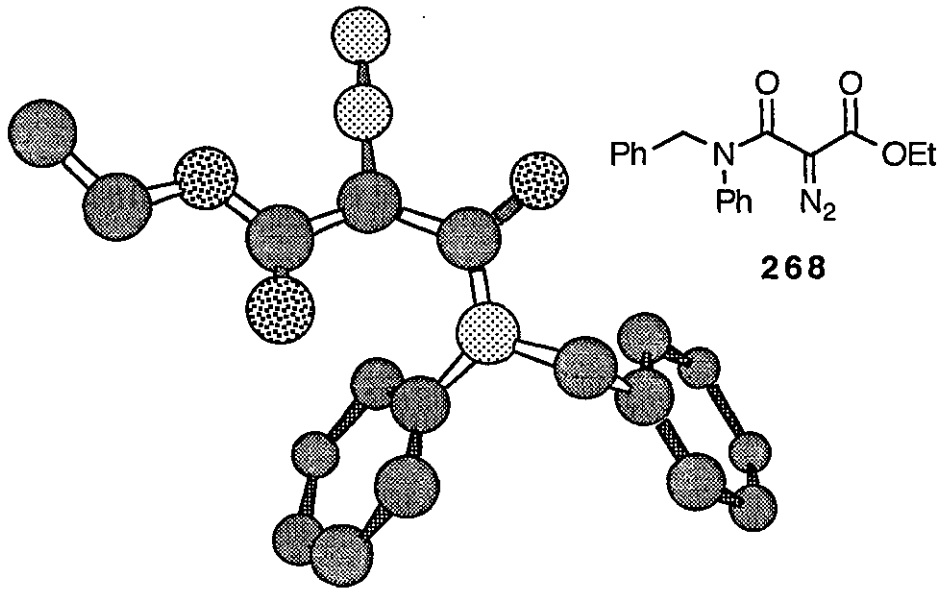
Using rhodium(II) trifluoroacetamide or rhodium(II) perfluorobutyramide as catalysts the reaction started quickly upon addition of catalyst (gas evolution was observed), but stopped within a minute. Addition of more

catalyst re-started the reaction briefly. After several days the reaction mixtures were shown by NMR to consist almost entirely of the initial cycloadduct **258** (**Scheme 105**). No carbene derived products were obtained from these reactions. However Padwa has reported[128] the isolation of oxindole **267** as the only product from the rhodium(II) trifluoroacetamide catalysed decomposition of this diazo compound.



267

Because of these complications we moved away from allyl diazoamides. The substrate **268** was prepared by reaction of ethyl 2-diazomalonyl chloride with *N*-benzylaniline in order to investigate the competition between β-lactam formation and oxindole formation. Crystals of **268** were suitable for X-ray crystallographic analysis. The solid state conformation is shown in **Figure 6** (full data given in **Appendix B**).

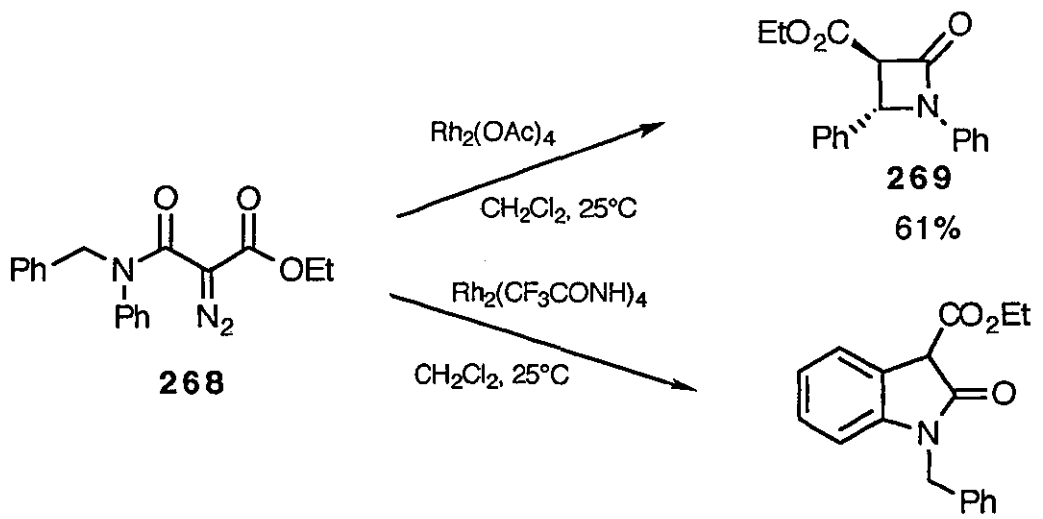


268

Figure 6

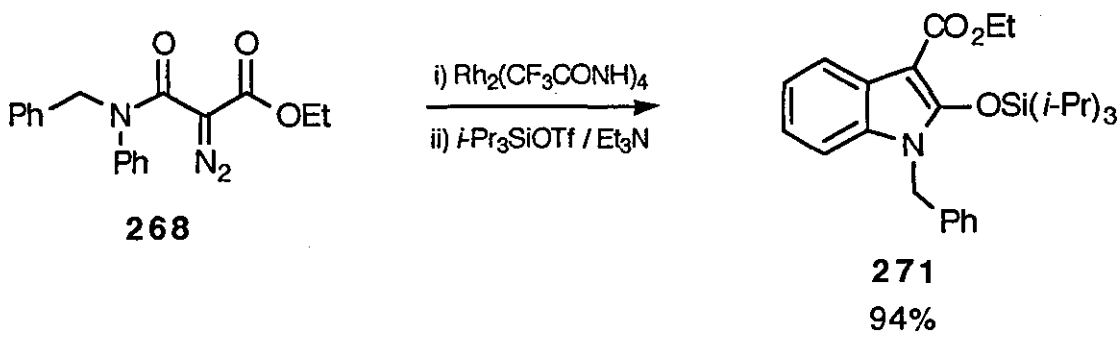
When **268** was decomposed in the presence of rhodium(II) acetate over 6 days, the β-lactam **269** was predominantly formed (61% isolated yield), with no evidence to suggest poisoning of catalyst. The balance of the material was shown to be oxindole **270** by NMR analysis of the crude reaction mixture. However with rhodium(II) trifluoroacetamide as catalyst, reaction was very

rapid: nitrogen evolution started immediately and after only 10 minutes the reaction mixture had changed from yellow (characteristic of diazo compounds) to colourless, and was shown by NMR to consist almost entirely of the oxindole **270**. This is formed by a formal insertion of the 'rhodium carbenoid' into a C-H bond in an aromatic system, although the reaction is probably better represented as an aromatic electrophilic substitution of the 'rhodium carbenoid'.[129]



Scheme 109

The oxindole **270** was found to be unstable to chromatography (silica gel, and basic and neutral alumina), but could be isolated as its triisopropylsilyl enol ether **271** in a one-pot process (**Scheme 110**).



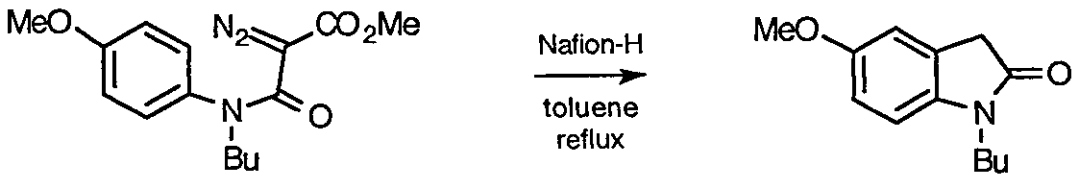
Scheme 110

Other catalysts gave rates of reaction and product distributions (determined by ^{1}H NMR analysis of crude reaction mixtures; normalised to **269** + **270** = 100%) as shown in **Table 1**.

Catalyst	reaction time	ratio **269**:**270**
rhodium(II) acetate	9 days	72:28
rhodium(II) trifluoroacetate	61 h	0:100
rhodium(II) perfluorobutyrate	121 h	7:93
rhodium(II) acetamide	145 h	19:81
rhodium(II) trifluoroacetamide	10 min	0:100
rhodium(II) perfluorobutyramide	10 min	0:100

Table 1

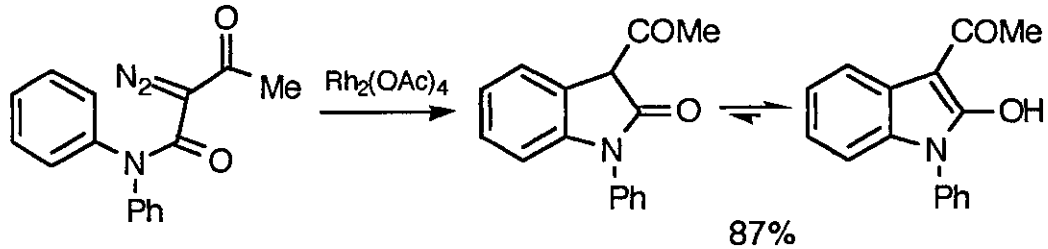
The cyclisation of diazoanilides to oxindoles is not unknown.[129-132] Wee has reported that Nafion-H catalysed decomposition of similar substrates to the above gives oxindoles with loss of the carbomethoxy group (*e.g.* **Scheme 111**).[130]



68%

Scheme 111

Of particular relevance to this discussion is the observation by Durst that although 3-acetyloxindoles can be prepared by the rhodium(II) acetate catalysed decomposition of suitable diazo-ketoamides (*e.g.* **Scheme 112**), this method fails for the corresponding diazo-ester-amides.[131]

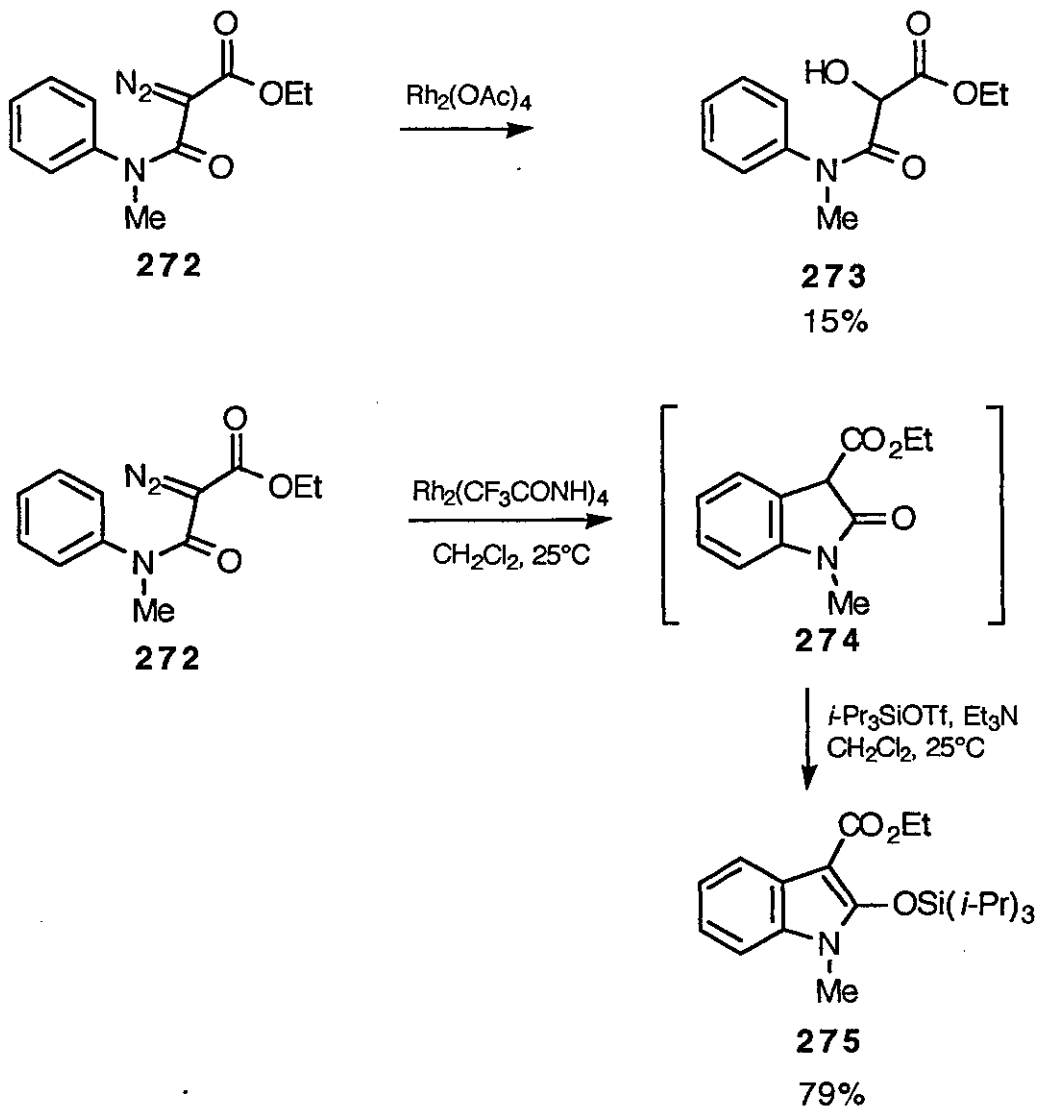


87%

Scheme 112

Instead, the rhodium(II) acetate catalysed decomposition of diazoamide **272** was reported to give only a product **273** derived from "adventitious water insertion".[131] Wee has reported[132] the formation of a β-lactam from the methyl ester analogue of **272** by 'carbene insertion' into a methyl C-H. Since the availability of ethyl 2-diazomalonyl chloride makes **272**

trivial to prepare, we decided to re-investigate its rhodium(II) catalysed decomposition. In our hands rhodium(II) acetate catalysis led only to a low yield of **273**, even though all glassware and solvents were thoroughly dried. However when **272** was decomposed in the presence of rhodium(II) trifluoroacetamide, only the oxindole **274**, characterised as its triisopropylsilyl enol ether **275**, was obtained (**Scheme 113**).



272 → **273** 15%

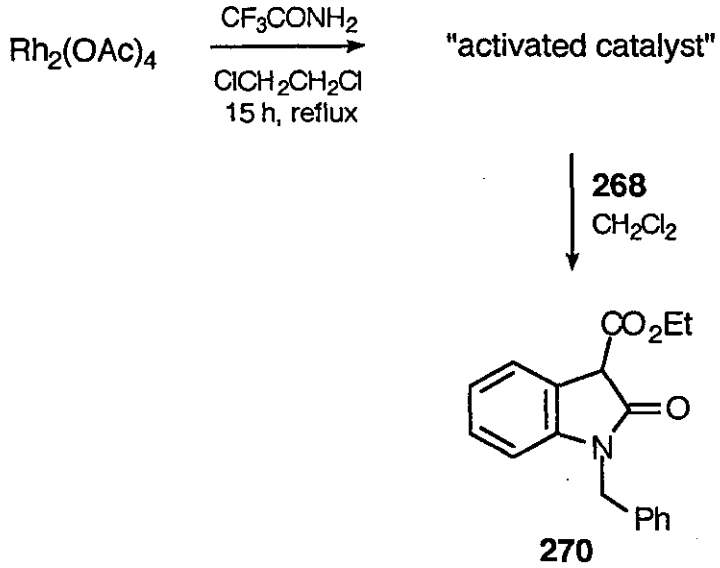
272 → **274** → **275** 79%

Scheme 113

3.3. *In situ* generation and use of rhodium(II) trifluoroacetamide

It is clear that rhodium(II) trifluoroacetamide is a superior catalyst for effecting insertion into C-H bonds in aromatic systems. An earlier report from our laboratories[18] revealed that this catalyst is particularly good for oxepane formation by O-H insertion (**Scheme 7**, Chapter 1). However the preparation

of this catalyst,[133] while simple, is often troublesome and unreliable. Low yields are common, and the catalyst is often of variable activity. Padwa[128] has offered rhodium(II) perfluorobutyramide as a catalyst which displays the same chemoselectivity as, and comparable rates of reaction to, rhodium(II) trifluoroacetamide, but is easier to prepare and purify. We felt that it might be possible to prepare rhodium trifluoroacetamide and use it without purification. To this end we heated a solution of rhodium(II) acetate in 1,2-dichloroethane with 2,2,2-trifluoroacetamide (20 equivalents) at reflux for 15 hours. After cooling to room temperature a solution of diazoamide **268** in dichloromethane was added. The only product formed was the oxindole **270** as before. The extended reaction time (4 hours instead of 10 minutes) is considered a small price to pay for the convenience of the protocol (**Scheme 114**) None of the β-lactam **269**, which would be formed by rhodium(II) acetate catalysis, was detected.



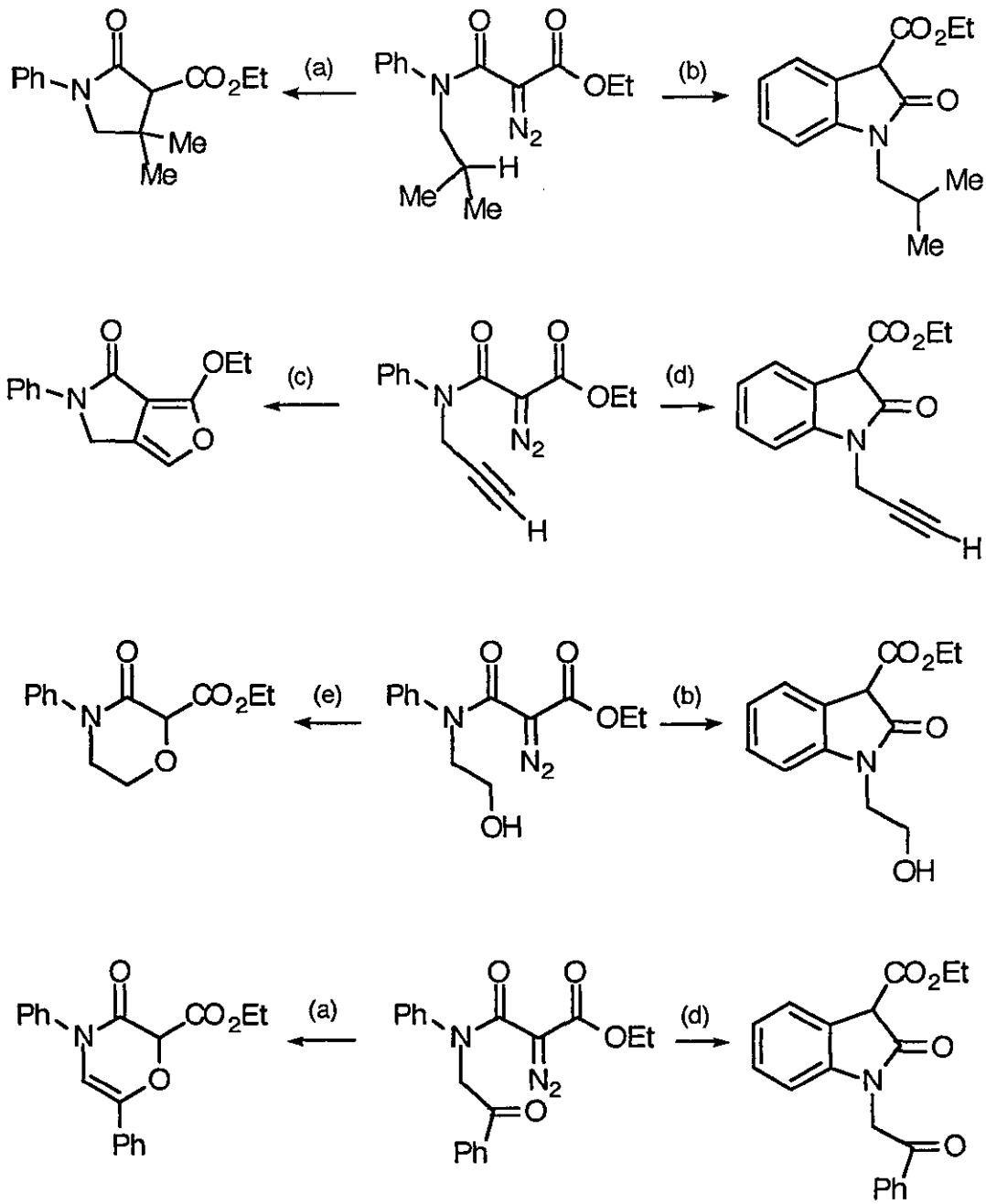
270

Scheme 114

3.4. Related competition experiments

As mentioned earlier, this work was carried out as part of a collaboration. A wider range of substrates were studied in order to define the catalyst selectivities. In all cases the above catalyst effects were supported, in that rhodium(II) trifluoroacetamide and rhodium(II) perfluorobutyramide favour oxindole formation, whereas rhodium(II) acetate favours products *other than* oxindoles. It is clear that, at least in these cases, the fluorinated amide- and the carboxylate-based catalysts are complementary. These results (chemistry

carried out by J. P. Marino Jr. under the direction of Prof. A. Padwa) are summarised in **Scheme 115**.[128]



(a) $Rh_2(OAc)_4$, benzene, reflux; (b) $Rh_2(C_3F_7CONH)_4$, CH_2Cl_2, 25°C

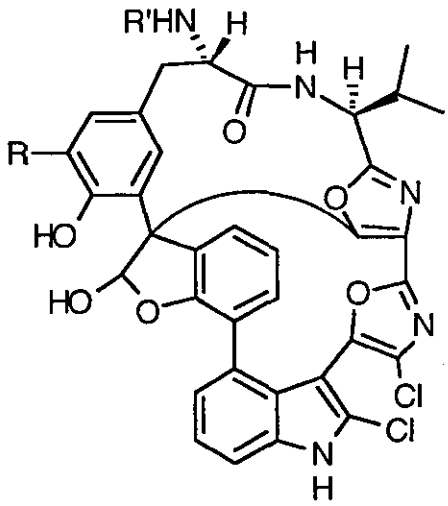
(c) $Rh_2(C_3F_7CO_2)_4$, benzene, reflux; (d) $Rh_2(CF_3CONH)_4$, CH_2Cl_2, 25°C

(e) $Rh_2(OAc)_4$, CH_2Cl_2, 25°C

Scheme 115

3.5. Attempted preparation of halogenated oxindoles

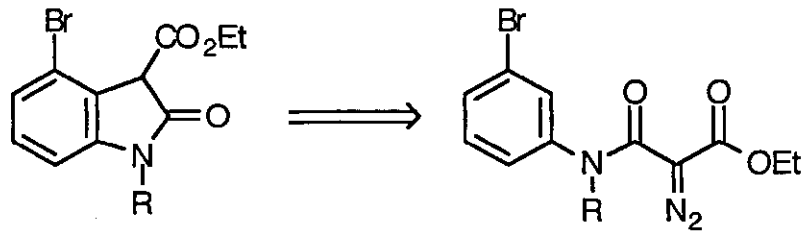
Diazonamides A and B[134] (**Figure 7**) are marine natural products which have received some attention within our group (see Chapter 4 for a more thorough discussion).



Diazonamide A: R = H, R' = $(CH_3)_2CH(NH_2)CO$
Diazonamide B: R = Br, R' = H

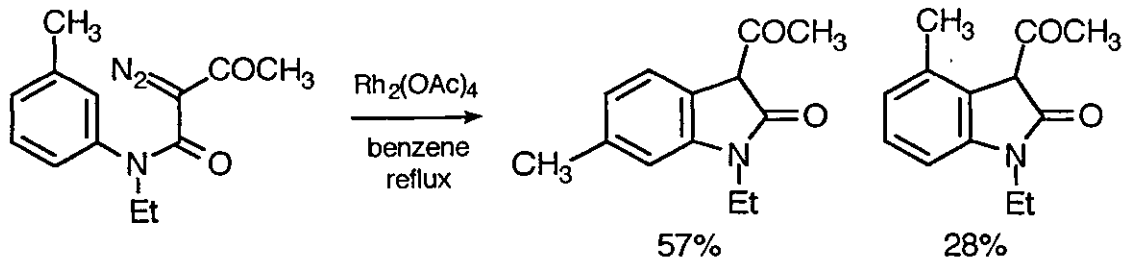
Figure 7

The indole ring can be prepared from an oxindole by a Vilsmeier-type acylation.[135] As mentioned in Chapter 4, a synthesis of diazonamide A or B requires a 4-substituted oxindole, which we felt could be prepared using rhodium carbene methodology. We chose a 4-bromooxindole, which can be disconnected to a 3-bromodiazoanilide as shown in **Scheme 116**. This would then allow introduction of the benzofuranol ring *via* a palladium catalysed cross-coupling reaction.



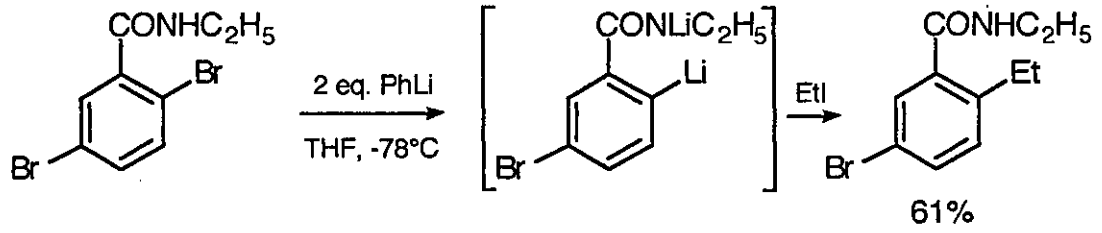
Scheme 116

However Doyle has shown[129] that aromatic C-H insertion in such systems favours the regioisomeric 6-substituted oxindole (**Scheme 117**). In order to prepare a 4-bromooxindole, the 6-position needs to be blocked. This should then produce a 4,7-disubstituted oxindole from which the substituent at the 7-position might be selectively removed.



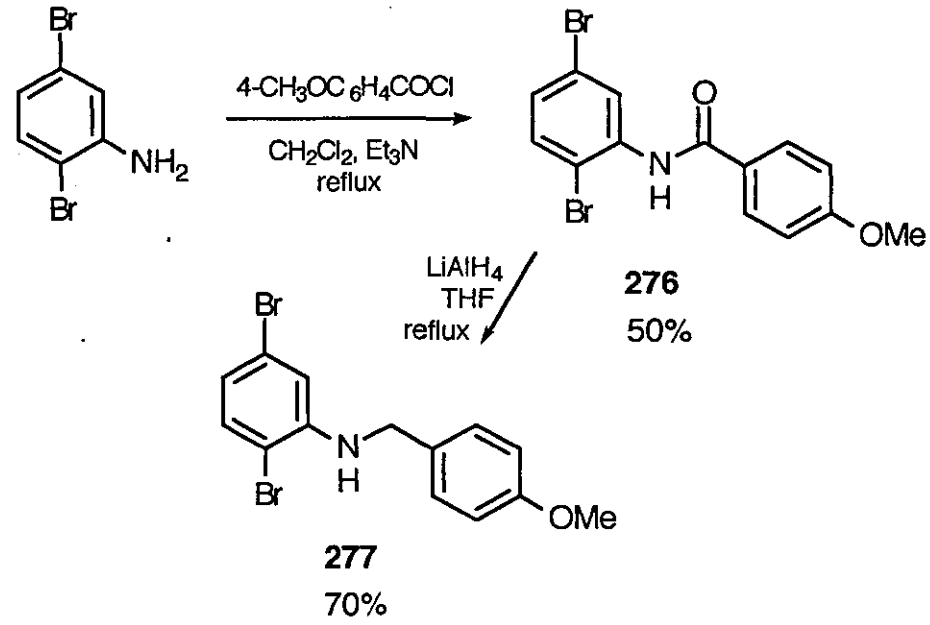
Scheme 117

The only suitable commercially available precursor was 2,5-dibromoaniline. This is clearly not ideal since the selective removal of one of the two bromine atoms is required, although since the 7-bromo is *ortho* to a nitrogen atom, by careful choice of the group on nitrogen, selective lithiation at the 7-position should be possible. Beak *et al.* have demonstrated one such selective lithiation (**Scheme 118**).[136]



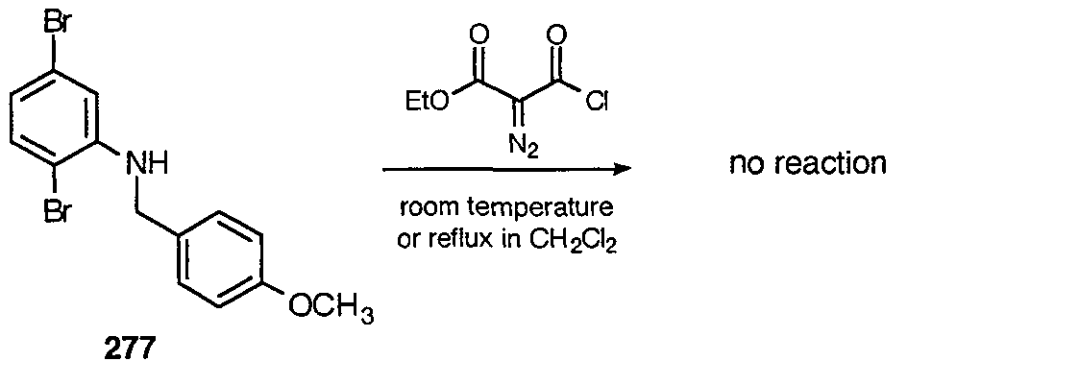
Scheme 118

2,5-Dibromoaniline was allowed to react with 4-methoxybenzoyl chloride to give the amide **276**. This was reduced by lithium aluminium hydride to give the secondary amine **277** (**Scheme 119**).

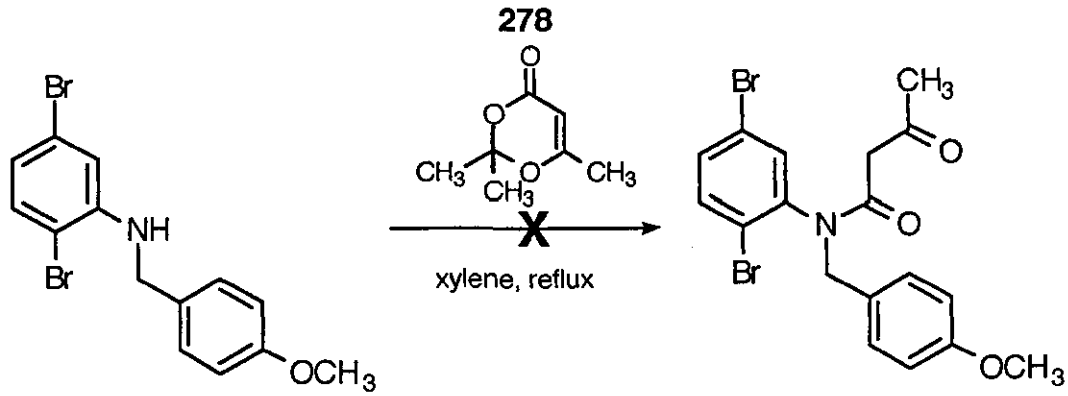


Scheme 119

Reaction of **277** with ethyl 2-diazomalonyl chloride (**252**) led only to recovery of the starting amine, even over an extended period of time or at elevated temperatures. Attempted reaction with the diketene equivalent 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**278**) in refluxing xylene also failed, giving only recovery of starting material (**Scheme 120**).



277



278

277

Scheme 120

This lack of reactivity most probably reflects the steric hindrance in the amine. Since 4-bromoindole can be readily prepared[137] by a Leimgruber-Batcho synthesis from 2-bromo-6-nitrotoluene, this route was not pursued further.

3.6. Conclusions

Rhodium(II) trifluoroacetamide is a particularly effective catalyst for oxindole formation from diazoanilides. Reactions are rapid and clean. A method has been developed which allows the generation and *in situ* use of this catalyst starting with the commercially available rhodium(II) acetate and 2,2,2-trifluoroacetamide. It is worth noting that both rhodium(II)

trifluoroacetamide and rhodium(II) perfluorobutyramide are insoluble in dichloromethane. While this fact probably does not have any great mechanistic implications (rhodium(II) perfluorobutyrate is soluble in dichloromethane, but favours oxindole formation, see **Table 1**) it means that the reactions are easy to follow visually. The disappearance of the characteristic yellow colour of the diazo compound is easy to see, as is the evolution of nitrogen from the catalyst surface. In rhodium(II) acetate catalysed reactions the green colour of the catalyst obscures the colour of the diazo compound.

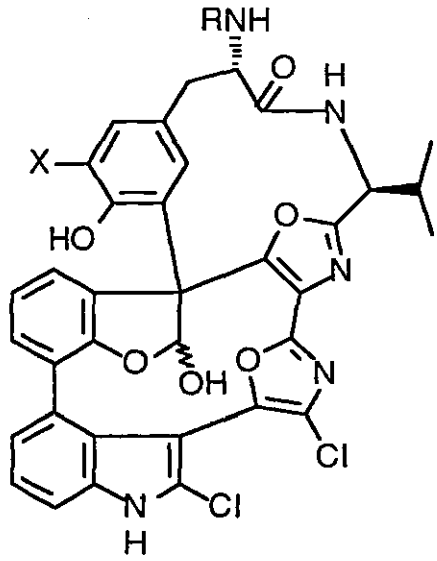
Chapter 4

Model studies towards the synthesis of Diazonamide A

Model studies towards the synthesis of Diazonamide A

4.1. Introduction

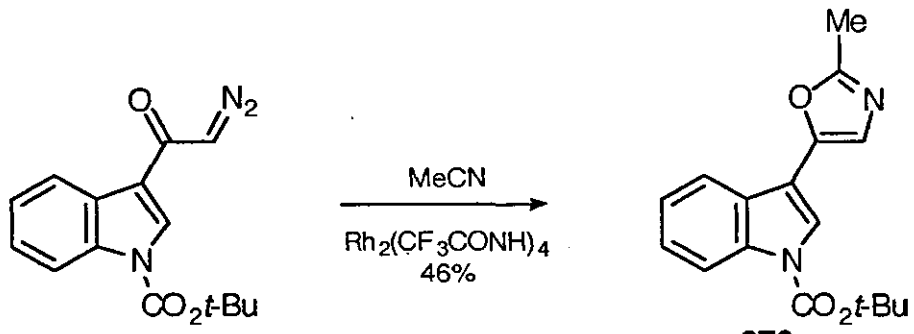
Diazonamides A and B (**Figure 8**) were recently isolated[134] from the colonial ascidian *Diazona chinensis*. These marine natural products have potent cytotoxic activity, and are therefore of great pharmacological interest, and their novel structure presents a formidable synthetic challenge.



Diazonamide A: X = H, R = $(CH_3)_2CHCH(NH_2)CO$-
Diazonamide B: X = Br, R = H

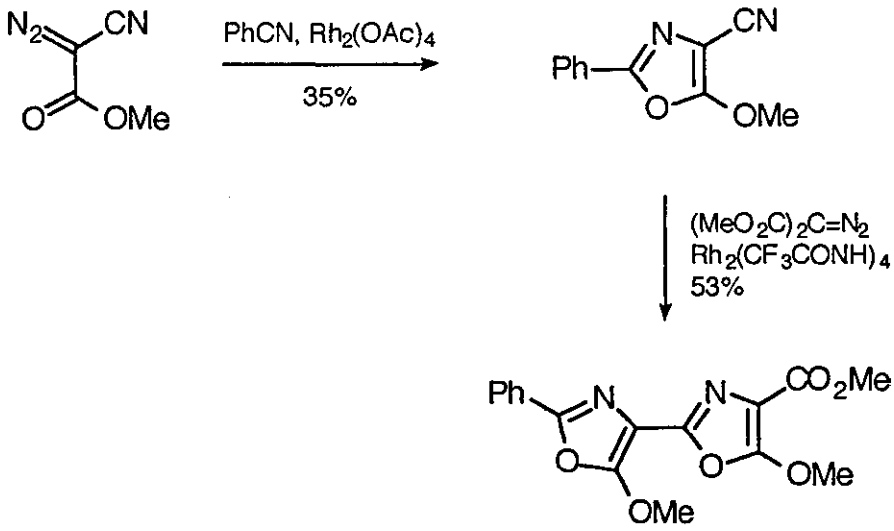
Figure 8

The diazonamides have a number of functional groups which are amenable to rhodium carbenoid methodology. The oxazole rings can be prepared by the cycloaddition reaction of a ketocarbene with a nitrile.[138] Recent work within our group has established this as a route to indole oxazoles **279** (**Scheme 121**)[139] and bis-oxazoles **280** (**Scheme 122**).[140]



279

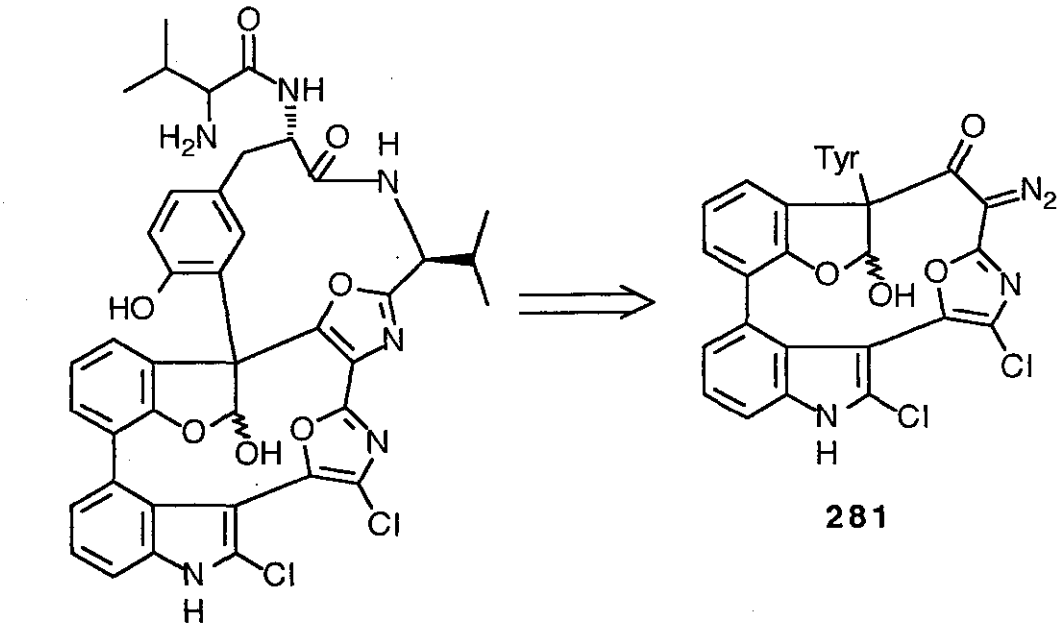
Scheme 121



280

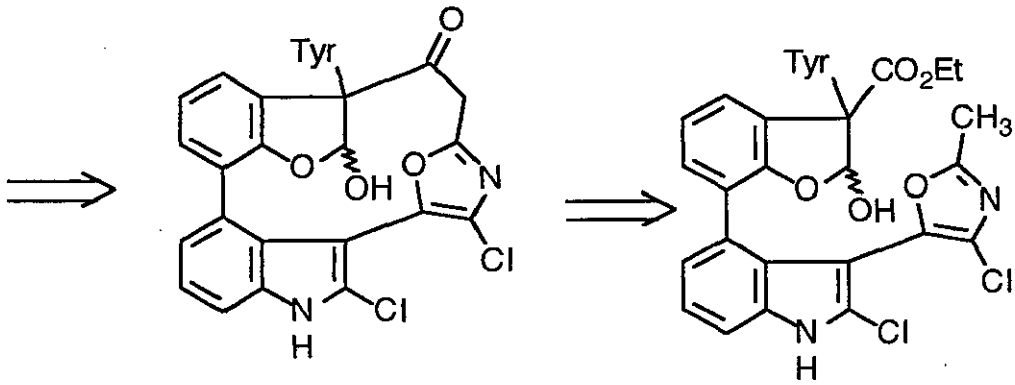
Scheme 122

The 'top oxazole' fragment within the diazonamide structure is clearly derived from valine, so that the ketocarbene + nitrile disconnection leads to valine nitrile. Recently oxazoles derived from valine nitrile have been prepared within our group.[141] Therefore disconnection of the amide bond of the pendant valine and the tyrosine-valine amide bond within the diazonamide core, followed by the disconnection of the oxazole leads to the diazo compound **281**. The diazo group could be introduced directly by a 'diazo transfer' reaction[142] to the 'active methylene' (*i.e.* sufficiently acidic) in **282**, which can be further disconnected to **283** (intramolecular reaction of the anion derived from the 2-methyloxazole with the benzofuran-3-ester), which we felt could be formed by a palladium catalysed cross coupling[143] of a 4-functionalised 3-indolyloxazole **284** and a suitable benzofuranone **285** (**Scheme 123**) followed by reduction of the lactone to the lactol.



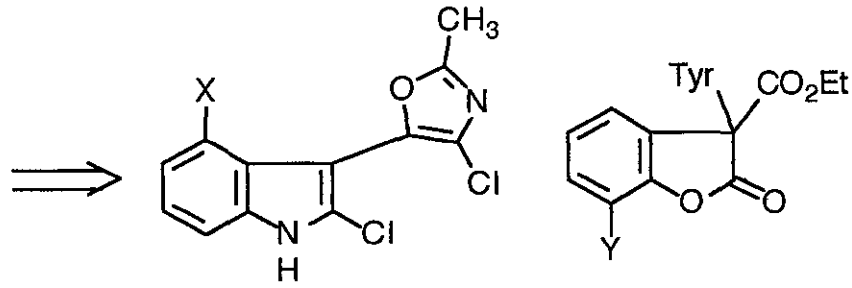
Diazonamide A

281



282

283



284

285

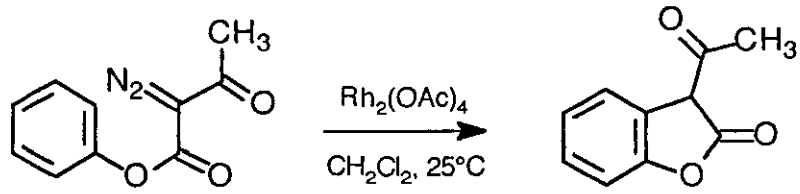
Tyr = tyrosine; X = halogen, Y = metal or X = metal, Y = halogen

Scheme 123

Since the preparation of oxazoles related to diazonamide A was being actively pursued by other workers in our group, studies were therefore undertaken as follows towards the benzofuranone ring of diazonamide A.

4.2. Preparation and elaboration of benzofuranones

3-Acetylbenzofuranones have been previously prepared by rhodium carbene chemistry (**Scheme 124**).[144]

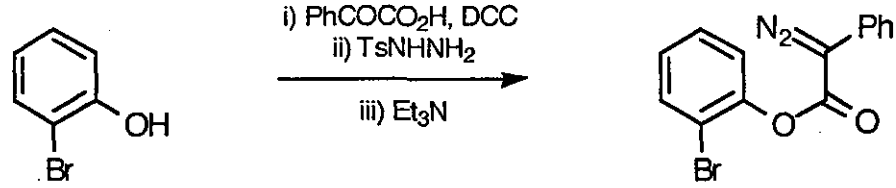


286 98%

Scheme 124

For an entry into the ring system of the diazonamides, we required a 3-arylbenzofuranone with a substituent at the 7- position suitable for a biaryl coupling (stannyl, halo, triflate, etc.). As a model compound we chose 7-bromo-3-phenylbenzofuranone (**288**).

The diazo precursor to this compound was prepared using a Bamford-Stevens reaction as follows. 2-Bromophenol was esterified with benzoylformic acid. Tosylhydrazone formation was followed by treatment with triethylamine to give the diazo compound **287**.

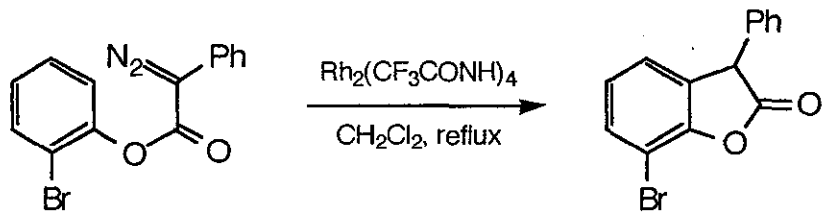


287
47% overall

Scheme 125

Treatment of this compound with either rhodium(II) acetate or rhodium(II) perfluorobutyramide at room temperature gave no isolable products. Increasing the temperature gave slightly better results. Slow addition of the diazo compound to rhodium(II) perfluorobutyramide in refluxing dichloromethane gave a complex mixture containing ca. 20% yield of the desired compound **288** (**Scheme 126**). Higher temperatures gave lower yields, as did using rhodium(II) acetate as catalyst at elevated temperatures.

Unfortunately the complexity of this reaction mixture meant that the product could not be obtained analytically pure.

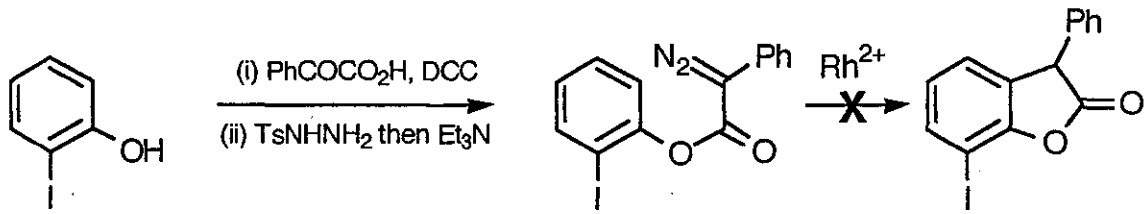


287 **288**

ca. 20%

Scheme 126

The chosen synthetic scheme required that the bromine in **288** be replaced by an aryl group *via* a palladium catalysed cross coupling,[143] which would presumably be easier to carry out using the corresponding iodo compound (**290**). Therefore **289** was prepared in an identical manner to the above. Decomposition of this compound by rhodium(II) salts under a wide range of conditions led to no identifiable products (**Scheme 127**).



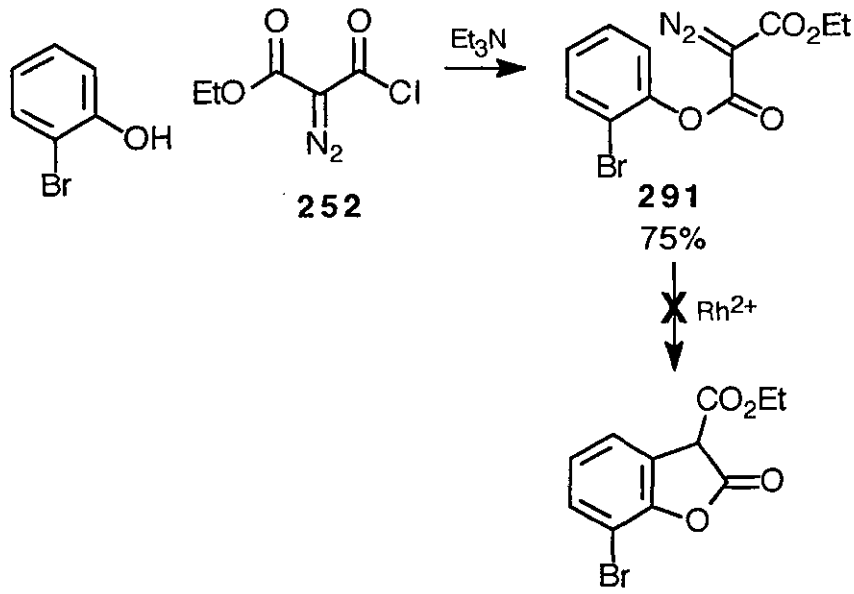
289 **290**

62%

Scheme 127

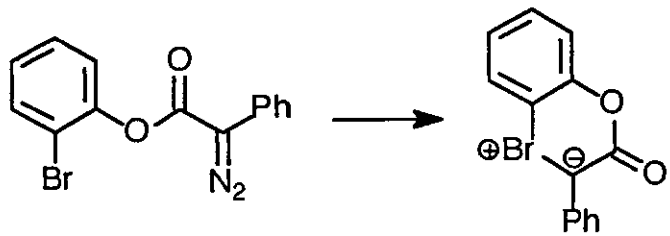
Presumably the deactivating effect that the halogen atoms have on the aromatic ring is partly to blame for this lack of reactivity. Also, the intermediate 'rhodium carbenoid' from **287** or **289** has only one electron withdrawing group. One might therefore expect it to be less electrophilic than that derived from **286** (**Scheme 124**).

The ester analogue **291** was prepared by reaction of 2-bromophenol with ethyl 2-diazomalonyl chloride (**252**). Rhodium(II) catalysed decomposition of this compound also failed to give identifiable products (**Scheme 128**) (Once again, the intermediate 'rhodium carbenoid' would be expected to be less electrophilic than that derived from **286**).



Scheme 128

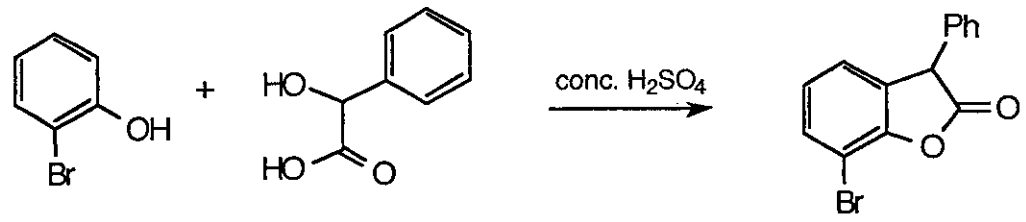
A further possible explanation for the failure of these reactions is that the presence of the *ortho*-bromine atom is directly affecting the course of the reaction by interception of the metallocarbene to give a six-membered ring bromonium ylide, *e.g.* **292**.[145]



292

Scheme 129

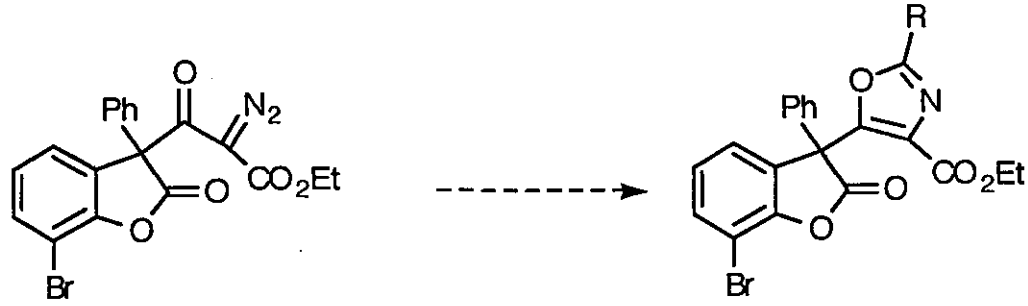
Since the preparation of the required benzofuranone was clearly not going to be as simple as at first anticipated, we felt it appropriate to prepare **288** using literature chemistry in order to test the next few steps in the planned synthesis first before expending a great deal of time solving a difficult problem. Also our inability to purify the benzofuranone prepared by this method meant that an alternative synthesis was required for characterisation purposes. The acid catalysed condensation of mandelic acid with 2-bromophenol gave a low yield of the desired benzofuranone **288**. However the low cost of the starting materials made this acceptable (**Scheme 130**).[146]



288
15%

Scheme 130

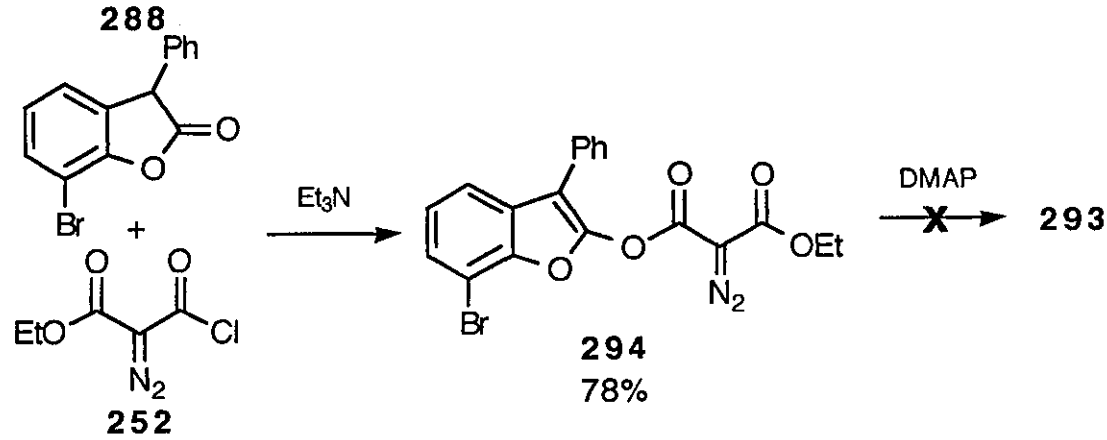
It has been shown that benzofuranones can be *O*-acylated using chloroformates, and that 4-dimethylaminopyridine (DMAP) catalyses *O*- to *C*-acyl migration in these systems.[147] Compound **293** would be particularly desirable, since it would serve as a precursor to the top oxazole ring in the diazonamides (**Scheme 131**).



293

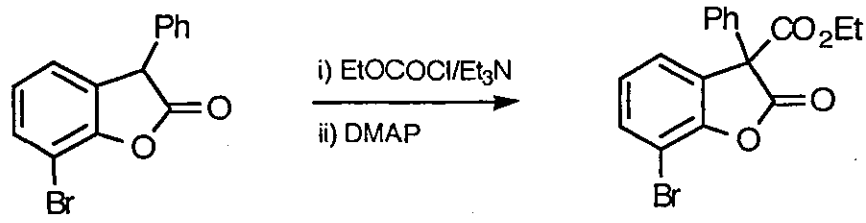
Scheme 131

Towards this end, the benzofuranone **288** was allowed to react with ethyl 2-diazomalonyl chloride (**252**) to give the *O*-acylated product **294**. However this compound failed to rearrange to **293** on treatment with DMAP (**Scheme 132**).



Scheme 132

Therefore the benzofuranone **288** was *C*-acylated[147] in a one pot procedure with ethyl chloroformate/triethylamine followed by addition of DMAP to give **295** in excellent yield. However although sodium hydride was used as the base in the literature report,[147] we found that triethylamine was superior in our case.



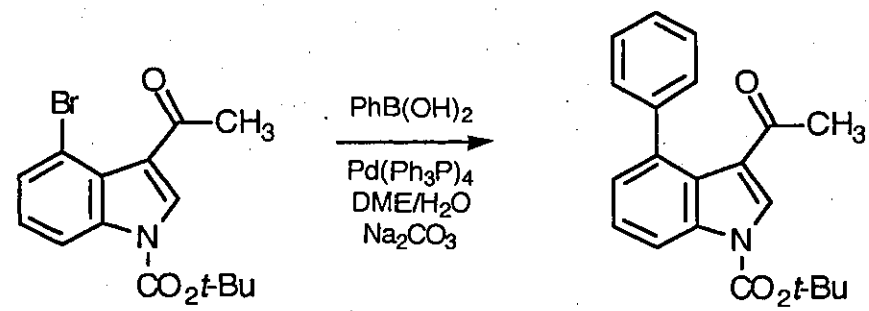
288 **295**

96%

Scheme 133

As a model reaction for the introduction of the indole ring into the 7-position of **295**, palladium catalysed cross coupling with phenyltrimethyltin was attempted. This reaction was carried out under a range of conditions: solvent (DMF, THF, DME), catalyst [$Pd_2(dba)_3$, $(Ph_3P)_4Pd$, $Pd(OAc)_2$, $(CH_3CN)_2PdCl_2$] and additives [Ph_3P, tri(2-furyl)phosphine] were all varied. In no case was there any evidence for a successful reaction. Since we had also to consider coupling a halogen-containing indole with a tin-containing benzofuranone, the reaction was also attempted on *tert*-butyl 3-acetyl-4-bromoindole-1-carboxylate (**296**), again with no success.

The Suzuki coupling protocol[148,149] was found to be more effective. The first model reaction tried, the coupling of *tert*-butyl 3-acetyl-4-bromoindole-1-carboxylate (**296**) with benzeneboronic acid, was successful, giving the 4-phenyl indole derivative **297** in 66% yield (**Scheme 134**).

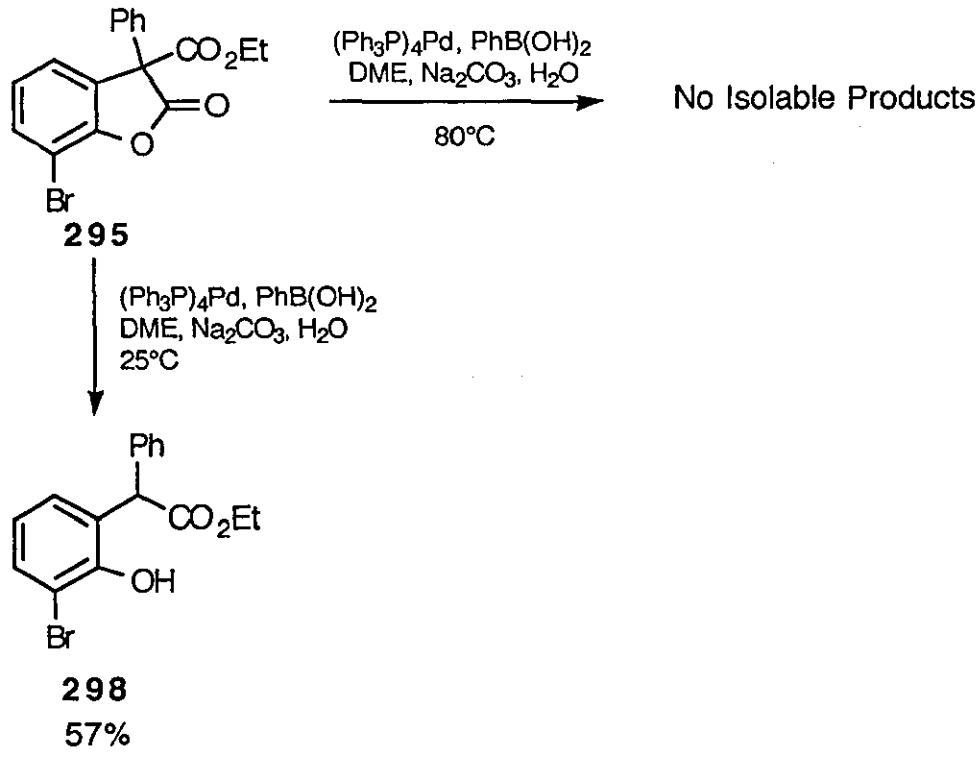


296 **297**

66%

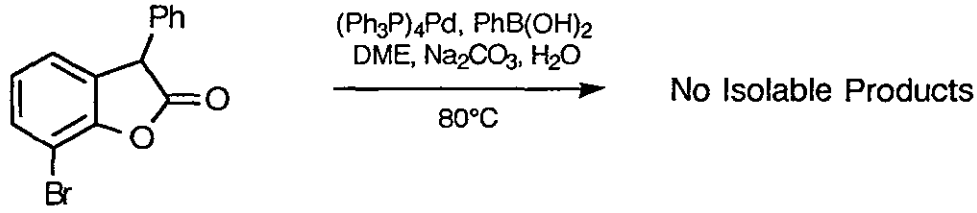
Scheme 134

The next step was to confirm that the benzofuranone **295** was robust enough to stand the Suzuki coupling conditions. Therefore the coupling reaction of **295** with benzeneboronic acid was attempted. Under the conditions used for the previous coupling (dimethoxyethane under reflux in the presence of aqueous sodium carbonate) no products could be isolated. However when the reaction was carried out at room temperature a 57% yield of the phenol **298** was isolated (**Scheme 135**). This is clearly formed by hydrolysis of the lactone and decarboxylation.



Scheme 135

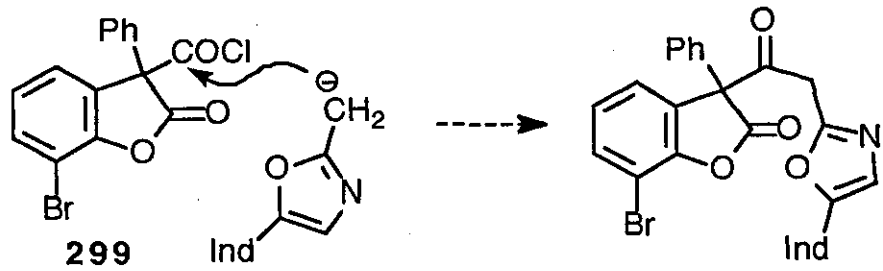
The coupling of the un-acylated benzofuranone **288** with benzeneboronic acid was attempted next. However upon addition of tetrakis(triphenylphosphine)palladium(0) to a solution of **288** in dimethoxyethane an intense purple colouration was observed. The reaction was continued despite this, but unfortunately neither products nor starting materials were recovered (**Scheme 136**). Presumably the palladium is forming a complex with the benzofuranone, and since the acylated benzofuranone gives no such colour change, then the complex is suspected to be a palladium enolate; attempts to isolate such a complex were unsuccessful.



288

Scheme 136

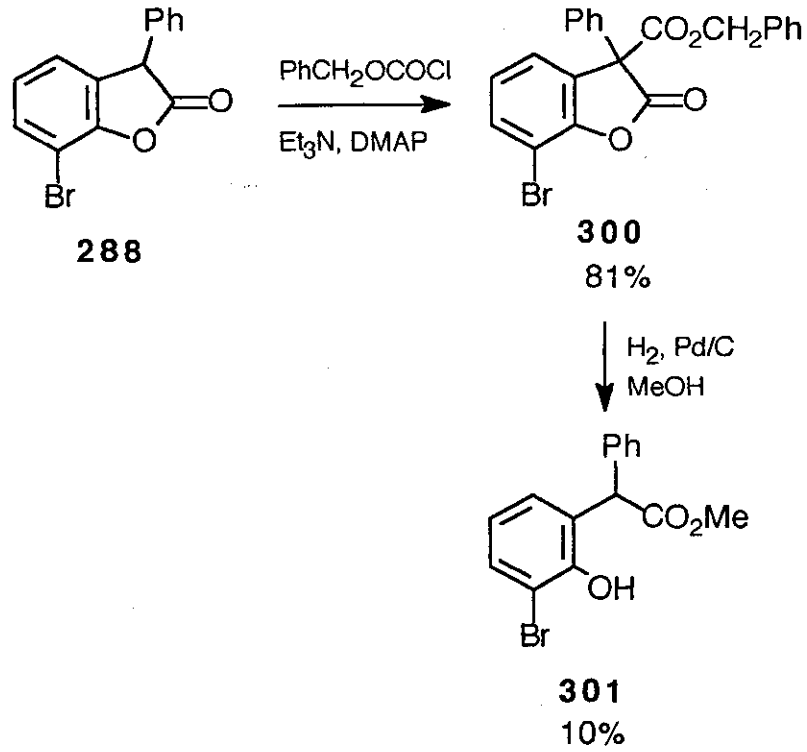
In parallel with this work, it was felt that the benzofuranone-3-acid chloride **299** would be a useful intermediate since it would allow coupling to a functionalised methyloxazole (**Scheme 137**). This approach would have some advantages - one could then carry out the cross coupling reaction in an intramolecular sense, and in particular a coupling in which both reaction partners contain a halogen becomes possible.[150] This would obviate the need for preparation of a boronic acid or organotin reagent.



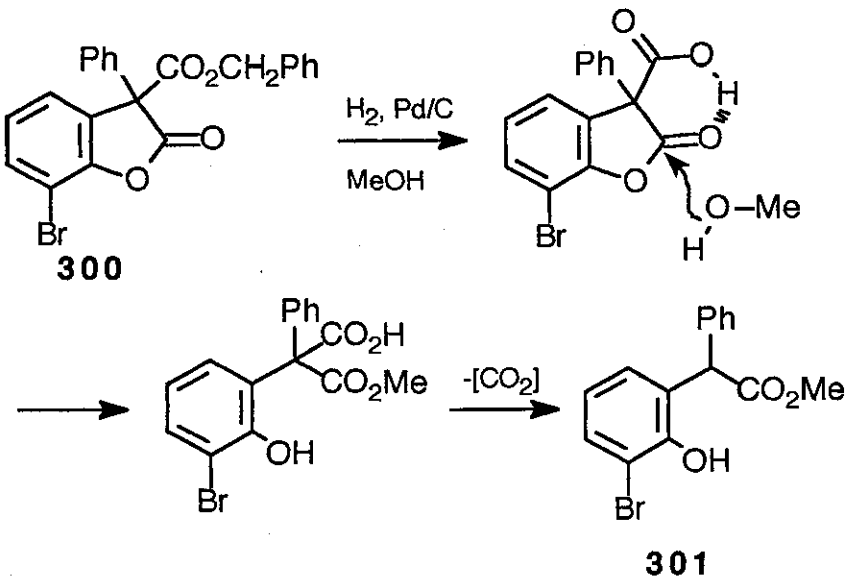
299

Scheme 137

This acid chloride would be prepared from the carboxylic acid, which might be prone to decarboxylation, and should be synthesised using as mild conditions as possible. We felt that hydrogenolysis of a benzyl ester fitted this criterion perfectly. Therefore **288** was allowed to react with benzyl chloroformate in the presence of triethylamine and 4-dimethylaminopyridine to give the unstable (see below) benzyl ester **300** in 81% yield. Hydrogenolysis of **300** in methanol gave a very low yield of the phenol **301** (**Scheme 138**). Since **288** is stable in the presence of methanol, this reaction presumably involves methanolysis of the intermediate acid (**Scheme 139**). Hydrogen bonding as shown would facilitate this process. The low yield obtained prevented full characterisation of **301**. However, comparison of the available data with that of the ethyl ester analogue **298** allowed the structure of **301** to be assigned with reasonable confidence. Hydrogenolysis of **300** in ethyl acetate led to no isolable products.



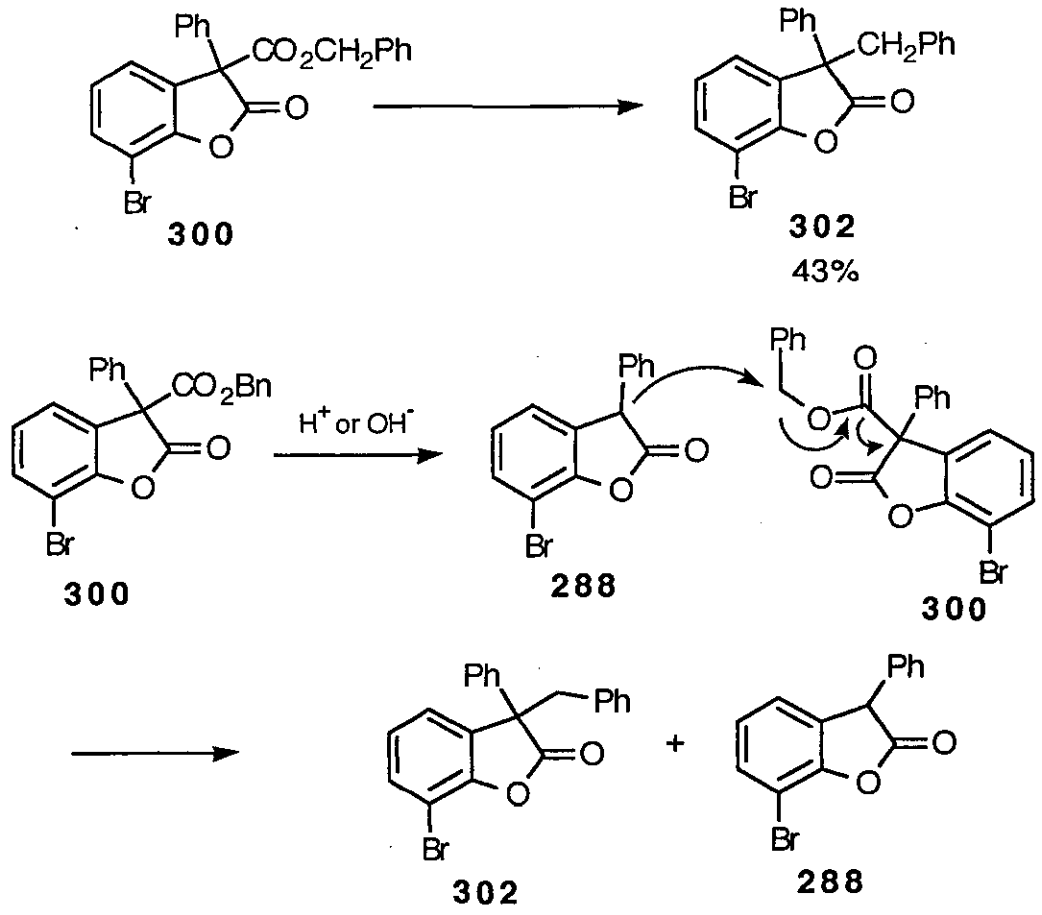
Scheme 138



Scheme 139

As mentioned above the benzyl ester **300** is unstable. We were somewhat surprised to find that the major decomposition product was **302**,. formed by loss of carbon dioxide. We have rationalised this as follows: a small amount of the unacylated benzofuranone is benzylated by **300** to give, after loss of CO_2, the product **302** and the benzofuranone **288**. This process is

therefore catalytic with respect to **288**, which could be formed from the benzyl ester by the action of either traces of acid or base (**Scheme 140**)



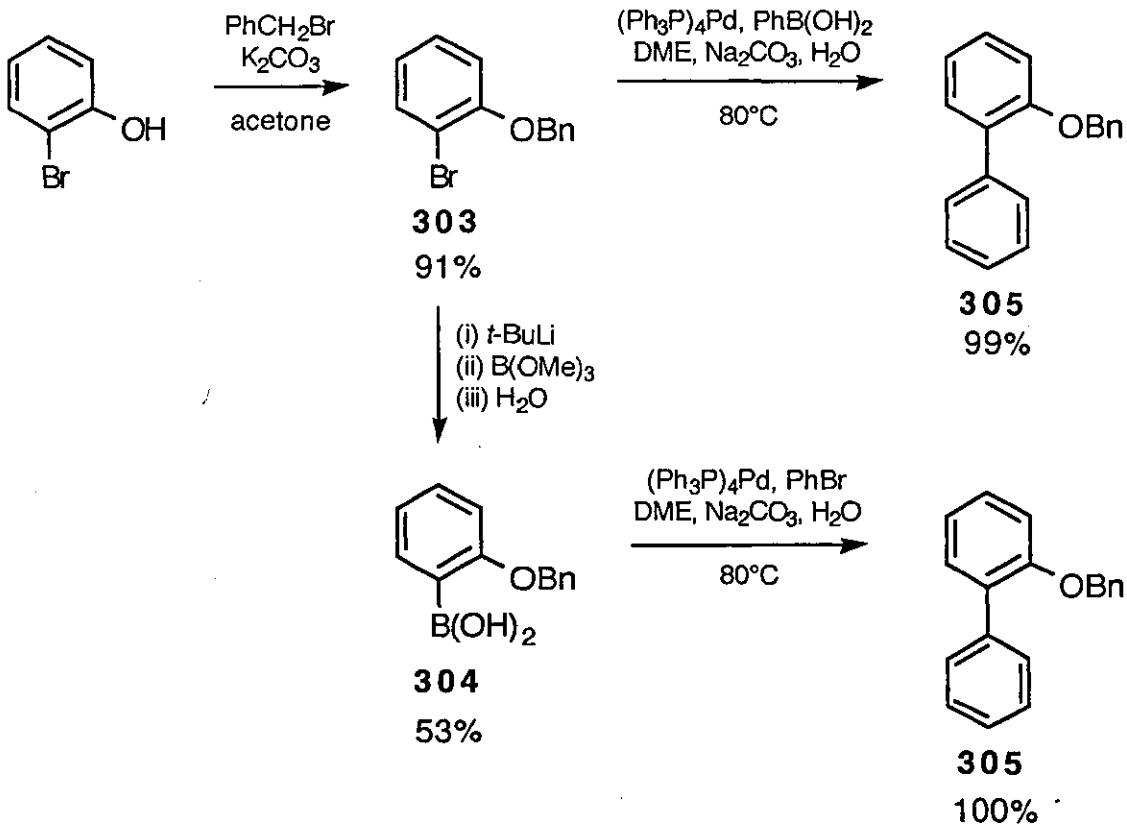
Scheme 140

4.3. Model Suzuki Coupling Reactions

Since the preparation of benzofuranones was found to be inefficient both by rhodium-carbenoid chemistry and literature chemistry, and palladium catalysed cross coupling reaction on these systems was unsuccessful in our hands, it was decided to prepare possible benzofuranone precursors in order to determine which were suitable for the Suzuki coupling protocol.

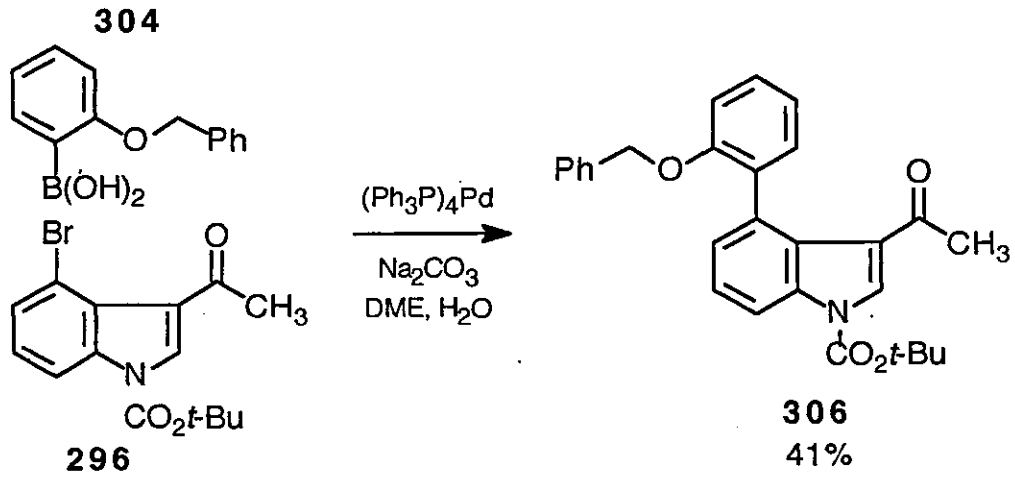
The simplest possible precursor to a 7-bromobenzofuranone is a protected 2-bromophenol. 2-Bromophenol was protected as its benzyl ether **303**. Coupling of this compound with commercially available benzeneboronic acid gave the biaryl **305** in 99% yield. We also felt it necessary to investigate incorporation of the boronic acid moiety into the benzofuranone precursor. The benzyl ether **303** was lithiated, and the resulting anion quenched with trimethyl borate to give, after aqueous work-up, the boronic acid **304**. This

coupled smoothly with bromobenzene to give the same biaryl **305** in quantitative yield.



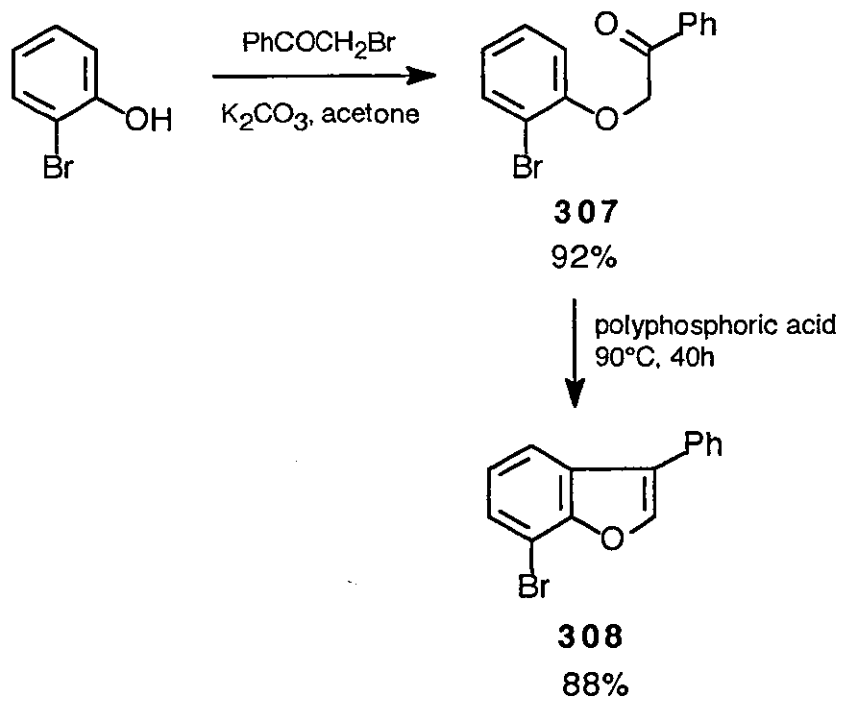
Scheme 141

The boronic acid **304** was also coupled with *tert*-butyl 3-acetyl-4-bromoindole-1-carboxylate (**296**) to give a 41% yield of the biaryl **306** (**Scheme 142**).



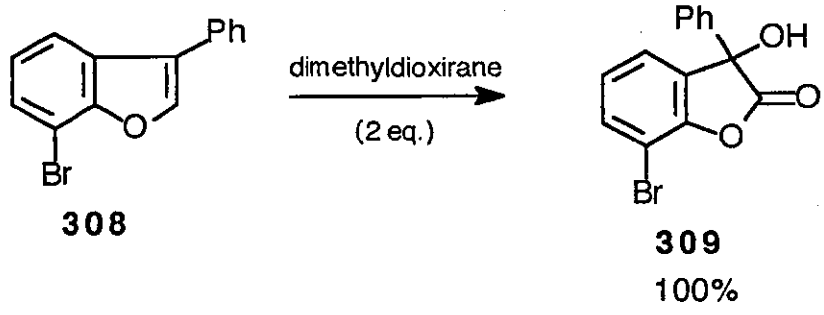
Scheme 142

There is literature precedent for the conversion of benzo[b]furans into benzofuranones.[151] The benzo[b]furan **308** was prepared as shown in **Scheme 143**.



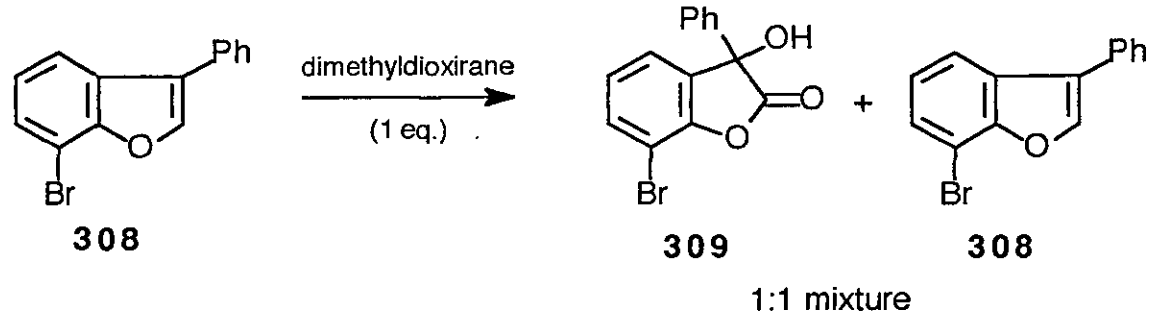
Scheme 143

Oxidation of this compound under literature conditions[151] (2 mole equivalents dimethyldioxirane) gave a quantitative yield of **309** in which the desired product (**288**) had been further oxidised.



Scheme 144

Use of a single equivalent of dimethyldioxirane gave an approximately 1:1 mixture of this over-oxidised product **309** and unreacted starting material **308**. Clearly the desired product is more readily oxidised than the starting material.

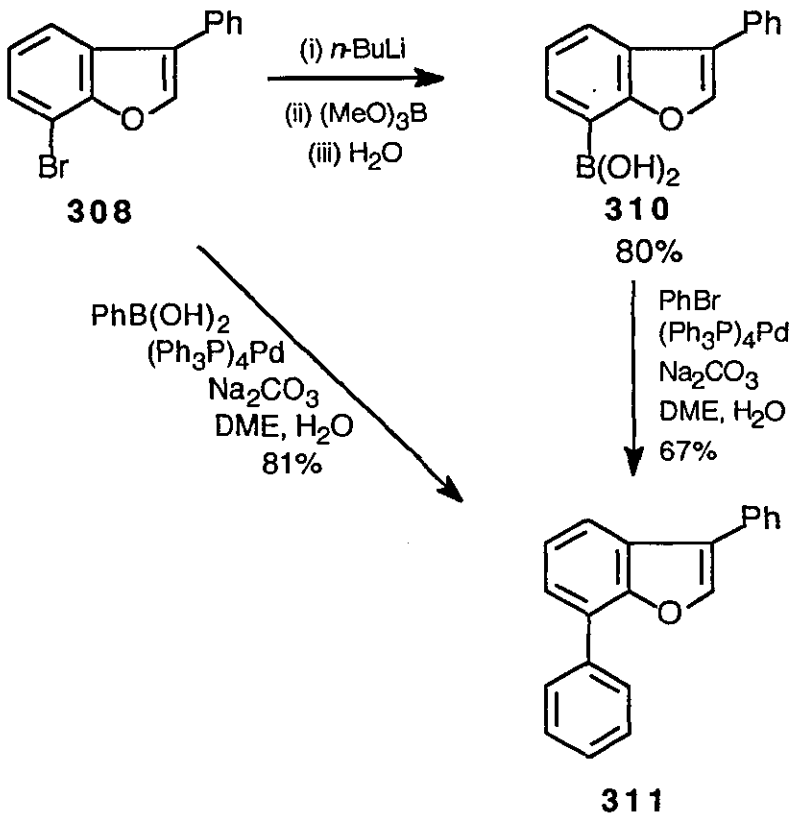


308 **309** **308**

1:1 mixture

Scheme 145

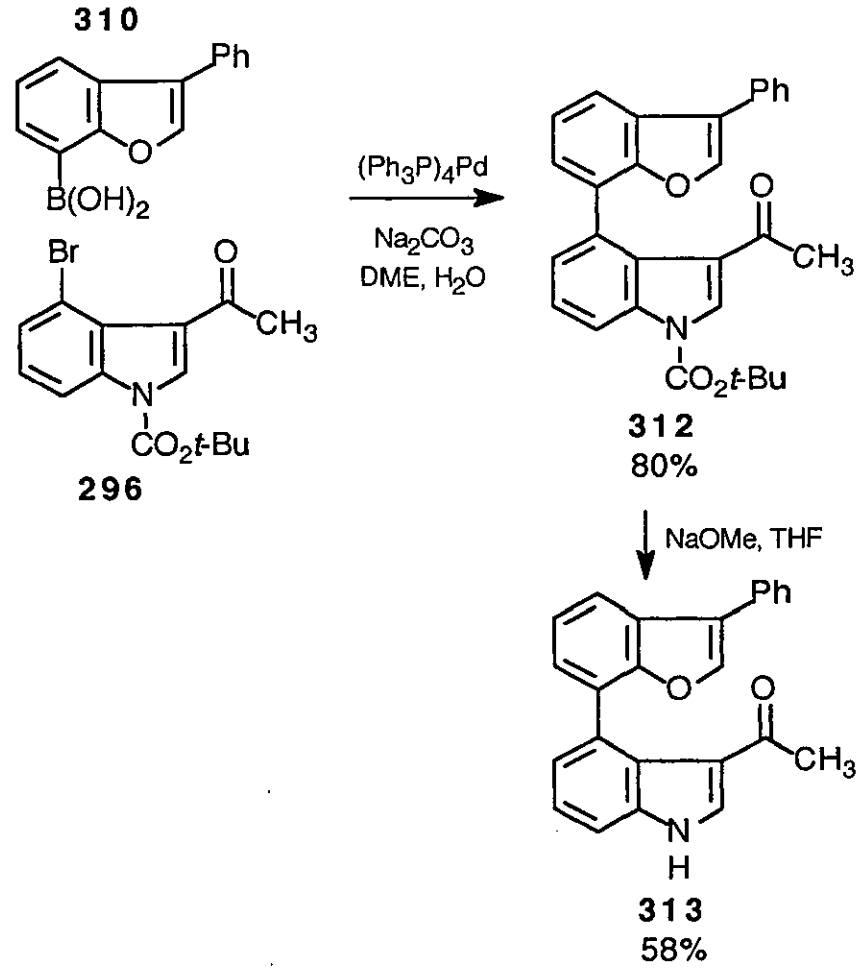
Although removal of the 3-hydroxy group in **309** was not addressed, 7-bromo-3-phenylbenzo[b]furan (**308**) can therefore be considered as a benzofuranone precursor. Conversion of **308** to the boronic acid **310** proceeded smoothly in 80% yield. Although we had found that for the preparation of **304** trimethyl borate could be replaced with triisopropyl borate, in this case using triisopropyl borate none of **310** was obtained; this is most likely due to steric demand at the anionic centre. Both **308** and **310** were phenylated as shown (**Scheme 146**) to give **311**.



308 **310** 80% **311**

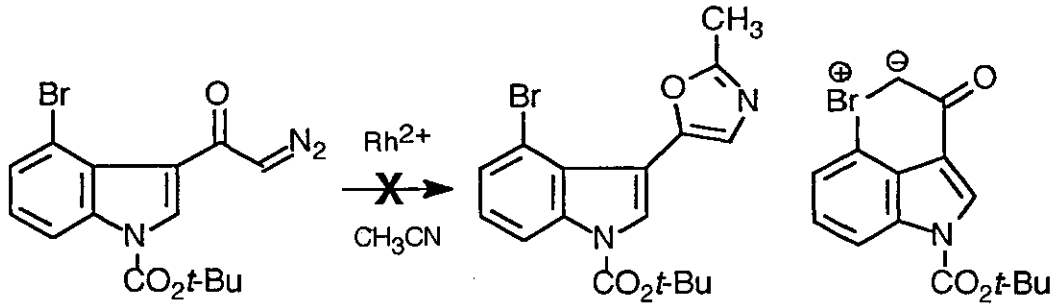
Scheme 146

Coupling of **310** with *tert*-butyl 3-acetyl-4-bromoindole-1-carboxylate (**296**) in this case proceeded to give **312** in a satisfying 80% yield, although this compound proved to be unstable, and the nitrogen protecting group had to be removed for characterisation purposes (**Scheme 147**). Since the 'top ring' in this compound is synthetically closer to a benzofuranone than in **306**, we felt that this was the route to be pursued.



Scheme 147

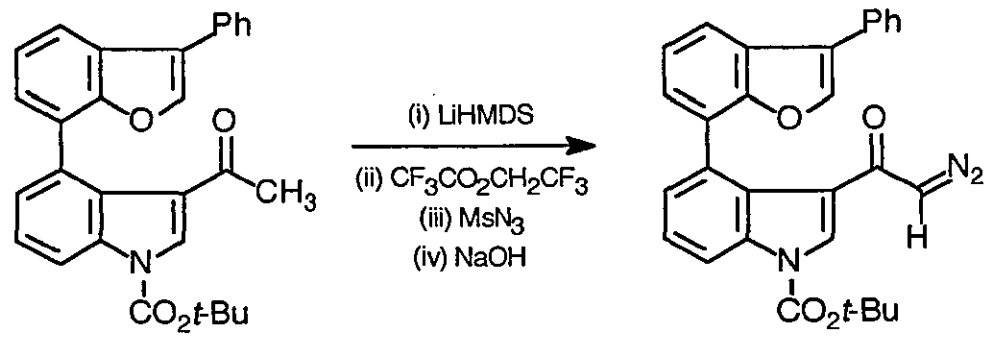
By this time it had become apparent that the oxazole formation reaction could not be carried out successfully on a 4-bromoindole derivative (**Scheme 148**).[141] Once again one can draw a six-membered bromonium ylide (**314**),[145] although we have no evidence for the intermediacy of this species.



314

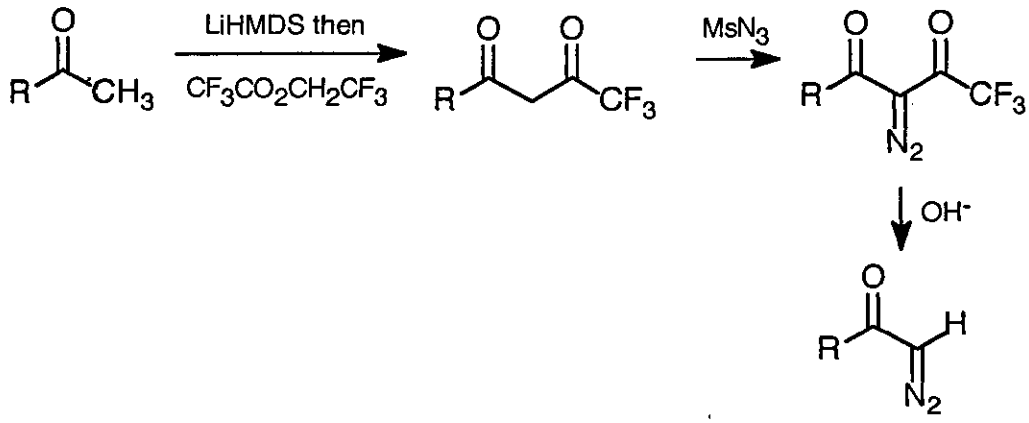
Scheme 148

It was therefore necessary to build up the oxazole on **312**. In order to accomplish this we needed to convert the acetyl group into a diazoacetyl group. This was carried out using the diazo-transfer procedure described by Danheiser *et al.*[152] In this, the methyl group is temporarily activated by the introduction of a trifluoroacetyl group. Diazo transfer to the 'active methylene' followed by removal of the trifluoroacetyl group during basic work-up led to the diazo compound **315** in 82% yield (**Scheme 149**).



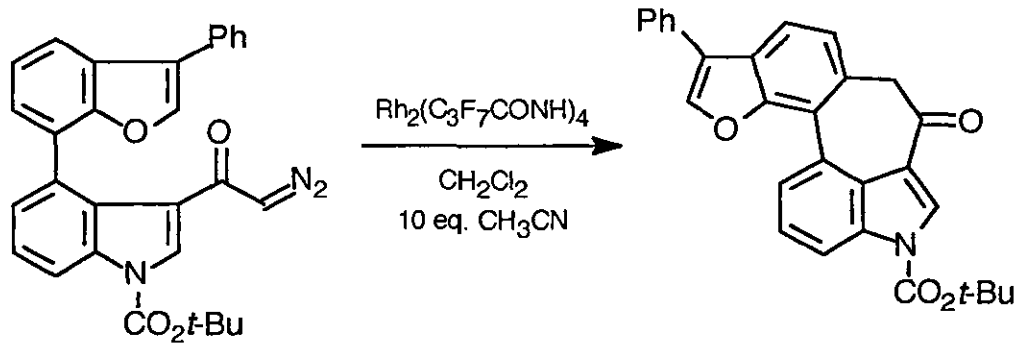
312 **315**
82%

Mechanism:



Scheme 149

However decomposition of this diazo compound by rhodium(II) perfluorobutyramide in the presence of excess acetonitrile led to none of the desired oxazole. Instead the 'carbene' inserted into the C-H bond at the 6-position of the benzofuran ring to give compound **316**, containing a 7-membered ring.



315 **316**
24%

Scheme 150

This result is somewhat disappointing but not entirely surprising. Rhodium(II) perfluorobutyramide has already been shown to be extremely effective for aromatic C-H insertion reactions (Chapter 3), and since this is an intramolecular reaction versus an intermolecular oxazole formation it might be expected to be the favoured process. It seems likely that the initial step in oxazole formation *via* 'rhodium carbenes' is co-ordination of the nitrile to the catalyst.[138,153] It was therefore hoped that interaction of the rhodium-nitrile complex with the diazo compound might lead to preferential oxazole formation. Clearly this was not the case. Using rhodium(II) acetate or rhodium(II) perfluorobutyrate as catalysts for this reaction was also unsatisfactory, and no products could be isolated.

4.4. Conclusions

The rhodium-carbenoid chemistry which is so effective for oxindole formation (Chapter 3) is very poor when applied to benzofuranones. The benzofuranone **288** prepared in this manner did not prove amenable to further modification as would be required for a synthetic approach to diazonamide A. Although a biaryl system **312** related to diazonamide A was prepared, oxazole formation from this compound proved unsuccessful.

Chapter 5

Experimental Section

5.1. General experimental points

Solvents were purified before use as follows. Diethyl ether was distilled from calcium chloride, and if necessary from sodium-benzophenone ketyl or lithium aluminium hydride. Ethyl acetate, chloroform and dichloromethane were distilled from phosphorus pentoxide. Toluene was distilled from sodium wire. Tetrahydrofuran was stored over sodium wire and distilled from sodium-benzophenone ketyl immediately prior to use. Ethanol was distilled from magnesium ethoxide. Methanol was distilled from magnesium methoxide. Light petroleum refers to the petroleum ether fraction boiling in the range 40 - 60°C, and was distilled from calcium chloride. Commercially available chemicals were generally used without further purification, except for tetrakis(triphenylphosphine)palladium(0) which was washed with ethanol, then with diethyl ether and dried under a stream of nitrogen.[149] However, where deemed necessary, reagents were purified according to procedures in 'Purification of Laboratory Chemicals'.[154]

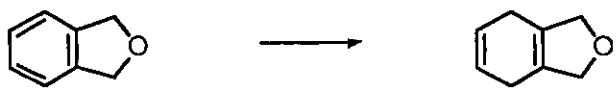
NMR spectra were recorded on a Bruker AC-250 spectrometer (operating at 250 MHz for ^{1}H NMR and 62.9 MHz for ^{13}C NMR) or on a Jeol QE300 (operating at 300 MHz for ^{1}H NMR and 75.48 MHz for ^{13}C NMR). NMR chemical shifts are quoted in ppm relative to tetramethylsilane as internal standard. Coupling constants are quoted in Hz. Electron impact mass spectra were recorded on a Kratos MS80 mass spectrometer with an ionising potential of 70 eV. Chemical ionisation mass spectra were recorded on a Finnigan MAT90 mass spectrometer. Infrared spectra were recorded in the range 4000 - 600 cm^{-1} on a Nicolet 250 FTIR spectrometer with internal calibration. Melting points points were recorded using an Electrotherm digital melting point apparatus, and are uncorrected.

Spectroscopic data is annotated with the following abbreviations: q - quartet; t - triplet; d - doublet; s - singlet; br - broad. Aromatic hydrogens, where not specifically assigned, are indicated by 'Ar_n', where 'n' is the number of hydrogens concerned. Due to the slow relaxation time as a result of the diazo group, diazo carbons are not always observed in ^{13}C NMR spectra, even when a relaxation delay is used.

All reactions were carried out under an atmosphere of dry nitrogen or argon, using oven- or flame-dried glassware.

5.2. Experimental for Chapter 2

1,3,4,7-Tetrahydrobenzo[c]furan (**212**)



212

Liquid ammonia (100 ml) was condensed into a round bottomed flask. Diethyl ether (19 ml), ethanol (18.3 ml) and phthalan (11.3 g, 94 mmol) were added sequentially followed by the addition, over 45 min, of sodium (6.5 g, 283 mmol). When the addition was complete, the ammonia was allowed to evaporate and water (100 ml) and diethyl ether (100 ml) added. The phases were separated and the aqueous phase extracted with diethyl ether (2 x 50 ml). The combined organic phases were dried over magnesium sulfate, concentrated *in vacuo* and purified by short path distillation to give the *title compound* (9.73 g, 85%) as a colourless liquid, b.p. 150°C at 15 mmHg (Found: M^+, 121.065. $C_8H_{10}O$ -H requires M, 121.0653); $\nu_{max.}$ (film) 3030, 2834, 1645, 1432, 1045, 1014, 957, 913, 893 and 815 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 5.78 (2 H, s, 2 x C*H*), 4.55 (4 H, s, 2 x C*H*$_2$O) and 2.66 (4 H, s, 2 x C*H*$_2$); δ_C(62.9 MHz; $CDCl_3$) 128.5 (C), 123.9 (CH), 77.3 (CH_2O) and 23.6 (CH_2); *m/z* (EI) 121 (M^+- H, 20%), 93 (65), 91 (100), 77 (60), 65 (30), 39 (35) and 29 (12).

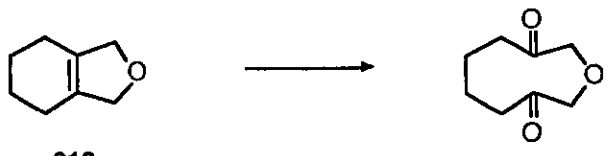
1,3,4,5,6,7-Hexahydrobenzo[c]furan (**213**)

212 **213**

A solution of 1,3,4,7-tetrahydrobenzo[c]furan (**212**) (1.22 g, 10 mmol) and tris(triphenylphosphine)rhodium(I) chloride (40 mg) in toluene (40 ml) was thoroughly degassed, then stirred under an atmosphere of hydrogen for 48 h. The solution was filtered through a pad of silica gel and the silica gel washed with diethyl ether (100 ml). After removal of the solvent *in vacuo* the residue was purified by flash column chromatography (eluent 3:1 light petroleum:diethyl ether) to give the *title compound* (902 mg, 73%) as a colourless liquid, b.p. 150°C at 15mmHg (Found: M^+, 125.0972. $C_8H_{12}O + H^+$ requires M, 125.0966); $\nu_{max.}$ (film) 2931, 2855, 1439, 1310, 1046, 908 and

806 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 4.51 (4 H, s, 2 x CH_2O), 2.1 - 1.9 (4 H, m, 2 x CH_2) and 1.7 - 1.6 (4 H, m, 2 x CH_2); δ_C (62.9 MHz; $CDCl_3$) 130.6 (C), 77.4 (CH_2O), 22.3 (CH_2) and 21.5 (CH_2); *m/z* (EI) 124 (M^+, 5%), 109 (6), 95 (10), 86 (34), 84 (55), 51 (40) and 49 (100).

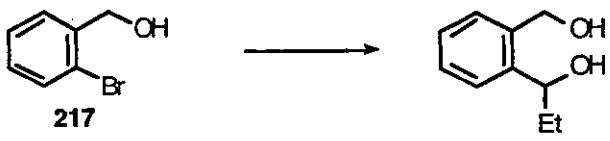
Oxonane-3,8-dione (**214**)



213 **214**

Sodium metaperiodate (3.51 g, 16.4 mmol) was added to a solution of 1,3,4,5,6,7-hexahydrobenzo[c]furan (**213**) (496 mg, 4 mmol) in tetrachloromethane (8 ml), acetonitrile (8 ml) and water (12 ml). Ruthenium(III) chloride hydrate (20 mg) was added and the reaction stirred vigorously for 24 h. Dichloromethane (50 ml) and water (50 ml) were added and the phases separated. The aqueous phase was extracted twice with dichloromethane (50 ml), and the combined organic phases dried over magnesium sulfate, filtered and concentrated *in vacuo* to give a dark oil which was purified by flash column chromatography (eluent 3:1 light petroleum:ethyl acetate) to give the *title compound* (365 mg, 58%) as a colourless oil (Found: M^+, 156.0785. $C_8H_{12}O_3$ requires M, 156.0786); $\nu_{max.}$ (film) 2937, 1714, 1447, 1256, 1161 and 1122 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 4.15 (4 H, s, 2 x CH_2O), 2.79 - 2.71 (4 H, m, 2 x CH_2CO) and 1.85 - 1.74 (4 H, m, 2 x CH_2); δ_C (62.9 MHz; $CDCl_3$) 212.9 (C=O), 79.9 (CH_2O), 36.5 (CH_2) and 23.7 (CH_2); *m/z* (EI) 156 (M^+, 2.3%), 126 (100), 98 (60), 83 (44), 70 (52), 55 (20) and 41 (19).

1-[(2-Hydroxymethyl)phenyl]propan-1-ol (**218**)

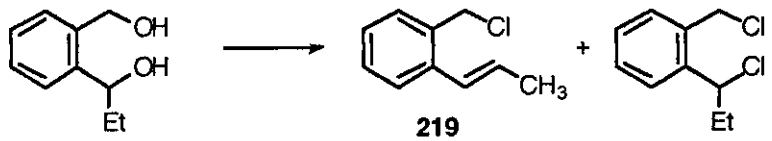


217 **218**

2-Bromobenzyl alcohol (9.35 g, 50 mmol) in THF (200 ml) was cooled to -78°C under an atmosphere of dry nitrogen. A 1.6 M solution of *n*-BuLi in hexanes (62.5 ml, 100 mmol) was added below -70°C to give a thick white suspension. After stirring for 30 min, propionaldehyde (5.8 g, 100 mmol) was

added and the reaction allowed to warm to room temperature to give a clear solution. 2N hydrochloric acid (50 ml) was added slowly and the phases then separated. The aqueous phase was extracted twice with diethyl ether (50 ml), and the combined organic phases washed with brine (50 ml). The organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the *title compound* (9.5 g, quantitative) as a colourless oil which was used without further purification; $\nu_{max.}$ (film) 3275 (br, OH), 2966, 2877, 1455, 1040, 1009 and 755 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.38 - 7.15 (4 H, m, Ar_4), 4.68 (1 H, t, *J* 6.9, C*H*OH), 4.58 and 4.46 (2 H, AB quartet, *J* 12.2, CH_2OH), 4.20 (2 H, br, OH), 1.77 (2 H, m, CH_2CH$_3$) and 0.89 (3 H, t, *J* 8.8, CH$_2$CH_3); δ_C (62.9 MHz; $CDCl_3$) 142.4 (C), 137.9 (C), 129.5 (CH), 128.2 (CH), 127.5 (CH), 126.6 (CH), 72.4 (CH), 62.9 (CH_2O), 30.0 (CH_2) and 10.6 (CH_3); *m/z* (EI) 137 (30%), 119 (100), 108 (63), 99 (20), 91 (69), 79 (63), 70 (42) and 58 (24).

Reaction of **218** *with hydrochloric acid*

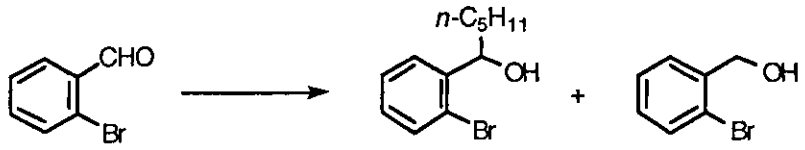


218 **219** **220**

Hydrochloric acid (50 ml) was added to the diol **218** (9.348g, *ca.* 50 mmol) and the biphasic solution stirred vigorously for 15 h. Water (50 ml) and diethyl ether (100 ml) were added and the phases separated. The aqueous phase was further extracted with diethyl ether (2 x 50 ml), and the combined organic phases washed with saturated sodium hydrogen carbonate solution to remove residual acid, then with water (2 x 50 ml). The organic phase was then dried over magnesium sulfate, filtered and concentrated *in vacuo* to give a dark oil. Short path distillation followed by flash column chromatography (eluent light petroleum) gave 1.172 g of a 2:1 mixture of **219** and **220**, b.p. 140°C at 2.5 mmHg (Found: M+, 166.0548. $C_{10}H_{11}{}^{35}Cl$ (**219**) requires M, 166.0549; Found: M+, 202.0300. $C_{10}H_{12}{}^{35}Cl_2$ (**220**) requires M, 202.0316); $\nu_{max.}$ (film) 2980, 1263, 963, 764, 732 and 671 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.58 - 7.18 (4 H of **219** + 4 H of **220**), 6.73 (1 H of **219**, dq, *J* 15.6 and 1.7, alkene), 6.18 (1 H of **219**, dq, *J* 15.6 and 6.6, alkene), 5.20 (1 H of **220**, m), 4.79 and 4.57 (2 H of **220**, AB quartet, *J* 11.7, CH_2Cl), 4.64 (2 H of **219**, s, CH_2Cl), 2.28 - 2.12 (2 H of **220**, m, CH_2CH$_3$), 1.93 (3 H of **219**, dd, *J* 6.6 and 1.7, CH_3) and 1.08 (3 H of **220**, t, *J* 7.3, CH_3); δ_C (62.9 MHz; $CDCl_3$) 140.6

(C), 137.5 (C), 134.8 (C), 133.6 (C), 130.4 (CH), 130.0 (CH), 129.5 (CH), 129.1 (CH), 128.9 (CH), 128.4 (CH), 127.4 (CH), 127.2 (CH), 127.0 (CH), 126.3 (CH), 60.0 (CH of **220**), 44.5 (CH_2), 43.4 (CH_2), 32.1 (CH_2 of **220**), 18.8 (CH_3 of **219**) and 11.8 (CH_3 of **220**); *m/z* (EI) 206 ($^{37}Cl^{37}Cl$-M$^+$of **220**, 0.4%), 204 ($^{37}Cl^{35}Cl$-M$^+$ of **220**, 1.1), 202 ($^{35}Cl^{35}Cl$-M$^+$ of **220**), 168 (^{37}Cl-M$^+$ of **219**, 8), 166 (^{35}Cl-M$^+$of **219**, 28), 131 (100), 115 (40) and 91 (38).

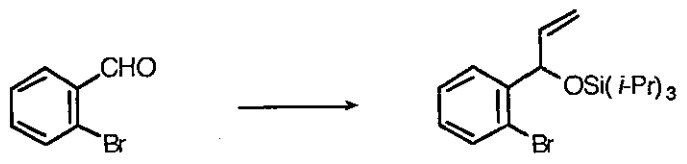
Reaction of 2-bromobenzaldehyde with n-pentylmagnesium bromide



221 **217**

A solution of 1-bromopentane (9.06 g, 60 mmol) was added dropwise to a suspension of magnesium turnings (1.458 g, 60 mmol) in THF (5 ml), with gentle heating until the magnesium started to dissolve, then external cooling as the formation of the organomagnesium reagent became exothermic. After all the magnesium turnings had dissolved, the solution was stirred for a further 10 min, then a solution of 2-bromobenzaldehyde (11.1 g, 60 mmol) in THF (15 ml) added over 30 min. After a further 30 min, water (20 ml) and 2N hydrochloric acid (20 ml) were added. The organic materials were extracted into diethyl ether (3 x 30 ml), and the combined organic phases washed with saturated brine, dried over magnesium sulfate and concentrated *in vacuo* to give a viscous yellow oil which was subjected to short path distillation. A solid sublimed at 90°C (0.6 mmHg) which was shown to be 2-bromobenzyl alcohol (**217**) [δ_H (250 MHz; $CDCl_3$) 7.52 - 7.42 (2 H, m), 7.32 - 7.25 (1 H, m), 7.15 - 7.04 (1 H, m), 4.69 (2 H, s) and 2.81 (1 H, br, OH)] by comparison with an authentic sample (Yield: 4.5g, 40%). The second product (b.p. 160°C at 0.4 mmHg) was impure **221** (Yield: 7.2 g, 47%) [δ_H (250 MHz; $CDCl_3$) 7.55 - 7.47 (2 H, m), 7.35 - 7.26 (1 H, m), 7.12 - 7.06 (1 H, m), 5.05 (1 H, dd, *J* 8.0 and 4.4), 3.1 (1 H, br, OH), 1.9 - 1.6 (2 H, m) 1.6 - 1.35 (6 H, m) and 0.9 - 0.85 (3 H, m)].

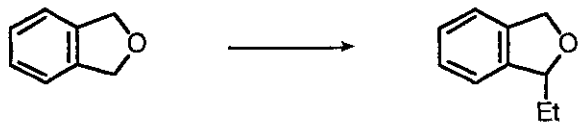
1-(2-Bromophenyl)-1-triisopropylsiloxyprop-2-ene (**222**)



222

To a solution of 2-bromobenzaldehyde (1.96 g, 10.6 mmol) in THF (20 ml) at 0°C was added a THF solution of vinylmagnesium bromide (10.6 ml, 10.6 mmol), keeping the temperature below 30°C by means of an ice/water bath. When the addition was complete, the reaction was quenched with 2N hydrochloric acid (20 ml) and the phases separated. The aqueous phase was extracted twice with diethyl ether (20 ml), and the combined organic phases dried over magnesium sulfate. The solution was filtered and the solvent removed *in vacuo* to give a yellow oil (2.534 g). This product was dissolved in dichloromethane (30 ml) and cooled to -5°C under an atmosphere of dry nitrogen. Triisopropylsilyl trifluoromethanesulfonate (3.24 g, 10.6 mmol) and 2,6-lutidine (1.13 g, 10.6 mmol) were added, and the solution allowed to warm to room temperature and stirred overnight. The reaction mixture was washed with water (20 ml) and brine (20 ml), dried over magnesium sulfate, filtered and concentrated *in vacuo* to an orange oil which was purified by flash column chromatography (eluent light petroleum) to afford the *title compound* (2.45 g, 62%) as a colourless oil (Found: M^+, 325.0621. $C_{18}H_{29}BrOSi$ - C_3H_7 requires M, 325.0624); $\nu_{max.}$ (film) 2959, 2867, 1465, 1140, 1025, 883 and 752 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.61 (1 H, dd, *J* 7.7 and 1.7, Ar_1), 7.47 (1 H, dd, *J* 8.0 and 1.2, Ar_1), 7.30 (1 H, td, *J* 7.7 and 1.2, Ar_1), 7.07 (1 H, td, *J* 7.9 and 1.7, Ar_1), 5.93 (1 H, ddd, *J* 17.1, 10.3 and 5.0, alkene), 5.66 (1 H, dt, *J* 5.0 and 1.5, ArC*H*OSi), 5.38 (1 H, dt, *J* 17.0 and 1.5, alkene), 5.06 (1 H, dt, *J* 10.3 and 1.5, alkene) and 1.20 - 1.0 (21 H, m, Si(C*HMe*$_2$)$_3$); δ_C (62.9 MHz; $CDCl_3$) 143.2 (C), 139.7 (CH), 132.2 (CH), 128.5 (CH), 128.3 (CH), 127.7 (CH), 121.4 (C), 113.4 (CH_2), 73.9 (CH), 17.9 (3 x CH) and 12.2 (6 x CH_3); *m/z* (EI) 327 (90%), 325 (87), 197 (9), 195 (10), 116 (100), 75 (17), 56 (19), 41 (24) and 27 (12).

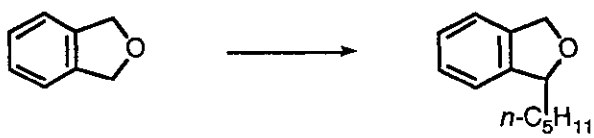
1-Ethyl-1,3-dihydrobenzo[c]furan (**223**)



223

A solution of phthalan (5.4 g, 45 mmol) in THF (150 ml) was cooled to -78°C under an atmosphere of argon. A solution of *tert*-butyllithium in pentane (29.1 ml, 49.5 mmol) was added dropwise and the resulting dark solution stirred at -78°C for 6 h. Iodoethane (12 ml, 150 mmol) was added over 15 min, during which time the colour of the solution faded and a precipitate formed. After a further 90 min at -78°C, methanol (45 ml) was added, the solution allowed to warm to room temperature and stirred for 12 h. The solvent was removed *in vacuo* and the residue partitioned between water (50 ml) and diethyl ether (50 ml). The aqueous phase was extracted with diethyl ether (2 x 50 ml), and the combined organic phase washed with water (25 ml) and brine (25 ml), then dried over magnesium sulfate, filtered, concentrated *in vacuo* and distilled to give the *title compound* (5.135 g, 77%) as a clear oil, b.p. 100°C at 5 mmHg (Found: M^+, 148.0885. $C_{10}H_{12}O$ requires M, 148.0888); $\nu_{max.}$ (film) 2967, 2850, 1461, 1050, 1019 and 744 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.28 - 7.15 (4 H, m, Ar_4), 5.20 (1 H, m, C*H*(Et)O), 5.08 (2 H, m, CH_2O), 1.93 and 1.76 (1 H each, m, C$H_2$$CH_3$), and 0.97 (3 H, t, *J* 7.4, CH_2CH_3); δ_C (62.9 MHz; $CDCl_3$) 141.8 (C), 139.5 (C), 127.2 (CH), 127.1 (CH), 121.1 (CH), 120.8 (CH), 84.9 (CH), 72.6 (CH_2O), 28.9 (CH_2) and 9.2 (CH_3); *m/z* (EI) 148 (M^+, 6%), 119 (100), 91 (40), 65 (10) and 39 (4).

1-Pentyl-1,3-dihydrobenzo[c]furan (**224**)

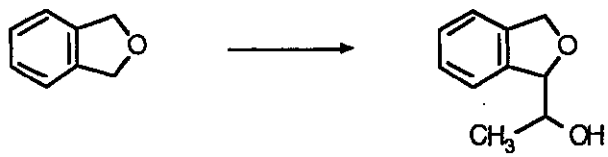


224

A solution of phthalan (18.6 g, 0.155 mol) in THF (350 ml) was cooled to -78°C under an atmosphere of nitrogen. A solution of *tert*-butyllithium in pentane (100 ml, 0.17 mol) was added at such a rate as to keep the internal temperature below -70°C. After stirring for 6 h at -78°C, 1-iodopentane (100 g, 0.51 mol) was added dropwise and the solution allowed to stir for a further 90 min. Methanol (150 ml) was then added, and the solution allowed to warm to

room temperature overnight. The solvent was removed *in vacuo* and the residue partitioned between water (200 ml) and diethyl ether (200 ml). The aqueous phase was extracted with diethyl ether (2 x 200 ml) and the combined organic phases then washed with water (200 ml) and saturated brine (200 ml). The organic phase was then dried over magnesium sulfate, filtered, concentrated *in vacuo* and distilled to give the *title compound* (25.37 g, 86%) as a colourless oil, b.p. 102°C at 3 mmHg (Found: M^+, 190.1359. $C_{13}H_{18}O$ requires M, 190.1358); $\nu_{max.}$ (film) 2955, 2857, 1461, 1037 and 746 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.27 - 7.15 (4 H, m, Ar_4), 5.24 (1 H, m, C*H*(pentyl)O), 5.06 (2 H, m, CH_2O), 1.80 and 1.68 (1 H each, m, CH_2), 1.48 - 1.28 (6 H, m, (CH_2)$_3$), and 0.88 (3 H, m, CH_3); δ_C (62.9 MHz; $CDCl_3$) 142.2 (C), 139.4 (C), 127.2 (CH), 127.1 (CH), 121.0 (CH), 120.8 (CH), 83.9 (CH), 72.4 (CH_2O), 36.2 (CH_2), 31.9 (CH_2), 24.8 (CH_2), 22.6 (CH_2) and 14.0 (CH_3); *m/z* (EI) 190 (M^+, 2%), 119 (100), 91 (25), 65 (5) and 32 (4).

1-(1-Hydroxyethyl)-1,3-dihydrobenzo[c]furan (**225**)



225

A solution of phthalan (2.4 g, 20 mmol) in THF (50 ml) was cooled to -78°C under an atmosphere of nitrogen. A solution of *tert*-butyllithium in pentane (12.9 ml, 22 mmol) was added dropwise, keeping the internal temperature below -70°C. After stirring for 6 h at -78°C, acetaldehyde (3.35 ml, 60 mmol) was added dropwise. After stirring for a further 90 min, methanol (20 ml) was added and the solution allowed to warm to room temperature overnight. The solvent was removed *in vacuo* and the residue partitioned between water (70 ml) and diethyl ether (70 ml). The aqueous phase was extracted with two 70 ml portions of diethyl ether, and the combined organic phases washed with water (70 ml) and saturated brine (70 ml). The organic phase was then dried over magnesium sulfate, filtered, concentrated *in vacuo*, distilled and further purified by flash column chromatography (eluent 1:1 light petroleum:diethyl ether) to give the *title compound* (2.007 g, 61%) as a colourless oil (1:1 mixture of diastereoisomers), b.p. 110°C at 0.05 mmHg (Found: M^+, 164.0841. $C_{10}H_{12}O_2$ requires M, 164.0837); $\nu_{max.}$ (film) 3425(br, OH), 2865, 1102, 1045 and 748 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.34 - 7.18 (4 H, m, Ar_4),

5.22 - 5.02 (3 H, m, benzylic H), 4.02 - 3.90 (1 H, m, C*H*OH), 2.37 and 2.20 (1 H, br, diastereomeric OH) and 1.32 and 1.16 (total 3 H, both d, *J* 6.4 and 6.5 respectively, diastereomeric CH_3); δ_C (62.9 MHz; $CDCl_3$) 139.9 (C), 139.8 (C), 138.6 (C), 138.4 (C), 128.0 (CH), 127.9 (CH), 127.4 (CH), 127.3 (CH), 122.1 (CH), 122.0 (CH), 121.1 (CH), 121.1 (CH), 88.1 (CH-O), 87.8 (CH-O), 73.6 (CH_2O), 72.8 (CH_2O), 70.9 (CHOH), 69.8 (CHOH), 18.5 (CH_3) and 17.7 (CH_3); *m/z* (EI) 164 (M^+, 0.3%), 134 (11), 119 (100), 105 (10) and 91 (35).

1-Ethyl-3-pentyl-1,3-dihydrobenzo[c]furan (**226**)

224 **226**

A solution of 1-pentyl-1,3-dihydrobenzo[c]furan (**224**) (25.37 g, 0.134 mol) in THF (350 ml) was cooled to -78°C under an atmosphere of argon. A 1.7 M solution of *tert*-butyllithium in pentane (100 ml, 0.17 mol) was added dropwise at -78°C. After stirring at -78°C for 6 h, iodoethane (40 ml, 0.5 mol) was added dropwise and stirring continued for a further 90 min. Methanol (150 ml) was then added and the solution allowed to warm to room temperature over 15 h. The solvent was removed *in vacuo* and the residue partitioned between water (100 ml) and diethyl ether (100 ml). The aqueous phase was extracted with diethyl ether (2 x 100 ml), and the combined organic phases washed with water (100 ml) and saturated brine (100 ml), then dried over magnesium sulfate, filtered and concentrated *in vacuo,* then distilled to give the *title compound* (24.03 g, 82%) as a colourless oil (mixture of diastereoisomers), b.p. 100°C at 1.4 mmHg (Found: M^+, 218.1667. $C_{15}H_{22}O$ requires M, 218.1671); $\nu_{max.}$ (film) 2959, 2857, 1459, 1050 and 749 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.27 - 7.12 (4 H, m, Ar_4), 5.27 - 5.10 (2 H, m, 2 x C*H*-O), 1.91 - 1.66 (4 H, m, 2 x CH_2), 1.51 - 1.28 (6 H, m, (CH_2)$_3$) and 1.02 - 0.86 (6 H, m, 2 x CH_3); δ_C (62.9 MHz; $CDCl_3$) 143.0 (C), 142.9 (C), 142.4 (C), 142.3 (C), 127.2 (CH), 121.2 (CH), 121.1 (CH), 121.1 (CH), 121.0 (CH), 83.9 (CH-O), 83.8 (CH-O), 83.2 (CH-O), 82.8 (CH-O), 36.8 (CH_2), 32.0 (CH_2), 32.0 (CH_2), 29.3 (CH_2), 25.1 (CH_2), 24.8 (CH_2), 22.6 (CH_2), 14.1 (CH_3), 9.5 (CH_3) and 9.1 (CH_3) (mixture of diastereoisomers, not fully resolved); *m/z* (EI) 218 (M^+, 0.7%), 189 (30), 147 (100), 129 (30), 119 (17), 91 (20) and 28 (16).

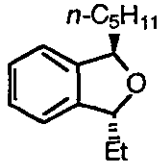
HPLC separation of the isomers of **226**

(Carried out by Mr Edwin Cole of Shell Research Ltd, Sittingbourne, Kent)

The isomers of **226** were separated by preparative HPLC using a Lichrosorb Si60 7 micron column 25 cm in length with an internal diameter of 50 mm. Eluent was 2% methyl *t*-butyl ether in hexane at a flow rate of 20 ml/min. Detection was by UV at 254 nm. The minor isomer **226trans** had a retention time of 18.5 min. The major isomer **226cis** had a retention time of 22 min.

10 g of **226** was separated in 0.5 g portions to give 3.04 g of **226trans** and 4.2 g of **226cis** (^{1}H NMR showed that this ratio does reflect that in the isomer mixture prepared by alkylation of **224**.

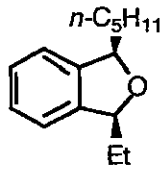
Data for **226trans**



226trans

Physical appearance: colourless oil (Found: M$^+$, 218.1672. $C_{15}H_{22}O$ requires M, 218.1671); $\nu_{max.}$ (film) 2931, 2850, 1465, 1050 and 744 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.27 - 7.12 (4 H, m, Ar_4), 5.28 - 5.20 (2 H, m, 2 x C*H*-O), 1.88 - 1.66 (4 H, m, 2 x CH_2), 1.44 - 1.28 (6 H, m, (CH_2)$_3$) and 0.96 - 0.85 (6 H, m, 2 x CH_3); δ_C (62.9 MHz; $CDCl_3$) 142.7 (C), 142.1 (C), 127.2 (CH), 127.1 (CH), 121.1 (CH), 121.0 (CH), 83.8 (CH-O), 83.1 (CH-O), 36.7 (CH_2), 31.9 (CH_2), 29.2 (CH_2), 24.7 (CH_2), 22.5 (CH_2), 14.0 (CH_3) and 9.0 (CH_3); *m/z* (EI) 218 (M$^+$, 1.3%), 189 (32), 147 (100), 129 (20), 117 (8) and 91 (10).

Data for **226cis**



226cis

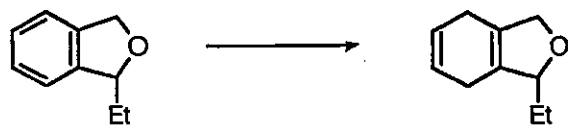
Physical appearance: colourless oil (Found: M$^+$, 218.1676. $C_{15}H_{22}O$ requires M, 218.1671); $\nu_{max.}$ (film) 2951, 2850, 1460, 1051, 1023 and 744 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.27 - 7.11 (4 H, m, Ar_4), 5.17 - 5.11 (2 H, m, 2 x C*H*-O),

2.09 - 1.64 (4 H, m, 2 x CH_2), 1.53 - 1.1.35 (6 H, m, $(CH_2)_3$) and 1.02 - 0.86 (6 H, m, 2 x CH_3); δ_C (62.9 MHz; $CDCl_3$) 142.9 (C), 142.3 (C), 127.1 (2 coincident CH), 121.0 (2 coincident CH), 83.7 (CH-O), 82.7 (CH-O), 36.7 (CH_2), 31.9 (CH_2), 29.2 (CH_2), 25.0 (CH_2), 22.5 (CH_2), 14.0 (CH_3) and 9.4 (CH_3); *m/z* (EI) 218 (M^+, 1%), 189 (35), 147 (100), 129 (18), 117 (7) and 91 (11).

Birch reduction of substituted 1,3-dihydrobenzo[c]furans: General procedure

Liquid ammonia (50 ml) was condensed into a round bottomed flask. Diethyl ether (6 ml), ethanol (5.3 ml, 90 mmol) and the appropriate 1,3-dihydrobenzo[c]furan (30 mmol) were added. Sodium (2.07 g, 90 mmol) was added over 30 min, and the solvent then allowed to evaporate. The residue was partitioned between water (50 ml) and diethyl ether (50 ml). The aqueous phase was extracted twice with diethyl ether (50 ml), and the combined organic phases washed with water (50 ml) then with saturated brine (50 ml). The organic phase was then dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified as described below.

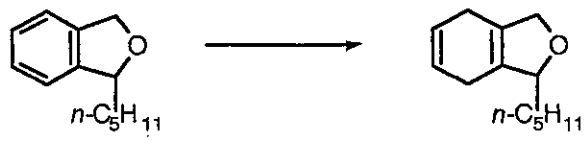
1-Ethyl-1,3,4,7-tetrahydrobenzo[c]furan (**227**)



223 **227**

1-Ethyl-1,3-dihydrobenzo[c]furan (**223**) (4.144 g, 28 mmol) was reduced according to the above general procedure to give, after distillation under reduced pressure, the *title compound* (3.64 g, 87%) as a colourless oil, b.p. 95°C at 9 mmHg (Found: M^+, 150.1044. $C_{10}H_{14}O$ requires M, 150.1045); $\nu_{max.}$ (film) 2964, 2825, 1046, 1019, 959 and 666 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 5.79 (2 H, s, alkene), 4.67 (1 H, m, C*H*-O), 4.47 (2 H, m, CH_2O), 2.58 (4 H, m, 2 x CH_2), 1.71 and 1.49 (1 H each, m, CH_2CH_3), and 0.91 (3 H, t, *J* 7.3, CH_3); δ_C (62.9 MHz; $CDCl_3$) 130.4 (C), 129.0 (C), 123.9 (alkene CH), 123.8 (alkene CH), 88.0 (CH-O), 76.4 (CH_2O), 26.8 (CH_2), 23.7 (CH_2), 23.5 (CH_2) and 8.6 (CH_3); *m/z* (EI) 150 (M^+, 5%), 121 (100), 103 (10), 91 (25), 77 (16) and 57 (6).

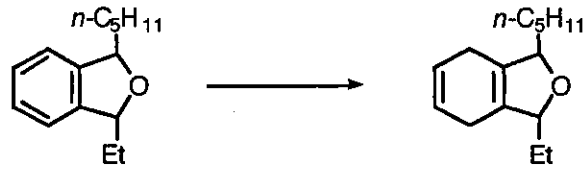
1-Pentyl-1,3,4,7-tetrahydrobenzo[c]furan (**228**)



224 **228**

Reduction of 1-pentyl-1,3-dihydrobenzo[c]furan (**224**) (2.85 g, 15 mmol) according to the above general procedure followed by distillation under reduced pressure gave the *title compound* (2.408 g, 84%) as a colourless oil, b.p. 110°C at 0.1 mmHg (Found: M^+, 192.1511. $C_{13}H_{20}O$ requires M, 192.1514); $\nu_{max.}$ (film) 2929, 2857, 1036, 958 and 666 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 5.78 (2 H, s, alkene), 4.69 (1 H, m, C*H*-O), 4.53 (2 H, m, CH_2O), 2.7 - 2.5 (4 H, m, 2 x CH_2), 1.7 - 1.2 (8 H, m, (CH_2)$_4$) and 0.89 (3 H, t, *J* 6.5, CH_3); δ_C (62.9 MHz; $CDCl_3$) 131.0 (C), 128.7 (C), 124.0 (alkene CH), 123.9 (alkene CH), 87.3 (CH-O), 76.3 (CH_2O), 34.3 (CH_2), 32.1 (CH_2), 24.5 (CH_2), 23.8 (CH_2), 23.6 (CH_2), 22.7 (CH_2) and 14.1 (CH_3); *m/z* (EI) 192 (M^+, 2%), 121 (100), 119 (14), 91 (20), 77 (10), 65 (4) and 43 (3).

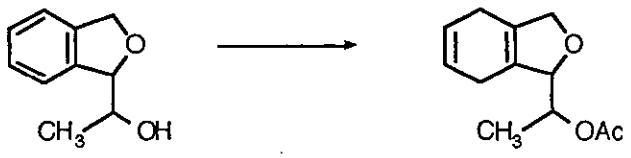
1-Ethyl-3-pentyl-1,3,4,7-tetrahydrobenzo[c]furan (**229**)



226 **229**

1-Ethyl-3-pentyl-1,3-dihydrobenzo[c]furan (**226**) was reduced by the general method described above. Purification by distillation gave the *title compound* (9.63g, 95%) as a colourless oil, b.p. 200°C at 3.5 mmHg (Found: M^+, 220.1830. $C_{15}H_{24}O$ requires M, 220.1827); $\nu_{max.}$ (film) 3030, 2929, 2824, 1464, 957 and 666 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 5.78 (2 H, br s, alkene), 4.7 (1 H, m, C*H*-O), 4.6 (1 H, m, C*H*-O), 2.6 (4 H, br s, 2 x CH_2), 1.8 - 1.25 (10 H, m, 5 x CH_2) and 0.96 - 0.86 (6 H, m, 2 x CH_3); δ_C (62.9 MHz; $CDCl_3$) 131.7 (C), 131.6 (C), 130.9 (C), 130.8 (C), 124.0 (alkene CH), 87.2 (CH-O), 87.1 (CH-O), 86.6 (CH-O), 86.2 (CH-O), 35.0 (CH_2), 34.5 (CH_2), 32.2 (CH_2), 32.1 (CH_2), 27.4 (CH_2), 26.9 (CH_2), 24.9 (CH_2), 24.4 (CH_2), 23.8 (CH_2), 23.8 (CH_2) 22.7 (CH_2), 22.7 (CH_2), 14.1 (CH_3), 14.1 (CH_3), 9.2 (CH_3) and 8.5 (CH_3) (mixture of diastereoisomers, not fully resolved); *m/z* (EI) 220 (M^+, 1%), 191 (58), 149 (100), 121 (18), 105 (22), 91 (30) and 79 (13).

1-(1,3,4,7-tetrahydrobenzo[c]furan-1-yl)ethyl acetate (**230**)



225 **230**

1-(1-Hydroxyethyl)-1,3-dihydrobenzo[c]furan (**225**) (984 mg, 6 mmol) was subjected to Birch reduction as described above. The crude product was dissolved in dichloromethane (10 ml). Acetic anhydride (0.714 g, 7 mmol), pyridine (0.5 ml) and 4-dimethylaminopyridine (20 mg) were added and the solution stirred for 15 h. The solution was diluted with dichloromethane (20 ml) and washed with copper sulfate solution (3 x 20 ml) then with water (2 x 20 ml), dried over magnesium sulfate, filtered and concentrated *in vacuo* to give an oil which was purified by flash column chromatography (eluent 9:1 light petroleum:diethyl ether) to give the *title compound* (0.872 g, 70% from **225**) as a colourless oil (Found: M^+, 208.1099. $C_{12}H_{16}O_3$ requires M, 208.1099); $\nu_{max.}$ (film) 1743, 1377, 1244 and 1052 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 5.78 - 5.76 (2 H, m, alkene), 5.10 - 4.97 (1 H, m, CHOAc), 4.82 - 4.47 (3 H, m, C*H*$_2$O and C*H*-O), 2.72 - 2.58 (4 H, m, 2 x C*H*$_2$), 2.09 (3 H of one diastereoisomer, s, COC*H*$_3$), 2.01 (3 H of other diastereoisomer, s, COC*H*$_3$), 1.25 (3 H of one diastereoisomer, d, *J* 6.5, C*H*$_3$) and 1.15 (3 H of other diastereoisomer, d, *J* 6.5, C*H*$_3$); δ_C (62.9 MHz; $CDCl_3$) 171.0 (C=O), 170.0 (C=O), 131.5 (C), 131.4 (C), 127.9 (C), 127.8 (C), 124.1 (alkene CH), 123.7 (alkene CH), 123.6 (alkene CH), 123.3 (alkene CH), 88.6 (CH-O), 88.4 (CH-O), 77.6 (CH_2O), 77.0 (CH_2O), 72.1 (CH-O), 70.5 (CH-O), 23.9 (CH_2), 23.8 (CH_2), 23.7 (CH_2), 21.3 (CO*C*H$_3$), 21.1 (CO*C*H$_3$), 15.6 (CH_3) and 13.2 (CH_3) (diastereoisomers, one of CH_2 peaks not distinct); *m/z* (EI) 208 (M^+, 0.5%), 148 (18), 121 (100), 119 (33), 103 (10), 93 (19), 91 (32), 77 (11) and 43 (10).

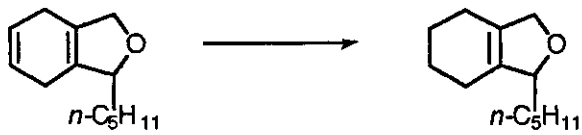
1-Ethyl-1,3,4,5,6,7-hexahydrobenzo[c]furan (**231**)

227 **231**

A degassed solution of **227** (600 mg, 4 mmol) in toluene (20 ml) containing tris(triphenylphosphine)rhodium(I) chloride (15 mg) was stirred under an

atmosphere of hydrogen for 17 h. The solution was then filtered through a pad of silica gel, concentrated *in vacuo* and purified by flash column chromatography (eluent light petroleum) to give the *title compound* (544 mg, 90%) as a colourless oil (Found: M^+, 152.1202. $C_{10}H_{16}O$ requires M, 152.1201); $\nu_{max.}$ (film) 2933, 2850, 1439, 1044 and 1019 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 4.65 (1 H, m, C*H*(Et)O), 4.47 (2 H, m, CH_2O), 1.93 (4 H, m, 2 x CH_2), 1.60 (5 H, m, 2 x CH_2 and one of C$H_2$$CH_3$), 1.44 (1 H, m, one of C$H_2$$CH_3$) and 0.88 (3 H, t, *J* 7.3, CH_3); δ_C (62.9 MHz; $CDCl_3$) 132.8 (C), 131.4 (C), 88.4 (CH-O), 76.8 (CH_2O), 27.0 (CH_2), 22.5 (CH_2), 22.4 (CH_2), 22.0 (CH_2), 21.8 (CH_2) and 8.6 (CH_3); *m/z* (EI) 152 (M^+, 9%), 135 (11), 123 (100), 95 (12), 79 (8), 67 (8) and 57 (8).

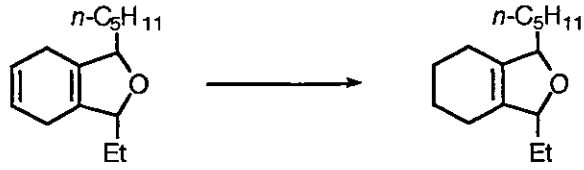
1-Pentyl-1,3,4,5,6,7-hexahydrobenzo[c]furan (**232**)



228 **232**

A degassed solution of 1-pentyl-1,3,4,7-tetrahydrobenzo[c]furan (**228**) (768 mg, 4 mmol) in toluene (20 ml) containing tris(triphenylphosphine)rhodium(I) chloride (15 mg) was stirred under an atmosphere of hydrogen for 48 h. After filtration through a pad of silica gel, the solvent was removed *in vacuo* and the residue purified by flash column chromatography (eluent light petroleum) to give the *title compound* (482 mg, 62%) as a colourless oil (Found: M^+, 194.1677. $C_{13}H_{22}O$ requires M, 194.1671); $\nu_{max.}$ (film) 2954, 2857, 1122, 1059 and 1036 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 4.63 (1 H, m, C*H*-O), 4.47 (2 H, m, CH_2O), 1.95 - 1.80 (4 H, m), 1.70 - 1.50 (5 H, m), 1.37 - 1.28 (7 H, m) and 0.88 (3 H, t, *J* 6.6, CH_3); δ_C (62.9 MHz; $CDCl_3$) 133.3 (C), 131.1 (C), 87.6 (CH-O), 76.6 (CH_2O), 34.5 (CH_2), 32.1 (CH_2), 24.5 (CH_2), 22.7 (CH_2), 22.6 (CH_2), 22.6 (CH_2), 22.5 (CH_2), 21.8 (CH_2) and 14.1 (CH_3); *m/z* (EI) 194 (M^+, 4%), 135 (10), 123 (100), 119 (9) and 95 (8).

1-Ethyl-3-pentyl-1,3,4,5,6,7-hexahydrobenzo[c]furan (**233**)



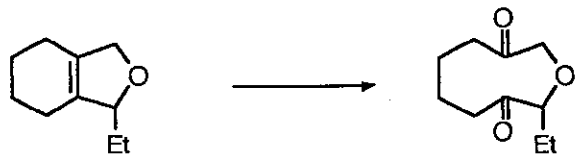
229 **233**

A suspension of 10% palladium on carbon (150 mg) in ethyl acetate (20 ml) was shaken for 15 min under an atmosphere of hydrogen (45 p.s.i.). A solution of 1-ethyl-3-pentyl-1,3,4,7-tetrahydrobenzo[c]furan (**229**) (6g, 27.3 mmol) in ethyl acetate (10 ml) was then added and the reaction mixture shaken vigorously under this pressure of hydrogen for 2 h. The catalyst was then removed by filtration through a pad of Celite® and the solution concentrated *in vacuo* to give the *title compound* (5.88g, 97%) as a colourless oil which was shown by NMR to contain *ca.* 10% of the corresponding 1,3-dihydrobenzo[c]furan (**226**) (Found: M^+, 222.1989. $C_{15}H_{26}O$ requires M, 222.1984); $\nu_{max.}$ (film) 2958, 2930, 2858, 1129, 1064 and 1048 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 4.65 - 4.45 (2 H, m, 2 x C*H*-O), 1.95 - 1.20 (18 H, m, 9 x CH_2) and 0.95 - 0.80 (6 H, m, 2 x CH_3); δ_C (75.48 MHz; $CDCl_3$) 134.3 (C), 134.0 (C), 133.4 (C), 133.1 (C), 87.3 (CH-O), 86.9 (CH-O), 86.3 (CH-O), 35.2 (CH_2), 34.8 (CH_2), 32.2 (CH_2), 32.1 (CH_2), 27.6 (CH_2), 27.1 (CH_2), 25.0 (CH_2), 24.4 (CH_2), 22.7 (CH_2), 22.6 (CH_2), 21.9 (CH_2), 14.1 (CH_3), 9.2 (CH_3) and 8.4 (CH_3) (mixture of diastereoisomers, not fully resolved); *m/z* (EI) 222 (M^+, 3.5%), 193 (60), 151 (100), 135 (7), 123 (7), 91 (8) and 81(9).

Oxidative ring expansion: General procedure

The substrate (0.66 mmol) was dissolved in tetrachloromethane (2 ml) and acetonitrile (2 ml). Water (3 ml), sodium metaperiodate (0.58 g, 2.7 mmol) and ruthenium(III) chloride hydrate (4 mg) were added and the resulting biphasic mixture was stirred rapidly for 24 h. The mixture was then diluted with dichloromethane (20 ml) and washed with water (3 x 20 ml). The organic phase was then dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the crude product which was purified as described below.

2-Ethyloxonane-3,8-dione (**234**)



231 **234**

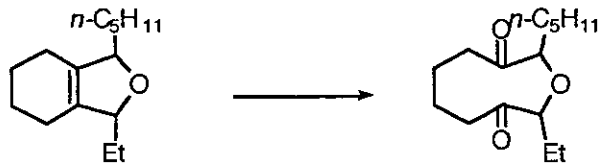
Oxidation of **231** (100 mg, 0.66 mmol) according to the general procedure described above was followed by flash column chromatography (eluent 3:1 light petroleum:diethyl ether) to give the *title compound* (59 mg, 49%) as a colourless oil (Found: M+, 184.1098. $C_{10}H_{16}O_3$ requires M, 184.1099); $\nu_{max.}$ (film) 2970, 2938, 1719 and 1113 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 4.42 and 3.90 (2 H, AB quartet, *J* 17.1, C*H*$_2$O), 3.64 (1 H, t, *J* 6.6, C*H*-O), 3.20 - 3.06 (2 H, m, C*H*$_2$), 2.29 - 2.14 (2 H, m, C*H*$_2$), 1.89 - 1.66 (6 H, m, 3 x C*H*$_2$) and 0.96 (3 H, t, *J* 7.4, C*H*$_3$); δ_C (62.9 MHz; $CDCl_3$) 214.9 (C=O), 212.9 (C=O), 90.8 (CH-O), 78.6 (CH_2O), 36.6 (CH_2), 35.6 (CH_2), 26.0 (CH_2), 24.5 (CH_2), 23.1 (CH_2) and 9.6 (CH_3); *m/z* (EI) 184 (M^+, 0.8%), 155 (M - C_2H_5, 10), 127 (22), 110 (16), 97 (17), 81 (100), 55 (20) and 41 (14).

2-Pentyloxonane-3,8-dione (**235**)

232 **235**

Oxidation of **232** (300 mg, 1.55 mmol) according to the general procedure described above, followed by flash column chromatography (eluent 3:1 light petroleum:diethyl ether) gave the *title compound* (124 mg, 35%) as a colourless oil (Found M^+, 226.1571. $C_{13}H_{22}O_3$ requires M, 226.1569); $\nu_{max.}$ (film) 2954, 2871, 1713, 1461 and 1114 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 4.41 and 3.90 (2 H, AB quartet, *J* 17.1, C*H*$_2$O), 3.71 (1 H, dd, *J* 7.3 and 5.9, C*H*-O), 3.21 - 3.08 (2 H, m, C*H*$_2$CO), 2.40 - 2.15 (2 H, m, C*H*$_2$CO), 1.89 - 1.62 (6 H, m, 3 x C*H*$_2$), 1.40 - 1.27 (6 H, m, (C*H*$_2$)$_3$CH$_3$) and 0.89 - 0.85 (3 H, m, C*H*$_3$); δ_C (62.9 MHz; $CDCl_3$) 214.9 (C=O), 212.8 (C=O), 89.5 (CH-O), 78.3 (CH_2O), 36.5 (CH_2), 35.3 (CH_2), 32.6 (CH_2), 31.4 (CH_2), 24.7 (CH_2), 24.4 (CH_2), 22.9 (CH_2), 22.3 (CH_2) and 13.8 (CH_3); *m/z* (EI) 226 (M^+, 0.2%), 155 (M - C_5H_{11}, 10), 127 (14), 81 (100), 55 (19) and 41 (18).

2-Ethyl-9-pentyloxonane-3,8-dione (**236**)



233 **236**

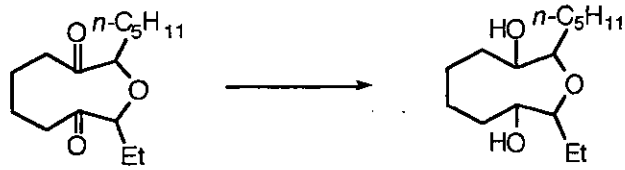
1-Ethyl-3-pentyl-1,3,4,5,6,7-hexahydrobenzo[c]furan (**233**) (880 mg, 3.96 mmol) was oxidised as described above. Purification by flash column chromatography (eluent 9:1 light petroleum:diethyl ether) gave the impure *title compound* (493 mg, 49%) as a pale yellow oil (mixture of diastereoisomers) (Found M^+, 254.1876. $C_{15}H_{26}O_3$ requires M, 254.1882); $\nu_{max.}$ (film) 2934, 2873, 1715, 1095 and 738 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 4.02 - 3.63 (2 H, m, 2 x C*H*-O), 3.06 - 2.10 (4 H, m, 2 x CH_2), 1.90 - 1.26 (14 H, m, 7 x CH_2) and 0.99 - 0.85 (6 H, m, 2 x CH_3); δ_C (62.9 MHz; $CDCl_3$) complex due to the presence of impurities, but including 88.4 (CH-O of major isomer), 87.4 (CH-O of major isomer), 80.9 (CH-O of minor isomer) and 79.7 (CH-O of minor isomer); ^1H-^{13}C correlation spectrum satisfactory; *m/z* (EI) 254 (M^+, 1%), 197 (8), 155 (18), 133 (21), 114 (26), 109 (100), 97 (26), 84 (23), 73 (22), 60 (37), 55 (41) and 41 (20).

Pentadeca-3,4,9,10-tetraone (**237**)

233 **237**

Oxidation of **233** as described above also yielded **237** (91 mg, 9%) as a yellow solid, m.p. 74 - 75°C (from light petroleum) (Found: MH^+, 269.1743. $C_{15}H_{24}O_4$ + H^+ requires M, 269.1753); $\nu_{max.}$ (CH_2Cl_2 solution) 2974, 2939, 1710, 1454, 1395 and 727 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 2.81 - 2.65 (8 H, m, 4 x CH_2), 1.65 - 1.53 (6 H, m, 3 x CH_3), 1.35 - 1.25 (4 H, m, 2 x CH_2), 1.07 (3 H, t, *J* 7.4, CH_2CH_3) and 0.88 (3 H, t, *J* 7.3, CH_2CH_3); δ_C (75.48 MHz; $CDCl_3$) 200.2 (C=O), 199.9 (C=O), 199.4 (C=O), 199.3 (C=O), 36.1 (CH_2), 35.8 (CH_2), 35.7 (CH_2), 31.4 (CH_2), 29.6 (CH_2), 22.8 (CH_2), 22.4 (3 coincident CH_2), 13.9 (CH_3) and 7.0 (CH_3); *m/z* (methane CI) 269 (MH^+, 16%), 251 (100), 221 (16), 169 (36), 167 (58) and 125 (64).

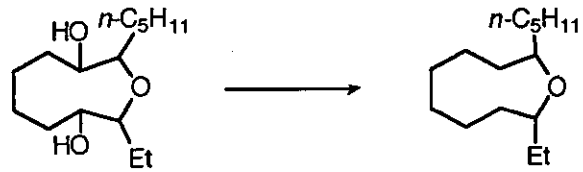
2-Ethyl-9-pentyloxonane-3,8-diol (**239**)



236 **239**

To a suspension of lithium aluminium hydride (615 mg, 15 mmol) in dry THF (7 ml) was added a solution of 2-ethyl-9-pentyloxonane-3,8-dione (**236**) (762 mg, 3 mmol) in dry THF (25 ml). The resulting solution was heated under reflux for 1h, then allowed to cool to room temperature and quenched with 2N hydrochloric acid (50 ml). The organic material was extracted with diethyl ether (3 x 50 ml) and the combined organic phases dried over magnesium sulfate and evaporated to dryness. Purification by flash column chromatography (eluent 1:1 light petroleum:diethyl ether) afforded the *title compound* (523 mg, 68%) as a viscous clear oil (Found: M^+, 258.2186. $C_{15}H_{30}O_3$ requires M, 258.2195); $\nu_{max.}$ (film) 3371 (br, OH), 2930, 2859, 1456 and 1045 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 3.9 - 3.7 (2H, m, 2 x C*H*OH), 3.6 - 3.1 (2H, m, 2 x C*H*-O), 2.1 - 1.95 (2H, br s, 2 x O*H*), 1.95 - 1.1 (18H, m, 9 x CH_2) and 1.0 - 0.8 (6H, m, 2 x CH_3); *m/z* (EI) 258 (M^+, 0.7%), 143 (42), 119 (42), 99 (42), 84 (69), 70 (73), 57 (76), 55 (68), 43 (71), 43 (100) and 29 (67).

Obtusan (mixture of diastereoisomers) (**216**)



239 **216**

Sodium hydride (150 mg, 60% dispersion in mineral oil, 3.7 mmol) was washed with hexane, dried and suspended in DMF (5 ml). A solution of 2-ethyl-9-pentyloxonane-3,8-diol (**239**) (191 mg, 0.74 mmol) in DMF (2 ml) was added dropwise, followed, after 5 min, by carbon disulfide (2 ml, excess, freshly filtered through basic alumina). After stirring for 30 min, iodomethane (2 ml, excess) was added dropwise and stirring continued for 90 min. Water (20 ml) was added and the organic material extracted into diethyl ether (3 x 20 ml). The combined organic phases were washed with water (6 x 20 ml), dried over magnesium sulfate, filtered and concentrated *in vacuo* to give an

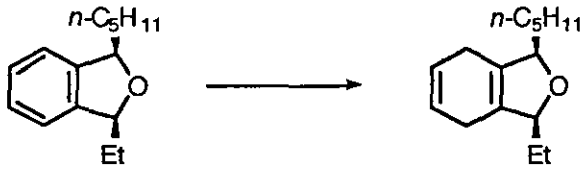
oil which was purified by flash column chromatography (eluent 9:1 light petroleum:diethyl ether) to give the bis-xanthate **240** (293 mg, 90%) as a mobile yellow oil which was used directly.

Thus a solution of the above xanthate (267 mg, 0.61 mmol) in benzene (CAUTION) with AIBN (20 mg) was heated to reflux. Tri-*n*-butyltin hydride (1.4 ml, 5.2 mmol) was added neat, and the solution heated under reflux for 45 min. The solution was allowed to cool to room temperature and concentrated *in vacuo* to a clear oil which was purified by flash column chromatography (eluent 99:1 light petroleum:diethyl ether) followed by short path distillation (Kugelrohr apparatus) to afford the *title compound*[87] (102 mg, 74%) as a clear liquid, b.p. 150°C at 4 mmHg (Found: M^+, 226.2299. $C_{15}H_{30}O$ requires M, 226.2297); $\nu_{max.}$ (film) 2957, 2927, 2859, 1465, 1158, 1141 and 1089 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 3.65 - 3.25 (2 H, m, C*H*-O-C*H*), 1.8 - 1.2 (22 H, m, 11 x CH_2) and 1.0 - 0.8 (6 H, m, 2 x CH_3); δ_C (62.9 MHz; $CDCl_3$) 81.1 (CH-O, *cis*),[87] 79.7 (CH-O, *cis*),[87] 76.3 (CH-O, *trans*), 75.4 (CH-O, *trans*), 36.4 (CH_2), 32.4 (CH_2), 32.2 (CH_2), 32.1 (CH_2), 32.0 (CH_2), 31.6 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 26.7 (CH_2), 26.6 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 25.3, (CH_2) 25.2 (CH_2), 22.8 (CH_2), 22.7 (CH_2), 14.1 (CH_3), 10.8 (CH_3) and 10.7 (CH_3) (mixture of diastereoisomers, not fully resolved); *m/z* (EI) 226 (M^+, 4%), 155 (10), 137 (12), 95 (36), 83 (59), 69 (64), 55 (948) and 41 (100).

Elaboration of single isomers of the 1,3-dihydrobenzo[c]furan ***226***

Separated isomers of **226** (For HPLC conditions see p. 113) were elaborated in an identical manner to the isomer mixture. Spectroscopic and related data for products is given below.

cis-1-Ethyl-3-pentyl-1,3,4,7-tetrahydrobenzo[c]furan (**229cis**)

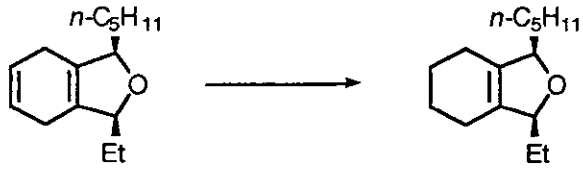


226cis **229cis**

Isolated as a colourless oil (3.60g, 89%), b.p. 170°C at 2mmHg (Found: M^+, 220.1828. $C_{15}H_{24}O$ requires M, 220.1827); $\nu_{max.}$ (film) 3029, 2958, 2929, 2857, 2823, 1465, 958 and 666 cm^{-1}; δ_H (300MHz; $CDCl_3$) 5.8 (2 H, br s,

alkene), 4.6 (2 H, br s, 2 x C*H*-O), 2.6 (4 H, br s, 2 x CH_2), 1.75 - 1.53 (2 H, m, CH_2), 1.5 - 1.2 (8 H, m, 4 x CH_2), 0.91 (3 H, t, *J* 7.5, CH_3) and 0.87 (3 H, t, *J* 6.6, CH_3); δ_C (75.48 MHz; $CDCl_3$) 131.8 (C), 131.0 (C), 124.1 (2 x CH, alkene), 87.2 (CH-O), 86.3 (CH-O), 35.0 (CH_2), 32.1 (CH_2), 27.5 (CH_2), 25.0 (CH_2), 23.9 (2 x CH_2), 22.7 (CH_2), 14.1 (CH_3) and 9.2 (CH_3); *m/z* (EI) 220 (M^+, 0.7%), 191 (46), 149 (100), 91 (39), 79 (27), 57 (32), 43 (40) and 29 (38).

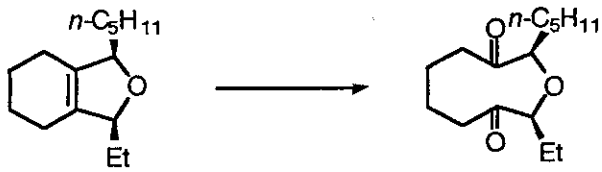
cis-1-Ethyl-3-pentyl-1,3,4,5,6,7-hexahydrobenzo[c]furan (**233cis**)



229cis **233cis**

Isolated as a colourless oil (3.23g, 100%) containing *ca.* 10% of the 1,3-dihydrobenzo[c]furan **226cis** (NMR analysis) (Found: M^+, 222.1987. $C_{15}H_{26}O$ requires M, 222.1984); $\nu_{max.}$ (film) 2931, 2858, 909 and 735 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 4.60 - 4.45 (2 H, m, 2 x C*H*-O), 1.95 - 1.20 (18 H, m, 9 x CH_2) and 0.95 - 0.80 (6 H, m, 2 x CH_3); δ_C (75.48 MHz; $CDCl_3$) 134.3 (C), 133.4 (C), 87.3 (CH-O), 86.4 (CH-O), 35.2 (CH_2), 32.1 (CH_2), 27.6 (CH_2), 25.0 (CH_2), 22.7 (CH_2), 22.6 (2 x CH_2), 21.9 (2 x CH_2), 14.1 (CH_3) and 9.2 (CH_3); *m/z* (EI) 222 (M^+, 4.1%), 193 (50), 151 (100), 147 (20), 81 (20), 57 (23), 41 (29) and 29 (32).

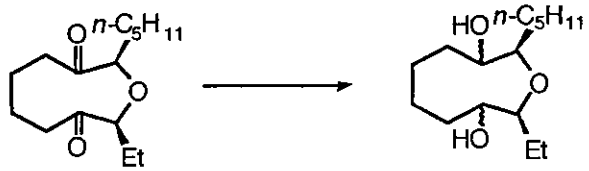
cis-2-Ethyl-9-pentyloxonane-3,8-dione (**236cis**)



233cis **236cis**

Isolated (1.174 g, 34%) as a pale oil (Found: M^+, 254.1880. $C_{15}H_{26}O_3$ requires M, 254.1882); $\nu_{max.}$ (film) 2957, 2934, 2873, 1713, 1464 and 1095 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 3.75 - 3.65 (2 H, m, 2 x C*H*-O), 2.4 - 1.2 (18 H, m, 9 x CH_2) and 1.0 - 0.8 (6 H, m, 2 x CH_3); δ_C (75.48 MHz; $CDCl_3$) complex due to the presence of impurities, but including 88.7 (CH-O) and 87.7 (CH-O); *m/z* (EI) 254 (M^+, 0.9%), 133 (61), 109 (80), 97 (39), 60 (60), 55 (100), 41 (99) and 29 (73).

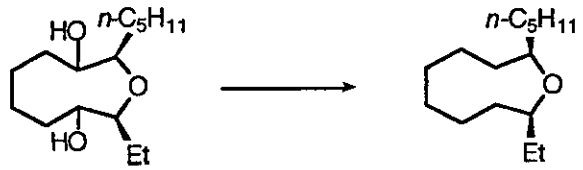
2-Ethyl-9-pentyloxonane-3,8-diol (**239cis**)



236cis **239cis**

Isolated (517 mg, 64%) as a colourless oil (Found: M^+, 258.2193. $C_{15}H_{30}O_3$ requires M, 258.2195); $\nu_{max.}$ (film) 3392 (br, OH), 2930, 2873, 1456, 1048 and 734 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 3.9 - 3.8 and 3.5 - 3.1 (4 H, m, 4 x C*H*-O), 2.6 - 2.4 (2 H, br, 2 x O*H*), 2.05 - 1.15 (18 H, m, 9 x CH_2) and 1.0 - 0.8 (6 H, m, 2 x CH_3); *m/z* (EI) 258 (M^+, 0.4%), 119 (41), 82 (82), 67 (100), 57 (58), 55 (69), 43 (52), 41 (95), 29(60) and 27 (49).

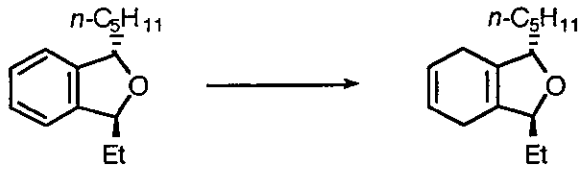
cis-obtusan (**216cis**)



239cis **216cis**

Treatment of **239cis** (400 mg, 1.55 mmol) as above led to the bis-xanthate **240cis** (523 mg, 77%) as a mobile yellow oil which was used directly.
Thus radical deoxygenation of the bis-xanthate **240cis** (400 mg, 0.91 mmol) gave the *title compound* (165 mg, 80%) as a single distereoisomer (Found: M^+, 226.2299. $C_{15}H_{30}O$ requires M, 226.2297); $\nu_{max.}$ (film) 2959, 2927, 2860, 1465 and 1089 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 3.45 - 3.25 (2 H, m, C*H*-O-C*H*), 1.85 - 1.20 (22 H, m, 11 x CH_2), 0.90 (3 H, t, *J* 7.5, CH_3) and 0.88 (3 H, t, *J* 6.9, CH_3); δ_C (62.9 MHz; $CDCl_3$) 81.2 (CH-O), 79.8 (CH-O), 36.5 (CH_2), 32.5 (CH_2), 32.3 (CH_2), 32.2 (CH_2), 29.2 (CH_2), 26.8 (CH_2), 26.7 (CH_2), 26.0 (CH_2), 22.9 (CH_2), 22.9 (CH_2), 22.8 (CH_2), 14.2 (CH_3) and 10.8 (CH_3); *m/z* (EI) 226 (M^+, 2.2%), 155 (5), 137 (6), 95 (22), 83 (41), 81 (29), 69 (43), 67 (29), 56 (41), 55 (88), 43 (59) and 41 (100).

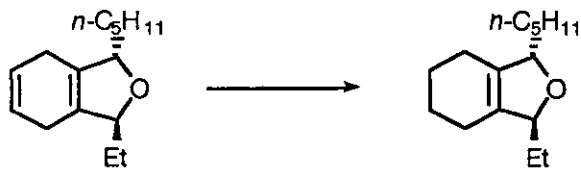
trans-1-Ethyl-3-pentyl-1,3,4,7-tetrahydrobenzo[c]furan (**229trans**)



226trans **229trans**

Birch reduction of **226trans** (2.8 g, 12.8 mmol) by the above general method gave **229trans** (2.58 g, 91%) as a colourless oil, b.p. 170°C at 2mmHg (Found: $M^{+\cdot}$ 220.1826. $C_{15}H_{24}O$ requires M, 220.1827); $\nu_{max.}$ (film) 3029, 2958, 2928, 2856, 2824, 1462, 958 and 668 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 5.8 (2 H, br s, alkene), 4.7 (2 H, br s, 2 x C*H*-O), 2.6 (4 H, br s, 2 x CH_2), 1.8 - 1.2 (10 H, m, 5 x CH_2) and 0.86 (6 H, two coincident triplets, *J* 7.4, 2 x CH_3); δ_C (75.48 MHz; $CDCl_3$) 131.6 (C), 130.1 (C), 124.1 (2 x alkene CH), 87.1 (CH-O), 86.6 (CH-O), 34.5 (CH_2), 32.2 (CH_2), 27.0 (CH_2), 24.4 (CH_2), 23.8 (2 x CH_2), 22.7 (CH_2), 14.1 (CH_3) and 8.5 (CH_3); *m/z* (EI) 220(M^+, 0.8%), 191(45), 149(100), 91(32), 79(19), 57(24), 43(25) and 29(24).

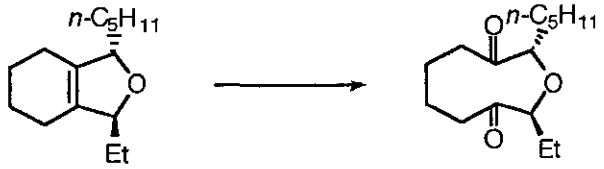
trans-1-Ethyl-3-pentyl-1,3,4,5,6,7-hexahydrobenzo[c]furan (**233trans**)



229trans **233trans**

Hydrogenation of **229trans** over palladium-on-carbon as described above gave **233trans** (2.03g, 100%) containing ca. 10% of the 1,3-dihydrobenzo[c]furan **226trans** (NMR analysis) (Found: M^+, 222.1984. $C_{15}H_{26}O$ requires M, 222.1984); $\nu_{max.}$ (film) 2929, 2857, 1458, 1053, 946 and 734 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 4.65 - 4.55 (2 H, m, 2 x C*H*-O), 1.95 - 1.8 (4 H, m, 2 x CH_2), 1.78 - 1.5 (6 H, m, 3 x CH_2), 1.5 - 1.2 (8 H, m, 4 x CH_2) and 0.8 - 0.95 (6 H, m, 2 x CH_3); δ_C (75.48 MHz; $CDCl_3$) 134.0 (C), 133.1 (C), 87.3 (CH-O), 86.9 (CH-O), 34.8 (CH_2), 32.3 (CH_2), 27.2 (CH_2), 24.4 (CH_2), 22.7 (3 x CH_2), 22.0 (2 x CH_2), 14.1 (CH_3) and 8.4 (CH_3); *m/z* (EI) 222 (M^+, 2.8%), 193 (47), 151 (100), 81 (22), 57 (28), 41 (34) and 29 (37).

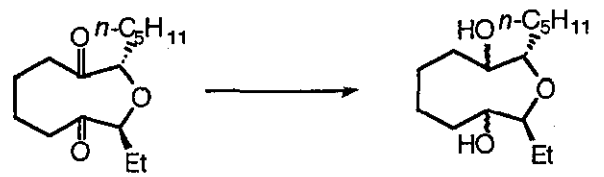
trans-2-Ethyl-9-pentyloxonane-3,8-dione (**236trans**)



233trans **236trans**

Oxidation of **233trans** according to the above general procedure gave **236trans** (1.214 g, 59%) as a pale oil (Found: M^+, 254.1889. $C_{15}H_{26}O_3$ requires M, 254.1882); $\nu_{max.}$ (film) 2936, 2863, 1717, 1463, 1186 and 1094 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 4.05 - 3.85 (2 H, m, C*H*-O-C*H*), 2.8 - 1.1 (18 H, m, 9 x CH_2) and 0.95 - 0.8 (6 H, m, 2 x CH_3); δ_C (74.48 MHz; $CDCl_3$) complex due to the presence of impurities, but including 81.3 (CH-O) and 80.1 (CH-O); *m/z* (EI) 254 (M^+, 0.5%), 133 (29), 109 (48), 99 (34), 84 (48), 67 (33), 60 (62), 57 (62), 55 (77), 41 (100), 29 (90) and 27 (70).

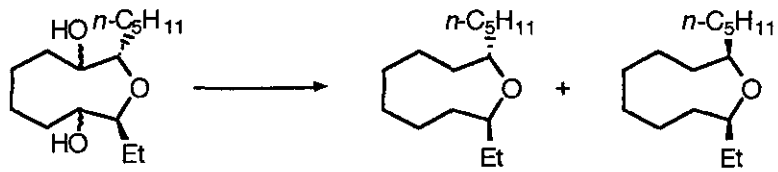
2-Ethyl-9-pentyloxonane-3,8-diol (**239trans**)



236trans **239trans**

Reduction of **236trans** as described above gave **239trans** (756 mg, 75%) as a slightly impure colourless oil (Found: M^+, 258.2194. $C_{15}H_{30}O_3$ requires M, 258.2195); $\nu_{max.}$ (film) 3392 (br, OH), 2931, 2860, 1458, 1122 and 1042 cm^{-1}; δ_H (250MHz; $CDCl_3$) 3.90 - 3.47 (4 H, m, 4 x C*H*-O), 2.22 (2 H, br, 2 x O*H*), 1.93 - 1.31 (18 H, m, 9 x CH_2) and 1.00 - 0.87 (6 H, m, 2 x CH_3); *m/z* (EI) 258 (M^+, 0.6%), 119 (30), 99 (32), 81 (44), 67 (68), 57 (71), 55 (62), 43 (63), 41 (100) and 29 (69).

*Deoxygenation of **239trans** to give a mixture of **216trans** and **216cis***



239trans **216trans** **216cis**

Treatment of **239trans** as described above gave the bis-xanthate **240trans** (647 mg, 76%) as a mobile yellow oil which was used directly.

Thus radical deoxygenation of the bis-xanthate **240trans** (110 mg, 0.25 mmol) as described above gave a 1.5:1 mixture (by ^{1}H NMR) of **216trans** and **216cis** (31 mg, 55%) as a colourless oil (Found: M$^+$, 226.2302. $C_{15}H_{30}O$ requires M, 226.2297); $\nu_{max.}$ (film) 2957, 2928, 2869, 1465, 1128, 1088, 1033 and 734 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 3.63 - 3.46 (2 H of **216trans**, m, C*H*-O-C*H*), 3.45 - 3.27 (2 H of **216cis**, m, C*H*-O-C*H*), 1.85 - 1.25 (22 H, m, 11 x CH_2) and 1.0 - 0.85 (6 H, m, 2 x CH_3); δ_C (62.9 MHz; $CDCl_3$) 81.1 (CH-O, **216cis**), 79.7 (CH-O, **216cis**), 76.3 (CH-O, **216trans**), 75.4 (CH-O, **216trans**), 36.3 (CH_2), 32.4 (CH_2), 32.2 (CH_2), 32.1 (CH_2), 32.0 (CH_2), 31.6 (CH_2), 29.2 (CH_2), 26.7 (CH_2), 26.6 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 26.1 (CH_2), 25.3 (CH_2), 25.2 (CH_2), 22.9 (CH_2), 22.8 (CH_2), 22.7 (CH_2), 14.1 (CH_3), 10.8 (CH_3) and 10.7 (CH_3) (mixture of diastereoisomers, not fully resolved); *m/z* (EI) 226 (M$^+$, 3.8%), 155 (11), 137 (17), 95 (37), 83 (59), 69 (60), 55 (95) and 41 (100).

2,3-Dihydro-1H-benzo[c]pyrrole (**244**)

244

A 1.0M solution of borane in THF (100 ml, 100 mmol) was added to a suspension of phthalimide (5.5 g, 37.5 mmol) in THF (9 ml) under an atmosphere of nitrogen over a period of 30 min. After the addition was complete, the resulting orange solution was heated under reflux for 16 h, then cooled to 0°C. Methanol (9.25 ml) was added over 30 min followed by 6N hydrochloric acid (10.5 ml), and the mixture heated under reflux for 1 h. The solution was then cooled to 0°C and 6N sodium hydroxide added until the reaction mixture had pH > 10. The phases were separated and the aqueous phase extracted with diethyl ether (2 x 50 ml). The combined organic phases were dried over potassium hydroxide pellets, filtered and concentrated *in vacuo* to give a brown oil which was purified by short path distillation (Kugelrohr apparatus) to give the *title compound* (1.898 g, 43%) as a pale oil, b.p. 70°C at 0.9mmHg (lit.[112] 48°C at 0.8mmHg); $\nu_{max.}$ (film) 3277 (br, NH), 2848, 1460, 1061 and 743 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.2 - 7.1 (4 H, m,

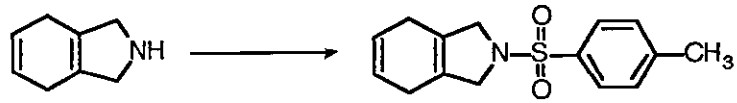
Ar_4), 4.16 (4 H, s, CH_2NCH_2) and 2.33 (1 H, br s, N*H*); δ_C (62.9 MHz, $CDCl_3$) 141.7 (C), 126.6 (CH), 122.6 (CH) and 52.9 (CH_2).

2,3,4,7-Tetrahydro-1H-benzo[c]pyrrole (**245**)

244 **245**

Liquid ammonia (40 ml) was condensed into a 100 ml 3-necked round bottomed flask. Diethyl ether (2.5 ml), ethanol (2.44 ml) and 2,3-dihydro-1*H*-benzo[c]pyrrole (**244**) (1.491 g, 12.5 mmol) were added in that order, followed by the addition, over 30 min, of sodium (0.86 g, 37.5 mmol). The ammonia was then allowed to evaporate, and water (20 ml) and diethyl ether (20 ml) added. The phases were separated and the aqueous phase extracted with diethyl ether (2 x 20 ml). The combined organic phase was dried over potassium hydroxide pellets, filtered and concentrated *in vacuo* to give the *title compound* (1.143 g, 75%) as an orange oil which was used without further purification; δ_H (250 MHz; $CDCl_3$) 5.77 (2 H, br s, alkene), 3.68 (4 H, s, CH_2NCH_2), 2.67 (4 H, s, 2 x CH_2) and 2.5 (1 H, br s, N*H*); δ_C(62.9 MHz; $CDCl_3$) 130.1 (C), 124.2 (alkene CH), 55.9 (CH_2N) and 25.2 (CH_2).

1,3,4,7-Tetrahydro-2-(4-toluenesulfonyl)-2H-benzo[c]pyrrole (**246**)

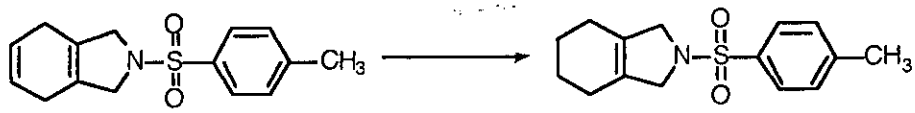


245 **246**

To the crude 2,3,4,7-tetrahydro-1*H*-benzo[c]pyrrole (**245**) (1.143 g, 9.45 mmol) was added *p*-toluenesulfonyl chloride (1.8 g, 9.45 mmol) and pyridine (7 ml), and the resulting dark solution heated under reflux for 30 min. The mixture was then poured into 2N hydrochloric acid (40 ml). The precipitate was collected by filtration and recrystallised from ethanol to give the *title compound* (2.211 g, 85%) as a buff coloured solid, m.p. 176 - 177°C (Found: C, 65.3; H, 6.2; N, 5.1. $C_{15}H_{17}NSO_2$ requires C, 65.4; H, 6.2; N, 5.1%); $\nu_{max.}$ ($CHCl_3$ solution) 3021, 1342, 1164, 1103 and 665 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.74 (2 H, d, *J* 8.4, Ar_2), 7.31 (2 H, d, *J* 8.4, Ar_2), 5.70 (2 H, s, alkene), 4.01 (4 H, s, CH_2NCH_2), 2.57 (4 H, s, 2 x CH_2) and 2.43 (3 H, s, CH_3); δ_C (62.9 MHz; $CDCl_3$) 143.4 (C), 134.0 (C), 129.8 (CH), 127.6 (CH), 123.5 (alkene CH),

122.6 (C), 56.9 (CH_2NCH_2), 24.6 (2 x CH_2) and 21.5 (CH_3); *m/z* (EI) 275 (M^+, 20%), 221 (20), 155 (100), 120 (95), 91 (80), 65 (30) and 35 (30).

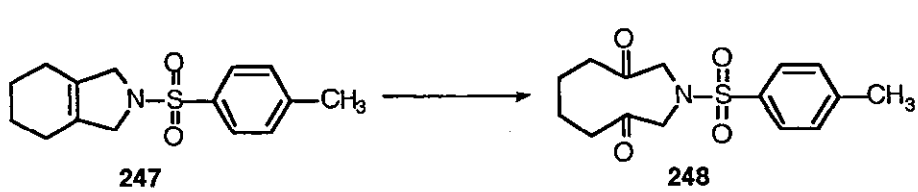
1,3,4,5,6,7-Hexahydro-2-(4-toluenesulfonyl)-2H-benzo[c]pyrrole (**247**)



246 **247**

A solution of 1,3,4,7-tetrahydro-2-(4-toluenesulfonyl)-2*H*-benzo[c]pyrrole (**246**) (275 mg, 1 mmol) and tris(triphenylphosphine)rhodium(I) chloride (30 mg) in degassed dry toluene (10 ml) was stirred under an atmosphere of hydrogen for 60 h. After removal of catalyst by filtration through a pad of silica gel, the solvent was removed *in vacuo* and the solid residue purified by flash column chromatography (eluent 3:1 light petroleum:diethyl ether) to give the *title compound* (225 mg, 81%) as a colourless solid , m.p. 133 - 134°C (Found C, 64.7; H, 6.8; N, 5.0. $C_{15}H_{19}NSO_2$ requires C, 64.95; H, 6.9; N, 5.0%); $\nu_{max.}$ (Nujol) 1340, 1162, 1099, 718 and 663 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.72 (2 H, d, *J* 8.4, Ar_2), 7.32 (2 H, d, *J* 8.4, Ar_2), 3.96 (4 H, s, CH_2NCH_2), 2.43 (3 H, s, CH_3), 2.0 - 1.8 (4 H, m, 2 x CH_2) and 1.7 - 1.5 (4 H, m, 2 x CH_2); δ_C (62.9 MHz; $CDCl_3$) 143.2 (C), 134.5 (C), 129.7 (CH), 127.6 (CH), 122.6 (alkene C), 57.1 CH_2NCH_2), 22.8 (2 x CH_2), 22.1 (2 x CH_2) and 21.5 (CH_3); *m/z* (EI) 277 (M^+, 2%), 155 (100), 122 (76), 91 (40), 65 (21), 41 (20) and 35 (18).

1-(4-Toluenesulfonyl)azonane-3,8-dione (**248**)



247 **248**

(a) By Ozonolysis

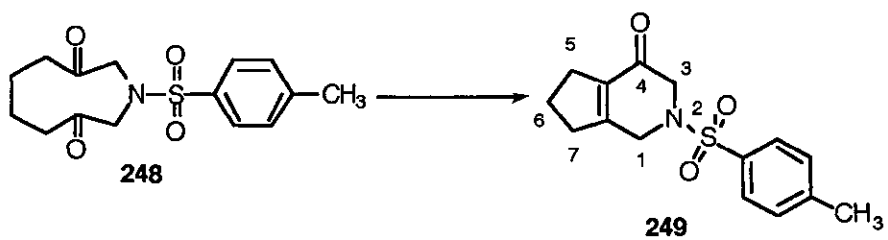
A solution of 1,3,4,5,6,7-hexahydro-2-(4-toluenesulfonyl)-2*H*-benzo[c]pyrrole (**247**) (100 mg, 0.36 mmol) in CH_2Cl_2 (50 ml) containing Sudan III dye[155] (trace) was ozonised at -78°C until the red colour was discharged. The solution was then purged with nitrogen for 15 min and methyl sulfide (0.5 ml) added. After stirring at room temperature for 30 min the volatiles were removed *in vacuo* to leave a brown solid which was recrystallised from

absolute ethanol to give the *title compound* (56 mg, 50%) as a colourless solid, m.p. 126 - 127°C (Found M^+ 309.1026, $C_{15}H_{19}NSO_4$ requires M, 309.1035); $\nu_{max.}$ ($CHCl_3$ solution) 3010, 1716, 1353, 1165 and 1090 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.68 (2 H, d, *J* 8.3, Ar_2), 7.37 (2 H, d, *J* 8.3, Ar_2), 3.70 (4 H, s, 2 x CH_2NCH_2), 3.1 - 2.9 (4 H, m, 2 x CH_2), 2.46 (3 H, s, CH_3) and 1.9 - 1.7 (4 H, m, 2 x CH_2); δ_C (62.9 MHz; $CDCl_3$) 209.4 (C=O), 144.9 (C), 133.7 (C), 130.3 (CH), 127.4 (CH), 60.4 (2 x CH_2N), 35.5 (2 x CH_2), 23.5 (2 x CH_2) and 21.6 (CH_3); *m/z* (EI) 309 (M^+, 0.2%), 154 (25), 136 (7), 126 (22), 98 (55), 81 (45), 65 (10) and 42(100).

(b) By action of $RuCl_3$/ $NaIO_4$

To 1,3,4,5,6,7-hexahydro-2-(4-toluenesulfonyl)-2*H*-benzo[c]pyrrole (**247**) (277 mg, 1 mmol) was added tetrachloromethane (2 ml), acetonitrile (2 ml) and water (3 ml). Sodium metaperiodate (877 mg, 4.1 mmol) and ruthenium(III) chloride hydrate (5 mg) were added and the reaction mixture stirred vigorously for 24 h. Dichloromethane (10 ml) and water (10 ml) were added and the phases separated. The aqueous phase was extracted twice with dichloromethane (10 ml), and the combined organic phases dried over magnesium sulfate, filtered and concentrated *in vacuo* to a grey solid which was recrystallised from absolute ethanol to give the *title compound* (216 mg, 70%) as an colourless solid, m.p. 125 - 126°C. Identical by ^1H and ^{13}C NMR to the same compound prepared by ozonolysis. Structure confirmed by single crystal X-ray diffraction analysis (**Appendix B**)

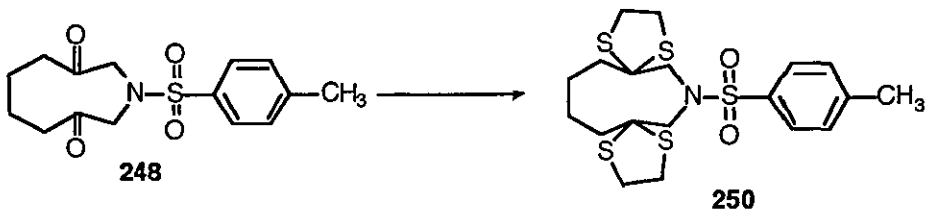
2-(4-Toluenesulfonyl)-1,2,3,4,5,6-hexahydro-7H-cyclopenta[c]pyrid-4-one (**249**)



A solution of 1-(4-toluenesulfonyl)azonane-3,8-dione (**248**) (205 mg, 0.66 mmol) and 4-toluenesulfonic acid (21 mg) in toluene (30 ml) was heated under reflux with removal of water (Dean-Stark) for 5 h. The solvent was removed *in vacuo* and the residue dissolved in dichloromethane (30 ml). The solution was washed with water (3 x 10 ml), dried over magnesium sulfate,

filtered and concentrated *in vacuo* to give a solid which was purified by flash column chromatography (eluent 1:1 light petroleum:diethyl ether) to give the *title compound* (171 mg, 89%) as a colourless solid, m.p. 122-123.5°C (Found: C, 61.85; H, 5.85; N, 4.8. $C_{15}H_{17}NO_3S$ requires C, 61.9; H, 5.8; N, 4.8%); $\nu_{max.}$ ($CHCl_3$ solution) 1679, 1354, 1271, 1168, 759 and 670 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.65 (2 H, d, *J* 8.4, Ar_2), 7.33 (2 H, d, *J* 8.4, Ar_2), 4.0 (2 H, br s, 1-CH_2N), 3.77 (2 H, s, 3-CH_2N), 2.55 (2 H, m, 7-CH_2), 2.45 - 2.35 (2 H, m, 5-CH_2), 2.43 (3 H, s, CH_3) and 1.95 - 1.8 (2 H, m, 6-CH_2); δ_C (62.9 MHz; $CDCl_3$) 189 (C=O), 160.2 (alkene C), 144.1 (aromatic C), 137.1 (aromatic C), 129.7 (aromatic CH), 128.1 (alkene C), 127.5 (aromatic CH), 52.5 (3-CH_2), 45.7 (1-CH_2), 35.5 (7-CH_2), 28.4 (5-CH_2), 21.6 (6-CH_2) and 21.5 (CH_3) (assignments made with the aid of correlation spectra and nOe data; *m/z* (EI) 291 (M^+, 3%), 223 (12), 136 (91), 108 (100), 91 (22) and 79 (19).

1-(4-Toluenesulfonyl)azonane-3,8-dione bis dithioketal (**250**)

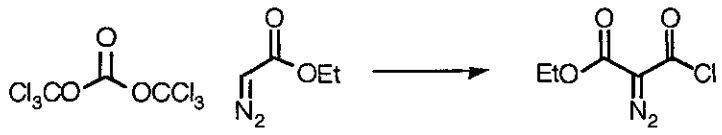


248 **250**

To a solution of 1-(4-toluenesulfonyl)-azonane-3,8-dione (**248**) (100 mg, 0.34 mmol) in dichloromethane (2 ml) was added ethane-1,2-dithiol (94 mg, 1 mmol) and freshly distilled boron trifluoride etherate (10 μl). After stirring for 12 h at room temperature, the solution was diluted with dichloromethane (50 ml) and washed with water (3 x 15 ml). The solution was then dried over magnesium sulfate, filtered and concentrated *in vacuo* to give a buff coloured solid which was recrystallised from ethanol to afford the *title compound* (101 mg, 68%) as colourless crystals, mp. 156-157°C (Found: C, 49.2; H, 5.9; N, 3.0. $C_{19}H_{27}NS_5O_2$ requires C, 49.5; H, 5.9; N, 3.0%); $\nu_{max.}$ (CH_2Cl_2 solution) 2915, 1440, 1348, 1163 and 1031 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.84 (2 H, d, *J* 8.2, Ar_2), 7.31 (2 H, d, *J* 8.2, Ar_2), 3.82 (4 H, s, 2 x CH_2N), 3.25 (8 H, s, 2 x S(CH_2)$_2$S), 2.17 (7 H, m, CH_3 and 2 x CH_2) and 1.27 - 1.22 (4 H, m, (CH_2)$_2$); δ_C (62.9 MHz; $CDCl_3$) 143.6 (C), 135.4 (C), 129.4 (CH), 128.4 (CH), 72.0 (2 x C), 63.0 (2 x CH_2N), 39.2 (4 x CH_2S + 2 x CH_2), 26.1 (2 x CH_2) and 21.6 (CH_3); *m/z* (EI) 461 (M^+, 0.6%), 309 (M - tosyl, 100), 277 (30), 212 (70), 184 (22), 155 (25), 105 (63) and 91 (49).

5.3. Experimental for Chapter 3

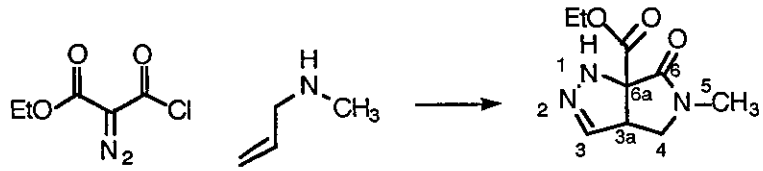
Ethyl 2-diazomalonyl chloride (**252**)



252

A solution of triphosgene (50.4 g, 0.168 mol) in benzene (225 ml) was cooled to 0°C. Pyridine (1.53 ml, 18 mmol) was added, and then ethyl diazoacetate (44 ml, 0.42 mol) was added at such a rate as to keep the temperature of the reaction mixture below 10°C. After warming to 25°C and stirring for 5 h, the solution was filtered through a pad of celite®, concentrated *in vacuo* and distilled under reduced pressure to give the *title compound* (39.57 g, 53%) as a yellow oil, b.p. 63°C at 2 mmHg (lit.[124] 60 - 62°C at 1.5 mmHg); $\nu_{max.}$ (film) 2155, 1765 and 1704 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 4.33 (2 H, q, *J* 7.1, OCH_2) and 1.32 (3 H, t, *J* 7.1, CH_3); δ_C (75.48 MHz; $CDCl_3$) 158.5 (C=O), 153.5 (C=O), 64.1 ($C=N_2$), 62.8 (CH_2) and 14.2 (CH_3).

Ethyl 1,3a,4,5,6,6a-hexahydro-5-methyl-6-oxopyrrolo[3,4-c]pyrazole-6a-carboxylate (**255**)

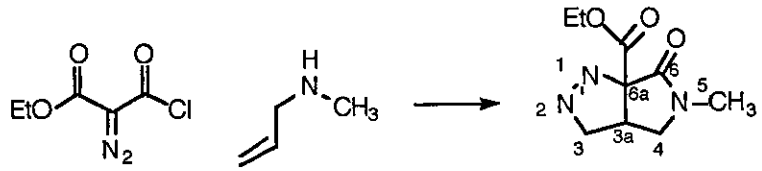


252 **255**

Ethyl 2-diazomalonyl chloride (**252**) (353 mg, 2 mmol) was added to a solution of *N*-methylallylamine (355 mg, 5 mmol) in dichloromethane (10 ml). After stirring at room temperature for 15 h, the solution was washed with 2N hydrochloric acid (2 x 10 ml), water (10 ml) and saturated brine (10 ml), then dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the crude product which was purified by flash column chromatography (eluent ethyl acetate) to give the *title compound* (390 mg, 93%) as a colourless oil (Found: M^+, 211.0956. $C_9H_{13}N_3O_3$ requires M, 211.0957); $\nu_{max.}$ (film) 3487, 3331, 2984, 2940, 2893, 1747, 1697, 1438, 1407, 1278, 1235 and 735 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 6.81 (1 H, d, *J* 0.6, 3-H), 6.68 (1 H, br s, N*H*), 4.40 (2 H, q, *J* 7.1, OCH_2), 4.06 (1 H, 3a-H), 3.91 (1 H, dd, *J* 10.0 and 8.2, 4-H), 3.50 (1

H, dd, *J* 10.0 and 1.9, 4-H), 3.03 (3 H, s, NC*H*$_3$) and 1.42 (3 H, t, *J* 7.1, CH_2CH_3); δ_C (62.9 MHz; $CDCl_3$) 169.0 (C=O), 168.3 (C=O), 143.2 (3-CH), 74.9 (6a-C), 62.6 (CH_2O), 50.9 (4-CH_2), 48.9 (3a-CH), 30.1 (NCH_3) and 14.1 (CH_3); *m/z* (EI) 211 (M^+, 7%), 182 (32), 137 (18), 95 (100), 81 (30), 43 (54) and 42 (38).

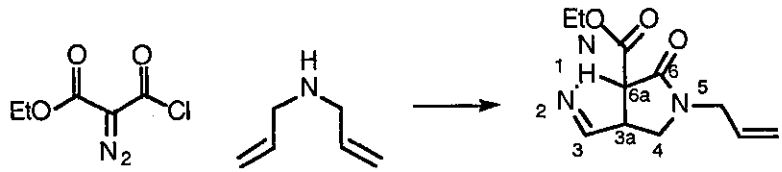
Ethyl 3,3a,4,5,6,6a-hexahydro-5-methyl-6-oxopyrrolo[3,4-c]pyrazole-6a-carboxylate (**254**)



252 **254**

Prepared in an identical manner as **255**, except that after addition of ethyl 2-diazomalonyl chloride (**252**) the reaction was stirred for only 5 min. Identical work-up led to the crude *title compound* (403 mg, 95%) as a colourless oil; δ_H (250 MHz; $CDCl_3$) 5.03 (1 H, dd, *J* 18.7 and 9.0, 3-H), 4.59 (1 H, dd, *J* 18.7 and 4.3, 3-H), 4.35 - 4.25 (2 H, m, OC*H*$_2$), 3.77 (1 H, dd, *J* 10.3 and 7.9, 4-H), 3.12 - 3.0 (2 H, m, 3a-H and 4-H), 2.85 (3 H, s, NC*H*$_3$) and 1.33 (3 H, t, *J* 7.4, CH_2CH_3) in good agreement with literature data.[126]

Ethyl 5-allyl-1,3a,4,5,6,6a-hexahydro-6-oxopyrrolo[3,4-c]pyrazole-6a-carboxylate (**256**)

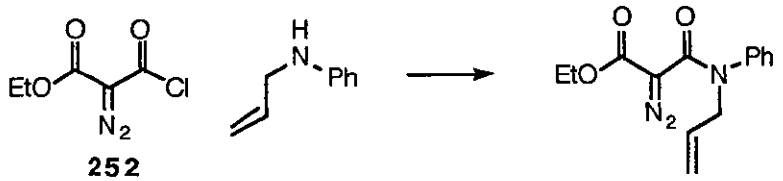


252 **256**

A solution of ethyl 2-diazomalonyl chloride (**252**) (353 mg, 2 mmol) in dichloromethane (2 ml) was added to a solution of diallylamine (388 mg, 4 mmol) in dichloromethane (15 ml). After stirring at room temperature for 5 min, the solution was washed with 2N hydrochloric acid (3 x 20 ml), then with saturated brine (20 ml) and dried over magnesium sulfate. Filtration and concentration *in vacuo* gave a colourless oil which was shown by infrared spectroscopy to contain only a trace of diazo compound. Purification by flash column chromatography (eluent diethyl ether) gave the *title compound* (340

mg, 72%) as a colourless oil (Found: M^+, 237.1108. $C_{11}H_{15}N_3O_3$ requires M, 237.1113); $\nu_{max.}$ (film) 3487, 3327, 2984, 2939, 1751, 1697, 1446, 1278, 1237, 1097, 1067 and 701 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 6.70 (1 H, d, *J* 1.4, 3-*H*), 6.60 (1 H, br s, N*H*), 5.70 (1 H, m, allyl C*H*), 5.21 (2 H, m, allyl CH=CH_2), 4.24 (2 H, q, *J* 7.2, OCH_2), 3.95 (3 H, m, allyl NCH_2 and 3a-*H*), 3.78 (1 H, dd, *J* 10.1 and 7.7, 4-*H*), 3.39 (1 H, dd, *J* 10.1 and 1.9, 4-*H*) and 1.31 (3 H, t, *J* 7.2, CH_3); δ_C (62.9 MHz; $CDCl_3$) 169.2 (C=O), 168.3 (C=O), 143.3 (3-CH), 131.1 (allyl CH), 118.3 (allyl CH_2), 75.0 (6a-C), 62.5 (CH_2O, 49.0 (4-CH_2), 48.4 (3a-CH), 45.4 (NCH_2) and 14.2 (CH_3); *m/z* (EI) 237 (M^+, 3.6%), 208 (33), 135 (19), 95 (100), 68 (30), 43 (62), 41 (69), 39 (43), 29 (36) and 27 (36).

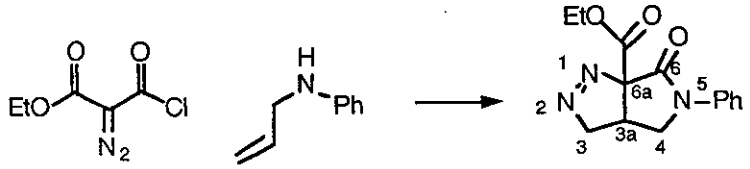
N-Allyl-N-phenyl-2-diazomalonamic acid ethyl ester (**257**)



252 **257**

Ethyl 2-diazomalonyl chloride (**252**) (353 mg, 2 mmol) in dichloromethane (5 ml) was added to a cooled (0°C) solution of *N*-allylaniline (266 mg, 2 mmol) and triethylamine (202 mg, 2 mmol) in dichloromethane (20 ml). After stirring for 5 min, the solution was concentrated *in vacuo* and rapidly purified by flash column chromatography (eluent 9:1 light petroleum:diethyl ether) to give the *title compound* (506 mg, 93%) as a bright yellow oil; $\nu_{max.}$ (film) 3070, 2984, 2938, 2127, 1722, 1696, 1636, 1596, 1497, 1384, 1304, 1111, 753 and 706 cm^{-1}; δ_H ($CDCl_3$) 7.5 - 7.2 (5 H, m, Ar_5), 5.97 - 5.84 (1 H, m, alkene H), 5.22 - 5.12 (2 H, m, alkene H), 4.43 - 4.39 (2 H, m, NCH_2), 4.01 (2 H, q, *J* 7.1, OCH_2) and 1.12 (3 H, t, *J* 7.1, CH_3).

Ethyl 3,3a,4,5,6,6a-hexahydro-6-oxo-5-phenylpyrrolo[3,4-c]pyrazole-6a-carboxylate (**258**)



252 **258**

Ethyl 2-diazomalonyl chloride (**252**) (353 mg, 2 mmol) in dichloromethane (2 ml) was added to a solution of *N*-allylaniline (532 mg, 4 mmol) in dichloromethane (15 ml). After stirring at room temperature for 5 min, the solution was washed with 2N hydrochloric acid (20 ml) and with water (20 ml), then dried over magnesium sulfate, filtered and concentrated *in vacuo*. The intermediate diazo compound was purified by flash column chromatography (eluent 9:1 light petroleum:diethyl ether) and allowed to stand at room temperature for 3 days, during which time cycloaddition occured to afford the *title compound* (507 mg, 78%) as a buff coloured solid; δ_H (250 MHz; $CDCl_3$) 7.37 - 7.14 (5 H, m, Ph), 5.09 (1 H, dd, *J* 18.7 and 9.0, 3-H), 4.66 (1 H, dd, *J* 18.7 and 4.3, 3-H), 4.35 - 4.27 (2 H, m, diastereotopic OCH_2), 4.20 (1 H, dd, *J* 10.4 and 8.2, 4-H), 3.50 (1 H, dd, *J* 10.4 and 2.7, 4-H), 3.16 - 3.10 (1 H, m, 3a-H) and 1.33 (3 H, t, *J* 7.2, CH_2CH_3); δ_C (62.9 MHz; $CDCl_3$) 166.0 (C=O), 162.8 (C=O), 138.0 (C), 129.0 (CH), 125.8 (CH), 120.3 (CH), 86.4 (3-CH_2), 62.9 (CH_2O), 54.7 (6a-C), 51.9 (4-CH_2), 31.2 (3a-CH) and 14.0 (CH_3).

N.B. This compound could not be obtained analytically pure since recrystallisation resulted in thermal nitrogen extrusion, and chromatography resulted in some hydrogen migration.

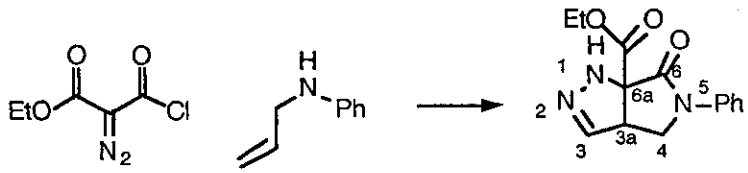
Ethyl 2,5-dihydro-4-methyl-2-oxo-1-phenyl-1H-pyrrole-3-carboxylate (**259**)

258 **259**

Crude ethyl 3,3a,4,5,6,6a-hexahydro-6-oxo-5-phenylpyrrolo[3,4-c]pyrazole-6a-carboxylate (**258**) (480 mg, 1.76 mmol) was dissolved in ethanol (5 ml) with gentle heating. After cooling, the *title compound* (154 mg, 36%) was isolated by filtration as a colourless solid, m.p. 141 - 142°C (Found: M^+, 245.1057. $C_{14}H_{15}NO_3$ requires M, 245.1052); $\nu_{max.}$ (CH_2Cl_2 solution) 3056, 2988, 1743, 1718, 1423, 1068 and 896 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.70 (2 H, m, Ar_2), 7.36 (2 H, t, *J* 7.8, Ar_2), 7.10 (1 H, m, Ar_1), 4.39 (2 H, q, *J* 7.2, OCH_2), 4.34 (2 H, s, NCH_2), 2.42 (3 H, s, CH_3) and 1.39 (3 H, t, *J* 7.2, OCH_2CH_3); δ_C (62.9 MHz; $CDCl_3$) 165.9 (C=O), 162.8 (C=O), 162.3 (C), 138.8 (C), 129.0 (CH), 125.8 (C), 124.1 (CH), 118.6 (CH), 60.9 (CH_2O), 54.7 (CH_2N), 15.2

(CH_3) and 14.3 (CH_3); *m/z* (EI) 245 (M^+, 91%), 199 (100), 173 (41), 143 (50), 104 (51), 77 (68) and 29 (24).

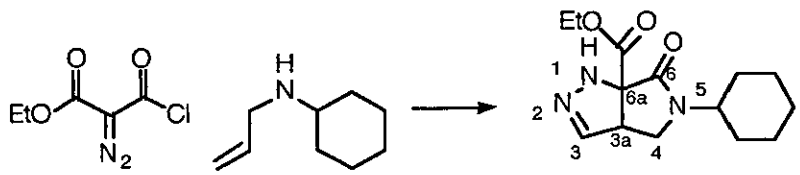
Ethyl 1,3a,4,5,6,6a-hexahydro-6-oxo-5-phenylpyrrolo[3,4-c]pyrazole-6a-carboxylate (**260**)



252 **260**

N-Allylaniline (266 mg, 2 mmol) and triethylamine (202 mg, 2 mmol) were dissolved in dichloromethane (20 ml). A solution of ethyl 2-diazomalonyl chloride (**252**) (353 mg, 2 mmol) in dichloromethane (2 ml) was added dropwise and the solution stirred for 5 min. The solution was then washed with 2N hydrochloric acid (2 x 20 ml) then with water (20 ml), dried over magnesium sulfate and concentrated *in vacuo* to give a yellow oil. Toluene (20 ml) was added and the solution heated under reflux for 17h. The solution was then allowed to cool to room temperature, washed with water, dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography (eluent light petroleum/diethyl ether/ethyl acetate) gave the *title compound* (326 mg, 60%) as a buff coloured solid, m.p. 113 - 114°C (from EtOH) (Found: C, 61.6; H, 5.6; N, 15.3%; $C_{14}H_{15}N_3O_3$ requires C, 61.5; H, 5.5; N, 15.4%); $\nu_{max.}$ (CH_2Cl_2 solution) 3349, 3070, 2990, 2904, 1755, 1704, 1595, 1503, 1410, 1310, 1271 and 746 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.60 - 7.15 (5 H, m, Ph), 6.78 (1 H, br s, N*H*), 6.74 (1 H, d, *J* 0.6, 3-H), 4.31 - 4.21 (3 H, m, O*CH*$_2$ and 4-*H*), 4.03 - 3.99 (1 H, m, 3a-*H*), 3.87 (1 H, dd, *J* 11.6 and 1.9, 4-*H*) and 1.28 (3 H, t, *J* 7.2, *CH*$_3$); δ_C (62.9 MHz; $CDCl_3$) 168.8 (C=O), 167.9 (C=O), 143.2 (3-CH), 138.1 (C), 129.0 (CH), 125.8 (CH), 120.5 (CH), 75.9 (6a-C), 62.6 (CH_2O), 50.1 (4-CH_2), 48.1 (3a-CH) and 14.0 (CH_3); *m/z* (EI) 273 (M^+, 3.5%), 245 (M-N_2, 6.1), 244 (19), 105 (100), 104 (45), 95 (40), 77 (63), 44 (41) and 39 (35).

Ethyl 5-cyclohexyl-1,3a,4,5,6,6a-hexahydro-6-oxopyrrolo[3,4-c]pyrazole-6a-carboxylate (**261**)

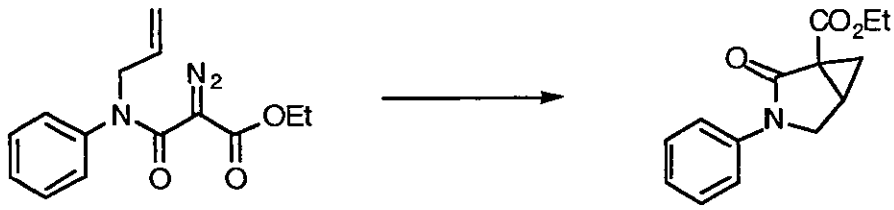


252 **261**

To a solution of *N*-allylcyclohexylamine (278 mg, 2 mmol) and triethylamine (202 mg, 2 mmol) in dichloromethane (10 ml) was added neat ethyl 2-diazomalonyl chloride (353 mg, 2 mmol). After stirring at room temperature for 5 min, the solution was washed with 2N hydrochloric acid (2 x 10 ml), water (10 ml) and saturated brine (10 ml), then dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the crude product which was purified by flash column chromatography (eluent 3:1 light petroleum:diethyl ether) to give the *title compound* (458 mg, 82%) as a viscous clear oil (Found: M+, 279.1585. $C_{14}H_{21}N_3O_3$ requires M, 279.1583); $\nu_{max.}$ (film) 3329, 3293, 2935, 2857, 1754, 1689, 1423, 1288, 1262, 1237, 1097, 1067, 738 and 703 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 6.66 (1 H, s, 3-H), 6.53 (1 H, br s exchangeable with D_2O, N*H*), 4.26 (2 H, q, *J* 7.1, OC*H*$_2$), 3.88 (2 H, m, cyclohexyl NC*H* and 3a-H), 3.72 (1 H, dd, *J* 9.9 and 7.5, 4-H), 3.42 (1 H, dd, *J* 9.9 and 1.6, 4-H), 1.83 - 1.66 (5 H, m, cyclohexyl), 1.43 - 1.27 (4 H, m, cyclohexyl), 1.30 (3 H, t, *J* 7.1, CH_2CH_3) and 1.20 - 1.05 (1 H, m, cyclohexyl); δ_C (62.9 MHz; $CDCl_3$) 168.7 (C=O), 168.1 (C=O), 143.3 (3-CH), 75.3 (6a-C), 62.3 (CH_2O), 51.7 (cyclohexyl N-CH), 48.7 (3a-CH), 44.8 (4-CH_2), 30.2 (cyclohexyl CH_2), 30.1 (cyclohexyl CH_2), 25.33 (cyclohexyl CH_2), 25.31 (cyclohexyl CH_2), 25.28 (cyclohexyl CH_2) and 14.0 (CH_3); *m/z* (EI) 279 (M+, 2.3%), 250 (21), 168 (11), 153 (13), 95 (18), 55 (27), 45 (44), 41 (21), 31 (100) and 27 (34).

Ethyl 3-aza-2-oxo-3-phenylbicyclo[3.1.0]hexane-1-carboxylate (**266**)

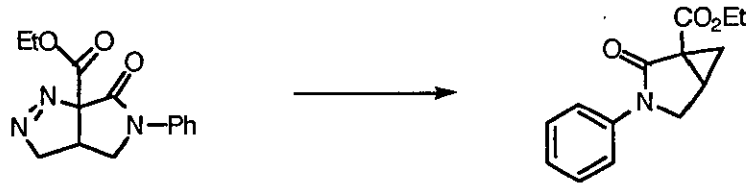
(a) By rhodium(II) catalysed decomposition of **257**



257 **266**

To a solution of *N*-allyl-*N*-phenyl-2-diazomalonamic acid ethyl ester (**257**) (200 mg, 0.73 mmol) in dry dichloromethane (10 ml) was added rhodium(II) acetate (10 mg), and the resulting solution stirred for 40 h. The solvent was removed *in vacuo* and the residue purified by flash column chromatography (eluent 1:1 light petroleum:diethyl ether) to give the *title compound* (10 mg, 6%) as a colourless solid, identical by ^1H and ^{13}C NMR with the same compound prepared by photolysis as described below.

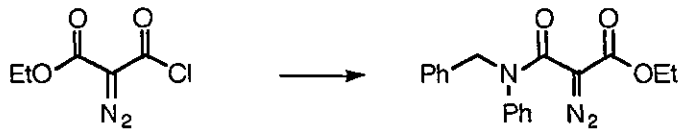
(b) By photolysis of **258**



258 **266**

A solution of ethyl 3,3a,4,5,6,6a-hexahydro-6-oxo-5-phenylpyrrolo[3,4-c]pyrazole-6a-carboxylate (**258**) (511 mg, 1.87 mmol) in 1,4-dioxan (50 ml) was irradiated for 24 h with a medium pressure mercury arc lamp (Southern New England Ultraviolet Company, Model #RPR-208). The solvent was removed *in vacuo* and the residue purified by flash column chromatography (eluent 1:1 light petroleum:diethyl ether) followed by recrystallisation (light petroleum/diethyl ether) to give the *title compound* (107 mg, 23%) as a colourless solid, m.p. 98.5 - 99.5°C (Found: M+, 245.1047. $C_{14}H_{15}NO_3$ requires M, 245.1052); $\nu_{max.}$ (CH_2Cl_2 solution) 3064, 2984, 2891, 1743, 1719, 1600, 1494, 1396, 1321, 1178 and 1096 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.57 (2 H, m, Ar_2), 7.34 (2 H, m, Ar_2), 7.16 (1 H, m, Ar_1), 4.27 (2 H, q, *J* 7.1, OCH_2), 4.10 (1 H, dd, *J* 10.3 and 5.9, one of NCH_2), 3.72 (1 H, d, *J* 10.3, one of NCH_2), 2.48 (1 H, m, CH), 2.03 (1 H, dd, *J* 8.0 and 4.5, one of CH_2), 1.33 (3 H, t, *J* 7.1, CH_3) and 1.27 (1 H, m, one of CH_2); δ_C (62.9 MHz; $CDCl_3$) 168.5 (C=O), 168.4 (C=O), 139.0 (C), 128.9 (CH), 124.7 (CH), 120.0 (CH), 61.6 (CH_2O), 48.4 (CH_2N), 32.8 (C), 22.1 (CH), 20.9 (CH_2) and 14.2 (CH_3); *m/z* (EI) 245 (M^+, 100%), 200 (16), 172 (41), 144 (34), 104 (43), 77 (57), 53 (24) and 29 (12).

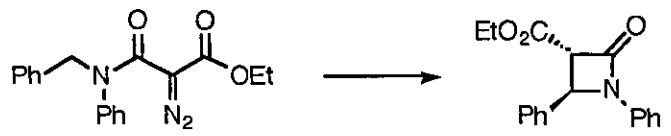
N-Benzyl-N-phenyl-2-diazomalonamic acid ethyl ester(**268**)



252 **268**

Ethyl 2-diazomalonyl chloride (**252**) (706 mg, 4 mmol) was added neat to a solution of *N*-benzylaniline (1.5 g, 8.2 mmol) in dichloromethane (50 ml). After stirring for 10 min at room temperature, the solution was washed with 2N hydrochloric acid (20 ml), water (20 ml) and saturated brine (20 ml), then dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography (eluent 3:1 light petroleum:ether) gave the *title compound* (1.15 g, 89%) as a bright yellow oil which crystallised on standing to a yellow solid, m.p. 78 - 79°C (from light petroleum/diethyl ether) (Found: M^+, 295.1195. $C_{18}H_{17}N_3O_3$ - N_2 requires 295.1208); $\nu_{max.}$ (CH_2Cl_2 solution) 3064, 2983, 2123, 1721, 1633, 1595, 1496, 1295 and 669 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.35 - 7.10 (10 H, m, 2 x Ph), 5.01 (2 H, s, NCH_2), 4.01 (2 H, q, *J* 7.1, OCH_2) and 1.12 (3 H, t, *J* 7.1, CH_3); δ_C (62.9 MHz; $CDCl_3$) 162 (C=O), 161 (C=O), 142.6 (C), 136.9 (C), 129.2 (CH), 128.4 (CH), 128.2 (CH), 127.4 (CH), 126.9 (CH), 126.3 (CH), 61.3 (CH_2O), 54.2 (CH_2N) and 14.1 (CH_3) (diazo carbon not observed); *m/z* (EI) 295 (M^+ - N_2, 4.7%), 249 (10), 222 (10), 103 (20), 91 (100), 86 (28), 84 (43), 77 (36), 65 (19), 49 (88), 44 (29) and 36 (36). Structure confirmed by single crystal X-ray diffraction analysis (**Appendix B**).

Ethyl 2-oxo-1,4-diphenylazetidine-3-carboxylate

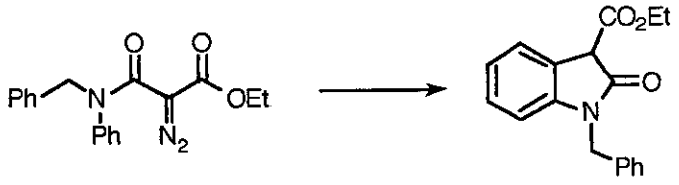


268 **269**

Rhodium(II) acetate (20 mg) was added to a solution of *N*-benzyl-*N*-phenyl-2-diazomalonamic acid ethyl ester (**268**) (250 mg, 0.77 mmol) in dry dichloromethane (40 ml). After stirring at room temperature for 6 days, the solution was concentrated *in vacuo* and purified by flash column chromatography (eluent 9:1 light petroleum:diethyl ether) to give the *title compound* (140 mg, 61%) as a colourless oil which crystallised on standing to

a colourless solid, m.p. 87 - 89°C (Found: C, 73.0; H, 5.8; N, 4.6%; $C_{18}H_{17}NO_3$ requires C, 73.2; H, 5.8; N, 4.8%); $\nu_{max.}$ (film) 2984, 1769, 1729, 1500, 1366, 1321, 1180 and 755 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.40 - 7.05 (10 H, m, 2 x Ph), 5.33 (1 H, d, *J* 2.6, PhC*H*NPh), 4.29 (2 H, q, *J* 7.1, OCH_2), 3.98 (1 H, d, *J* 2.6, COC*H*) and 1.33 (3 H, q, *J* 7.1, CH_3); δ_C (62.9 MHz; $CDCl_3$) 166.3 (C=O), 159.3 (C=O), 137.2 (C), 136.3 (C), 129.3 (CH), 129.1 (CH), 129.0 (CH), 126.2 (CH), 124.4 (CH), 117.2 (CH), 63.6 (CH), 62.1 (CH_2O), 57.5 (CH) and 14.2 (CH_3); *m/z* (EI) 295 (M^+, 20%), 176 (50), 131 (100), 115 (19), 103 (26), 91 (27), 77 (52) and 29 (29).

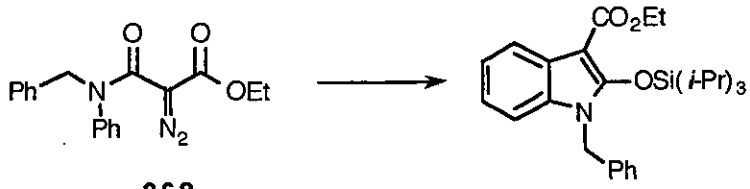
Ethyl 1-benzyl-2-oxoindole-3-carboxylate (**270**)



268 **270**

Rhodium(II) trifluoroacetamide (5 mg) was added to a solution of *N*-benzyl-2-*N*-phenyl-2-diazomalonamic acid ethyl ester (**268**) (150 mg, 0.46 mmol) in dichloromethane (25 ml). After 10 min the solvent was removed *in vacuo* to give the essentially pure *title compound* (135 mg, 99%) as a solid (green due to catalyst); δ_H (250 MHz; $CDCl_3$) 7.33 - 7.00 (8 H, m, Ar_8), 6.70 (1 H, d, *J* 7.8, Ar_1), 5.06 and 4.81 (2 H, AB quartet, *J* 15.7, PhCH_2), 4.52 (1 H, s, C*H*CO_2Et), 4.23 (2 H, m, distereotopic OCH_2) and 1.30 (3 H, t, *J* 7.1, CH_3).

Ethyl 1-benzyl-2-(triisopropylsiloxy)indole-3-carboxylate



268 **271**

Rhodium(II) trifluoroacetamide (1.5 mg) was added to a solution of *N*-benzyl-*N*-phenyl-2-diazomalonamic acid ethyl ester (**268**) (283 mg, 0.88 mmol) in dichloromethane (10 ml). After stirring at room temperature for 10 min, triisopropylsilyl trifluoromethanesulfonate (300 mg, 0.98 mmol) and triethylamine (100 mg, 1 mmol) were added. After a further 5 min, the solution was diluted with dichloromethane (10 ml), washed with water (2 x 10 ml),

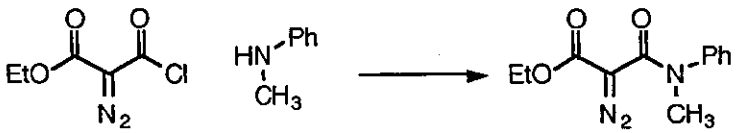
dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography (eluent 99:1 light petroleum:diethyl ether) gave the *title compound* (376 mg, 94%) as a colourless solid, m.p. 77 -78°C (Found: M^+, 451.2547. $C_{27}H_{37}NO_3Si$ requires M, 451.2543); $\nu_{max.}$ (CH_2Cl_2 solution) 3050, 2951, 2878, 1702, 1543, 1470, 1456, 1423, 1218, 1145, and 773 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 8.0 (1 H, m, indole 4-H), 7.23 - 7.01 (8 H, m, Ar_8), 5.27 (2 H, s, PhCH_2), 4.37 (2 H, q, *J* 7.1, OCH_2), 1.50 (3 H, heptet, *J* 7.7, 3 x isopropyl C*H*), 1.44 (3 H, t, *J* 7.1, CH_3CH_2) and 1.08 (18 H, d, *J* 7.7, 6 x isopropyl CH_3); δ_C (62.9 MHz; $CDCl_3$) 164.8 (C=O), 153.2 (C), 136.3 (C), 131.2 (C), 128.6 (CH), 127.4 (CH), 126.1 (CH), 125.2 (C), 121.7 (CH), 121.1 (CH), 120.8 (CH), 109.2 (CH), 89.1 (C), 59.0 (CH_2O), 44.7 (CH_2N), 17.9 (CH_3 of isopropyl), 14.7 (CH_3 of ester) and 14.3 (CH of isopropyl); *m/z* (EI) 451 (M^+, 7.5%), 408 (100), 380 (15), 223 (10), 91 (96) and 59 (15).

Evaluation of other catalysts for the decomposition of ***268***

The catalyst* (1 mol%) was added to a solution of *N*-benzyl-*N*-phenyl-2-diazomalonamic acid ethyl ester (**268**) (100 mg, 0.31 mmol) in dichloromethane (10 ml). When all the diazo compound had been consumed (TLC analysis) the solvent was removed *in vacuo* and the residue examined by ^1H NMR. In this way the ratio of **269**:**270** was determined. Results are recorded in **Table 1**, p.76.

*catalysts used: rhodium(II) trifluoroacetate, rhodium(II) perfluorobutyrate, rhodium(II) acetamide and rhodium(II) perfluorobutyramide.

N-Methyl-N-phenyl-2-diazomalonamic acid ethyl ester (**272**)

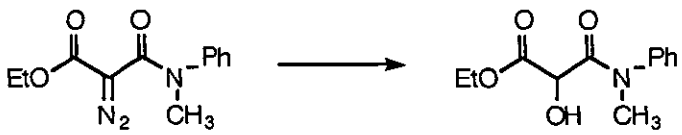


252 **272**

A solution of ethyl 2-diazomalonyl chloride (**252**) (706 mg, 4 mmol) in dichloromethane (5 ml) was added to a solution of *N*-methylaniline (856 mg, 8 mmol) in dichloromethane (30 ml). After stirring at room temperature for 5 min, the solution was washed with 2N hydrochloric acid (50 ml) and water (50 ml), then dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by flash chromatography (eluent 4:1 to 1:1 light petroleum:diethyl

ether) to give the *title compound* (930 mg, 94%) as a yellow solid, m.p. 66 - 67°C (from light petroleum:diethyl ether) (Found: C, 58.2; H, 5.3; N, 17.0%; $C_{12}H_{13}N_3O_3$ requires C, 58.3; H, 5.3; N, 17.0%); $\nu_{max.}$ (CH_2Cl_2 solution) 2984, 2127, 1722, 1629, 1596, 1423, 1370, 1277 and 766 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.40 - 7.20 (5 H, m, Ar_5), 4.02 (2 H, q, *J* 7.1, OCH_2), 3.39 (3 H, s, NCH_3) and 1.13 (3 H, t, *J* 7.1, CH_2CH_3); δ_C (62.9 MHz; $CDCl_3$) 162.0 (C=O), 161.1 (C=O), 144.0 (C), 129.5 (CH), 126.9 (CH), 125.8 (CH), 61.4 (CH_2O), 38.7 (NCH_3) and 14.3 (CH_3) (diazo carbon not observed); *m/z* (EI) 247 (M^+, 1.8%), 219 (21), 173 (60), 147 (55), 146 (72), 118 (53), 105 (34), 91 (35), 77 (100) and 29 (84).

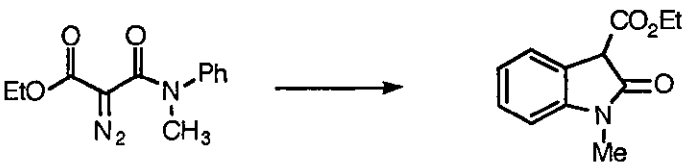
N-Methyl-N-phenyl-2-hydroxymalonamic acid ethyl ester (**273**)



272 **273**

Rhodium(II) acetate (2 mg) was added to a solution of *N*-methyl-*N*-phenyl-2-diazomalonamic acid ethyl ester (**272**) (56 mg, 0.23 mmol) in dichloromethane (5 ml). After stirring at room temperature for 8 days, the solvent was removed *in vacuo* and the residue purified by flash column chromatography (eluent 4:1 to 1:1 light petroleum:diethyl ether) to give the *title compound* (8 mg, 15%) as a colourless oil; δ_H (250 MHz; $CDCl_3$) 7.55 - 7.20 (5 H, m, Ar_5), 4.60 (1 H, d, *J* 8.7, O*H*), 4.09 (2 H, m, OCH_2), 3.96 (1 H, d, *J* 8.7, C*H*OH), 3.36 (3 H, s, NCH_3) and 1.21 (3 H, t, *J* 7.2, CH_3); δ_C (62.9 MHz; $CDCl_3$) 169.5 (C=O), 168.2 (C=O), 141.7 (C), 129.9 (CH), 128.7 (CH), 127.8 (CH), 69.2 (CHOH), 62.0 (CH_2O), 38.2 (CH_3N) and 13.9 (CH_3) in good agreement with literature data.[131]

Ethyl 1-methyl-2-oxoindole-3-carboxylate (**274**)

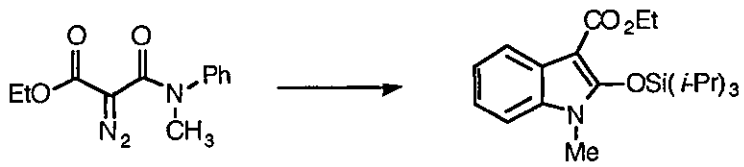


272 **274**

Rhodium(II) trifluoroacetamide (5 mg) was added to a solution of *N*-methyl-*N*-phenyl-2-diazomalonamic acid ethyl ester (**272**) (200 mg, 0.81 mmol) in

dichloromethane (15 ml). After stirring at room temperature for 10 min, the solvent was removed *in vacuo* to afford the essentially pure *title compound* (137 mg, 77%) as a pale green oil (colour due to catalyst); δ_H (250 MHz; $CDCl_3$) 7.35 (2 H, m, Ar_2), 7.08 (1 H, m, Ar_1), 6.80 (1 H, m, Ar_1), 4.42 (1 H, s, $CHCO_2Et$), 4.26 (2 H, m, diastereotopic OCH_2), 3.23 (3 H, s, NCH_3) and 1.28 (3 H, t, *J* 7.1, OCH_2CH_3).

Ethyl 1-methyl-2-(triisopropylsiloxy)indole-3-carboxylate (**275**)



272 **275**

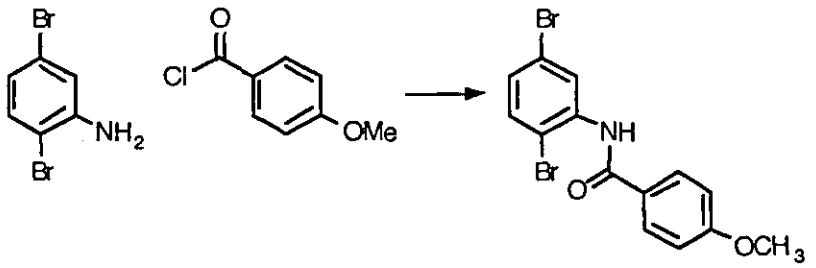
Rhodium(II) trifluoroacetamide (1 mg) was added to a solution of *N*-methyl-*N*-phenyl-2-diazomalonamic acid ethyl ester (**272**) (83 mg, 0.34 mmol) in dichloromethane (5 ml). After stirring at room temperature for 15 min, triisopropylsilyl trifluoromethanesulfonate (107 mg, 0.35 mmol) and triethylamine (35 mg, 0.35 mmol) were added. After 10 min, the solution was washed with water (2 x 10 ml), dried over magnesium sulfate, concentrated *in vacuo* and purified by flash column chromatography (eluent light petroleum) to afford the *title compound* (100 mg, 79%) as a colourless solid, m.p. 56 - 57°C (Found: M^+, 375.2235. $C_{21}H_{33}NO_3Si$ requires M, 375.2230); $\nu_{max.}$ (CH_2Cl_2 solution) 2947, 2868, 1693, 1533, 1473, 1174, 1097 and 755 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 8.03 - 7.99 (1 H, m, Ar_1), 7.22 - 7.16 (3 H, m, Ar_3), 4.36 (2 H, q, *J* 7.1, OCH_2), 3.59 (3 H, s, NCH_3), 1.55 (3 H, heptet, *J* 7.6, $Si(CHMe_2)_3$), 1.42 (3 H, t, *J* 7.1, CH_2CH_3) and 1.16 (18 H, d, *J* 7.6, $Si(CH(CH_3)_2)_3$); δ_C (62.9 MHz; $CDCl_3$) 164.7 (C), 153.2 (C), 131.3 (C), 125.2 (C), 121.5(CH), 120.9 (CH), 120.8 (CH), 108.3 (CH), 89.3 (C), 58.9 (CH_2O), 27.8 (CH_3N), 17.8 (isopropyl CH_3), 14.7 (ester CH_3) and 14.1 (isopropyl CH); *m/z* (EI) 375 (M^+, 8.3%), 332 (100), 304 (27), 218 (8), 173 (11), 131 (17), 103 (19), 73 (18) and 59 (34).

In situ generation and use of rhodium(II) trifluoroacetamide

A solution of rhodium(II) acetate (10 mg, 0.0226 mmol) and 2,2,2-trifluoroacetamide (50 mg, 0.44 mmol) in 1,2-dichloroethane (5 ml) was heated at reflux overnight under a nitrogen atmosphere. The solution was

then allowed to cool to room temperature, and a solution of diazoamide **268** (50 mg, 0.155 mmol) in dichloromethane (10 ml) was added dropwise. After stirring at room temperature for 4 hours all the diazo compound had been consumed (TLC analysis). The solvent was removed *in vacuo* and the reaction mixture examined by ^{1}H NMR (250 MHz; $CDCl_3$). Only the oxindole **270** was detectable in the crude NMR. No β-lactam **269** was formed.

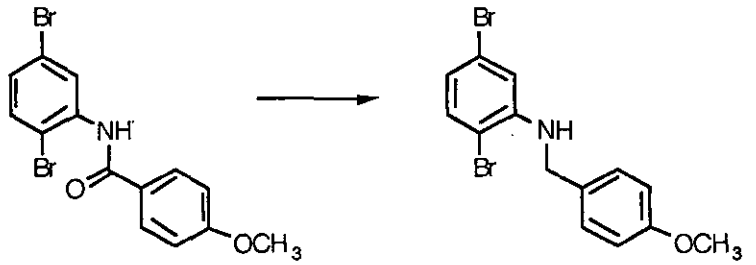
N-(2,5-dibromophenyl)-4-methoxybenzamide (**276**)



276

Triethylamine (2.42 g, 24 mmol) and *p*-anisoyl chloride (4.09 g, 24 mmol) were added to a solution of 2,5-dibromoaniline (5.48 g, 21.8 mmol) in dichloromethane (100 ml). After heating under reflux for 1 h, the solution was allowed to cool to room temperature, washed with saturated sodium bicarbonate solution (50 ml), 2N hydrochloric acid (50 ml) and saturated brine (50 ml), then dried over sodium sulfate, filtered, concentrated *in vacuo* and recrystallised from aqueous ethanol to give the *title compound* (4.21 g, 50%) as a colourless solid, m.p. 122 - 123°C (Found: C, 43.3; H, 2.6; N, 3.6%. $C_{14}H_{11}Br_2NO_2$ requires C, 43.7; H, 2.9; N, 3.6%); $\nu_{max.}$ (CH_2Cl_2 solution) 1684, 1608, 1579, 1504, 1401, 1270, 757 and 707 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 8.78 (1 H, d, *J* 2.4, Ar_1), 8.35 (1 H, br s, N*H*), 7.87 (2 H, d, *J* 8.9, *p*-methoxyphenyl), 7.40 (1 H, d, *J* 8.5, Ar_1), 7.11 (1 H, dd, *J* 8.5 and 2.4, Ar_1), 6.99 (2 H, d, *J* 8.9, *p*-methoxyphenyl) and 3.87 (3 H, s, O*CH*$_3$); δ_C (62.9 MHz; $CDCl_3$ + d_6-DMSO) 164.5 (C=O), 162.8 (*C*-CO), 137.0 (C), 133.0 (CH), 128.9 (CH), 127.8 (CH), 125.9 (C), 124.5 (CH), 121.7 (C), 114.0 (CH), 112.5 (C) and 55.4 (CH_3O); *m/z* (EI) 387 (M^+, 2%), 385 (3), 383 (2), 306 (10), 304 (10), 135 (100), 92 (13) and 77 (19).

N-(2,5-Dibromophenyl)-4-methoxybenzylamine (**277**)

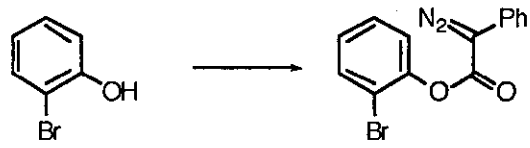


276 **277**

A solution of *N*-(2,5-dibromophenyl)-4-methoxybenzamide (**276**) (2.89 g, 7.5 mmol) in THF (40 ml) was added to a suspension of lithium aluminium hydride (0.285 g, 7.5 mmol) in THF (5 ml). The solution was heated under reflux for 24 h, then allowed to cool to room temperature and carefully quenched with water (50 ml). Dichloromethane (50 ml) was added and the phases separated. The aqueous phase was extracted with dichloromethane (2 x 50 ml), and the combined organic phases washed with saturated sodium bicarbonate solution (50 ml), dried over sodium sulfate, filtered and concentrated *in vacuo* to give the crude product which was recrystallised from aqueous ethanol to afford the *title compound* (1.952 g, 70%) as a colourless solid, m.p. 66 - 67°C (Found: C, 45.3; H, 3.2; N, 3.6. $C_{14}H_{13}Br_2NO$ requires C, 45.3; H, 3.5; N, 3.8); $\nu_{max.}$ (CH_2Cl_2 solution) 3408 (br, NH), 1611, 1587, 1512, 1248, 1016 and 829 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.28 (2 H, d, *J* 8.6, *p*-methoxyphenyl), 7.27 (1 H, d, *J* 8.4, 3-H), 6.91 (2 H, d, *J* 8.6, *p*-methoxyphenyl), 6.75 (1 H, d, *J* 2.2, 6-H), 6.69 (1 H, dd, *J* 8.4 and 2.2, 4-H), 4.67 (1 H, br m, NH), 4.28 (2 H, br d, *J* 5.3, NCH_2) and 3.83 (3 H, s, OCH_3); δ_C (62.9 MHz; $CDCl_3$) 159.0 (C), 145.8 (C), 133.2 (CH), 129.7 (C), 128.6 (CH), 122.2 (C), 120.5 (CH), 114.2 (CH), 114.1 (CH), 108.0 (C), 55.2 (CH_3O) and 47.4 (CH_2N); *m/z* (EI) 371 (M^+, 7%), 135 (8) and 121 (100).

5.4. Experimental for Chapter 4

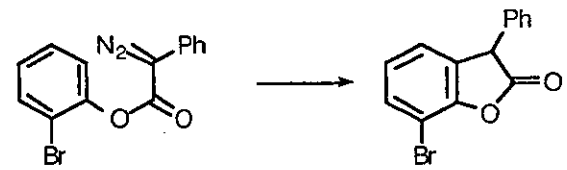
2-Bromophenyl 2-diazo-2-phenylacetate (**287**)



287

Benzoylformic acid (2.33 g, 15.5 mmol) and 2-bromophenol (2.6 g, 15 mmol) were dissolved in dichloromethane (50 ml). The solution was cooled to 0°C and dicyclohexylcarbodiimide (3.09 g, 15 mmol) was added, and the solution stirred at room temperature for 1 h. The solution was filtered, concentrated *in vacuo* and purified by flash column chromatography (eluent 4:1 light petroleum:diethyl ether) to give the intermediate α-ketoester (3.447 g, 75%) as a colourless oil. A solution of this α-ketoester (4 g, 13.1 mmol) and 4-toluenesulfonylhydrazide (2.44 g, 13.1 mmol) in toluene (100 ml) was heated under reflux with removal of water (Dean-Stark) for 3 h. The toluene was then removed *in vacuo* and dichloromethane (100 ml) added. Triethylamine (1.5 ml, 15 mmol) was added and the solution stirred for 5 min at room temperature. The organic solution was then washed with water (50 ml) and saturated brine (50 ml), then dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by flash column chromatography (eluent 99:1 light petroleum:diethyl ether) to give the *title compound* (2.62 g, 47% from 2-bromophenol) as a yellow oil which solidified to a waxy yellow solid, m.p. 54 - 55°C (Found: M^+, 315.9849; $C_{14}H_9{}^{79}BrN_2O_2$ requires M, 315.9848); $\nu_{max.}$ (film) 2095, 1725, 1472, 1212 and 1129 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.63 (1 H, dd, *J* 8.0 and 1.5), 7.57 - 7.52 (2 H, m), 7.45 - 7.36 (2 H, m), 7.34 (1 H, dd, *J* 7.1 and 1.5), 7.31 - 7.19 (2 H, m) and 7.14 (1 H, ddd, *J* 8.0, 7.1 and 1.9); δ_C (62.9 MHz; $CDCl_3$) 162.4 (C=O), 147.8 (C), 133.4 (CH), 129.1 (CH), 128.5 (CH), 127.5 (CH), 126.3 (CH), 124.8 (C), 124.2 (CH), 124.1 (CH) and 116.4 (C) (diazo carbon not observed); *m/z* (EI) 318 (^{81}Br-M^+, 2%), 316 (^{79}Br-M^+, 2), 261 (12), 259 (12), 209 (42), 105 (100), 89 (79), 77 (55), 63 (43) and 28 (44).

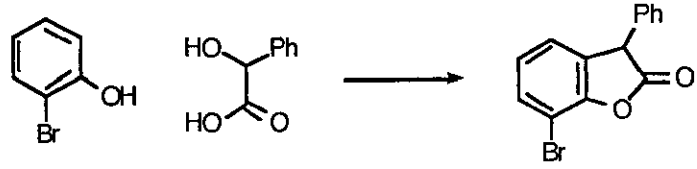
Rhodium(II) catalysed decomposition of ***287***



287 **288**

A solution of 2-bromophenyl 2-diazo-2-phenylacetate (**287**) (1 g, 3.15 mmol) in dichloromethane (25 ml) was added over 20 min to a refluxing suspension of rhodium(II) perfluorobutyramide (5 mg) in dichloromethane (15 ml). The solution was heated under reflux for a further 20 min, then allowed to cool to room temperature and concentrated *in vacuo*. Extensive flash column chromatography (eluent 9:1 light petroleum:diethyl ether) led to an impure sample of 7-bromo-3-phenylbenzofuran-2-one (**288**) (180 mg, 20%). Spectroscopic data for this compound are given below.

7-Bromo-3-phenylbenzofuran-2-one (**288**)

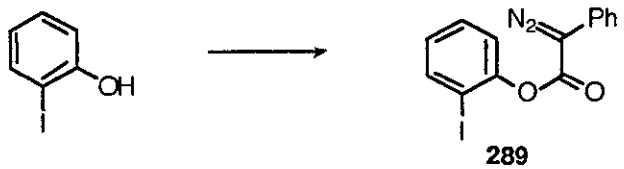


288

A mixture of 2-bromophenol (21.12 g, 122 mmol) and mandelic acid (18.54 g, 122 mmol) were cooled to 0°C. 70% Sulfuric acid (30 ml) was added at 0°C, and the resulting dark solution heated to 110°C for 1 h. After cooling to room temperature, water (50 ml) and dichloromethane (50 ml) were added. The phases were separated and the organic phase washed thoroughly with saturated aqueous sodium hydrogen carbonate solution. The organic phase was then dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by flash column chromatography (eluent 9:1 light petroleum:diethyl ether) to afford the *title compound* (5.106 g, 15%) as a colourless solid, m.p. 82 - 83°C (from light petroleum/diethyl ether) (Found: C, 58.4; H, 2.9%. $C_{14}H_9BrO_2$ requires C, 58.2; H, 3.1%); $\nu_{max.}$ (CH_2Cl_2 solution) 1818, 1446, 1065 and 1048 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.52 (1 H, dt, *J* 7.9 and 1.2, Ar_1), 7.4 - 7.3 (3 H, m, Ar_3), 7.25 - 7.2 (2 H, m, Ar_2), 7.14 (1 H, dt, *J* 7.5 and 1.2, Ar_1), 7.06 (1 H, t, *J* 7.9, Ar_1) and 4.98 (1 H, s, C*H*Ph); δ_C (62.9 MHz; $CDCl_3$) 173.3 (C=O), 151.7 (C), 134.4 (C), 132.7 (CH), 129.2 (CH), 128.4 (CH), 128.3

(C), 128.2 (CH), 125.6 (CH), 124.1 (CH), 103.6 (C) and 50.6 (*C*HPh); *m/z* (EI) 290 (^{81}Br-M$^+$, 18%), 288 (^{79}Br-M$^+$, 18), 261 (43), 259 (42), 210 (54), 181 (80), 152 (48), 84 (77), 64 (76) and 49 (100).

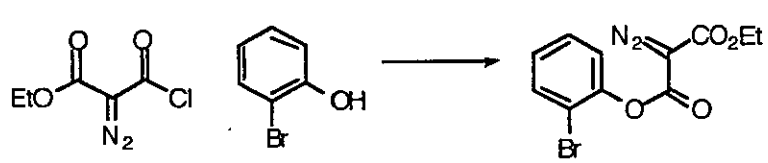
2-Iodophenyl 2-diazo-2-phenylacetate (**289**)



289

Dicyclohexylcarbodiimide (2.06 g, 10 mmol) was added to a cooled (0°C) solution of benzoylformic acid (1.5 g, 10 mmol) and 2-iodophenol (2.2 g, 10 mmol) in dichloromethane (20 ml). After stirring at room temperature for 1 h, the solution was filtered, concentrated *in vacuo* and purified by flash column chromatography (eluent 9:1 light petroleum:diethyl ether) to give the intermediate α-ketoester (3.4 g, 97%) as a colourless oil. To a sample of this compound (1 g, 2.8 mmol) in toluene (15 ml) was added 4-toluenesulfonyl hydrazide (0.53 g, 2.8 mmol) and the solution heated under reflux with separation of water (Dean-Stark) for 3 h. After cooling to room temperature, triethylamine (5 drops) was added and the solution stirred for 30 min. The solvent was removed *in vacuo* and the residue purified by flash column chromatography (eluent light petroleum to 9:1 light petroleum:diethyl ether) to give the *title compound* (666 mg, 64%) as a waxy yellow solid, m.p. 79 - 81°C (Found: M$^+$, 363.9714; $C_{14}H_9IN_2O_2$ requires M, 363.9711); $\nu_{max.}$ (CH_2Cl_2 solution) 2094, 1726, 1207, 1126 and 730 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.86 (1 H, dd, *J* 8.0 and 1.5), 7.59 - 7.54 (2 H, m), 7.46 - 7.36 (3 H, m), 7.29 - 7.19 (2 H, m) and 7.00 (1 H, ddd, *J* 9.1, 7.5 and 1.6); δ_C (62.9 MHz; $CDCl_3$) 162.2 (C=O), 150.5 (C), 139.4 (CH), 129.3 (CH), 129.0 (CH), 127.7 (CH), 126.2 (CH), 124.7 (C), 124.0 (CH), 123.3 (CH) and 90.4 (C-I) (diazo carbon not observed); *m/z* (EI) 364 (M$^+$, 2.8%), 336 (16), 307 (22), 220 (60), 209 (49), 105 (100), 98 (52), 77 (54) and 63 (40).

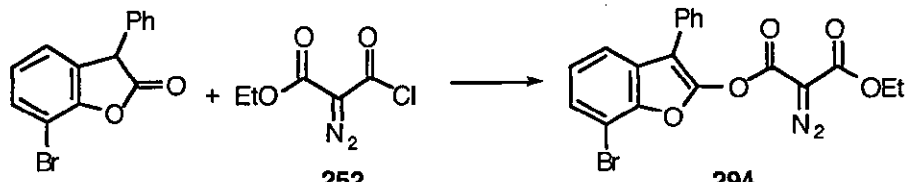
Ethyl 2-bromophenyl 2-diazomalonate (**291**)



252 **291**

2-Bromophenol (692 mg, 4 mmol) and triethylamine (404 mg, 4 mmol) were dissolved in dichloromethane (2 ml). This solution was added dropwise to a solution of ethyl 2-diazomalonyl chloride (**252**) (706 mg, 4 mmol) in dichloromethane (10 ml). After stirring for 30 min, the solution was washed with 2N hydrochloric acid (15 ml), water (15 ml) and saturated brine (15 ml). The solution was then dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by flash column chromatography (eluent 9:1 light petroleum:diethyl ether) to give the *title compound* (934 mg, 75%) as a yellow oil (Found: M^+, 313.9736. $C_{11}H_9{}^{81}BrN_2O_4$ requires M, 313.9727); $\nu_{max.}$ (film) 2144, 1774, 1712, 1333, 1212, 1045 and 754 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.56 (1 H, dd, *J* 8.0, 1.2, Ar_1), 7.30 - 7.20 (2 H, m, Ar_2), 7.09 (1 H, t, *J* 8.0, Ar_1), 4.32 (2 H, q, *J* 7.1, OCH_2) and 1.31 (3 H, t, *J* 7.1, CH_3); δ_C (62.9 MHz; $CDCl_3$) 160.4 (C=O), 158.0 (C=O), 147.2 (C), 133.3 (CH), 128.4 (CH), 127.6 (CH), 123.9 (CH), 115.9 (C-Br), 62.0 (CH_2O) and 14.2 (CH_3) (diazo carbon not observed, even with 3 sec relaxation delay); *m/z* (EI) 314 (M^+, 1.9%), 312 (1.9), 286 (1), 284 (1), 174 (18), 141 (60), 49 (73) and 29 (100).

7-Bromo-3-phenylbenzofuran-2-yl ethyl 2-diazomalonate (**294**)

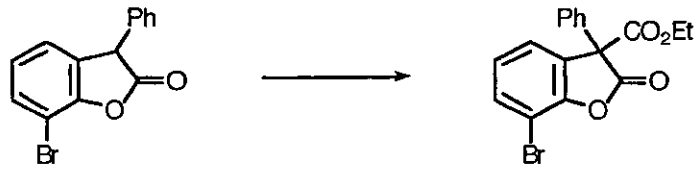


288 **252** **294**

7-Bromo-3-phenylbenzofuran-2-one (**288**) (80 mg, 0.28 mmol) was dissolved in dichloromethane (5 ml). A solution of ethyl 2-diazomalonyl chloride (**252**) (71 mg, 0.4 mmol) in dichloromethane (1 ml) was added, followed by triethylamine (3 drops). After 2 min, the solution was washed with water (5 ml) and saturated sodium bicarbonate solution (5 ml), then dried over sodium sulfate, filtered and concentrated *in vacuo* to give the crude product which was purified by flash column chromatography (eluent 9:1 light petroleum:diethyl ether) to give the *title compound* (93 mg, 78%) as a pale yellow oil (Found: M^+, 401.9919. $C_{19}H_{13}{}^{81}BrN_2O_5$ - N_2 requires M, 401.9927); $\nu_{max.}$ (film) 2150, 1786, 1735, 1322, 1201 and 1028 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.64 (1 H, dd, *J* 7.9 and 1.1, Ar_1), 7.58 - 7.39 (6 H, m, Ar_6), 7.19 (1 H, t, *J* 7.9, Ar_1), 4.37 (2 H, q, *J* 7.1, OCH_2) and 1.37 (3 H, t, *J* 7.1, CH_3); δ_C (62.9 MHz; $CDCl_3$) 178.5 (C=O), 159.8 (C=O), 148.4 (C), 147.3 (C), 129.5 (C), 129.0 (CH), 128.9 (C), 128.1 (CH), 127.9 (CH), 127.7 (CH), 124.7 (CH),

119.3 (CH), 107.1 (C), 104.0 (C), 62.4 (CH_2O), 14.3 (CH_3) (diazo carbon not observed); *m/z* (EI) 402 (0.1%), 400 (0.1), 289 (4), 287 (3), 141 (14), 41 (15) and 29 (100).

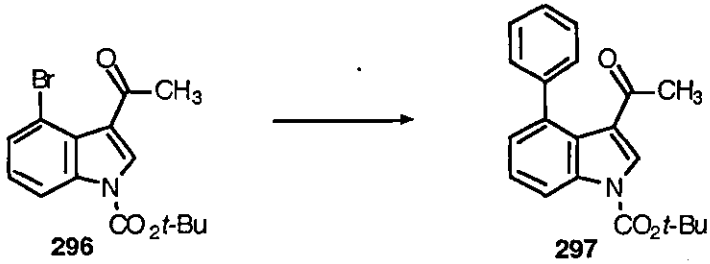
Ethyl 7-bromo-2-oxo-3-phenylbenzo[b]furan-3-carboxylate (**295**)



288 **295**

7-Bromo-3-phenylbenzofuran-2-one (**288**) (500 mg, 1.73 mmol) was dissolved in dichloromethane (30 ml). Ethyl chloroformate (250 mg, 2.3 mmol) and triethylamine (200 mg, 2 mmol) were added, and the solution stirred for 5 min. 4-Dimethylaminopyridine (5 mg) was added to give an intense purple solution which faded to colourless over 15 h. The solution was diluted with dichloromethane (20 ml) and washed with water (50 ml) and saturated brine (50 ml), then dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by flash column chromatography (eluent 4:1 light petroleum:diethyl ether) to give the *title compound* (597 mg, 96%) as a colourless solid (Found: M^+, 361.9987. $C_{17}H_{13}{}^{81}BrO_4$ requires M, 361.9978); $\nu_{max.}$ (CH_2Cl_2 solution) 2977, 1822, 1740, 1444, 1239, 969 and 739 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.61 (1 H, dd, *J* 8.1 and 1.2, 4-C*H* or 6-C*H*), 7.46 (1 H, dd, *J* 7.6 and 1.2, 4-C*H* or 6-C*H*), 7.40 - 7.30 (5 H, m, Ph), 7.18 (1 H, t, *J* 7.4, 5-C*H*), 4.35 - 4.19 (2 H, m, OCH_2) and 1.25 (3 H, t, *J* 7.1, CH_3); δ_C (62.9 MHz; $CDCl_3$) 169.9 (C=O), 167.1 (C=O), 151.6 (C), 134.1 (C), 133.8 (CH), 129.01 (CH), 128.98 (CH), 127.4 (CH), 126.9 (C), 125.7 (CH), 125.1 (CH), 104.0 (C), 63.3 (CH_2O) and 13.9 (CH_3); *m/z* (EI) 362 (^{81}Br-M^+, 10%), 360 (^{79}Br-M^+, 10), 318 (14), 316 (14), 290 (96), 288 (100), 261 (44), 259 (42), 209 (32), 180 (45), 152 (90) and 29 (66).

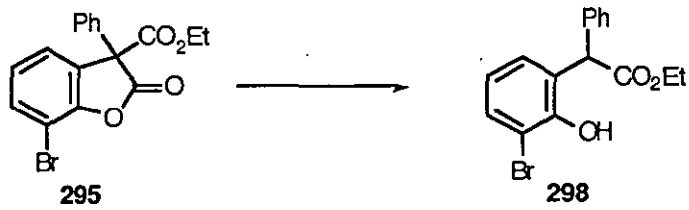
t-Butyl 3-acetyl-4-phenylindole-1-carboxylate (**297**)



296 **297**

t-Butyl 3-acetyl-4-bromoindole[156] (1.014 g, 3 mmol) was dissolved in dimethoxyethane (50 ml) and the solution degassed under reduced pressure. Tetrakis(triphenylphosphine)palladium(0) (100 mg) was added and the resulting yellow solution further degassed, then stirred at room temperature for 10 min. 2M Aqueous sodium carbonate solution (6 ml) was then added followed by benzeneboronic acid (550 mg, 4.5 mmol). The solution was then degassed and heated under reflux for 14 h, then cooled and partitioned between diethyl ether (100 ml) and water (100 ml). The organic phase was washed with saturated sodium bicarbonate solution (50 ml), water (50 ml) and finally saturated brine (50 ml), then dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by flash column chromatography (eluent 3:2 light petroleum:dichloromethane) to give the *title compound* (667 mg, 66%) as a waxy solid, m.p. 112 - 113°C (Found: M^+, 335.1515; $C_{21}H_{21}NO_3$ requires M, 335.1521); $\nu_{max.}$ (CH_2Cl_2 solution) 2958, 1744, 1684, 1420, 1370, 1255, 1151 and 757 cm^{-1}; δ_H (250 MHZ; $CDCl_3$) 8.25 (1 H, dd, *J* 8.3 and 1.0, 5-H or 7-H), 8.03 (1 H, s, 2-H), 7.48 - 7.36 (6 H, m, Ar_6), 7.29 (1 H, dd, *J* 7.5 and 1.0, 5-H or 7-H), 1.90 (3 H, s, $COCH_3$) and 1.70 (9 H, s, *t*-Bu); δ_C (62.9 MHz; $CDCl_3$) 195.9 (C=O), 149.0 (C=O), 142.0 (C), 136.4 (C), 136.2 (C), 130.1 (CH), 128.5 (CH), 128.4 (CH), 127.3 (CH), 125.4 (CH), 125.3 (CH), 124.8 (C), 124.1 (C), 114.1 (CH), 85.0 (CMe_3), 29.3 (CH_3) and 28.1 ($C(CH_3)_3$); *m/z* (EI) 335 (M^+, 4.1%), 279 (13), 235 (13), 220 (33), 57 (100), 41 (41) and 29 (19).

Ethyl 2-(3-bromo-2-hydroxyphenyl)-2-phenylacetate (**298**)



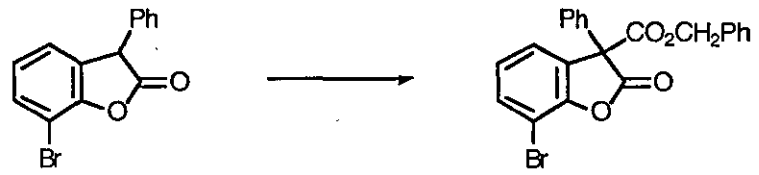
295 **298**

From the attempted Suzuki reaction between ethyl 7-bromo-2-oxo-3-phenylbenzo[b]furan-3-carboxylate (**295**) and benzeneboronic acid as follows:

A solution of ethyl 7-bromo-2-oxo-3-phenylbenzo[b]furan-3-carboxylate (**295**) (100 mg, 0.28 mmol) in dimethoxyethane (8 ml) was degassed. Tetrakis(triphenylphosphine)palladium(0) (30 mg) was added and the solution further degassed. After stirring for 10 min, a 2M aqueous solution of sodium

carbonate (0.5 ml, 1 mmol) was added followed by benzeneboronic acid (65 mg, 0.5 mmol), and the solution was degassed then stirred under an atmosphere of nitrogen for 150 h. Dichloromethane (50 ml) was added and the solution washed with water (50 ml) and saturated brine (50 ml), then dried over magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography (eluent 9:1 light petroleum:dichloromethane) afforded the *title compound* (53 mg, 57%) as a colourless oil (Found: M^+, 336.0184. $C_{16}H_{15}{}^{81}BrO_3$ requires M, 336.0185); $\nu_{max.}$ (film) 3520 (br, OH), 1735, 1450, 1240, 1175 and 700 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.42 - 7.27 (6 H, m, Ar_6), 7.05 (1 H, dd, *J* 7.7 and 1.2, Ar_1), 6.77 (1 H, t, *J* 7.7, Ar_1), 6.72 (1 H, s, exchangeable with D_2O, O*H*), 5.30 (1 H, s, C*H*CO_2Et), 4.25 (2 H, qd, *J* 7.1 and 0.8, OC*H*$_2$) and 1.28 (3 H, t, *J* 7.1, C*H*$_3$); δ_C (62.9 MHz; $CDCl_3$) 172.6 (C=O), 150.0 (C), 137.0 (C), 131.1 (CH), 129.2 (CH), 128.84 (C), 128.79 (CH), 128.6 (CH), 127.4 (CH), 121.4 (CH), 110.9 (C), 61.4 (CH_2O), 52.1 (CH) and 14.1 (CH_3); m/z (EI) 336 (^{81}Br-M^+, 16%), 334 (^{79}Br-M^+, 16), 290 (26), 288 (26), 263 (64), 261 (100), 181 (53), 152 (58), 76 (24) and 29 (38).

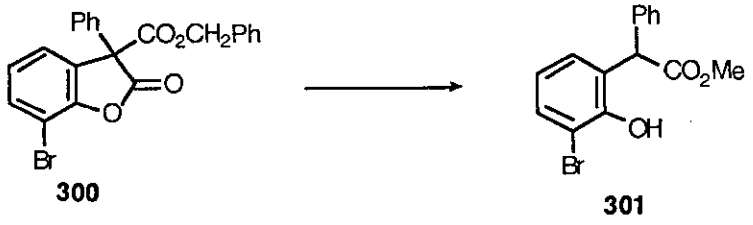
Benzyl 7-bromo-2-oxo-3-phenylbenzo[b]furan-3-carboxylate (**300**)



288 **300**

7-Bromo-3-phenylbenzofuran-2-one (**288**) (150 mg, 0.52 mmol) was dissolved in dichloromethane (12 ml). Benzyl chloroformate (97 mg, 0.57 mmol) and triethylamine (60 mg, 0.6 mmol) were added. After stirring at room temperature for 5 min, 4-dimethylaminopyridine (5 mg) was added and the solution stirred for 10 min. The solution was diluted with dichloromethane (20 ml), washed with water (20 ml) and saturated brine (20 ml), then dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography (eluent 4:1 light petroleum:diethyl ether) gave the unstable *title compound* (178 mg, 81%) as a colourless oil; $\nu_{max.}$ (film) 3031, 1820, 1748, 1444, 1218, 911 and 738 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.7 - 7.0 (13 H, m, Ar_{13}) and 5.26 and 5.22 (2 H, AB quartet, *J* 12.3, CH_2O).

Methyl 2-(3-bromo-2-hydroxyphenyl)-2-phenylacetate (**301**)



300 **301**

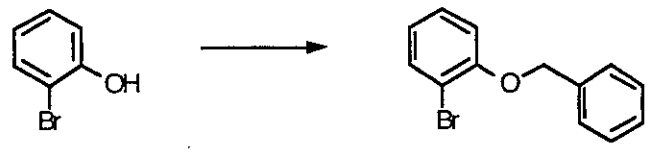
Benzyl 7-bromo-2-oxo-3-phenylbenzo[b]furan-3-carboxylate (**300**) (79 mg, 0.19 mmol) was dissolved in methanol (5 ml). 10% Palladium-on-carbon (5 mg) was added and the solution stirred under an atmosphere of hydrogen for 2 h. The solution was then filtered, concentrated *in vacuo*, and purified by flash column chromatography to give the *title compound* (6 mg, 10%) as a colourless oil; δ_H (250 MHz; $CDCl_3$) 7.30 - 7.09 (7 H, m, Ar_6 + OH), 6.92 - 6.87 (2 H, m, Ar_2), 5.16 (1 H, s, C*H*Ph) and 3.82 (3 H, s, OCH_3).

3-Benzyl-7-bromo-3-phenylbenzofuran-2-one (**302**)

300 **302**

A sample of benzyl 7-bromo-2-oxo-3-phenylbenzo[b]furan-3-carboxylate (**300**) (731 mg, 1.73 mmol) was allowed to stand at room temperature for 48 h, during which time the compound solidified. Purification by flash column chromatography (eluent 4:1 light petroleum:diethyl ether) gave the *title compound* (314 mg, 43%) as a colourless solid, m.p. 102 - 103°C (Found: C, 66.6; H, 3.7%. $C_{21}H_{15}BrO_2$ requires C, 66.5; H, 4.0%); $\nu_{max.}$ (CH_2Cl_2 solution) 1806, 1442, 1068, 1050 and 698 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.51 - 7.46 (2 H, m, Ar_2), 7.41 - 7.31 (4 H, m, Ar_4), 7.13 - 7.01 (5 H, m, Ar_5), 6.87 - 6.82 (2 H, m, Ar_2) and 3.70 and 3.35 (2 H, AB quartet, *J* 13.2, CH_2Ph); δ_C (62.9 MHz; $CDCl_3$) 175.9 (C=O), 150.9 (C), 137.8 (C), 134.3 (C), 132.4 (CH), 130.5 (C), 129.9 (CH), 128.9 (CH), 128.3 (CH), 128.1 (CH), 127.4 (CH), 126.9 (CH), 124.9 (CH), 124.8 (CH), 103.6 (C-Br), 58.4 (C) and 45.0 (CH_2); *m/z* (EI) 380 (^{81}Br-M$^+$, 4%), 378 (^{79}Br-M$^+$, 4), 289 (3), 287 (3), 152 (9) and 91 (100).

2-(Benzyloxy)bromobenzene (**303**)



303

Potassium carbonate (13.8 g, 0.1 mol) was added to a solution of 2-bromophenol (17.3 g, 0.1 mol) and benzyl bromide (17.1 g, 0.1 mol), and the resulting suspension heated under reflux for 3 h. The solvent was removed *in vacuo* and the residue partitioned between water (100 ml) and dichloromethane (100 ml). The organic phase was extracted twice with dichloromethane (100 ml), and the combined organic phases dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by short path distillation to give the *title compound* (24.0 g, 91%) as a colourless liquid, b.p. 180°C at 2 mmHg (Found: M^+, 261.9985. $C_{13}H_{11}{}^{79}BrO$ requires M, 261.9994); $\nu_{max.}$ (film) 3064, 3033, 1587, 1479, 1278, 1248, 1053, 1031 and 747 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.58 (1 H, dd, *J* 7.9 and 1.6, Ar_1), 7.51 (2 H, m, Ar_2), 7.48 - 7.21 (3 H, m, Ar_3), 7.29 (1 H, m, Ar_1), 6.95 (1 H, dd, *J* 8.2 and 1.4, Ar_1), 6.86 (1 H, td, *J* 7.6 and 1.4, Ar_1) and 5.17 (2 H, s, OCH_2); δ_C (62.9 MHz; $CDCl_3$) 154.9 (C), 136.4 (C), 133.3 (CH), 128.5 (CH), 128.3 (CH), 127.8 (CH), 126.9 (CH), 122.0 (CH), 113.8 (CH), 112.4 (C) and 70.6 (CH_2O). *m/z* (EI) 264 (^{81}Br-M^+, 10%), 262 (^{79}Br-M^+, 10), 91 (100) and 65 (11).

2-Benzyloxybenzeneboronic acid (**304**)

303 **304**

A solution of 2-(benzyloxy)bromobenzene (**303**) (7.89 g, 30 mmol) in THF (200 ml) was cooled to -78°C under an atmosphere of nitrogen. A 1.7M solution of *tert*-butyllithium in pentane (23 ml, 40 mmol) was added at such a rate as to keep the internal temperature below -70°C. After stirring at -78°C for 30 min, trimethylborate (20 ml, excess) was added rapidly in one portion. After stirring for a further 30 min, the solution was allowed to warm to room temperature, stirred for a further 1 h, then poured into 0.001N hydrochloric acid (300 ml). The mixture was extracted with dichloromethane (2 x 100 ml),

and the combined organic phases dried over sodium sulfate. The solution was then filtered, concentrated *in vacuo* and recrystallised (light petroleum/dichloromethane with 1 drop of water) to give the *title compound* (3.65 g, 53%) as a colourless solid, m.p. 91 - 92°C (Found: M^+, 228.0969. $C_{13}H_{13}BO_3$ requires M, 228.0958) ; $\nu_{max.}$ (CH_2Cl_2 solution) 3389 (br, OH), 1601, 1453, 1344, 1002 and 694 cm^{-1}; δ_H (250 MHz; $CDCl_3/d_6$-DMSO) 7.88 (1 H, dd, *J* 7.2 and 1.7, Ar_1), 7.45 - 7.30 (6 H, m, Ar_6), 7.04 - 6.95 (2 H, m, Ar_2), 6.62 (2 H, s, exchangeable with D_2O, 2 x O*H*) and 5.11 (2 H, s, OCH_2); δ_C (62.9 MHz; $CDCl_3/d_6$-DMSO) 163.8 (C), 137.0 (CH), 135.9 (C), 132.8 (CH), 128.9 (CH), 128.5 (CH), 127.7 (CH), 121.5 (CH), 111.3 (CH) and 70.4 (CH_2O) (C-B not observed); *m/z* (EI) 228 (M^+, 7%), 184 (7), 91 (100) and 65 (10).

2-Benzyloxybiphenyl (**305**)

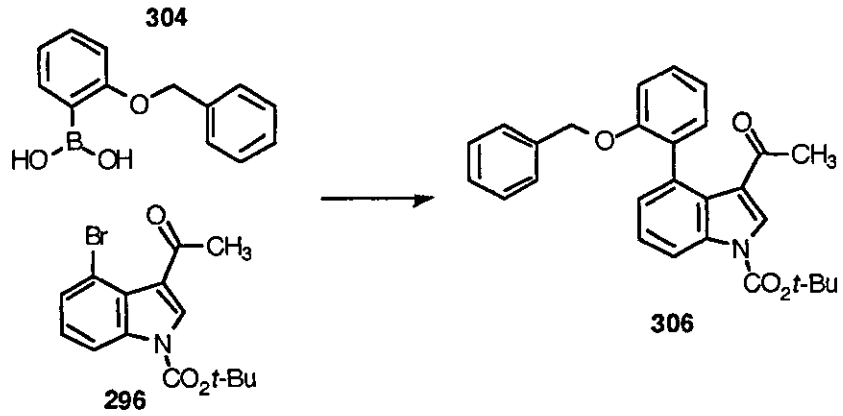
303 **305**

A solution of 2-(benzyloxy)bromobenzene (**303**) (263 mg, 1 mmol) in 1,2-dimethoxyethane (18 ml) was degassed under reduced pressure. Tetrakis(triphenylphosphine)palladium(0) (60 mg) was added and the solution was further degassed. 2M Aqueous sodium carbonate solution (1 ml, 2 mmol) was added followed by benzeneboronic acid (183 mg, 1.5 mmol). After further degassing, the solution was heated under reflux for 8 h. The solution was allowed to cool to room temperature and partitioned between dichloromethane (50 ml) and water (50 ml). The organic phase was washed with water (50 ml) then saturated brine (50 ml), then dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by flash column chromatography (eluent 49:1 light petroleum:diethyl ether) to give the *title compound* (256 mg, 99%) as a colourless oil, b.p. 220°C at 0.8 mmHg (Found: M^+, 260.1202; $C_{19}H_{16}O$ requires M, 260.1201); $\nu_{max.}$ (film) 3030, 1482, 1434, 1225, 753 and 697 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.64 - 7.59 (2 H, m, Ar_2), 7.47 - 7.25 (10 H, m, Ar_2), 7.11 - 7.04 (2 H, m, Ar_2) and 5.07 (2 H, s OCH_2); δ_C (62.9 MHz; $CDCl_3$) 155.6 (C), 138.5 (C), 137.2 (C), 134.9 (C), 131.0 (CH), 129.6 (CH), 128.5 (CH), 128.4 (CH), 127.9 (CH), 127.5 (CH),

126.9 (CH), 126.8 (CH), 121.3 (CH), 113.4 (CH) and 70.5 (CH_2); *m/z* (EI) 260 (M^+, 18%), 91 (100), 84 (13) and 49 (20).

The same compound was obtained (100% yield) from an identical coupling reaction between 2-(benzyloxy)benzeneboronic acid (**304**) and bromobenzene.

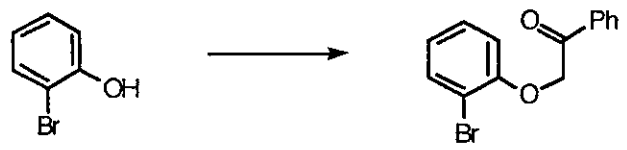
t-Butyl 3-acetyl-4-(2-benzyloxyphenyl)indole-1-carboxylate (**306**)



A solution of *t*-butyl 3-acetyl-4-bromoindole-1-carboxylate[156] (**296**) (338 mg, 1 mmol) in dimethoxyethane (18 ml) was degassed under reduced pressure. Tetrakis(triphenylphosphine)palladium(0) (60 mg) was added, followed by further degassing and the solution stirred for 10 min. A 2M aqueous solution of sodium carbonate (2 ml , 4 mmol) was added, followed by 2-benzyloxybenzeneboronic acid (**304**) (342 mg, 1.5 mmol), and the solution heated under reflux for 14 h. The solution was allowed to cool to room temperature, diluted with dichloromethane (50 ml) and washed with water (3 x 30 ml). The organic phase was dried over magnesium sulfate, concentrated *in vacuo* and purified by flash column chromatography (eluent 3:2 light petroleum:dichloromethane) to give the *title compound* (181 mg, 41%) as a colourless oil (Found: M^+, 441.1948. $C_{28}H_{27}NO_4$ requires M, 441.1940); $\nu_{max.}$ (film) 2977, 1740, 1683, 1421, 1370, 1255, 1149 and 755 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 8.23 (1 H, dd, *J* 8.3 and 1.05, Ar_1), 8.00 (1 H, s, indole 2-H), 7.44 (1 H, t, *J* 7.5, Ar_1), 7.36 - 7.29 (3 H, m, Ar_3), 7.20 - 7.17 (3 H, m, Ar_3), 7.11 - 7.02 (3 H, m, Ar_3), 6.96 (1 H, dd, *J* 8.5 and 1.2, Ar_1), 4.94 (2 H, s, OCH_2), 2.05 (3 H, s, $COCH_3$) and 1.71 (9 H, s, $C(CH_3)_3$); δ_C (62.9 MHz; $CDCl_3$) 194.0 (ketone C=O), 155.8 (C=O), 149.2 (C), 137.3 (C), 136.0 (C), 133.1 (C), 132.0 (C), 130.5 (CH), 130.4 (CH), 128.7 (CH), 128.1 (CH), 127.3 (CH), 126.8 (CH), 126.5 (CH), 125.7 (C), 125.1 (CH), 124.5 (C), 121.0 (CH),

114.1 (CH), 112.6 (CH), 85.0 (*C*Me$_3$), 70.0 (CH_2O), 28.7 (CH_3) and 28.2 (C(*C*H$_3$)$_3$); *m/z* (EI) 441 (M^+, 7.5%), 342 (9), 299 (17), 208 (10), 91 (82), 57 (81) and 41 (100).

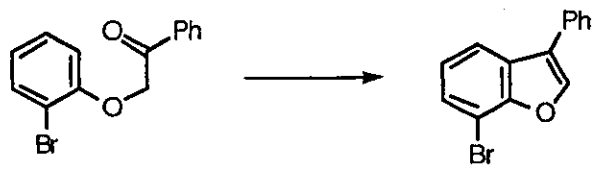
2-(2-Bromophenoxy)-1-phenylethan-1-one (**307**)



307

Potassium carbonate (10 g, 72 mmol) was added to a solution of phenacyl bromide (14.4 g, 72 mmol) and 2-bromophenol (12.5 g, 72 mmol) in acetone (40 ml), and the resulting suspension heated under reflux for 4 h. The suspension was then allowed to cool to room temperature and poured into water (300 ml). The precipitate was collected by filtration and recrystallised from absolute ethanol to afford the *title compound* (19.3 g, 92%) as a colourless solid, m.p. 114 - 115°C (Found: C, 57.5; H, 3.6%. $C_{14}H_{11}BrO_2$ requires C, 57.8; H, 3.8%); $\nu_{max.}$ (CH_2Cl_2 solution) 1706, 1479 and 1220 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 8.06 - 8.00 (2 H, m, Ar_2), 7.66 - 7.46 (4 H, m, Ar_4), 7.22 (1 H, td, *J* 7.9 and 1.6, Ar_1), 6.90 - 6.81 (2 H, m, Ar_2) and 5.33 (2 H, s, C*H*$_2$O); δ_C (62.9 MHz; $CDCl_3$) 194.0 (C=O), 154.5 (C), 134.3 (C), 133.9 (CH), 133.6 (CH), 128.8 (CH), 128.4 (CH), 128.2 (CH), 122.8 (CH), 113.8 (CH), 112.3 (C-Br) and 71.8 (CH_2O); *m/z* (EI) 292 (^{81}Br-M^+, 0.5%), 290 (^{79}Br-M^+, 0.5), 211 (20), 105 (100), 77 (36) and 41 (74).

7-Bromo-3-phenylbenzo[b]furan (**308**)



307 **308**

Polyphosphoric acid (30 g) was pre-heated to 80°C for 20 min. 2-(2-bromophenoxy)-1-phenylethan-1-one (**307**) (5.82 g, 20 mmol) was added in one portion and the viscous mixture heated at 90°C with stirring for 40 h. Water (50 ml) was added and precipitate collected by filtration. Recrystallisation from absolute ethanol gave the *title compound* (4.78 g, 88%) as a colourless solid, m.p. 73 - 74°C (Found: C, 61.5; H, 3.1%. $C_{14}H_9BrO$

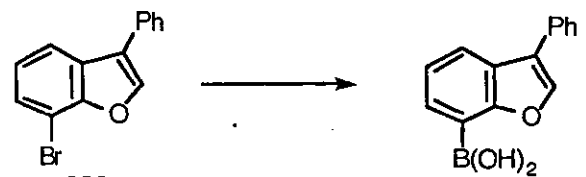
requires C, 61.6; H, 3.3%); $\nu_{max.}$ (CH_2Cl_2 solution) 3111, 3052, 1444, 1229, 1104 and 696 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.84 (1 H, s, 2-H), 7.76 (1 H, dd, *J* 7.8 and 1.0, Ar_1), 7.63 - 7.58 (2 H, m, Ar_2), 7.53 - 7.35 (4 H, m, Ar_4) and 7.18 (1 H, t, *J* 7.85, Ar_1); δ_C (62.9 MHz; $CDCl_3$) 152.9 (C), 141.9 (CH), 131.5 (C), 129.1 (CH), 127.92 (C), 127.89 (CH), 127.7 (CH), 127.6 (CH), 124.4 (CH), 123.2 (C), 119.7 (CH) and 104.7 (C-Br); *m/z* (EI) 274 (^{81}Br-M$^+$, 98%), 272 (^{79}Br-M$^+$, 100), 165 (80), 82 (48) and 63 (20).

7-Bromo-3-hydroxy-3-phenylbenzofuran-2-one (**309**)

308 **309**

A cooled (-78°C) solution of dimethyldioxirane[157] (0.0976M in acetone, 4 ml, 0.39 mmol) was rapidly added to a cooled (-78°C) solution of 7-bromo-3-phenylbenzo[b]furan (**308**) (50 mg, 0.18 mmol) in acetone (1.5 ml). The solution was stirred at -78°C for 1 h, then allowed to warm to room temperature overnight. The solvent was removed *in vacuo* to afford the pure *title compound* (56 mg, 100%) as a colourless oil (Found: M$^+$, 305.9713. $C_{14}H_9{}^{81}BrO_3$ requires M, 305.9716); $\nu_{max.}$ (film) 3420 (br, OH), 1817, 1440 and 1044 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.55 (1 H, dd, *J* 7.1 and 1.3), 7.39 - 7.34 (5 H, m), 7.25 (1 H, dd, *J* 7.5 and 1.3), 7.09 (1 H, t, *J* 7.6) and 3.7 - 3.2 (1 H, br s, exchangeable with D_2O, OH); δ_C (62.9 MHz; $CDCl_3$) 174.8 (C=O), 151.1 (C), 138.3 (C), 134.2 (CH), 131.0 (C), 129.3 (CH), 129.0 (CH), 126.3 (CH), 125.4 (CH), 124.2 (CH), 104.1 (C-Br) and 78.0 (3-C); *m/z* (EI) 306 (^{81}Br-M$^+$, 4%), 304 (^{79}Br-M$^+$, 3%), 279 (10), 278 (19), 277 (20), 276 (18), 275 (13), 105 (22), 58 (38) and 43 (100)

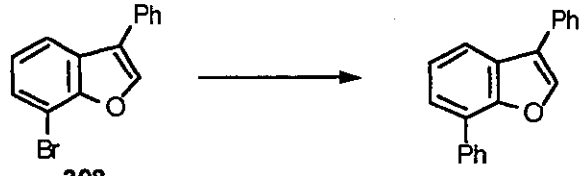
3-Phenylbenzo[b]furan-7-boronic acid (**310**)



308 **310**

A solution of 7-bromo-3-phenylbenzo[b]furan (**308**) (5 g, 18.3 mmol) in dry THF (200 ml) was cooled to -78°C under an atmosphere of nitrogen. *n*-Butyllithium (15.4 ml of a 2.5M solution in hexanes, 38.5 mmol) was added dropwise, and the resulting solution stirred at -78°C for 30 min. Trimethylborate (15 ml, excess) was added rapidly in one portion and the solution stirred at -78°C for 1 h, then allowed to warm to room temperature and poured into 0.001N hydrochloric acid. The product was extracted into dichloromethane (3 x 100 ml), and the combined organic phases dried over sodium sulfate, filtered and concentrated *in vacuo* to give a solid which was recrystallised (dichloromethane/light petroleum with 1 drop of water) to afford the *title compound* (3.491 g, 80%) as a colourless powder, m.p. 107 - 108°C (Found M^+, 238.0800; $C_{14}H_{11}BO_3$ requires M, 238.0801); $\nu_{max.}$ (CH_2Cl_2 solution) 3276 (br, OH), 2964, 2924, 1364, 1265 and 737 cm^{-1}; δ_H (250 MHz; $CDCl_3$/DMSO-d_6) 7.91 (1 H, dd, *J* 7.8 and 1.6, Ar_1), 7.88 (1 H, s, 2-H), 7.85 (1 H, dd, *J* 7.3 and 1.6, Ar_1), 7.67 - 7.36 (5 H, m, Ar_5), 7.34 (1 H, dd, *J* 7.8 and 7.3, Ar_1) and 7.15 (2 H, s, exchangeable with D_2O, $B(OH)_2$); δ_C (62.9 MHz; $CDCl_3$/DMSO-d_6) 160.8 (C), 141.1 (CH), 131.7 (C), 131.1 (CH), 128.9 (CH), 127.4 (CH), 127.2 (CH), 125.1 (C), 122.8 (CH), 122.3 (CH), 122.3 (C-B, $J_{C\text{-}B}$ 94 Hz) and 111.6 (C); *m/z* (EI) 238 (M^+, 52%), 194 (100), 165 (74) and 45 (97).

3,7-Diphenylbenzo[b]furan (**311**)



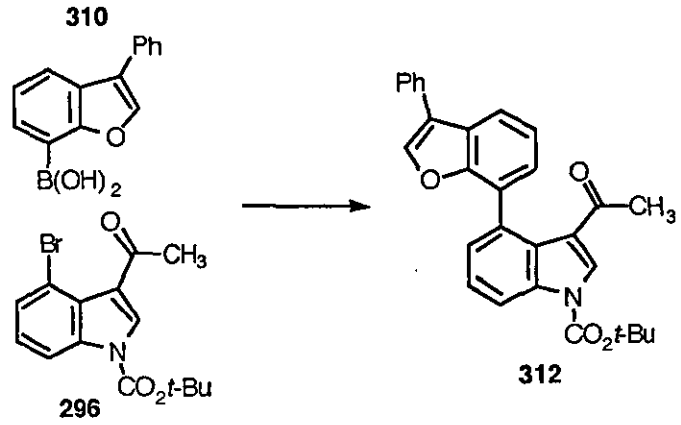
308 **311**

Tetrakis(triphenylphosphine)palladium(0) (60 mg) was added to a degassed solution of 3-phenyl-7-bromobenzo[b]furan (**308**) (273 mg, 1 mmol) in dimethoxyethane (18 ml). The solution was further degassed and aqueous sodium carbonate (1 ml of a 2N solution, 2 mmol) and benzeneboronic acid (183 mg, 1.5 mmol) were added and the solution heated under reflux for 8 h. The solution was then allowed to cool to room temperature, diluted with dichloromethane (30 ml) and washed with water (30 ml), then with saturated brine (30 ml). The solution was dried over magnesium sulfate, filtered and concentrated *in vacuo*. Recrystallisation from ethanol afforded the *title compound* (220 mg, 81%) as a colourless solid, m.p. 96 - 97°C (Found: M^+,

270.1052; $C_{20}H_{14}O$ requires M, 270.1045); $\nu_{max.}$ (KBr) 3064, 3061, 1409, 1123, 760 and 698 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.89 - 7.85 (2 H, m, Ar_2), 7.81 (1 H, s, 2-H), 7.80 (1 H, dd, *J* 7.7 and 1.3, Ar_1), 7.67 - 7.63 (2 H, m, Ar_2) and 7.53 - 7.32 (8 H, m, Ar_8); δ_C (62.9 MHz; $CDCl_3$) 141.4 (CH), 136.4 (C), 132.0 (C), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.5 (C), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.2 (C), 126.0 (C), 124.2 (CH), 123.5 (CH), 122.4 (C) and 119.5 (CH); *m/z* (EI) 270 (M^+, 100%), 241 (15), 239 (16) and 165 (12).

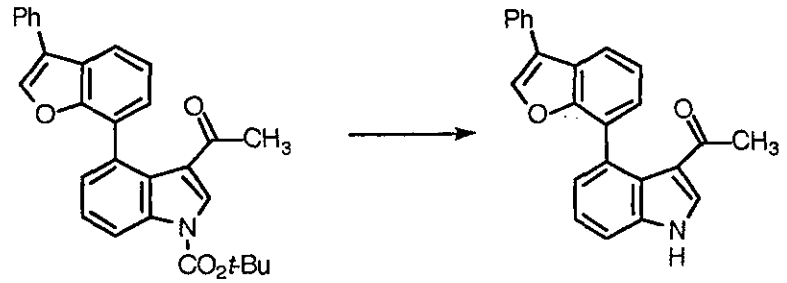
The same compound was produced (67% yield) by an identical coupling reaction between 3-phenylbenzo[b]furan-7-boronic acid (**310**) and bromobenzene.

tert-Butyl 3-acetyl-4-(3-phenylbenzo[b]furan-7-yl)indole-1-carboxylate (**312**)



A solution of *tert*-butyl 3-acetyl-4-bromoindole-1-carboxylate[156] (**296**) (338 mg, 1 mmol) in 1,2-dimethoxyethane (15 ml) was degassed. Tetrakis(triphenylphosphine)palladium(0) (30 mg) was added and the solution further degassed. A 2M aqueous solution of sodium carbonate (1.5 ml, 3 mmol) was added followed by 3-phenylbenzo[b]furan-7-boronic acid (**310**) (357 mg, 1.5 mmol) and the solution further degassed, then heated under reflux for 15 h. Dichloromethane (50 ml) was added and the solution washed with water (2 x 30 ml), then dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography (eluent dichloromethane) gave the *title compound* (359 mg, 80%) as a colourless foam; δ_H (250 MHz; $CDCl_3$) 8.37 (1 H, dd, *J* 6.8 and 2.6, Ar_1), 8.18 (1 H, s, Ar_1), 7.89 (1 H, dd, *J* 7.1 and 2.1, Ar_1), 7.73 - 7.69 (3 H, m, Ar_3), 7.56 - 7.32 (7 H, m, Ar_7), 2.10 (3 H, s, $COCH_3$) and 1.75 (9 H, s, $C(CH_3)_3$).
This compound was characterised after removal of the nitrogen protecting group as described below.

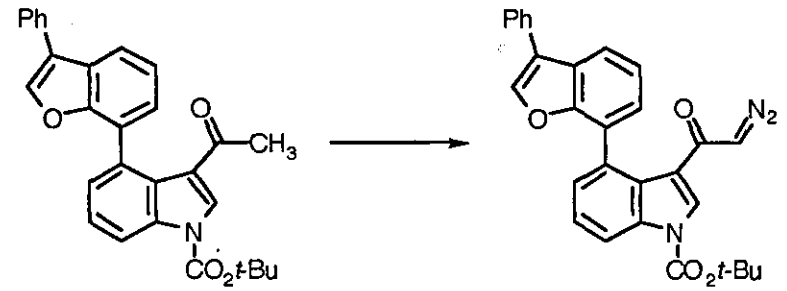
3-Acetyl-4-(3-phenylbenzo[b]furan-7-yl)indole (**313**)



312 **313**

Sodium methoxide (30% in methanol) was added to a solution of **312** (120 mg, 0.27 mmol) in THF (3 ml). After stirring for 30 min, dichloromethane (30 ml) was added and the solution washed with water (30 ml) and saturated brine (30 ml). The solution was then dried over magnesium sulfate, filtered, concentrated *in vacuo* and recrystallised from acetone to give the title compound (54 mg, 58%) as a colourless solid, m.p. 257 - 257°C (dec.) (Found: C, 81.9; H, 5.0; N, 3.9%. $C_{24}H_{17}NO_2$ requires C, 82.0; H, 4.9; N, 4.0%); $\nu_{max.}$ (CH_2Cl_2 solution) 3456, 1722, 1602 and 1121 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 10.6 (1 H, br s, N*H*), 8.22 (1 H, m, Ar_1), 8.06 (1 H, s, Ar_1), 7.85 (1 H, dd, *J* 6.8 and 2.2, Ar_1), 7.74 (2 H, d, *J* 7.5, Ar_2), 7.61 - 7.48 (3 H, m, Ar_3), 7.41 - 7.23 (5 H, m, Ar_5) and 2.2 (3 H, s, $COCH_3$); δ_C (62.9 MHz; $CDCl_3$) 196.1 (C=O), 158.6 (C), 146.6 (CH), 142.8 (C), 138.7 (CH), 137.0 (C), 135.1 (C), 134.1 (CH), 133.4 (C), 133.0 (C), 132.3 (CH), 132.0 (CH), 130.0 (C), 129.3 (CH), 129.2 (CH), 127.8 (CH), 127.7 (CH), 126.4 (C), 124.5 (C), 123.4 (CH), 117.0 (CH) and 32.9 (CH_3); *m/z* (EI) 351 (M^+, 100%), 336 (41), 139 (15) and 43 (30).

t-Butyl 3-diazoacetyl-4-(3-phenylbenzo[b]furan-7-yl)indole-1-carboxylate (**315**)

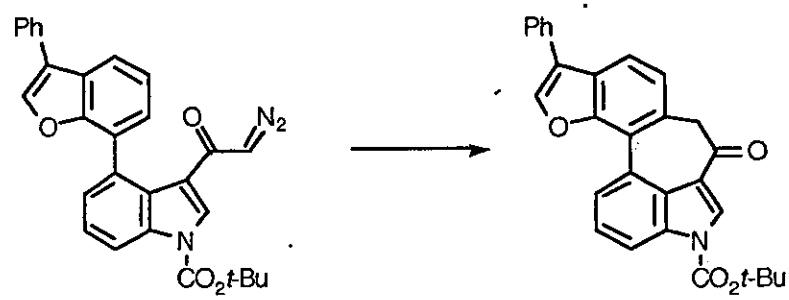


312 **315**

Hexamethyldisilazane (194 mg, 0.25 ml, 1.2 mmol) in THF (2 ml) was cooled to 0°C under a nitrogen atmosphere. A 2.5M solution of *n*-butyllithium in

hexanes (0.48 ml, 1.2 mmol) was added and the solution stirred for 10 min. The solution was cooled to -78°C and **312** (451 mg, 1 mmol) in THF (3 ml) added dropwise. After stirring at -78°C for 45 min, 2,2,2-trifluoroethyl trifluoroacetate (235 mg, 0.16 ml, 1.2 mmol) was added rapidly in one portion. The solution was stirred at -78°C for 30 min, then poured into 5% aqueous hydrochloric acid (30 ml) and dichloromethane (30 ml). The phases were separated and the aqueous phase extracted twice with dichloromethane (30 ml). The combined organic phases were washed with saturated brine (2 x 30 ml) and concentrated *in vacuo* to give 680 mg of an oil which was immediately dissolved in acetonitrile (10 ml). Triethylamine (120 mg, 1.2 mmol), water (1 drop) and methanesulfonyl azide (150 mg, 1.2 mmol) were added and the solution stirred overnight at room temperature in the dark. The solution was concentrated *in vacuo* to a volume of *ca.* 10 ml, and dichloromethane (50 ml) added. The solution was then washed with 10% aqueous NaOH solution (3 x 30 ml), then with saturated brine (30 ml), then dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by flash column chromatography (eluent 3:2 dichloromethane:light petroleum) to give the *title compound* (393 mg, 82%) as a yellow oil; $\nu_{max.}$ (film) 2101, 1744, 1626, 1296 and 1152 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 8.35 (1 H, m, Ar_1), 8.04 (1 H, s, Ar_1), 7.85 (1 H, dd, *J* 7.2 and 1.9, Ar_1), 7.70 (1 H, s, Ar_1), 7.67 - 7.63 (2 H, m, Ar_2), 7.52 - 7.37 (7 H, m, Ar_7), 4.68 (1 H, s, C*H*(N_2)) and 1.69 (9 H, s, C(CH_3)$_3$); δ_C (250 MHz; $CDCl_3$) 182.9 (C=O), 153.5 (C=O), 149.0 (C), 141.4 (CH), 136.2 (C), 131.9 (C), 129.8 (C), 129.0 (CH), 128.8 (CH), 127.66 (CH), 127.57 (CH), 126.4(C), 126.2 (C), 126.0 (CH), 125.8 (C), 125.4 (CH), 125.0 (CH), 123.5 (CH), 122.8 (C), 120.0 (CH), 115.2 (CH), 114.5 (C), 85.0 (*C*Me_3) and 28.1 (C(CH_3)$_3$) (diazo carbon not observed); *m/z* (EI) 309 (100%), 280 (16) and 252 (13).

Rhodium (II) perfluorobutyramide catalysed decomposition of t-butyl 3-diazoacetyl-4-(3-phenylbenzo[b]furan-7-yl)indole-1-carboxylate (**315**)



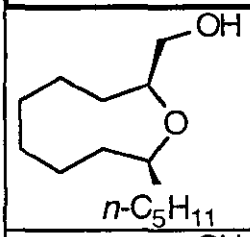
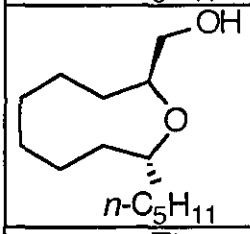
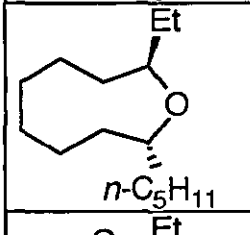
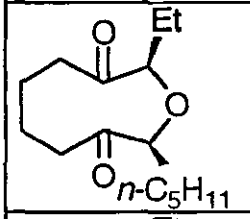
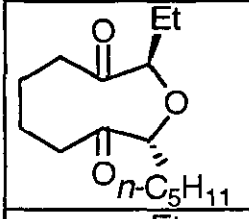
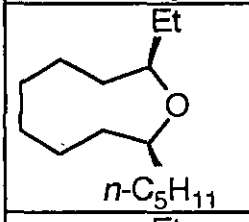
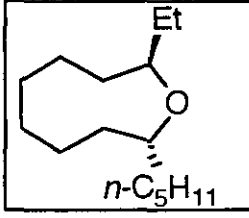
315 **316**

A solution of **315** (98 mg, 0.205 mmol) in chloroform (5 ml) was added over 8 h to a suspension of rhodium(II) perfluorobutyramide (1 mg) in chloroform (3 ml) containing acetonitrile (82 mg, 2 mmol). The solvent was then removed *in vacuo* and the residue purified twice by flash column chromatography (eluent 3:2 dichloromethane:light petroleum) to give the **316** (22 mg, 24%) as a colourless oil (Found: M^+, 449.1638. $C_{29}H_{23}NO_4$ requires M, 449.1627); $\nu_{max.}$ (film) 1746, 1686, 1546, 1258 and 1149 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 8.41 (1 H, dd, *J* 7.8 and 0.8, indole 5-H or 7-H), 8.33 (1 H, dd, *J* 8.3 and 0.8, indole 5-H or 7-H), 8.27 (1 H, s, indole 2-H or benzo[b]furan 2-H), 7.83 (1 H, s, indole 2-H or benzo[b]furan 2-H), 7.81 (1 H, d, *J* 7.9, benzo[b]furan 4-H or 5-H), 7.68 - 7.61 (3 H, m, Ar_3), 7.52 - 7.46 (2 H, m, Ar_2), 7.42 - 7.39 (1 H, m, Ar_1), 7.37 (1 H, d, *J* 7.9, benzo[b]furan 4-H or 5-H), 4.09 (2 H, s, $COCH_2$) and 1.70 (9 H, s, $C(CH_3)_3$); δ_C (62.9 MHz; $CDCl_3$) 190.1 (C=O), 153.8 (C=O), 149.0 (C), 141.4 (CH), 136.1 (C), 131.7 (C), 129.1 (CH), 129.2 (CH), 127.7 (2 x CH), 127.6 (C), 126.8 (C), 126.6 (CH), 126.5 (CH), 125.3 (CH), 122.4 (C), 122.1 (C), 121.9 (C), 120.6 (CH), 115.2 (CH), 85.5 (CMe_3), 52.5 (CH_2CO) and 28.1 ($C(CH_3)_3$) (2 quaternary carbons not seen); ^1H-^1H and ^1H-^{13}C correlation spectra consistent with the proposed structure; *m/z* (EI) 449 (M^+, 20%), 394 (12), 349 (41), 320 (26), 57 (47), 56 (59), 43 (61) and 41 (100).

Appendices

Appendix A: ^{13}C NMR data for oxonanes

Table 2: ^{13}C NMR data for 2,9-disubstituted oxonanes (2-C and 9-C)

Structure	Chemical shifts (ppm)	Reference
	82.4, 82.6	87
	75.5, 78.85	87
	75.41, 76.35	87
	87.7, 88.7	This thesis (**236cis**)
	80.1, 81.3	This thesis (**236trans**)
	79.8, 81.2	This thesis (**216cis**)
	75.4, 76.3	This thesis (**216trans**)

Appendix B: Crystal structure data

Crystal Structure of 1-(4-toluenesulfonyl)azonane-3,8-dione (**248**)

Crystals of **248** were grown from ethanol. A crystal of dimensions 1.8 x 0.5 x 0.3 mm was chosen for data collection and mounted about the crystallographic b axis. Unit cell dimensions were obtained from oscillation and Weissenberg photographs and partially refined by least-squares refinement of 18 reflections in the h0l plane using a Stöe Stadi-2 Weissenberg diffractometer.

Crystal Data

$C_{15}H_{19}NSO_4$, M_r 309.36. monoclinic: a = 11.263(11), b = 5.63(1), c = 23.915(19) Å. β = 95.38(7). V = 1509.79 Å^3, F(0,0,0) = 656.
Space group $P2_1/c$, Z = 4, ρ_c = 1.361 gcm^{-3}.
Mo K_α radiation, λ = 0.71069 Å, μ = 1.84cm^{-1}.

Data Collection

Intensity data were collected on a Stöe Stadi-2 Weissenberg diffractometer using an ω scan, allowing the measurement of 2677 unique reflections of which 2110 had $F/\sigma(F) > 6$.
max. sin Θ/λ = 0.6, h-13 → 13, k 0 → 5, l -28 → 28.
Data were corrected for Lorentz and polarisation effects but not absorption ($t_{max.}$ = 0.97, $t_{min.}$ = 0.85).

Structure solution and refinement

The structure was solved by direct methods (SHELX76) and refined by full-matrix least-squares refinement. Non-hydrogen atoms were allowed anisotropic temperature factors. Hydrogen atoms were found from difference map and refined isotropically.
The refinement converged with R = 0.0637, R_W = 0.0637 (unit weights). Maximum shift/error = 0.01; electron density residuals in the final difference map -0.4 → +0.3 eÅ^{-3}.

Figure 9
Unit cell of azonane **248** (hydrogen atoms omitted for clarity).

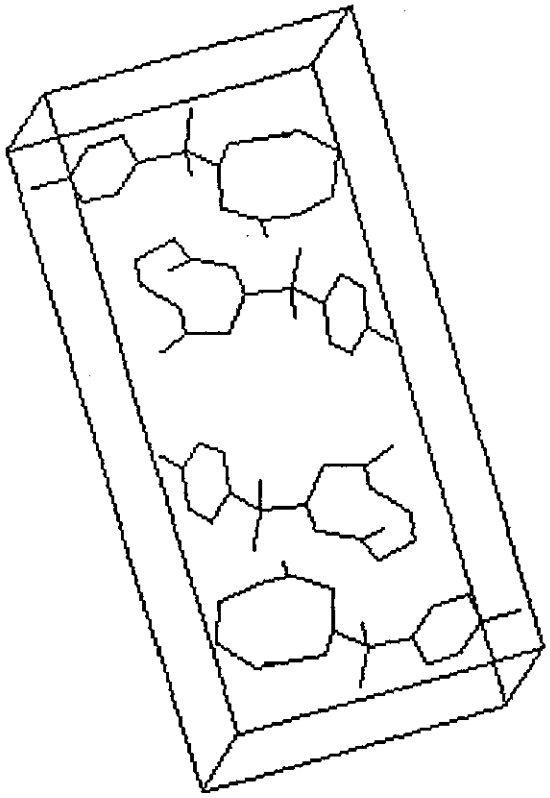


Figure 10
Three dimensional representation of azonane **248** (hydrogen atoms omitted for clarity).

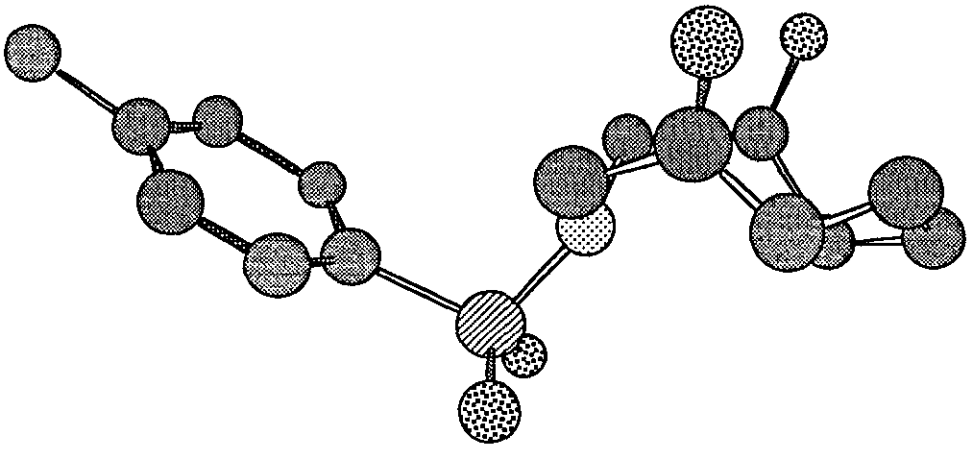


Table 3

Selected bond Lengths (Å) for azonane **248**

O(1)	- S(1)	1.427 (3)	C(4)	- C(3)	1.376 (5)
O(2)	- S(1)	1.433 (3)	C(7)	- C(3)	1.513 (6)
N(1)	- S(1)	1.639 (3)	C(5)	- C(4)	1.389 (6)
C(6)	- S(1)	1.753 (4)	C(6)	- C(5)	1.376 (5)
C(9)	- O(3)	1.212 (5)	C(9)	- C(8)	1.516 (5)
C(14)	- O(4)	1.218 (5)	C(10)	- C(9)	1.496 (6)
C(8)	- N(1)	1.460 (4)	C(11)	- C(10)	1.526 (5)
C(15)	- N(1)	1.466 (5)	C(12)	- C(11)	1.514 (7)
C(2)	- C(1)	1.383 (6)	C(13)	- C(12)	1.537 (5)
C(6)	- C(1)	1.379 (5)	C(14)	- C(13)	1.492 (5)
C(3)	- C(2)	1.374 (5)	C(15)	- C(14)	1.515 (5)

Table 4

Selected bond angles for azonane **248**

O(2)	- S(1)	- O(1)	120.0 (2)	C(1)	- C(6)	- S(1)	119.2 (3)
N(1)	- S(1)	- O(1)	106.6 (2)	C(5)	- C(6)	- S(1)	120.2 (3)
N(1)	- S(1)	- O(2)	105.9 (2)	C(5)	- C(6)	- C(1)	120.4 (3)
C(6)	- S(1)	- O(1)	108.6 (2)	C(9)	- C(8)	- N(1)	112.1 (3)
C(6)	- S(1)	- O(2)	109.3 (2)	C(8)	- C(9)	- O(3)	118.6 (4)
C(6)	- S(1)	- N(1)	105.4 (2)	C(10)	- C(9)	- O(3)	123.4 (3)
C(8)	- N(1)	- S(1)	118.7 (2)	C(10)	- C(9)	- C(8)	117.9 (3)
C(15)	- N(1)	- S(1)	117.4 (2)	C(11)	- C(10)	- C(9)	114.3 (4)
C(15)	- N(1)	- C(8)	114.9 (3)	C(12)	- C(11)	- C(10)	115.2 (3)
C(6)	- C(1)	- C(2)	119.0 (3)	C(13)	- C(12)	- C(11)	115.6 (4)
C(3)	- C(2)	- C(1)	122.2 (4)	C(14)	- C(13)	- C(12)	113.2 (4)
C(4)	- C(3)	- C(2)	117.5 (4)	C(13)	- C(14)	- O(4)	122.3 (4)
C(7)	- C(3)	- C(2)	121.2 (4)	C(15)	- C(14)	- O(4)	119.0 (4)
C(7)	- C(3)	- C(4)	121.3 (4)	C(15)	- C(14)	- C(13)	118.8 (4)
C(5)	- C(4)	- C(3)	122.0 (3)	C(14)	- C(15)	- N(1)	109.2 (3)
C(6)	- C(5)	- C(4)	118.9 (4)				

Crystal Structure of N-benzyl-N-phenyl-2-diazomalonamic acid ethyl ester (**268**)

Crystals of **268** were grown from light petroleum/ether. All crystals examined suffered from problems of twinning. A crystal of dimensions 1.0 x 0.7 x 1.0mm was chosen for data collection and mounted about the crystallographic c axis. Unit cell dimensions were obtained from oscillation and Weissenberg photographs and partially refined by least-squares refinement of 24 reflections in the hk0 plane using a Stöe Stadi-2 Weissenberg diffractometer.

Crystal Data

$C_{12}H_{17}N_3O_3$, M_r 251.283. monoclinic: a = 11.00(1), b = 18.99(1), c = 11.82(2) Å. β = 136.1(1). V = 1710.35 $Å^3$, F(0,0,0) = 536.
Space group $P2_1/a$, Z = 4, $\rho_c = 0.976\ gcm^{-3}$.
Mo K_α radiation, $\lambda = 0.71069$ Å, $\mu = 0.44cm^{-1}$.

Data Collection

Intensity data were collected on a Stöe Stadi-2 Weissenberg diffractometer using an ω scan, allowing the measurement of 3066 unique reflections of which 2152 had $I/\sigma(I) > 3$.
max. $\sin\Theta/\lambda = 0.6$, h-12 → 9, k 0 → 22, l 0 → 11.
Data were corrected for Lorentz and polarisation effects but not absorption ($t_{max.} = 0.97$, $t_{min} = 0.96$).

Structure solution and refinement

The structure was solved by direct methods (SHELXS) and refined by full-matrix least-squares refinement. Non-hydrogen atoms were allowed anisotropic temperature factors. Phenyl hydrogen atoms were placed in calculated positions with isotropic temperature factors unrestrained. 4 other hydrogen atoms were found from difference map and refined isotropically. The remaining 4 hydrogen atoms were not found.
The refinement converged with R = 0.11, $R_W = 0.11$ ($w = 116.3238/s^2(F) + 0.000063F^2$).
Maximum shift/error = 0.02; electron density residuals in the final difference map ± $0.4eÅ^{-3}$
The relatively high R factor reflects the quality of data obtained from a twinned crystal.

Figure 11
Unit cell of diazoamide **268** (hydrogen atoms omitted for clarity)

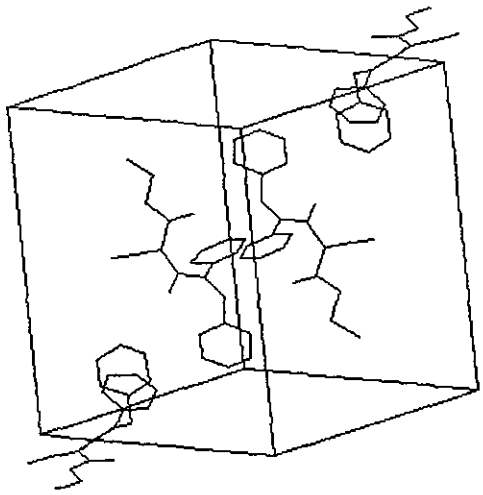


Figure 12
Three dimensional representation of diazoamide **268** (hydrogen atoms omitted for clarity)

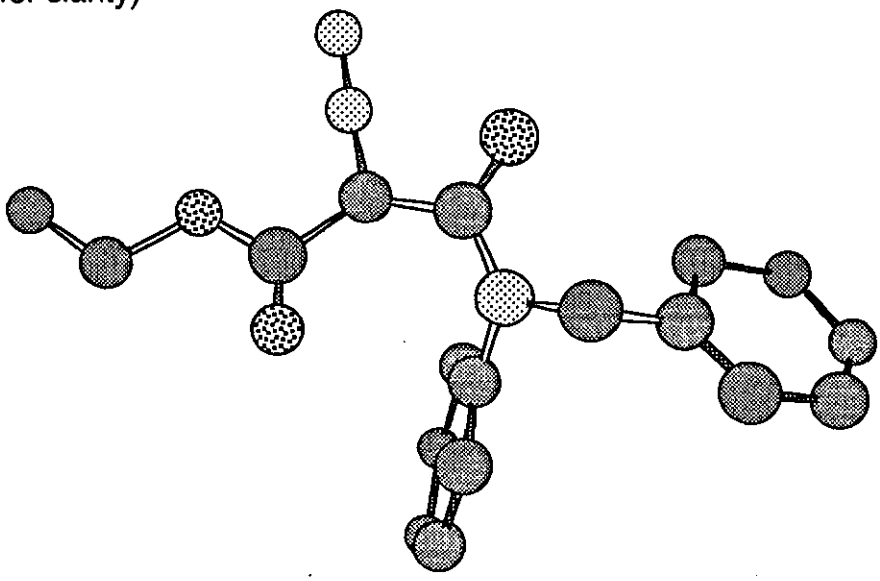


Table 5

Selected bond lengths (Å) for diazoamide **268**

C(5)	- O(1)	1.231 (5)	C(4)	- C(5)	1.482 (7)
C(3)	- O(2)	1.368 (6)	C(17)	- C(18)	1.397 (7)
C(2)	- O(2)	1.472 (6)	C(6)	- C(7)	1.525 (6)
C(14)	- C(13)	1.374 (7)	C(12)	- C(7)	1.397 (8)
N(1)	- C(13)	1.443 (5)	C(8)	- C(7)	1.392 (8)
C(18)	- C(13)	1.404 (7)	C(16)	- C(15)	1.384 (9)
C(3)	- O(3)	1.195 (6)	C(17)	- C(16)	1.380 (9)
C(15)	- C(14)	1.388 (7)	C(11)	- C(12)	1.395 (8)
C(5)	- N(1)	1.362 (6)	C(11)	- C(10)	1.354 (10)
C(6)	- N(1)	1.493 (7)	C(9)	- C(10)	1.390 (10)
C(4)	- C(3)	1.464 (7)	C(1)	- C(2)	1.495 (11)
C(4)	- N(2)	1.329 (7)	C(8)	- C(9)	1.411 (9)
N(3)	- N(2)	1.123 (6)			

Table 6

Selected bond angles for diazoamide **268**

C(2)	- O(2)	- C(3)	114.9 (4)	C(5)	- C(4)	- C(3)	128.5 (5)
N(1)	- C(13)	- C(14)	119.8 (5)	C(5)	- C(4)	- N(2)	112.8 (4)
C(18)	- C(13)	- C(14)	120.9 (5)	C(17)	- C(18)	- C(13)	118.9 (5)
C(18)	- C(13)	- N(1)	119.3 (4)	C(12)	- C(7)	- C(6)	121.5 (5)
C(15)	- C(14)	- C(13)	119.2 (6)	C(8)	- C(7)	- C(6)	118.2 (5)
C(5)	- N(1)	- C(13)	124.3 (4)	C(8)	- C(7)	- C(12)	120.3 (5)
C(6)	- N(1)	- C(13)	115.5 (4)	C(16)	- C(15)	- C(14)	121.0 (6)
C(6)	- N(1)	- C(5)	119.0 (4)	C(17)	- C(16)	- C(15)	119.8 (5)
O(3)	- C(3)	- O(2)	125.0 (5)	C(16)	- C(17)	- C(18)	120.2 (6)
C(4)	- C(3)	- O(2)	110.2 (5)	C(7)	- C(6)	- N(1)	112.5 (4)
C(4)	- C(3)	- O(3)	124.8 (5)	C(11)	- C(12)	- C(7)	119.7 (6)
N(3)	- N(2)	- C(4)	178.5 (5)	C(9)	- C(10)	- C(11)	119.9 (6)
N(1)	- C(5)	- O(1)	121.3 (5)	C(10)	- C(11)	- C(12)	120.9 (7)
C(4)	- C(5)	- O(1)	119.0 (4)	C(1)	- C(2)	- O(2)	105.9 (5)
C(4)	- C(5)	- N(1)	119.7 (4)	C(8)	- C(9)	- C(10)	120.9 (7)
N(2)	- C(4)	- C(3)	116.2 (5)	C(9)	- C(8)	- C(7)	118.2 (7)

Appendix C: Molecular modelling[158]

Calculations were carried out using Sybyl 6.03 (Tripos Associates) running on an Evans and Sutherland workstation. The minimum energy conformation of **261** was found by a random search using the Powell method with gradient termination. Conformational analysis was performed by fixing the pyrrolopyrazole ring and cyclohexane ring, and rotating the cyclohexane ring relative to the pyrrolopyrazole ring using a systematic search (Clearly this is not ideal, since in reality both the cyclohexane and pyrrolopyrazole rings will be able to alter their conformations in order to permit rotation. In reality the energy barrier to rotation, while still significant, will be less than calculated by this method).

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