UNIVERSITY OF SOUTHAMPTON

FACULTY OF SCIENCE

Department of chemistry

SYNTHESIS OF MEDIUM SIZED RING BY RADICAL *IPSO*-SUBSTITUTION

BY

Nathalie Sylvie L'Hélias

Thesis for the degree of Doctor of Philosophy

January 2005

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF SCIENCE
SCHOOL OF CHEMISTRY

Doctor of Philosophy

SYNTHESIS OF MEDIUM SIZED RING BY RADICAL *IPSO*-SUBSTITUTION

by Nathalie Sylvie L'Hélias

A new approach to seven, eight and nine membered ring synthesis involving a radical *ipso*-substitution is described. The method involves treatment of a 2-iodobenzyl-indanone or tetralone with tributyltin hydride and AIBN. Addition of the resulting aryl radical to the pendant carbocycle then occurred in a 5-*exo*-trig manner to the ring junction. Fragmentation of the resulting radical intermediate lead to rearomatisation of the arene and to the formation of a highly stabilised radical.

With tetralone derivatives the 5-*exo*-trig *ipso*-cyclisation competed with 6-*endo*/*exo*-*ortho*-addition while in the case of benzocyclobutane a competing 5-*exo* trig cyclisation to a nitrile was observed in addition to the formation of the seven membered ring.

A study on the use of tetrakistrimethylsilyl silane-TBAF for the reduction of the aryl halides is also presented.

Contents

Preface

The research described in this thesis was carried out under the supervision of Dr D. C. Harrowven at the University of Southampton between October 2001 and October 2004. No part of this thesis has previously been submitted for a degree.

To my Mother and Olivier

Acknowledgements

I wish to thank my supervisor David Harrowven for his advice, his support and all the proof-reading.

I also wish to thank A. Ganesan and Jonathan Moseley for their advice and support. G. John Langley and Julie Herniman for mass spectrometry, Joan Street and Neil Wells for NMR services and Stuart Flanagan for the X-Ray.

The Harrowven group past and present.

AstraZeneca for the financial support.

I also wish to deeply thank my mother and my brother for their support in whatever I do.

Abbreviations

ABCN,VAZO	1,1'-azobis(cyclohexanecarbonitrile)
Ac	acetyl
AIBN	azobisisobutyronitrile
app.	apparent
Ar	aryl
aq.	aqueous
Bn	benzyl
br.	broad
Bu	butyl
^{n}Bu	*n*-butyl
^{t}Bu	tert-butyl
18-c-6	18-crown-6
CHN	combustion analysis
CI	chemical ionisation
d	doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DEPT	Distortionless Enhancement through Polarisation Transfer
DMF	*N,N'*-dimethylformamide
DMSO	dimethylsulfoxide
DPDC	diisopropylperoxydicarbonate
d.r.	diastereomeric ratio
DTBP	di-*tert*-butylperoxide
EDG	electron-donating group
EI	electron ionisation, electron impact
ES	electrospray
Et	ethyl
Ether	diethyl ether
EWG	electron-withdrawing group
FT	Fourier Transform
GC	gas chromatography

h	hour(s)
HRMS	high resolution mass spectrometry
hν	visible and ultraviolet radiation
Hz	hertz
IR	infrared
LDA	lithium diisopropylamide
lit.	literature
LRMS	low resolution mass spectrometry
m	multiplet
m	*meta*
M	mol/L
Me	methyl
Mes	mesitylenesulfonyl
min	minute(s)
MP	melting point
MS	mass spectrometry
NMR	nuclear magnetic resonance spectroscopy
o	*ortho*
obs.	obscure
p	*para*
petrol	petroleum ether (40/60)
Ph	phenyl
Ppm	parts per million
^{i}Pr	isopropyl
q	quartet
r.t.	room temperature
s	singlet
sat.	saturated
SM	starting material
t	triplet
TBACl	tetrabutylammonium chloride
TBAF	tetrabutylammonium fluoride
THF	tetrahydrofuran

Ts	tosyl
W	weak

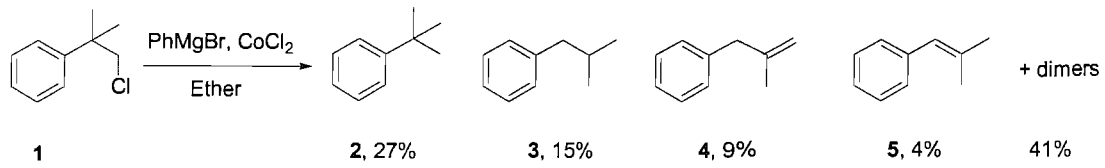
Chapter 1 Radical induced aryl migration to carbon

Chapter 1 Radical induced aryl migration to carbon.

This introduction summarises the work carried out in the area of radical aryl migration reactions. Studer *et al.* recently reviewed the topic, covering research from 1911 to 2001.[1]

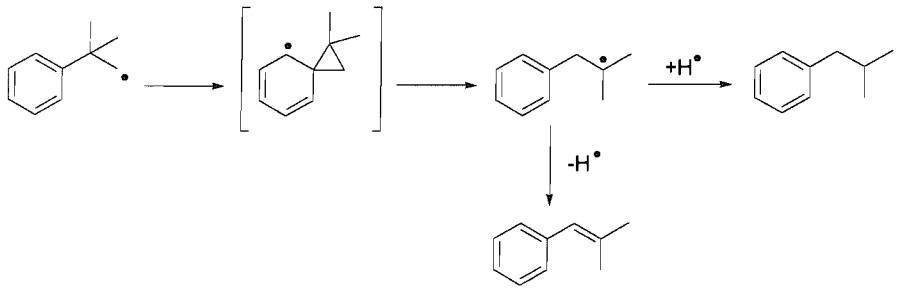
1.1 The neophyl rearrangement (1,2-aryl migration).

In 1911 Wieland reported the first example of an addition of a carbon-centred radical to an arene.[2] 30 years later, Urry *et al.* revisited the so-called "neophyl type rearrangement" and found that treatment of **1** with phenylmagnesium bromide and cobalt chloride led to a range of products that included three compounds (**3-5**) with a rearranged carbon skeleton.[3]



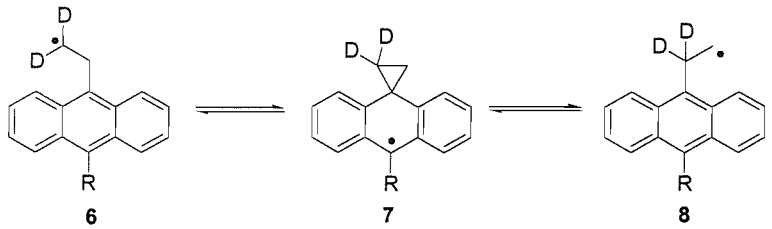
Scheme 1

The formation of **3-5** gave the proof that a rearrangement had occurred (Scheme 2). The rearrangement is believed to proceed *via* a neophyl radical intermediate. This radical adds to the *ipso* carbon of the vicinal arene by a 3-*exo*-trig cyclisation. Then, after fragmentation of the cyclopropane, the benzene ring is restored with generation of the more stable tertiary alkyl radical. This radical intermediate either gains or loses a hydrogen atom, though a mechanism that has yet to be fully understood.



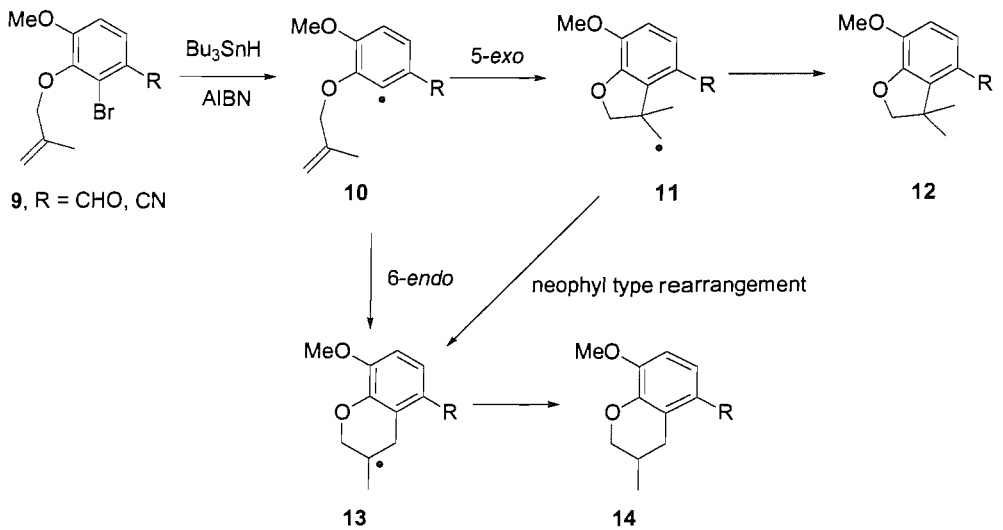
Scheme 2

Leardini *et al.* showed that alkyl radicals **6** and **8** interconvert *via* spiro-octadienyl radical intermediate **7** (Scheme 3).[4] The rate of reaction was dependent on the nature of R with a lower limit for the rate constant of 5 x 10^7 s^{-1}. From this they concluded that the neophyl type rearrangement was a slow process.



Scheme 3

In 1986 Parker *et al.* reported that *o*-bromoaryl allyl ether **9**, when treated under radical forming conditions (Bu_3SnH, AIBN), underwent a 5-*exo*-trig cyclisation to **13**.[5] This intermediate could then undergo a neophyl type rearrangement to give **14** (Scheme 4), the same product as given by a 6-*endo* cyclisation of **10**.

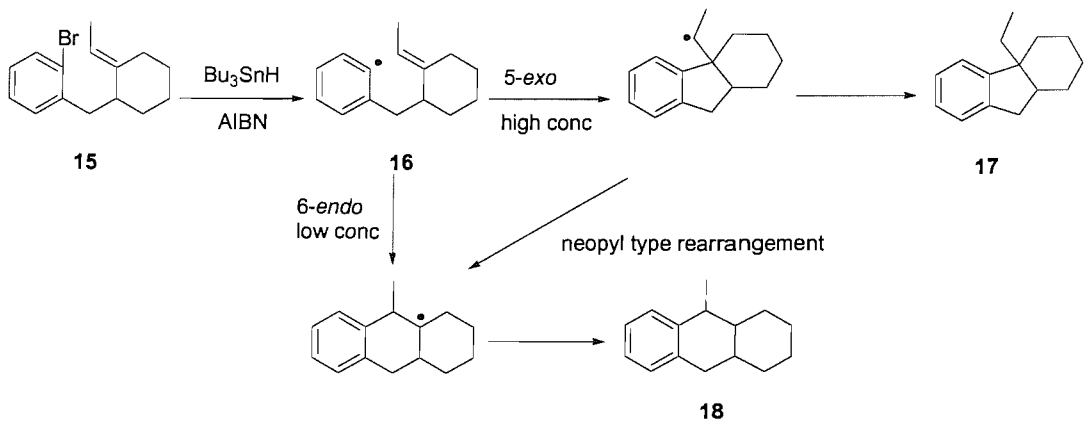


Scheme 4

Later, the reaction was revised by Beckwith who showed that the neophyl type rearrangement became predominant under certain conditions.[6] Although it was found that the neophyl type rearrangement was a relatively slow process (rate constant $k_r = 1.4x10^5$ s^{-1}

at 80 °C for **11** to **12**), it became significant when reactions were conducted at high temperature and low concentration of Bu_3SnH. Beckwith went on to show that the neophyl type rearrangement was faster for radicals adding to the naphthalene nucleus compared to those adding to a benzene. Addition was facilitated by the presence of an electron withdrawing substituent on the arene.

Ishibashi *et al.* observed a similar result when aryl bromide **15** was placed under radical forming conditions. At high concentrations of Bu_3SnH, the product derived from a 5-*exo*-trig cyclisation **17** became predominant (1 : 7, *endo* : *exo*). At low concentrations of Bu_3SnH, however, **15** gave mostly the "6-*endo* cyclised" compound **18** implicating the neophyl rearrangement (Scheme 5).[7, 8]



Scheme 5

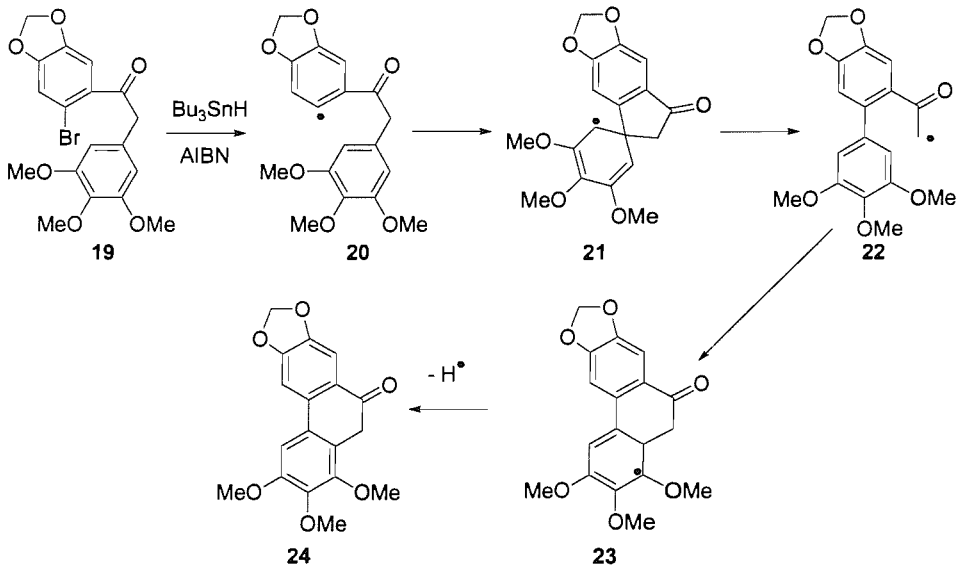
Ishibashi *et al.* also observed a related neophyl type rearrangement as a side reaction in the synthesis of mesembranol and elwesine.[9]

1.2 1,4-Aryl migration

1.2.1 From carbon to carbon

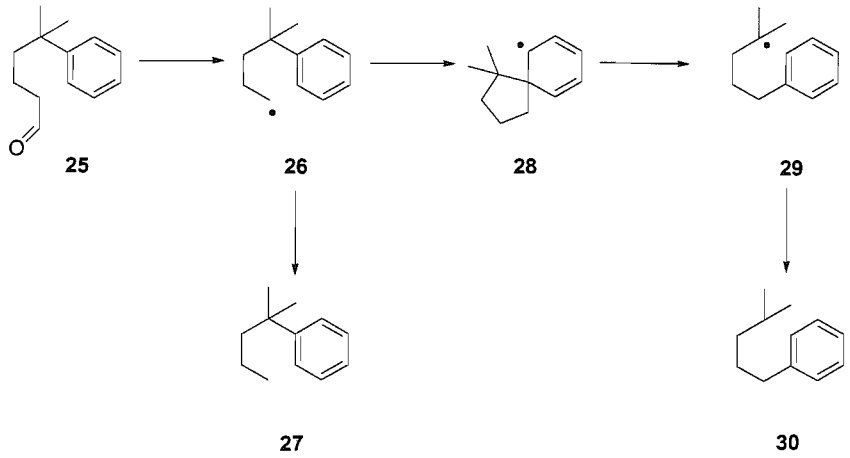
Related 1,4-aryl migrations are more common and have greater synthetic potential. Indeed, Narasimhan and Aidhen employed a radical induced 1,4-aryl migration reaction in a synthesis of steganone.[10] Thus, when ketone **19** was treated under radical forming

conditions it gave dihydrophenanthrenone **24** in 23 % yield. Its formation was presumed to result from attack of the aryl radical **20** on the *ipso* carbon of the adjacent arene. Fragmentation of the resulting spirocycle **21** then gave **22**. Cyclisation to the *ortho*-carbon of the trimethoxyarene followed to give **23**, which then collapsed to **24** (Scheme 6).



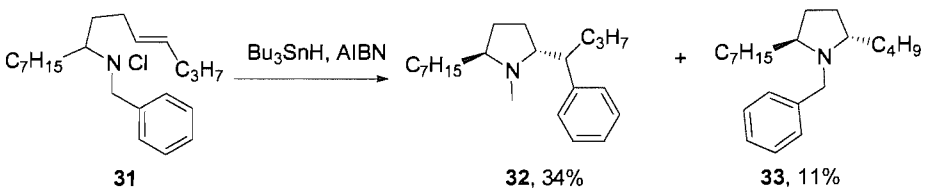
Scheme 6

Winstein *et al.* were the first to report an example of a radical induced 1,4-aryl shift (Scheme 7). It was observed during the decarbonylation of aldehyde **25**, which led to both **27** and **30**. The rearrangement can be explained by the 5-*exo*-trig cyclisation of **26** to **28**, and subsequent fragmentation to **29**.[11] Julia later revisited the reaction, and drew the same conclusion about its mechanism.[12]



Scheme 7

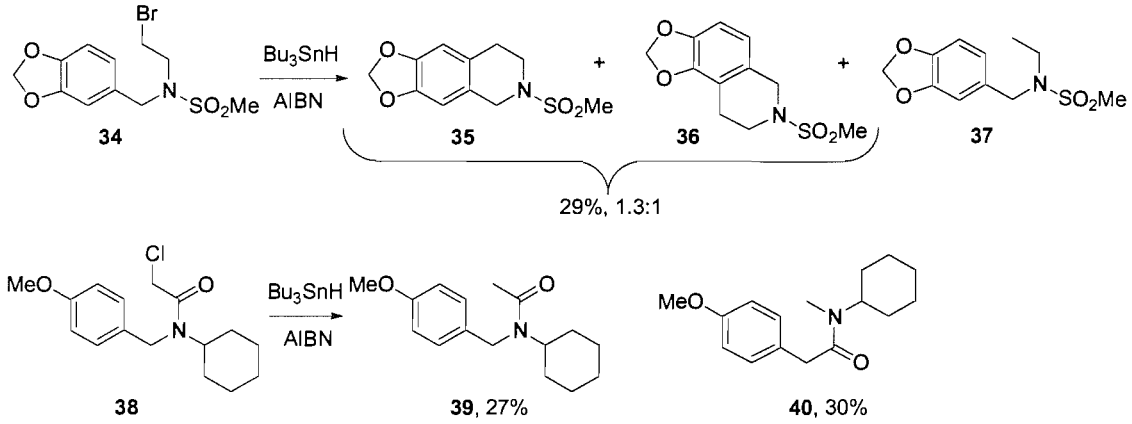
Tokuda *et al.* reported some stereoselective *ipso*-substitution reactions from various *N*-chloroamines under radical forming conditions leading to 1,4-phenyl-migrated *N*-methyl-2,5-disubstituted pyrrolidines. Thus, on treatment of **31** with tributyltin hydride and AIBN, cyclisation to the pendant alkene was followed by a 5-*exo*-trig cyclisation to the arene. Fragmentation and H-atom abstraction then gave **32**, as a single stereoisomer (Scheme 8). [13] The nature of the arene had some influence on the course of the reaction, as the presence of an electron-donating group in *para*-position lowered the overall yield significantly.



Scheme 8

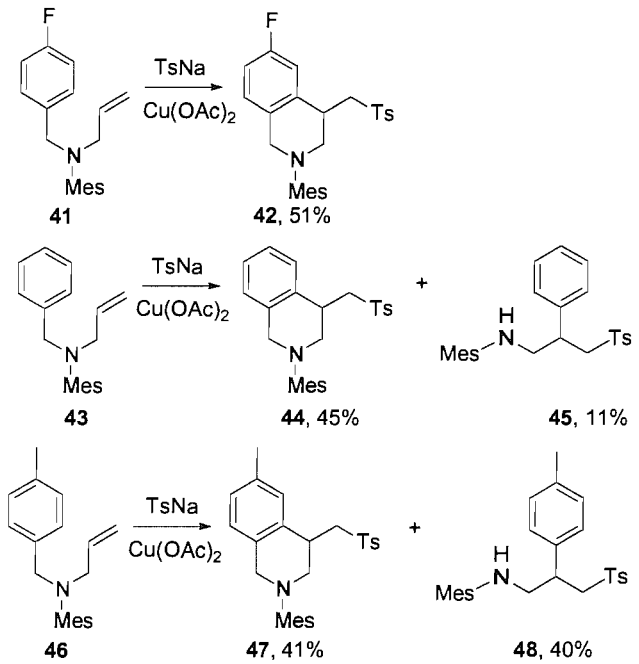
Ishibashi *et al.* carried out some comparative studies on the behaviour of sulfonamides and amides when serving as tethers in radical additions to arenes. Sulfonamide **34**, when reacted under radical forming conditions gave products **35** and **36** derived from *ortho*-cyclisation, whereas under the same conditions amide **38** yielded amide **40** derived from *ipso*-cyclisation and fragmentation. In each case a significant amount of reduced

compound was isolated. The difference in behaviour was attributed to the stability of the first formed radical intermediate.[14]



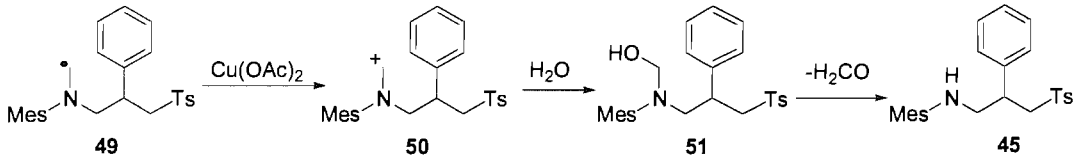
Scheme 9

Chuang *et al.* investigated the behaviour of some related aryl sulfonamines and found that electron-withdrawing groups on the aromatic ring promoted the *ortho*-cyclisation pathway while electron donating substituents promoted *ipso*-substitution (Scheme 10).[15]



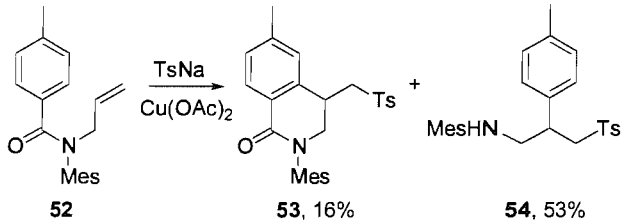
Scheme 10

The formation of **45** (and **48**) occurred *via* the mechanism described in the Scheme 11. **49** resulting from the p-toluenesulfonyl radical addition to **43**, followed by an *ipso*-cyclisation to give a cyclohexadienyl radical and an elimination, undergoes oxidation by copper(II) acetate, followed by addition of water and hydrolysis to produce **45**.



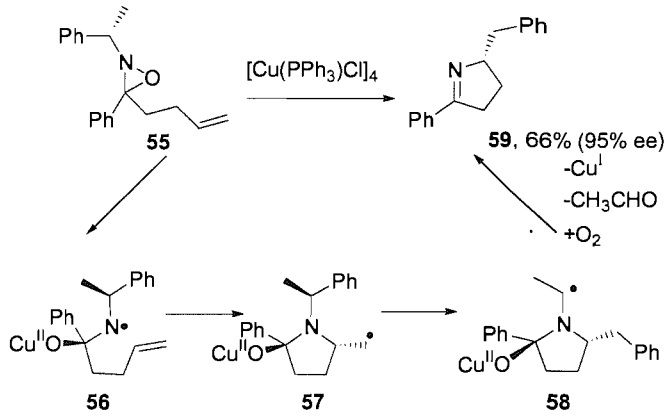
Scheme 11

The behaviour of the related aryl amides was then investigated.[15, 16] It was found that the additional carbonyl group strongly influences the course of the reaction, biasing it in favour of *ipso*-substitution (Scheme 12).



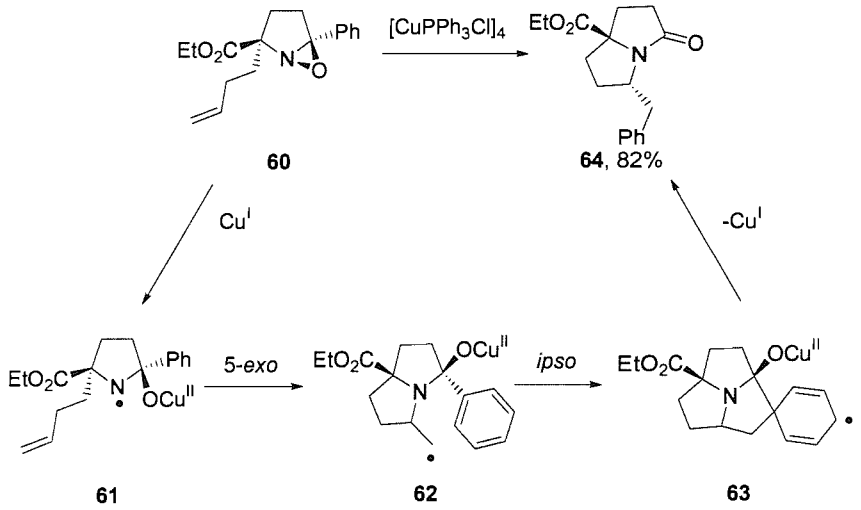
Scheme 12

Aubé *et al.* observed a stereoselective aryl migration reaction when oxaziridine **55** was treated with $[Cu(PPh_3)_4Cl]_4$. The reaction was triggered by addition of the nitrogen centred radical intermediate **56** to the proximal alkene. Cyclisation to the arene (**57→58**) was then followed by fragmentation to **59** (Scheme 13). No details were given as to how this final stage occurs.[17]



Scheme 13

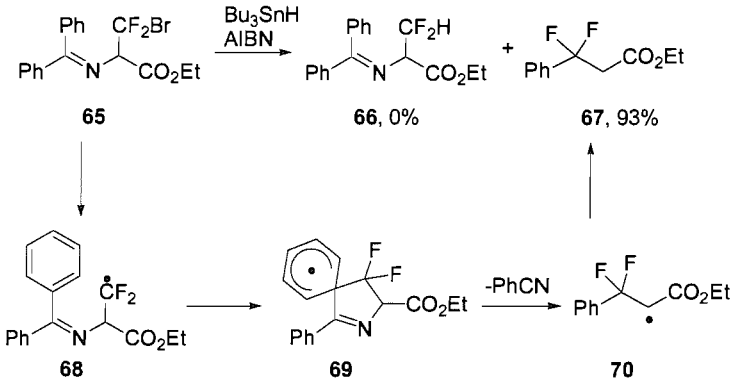
More recently Black *et al.* studied the ring opening of some oxaziridines with the same copper(I) complex to gain an insight into the stereoselectivity of the *ipso*-substitution-fragmentation process. Treatment of oxaziridine **60** likewise led to nitrogen centred radical **61** which underwent cyclisation to the proximal alkene to generate carbon centred radical **62**. *Ipso*-addition to the arene and fragment then yielded bicycle **64** as a single diastereoisomer in 63% yield. [18]



Scheme 14

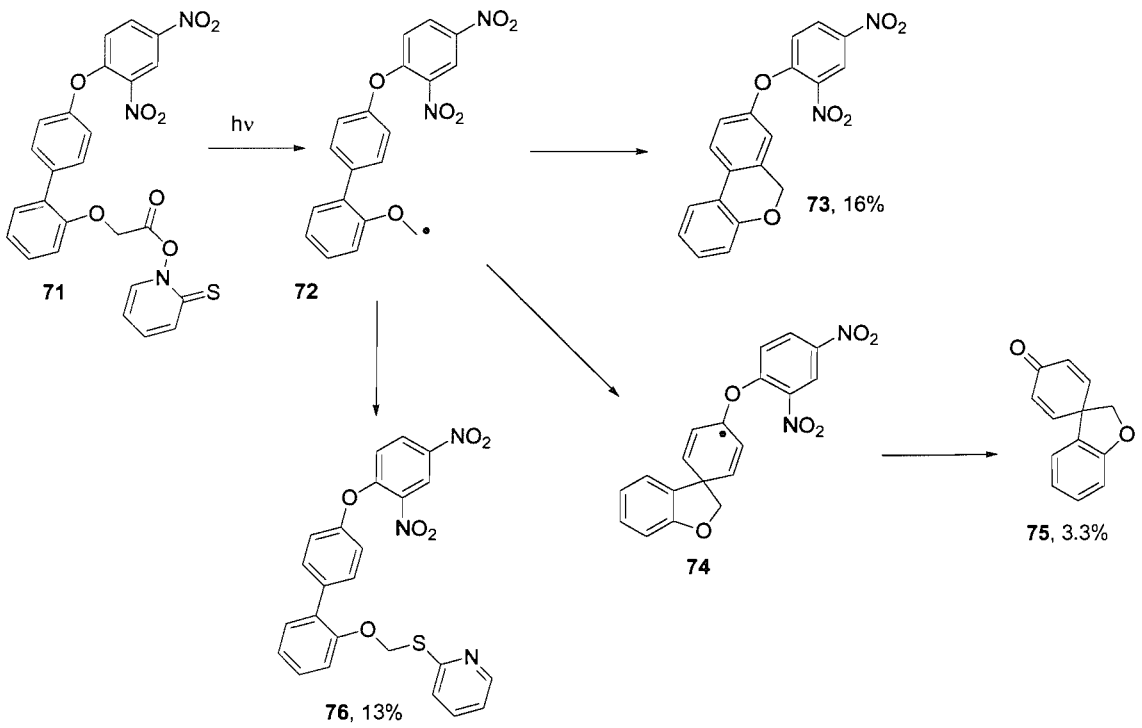
Imines have been explored as a tether for *ipso*-substitution reactions by Uneyama *et al.* Thus, the 3-bromo-3,3-difluoroalanine Schiff base **65** was easily synthesised and

transformed under radical forming conditions to the rearranged product **67** in very high yield (Scheme 15). [19]



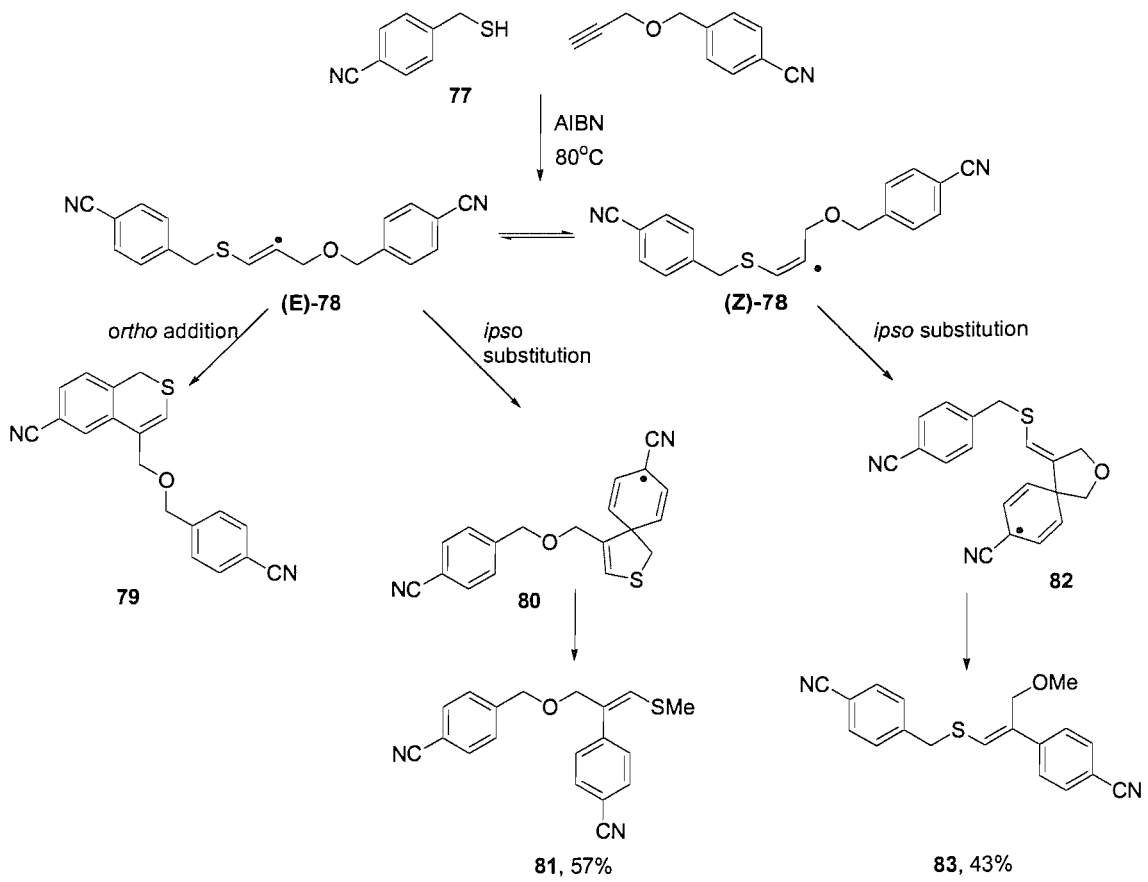
Scheme 15

Ipso-substitution has been examined as a way to access dibenzocyclooctadiene lignans. To that end, aryloxy radical **72** was formed by Barton decarboxylation of **71** and underwent a 6-*endo*/*exo*-trig cyclisation to form **73** in 16% yield. Other products identified were the biaryl **76** and tricycle **75** (Scheme 16). [20]



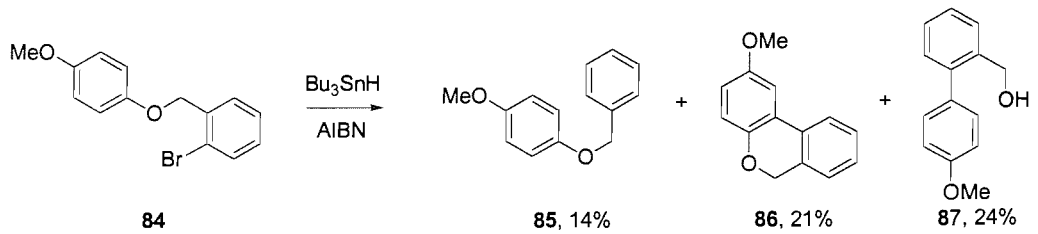
Scheme 16

Montevecchi *et al.* observed products formed from radical *ipso*-substitution when thiol **77** was added to benzyl propargyl ethers. Thus, **78** was generated by regioselective addition of the 4-cyanotoluenesulfanyl radical to alkyne. The product of *ortho*-cyclisation **79** was not observed in this case, the two products **81** and **83** being derived from *ipso*-substitution to the proximal arenes. [21]



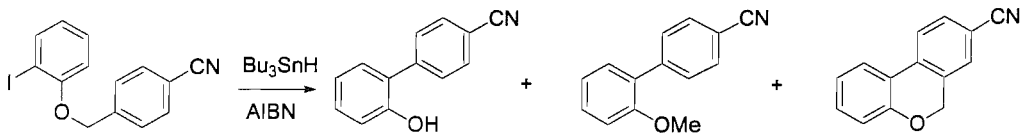
Scheme 17

Bowman *et al.* attempted to prepare 6*H*-benzo[*c*]chromen-6-ones from aryl benzoates and found these to be unsuitable substrates. The corresponding arylbenzyl ethers, by contrast, did give the desired reaction, albeit in low yield. Indeed, in many cases products derived from an *ipso*-substitution pathway were formed in higher yield than the desired compound (Scheme 18). [22]



Scheme 18

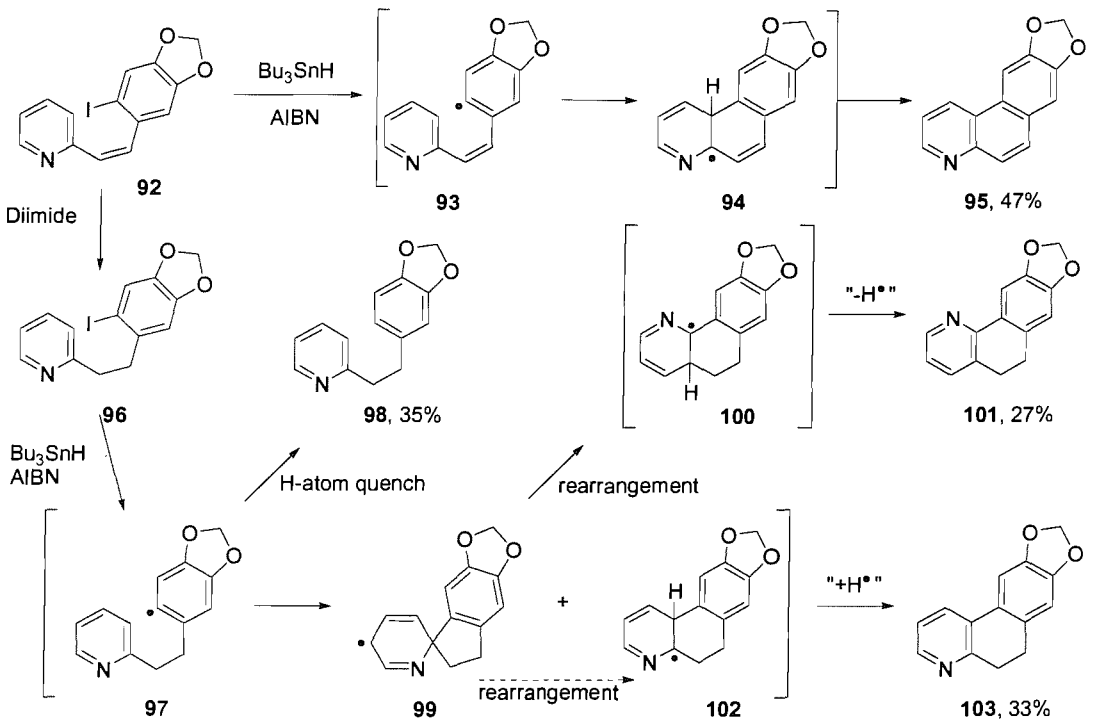
Recently, Harrowven *et al.* described a method of preparing biaryls and triaryls from benzyl iodoaryl ethers. For example, treatment of **88** with tributyltin hydride under standard radical forming conditions gave phenol **89** as the major product, together with the corresponding methyl ether **90** and tricycle **91**. The formation of **89** was not expected and further investigation is needed to understand how the methylene fragment is lost. Products **90** and **91** each result from *ipso*-cyclisation followed by a fragmentation to rearomatise the aromatic ring.[23]



88 **89**, 46% **90**, 6% **91**, 27%

Scheme 19

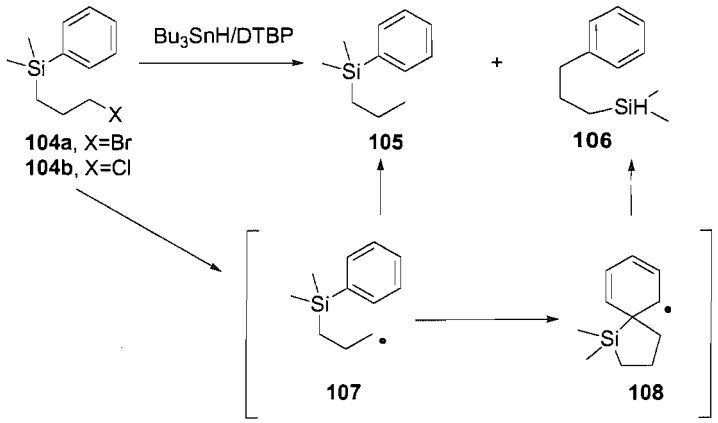
Harrowven *et al.* also discovered that intramolecular radical additions to pyridine were often favourable processes. It was shown that addition to C2, C3 and C4 were all facile process and that the tether played an important role in determining the course of the reaction. Indeed with a *cis*-alkene as a tethering group, aryl radical intermediates underwent *ortho*-cyclisation (by a 6-*exo/endo*-trig course) often in very good yields. However, when a more flexible alkane tether was used, both the reduction of the halogen and 5-*exo*-trig cyclisation modes became competitive with *ortho*-cyclisation (Scheme 20). [24, 25]



Scheme 20

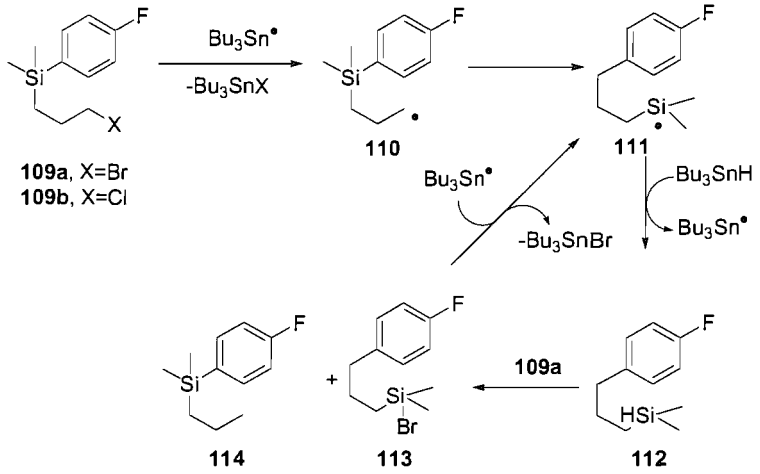
1.2.2 From silicon to carbon

Wilt *et al.* were the first to report a 1,4-aryl migration from silicon to carbon. [26] He found that the α-silyl radicals did not undergo 3-*exo*-trig cyclisation to an arene, reasoning that the silacyclopropane intermediate would be too strained. However, when bromide **104a** was treated with Bu_3SnH/ DTBP it gave a mixture of **105** and **106**, implicating the spirocyclic intermediate **108**. As expected, at concentrations of Bu_3SnH higher than 3.0 M rearrangement was not observed. The result showed that a 1,4-aryl shift from silicon to carbon is generally less facile than a 1,2-aryl shift from carbon to carbon. Interestingly, the nature of the halide also influenced the outcome of the reaction. With alkyl chlorides more rearranged product was observed compared to the corresponding alkyl bromide treated under the same conditions. This difference in behaviour decreased when dilution was increased.



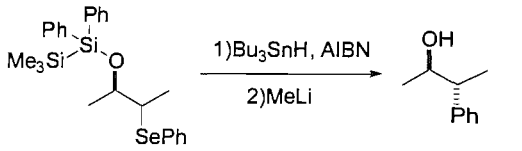
Scheme 21

This unusual behaviour suggested that the silane product (e.g. **112**) could reduce alkyl bromides such as **109a** but was inert towards the corresponding alkyl chloride **109b** (Scheme 22).



Scheme 22

Studer *et al.* observed several high yielding 1,4-aryl migrations from silicon to an alkyl radical with silyl ethers such as **115**. No products derived from *ortho* attack of the phenyl ring were observed, and best yields were obtained for the migration of the unfunctionalized phenyl group rather than substituted arenes.

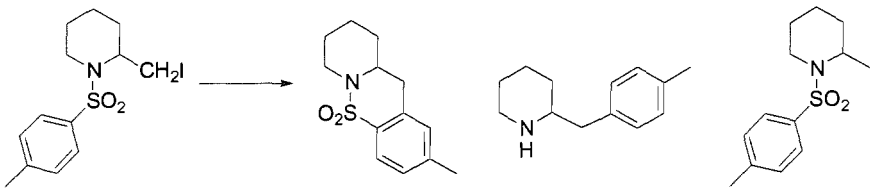


115 **116**, 81%
dr (*u:l*= 14:1)

Scheme 23

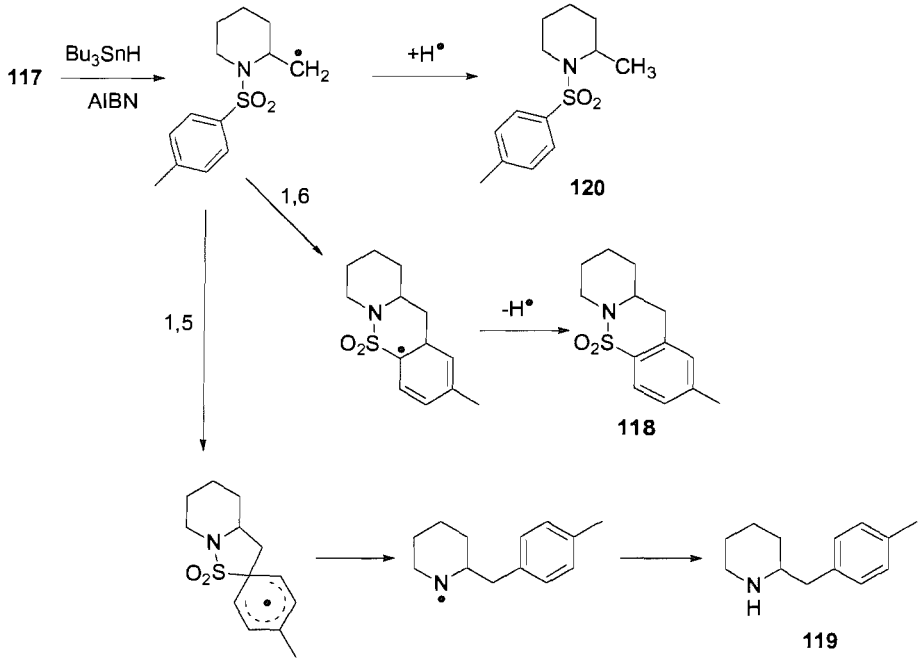
1.2.3 From sulfur to carbon

Speckamp *et al.* investigated the radical induced migration of the *p*-tolyl group in *p*-toluenesulfonamides. They showed that when **117** was placed under radical forming conditions it gave rise to three products **118-120**. The first, **118**, was formed as a result of *ortho* addition of the radical intermediate to the arene while **119** resulted from an *ipso* attack on the arene followed by extrusion of sulfur dioxide. **120** was formed by direct reduction of the starting material (Scheme 24). The reaction conditions employed had a significant influence over the course of the reaction. It was noted that at room temperature *ortho*-cyclisation predominated while at 190 °C rearrangement was the dominant pathway. When hexabutyltin and di-*tert*-butyl peroxide were used to facilitate the reaction at reflux in benzene, **118** was obtained in 64% yield and the reduced product **120** was completely suppressed (Scheme 24). [27]



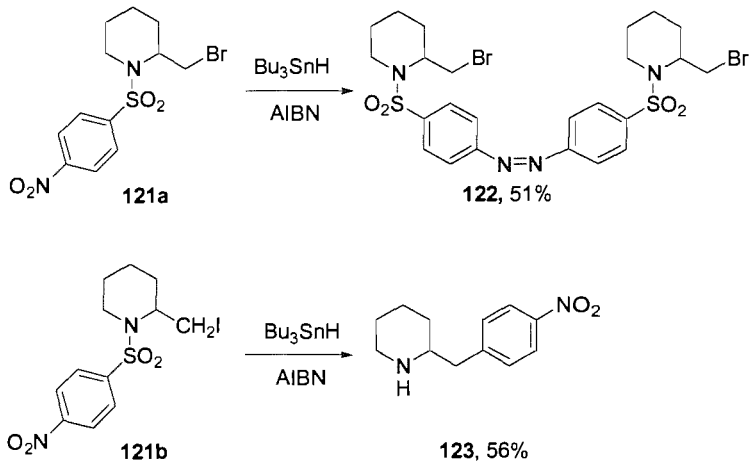
117 **118** **119** **120**

reflux, benzene, Bu_3SnH/AIBN	45%	32%	23%
22 °C, anisole, Bu_3SnH/AIBN	68%	0%	30%
190 °C, diphenyl ether, Bu_3SnH/AIBN	26%	64%	9%
reflux, benzene, $(Bu_3Sn)_2$/^{t}BuOO^{t}Bu	64%	25%	0%



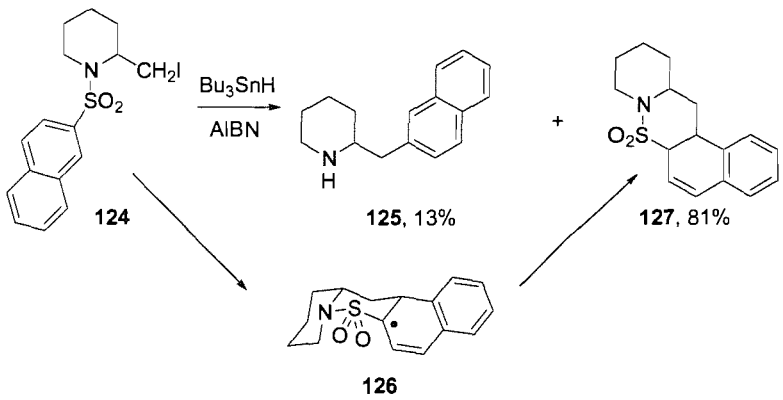
Scheme 24

Speckamp *et al.* went on to study the effect of substituents on the outcome of the reaction. They showed that the course of the reaction was often influenced by the choice of halide in the starting material. With the 4-nitroarene derivative **121b**, for example, the iodide gave the product of ipso-substitution **123** in 56% yield whereas the corresponding bromide **121a** gave dimer **122** in 51% yield by reduction of the nitro group (Scheme 25). [28]



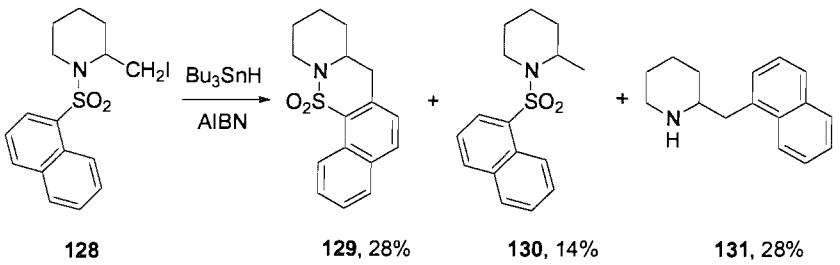
Scheme 25

A surprising result was noted when naphthyl sulfonamides **124** and **128** were examined. In the case of **124**, dihydronaphthalene **127** was formed in 81% yield rather than the corresponding naphthalene. In this case the radical intermediate **126** is stabilised by conjugation to both the double bond and the sulfonamide group.



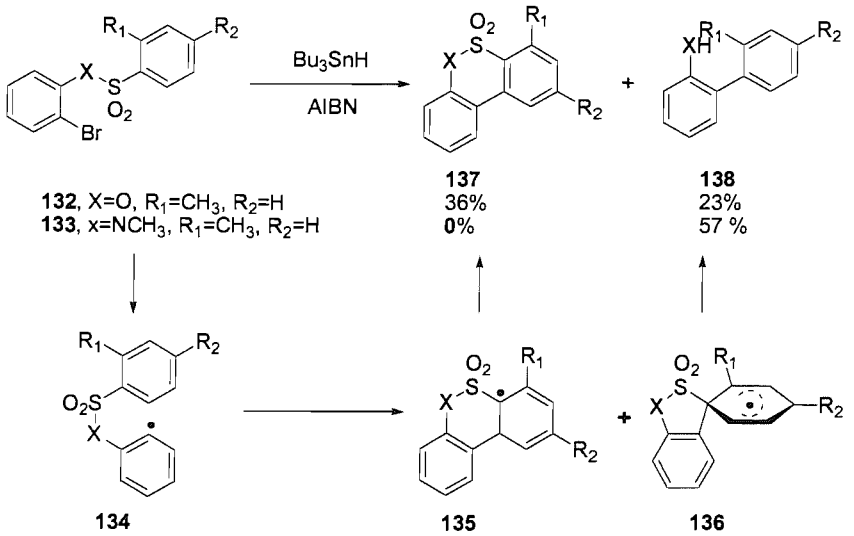
Scheme 26

By contrast, the isomeric naphthalene **128** gave a complex product mixture (Scheme 27), including both the rearranged product **131** and naphthalene **129**. Notably, the radical intermediate in this case is not stabilised by conjugation to an alkene and consequently rearomatisation becomes the favoured process. A similar aryl migration has been observed by Clive *et al.* [29]



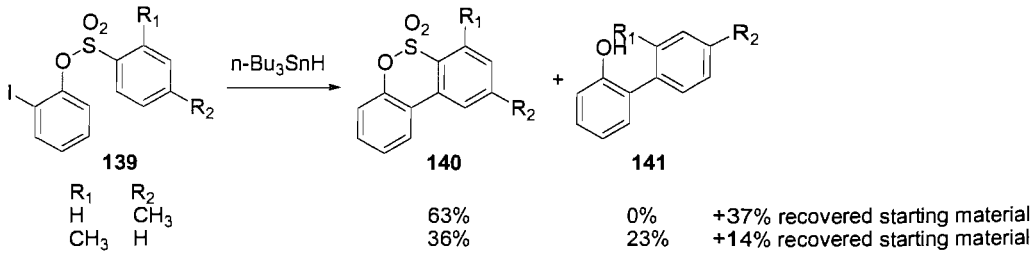
Scheme 27

Motherwell *et al.* used the method to develop a new route to biaryls and heterobiaryls. Aryl radicals were chosen as the radical donor as the main focus of their study was to understand the factors influencing the selectivity of the reaction toward either *ortho*-addition or *ipso*-substitution. It was noticed that when X=NMe *ipso*-substitution became the dominant pathway (Scheme 28). [30, 31]



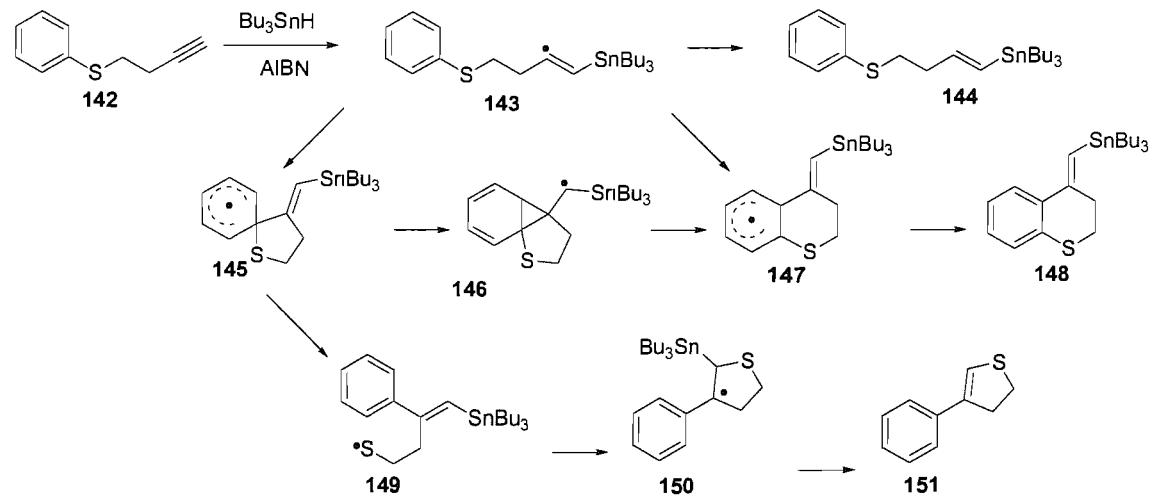
Scheme 28

It was shown that an *ortho*-methyl group on the acceptor arene also biased reactions in favour of *ipso*-substitution (Scheme 29). Presumably, steric encumbrance pushes the equilibrium between **135** and **136** toward formation of the latter. A carbomethoxy group on the *ortho* carbon of the arene acceptor likewise promoted *ipso*-substitution while the same substituent placed in the *meta* position promoted 1,6-addition to the two *ortho* positions.



Scheme 29

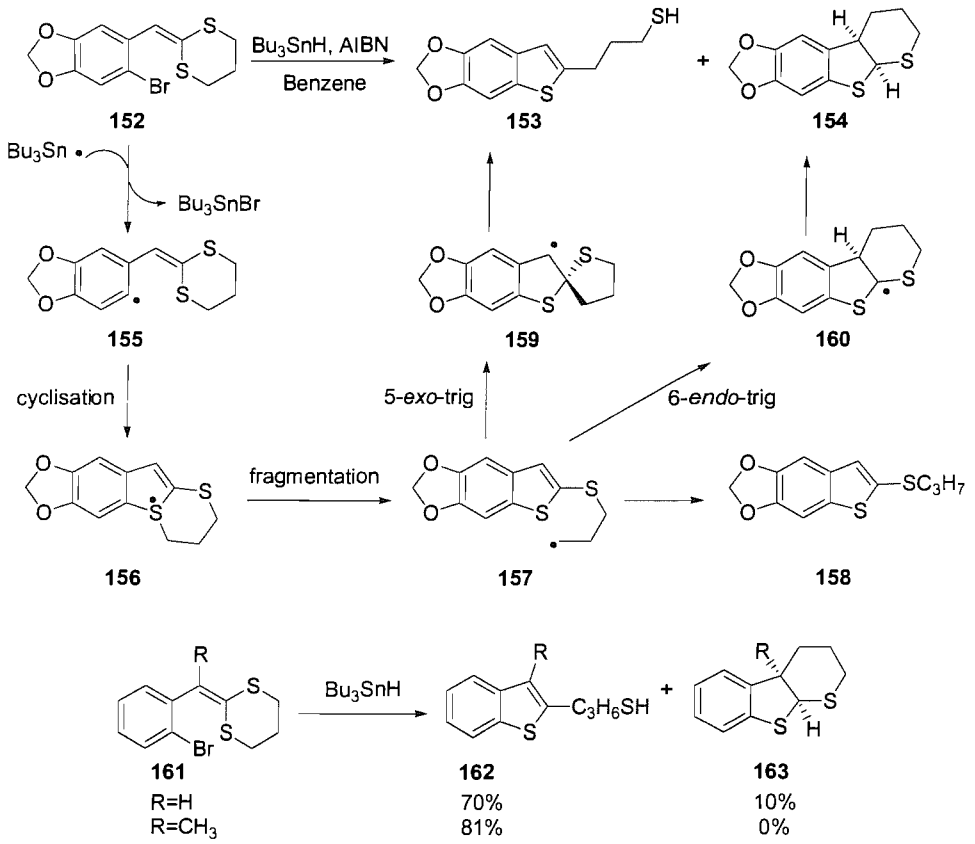
Montevecchi *et al.* observed a similar aryl migration when sulfide **142** was treated with tributyltin hydride and AIBN. In this case, a number of different pathway were followed. *Ipso*-substitution to **145** was followed in part by a second cyclisation to cyclopropane **146**. This in turn collapsed to **147** a precursor of **148**. Alternatively, fragmentation of the C-S bond in **145** gave sulfur centred radical **149**. This was then captured by the vicinal alkene in a 5-*endo*-trig cyclisation leading to the formation of stannane **150**. Elimination of tributyltin radical then gave dihydrothiophene **151**. An hydrogen abstraction by the radical **143** would lead to **144**. These three products were afforded in a 1:2:3 ratio in 85% yield.[32]



Scheme 30

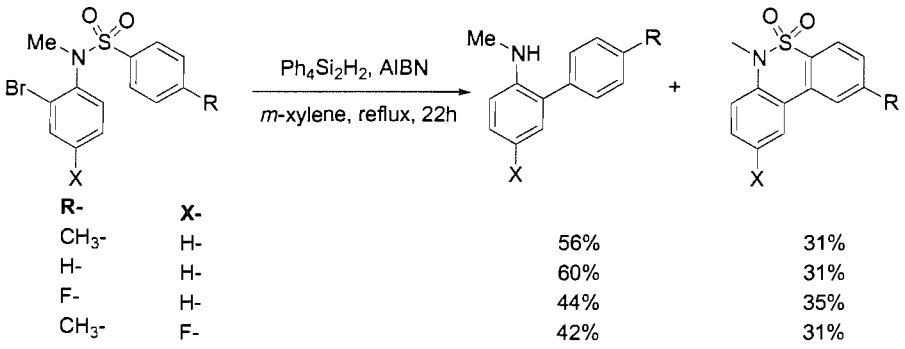
Earlier, Harrowven had observed a related rearrangement within a cascade sequence leading to benzo[*b*]thiophenes. Thus, treatment of **152** with tributyltin hydride and AIBN initiated a 5-*exo*-cyclisation to sulfur leading to the formation of carbon centred radical intermediate **157**. A second cyclisation to the benzo[*b*]thiophene next gave **159** which

rearomatised by ejection of a sulfur centred radical intermediate to give **153** on work-up. Two minor products were also isolated; the tetracyclic thioacetal **154** resulting from a 6-*endo*-trig cyclisation of **157** to **160** and the benzo[*b*]thiophene **158** derived from **157** by H-atom abstraction. It was noted that increased steric hindrance on the olefin, *e.g.* **161**, biased the reaction in favour of the benzo[*b*]thiophene **162** (Scheme 31).[33, 34]



Scheme 31

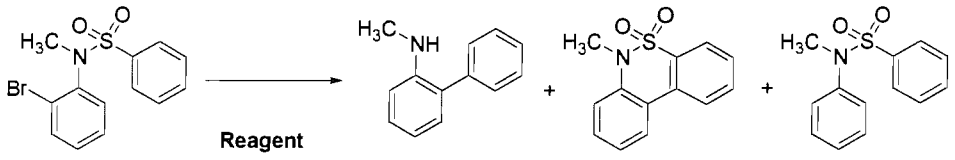
Togo *et al.* have studied the effect of substituents on the *ipso*-substitution reactions of various sulfonamides.[35] The study showed that an electron-withdrawing substituent in the *para*-position of the radical acceptor decreases the yield of *ipso*-substitution products. Introduction of an electron-withdrawing substituent in the aniline moiety of the sulfonamide likewise reduced the amount of the *ipso*-substitution product formed (Scheme 32).



R-	X-		
CH_3-	H-	56%	31%
H-	H-	60%	31%
F-	H-	44%	35%
CH_3-	F-	42%	31%

Scheme 32

They found that the optimum conditions to perform a radical *ipso*-substitution reaction employed 1,1,2,2-tetraphenyl-disilane as a mediator and AIBN as an initiator (Scheme 33).

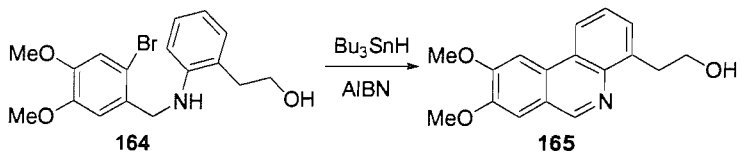


Reagent			
Ph_2SiH_2	20%	23%	-
n-Bu_3SnH	41%	37%	18%
$(TMS)_3SiH$	56%	22%	-
$Ph_4Si_2H_2$	60%	31%	-

Scheme 33

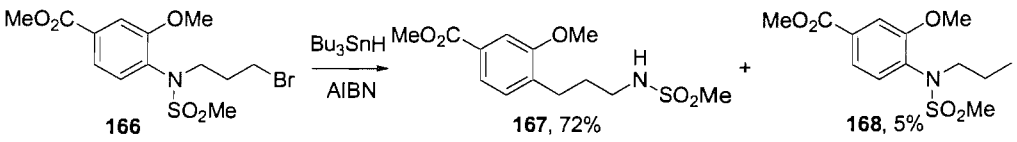
1.2.4 From nitrogen to carbon

Lobo *et al.* used a radical induced *ortho*-cyclisation as a key step in the synthesis of several alkaloid natural products. Notably for aryl bromide **164** no *ipso* cyclisation was observed (Scheme 34). [36, 37]



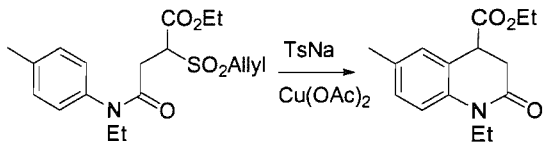
Scheme 34

By way of contrast, Lee showed that sulfonamide **166** gave the rearrangement product **167** in high yield demonstrating the need to stabilise a nitrogen centred radical in order to induce fragmentation. It was also shown that radical additions with sulfonamides such as **166** proceed by *ipso*-substitution alone leading to **167**. The best yield was obtained when an electron donating and a withdrawing group were placed respectively on the *ortho* and *para* position of the arene acceptor (Scheme 35).[38] It was concluded that the efficiency of such aryl migration from nitrogen to carbon depends strongly on the stability of the intermediate spiro cyclohexadienyl radicals. Radical *ipso* attack is most efficient if the intermediate is "captodatively" stabilized, and homolytic cleavage of the C-N bond for rearomatisation is kinetically favourable.



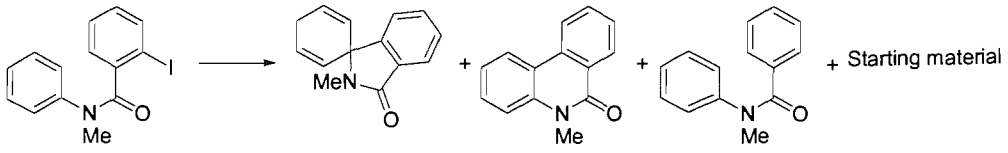
Scheme 35

Chuang *et al.* have described a related reaction with amide **169**. Here , the only product observed resulted from *ortho*-cyclisation to the arene (Scheme 36).



Scheme 36

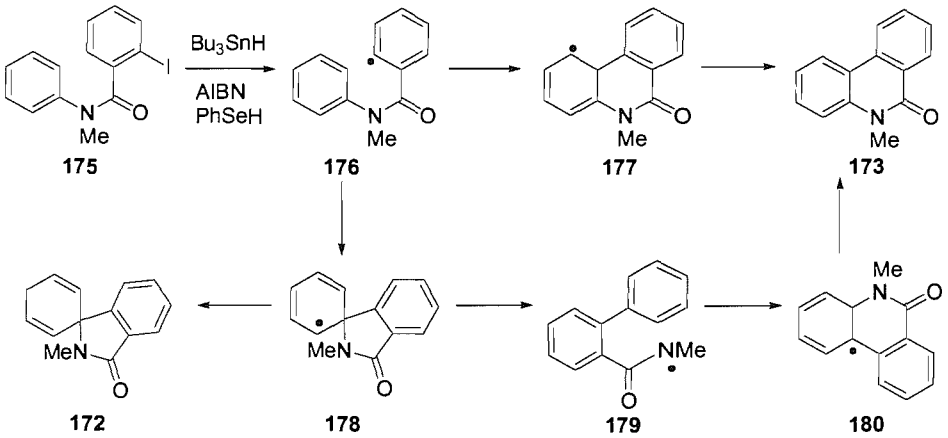
Crich [39] and Bowman [40-42] each investigated the *ortho/ipso* addition of related aryl radical intermediates tethered to an arene by an amide linkage. A number of products were formed in each case, all in low yield. Notably one of these was spirocycle **172**, showing that the amide is a poor radical leaving group (Scheme 37).



	171	172	173	174	
Bu_3SnH/AIBN		0%	12%	23%	37%
Bu_3SnH/PhSeH/AIBN		43%	22%	22%	0%

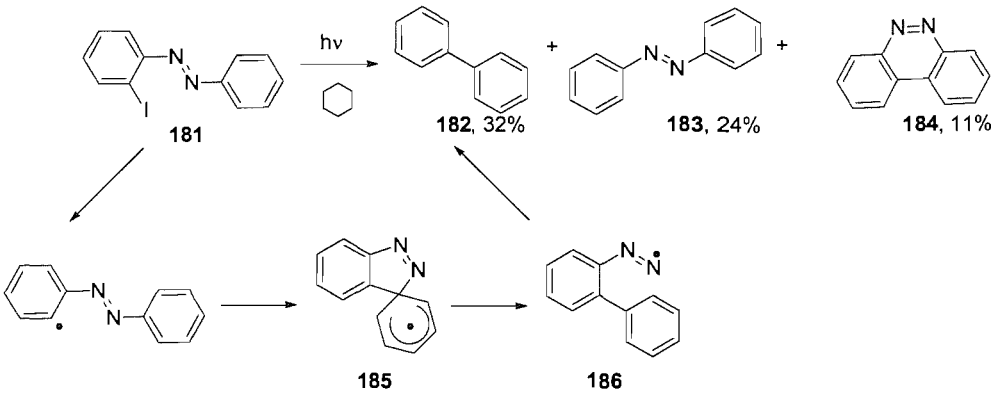
Scheme 37

It was suggested that **173** resulted from the rearrangement of **178** rather than a direct *ortho*-addition (Scheme 38). This conclusion was based on the observation that the yield of spirocycle **172** increased significantly on addition of benzene selenol. Crich concluded that "benzeneselenol catalysed the chain propagation by quenching of the kinetically cyclised radical **178** before it could undergo rearrangement to **173**".



Scheme 38

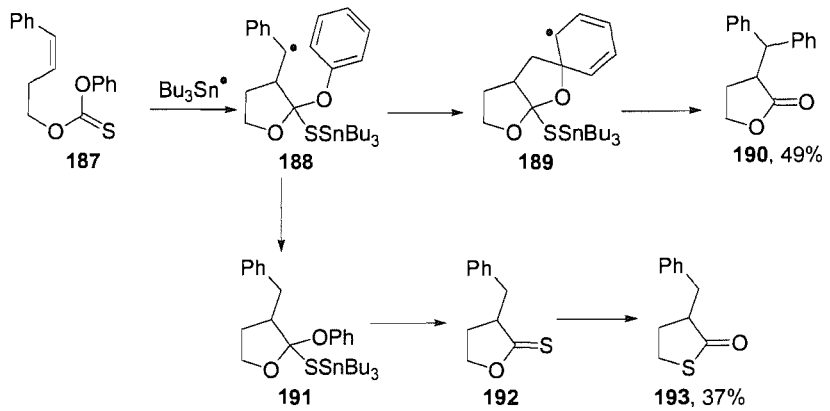
An interesting synthesis of biaryls has been achieved by photolysis of *trans*-diazobenzene iodides such as **181** in cyclohexane.[43] Three reaction pathways were noted: reduction of the halogen in the starting material leading to **183**, *ipso*-substitution *via* **185** leading to phenyl **182**, and the *ortho*-addition to **184**.



Scheme 39

1.2.5 From oxygen to carbon

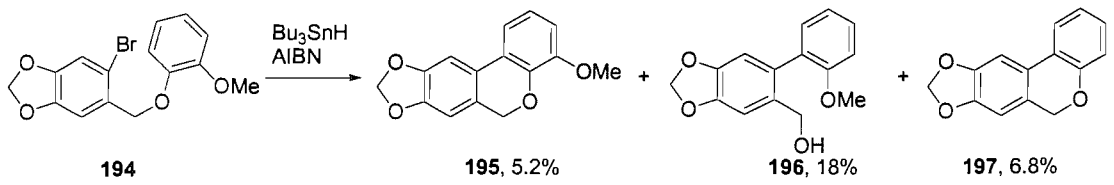
In 1989, Bachi *et al.* reported a new route to thionolactones involving radical *ipso*-substitution (Scheme 40). The formation of γ-lactone **190** from **187** implicated the formation of **188**, radical cyclisation to **189** and fragmentation of the C-O bond to give **190**. Loss of tributyltinthiyl radical presumably provides a strong driving force for the scission of the ether.



Scheme 40

Lobo *et al.* have reported a series of related *ipso*-substitution reactions leading to biaryls. Thus, when **194** was treated with tributyltin hydride and AIBN, *ortho*-cyclisation and *ipso*-substitution was each observed as significant pathway. In the latter case, ejection of the

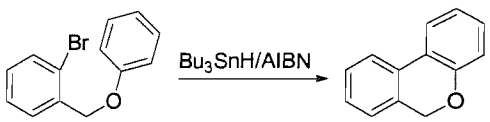
benzoxyl radical was followed by H-atom abstraction to give **196** in 18% yield (Scheme 41). [44]



194 **195**, 5.2% **196**, 18% **197**, 6.8%

Scheme 41

For substrates lacking oxygen substituents on the arenes, such as **198**, only the product of *ortho*-cyclisation **199** was given (Scheme 42).

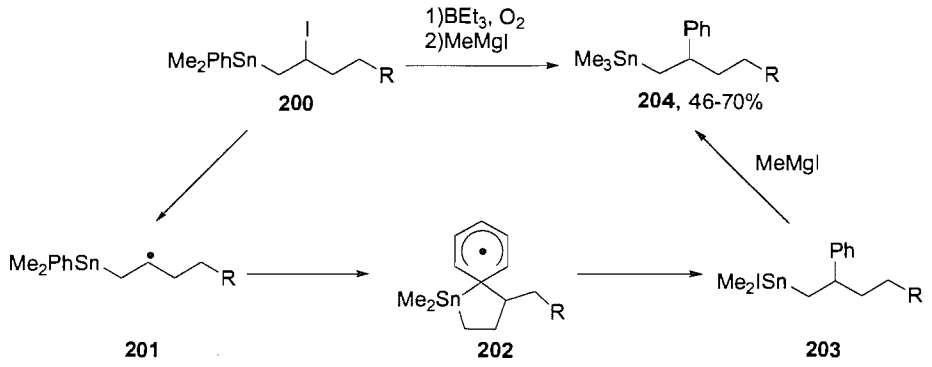


198 **199**, 48%

Scheme 42

1.2.6 From tin to carbon

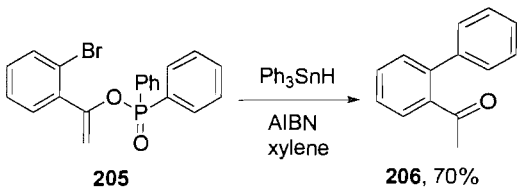
Only one example has been found of a radical induced 1,4-aryl migration from tin to carbon. It was reported by Oshima *et al.*, who induced the radical cyclisation of **200** with triethylborane (Scheme 43). The reaction afforded mainly the trimethyl stannane derivative **204** and yields for a series of related reactions were good to excellent. [45]



Scheme 43

1.2.7 From phosphorus to carbon

Clive *et al.* investigated the synthesis of biaryls by intramolecular *ipso*-substitution of phosphinates. The process involved a migration of an aryl ring from phosphorus to carbon. Best results were obtained with enol phosphinates akin to **205**, which gave biaryl **206** in 70% yield (Scheme 44). [46, 47]

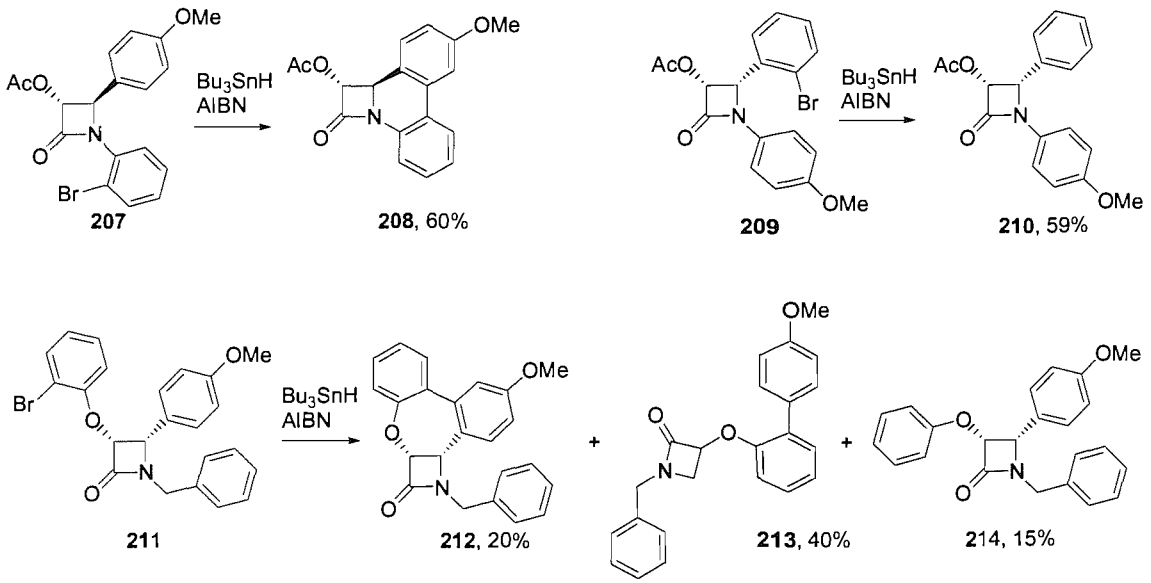


Scheme 44

1.3 1,5-aryl migrations

1.3.1 From carbon to carbon

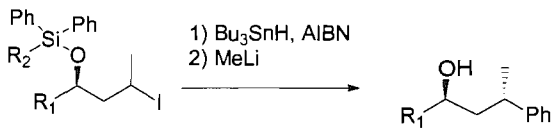
Alcaide *et al.* studied a series of cyclisation reactions involving β-lactams. They focused, their investigation on the influence of substituents in the aromatic acceptor ring on the regioselectivity of aryl radical addition to a vicinal arene. Some of the findings are summarised in Scheme 45. [48]



Scheme 45

1.3.2 From silicon to carbon

Studer *et al.* have conducted extensive studies on the stereoselectivity of 1,5-aryl migration from silicon to carbon. The effect of substituents on both the silicon and the aliphatic chain have each been examined (Scheme 46).[49, 50] It was found that a substituent on the ethereal carbon (R_1) had little impact on the stereoselectivity of such reaction. The yield of the reaction was however greatly affected by the nature of R_2, the highest yield being obtained when R_2=$SiMe_3$. Diastereoselectivity was good in all cases (10:1 with **215a-c** and 6:1 with **215d**).

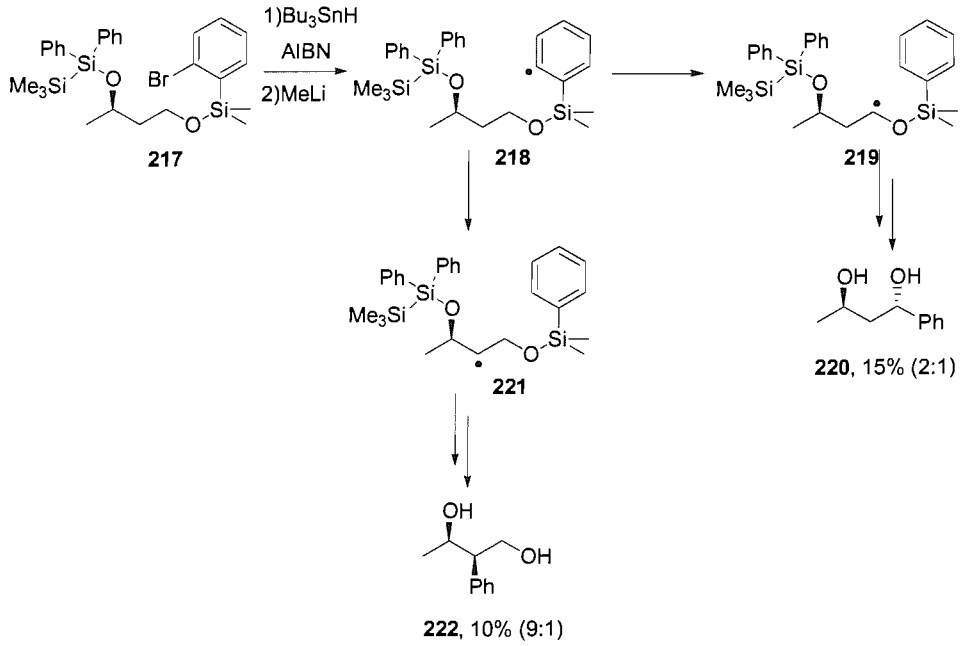


216

215a R_2= $SiMe_3$	70%
215b R_2=$GeMe_3$	57%
215c R_2=$SnMe_3$	35%
215d R_2=CMe_3	33%

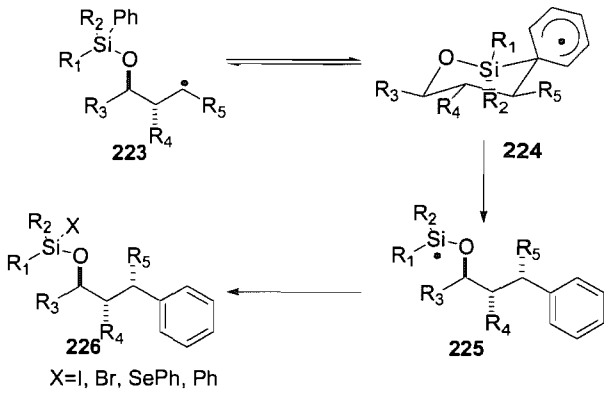
Scheme 46

The nature of the attacking radical was also investigated. For example, treatment of **217** under standard radical forming conditions induced both 1,4- and 1,6-aryl migration (Scheme 47) *via* the two radical intermediates **219** and **221**. The products isolated following treatment with MeLi being diols **220** and **222**.



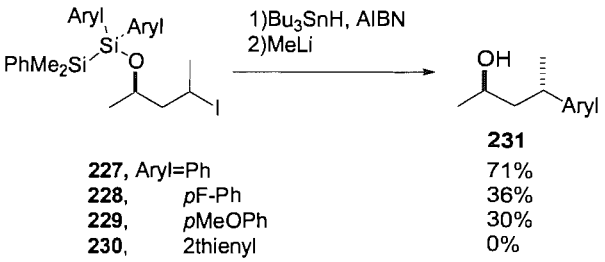
Scheme 47

The stereoselectivity observed was explained by invoking a chair like transition state **224** when the radical **223** adds to the *ipso* carbon of the phenyl group (Scheme 48). Fragmentation of the carbon to silicon bond and quenching of the radical gives **226**.



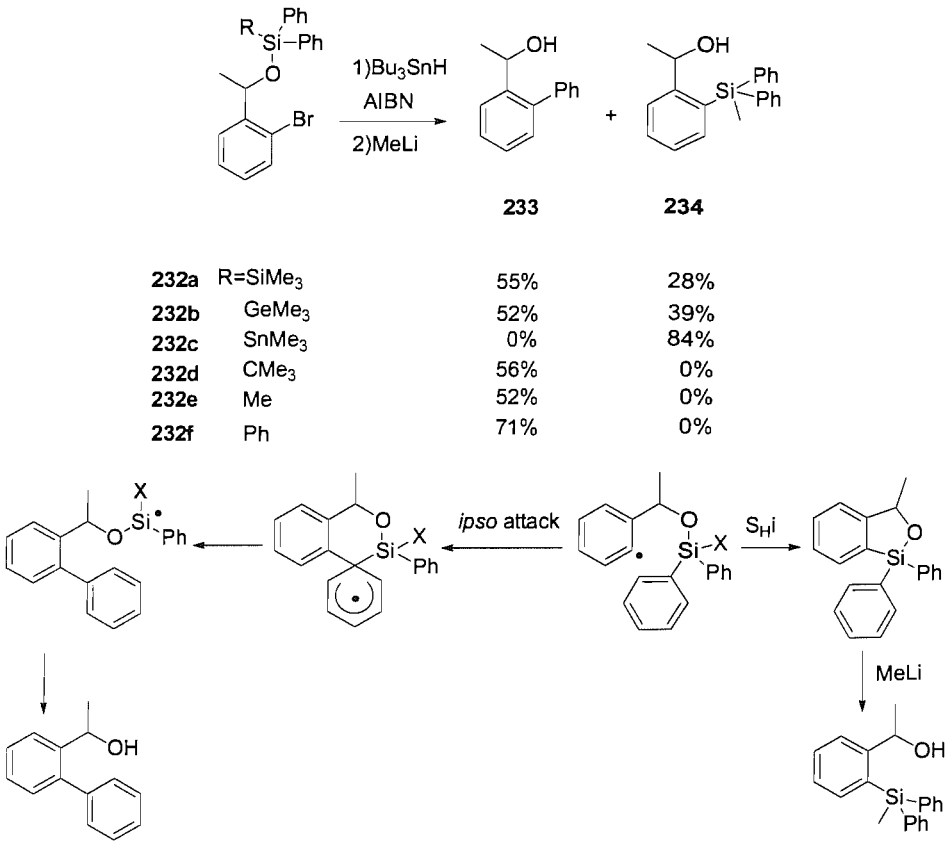
Scheme 48

The scope of such reactions was extended by changing the aryl group attached to silicon. Of the systems studied, migration was most efficient with a phenyl group, functionalised arenes being transferred less efficiently (Scheme 49).



Scheme 49

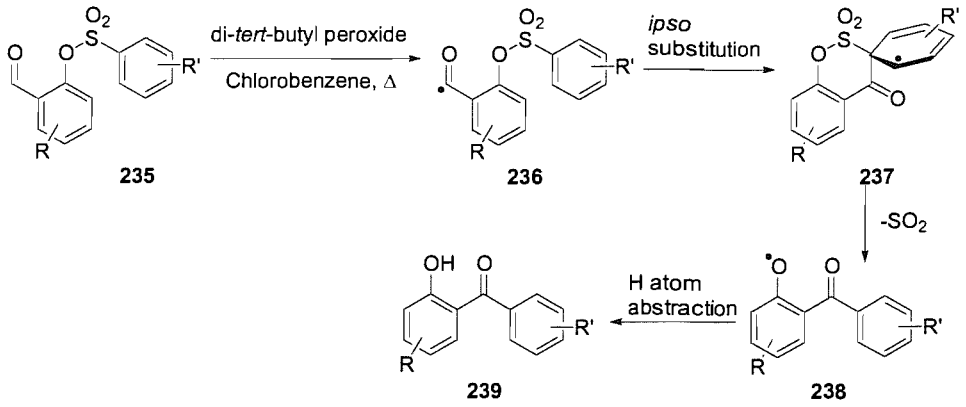
The same group also developed a related method of preparing biaryls by aryl migration.[50] They prepared several diphenylsilyl derivatives **232** and placed them under radical forming conditions (Scheme 50). It was found that substituents on the aryl attached to silicon strongly influenced the outcome of the reaction leading to either **233** or **234**. The latter was observed as significant product when homolytic substitution at silicon (S_Hi) was favourable (**232a-c**). Indeed, with the stannylated silyl ether **232c** it was the only observed product, formed in 84%. By contrast **233** was the only product observed when alkyl or phenyl groups were attached to silicon. In such cases biaryls were generally formed in moderate to good yields (52-71%).



Scheme 50

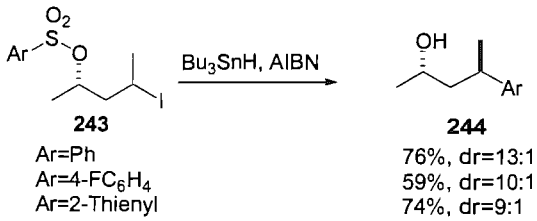
1.3.3 From sulfur to carbon

Analogous reactions have been reported with aryl sulfonyl esters (Scheme 51).[51] In the example highlighted in Scheme 51, best results were obtained when R=H and R'=4-CH_3, when benzophenone **239** was produced in an isolated yield of 80%. Electron donating and electron withdrawing groups were each tolerated in the aromatic sulfonyl acceptor ring. However the incorporation of a methoxy group in the donor ring resulted in a much lower yield.



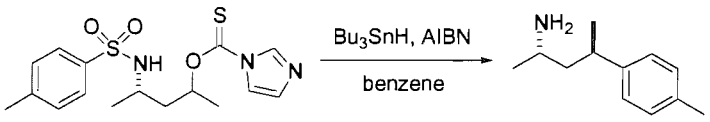
Scheme 51

Studer *et al.* extended their earlier work with silanes to uncover a series of stereoselective *ipso*-substitution reaction of sulfonates.[52, 53] The stereoselectivity observed was readily explained by invoking a chair like transition state akin to that discussed in Scheme 48, with substituents preferentially adopting an equatorial orientation.

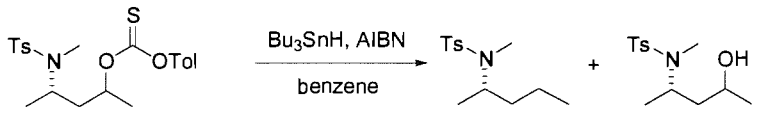


Scheme 52

The 1,5-aryl migration in the sulfonamides was not as efficient as in the sulfonate series described above but could be achieved with complete stereocontrol (Scheme 53).



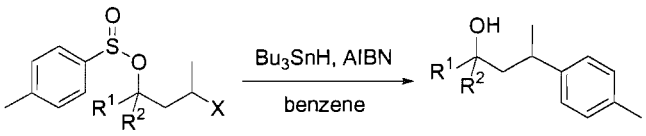
245 **246**, 37%, *u:l* 95:5



247 **248**, 69% **249**, 5%

Scheme 53

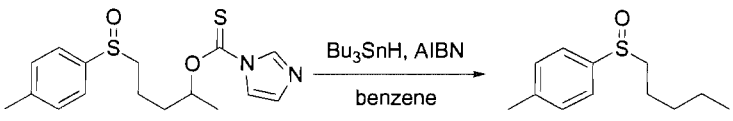
The 1,5-aryl migration from sulfur to carbon in arenesulfinates proved to be far less efficient. Indeed of the few substrates examined, **250a-d**, only one gave the desired rearrangement in greater than 10% yield (Scheme 54).



250a, R^1=R^2=H, X=Br — **251**, 6%
250b, R^1=R^2=H, X=I — **252**, 0%
250c, R^1=Me, R^2=H, X=Br — **253**, 20%, u:l=10:1
250d, R^1= R^2=Me, X=Br — **254**, 9%

Scheme 54

Interestingly no 1,5-aryl migration was observed with arenesulfoxides **255**. In this case the product of reduction **256** was recovered in near quantitative yield (Scheme 55). A 1,5-aryl migration from sulfur to carbon involving a sulfide related to that described in Scheme 16 has been reported.[32]

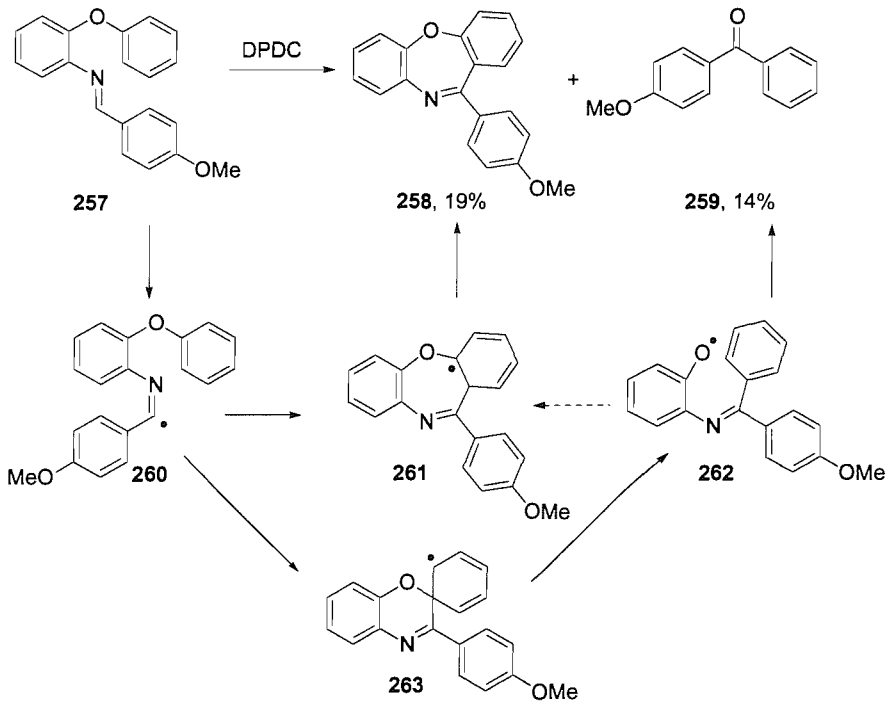


255 **256**, 96%

Scheme 55

1.3.4 From oxygen to carbon

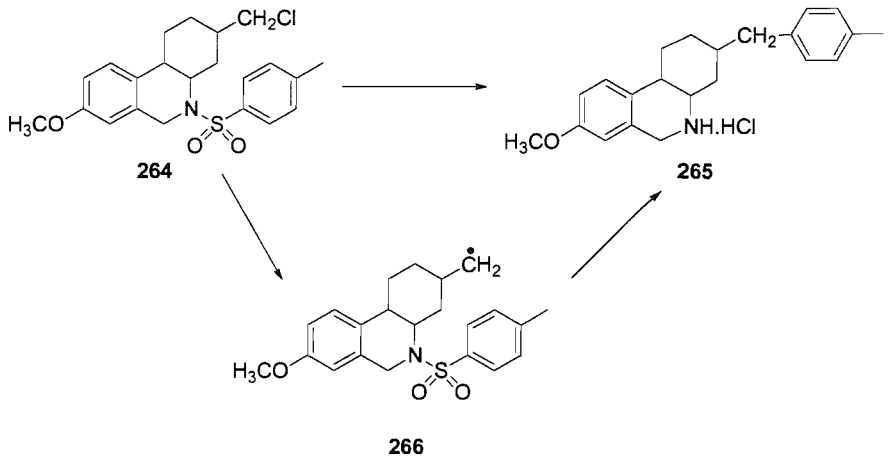
Nanni reported an interesting, if low yielding aryl migration from oxygen to carbon. Radical intermediate **260** was readily generated from imine **257**. *Ortho* cyclisation and rearomatisation of this intermediate led to oxazepine **258**. *Ipso* cyclisation led to ketone **259** after fragmentation of the intermediate spirocycle **263** and hydrolysis of the thus formed imine **262**.[54, 55]



Scheme 56

1.4 1,6-aryl migration

The first report of an aryl migration from a sulfur to a carbon was made by Speckamp *et al.* who found that chloride **264** was transformed into amine **265** in 50% yield when treated under standard radical forming conditions. The result can be explained by the addition of the alkyl radical **266** to the *ipso* carbon of the vicinal aryl. Fragmentation of the carbon-sulfur bond and elimination of sulfur dioxide led to the formation of **265** (Scheme 55). [56]



Scheme 57

1.5 Conclusion

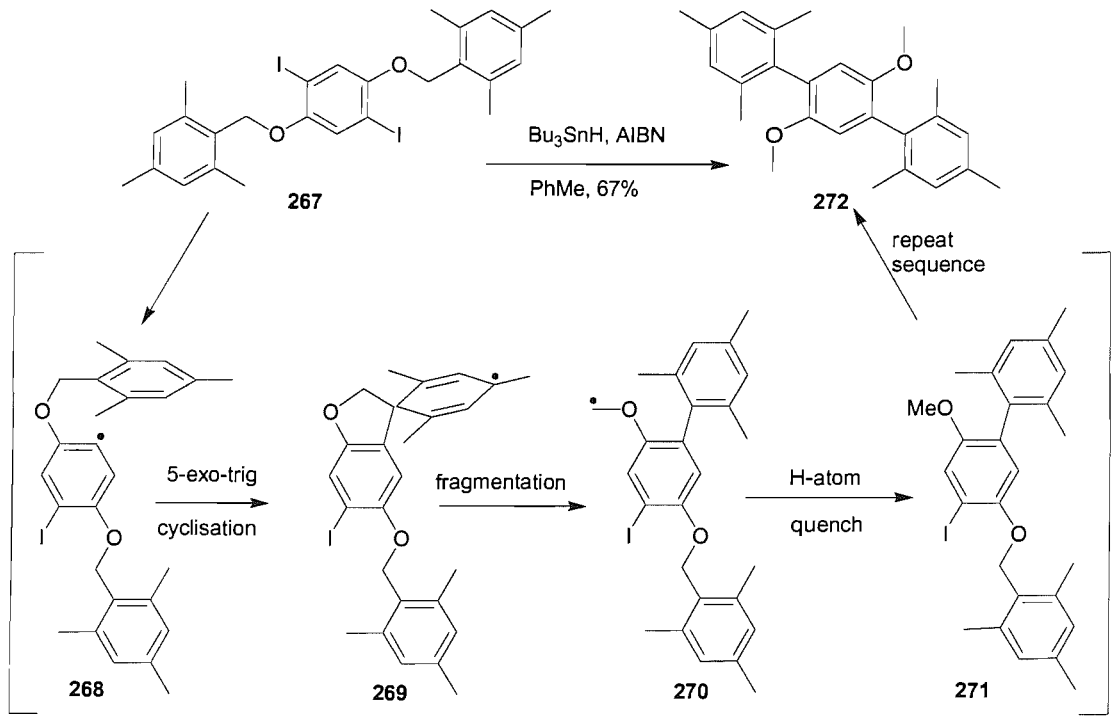
A large variety of radical *ipso*-substitutions have been reported. The nature and the position of the substituents on the aryl seem to have a profound influence on the course of the reaction not only determining the yield of the reaction but also its regioselectivity. The nature of the tethering chain and the method of radical generation may also influence the course of a reaction particularly in respect of regioselectivity. The main limitation of the method relates to the number of side reactions that can occur, mainly arising from competitive *ortho* addition to the aryl acceptor, reduction of the starting material or side reactions of the radical intermediate formed on fragmentation.

Chapter 2 Synthesis of 8-membered rings by radical *ipso*-substitution

Chapter 2 Synthesis of 8-membered rings by radical *ipso*-substitution

2.1 Background

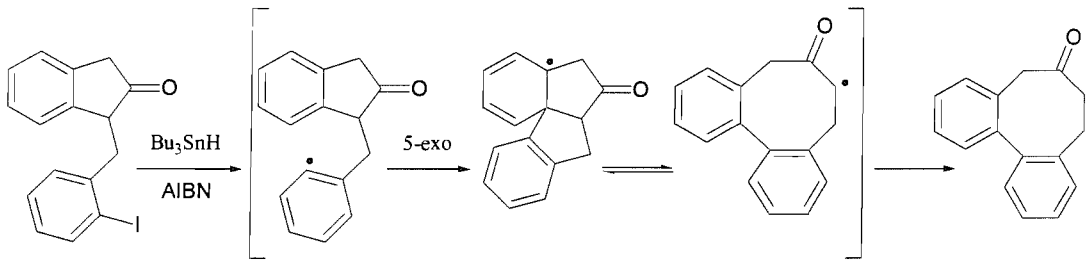
Radical *ipso*-substitution has been widely studied as indicated in Chapter one. Our group's interest in radical chemistry has prompted the discovery of several high yielding transformations initiated by the addition of carbon centred radical intermediates to arenes.[23, 57, 58] The program described in this thesis was inspired by the observation that diiodide **267**, when exposed to tributyltin hydride under standard radical forming conditions, was transformed into the terphenyl **272** in 67% yield (Scheme 58).



Scheme 58

2.2 Synthesis of 8-membered rings by radical *ipso*-substitution

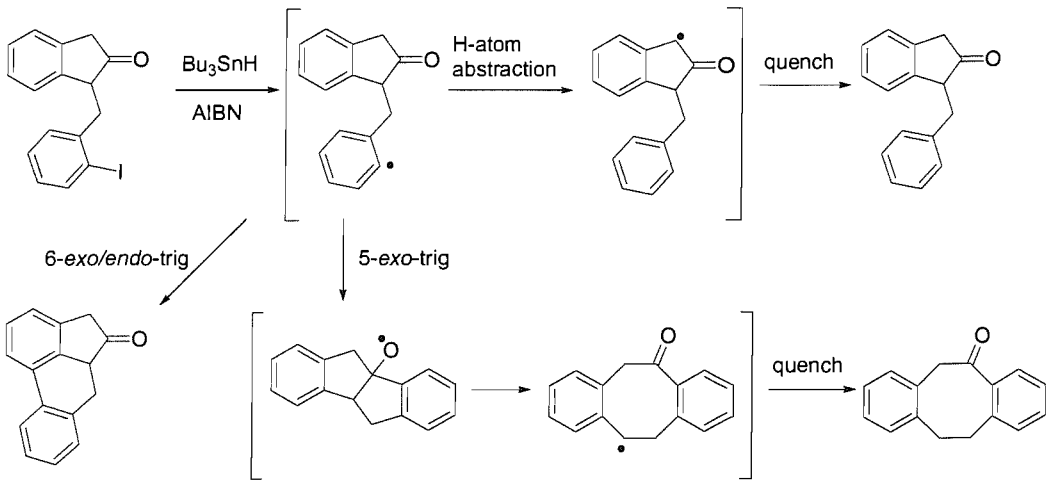
Our plan was to extend the radical *ipso*-substitution chemistry towards medium ring synthesis through the development of a new ring expansion protocol (Scheme 59). The idea was to incorporate the radical leaving group within an indane ring. In that way, cyclisation of an intermediate such as **274** could be followed by fragmentation of the resulting tetracycle **275** leading to the formation of a medium-sized ring **276**. H-atom abstraction from tributyltin hydride would then complete the sequence giving **277**.



273 **274** **275** **276** **277**

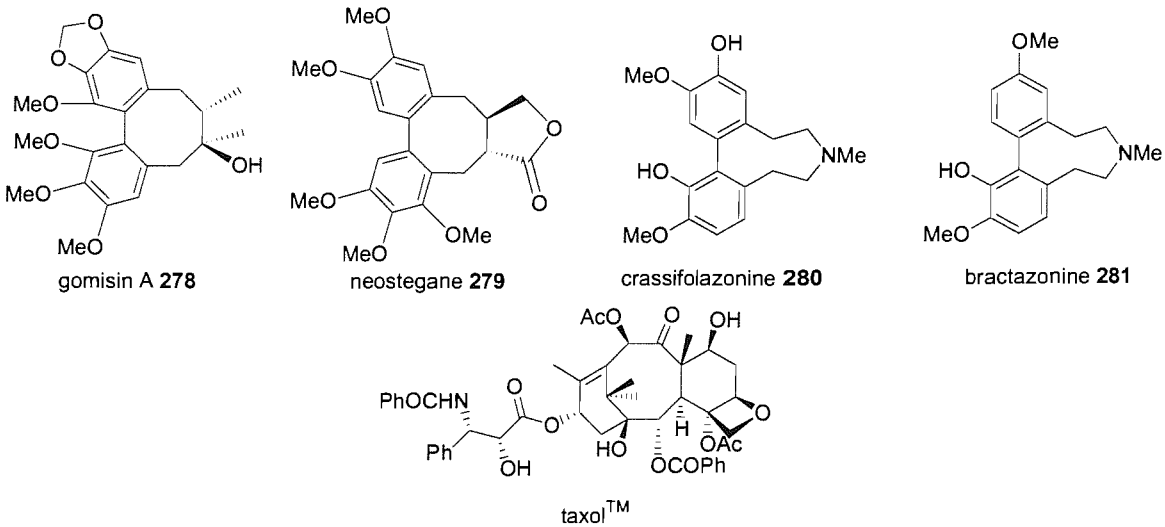
Scheme 59

The main problem of this approach is that the 5-*exo*-trig radical cyclisation would have to compete with alternative pathways such as i)*ortho*-cyclisation, ii)hydrogen atom abstraction from the benzylic centre and iii)5-*exo*-trig cyclisation to the ketone (Scheme 60). As each of these processes is well documented in the literature we were curious to see which, if any, would predominate.[59]



Scheme 60

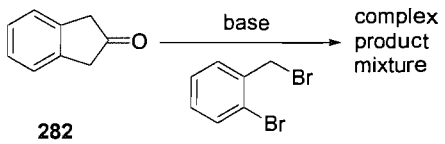
One class of compounds that is ideally suited to synthesis using our methodology is the stegane series of lignans, *e.g.* gomisin A **278** and neostegane **279**,[60-62] as these contain a biaryl unit within an eight membered carbocyclic ring (Scheme 61). Furthermore, if the methodology could be extended to tetralones and heterocyclic analogues, syntheses of the alkaloids crassifolazonine **280** and bractazonine **281** might be achievable. It might also provide a route to the carbocyclic framework of taxol™.



Scheme 61

2.2.1 Synthesis of the precursors.

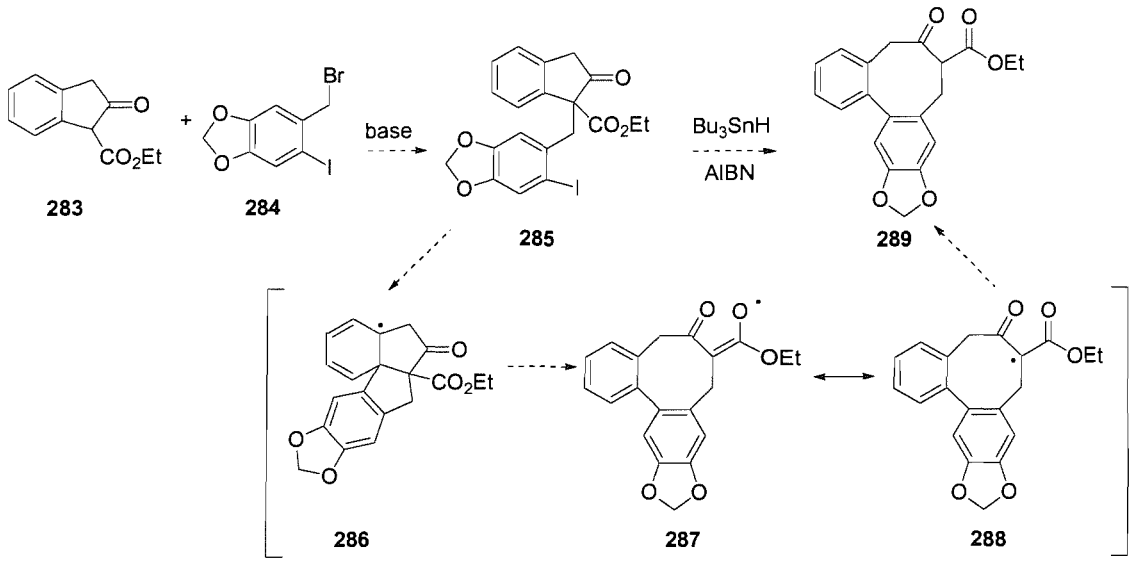
Our plan was to prepare indanone derivatives by the method outlined in Scheme 62. Initial attempts to deprotonate 2-indanone and quench the resulting enolate with 2-bromobenzyl bromide were unsuccessful. Indeed, several substitutions occurred and it was impossible to see by NMR if the desired product was formed. Moreover, it was found that commercial 2-indanone contained several impurities adding to the difficulty of separating the product mixture.



282

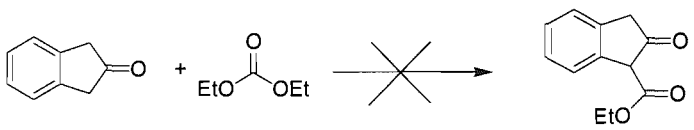
Scheme 62

To overcome these difficulties we decided to use ketoester **283** rather than 2-indanone as our starting material. In this case, one α-hydrogen is much more acidic than the others. Consequently, single deprotonation and therefore single substitution could be carried out. Moreover, it was hoped that the ester function might afford a further advantage, promoting the 5-*exo*-trig cyclisation **285**→**289** through steric butressing (Thorpe-Ingold effect) while helping to stabilise the radical intermediate **287** formed on fragmentation of the indane ring.



Scheme 63

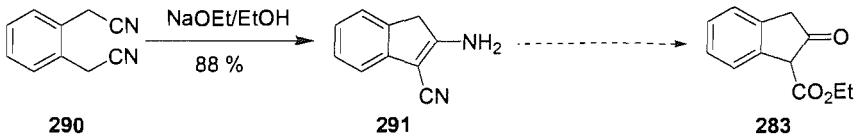
Three routes to ketoester **283** were investigated. In the first we sought to trap the enolate derived from 2-indanone with diethyl carbonate. Unfortunately, the reaction failed to produce anything but recovered starting material (Scheme 64).



reagents and conditions: NaH, ether, 9h

Scheme 64

We next sought to prepare **283** by cyclisation of bis-nitrile **290** to indane **291**, followed by ethanolysis. Several bases were examined in an attempt to promote the formation of **291**, (Table 1). Our efforts were finally rewarded when the desired transformation was accomplished in 88% yield through the action of sodium ethoxide in ethanol. Unfortunately, all attempts to effect the hydrolysis/ethanolysis of **291** to **283** met with failure.



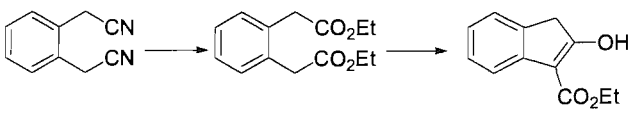
290 291 283

Scheme 65

Table 1: Attempted cyclisation of 290 to 291

Base	eq	Temperature	Yield
tBuLi	1.2	-78 °C→rt	-
tBuLi	2	-78 °C→rt	-
tBuLi	3	-78 °C→rt	-
tBuOK	1.5	0 °C→rt	-
NaOEt	1.5	0 °C→rt	88 %

Contemporaneous studies had shown that the conversion of bis-nitrile **290** to bis-ester **292** could be readily achieved using sulfuric acid in ethanol (Scheme 66). Initial attempts to effect its cyclisation to ketoester **283** gave some of the desired product, albeit in low yield. Extensive optimisation improved the yield to 62%; some of the key experiments being summarised in Table 2. Spectroscopic analysis of the product showed that it existed primarily in the enol form.



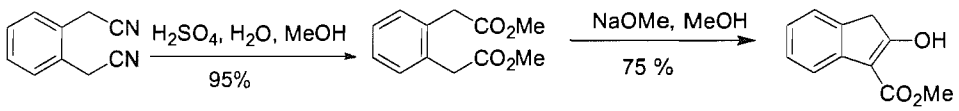
290 292 283

Scheme 66

Table 2: Cyclisation of 292 to 283 using NaOEt in EtOH.

Temperature	Time	Yield
0 °C	12 h	11 %
20 °C	16 h	10 %
80 °C	2 h	46 %
80 °C	3 h	62 %
80 °C	16 h	25 %

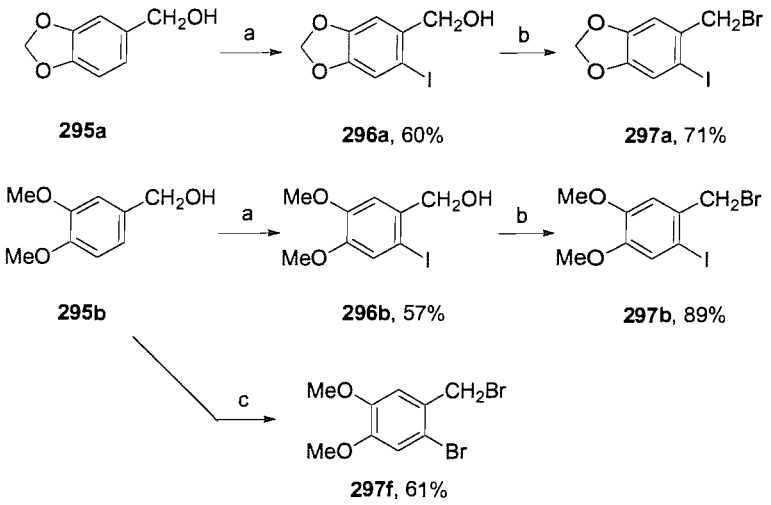
The approach was next extended to the corresponding methyl ester **294** in order to simplify NMR analysis of subsequent products. The reaction conditions employed in the synthesis of the ethyl ester proved equally rewarding, giving **294** in a satisfying 71% overall yield when conducted on a multigram scale (Scheme 67).



290 **293** **294**

Scheme 67

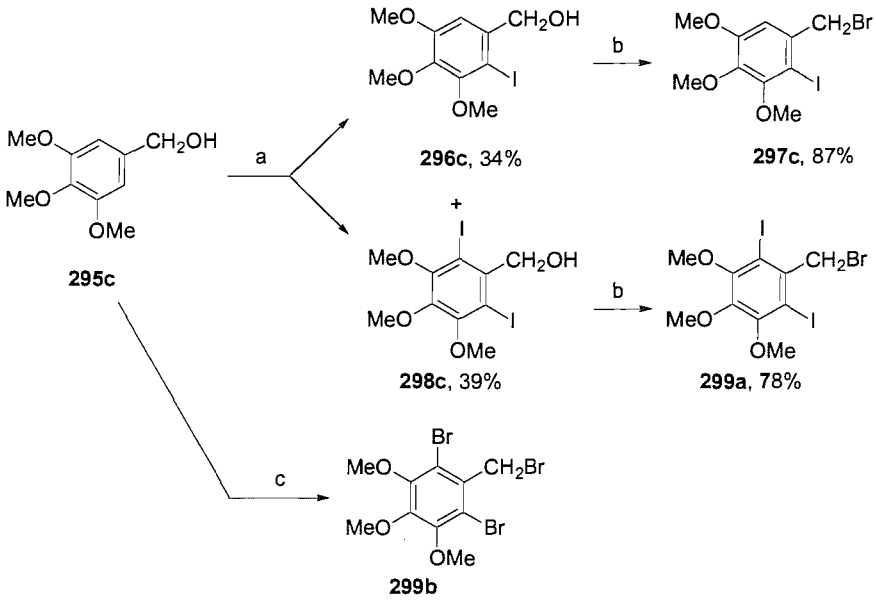
With the indanone to hand, work began on the preparation of various *ortho*-halobenzyl bromides. Thus, benzyl alcohols **295a** and **295b** were iodinated with iodine and silver trifluoroacetate, then converted to the corresponding bromides **297a** and **297b** by treatment with phosphorus tribromide (Scheme 68).



reagents and conditions: a)I_2, CF_3CO_2Ag, $CHCl_3$. b)PBr_3, benzene. c)Br_2, AcOH

Scheme 68

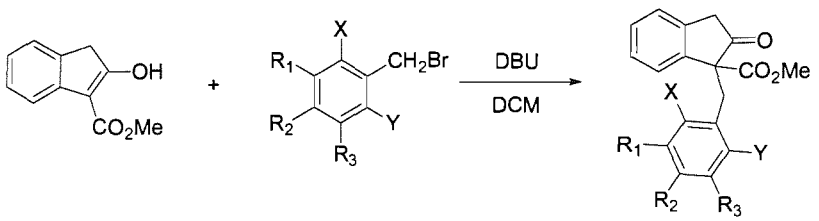
It was observed that when 3,4,5-trimethoxybenzyl alcohol was iodinated with iodine and the silver salt, both mono and di-iodinated products **296c** and **298c** were formed in 34% and 39% yield respectively. Both compounds were readily brominated with phosphorus tribromide to give **297c** and **299a** respectively (Scheme 69). Tribromide **299b** was also prepared through the action of bromine in acetic acid on alcohol **295c**.



reagents and conditions: a)I_2, CF_3CO_2Ag, $CHCl_3$. b)PBr_3, benzene. c)Br_2, AcOH

Scheme 69

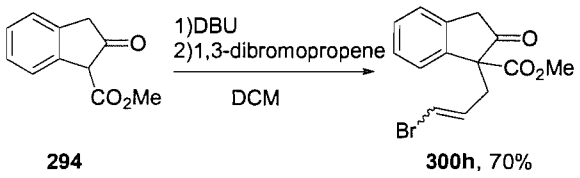
Our next task was to couple these bromides to ketoester **294**. Pleasingly deprotonation of **294** with DBU followed by addition of the different bromides **297a-c**, **297e** and **299a-b** achieved the desired alkylation in modest to excellent yield. Product **300e** was obtained in 76% yield from commercially available 2-iodobenzyl bromide (Scheme 70).



300a,	$R_1R_2=OCH_2O$ R_3=X=H Y=I	40%
300b,	$R_1=R_2=OCH_3$ R_3=H X=H Y=I	97%
300c,	$R_1=R_2=R_3=OCH_3$ X=H Y=I	85%
300d,	$R_1=R_2=R_3=OCH_3$ X=Y=I	70%
300e,	$R_1=R_2=R_3$=X=H Y =I	76%
300f,	$R_1=R_2=OCH_3$ R_3=H X=H Y=Br	40%
300g,	$R_1=R_2=R_3=OCH_3$ X=Y=Br	56%

Scheme 70

The stage was now set to test the ring expansion methodology. In order to extend this methodology to vinyl radical intermediates, precursor **300h** was also synthesised from indanone **294** and 1,3-dibromopropene (Scheme 71).

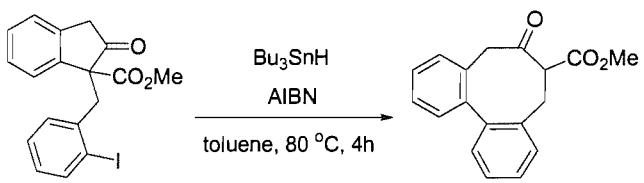


294 **300h**, 70%

Scheme 71

2.2.2 The ring expansion reaction

Thus, precursor **300e** was treated under standard radical forming conditions using 1.1 equivalent of tributyltin hydride and 0.2 equivalent of AIBN in toluene. From the complex product mixture given we were encouraged to isolate cyclooctanone **301e**, albeit in a disappointing 11% yield. Extended reaction times and slow addition of tributyltin hydride each proved deleterious. Indeed, curiously the product seemed to be quite unstable and prone to degradation under the reaction conditions to baseline material. Only by quenching the reaction after four hours was it possible to isolate and characterise **301e** (Scheme 72).

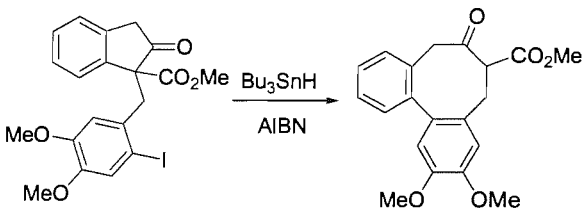


300e **301e**, 11%

Scheme 72

Several attempts were made to improve the yield but to no avail. For example, we hoped that it might be possible to keep the temperature low using triethylborane as the initiator. However, when placed under an oxygen atmosphere with 1.1 equivalent of tributyltin hydride at room temperature, only the starting material was recovered.

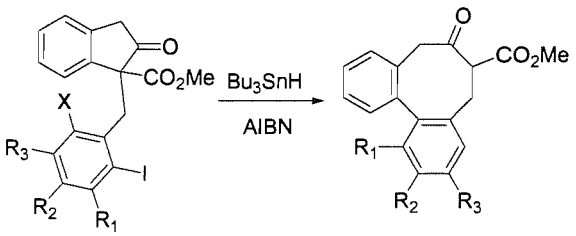
Undaunted by these observations the ring expansion was next applied to the dimethoxy-derivative **300b**. To our delight, cyclooctanone **301b** was formed as the major product in 70% yield as a 1:1 mixture of diastereoisomers using the standard radical cyclisation methodology (Scheme 73).



300b **301b**, 70%

Scheme 73

Encouraged by this good result, several related cyclisations were carried out in order to determine the scope of the reaction (Scheme 74).

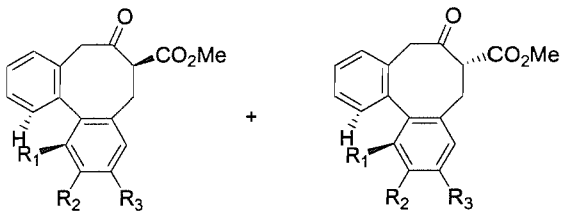


	301
300a, R_1=H R_2R_3=OCH_2O X=H	81%
300c, R_1=R_2=R_3=OCH_3 X=H	69%
300d, R_1=R_2=R_3=OCH_3 X=I	96%

Scheme 74

All these cyclisations proceed in good to very good yield. The best result was obtained with diiodide **300d**, which gave the ring expansion product in 96% yield. Presumably yields were elevated in this case as each of the two C-I bonds provides an opportunity for the reaction to proceed. Notably, all these molecules have an asymmetric centre and display atropisomerism about the biaryl linkage. In each case the product was given as a 1:1 mixture of diastereoisomers. However, on recrystallisation from methanol **301a** yielded a single diastereoisomer which proved stable to NMR analysis.

Moreover, after analysis of the X-Ray obtained from a diastereoisomer of **301b** it clearly appeared that the proton between the two carbonyls was not particularly acidic as it was not perpendicular to these carbonyls (figure 1). This could explain why only one diastereoisomer was given following recrystallisation.



Scheme 75

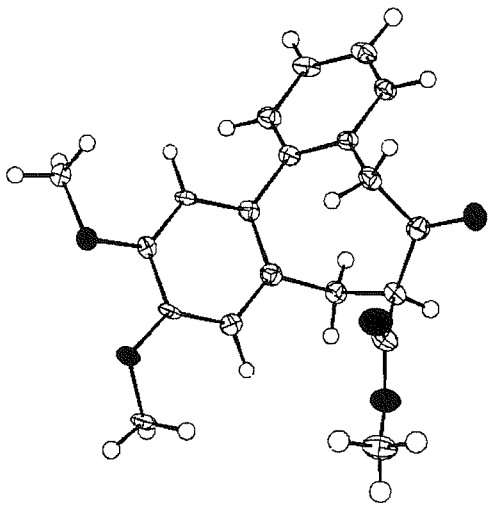
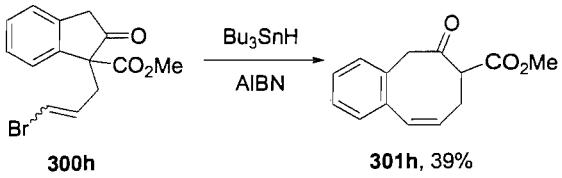


Figure 1

The methodology was next extended to vinyl bromide **300h**. Here too, exposure to tributyltin hydride under standard radical forming conditions induced a ring expansion leading to dihydrobenzocyclooctene **301h** in a modest 39% yield.



300h **301h**, 39%

Scheme 76

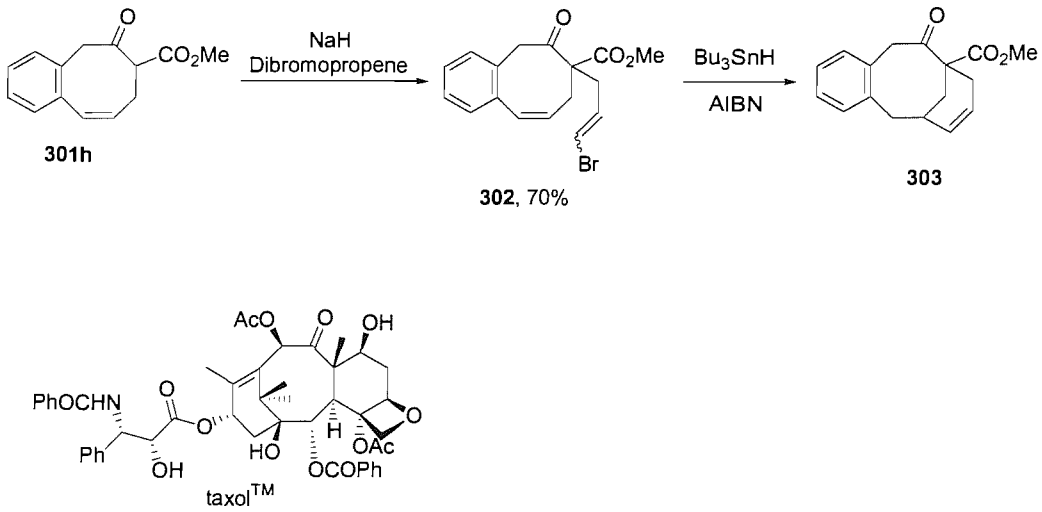
From these results it is evident that radical *ipso*-substitution can outpace *ortho*-cyclisation, 5-*exo*-trig cyclisation to a ketone and benzylic H-atom abstraction. The method gives rapid access to benzo-cyclooctanones and does not require high dilution to achieve good yields. Curiously, substitution in the donor ring appears to play a significant role in determining the course of the reaction with substrates containing methoxy and methylenedioxy substituents giving substantially higher yields compared to the unsubstituted derivatives.

Chapter 3 Synthesis of 9-membered rings by radical *ipso*-substitution

Chapter 3 Synthesis of 9-membered rings by radical *ipso*-substitution

3.1 Toward the synthesis of the taxol™ ring system

The results obtained with vinyl bromide **301h** led us to consider the possibility of constructing the taxol™ ring system from **303**. In principle, the 6-8-6 ring system might be accessed by means of a second alkylation and radical cyclisation sequence as indicated in Scheme 77.

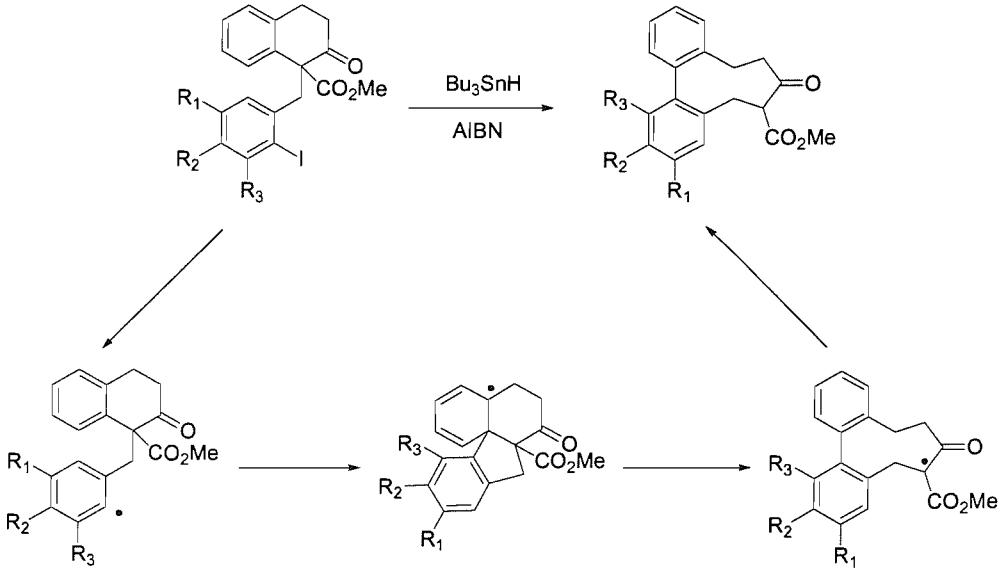


Scheme 77

To that end, cyclooctane **301h** was deprotonated with sodium hydride and alkylated with 1,3-dibromopropene. The product **302** was obtained in 70% yield as a 1:1 mixture of (E)- and (Z)-isomers. These were then exposed to standard radical forming conditions. Alas, none of the desired product **303** was identified in the resulting product mixture. Several conditions were explored in an attempt to facilitate the radical cyclisation, including both microwave and thermal heating. Unfortunately all of them failed. At this time we are unsure as to the reasons for this failure. It may be due to H-atom abstraction from the

proximal allylic carbon; addition of $Bu_3Sn^{\bullet}$ to one of the alkenes or cyclisation to the vicinal ketone.

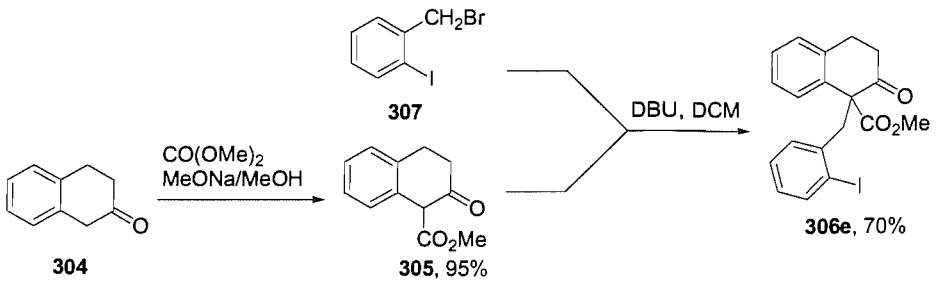
Following the good results obtained in forming the 8-membered ring system from indanones, the synthesis of the 9-membered rings by expansion of tetralones seemed a logical extension. The mechanism of the proposed reaction is detailed in scheme **78**.



Scheme 78

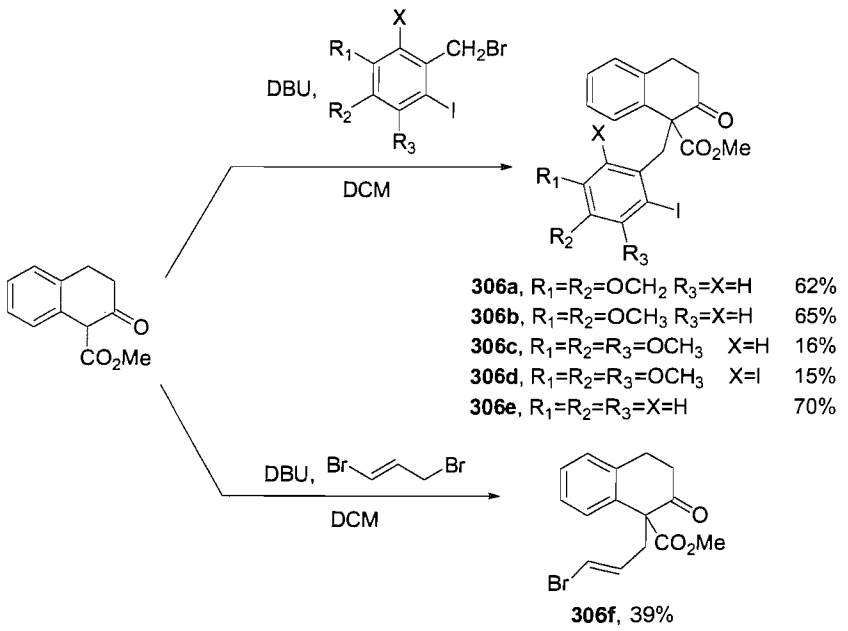
3.2 Synthesis of the precursors

The required precursors were readily prepared from tetralones **304**. Deprotonation with NaOMe facilitated condensation with dimethyl carbonate to afford β-ketoester **305** in 95% yield. A second deprotonation with DBU next facilitated alkylation with benzyl bromide **307** to afford precursor **306** in 70% (Scheme 79).



Scheme 79

Several *ortho*-iodobenzyl bromides were then synthesised, as described in the previous Chapter, and united with tetralone **305** to give **306a-e**. The yield for the trimethoxy-derivatives **306c,d** was poor due to decomposition of the benzyl bromide under the reaction conditions. Otherwise yields were generally good with this method (Scheme 80).

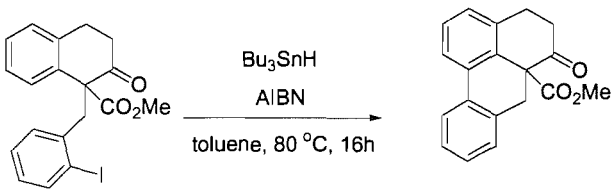


Scheme 80

3.3 The ring expansion reaction

The precursor **306e** was placed under standard radical forming conditions using 1.1 equivalent of tributyltin hydride and 0.2 equivalent of AIBN in toluene. Analysis of the product mixture revealed that the planned expansion of the tetralone to a 9-membered ring

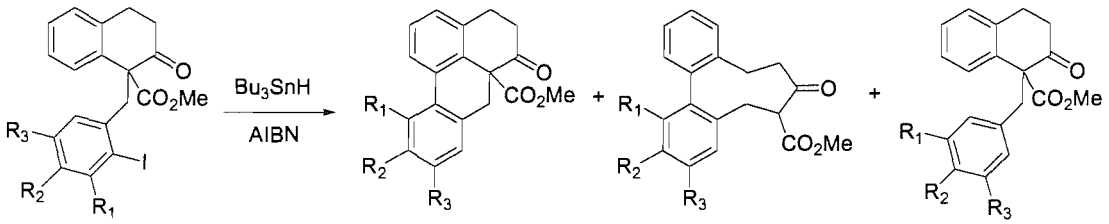
had not taken place. Rather, *ortho*-cyclisation to tetracycle **308e** had occurred in 80% yield.



306e **308e**, 80%

Scheme 81

By way of contrast, the trimethoxy-derivative **306c** gave the ring expanded material **308c** (figure 2) together with the product of halide reduction **309c** while the methylenedioxy derivative **306a** gave the products of *ortho*- and *ipso*-cyclisation, **310a** and **308a** (figure 3), respectively.



R_1=H, R_2=R_3=OCH_2
R_1=R_2=R_3=OCH_3

310a, 45%
310c, 0%

308a, 45%
308c, 35%

309a, 0%
309c, 35%

Scheme 82

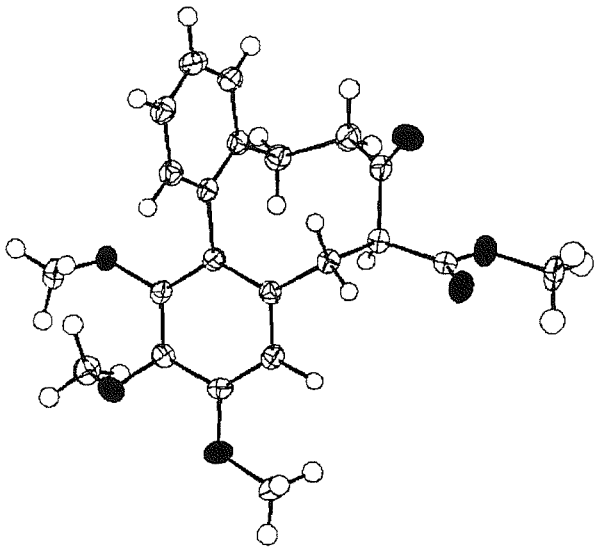


Figure 2

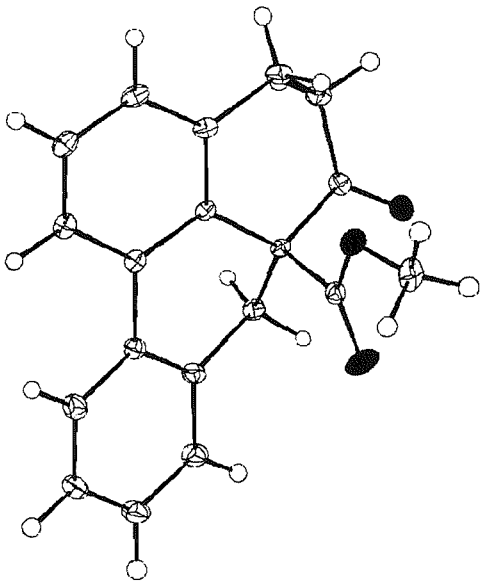
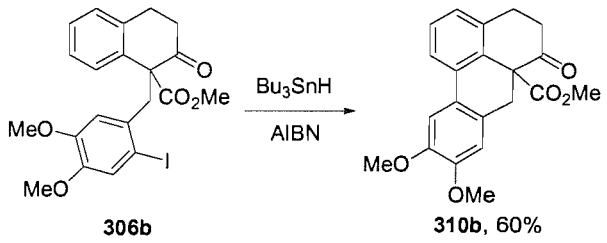


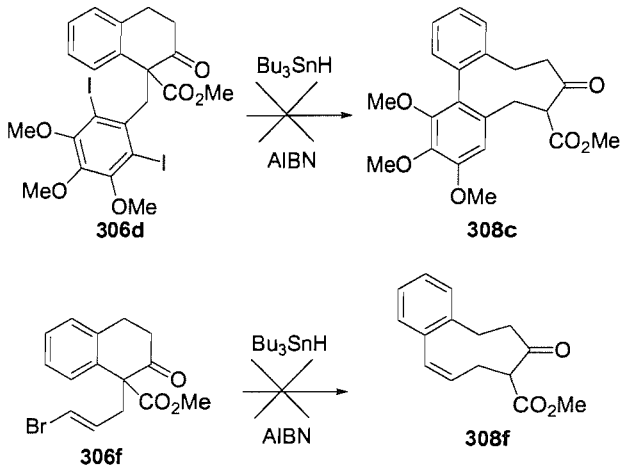
Figure 3

Somewhat surprised by this result, we next attempted the ring expansion with the electron rich substrates **306b-d**. The dimethoxy-derivative **306b** likewise gave tetracycle **310b** as the only identifiable product of the reaction in 60% yield (Scheme 83).



Scheme 83

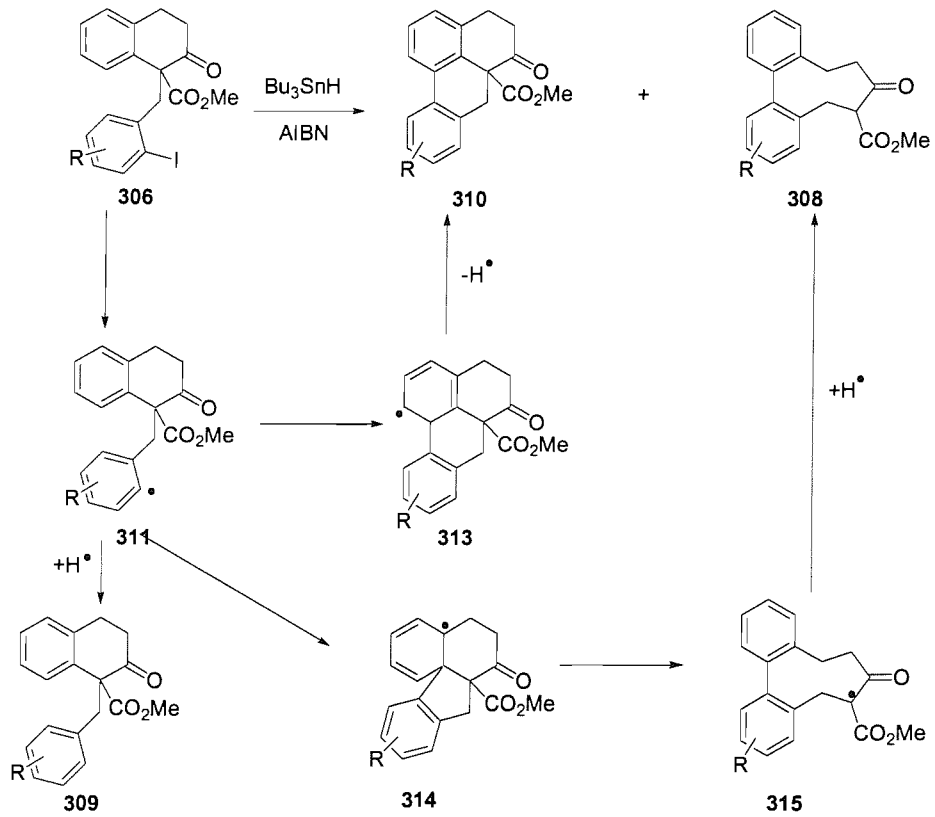
All attempts to cyclise diiodide **306d** and bromide **306f** failed. The reason for this is unclear, the starting material appearing to degrade to baseline material under the reaction conditions. The steric hindrance of the two halogens in the case of **306d** was probably responsible for this lack of stability (Scheme 84). For **306f**, the strength of the carbon-bromine bond leads to a lack of reactivity which was manifest by substantial quantities of the starting material.



Scheme 84

From these results it is evident that a precursor such as **306** can cyclise to the *ipso*-position of the tetralone to give **314**. When that occurs the spirocycle **314** collapses with

rearomatisation to the 9-membered ring **308**. Alternatively, cyclisation of **306** can occur to the *ortho* position of the tetralone affording tetracycle **310**. That the course of these reactions is strongly influenced by substituents on the donor aryl radical is a surprising and noteworthy observation. In some cases, the preference for *ortho*-cyclisation over *ipso*-substitution might be explained by steric influences. In particular, we had noticed that the presence of a methoxy group *ortho* to the radical intermediate greatly favours the *ipso*-cyclisation pathway. It is interesting to note that only one diastereoisomer of the 9-membered ring was observed, possibly indicating that the biaryl linkage is free to rotate at ambient temperature.



Scheme 85

These experiments also show that the efficiency of these ring expansion reactions is also influenced by the nature of the saturated ring attached to the radical acceptor. For the indanone derivatives, 6-*endo*/*exo*-trig cyclisation is harder to achieve as the transition state

leading to *ortho*-addition is strained. As the size of the saturated ring is increased, that barrier to *ortho*-cyclisation lessens making it the dominant pathway in many cases.

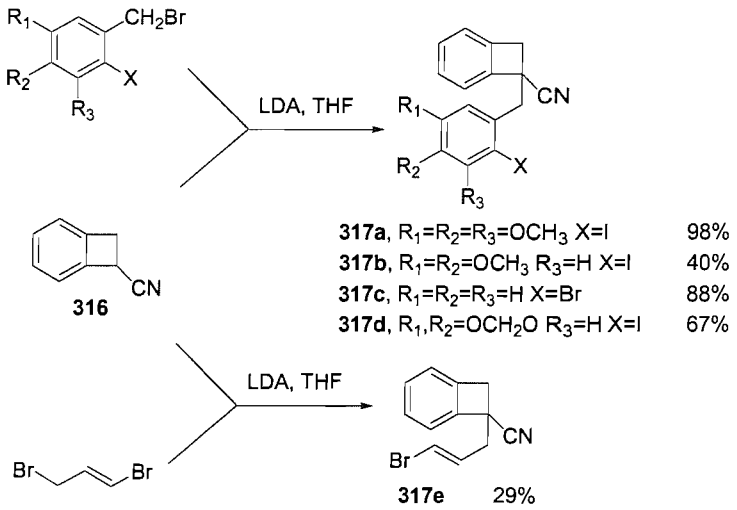
Chapter 4 Synthesis of 7-membered rings by radical *ipso*-substitution

Chapter 4 Synthesis of 7-membered rings by radical *ipso*-substitution

Mindful of the preceeding observations, we next sought to extend the methodology towards the formation of 7-membered ring systems. In this case we needed a benzocyclobutane precursor that was amenable to the *ipso*-cyclisation and fragmentation sequence.

4.1 Synthesis of the precursors

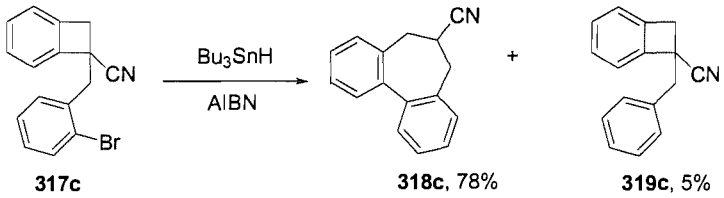
The precursors we required were synthesised from benzocyclobutane carbonitrile **316** and a series of *ortho*-halobenzyl bromides as indicated in Scheme 86. All were given in modest to excellent yield.



Scheme 86

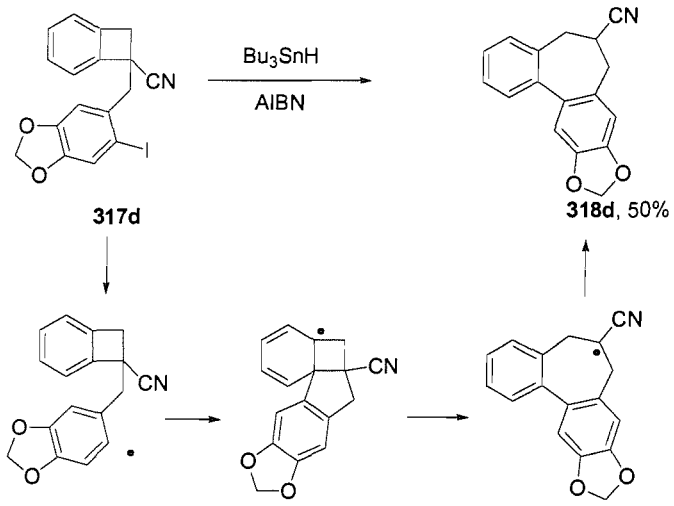
4.2 The ring expansion reaction

The ring expansion reaction was first carried out on the unsubstituted derivative **317c**. Pleasingly the 7-membered ring was obtained in 78% yield along with the product of reduction **319c**, formed in 5% yield (Scheme 87).



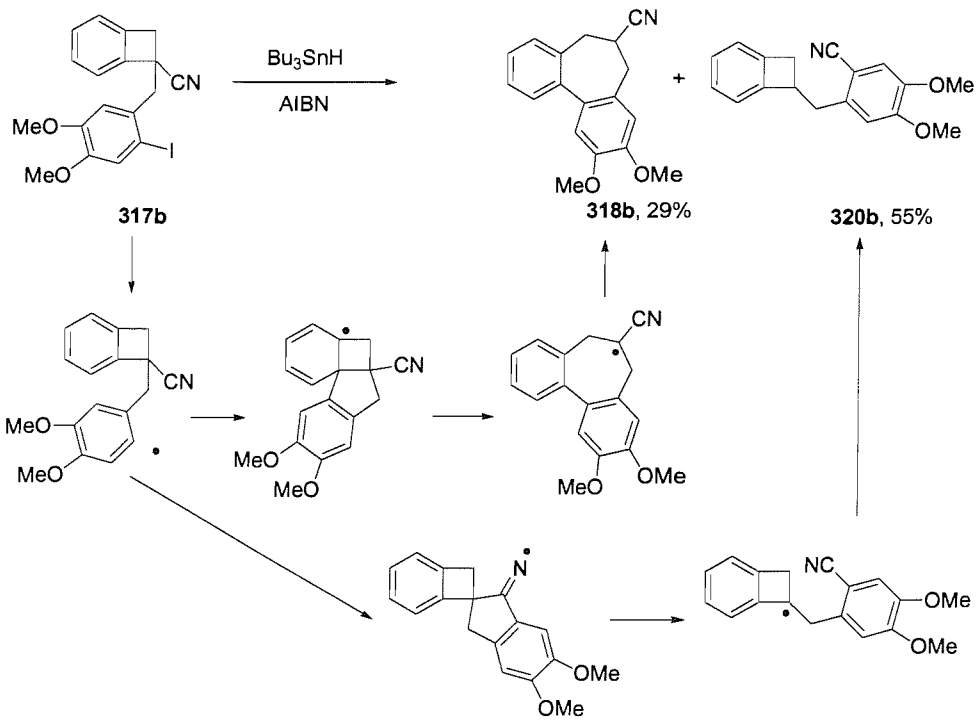
Scheme 87

The ring expansion was then carried out on some electron-rich aryl derivatives. When the methylenedioxy-derivative **317d** was treated using analogous conditions it was smoothly transformed into the corresponding dibenzocycloheptane **318d** in 50% yield (Scheme 88).



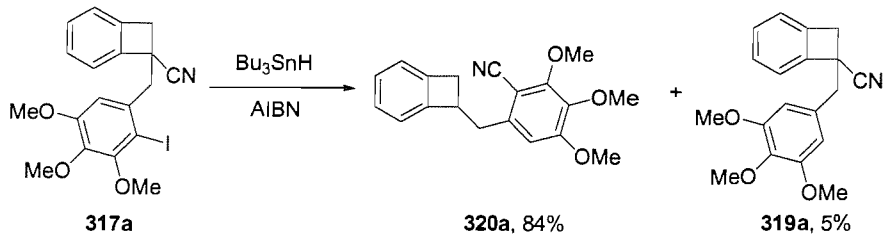
Scheme 88

By way of contrast the anticipated ring expansion product **318b** was only a minor product when the corresponding dimethoxy-derivative **317b** was treated analogously (Scheme 89). The major product in this case was the rearranged nitrile **320b**, which was given in 55% yield.



Scheme 89

This alternative pathway was even more pronounced with the trimethoxy derivative **317a.** In this case none of the anticipated cycloheptane was furnished. Nitrile **320a** being given in 84% yield together with traces of the reduced material **319a.**



Scheme 90

These results provide a stark illustration of how ether substituents on the aryl radical donor may influence the course of radical reaction. The effect is undoubtedly electronic in nature though further experimentation and/or modelling is needed. The ring expansion reaction was then carried out on the derivative **317e**. Unfortunately a complex reaction mixture was obtained and no compound of cyclisation could be detected.

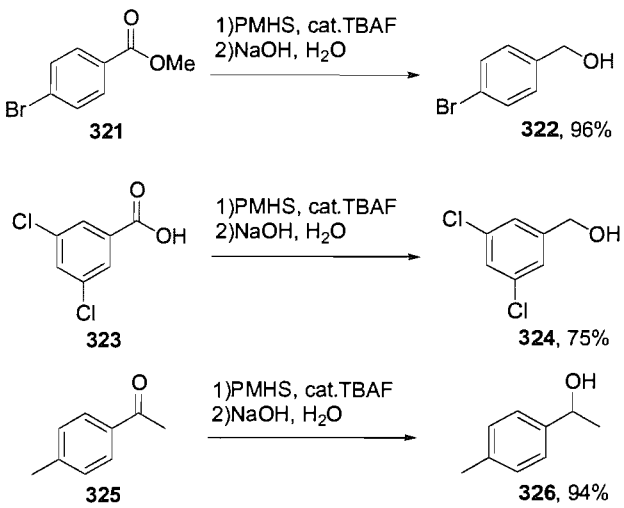
Chapter 5 The reduction of aryl halides with tetrakis(trimethylsilyl)silane-tetrabutylammonium fluoride reagents and related combination

Chapter 5 The reduction of aryl halides with tetrakis(trimethylsilyl)silane-tetrabutylammonium fluoride reagents and related combination

Previous work within the Harrowven group had shown that a combination of tributyltin hydride (or hexabutylditin) and tetrabutylammonium fluoride was capable of reducing aryl halides to the corresponding arene. The reaction was shown to proceed by halogen-metal exchange and protonation, *vide supra*. Mindful of this, we recognised that many of the substrates we had to hand, could be used in this the reaction. Moreover, they offered the possibility of cyclisation of the organometallic intermediate to the vicinal carbonyl or nitrile and hence there was potentially a mild and useful new C-C bond forming reaction to be uncovered.

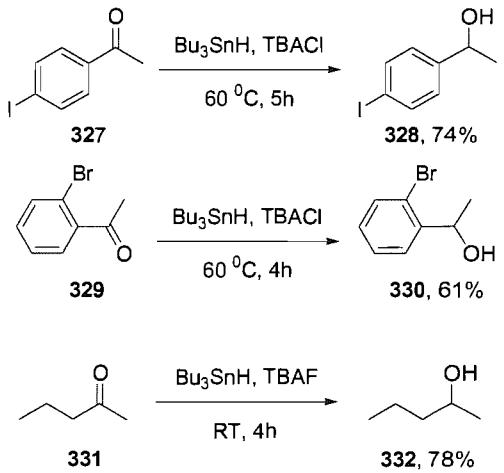
5.1 Background

Lawrence *et al.* reported the use of tetrabutylammonium fluoride and polymethylhydrosiloxane for the reduction of aryl esters, acids, ketones and aldehydes to the corresponding alcohols in good yield (Scheme 91).[63] It is interesting to note that in many of the case examined a halogen substituted on the aromatic ring remained untouched by the reagent combination.



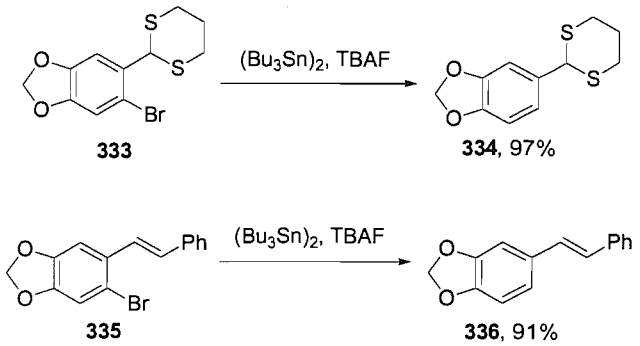
Scheme 91

Shibata *et al.* have also described the reduction of ketones with a combination of tributyltin hydride and tetrabutylammonium chloride or fluoride (Scheme 92).[64] Here too, halogen substituents on the aromatic ring were unaffected under the reaction conditions.



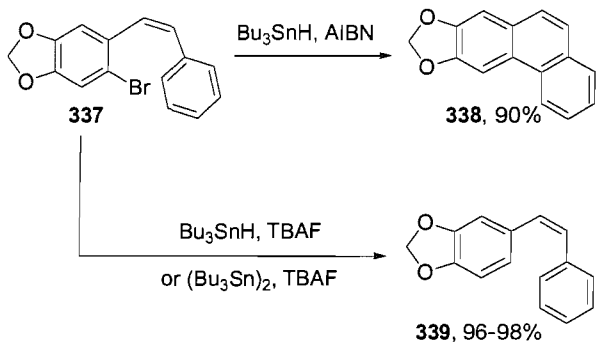
Scheme 92

Harrowven and Guy then made the interesting discovery that aryl bromides and iodides were readily reduced by a combination of tributyltin hydride (or hexabutylditin) and tetrabutylammonium fluoride (Scheme 93).[65] All the reactions explored proceeded in good to excellent yield.



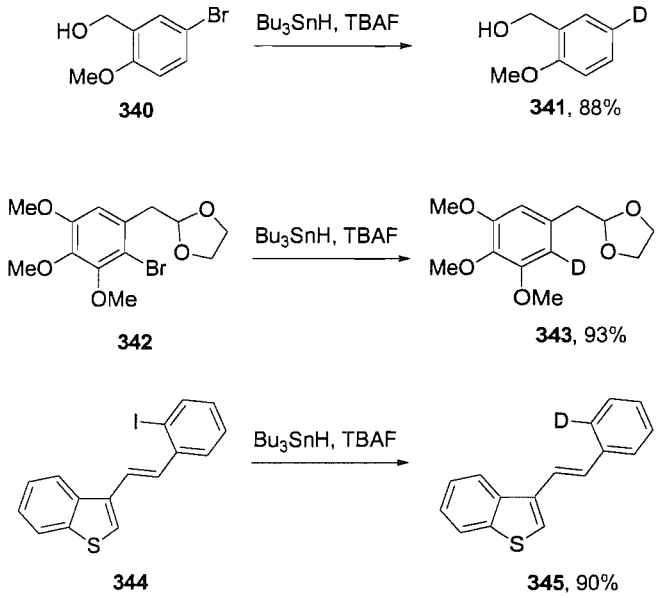
Scheme 93

The mechanism of these reactions was investigated. To test whether free radical intermediates were involved, the *cis*-bromostilbene **337** was subjected to both Bu_3SnH-TBAF and hexabutylditin-TBAF reagent combinations. In each case the *cis*-stilbene **339** was formed rather than phenanthrene **338**, the product afforded when a radical reaction is involved (Scheme 94).



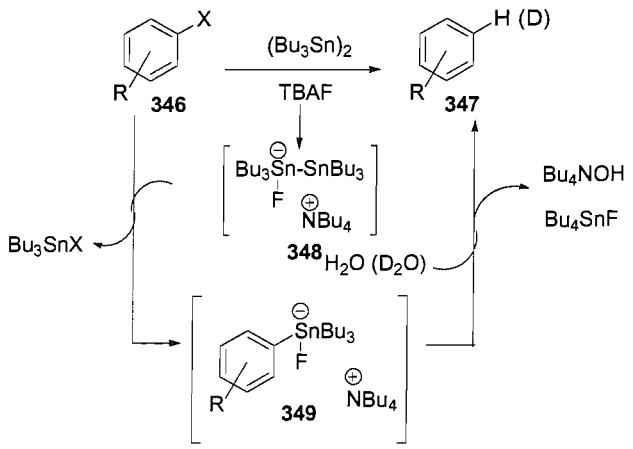
Scheme 94

It was concluded that the likely mechanism for the reduction was a halogen to metal exchanged followed by a protonation. The residual water in TBAF was exchanged for D_2O and used in several reductions. In each case the deuterated products were isolated in excellent yield (Scheme 95).



Scheme 95

It was then postulated that hexabutylditin and TBAF first interact to form **348**. Halogen to metal exchange follows producing tributyltin halide and the complex **349**. Protonation with water (or deuteration with D_2O) then gives **347** (Scheme 96).

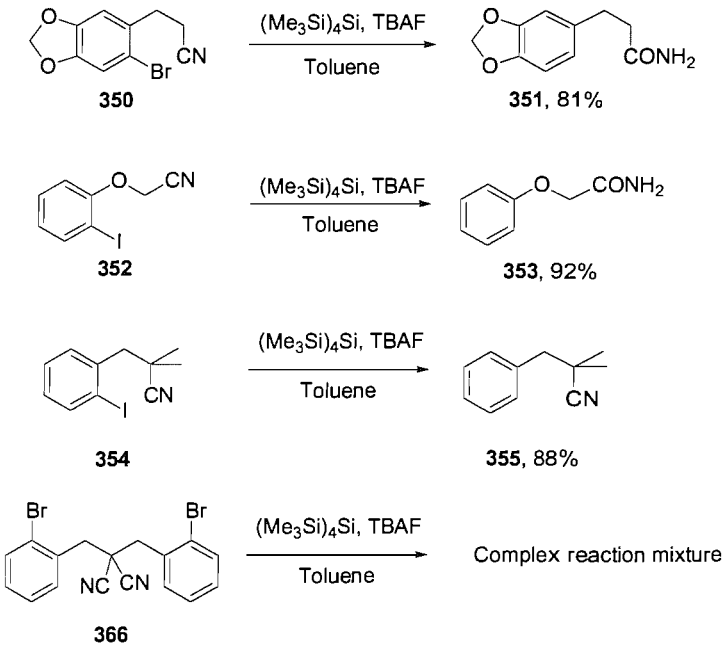


Scheme 96

5.2 Investigating the scope of the reaction

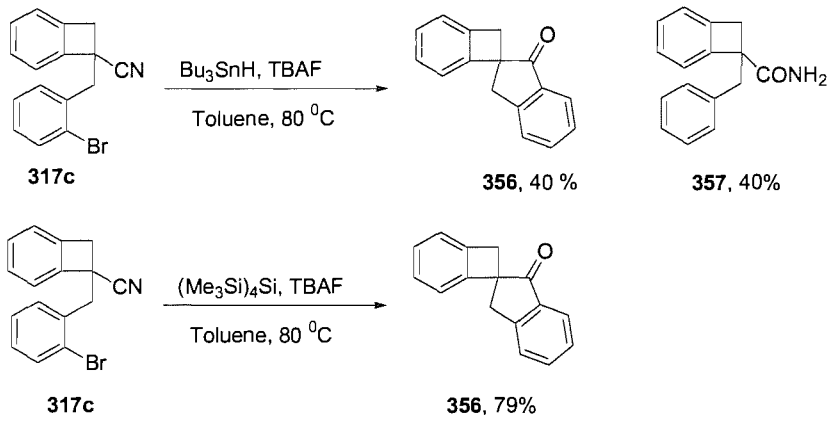
The use of organotin reagents limits the appeal of the method, due to their toxicity and difficulty associated with their removal. We decided to examine the effectiveness of some

silicon based alternatives in the hope that these might be equally effective. Pleasingly a combination of tetrakis(trimethylsilyl)silane and TBAF proved to be highly effective for the reduction of aryl bromides and iodides (Scheme 97). Under the reaction conditions employed, primary nitriles were readily hydrolysed to the corresponding primary amide, while tertiary nitriles were generally unaffected. Placed under the same reaction conditions compound **366** gave a complex reaction mixture. No product of reduction could be identified.



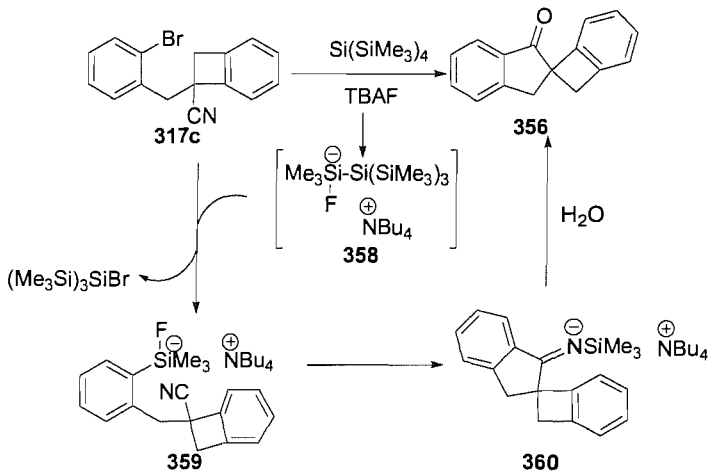
Scheme 97

In each of the cases illustrated above, cyclisation of the organosilicon intermediate to the proximal nitrile was outpaced by protonation. However, when compound **317c** reacted with tributyltin hydride and TBAF, two products were given. These were identified as the cyclised product **356** (40% yield) and the reduced compound **357** (40% yield). Pleasingly when the same starting material was treated with a combination of tetrakis(trimethylsilyl) silane and tetrabutylammonium fluoride only the cyclised compound **356** was isolated in 79% yield. Notably the use of tetrakis(trimethylsilyl)silane not only increased the yield of cyclised product, it also suppressed the reduction product (Scheme 98).



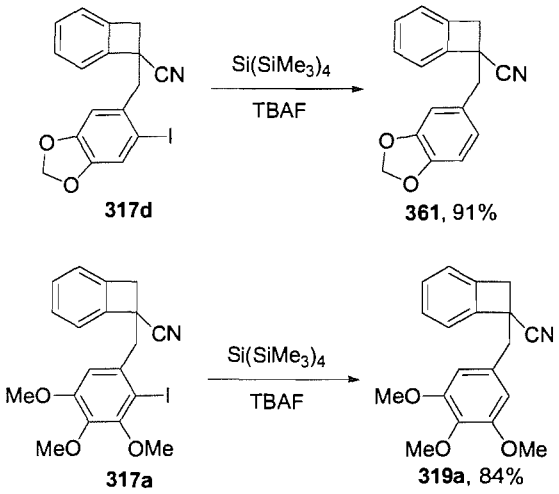
Scheme 98

Our postulate for the mechanism of this reaction is depicted in Scheme 99. In essence it is the same mechanism to that envoked for the reduction of the aryl halide though in this case a nitrile, rather than a proton, serves as the electrophile. Tetrakis(trimethylsilyl)silane and TBAF first interact to form **358**. Halogen to metal exchange follows to produce tris(trimethylsilyl)silyl halide and the ate complex **359**. Cyclisation to the nitrile and hydrolysis then afford **356**.



Scheme 99

To investigate the scope of the reaction, some related substrates **317a** and **317d** were treated analogously. Surprisingly, and for reasons that remain unclear, each gave only the products derived from reduction of the carbon to iodine bond (Scheme 100).



Scheme 100

Work is on-going within the group aimed at trying to understand the factors that determine which course is followed. At this stage we can say that the reagent combination of tetrakis(trimethylsilyl)silane and TBAF is effective for the reduction of aromatic bromides and iodides under mild conditions. This reaction is believed to proceed *via* halogen to metal exchange followed by protonation. In one case cyclisation has been observed to a nitrile providing some further evidence for the mechanistic postulate. Additionally we have observed that unencumbered nitriles are susceptible to hydrolyse under the reaction conditions.

Chapter 6 Experimental section

Chapter 6 Experimental section

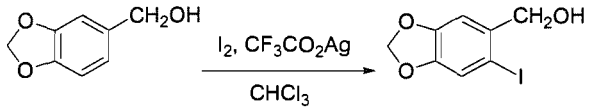
6.1 General procedures and analytical instrumentation

Where column chromatography was undertaken, Merck silica gel 60 (0.040-0.063, 230-400 mesh ASTM) was used. Infrared (IR) spectroscopy was performed using a Nicolet Impact 400 Thunderdome spectrometer as indicated. Positions of absorption maxima are quoted in cm^{-1}. Letters give an indication of the relative strength of the peak (w = weak, m = moderate, s = strong, br = broad, v = very). UV-visible spectroscopy was performed on either a Pye Unicam SP8-400 spectrophotometer or a Shimadzu UV-240 Graphicord spectrophotometer as solutions in dichloromethane or methanol as indicated in the script. ^{1}H and ^{13}C NMR spectroscopy was performed on a Bruker 300 MHz spectrometer. The solvents used are indicated in the text. Chemical shifts are quoted as δ-values in ppm. The abbreviations used in the recorded data for the NMR spectra are: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, br = broad. Chemical ionisation (CI) mass spectroscopy was performed on a Thermoquest Trace GCMS spectrometer. Electrospray (ES) mass spectroscopy was performed on a Micromass Platform (MP) spectrometer. Melting points were performed on a Griffin melting point apparatus, and are uncorrected.

When necessary, solvents were distilled before use.

6.2 Synthetic procedures

6-Iodo-benzo[1,3]dioxole-5-methanol (6-iodopiperonyl alcohol) (296a)[66]



mw = 278 g/mol

$C_8H_7O_3I$

CAS = 69048-76-6

To a stirred solution of piperonyl alcohol (2.00 g, 13.1 mmol) and silver trifluoroacetate (4.36 g, 19.7 mmol) in dry chloroform (20 mL) at 0 °C under nitrogen, was added iodine (5.00 g, 19.7 mmol) in one portion. The resulting yellow mixture was maintained at 0 °C for 5 minutes and then filtered through celite. The filtrate was washed with sodium thiosulfate (20 mL) and this aqueous suspension was extracted with chloroform (4 x 20 mL). The organic phases were then combined and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield a powdery solid, which was recrystallised from chloroform to afford the product as a cream powdery solid (2.19 g, 7.90 mmol, 60%).

Data for **296a** were consistent with literature values.

MP 102-104 °C (ether/petrol) lit[66] 106-107 °C

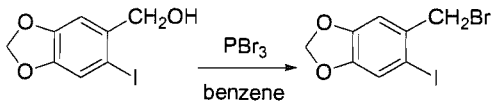
FT-IR (neat, cm^{-1}): 1474 (s), 1225 (s), 1100 (w), 1037 (s), 927 (m), 858 (m), 842 (m), 783 (m).

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.24 (1H, s, C**H**$_{AR}$), 6.99 (1H, s, C**H**$_{AR}$), 5.98 (2H, s, OC**H**$_2$O), 4.59 (2H, s, C**H**$_2$OH), 1.94 (1H, s, O**H**).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 148.7 (**C**$_{AR}$), 148.0 (**C**$_{AR}$), 136.3 (**C**$_{AR}$), 118.6 (**C**H$_{AR}$), 109.2 (**C**H$_{AR}$), 101.8 (O**C**H$_2$O), 85.5 (**C**$_{AR}$I), 69.3 (**C**H$_2$OH).

LRMS(CI) 278 (M^+, 24%), 261 ($[M-OH]^+$, 36%), 151 ($[M-I]^+$, 58%), 135 (100%), 63 (16%) amu.

(6-Iodo-1,3-benzodioxolo-5-yl)methyl bromide (297a)[66]



mw = 340.82 g/mol

$C_8H_6O_2BrI$

To a cooled solution (0 °C) of the alcohol **296a** (4.30 g, 15.48 mmol) in benzene (50 mL) was added phosphorus tribromide (0.51 mL, 1.46 g, 5.41 mmol) dropwise over 5 minutes. The mixture was allowed to warm to room temperature and stirred for 2 hours. The mixture was then concentrated *in vacuo* and the residue partitioned between dichloromethane (20 mL) and water (20 mL). The organic phase was washed with sat. $NaHCO_3$ (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound as a cream powder (4.92 g, 14.44 mmol, 93%).

Data for **297a** were consistent with literature values.

MP 74-76 °C (petrol)[66] lit 72 °C.

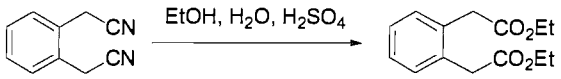
FT-IR (neat, cm^{-1}): 3101 (w), 3030 (w), 2964 (w), 1493 (s), 1479 (s), 1379 (m), 1252 (s), 1233 (s), 1114 (m), 1034 (m), 925 (s), 864 (s).

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.25 (1H, s, CH_{AR}), 6.97 (1H, s, CH_{AR}), 5.99 (2H, s, OCH_2O), 4.56 (2H, s, CH_2Br).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 148.8 (2 x $C_{AR}O$), 133.4 (C_{AR}), 119.1 (CH_{AR}), 110.2 (CH_{AR}), 102.2 (OCH_2O), 89.0 ($C_{AR}I$), 39.7 (CH_2Br).

LRMS(CI) 342 ($[M^{81}Br]^+$, 5%), 340 ($[M^{79}Br]^+$, 5%), 278 (12%), 262 ($[MH\text{-}Br]^+$, 100%), 135 ($[MH\text{-}Br\text{-}I]^+$, 38%), 77 (14%) amu.

(2-Ethoxycarbonylmethyl-phenyl)-acetic acid ethyl ether (292)[67]



mw = 250 g/mol

$C_{14}H_{18}O_4$

CAS = 17532-66-0

A solution of dinitrile **290** (2.26 g, 14 mmol) in ethanol (8 mL), H_2O (0.8 mL) and concentrated sulfuric acid (3.6 mL) was stirred at reflux for 18 h. After cooling and adding H_2O (20 mL), the organic layer was extracted with ether (3 x 20 mL). The combined organic phases were washed with H_2O (20 mL) and saturated $NaHCO_3$ (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the title compound as a yellow oil (2.79 g, 11.1 mmol, 80%).

Data for **292** were consistent with literature values.

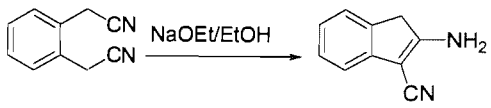
FT-IR (neat, cm^{-1}): 2981 (w), 1727 (s), 1248 (m), 1151 (s), 1027 (m).

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.24 (4H, s, 4 x CH_{AR}), 4.06 (4H, q, *J*=7.1 Hz, CH_2CH_3), 3.65 (4H, s, 2 x CH_2CO_2Et), 1.16 (6H, t, *J*=7.1 Hz, 2 x CH_2CH_3).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 171.2 (2 x **C**O), 133.4 (2 x C_{AR}), 130.9 (2 x CH_{AR}), 127.6 (2 x CH_{AR}), 60.9 (2 x $CO_2CH_2CH_3$), 39.0 (2 x CH_2CO_2Et), 14.2 (2 x CH_2CH_3).

LRMS(CI) 268 ($[M+NH_4]^+$, 20%), 251 ($[MH]^+$, 100%), 222 (53%), 204 (62%), 176 (77%), 147 (54%), 130 (40%), 104 (62%), 91 (38%) amu.

2-Amino-*3H*-indene-1-carbonitrile (291)[68]



mw = 156 g/mol

$C_{10}H_8N_2$

Metallic sodium (0.22 g, 9.6 g atom) was added slowly at 0 °C to ethanol (20 mL) under nitrogen. After complete dissolution, dinitrile **290** (1.00 g, 6.4 mmol) was added in one portion. The reaction was stirred for 30 min at 0 °C then warmed to room temperature and stirred for 16 h. Silica was added to the resulting mixture and the solvent was removed *in vacuo*. Purification by column chromatography (silica gel, AcOEt/petrol, 20/80) afforded the title compound (0.88 g, 5.6 mmol, 87%) as a dark purple powder.

Data for **291** were consistent with literature values.

MP 190-192 °C lit[68] 193 °C

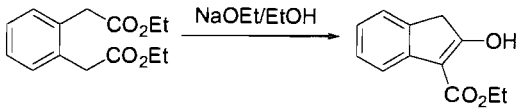
FT-IR (neat, cm^{-1}): 1637 (w), 1568 (w), 1456 (w), 1263 (s), 1095 (br), 815 (s), 753 (s).

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.44 (1H, d, J = 7.2 Hz, C**H**$_{AR}$), 7.23 (2H, m, 2 x C**H**$_{AR}$), 7.03 (1H, t, J = 7.2 Hz, C**H**$_{AR}$), 5.11 (2H, s, N**H**$_2$), 3.79 (2H, s, C**H**$_2$CNH$_2$).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 165.5 (**C**N), 133.0 (2 x **C**$_{AR}$), 128.3 (**C**H$_{AR}$), 127.7 (**C**H$_{AR}$), 123.4 (**C**H$_{AR}$), 123.1 (**C**H$_{AR}$), 117.4 (**C**H$_{AR}$), 117.0 (**C**CN), 38.7 (**C**H$_2$CNH$_2$).

LRMS(CI) 174 ([M+NH$_4$]$^+$, 20%), 156 (M$^+$, 100%), 127 (6%), 102 (8%), 77 (5%) amu.

2-Hydroxy-*3H*-indene-1-carboxylic acid ethyl ester (283)[69, 70]



mw = 204 g/mol

$C_{12}H_{12}O_3$

Metallic sodium (0.39 g, 17.1 g atom) was added slowly at 0 °C to ethanol (20 mL) under nitrogen. After complete dissolution, diester **292** (1.94 g, 7.8 mmol) in THF (2 mL) was added in one portion. The reaction was stirred for 30 min at 0 °C then at reflux for 16 h. Following continuous extraction of the reaction mixture with EtOAc for 24 h (150 mL). The solvent was removed *in vacuo* leaving yellow oil. Purification by column chromatography (silica gel, AcOEt/petrol 20/80), afforded the title compound (0.40 g, 1.96 mmol, 25%), as yellow oil.

Data for **283** were consistent with literature values.

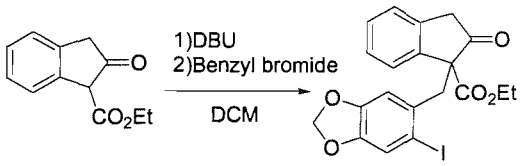
FT-IR (neat, cm^{-1}): 2979 (s), 2926 (s), 1654 (s).

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.62 (1H, d, J = 7.6 Hz, C**H**$_{AR}$), 7.28 (2H, m, 2 x C**H**$_{AR}$), 7.13 (1H, t, J = 7.6 Hz, C**H**$_{AR}$), 4.15 (2H, q, J = 7.1 Hz, C**H$_2$**CH$_3$), 3.72 (2H, s, C**H$_2$**CO)

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 171.3 (**C**O), 169.1 (**C**O$_2$), 132.2 (**C**$_{AR}$), 127.5 (**C**H$_{AR}$), 122.7 (**C**H$_{AR}$), 120.5 (**C**H$_{AR}$), 119.1 (**C**H$_{AR}$), 112.4 (**C**CO), 58.6 (**C**H$_2$CH$_3$), 39.0 (**C**H$_2$CO), 14.4 (CH$_2$**C**H$_3$).

LRMS(CI) 132 ([M-CO_2Et]$^+$, 40%), 104 (100%), 78 (22%), 63 (10%) amu.

1-(6-Iodo-benzo[1,3]dioxol-5-ylmethyl)-2-oxo-indan-1-carboxylic acid ethyl ester (285)



mw = 464 g/mol

$C_{20}H_{17}O_5I$

DBU (0.13 mL, 0.86 mmol) was added to a solution of indanone **283** (0.16 g, 0.78 mmol) in dichloromethane (10 mL). The mixture was stirred for 1 hour then benzyl bromide **297a** (0.30 g, 1.02 mmol) was added. After 60 hours, H_2O (10 mL) was added and the aqueous phase extracted with dichloromethane (2 x 20 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, ether/petrol 5/95) afforded the title compound **285** (0.14 g, 0.31 mmol, 40%) as a yellow solid.

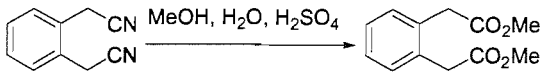
MP 117-119 °C

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.29 (3H, m, 3 x C**H**$_{AR}$), 7.09 (2H, m, 2 x C**H**$_{AR}$), 6.66 (1H, s, C**H**$_{AR}$), 5.90 (2H, d, J = 5.34 Hz, OC**H**$_2$O), 4.14 (2H, m, C**H**$_2$CH$_3$), 3.70-3.45 (4H, br, C**H**$_2$CO, C**H**$_2$C$_{AR}$C$_{AR}$I), 1.14 (3H, t, J = 7.05, CH$_2$C**H**$_3$).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 211.2 (**C**O), 170.0 (**C**O$_2$), 148.3 (**C**$_{AR}$O), 147.3 (**C**$_{AR}$O), 140.0 (**C**$_{AR}$), 137.3 (**C**$_{AR}$), 132.1 (**C**$_{AR}$), 128.8 (**C**H$_{AR}$), 127.6 (**C**H$_{AR}$), 125.6 (**C**H$_{AR}$), 124.9 (**C**H$_{AR}$), 118.7 (**C**H$_{AR}$), 109.8 (**C**H$_{AR}$), 101.7 (O**C**H$_2$O), 91.7 (**C**$_{AR}$I), 66.4 (O$_2$C**C**CO), 62.1 (O**C**H$_2$), 43.8 (**C**H$_2$CO), 43.3 (**C**H$_2$C$_{AR}$C$_{AR}$I), 14.0 (CH$_2$**C**H$_3$).

LRMS(CI) 464 (M^+, 6%), 337 ([M-I]$^+$, 14%), 320 (18%), 292 (8%), 261 (100%), 235 (14%), 178 (10%), 135 (14%) amu.

(2-Methoxycarbonylmethyl-phenyl)-acetic acid methyl ester (293)[67]



mw = 222 g/mol

$C_{12}H_{14}O_4$

A solution of dinitrile **290** (3.00 g, 19.2 mmol) in methanol (12 mL), H_2O (1.2 mL) and concentrated sulfuric acid (5 mL) was stirred at reflux for 18 h. After cooling and addition of water (20 mL), the organic phase was separated with ether (3 x 20 mL) and washed with H_2O (20 mL) and sat. $NaHCO_3$ (20 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo* to yield **293** (4.14 g, 18.6 mmol, 97%) as a colourless oil.

Data for **293** were consistent with literature values.

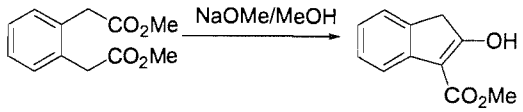
FT-IR (neat, cm^{-1}): 1736 (s), 1436 (m), 1341 (w), 1259 (m), 1160 (m), 1009 (m).

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.25 (4H, s, 4 x CH_{AR}), 3.72 (4H, s, 2 x CH_2), 3.66 (6H, s, 2 x OCH_3).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 171.7 (2 x CO_2), 133.3 (2 x C_{AR}), 131.0 (2 x CH_{AR}), 127.8 (2 x CH_{AR}), 52.2 (2 x OCH_3), 38.8 (2 x CH_2).

LRMS(CI) 240 ($[M+NH_4]^+$, 8%), 223 ($[M+H]^+$, 100%), 208 (14%), 190 ($[M-CH_3OH]^+$, 100%), 176 (20%), 163 ($[M- CO_2Me]^+$, 46%), 130 (24%), 103 (42%), 91 (15%), 78 (22%), 59 (10%) amu.

2-Hydroxy-*3H*-indene-1-carboxylic acid methyl ester (294)[71]



mw = 190 g/mol

$C_{11}H_{10}O_3$

Metallic sodium (2.88 g, 126 mmol) was added slowly at 0 °C to methanol (120 mL) under nitrogen. After complete dissolution, diester **293** (12.71 g, 57 mmol) was added in one portion. The reaction was warmed to room temperature and stirred for 30 minutes then heated at reflux for 3 h. Following extraction with ether (2 x 20 mL) and water (20 mL), the aqueous phase was acidified to pH 1 with 2N HCl (100 mL) and extracted with ether (2 x 20 mL). The combined organic phases were dried ($MgSO_4$), concentrated *in vacuo* to leave a white solid and purified by column chromatography (silica gel, ether/petrol, 30/70) to afford the title compound **294** (8.31 g, 43.7 mmol, 76%) as a light blue solid.

Data for **294** were consistent with literature values.

MP 55-57 °C (ether/petrol)

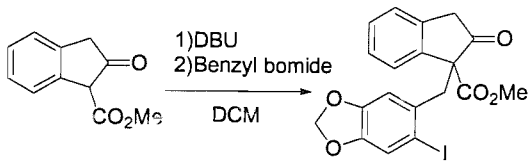
FT-IR (neat, cm^{-1}): 3182 (v), 2950 (m), 1666 (s), 1593 (s), 1476 (s), 1440 (s), 1323 (s), 1165 (s), 1046 (s), 781 (s) amu.

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 11.03 (1H, s, O**H**), 7.60 (1H, d, J = 7.5 Hz, C$\mathbf{H}_{AR}$), 7.33-7.26 (2H, m, 2 x C$\mathbf{H}_{AR}$), 7.13 (1H, t, J = 6.4 Hz, C$\mathbf{H}_{AR}$), 3.97 (3H, s, C$\mathbf{H}_3$), 3.60 (2H, s, C$\mathbf{H}_2$COH).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 180.9 (**C**O_2), 139.9 (**C**OH), 133.2 (2 x **C**$_{AR}$), 127.2 (**C**H$_{AR}$), 123.9 (**C**H$_{AR}$), 123.7 (**C**H$_{AR}$), 120.3 (**C**H$_{AR}$), 105.2 (COCCOH), 51.7 (**C**H_3), 37.8 (**C**H_2COH).

LRMS(CI) 132 ([M-CO_2Me]$^+$, 42%), 104 (100%), 78 (20%) amu.

1-(6-Iodo-benzo[1,3]dioxol-5 yl methyl)-2-oxo-indan-1-carboxylic acid methyl ester (300a)



mw = 450 g/mol

$C_{19}H_{15}O_5I$

DBU (1.88 mL, 12.6 mmol) was added to a solution of indanone **294** (2.00 g, 10.5 mmol) in dichloromethane (75 mL). The mixture was stirred for 1 hour then benzyl bromide **297a** (4.30 g, 12.6 mmol) was added. After 16 hours, H_2O (10 mL) was added and the aqueous phase extracted with dichloromethane (2 x 20 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, ether/petrol, 10/90) gave the title compound **300a** (2.65 g, 5.89 mmol, 56%) as a yellow solid.

MP 114–115 °C (ether/petrol).

FT-IR (neat, cm^{-1}): 2951 (w), 2898 (w), 1759 (s), 1735 (s), 1477 (s), 1229 (s), 1038 (s), 932 (s), 731 (s).

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.31-7.22 (3H, m, 3 x CH_{AR}), 7.09 (1H, s, CH_{AR}), 7.06 (1H, d, J = 7.7 Hz, CH_{AR}), 6.64 (1H, s, CH_{AR}), 5.88 (2H, d, J = 6.9 Hz, OCH_2O), 3.70-3.45 (4H, br, CH_2CO, $CH_2C_{AR}C_{AR}I$), 3.65 (3H, s, OCH_3).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 211.0 (CO), 170.5 (CO_2), 148.3 ($C_{AR}O$), 147.4 ($C_{AR}O$), 139.9 (C_{AR}), 137.3 (C_{AR}), 131.9 (C_{AR}), 128.9 (CH_{AR}), 127.7 (CH_{AR}), 125.7 (CH_{AR}), 124.9 (CH_{AR}), 118.7 (CH_{AR}), 109.8 (CH_{AR}), 101.7

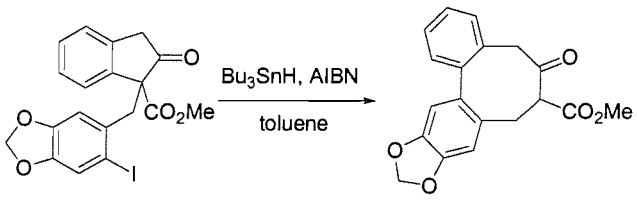
(OCH_2O), 91.8 ($C_{AR}I$), 66.3 (COCCO), 53.2 (OCH_3), 43.9 (CH_2CO), 43.3 (CH_2).

LRMS(CI) 450 (M^+, 4%), 324 ($[MH-I]^+$, 8%), 306 (25%), 261 (100%), 235 (26%), 189 (20%) amu.

HRMS(ES) Found M+Na: 472.9851; $C_{19}H_{15}O_5INa$ requires 472.9856

CHN Calculated C 50.69, H 3.36. Found C 50.87, H 3.40.

Methyl 6 oxo 5,6,7,8 tetrahydrobenzo[3′,4′]cycloocta[4,5]benzo[*d*][1,3]dioxole-7-carboxylate (301a)



mw = 324 g/mol

$C_{19}H_{16}O_5$

To a solution of indanone **300a** (0.35 g, 0.77 mmol) in toluene (30 mL) under nitrogen, was added Bu_3SnH (0.314 mL, 1.20 mmol) and AIBN (13 mg, 0.07 mmol). The mixture was stirred at 80 °C for 3 hours then additional Bu_3SnH (0.341 mL, 1.2 mmol) and AIBN (13 mg, 0.07 mmol) were added. The reaction was stirred at 80 °C for a further 16 hours then cooled to room temperature. Aqueous potassium fluoride (10% w/v, 20 mL) was added and the resulting mixture stirred vigorously for 24 hours. The organic phase was washed with brine (2 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 0-5% ether/toluene) afforded the title compound **301a** (87 mg, 0.27 mmol, 35%) as a white powder.

MP 147-149 °C

FT-IR (neat, cm^{-1}): 2916 (br), 2358 (s), 1739 (s), 1706 (s), 1502 (m), 1479 (s), 1218 (s), 1029 (m).

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.40-7.26 (4H, m, 4 x C**H**$_{AR}$), 6.86 (1H, s, C**H**$_{AR}$), 6.78 (1H, s, C**H**$_{AR}$), 6.03 (2H, s, OC**H**$_2$O), 3.76 (3H, s, OC**H**$_3$), 3.92-3.62 (1H, m, COC**H**CO), 3.64 (1H, d, J = 11.5 Hz, C**H**$_2$CO), 3.41 (1H, d, J = 11.5 Hz, C**H**$_2$CO), 2.91 (1H, dd, J = 14.2, 2.9 Hz, C**H**HCHCO), 2.78 (1H, dd, J = 14.0, 11.8 Hz, CH**H**CHCO).

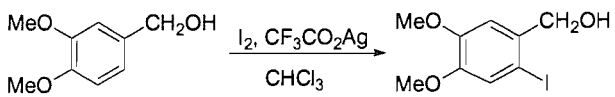
^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 203.3 (**C**O), 171.0 (**C**O$_2$), 148.0 (**C**$_{AR}$O), 147.2 (**C**$_{AR}$O), 140.9 (**C**$_{AR}$), 133.7 (**C**$_{AR}$), 132.6 (**C**$_{AR}$), 131.0 (**C**$_{AR}$), 129.8 (**C**H$_{AR}$), 129.5 (**C**H$_{AR}$), 128.3 (**C**H$_{AR}$), 128.0 (**C**H$_{AR}$), 109.5 (2 x **C**H$_{AR}$), 101.5 (O**C**H$_2$O), 59.4 (CO**C**HCO), 52.4 (O**C**H$_3$), 48.1 (**C**H$_2$CO), 32.4 (**C**H$_2$).

LRMS(CI) 266 ([M-CO_2CH_3]$^+$, 100%), 238 (22%), 223 (32%), 193 (14%), 165 (60%), 152 (22%), 139 (10%) amu.

HRMS(ES) Found 2M+Na: 671.1889; $C_{38}H_{32}O_{10}Na$ requires 671.1887.

CHN Calculated C 70.36, H 4.97. Found C 69.97, H 4.93.

4,5-Dimethoxy-2-iodobenzyl alcohol (296b)[72]



mw = 294 g/mol

$C_9H_{11}O_3I$

To a stirred suspension of the alcohol **295b** (5.00 g, 29.73 mmol) and silver trifluoroacetate (9.85 g, 44.59 mmol), in dry chloroform (60 mL) at 0 °C under nitrogen was added iodine (8.30 g, 32.70 mmol) in one portion. The resulting yellow mixture was maintained at 0 °C for 5 minutes and then filtered through celite. The filtrate was washed with sat. sodium thiosulfate (20 mL) and this aqueous suspension extracted with chloroform (4 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to a pale yellow solid. Recrystallisation from chloroform/petrol gave the title product as a cream powder (6.73 g, 22.89 mmol, 77%).

Data for **296b** were consistent with literature values.

MP 93-95 °C (ether) lit[72] 94-96 °C

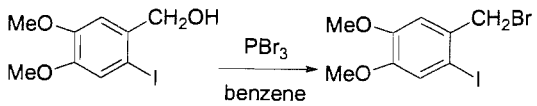
FT-IR (neat, cm^{-1}): 3484 (br), 2934 (br), 1501 (s), 1257 (s), 1155 (s), 1026 (s), 791 (m), 731 (m).

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.19 (1H, s, C**H**$_{AR}$), 6.97 (1H, s, C**H**$_{AR}$), 4.57 (2H, s, C**H**$_2$OH), 3.84 (3H, s, OC**H**$_3$), 3.83 (3H, s, OC**H**$_3$), 2.39 (1H, s, O**H**).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 149.5 (**C**$_{AR}$O), 148.9 (**C**$_{AR}$O), 135.3 (**C**$_{AR}$), 121.5 (**C**H$_{AR}$), 111.6 (**C**H$_{AR}$), 85.4 (**C**$_{AR}$I), 69.1 (**C**H$_2$OH), 56.3 (O**C**H$_3$), 56.1 (O**C**H$_3$).

LRMS(CI) 294 (M^+, 66%), 277 ($[M\text{-}OH]^+$, 100%), 167 ($[M\text{-}I]^+$, 31%), 151 (72%), 139 (12%) amu.

4,5-Dimethoxy-2-iodo benzyl bromide (297b)[73]



mw = 357 g/mol

$C_9H_{10}O_2BrI$

To a cooled solution (0 °C) of the alcohol **296b** (6.73 g, 22.90 mmol) in benzene (70 mL) was added phosphorus tribromide (0.76 mL, 2.16 g, 8.01 mmol) dropwise over 5 minutes. After 2 hours at room temperature the mixture was concentrated *in vacuo* and portioned between dichloromethane (40 mL) and water (20 mL). The organic phase was washed with sat. $NaHCO_3$ (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound **297b** as a yellow pale powder (7.50 g, 21.02 mmol, 92%).

Data for **297b** were consistent with literature values.

MP 87-89 °C (ether) lit[73] 89-90 °C (ether).

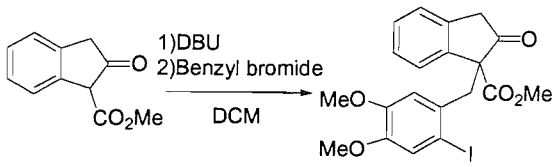
FT-IR (neat, cm^{-1}): 2955 (br), 1593 (m), 1501 (s), 1375 (m), 1256 (s), 1206 (s), 1164 (s), 1024 (m).

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.24 (1H, s, CH_{AR}), 6.97 (1H, s, CH_{AR}), 4.60 (2H, s, CH_2Br), 3.89 (3H, s, OCH_3), 3.88 (3H, s, OCH_3).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 149.7 (2 x C_{AR}), 132.5 (C_{AR}), 121.9 (CH_{AR}), 112.8 (CH_{AR}), 88.7 ($C_{AR}I$), 56.3 (OCH_3), 56.1 (OCH_3), 39.6 (CH_2Br).

LRMS(CI) 358 ($[M^{81}Br]^+$, 2%), 356 ($[M^{79}Br]^+$, 2%), 277 ($[M\text{-}Br]^+$, 87%), 170 (20%), 152 (100%), 137 (20%), 109 (10%) amu.

1-(2-Iodo-4,5-dimethoxybenzyl)-2-oxo-indan-1-carboxylic acid methyl ester (300b)



mw = 466 g/mol

$C_{20}H_{19}O_5I$

DBU (0.84 mL, 5.60 mmol) was added to a solution of indanone **294** (0.88 g, 4.60 mmol) in dichloromethane (70 mL) under nitrogen. The reaction was stirred for 45 minutes then the aryl bromide **297b** (2.00 g, 5.60 mmol) was added. After 60 hours, water (10 mL) was added and the aqueous phase extracted with dichloromethane (2 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, ether/petrol, 1:1) afforded the title compound **300b** (2.09 g, 4.40 mmol, 97%) as a pale yellow powder.

MP 117-119 °C (ether/petrol)

FT-IR (neat, cm^{-1}): 2952 (br), 1760 (s), 1735(s), 1596 (m), 1505 (s), 1462 (m), 1250 (s), 1163 (s), 1027 (m), 912 (m), 731 (s).

^{1}H NMR δ (300 MHz, $CDCl_3$): 7.33-7.26 (4H, m, 4 x C**H**$_{AR}$), 7.09 (1H, s, C**H**$_{AR}$), 6.35 (1H, s, C**H**$_{AR}$), 3.78 (3H, s, OC**H**$_3$), 3.68 (3H, s, OC**H**$_3$), 3.50 (3H, s, OC**H**$_3$), 3.78-3.50 (3H, m, C**H**$_2$ & C**H**H), 3.18 (1H, d, J=22.7 Hz, C**H**H).

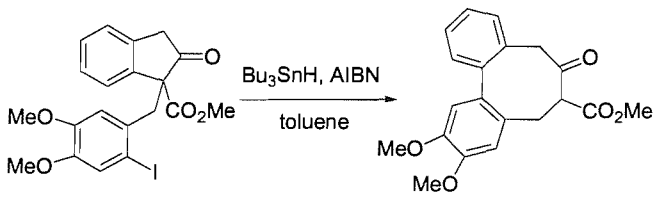
^{13}C NMR δ (75 MHz, $CDCl_3$): 210.9 (**C**O), 170.6 (**C**O_2), 148.6 (**C**$_{AR}$O), 148.2 (**C**$_{AR}$O), 140.3 (**C**$_{AR}$), 137.8 (**C**$_{AR}$), 130.7 (**C**$_{AR}$), 128.9 (**C**H$_{AR}$), 127.9 (**C**H$_{AR}$), 125.4 (**C**H$_{AR}$), 125.1 (**C**H$_{AR}$), 121.6 (**C**H$_{AR}$), 112.4 (**C**H$_{AR}$), 91.2 (**C**$_{AR}$I), 66.4 (CO**C**CO), 56.0 (O**C**H$_3$), 55.5 (O**C**H$_3$), 53.1 (CO_2**C**H$_3$), 43.8 (**C**H_2CO), 43.3 (**C**H_2).

LRMS(CI) 484 ($[M+NH_4]^+$, 8%), 466 (M^+, 4%), 340 ($[MH-I]^+$, 10%), 277 (100%), 151 (30%) amu.

HRMS(ES) Found M+Na: 489.0173; $C_{20}H_{19}O_5NaI$ requires 489.0169

CHN Calculated C 51.52, H 4.11. Found C 51.62, H 4.19.

2,3-Dimethoxy-7-oxo-5,6,7,8-tetrahydrodibenzo[*a,c*]cyclooctene-6-carboxylic acid methyl ester (301b)



mw = 340 g/mol

$C_{20}H_{20}O_5$

To a solution of indanone **300b** (1.00 g, 2.10 mmol) in toluene (30 mL) was added tributyltin hydride (0.87 mL, 0.94 g, 3.21 mmol) and AIBN (35 mg, 0.21 mmol). After heating at 80 °C for 3 hours, the reaction mixture was cooled to room temperature and stirred vigorously with potassium fluoride (10% w/v, 20 mL) for 24 hours. The resulting mixture was extracted with ether (10 mL) and the combined organic phases washed with brine (2 x 30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (1:1 ether/petrol) yielded the title compound as a white solid (0.50 g, 1.47 mmol, 70%) as a 1:1 mixture of diastereoisomers.

MP 168-170 °C

FT-IR (neat, cm^{-1}): 2951 (br), 2359 (m), 1741 (s), 1707 (s), 1518 (s), 1240 (s), 1146 (s), 1024 (m).

^{1}H NMR δ (400 MHz, $CDCl_3$): 7.43-7.26 (8H, m, 8 x C**H**$_{AR}$), 6.95 (1H, s, C**H**$_{AR}$), 6.93 (1H, s, C**H**$_{AR}$), 6.88 (1H, s, C**H**$_{AR}$), 6.86 (1H, s, C**H**$_{AR}$), 4.03 (3H, s, OC**H**$_3$), 3.99 (3H, s, OC**H**$_3$), 3.98 (3H, s, OC**H**$_3$), 3.97 (3H, s, OC**H**$_3$), 3.94 (1H, d, J = 11.8 Hz, C**H**HCO), 3.84 (3H, s, OC**H**$_3$), 3.80 (3H, s, OC**H**$_3$), 3.76 (1H, dd, J = 12.3, 2.6 Hz, COC**H**CO), 3.70 (1H, d, J = 11.3 Hz, C**H**HCO), 3.59 (1H, app t, J = 4.5 Hz, COC**H**CO), 3.51 (1H, d, J = 12.0 Hz, C**H**HCO), 3.47 (1H, d, J = 11.3 Hz, C**H**HCO), 3.27 (1H, dd, J = 14.6, 5.5 Hz, C**H**HCHCO), 3.03 (1H, dd, J = 14.5, 2.6 Hz, C**H**HCHCO), 2.88 (1H, dd, J = 14.5, 12.3 Hz, C**H**HCHCO), 2.84 (1H, dd, J = 14.5, 3.7 Hz, C**H**HCHCO).

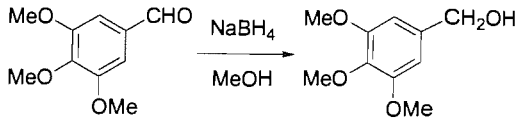
^{13}C NMR δ (75 MHz, $CDCl_3$): 204.2 (**C**O), 203.5 (**C**O), 171.1 (**C**O$_2$), 170.2 (**C**O$_2$), 149.1 (**C**$_{AR}$O), 148.4 (**C**$_{AR}$O), 148.3 (**C**$_{AR}$O), 148.2 (**C**$_{AR}$O), 141.3 (**C**$_{AR}$), 140.8 (**C**$_{AR}$), 133.5 (**C**$_{AR}$), 133.1 (**C**$_{AR}$), 132.8 (**C**$_{AR}$), 132.5 (**C**$_{AR}$), 129.8 (**C**H$_{AR}$), 129.7 (**C**H$_{AR}$), 129.6 (**C**$_{AR}$), 129.4 (**C**H$_{AR}$), 129.3 (**C**H$_{AR}$), 128.1 (**C**H$_{AR}$), 128.0 (**C**H$_{AR}$), 127.8 (**C**H$_{AR}$), 127.6 (**C**H$_{AR}$), 127.3 (**C**$_{AR}$), 113.5 (**C**H$_{AR}$), 112.22 (**C**H$_{AR}$), 112.20 (**C**H$_{AR}$), 112.1 (**C**H$_{AR}$), 59.4 (CO**C**HCO), 56.4 (CO**C**HCO), 59.1 (O**C**H$_3$), 56.0 (O**C**H$_3$), 55.9 (O**C**H$_3$), 55.9 (O**C**H$_3$), 52.3 (O**C**H$_3$), 52.2 (O**C**H$_3$), 48.0 (**C**H$_2$CO), 47.9 (**C**H$_2$CO), 32.1 (**C**H$_2$CHCO), 32.0 (**C**H$_2$CHCO).

LRMS(CI) 300 (100%), 283 (54%), 265 (46%), 239 (10%), 165 (8%) amu.

HRMS(CI) Found 2M+Na: 703.2515; $C_{40}H_{40}O_{10}Na$ requires 703.2513.

CHN Calculated C 70.58, H 5.92. Found C 70.43, H 5.92.

3,4,5-Trimethoxy benzyl alcohol (295c)[74]



mw = 198 g/mol

$C_{10}H_{14}O_4$

CAS = 384-31-1

To a solution of 3,4,5-trimethoxybenzaldehyde (0.50 g, 25.40 mmol) in methanol (50 mL) at 0 °C, was added sodium borohydride (1.06 g, 28.00 mmol) portionwise over 5 minutes. After 30 minutes, the solvent was removed under reduced pressure. The residue was diluted with dichloromethane (20 mL) and washed with brine (2 x 20 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to afford the title alcohol **295c** (5.02 g, 25.30 mmol, 99%) as a colourless oil.

Data for **295c** were consistent with literature values.

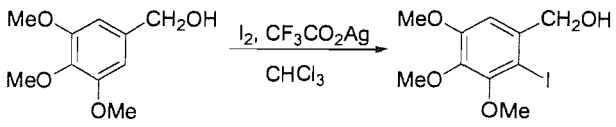
FT-IR (neat, cm^{-1}): 3446 (br), 2940 (s), 2359 (s), 1592 (s), 1506 (s), 1458 (s), 1330 (s), 1235 (s), 1126 (s).

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 6.60 (2 H, s, 2 x CH_{AR}), 4.63 (2H, s, CH_2OH), 3.86 (6H, s, 2 x OCH_3), 3.83 (3H, s, OCH_3), 1.87 (1H, s, OH).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 153.4 (C_{AR}), 137.3 ($C_{AR}O$), 136.8 (2 x $C_{AR}O$), 103.8 (2 x CH_{AR}), 65.6 (CH_2OH), 61.0 (OCH_3), 56.2 (2 x OCH_3).

LRMS(CI) 199 ($[MH]^+$, 70%), 181 ($[M\text{-}OH]^+$, 100%), 155 (6%), 127 (14%), 95 (7%) amu.

2-Iodo-3,4,5-trimethoxy benzyl alcohol (296c)[75]



mw = 324 g/mol

$C_{10}H_{13}O_4I$

CAS = 6449-45-5

To a stirred suspension of alcohol **295c** (3.00 g, 15 mmol) and silver trifluoroacetate (5.01 g, 23 mmol) in dry chloroform (45 mL) at 0 °C under nitrogen was added iodine (5.76 g, 23 mmol) in one portion. The resulting yellow mixture was maintained at 0 °C for 5 minutes then filtered. The filtrate was washed with sat. sodium thiosulfate (20 mL) and this aqueous suspension was extracted with chloroform (4 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to yield **296c** (1.63 g, 5.00 mmol, 34%) as a white powder.

Data for **296c** were consistent with literature values.

MP 46-48 °C lit[75] 57-59 °C

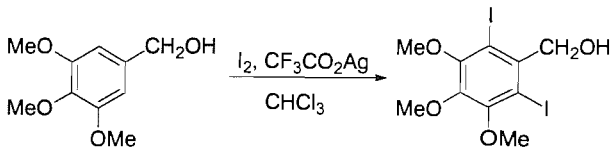
FT-IR (neat, cm^{-1}): 3446 (br), 2935 (s), 2359 (s), 1560 (m), 1477 (s), 1390 (s), 1323 (s), 1103 (s), 1005 (s).

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 6.92 (1H, s, C**H**$_{AR}$), 4.65 (2H, s, C**H$_2$**OH), 3.88 (6H, s, 2 x OC**H$_3$**), 3.86 (3H, s, OC**H$_3$**), 2.24 (1H, s, O**H**).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 154.3 (**C**$_{AR}$O), 153.4 (**C**$_{AR}$O), 141.8 (**C**$_{AR}$O), 138.7 (**C**$_{AR}$), 108.4 (**C**H$_{AR}$), 84.9 (**C**$_{AR}$I), 69.8 (**C**H$_2$OH), 61.4 (O**C**H$_3$), 61.2 (O**C**H$_3$), 56.5 (O**C**H$_3$).

LRMS(CI) 324 (M^+, 84%), 307 ($[M\text{-}OH]^+$, 100%), 198 ($[MH\text{-}I]^+$, 70%), 181 (88%), 167 (12%), 127 (12%) amu.

2,6-Diiodo-3,4,5-trimethoxy benzyl alcohol (298c)



mw = 450 g/mol

$C_{10}H_{12}O_4I_2$

To a suspension of alcohol **295c** (3.00 g, 15.00 mmol) and silver trifluoroacetate (5.01 g, 23.00 mmol) in dry chloroform (45 mL) at 0 °C under nitrogen was added iodine (5.76 g, 23.00 mmol) in one portion. The resulting yellow mixture was maintained at 0 °C for 5 minutes then filtered. The filtrate was washed with sat. sodium thiosulfate (20 mL) and this aqueous suspension was extracted with chloroform (4 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to yield **298c** (2.65 g, 5.80 mmol, 39%) as a white powder.

MP 82-84 °C (chloroform)

FT-IR (neat, cm^{-1}): 3320 (br), 2935 (s), 2359 (m), 1459 (s), 1402 (s), 1371 (s), 1309 (s), 1082 (s), 1006 (s).

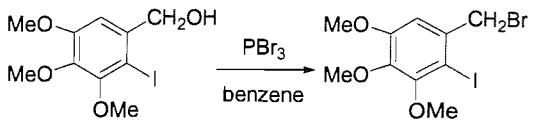
^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 5.15 (2H, s, CH_2OH), 3.90 (3H, s, OCH_3), 3.88 (6H, s, 2 x OCH_3).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 154.4 (2 x $C_{AR}O$), 145.3 ($C_{AR}O$), 139.8 (C_{AR}), 92.9 (2 x $C_{AR}I$), 75.2 (CH_2OH), 61.4 (OCH_3), 61.2 (2 x OCH_3).

LRMS(CI) 450 (M^+, 50%), 433 ($[M-OH]^+$, 56%), 324 ($[MH-I]^+$, 14%), 307 ($[MH-OH-I]^+$, 26%), 194 ($[M-2I-2H]^+$, 98%), 183 (100%) amu.

HRMS(CI) Found M+Na: 472.8715; $C_{10}H_{12}O_4NaI_2$ requires 472.8717.

2-Iodo-3,4,5-trimethoxy benzyl bromide (297c)[75]



mw =387 g/mol

$C_{10}H_{12}O_3BrI$

To a cooled solution (0 °C) of the alcohol **296c** (1.37 g, 4.20 mmol) in benzene (20 mL) was added phosphorus tribromide (0.14 mL, 0.40 g, 1.50 mmol) dropwise over 1 minute. The mixture was allowed to warm to room temperature, stirred for 2 hours, then concentrated *in vacuo*. The residue was partitioned between dichloromethane (40 mL) and water (20 mL). The organic phase was washed with sat. $NaHCO_3$ (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the title product **297c** as a cream powder (1.42 g, 3.60 mmol, 87%).

Data for **297c** were consistent with literature values.

MP 39-41 °C

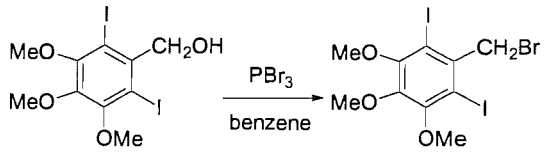
FT-IR (neat, cm^{-1}): 2935 (m), 2359 (s), 2341 (s), 1479 (s), 1386 (s), 1333 (s), 1100 (s), 1003 (m).

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 6.90 (1H, s, C**H**$_{AR}$), 4.64 (2H, s, C**H**$_2$Br), 3.89 (9H, s, 3 x OC**H**$_3$).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 153.9 (**C**$_{AR}$O), 153.7 (**C**$_{AR}$O), 142.0 (**C**$_{AR}$O), 135.6 (**C**$_{AR}$), 109.7 (**C**H$_{AR}$), 88.5 (**C**$_{AR}$I), 61.1 (O**C**H$_3$), 60.9 (O**C**H$_3$), 56.3 (O**C**H$_3$), 39.7 (**C**H$_2$Br).

LRMS(CI) 388 ($[M^{81}Br]^+$, 2%), 386 ($[M^{79}Br]^+$, 2%), 361 (20%), 307 ($[M\text{-}Br]^+$, 70%), 183 (100%), 167 (25%) amu.

2,6-Diiodo-3,4,5-trimethoxy benzyl bromide (299c)



mw = 513 g/mol

$C_{10}H_{11}O_3BrI_2$

To a cooled solution (0 °C) of the alcohol **298c** (2.50 g, 5.70 mmol) in benzene (30 mL) was added phosphorus tribromide (0.19 mL, 0.54 g, 2.00 mmol) dropwise over 1 minute. The mixture was allowed to warm to room temperature, stirred for 2 hours, then concentrated *in vacuo*. The residue was portioned between dichloromethane (40 mL) and water (20 mL). The organic phase was washed with sat. $NaHCO_3$ (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the title product **299c** as a cream powder (2.24 g, 4.30 mmol, 78%).

MP 86-88 °C (ether/petrol)

FT-IR (neat, cm^{-1}): 2932 (m), 2359 (s), 1458 (s), 1401 (s), 1372 (s), 1316 (s), 1206 (s), 1076 (s), 953 (s).

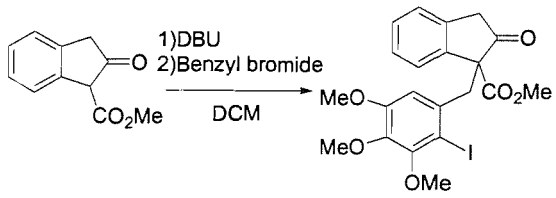
^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 5.02 (2H, s, C**H$_2$**Br), 3.90 (3H, OC**H$_3$**), 3.87 (6H, s, 2 x OC**H$_3$**).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 154.3 (2 x **C$_{AR}$**O), 145.0 (**C$_{AR}$**O), 136.7 (**C$_{AR}$**), 92.8 (2 x **C$_{AR}$**I), 61.2 (O**C**H$_3$), 61.0 (2 x O**C**H$_3$), 47.0 (**C**H$_2$Br).

LRMS(CI) 514 ($[M^{81}Br]^+$, 5%), 512 ($[M^{79}Br]^+$, 5%), 450 (18%), 434 ($[MH\text{-}Br]^+$, 96%), 419 (12%), 308 (100%), 182 (92%) amu.

HRMS(ES) Found M: 511.7982; $C_{10}H_{11}O_3{}^{79}BrI_2$ requires 511.7981.

1-(2-Iodo-3,4,5-trimethoxy-benzyl)-2-oxo-indan-1-carboxylic acid methyl ester (300c)



mw = 496 g/mol

$C_{22}H_{21}O_6I$

DBU (0.47 mL, 3.15 mmol) was added to a solution of indanone **294** (0.50 g, 2.60 mmol) in dichloromethane (70 mL). The reaction was stirred for 45 minutes then benzyl bromide **297c** (1.22 g, 3.15 mmol) was added. After 16 hours, water (10 mL) was added. The aqueous phase was extracted with dichloromethane (2 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, ether/petrol, 1:1) afforded the compound **300c** (1.09 g, 2.20 mmol, 85%) as a pale yellow powder.

MP 144-146 °C

FT-IR (neat, cm^{-1}): 2931 (m), 2354 (s), 1753 (s), 1729 (s), 1479 (s), 1384 (s), 1233 (s), 1100 (s).

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.29-7.23 (3H, m, 3 x CH_{Ar}), 7.07 (1H, d, J = 8.1 Hz, CH_{AR}), 6.44 (1H, s, CH_{AR}), 3.80 (3H, s, OCH_3), 3.76-3.74 (2H, m, CH_2), 3.75 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 3.65 (1H, obs d, J = 22.8 Hz, CH_2), 3.58 (3H, s, OCH_3), 3.34 (1H, d, J = 22.8 Hz, CH_2).

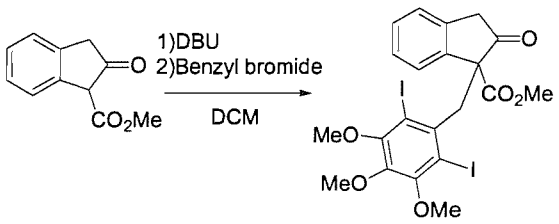
^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 211.0 (CO), 170.8 (CO_2), 153.3 ($C_{AR}O$), 153.2 ($C_{AR}O$), 141.4 ($C_{AR}O$), 140.4 (C_{AR}), 137.9 (C_{AR}), 134.6 (C_{AR}), 129.1 (CH_{AR}), 128.0 (CH_{AR}), 125.8 (CH_{AR}), 125.2 (CH_{AR}), 109.7 (CH_{AR}), 92.4

($C_{AR}I$), 66.6 (COCCO), 61.3 (OCH_3), 60.9 (OCH_3), 56.1 (OCH_3), 53.4 (OCH_3), 44.1 (CH_2), 43.5 (CH_2).

LRMS(CI) 514 ($[M+NH_4]^+$, 6%), 370 ($[M-I]^+$, 62%), 353 (26%), 307 (100%), 183 (69%) amu.

HRMS(ES) Found M+Na: 519.0265; $C_{21}H_{21}O_6NaI$ requires 519.0275.

1-(2,6-Diiodo-3,4,5-trimethoxy-benzyl)-2-oxo-indan-1-carboxylic acid methyl ester (300d)



mw = 622 g/mol

$C_{21}H_{20}O_6I_2$

DBU (0.47 mL, 3.15 mmol) was added to a solution of indanone **294** (0.50 g, 2.60 mmol) in dichloromethane (70 mL). The reaction was stirred for 45 minutes then benzyl bromide **299c** (1.62 g, 3.15 mmol) was added. After 16 hours water (10 mL) was added and the aqueous phase extracted with dichloromethane (2 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, ether/petrol, 1:1) afforded the title compound **300d** (1.13 g, 1.81 mmol, 70%) as a pale yellow powder.

MP 103-105 °C (ether/petrol)

FT-IR (neat, cm^{-1}): 2935 (m), 1764 (s), 1732 (s), 1403 (s), 1371 (s), 1228 (s), 1083 (s), 1002 (s).

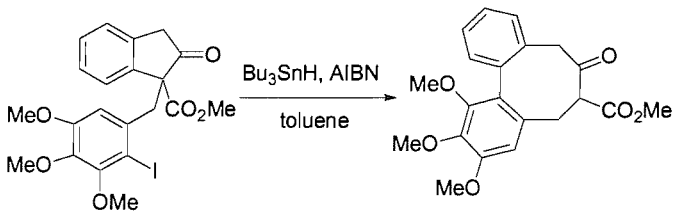
^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.27-7.18 (2H, m, 2 x CH_{AR}), 7.00 (1H, t, J = 8.0 Hz, CH_{AR}), 6.74 (1H, d, J = 8.0 Hz, CH_{AR}), 4.62 (1H, d, J = 15.0 Hz, CH_2CO), 4.19 (1H, d, J = 15.0 Hz, CH_2CO), 3.86 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.72 (6H, s, 2 x OCH_3), 3.88-3.72 (2H, m, CH_2).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 210.9 (CO), 169.9 (CO_2), 153.7 (2 x $C_{AR}O$), 143.7 ($C_{AR}O$), 140.1 (C_{AR}), 139.2 (C_{AR}), 137.8 (C_{AR}), 128.4 (CH_{AR}), 126.9 (CH_{AR}), 126.8 (CH_{AR}), 124.4 (CH_{AR}), 96.0 (2 x $C_{AR}I$), 64.0 (COCCO), 61.3 (OCH_3), 60.8 (2 x OCH_3), 53.7 (OCH_3), 51.3 (CH_2), 43.7 (CH_2).

LRMS(CI) 495 ($[M-I]^+$, 36%), 435 (6%), 369 ($[MH-2I]^+$, 100%), 340 (46%), 309 (18%), 281 (56%) amu.

HRMS(ES) Found M+Na: 644.9254; $C_{21}H_{20}O_6NaI_2$ requires 644.9241.

1,2,3-Trimethoxy-7-oxo-5,6,7,8-tetrahydro-dibenzo[*a*,*c*]cyclooctene-6-carboxylic acid methyl ester (301c)



mw = 370 g/mol

$C_{21}H_{22}O_6$

To a solution of indanone **300c** (0.68 g, 1.38 mmol) in toluene (60 mL) was added tributyltin hydride (0.56 mL, 0.60 g, 2.07 mmol) and AIBN (23 mg, 0.14 mmol). The reaction mixture was heated at 80 °C for 3 hours then cooled to room temperature, and stirred vigorously with potassium fluoride (10% w/v, 20 mL) for 24 hours. The resulting mixture was extracted with ether (10 mL) and the combined organic phases washed with brine (2 x 30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column

chromatography (1:1 ether/petrol) yielded the title compound as a yellow oil (0.35 g, 0.94 mmol, 69%) as a 1:1 mixture of diastereoisomers.

MP 203-205 °C

FT-IR (neat, cm^{-1}): 2931 (v), 2841 (w), 1739 (s), 1710 (s), 1597 (s), 1483 (s), 1450 (s), 1393 (s), 1195 (s), 1147 (s), 1100 (s), 1006 (s) amu.

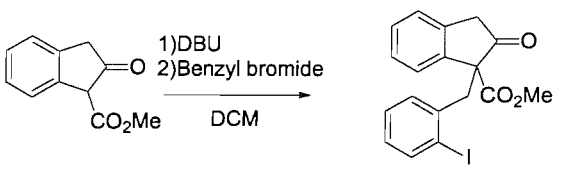
^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.44-7.27 (4H, m, 4 x CH_{AR}), 6.67 (1H, s, CH_{AR}), 3.92 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.81 (1H, d, J = 12.2 Hz, CHH), 3.73 (3H, s, OCH_3), 3.61-3.46 (1H, obs dd, $CHCO_2CH_3$), 3.56 (3H, s, OCH_3), 3.46 (1H, d, J = 12.2 Hz, CHH), 3.14 (1H, dd, J = 14.3, 5.1 Hz, CHH), 2.69 (1H, dd, J = 14.3, 4.6 Hz, CHH).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 203.9 (CO), 170.4 (CO_2), 153.0 (C_{AR}), 151.0 (C_{AR}), 141.9 (C_{AR}), 136.9 (C_{AR}), 133.2 (C_{AR}), 131.6 (C_{AR}), 131.0 (CH_{AR}), 130.0 (CH_{AR}), 128.2 (CH_{AR}), 127.5 (C_{AR}), 127.3 (CH_{AR}), 109.7 (CH_{AR}), 61.2 (CH or CH_3), 60.9 (CH or CH_3), 56.7 (CH_3), 56.1 (CH_3), 52.4 (CH_3), 48.4 (CH_2), 32.4 (CH_2).

LRMS(CI) 312 ($[MH-CO_2CH_3]^+$, 100%), 297 (5%), 269 (10%), 256 (22%) amu.

HRMS(ES) Found M: 371.1492; requires 371.1489.

1-(2-Iodo-benzyl)-2-oxo-indan-1-carboxylic acid methyl ester (300e)



mw = 406 g/mol

$C_{18}H_{15}O_3I$

DBU (0.94 mL, 6.31 mmol) was added to a solution of indanone **294** (1.00 g, 5.26 mmol) in dichloromethane (65 mL). The reaction was stirred for 45 minutes then benzyl bromide (1.87 g, 6.31 mmol) was added. After 16 hours, water (10 mL) was added and the aqueous phase extracted with dichloromethane (2 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, ether/petrol, 1:1) afforded the title compound **300e** (1.63 g, 4.03 mmol, 76%) as a pale yellow powder.

MP 100-102 °C (ether/petrol)

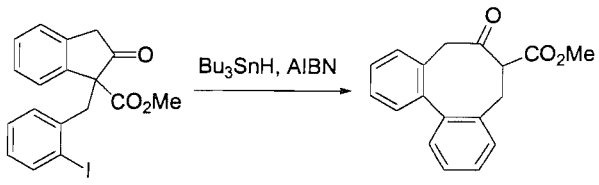
FT-IR (neat, cm^{-1}): 3061 (m), 2951 (m), 1759 (s), 1737 (s), 1434 (s), 1234 (s), 1012 (s).

^{1}H NMR δ ppm (300 MHZ, $CDCl_3$): 7.67 (1H, d, J = 7.7 Hz, C**H**$_{AR}$), 7.22-7.17 (3H, m, 3 x C**H**$_{AR}$), 7.10-7.03 (3H, m, 3 x C**H**$_{AR}$), 6.78 (1H, m, C**H**$_{AR}$), 3.79 (1H, d, J = 14.5 Hz, C**H**H), 3.71 (1H, d, J = 14.5 Hz, CH**H**), 3.64 (3H, s, OC**H**$_3$), 3.63 (1H, d, J = 22.8 Hz, CH**H**), 3.37 (1H, d, J = 22.8 Hz, C**H**H).

^{13}C NMR δ ppm (75 MHZ, $CDCl_3$): 211.4 (**C**O), 170.8 (**C**O_2), 140.5 (**C**H$_{AR}$), 140.1 (**C**$_{AR}$), 139.2 (**C**$_{AR}$), 130.5 (**C**H$_{AR}$), 129.2 (**C**H$_{AR}$), 128.8 (**C**H$_{AR}$), 128.6 (**C**H$_{AR}$), 128.0 (**C**H$_{AR}$), 126.0 (**C**H$_{AR}$), 125.2 (**C**H$_{AR}$), 104.1 (**C**$_{AR}$I), 66.6 (CO**C**CO), 53.4 (O**C**H$_3$), 44.0 (**C**H$_2$), 43.6 (**C**H$_2$).

LRMS(CI) 424 ($[M+NH_4]^+$, 100%), 407 ($[MH]^+$, 53%), 375 ($[M-OCH_3]^+$, 10%), 298 (20%), 279 ($[M-I]^+$, 34%), 263 (20%), 249 (8%) amu.

7-oxo-5,6,7,8-tetrahydro-dibenzo[a,c]cyclooctene-6-carboxylic acid methyl ester (301e)



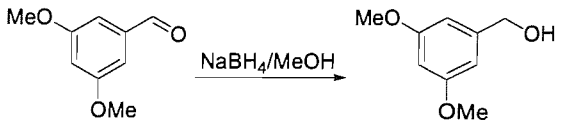
mw = 280 g/mol

$C_{18}H_{16}O_3$

To a solution of indanone **300e** (0.66 g, 1.63 mmol) in toluene (55 mL) was added tributyltin hydride (0.66 mL, 0.71 g, 2.45 mmol) and AIBN (27 mg, 0.16 mmol). The reaction mixture was heated at 80 °C for 4 hours then cooled to room temperature, and stirred vigorously with potassium fluoride (10% w/v, 20 mL) for 24 hours. The resulting mixture was extracted with ether (10 mL) and the combined organic phases washed with brine (2 x 30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (1:1 ether/petrol) yielded the title compound as a yellow pale oil (0.05 g, 0.18 mmol, 11%) as a 1:1 mixture of diastereoisomers A and B.

^{1}H NMR 7.35-7.27 (16H, m, 8 x C**H**$_{AR}$ of A + 8 x C**H**$_{AR}$ of B), 3.85 (1H, d, J = 13.1 Hz, C**H**H of A), 3.78 (3H, s, OC**H**$_3$), 3.73 (3H, s, OC**H**$_3$), 3.71-3.39 (5H, m, CH**H** of A + C**H**H of B + C**H**CO_2CH_3 of A and B), 3.26 (1H, dd, J = 14.1, 5.4 Hz, CH**H** of A), 3.03 (1H, dd, J = 13.7, 2.8 Hz, C**H**H of B), 2.85 (1H, dd, J = 14.1, 4.2 Hz, C**H**H of A), 2.91-2-80 (1H, obs dd, CH**H** of B).

3,5-Dimethoxy benzyl alcohol (295d)[76]



mw = 168 g/mol

$C_9H_{12}O_3$

CAS 705-76-0

To a solution of 3,5-dimethoxy benzaldehyde (0.42 g, 2.53 mmol) in methanol (5 mL) at 0 °C, was added sodium borohydride (0.10 g, 2.78 mmol) portion wise over 5 minutes. The mixture was stirred for 30 minutes then the solvent was removed under reduced pressure. The residue was diluted with dichloromethane (20 mL) and washed with brine (2 x 20 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound (0.40 g, 2.40 mmol, 95%) as white crystals.

Data for **295d** were consistent with literature values.

MP 39-41 °C (ether/petrol) lit[76] 44-45 °C (ether/petrol)

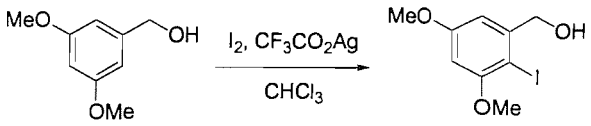
FT-IR (neat, cm^{-1}): 3341 (br), 2947 (br), 1600 (s), 1458 (s), 1294 (s), 1206 (s), 1149 (s), 1010 (s), 828 (s).

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 6.53 (2H, d, J = 2.0 Hz, 2 x C**H**$_{AR}$), 6.39 (1H, t, J = 2.0 Hz, C**H**$_{AR}$), 4.63 (2H, s, C**H$_2$**OH), 3.79 (6H, s, 2 x OC**H$_3$**), 1.86 (1H, s, O**H**).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 161.1 (2 x **C**$_{AR}$), 143.5 (**C**$_{AR}$), 104.6 (2 x **C**H$_{AR}$), 99.7 (**C**H$_{AR}$), 65.4 (**C**H$_2$OH), 55.5 (2 x OCH$_3$).

LRMS(CI) 169 ($[MH]^+$, 100%), 151 ($[M\text{-}OH]^+$, 20%), 139 ($[MH_2\text{-}\ CH_2OH]^+$, 26%), 125 (8%) amu.

3,5-Dimethoxy-2-iodo benzyl alcohol (296d)[77, 78]



mw = 294 g/mol

$C_9H_{11}O_3I$

CAS 74726-77-5

To a stirred solution of the alcohol (3.41 g, 20.3 mmol) and silver trifluoroacetate (5.38 g, 24.3 mmol) in dry chloroform (130 mL) at 0 °C under nitrogen, was added iodine (5.67 g, 22.3 mmol) in one portion. The resulting yellow mixture was allowed to warm to room temperature, stirred for 1 hour and then filtered through celite. The filtrate was washed with sodium thiosulfate (20 mL) and this aqueous suspension was extracted with chloroform (4 x 20 mL). The organic phases were then combined, and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield (5.90 g, 20.1 mmol, 99%) as a cream powdery solid.

Data for **296d** were consistent with literature values.

MP 77-79 °C (petrol/ether) lit[77] 96-97 °C (dichloromethane/petrol)

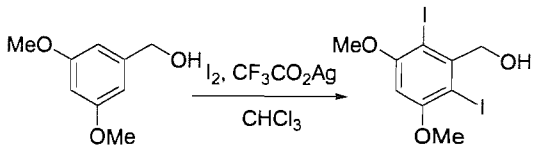
FT-IR (neat, cm^{-1}): 3418 (v), 1639 (m), 1578 (m), 1313 (m), 1162 (w).

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 6.74 (1H, d, J = 2.0 Hz, C**H**$_{AR}$), 6.40 (1H, d, J = 2.0 Hz, C**H**$_{AR}$), 4.69 (2H, s, C**H**$_2$OH), 3.87 (3H, s, OC**H**$_3$), 3.84 (3H, s, OC**H**$_3$), 1.97 (1H, s, O**H**).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 161.5 (2 x **C**$_{AR}$O), 145.0 (**C**$_{AR}$), 105.3 (**C**H$_{AR}$), 98.2 (**C**H$_{AR}$), 94.8 (**C**$_{AR}$I), 69.8 (**C**H$_2$OH), 56.6 (O**C**H$_3$), 55.7 (O**C**H$_3$).

LRMS(CI) 295 ([MH]$^+$, 26%), 169 ([MH$_2$-I]$^+$, 96%), 153 (100%), 139 (28%), 109 (8%) amu.

2,6-Diiodo-3,5-dimethoxy benzyl alcohol (298d)



mw = 420 g/mol

$C_9H_{10}I_2O_3$

To a stirred solution of the alcohol (1.36 g, 8.09 mmol) and silver trifluoroacetate (2.68 g, 12.1 mmol) in dry chloroform (30 mL) at 0 °C under nitrogen, was added iodine (3.08 g, 12.1 mmol) in one portion. The resulting yellow mixture was allowed to warm to room temperature, stirred for 1 hour then filtered through celite. The filtrate was washed with sodium thiosulfate (20 mL) and this aqueous suspension was extracted with chloroform (4 x 20 mL). The organic phases were then combined and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield (1.02 g, 2.43 mmol, 30%) as a cream powdery solid.

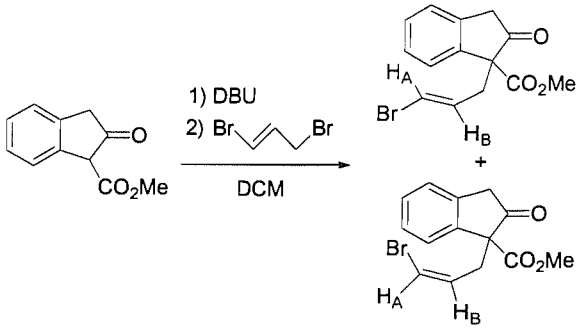
MP 156-158 °C (ether/petrol)

FT-IR (neat, cm^{-1}): 3437 (v), 3002 (br), 1777 (s), 1739 (s), 1337 (s), 1209 (s), 1157 (s).

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 6.44 (1H, s, C**H**$_{AR}$), 5.87 (2H, s, C**H$_2$**OH), 3.93 (6H, s, 2 x OC**H$_3$**).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 159.8 (2 x **C**$_{AR}$O), 138.5 (**C**$_{AR}$), 95.9 (**C**H$_{AR}$), 83.1 (2 x **C**$_{AR}$I), 79.1 (**C**H$_2$OH), 57.0 (2 x OCH$_3$).

1-(3-Bromo-allyl)-2-oxo-indan-1-carboxylic acid methyl ester (300h)



mw = 309 g/mol

$C_{14}H_{13}BrO_3$

DBU (0.94 mL, 6.31 mmol) was added to a solution of indanone **294** (1.00 g, 5.26 mmol) in dichloromethane (100 mL). After 1 hour, 1,3-dibromopropene (0.63 mL, 6.31 mmol) was added. After a further 40 hours, H_2O (10 mL) was added. The aqueous phase was extracted with dichloromethane (2 x 20 mL) and the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, ether/petrol, 10/90) afforded a 1:1 mixture of the title (E)-**300h** and (Z)-**300h** (1.14 g, 3.69 mmol, 70%) as a yellow oil.

FT-IR (neat, cm^{-1}): 3068 (w), 2945 (w), 1753 (v), 1729 (v), 1431 (m), 1237 (s), 1133 (m).

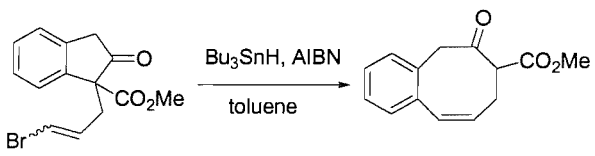
^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.36-7.34 (8H, m, 8 x C**H**$_{AR}$), 6.15 (1H, d, J = 7.1 Hz, **H**$_A$ cis), 6.04 (1H, d, J = 13.6 Hz, **H**$_A$ trans), 5.80-5.74 (2H, m, **H**$_B$ cis and trans), 3.82 (1H, d, J = 22.7 Hz, C**H**HCO), 3.78 (1H, d, J = 22.6 Hz, C**H**HCO), 3.65 (3H, s, OC**H**$_3$), 3.63 (3H, s, OC**H**$_3$), 3.53 (1H, d, J = 22.6 Hz, CH**H**CO), 3.48 (1H, d, J = 22.7 Hz, CH**H**CO), 3.14 (1H, ddd, J = 15.1, 7.0, 1.5 Hz, C**H**HCH$_B$ cis), 3.06 (1H, ddd, J = 15.1, 7.0, 1.5 Hz, CH**H**CH$_B$ cis), 2.91 (2H, m, C**H**$_2$CHB trans).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 170.0 (2 x **C**O), 157.0 (2 x **C**O_2), 140.1 (**C**H_{AR}), 139.5 (**C**H_{AR}), 137.6 (**C**H_{AR}), 137.5 (**C**H_{AR}), 131.0 (**C**H_B cis or trans), 129.1 (2 x **C**H_{AR}), 128.5 (**C**H_B cis or trans), 128.2 (2 x **C**H_{AR}), 125.4 (**C**H_{AR}), 125.2 (**C**H_{AR}), 124.5 (**C**H_{AR}), 124.3 (**C**H_{AR}), 111.5 (**C**H_A cis or trans), 109.1 (**C**H_A cis or trans), 64.7 (**C**CO_2CH_3 cis or trans), 64.1 (**C**CO_2CH_3 cis or trans), 53.1 (2 x O**C**H_3), 43.3 (2 x **C**H_2CO), 37.5 (**C**H_2C_B cis or trans), 34.6 (**C**H_2C_B cis or trans).

LRMS(CI) 328 ([M(^{81}Br)+NH_4]$^+$, 48%), 326 ([M(^{79}Br)+NH_4]$^+$, 48%), 310 ([M(^{81}Br)]$^+$, 32%), 308 ([M(^{79}Br)]$^+$, 32%), 229 ([M-Br]$^+$, 100%), 189 (38%), 169 (48%), 141 (82%), 115 (64%) amu.

HRMS(ES) Found M+Na+Br: 330.9940; $C_{14}H_{13}O_3NaBr$ requires 330.9942.

(Z)-6-Oxo-5,6,7,8-tetrahydro-benzocyclooctene-7-carboxylic acid methyl ester (301h)



mw = 230 g/mol

$C_{14}H_{14}O_3$

To a solution of indanone **300h** (1.07 g, 3.47 mmol) in toluene (140 mL) were added Bu_3SnH (1.40 mL, 5.21 mmol) and AIBN (57 mg, 0.35 mmol). The mixture was stirred at 80 °C for 16 hours then further Bu_3SnH (1.40 mL, 5.21 mmol) and AIBN (57 mg, 0.35 mmol) were added. The reaction heated at 80 °C for 24 hours then cooled to room temperature. Aqueous potassium fluoride (10% w/v, 20 mL) was added and the resulting mixture stirred vigorously for 24 hours. The organic phase was washed with brine (2 x 20 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (silica gel, 40% ether/petrol) afforded the title compound **301h** (311 mg, 1.35 mmol, 39%) as a white powder.

MP 51-53 °C (ether/petrol)

FT-IR (neat, cm^{-1}): 3011 (w), 2945 (w), 1743 (s), 1706 (s), 1436 (m), 1351 (w), 1289 (m), 1166 (m).

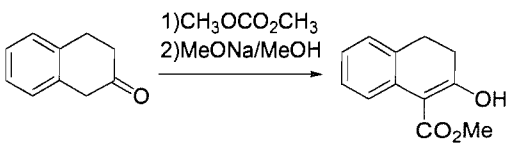
^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.25-7.16 (4H, m, 4 x C**H**$_{AR}$), 6.73 (1H, d, J = 11.6 Hz, C**H** alkene), 6.09 (1H, dt, J = 11.6, 6.7 Hz, C**H** alkene), 3.94 (1H, d, J = 12.4 Hz, CH**H**CO), 3.71 (3H, s, OC**H$_3$**), 3.69 (1H, obs d, J = 12.4 Hz, C**H**HCO), 3.61 (1H, dd, J = 10.1, 3.2 Hz, C**H**CO_2CH_3), 2.64-2.54 (2H, m, C**H$_2$**$CHCO_2CH_3$).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 204.2 (**C**O), 170.5 (**C**O_2), 136.8 (**C**$_{AR}$), 132.6 (**C**$_{AR}$), 131.0 (**C**H), 130.4 (**C**H), 129.4 (**C**H), 129.3 (**C**H), 127.9 (**C**H), 127.6 (**C**H), 52.7 (**C**HCO_2CH_3), 52.4 (O**C**H_3), 48.4 (**C**H_2CO), 28.2 (**C**$H_2CHCO_2CH_3$).

LRMS(CI) 190 (100%), 172 ($[M-CO_2CH_3]^+$, 95%), 144 (65%), 129 (78%), 115 (86%) amu.

HRMS(ES) Found 2M+Na: 483.1782; requires 483.1778.

2-hydroxy-3,4-dihydro naphthalene-1-carboxylic acid methyl ester (305)[79]



mw = 204 g/mol

$C_{12}H_{12}O_3$

To a mixture of dimethyl carbonate (11.55 mL, 137 mmol) and tetralone **304** (1.00 g, 6.85 mmol) at 0 °C was added a solution of sodium methoxide (0.19 g, 8.22 mmol) in methanol dropwise. The mixture was heated at 80 °C for 2 hours then cooled at 0 °C. HCl was added (2M, 30 mL) followed after 5 minutes by ethyl acetate. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 10% ether/petrol) afforded the title compound **305** (1.33 g, 6.52 mmol, 95%) as a colourless oil.

Data for **305** were consistent with literature values.

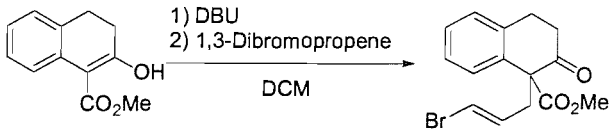
FT-IR (neat, cm^{-1}): 2950 (m), 1725 (m), 1630 (s), 1597 (s), 1488 (s), 1431 (s), 1308 (s), 1228 (s), 1053 (m)

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 10.68 (1H, s, O**H**), 7.76 (1H, d, J = 7.8 Hz, C$\mathbf{H}_{AR}$), 7.28-7.10 (3H, m, 3 x C$\mathbf{H}_{AR}$), 3.96 (3H, s, OC$\mathbf{H}_3$), 2.87 (2H, t, J = 7.4 Hz, CH**H**COH), 2.59 (2H, t, J = 7.4 Hz, C**HH**).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 178.5 (**C**O_2), 172.6 (**C**O), 133.3 (**C**$_{AR}$), 131.4 (**C**$_{AR}$), 127.3 (**C**H$_{AR}$), 126.5 (**C**H$_{AR}$), 126.0 (**C**H$_{AR}$), 125.1 (**C**H$_{AR}$), 100.0 (**C**CO_2CH_3), 51.9 (O**C**H_3), 29.6 (**C**H_2CO), 27.9 (**C**H_2).

LRMS(CI) 146 ([MH-CO_2CH_3]$^+$, 100%), 104 (88%), 91 (14%), 65 (14%) amu.

1-((*E*)-3-Bromo-allyl)-2-oxo-1,2,3,4-tetrahydro-naphtalene-1-carboxylic acid methyl ester (306f)



mw = 323 g/mol

$C_{15}H_{15}BrO_3$

DBU (0.66 mL, 4.41 mmol) was added to a solution of tetralone **305** (0.60 g, 2.94 mmol) in dichloromethane (33 mL). After 1 hour, 1,3-dibromopropene (0.88 g, 4.41 mmol) was added, followed after a further 16 hours by H_2O (10 mL). The aqueous phase was extracted with dichloromethane (2 x 20 mL) then the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, ether/petrol, 10/90) afforded the title compound (0.70 g, 2.18 mmol, 74%) as a colourless oil.

FT-IR (neat, cm^{-1}): 3063 (w), 2945 (m), 1739 (s), 1715 (s), 1427 (m), 1237 (s), 1218 (s), 939 (m).

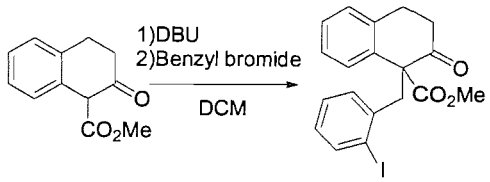
^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.31-7.22 (4H, m, 4 x C**H**$_{AR}$), 5.96 (1H, d, J = 13.6 Hz, C**H**Br), 5.72 (1H, ddd, J = 13.6, 9.2, 6.7 Hz, C**H**CHBr), 3.63 (3H, s, OC**H**$_3$), 3.18-2.84 (5H, m, CH**H** + 2 x C**H**$_2$), 2.61 (1H, ddd, J = 14.5, 6.9, 4.4 Hz, CH**H**).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 207.8 (**C**O), 170.9 (**C**O$_2$), 136.5 (**C**), 135.1 (**C**), 131.6 (**C**H), 128.8 (**C**H), 128.0 (**C**H), 127.6 (**C**H), 126.9 (**C**H), 108.9 (**C**H), 62.2 (COCCO), 53.1 (O**C**H$_3$), 40.2 (**C**H$_2$), 39.3 (**C**H$_2$), 27.7 (**C**H$_2$).

LRMS(CI) 342 ([M(^{81}Br)+ NH_4]$^+$, 8%), 340 ([M(^{79}Br)+NH_4]$^+$, 8%), 325 ([M(^{81}Br)+H]$^+$, 42%), 323 ([M(^{79}Br)+H]$^+$, 42%), 243 (94%), 215 (88%), 183 (100%), 155 (44%), 141 (86%), 128 (62%), 115 (98%) amu.

HRMS(ES) Found 2M(^{79}Br)+Na: 667.0305; $C_{30}H_{30}O_6Br_2Na$ requires 667.0302.

1-(2-Iodo-benzyl)-2-oxo-1,2,3,4-tetrahydro-naphtalene-1-carboxylic acid methyl ester (306e)



mw = 420 g/mol

$C_{19}H_{17}O_3I$

DBU (0.55 mL, 3.68 mmol) was added to a solution of tetralone **305** (0.50 g, 2.45 mmol) in dichloromethane (33 mL). After 1 hour, the benzyl bromide (1.09 g, 3.68 mmol) was added followed after 16 hours by H_2O (10 mL). The aqueous phase was extracted with dichloromethane (2 x 20 mL) and the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, ether/petrol, 10/90) afforded the title compound **306e** (0.74 g, 1.76 mmol, 72%) as a white solid.

MP 85-87 °C (petrol)

FT-IR (neat, cm^{-1}): 2945 (w), 1739 (s), 1710 (s), 1427 (m), 1228 (s), 1214 (s), 1010 (m).

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.70 (1H, dd, J = 7.8, 1.3 Hz, C**H**$_{AR}$), 7.28-7.21 (3H, m, 3 x C**H**$_{AR}$), 7.12-7.04 (2H, m, 2 x C**H**$_{AR}$), 6.86-6.79 (2H, m, 2 x C**H**$_{AR}$), 3.98 (1H, d, J = 14.0 Hz, CH**H**CO), 3.70 (3H, s, OC**H**$_3$), 3.66 (1H, d, J = 14.0 Hz, CH**H**CO), 2.78 (1H, dt, J = 14.7, 5.4 Hz, CH**H**), 2.67 (1H,

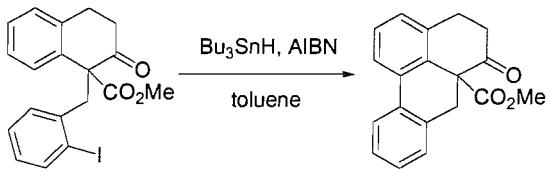
dt, J = 10.9, 5.5 Hz, C**H**H), 2.50 (1H, dt, J = 14.7, 5.4 Hz, C**H**H), 2.23 (1H, m, CH**H**).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 208.8 (**C**O), 171.7 (**C**O_2), 140.2 (**C**H_{AR}), 139.1 (**C**$_{AR}$), 136.6 (**C**$_{AR}$), 135.2 (**C**$_{AR}$), 131.1 (**C**H_{AR}), 128.7 (**C**H_{AR}), 128.6 (**C**H_{AR}), 128.5 (**C**H_{AR}), 128.0 (**C**H_{AR}), 127.8 (**C**H_{AR}), 127.4 (**C**H_{AR}), 102.7 (**C**$_{AR}$I), 64.4 (COCCO), 53.1 (O**C**H_3), 46.3 (**C**H_2), 39.1 (**C**H_2), 27.0 (**C**H_2).

LRMS(CI) 438 ($[M+NH_4]^+$, 24%), 421 (MH^+, 100%), 389 (32%), 293 ($[M-I-H]^+$,76%), 233 (84%), 217 (56%) amu.

HRMS(ES) Found 2M+Na: 863.0369; $C_{38}H_{34}O_6I_2Na$ requires 863.0336.

6-Oxo-5,6-dihydro-4*H*,7*H*-benzo[*de*]anthracene-6a-carboxylic acid methyl ester (308e)



mw = 292 g/mol

$C_{19}H_{16}O_3$

To a solution of iodide **306e** (0.27 g, 0.64 mmol) in toluene (35 mL) under nitrogen, were added Bu_3SnH (0.26 mL, 0.96 mmol) and AIBN (10 mg, 0.06 mmol). The mixture was heated at 80 °C for 16 hours then cooled to room temperature. Aqueous potassium fluoride (10% w/v, 20 mL) was added and the resulting mixture stirred vigorously for 24 hours. The organic phase was washed with brine (2 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 10% ether/toluene) afforded the title compound **308e** (151 mg, 0.52 mmol, 81%) as a white powder.

MP 108-110 °C (ether/petrol)

FT-IR (neat, cm^{-1}): 2950 (w), 2354 (w), 1743 (s), 1710 (s), 1431 (m), 1223 (s), 1166 (s).

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.75 (2H, app t, J = 7.3 Hz, 2 x CH_{AR}), 7.40-7.22 (5H, m, 5 x CH_{AR}), 3.71 (1H, d, J = 15.7 Hz, $CHHCCO_2CH_3$), 3.51 (3H, s, OCH_3), 3.42 (1H, ddd, J = 16.4, 11.7, 5.9 Hz, CHHCO), 3.09 (1H, ddd, J = 16.0, 6.0, 4.0 Hz, $CHHCH_2CO$), 3.06 (1H, d, J = 15.7 Hz, $CHHCCO_2CH_3$), 2.96 (1H, ddd, J = 16.0, 6.4, 4.0 Hz, $CHHCH_2CO$), 2.66 (1H, ddd, J = 16.4, 11.7, 6.0 Hz, CHHCO).

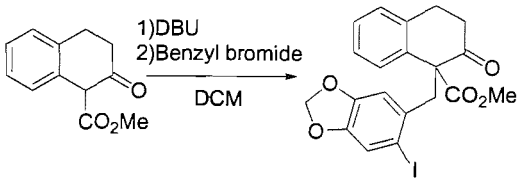
^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 206.8 (CO), 169.4 (CO_2), 136.7 (C_{AR}), 135.0 (C_{AR}), 133.6 (C_{AR}), 132.9 (C_{AR}), 131.5 (C_{AR}), 128.9 (CH_{AR}), 128.6 (CH_{AR}), 128.4 (CH_{AR}), 127.8 (CH_{AR}), 127.5 (CH_{AR}), 123.9 (CH_{AR}), 122.9 (CH_{AR}), 58.3 ($COCCO_2CH_3$), 53.0 (OCH_3), 37.3 (CH_2), 35.2 (CH_2), 28.3 (CH_2).

LRMS(CI) 310 ($[M+ NH_4]^+$, 8%), 293 ($[MH]^+$, 50%), 275 (10%), 233 (100%), 215 (20%), 202 (35%), 191 (56%), 165 (14%), 152 (5%), 59 (50%).

HRMS(EI) Found M: 292.10990; $C_{19}H_{16}O_3$ requires 292.10994.

CHN Calculated C 78.06, H 5.52. Found C 77.90 H 5.47.

1-(6-Iodo-benzo[1,3]dioxol-5ylmethyl)-2-oxo-1,2,3,4-tetrahydro-naphtalene-1-carboxylic acid methyl ester (306a)



mw = 464 g/mol

$C_{20}H_{17}O_5I$

DBU (2.55 mL, 16.94 mmol) was added to a solution of tetralone **305** (2.88 g, 14.11 mmol) in dichloromethane (150 mL). The mixture was stirred for 1 hour then the benzyl bromide (5.77 g, 16.94 mmol) was added. The reaction mixture was stirred under nitrogen for 16 hours. H_2O (30 mL) was added and the aqueous phase extracted with dichloromethane (2 x 20 mL), washed with brine (20 mL), dried ($MgSO_4$) concentrated *in vacuo*. Purification by column chromatography (silica gel, ether/petrol, 10/90) afforded the title compound **306a** (4.06 g, 8.75 mmol, 62%) as a white solid.

MP 110-112 °C (petrol/ether)

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.18-7.13 (4H, m, C**H**$_{Ar}$), 7.10 (1H, s, C**H**$_{Ar}$), 6.40 (1H, s, C**H**$_{Ar}$), 5.90 (1H, d, J = 1.1 Hz, OC**H**$_2$O), 5.89 (1H, d, J = 1.1 Hz, OC**H**$_2$O), 3.87 (1H, d, J = 14.3 Hz, C**H**HCCO), 3.68 (3H, s, OC**H**$_3$), 3.56 (1H, d, J = 14.3 Hz, CH**H**CCO), 2.92-2.83 (1H, m, CH**H**), 2.77-2.44 (3H, m, C**H**H and C**H**H).

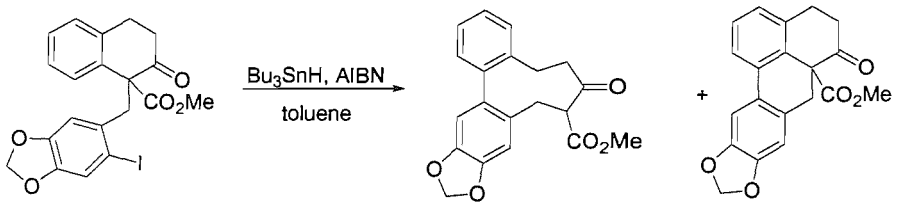
^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 208.6 (**C**O), 171.7 (**C**O$_2$), 148.0 (**C**$_{Ar}$O), 147.3 (**C**$_{Ar}$O), 136.6 (**C**$_{Ar}$), 135.3 (**C**$_{Ar}$), 132.1 (**C**$_{Ar}$), 128.6 (**C**H$_{Ar}$), 128.0 (**C**H$_{Ar}$), 127.3 (**C**H$_{Ar}$), 119.1 (**C**H$_{Ar}$), 110.7 (**C**H$_{Ar}$), 101.7 (O**C**H$_2$O), 90.5 (**C**$_{Ar}$I), 64.4 (CO**C**CO), 53.1 (O**C**H$_3$), 46.2 (**C**H$_2$), 39.1 (**C**H$_2$), 27.4 (**C**H$_2$).

LRMS(CI) 466 ([MH$_2$]$^+$, 2%), 337 ([M-I]$^+$, 10%), 281 (10%), 261 (100%), 202 (84%), 135 (15%) amu.

HRMS(ES) Found M+Na: 487.0012; $C_{20}H_{17}O_5INa$ requires 487.0013.

CHN Calculated C 51.74, H 3.69. Found C 51.36, H 3.64.

Methyl6oxo,5,6,12c-tetrahydrobenzo[3',4']cyclonona[4,5]benzo[*d*][1,3]dioxol-6-7-carboxylic acid methyl ester (308a) and 6-Oxo-3a,5,6,12c-tetrahydro-*4H,7H*-9,11-dioxa-benzo[*fg*]cyclopenta[*b*]anthracene-6a-carboxylic acid methyl ester (310a)

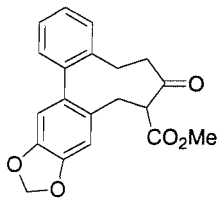


mw =338 g/mol mw=336 g/mol

$C_{20}H_{18}O_5$ $C_{20}H_{16}O_5$

To a solution of tetralone **306a** (1.13 g, 2.44 mmol) in toluene (95 mL) under nitrogen, was added Bu_3SnH (0.98 mL, 3.66 mmol) and AIBN (0.2 g, 1.22 mmol). The mixture was stirred at 80 °C for 50 hours and then cooled to room temperature. Aqueous potassium fluoride (10% w/v, 20 mL) was added and the resulting mixture stirred vigorously for 24 hours. The organic phase was washed with brine (2 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 10% ether/toluene) afforded the title compounds **308a** (0.72 g, 1.07 mmol, 45%) and **310a** (0.72 g, 1.07 mmol, 45%) both as white powders.

Methyl6oxo,5,6,12c-tetrahydrobenzo[3',4']cyclonona[4,5]benzo[*d*][1,3]dioxol-6-7-carboxylic acid methyl ester (308a)



MP 126-128 °C (ether/petrol)

FT-IR (neat, cm^{-1}): 2945 (w), 2897 (w), 1743 (s), 1706 (s), 1474 (s), 1266 (m), 1214 (s), 1039 (s).

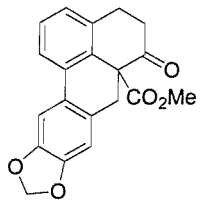
^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.33-7.24 (3H, m, 3 x C**H**$_{Ar}$), 7.09 (1H, d, J = 7.1 Hz, C**H**$_{Ar}$), 6.75 (1H, s, C**H**$_{Ar}$), 6.61 (1H, s, C**H**$_{Ar}$), 6.00 (2H, d, J = 3.3 Hz, OC**H**$_2$O), 3.69 (3H, s, OC**H**$_3$), 3.67 (1H, dd, J = 13.8, 10.0 Hz, C**H**H), 3.07 (1H, dd, J = 14.5, 3.5 Hz, C**H**H), 2.96-2.89 (1H, m, CH**H**), 2.70 (1H, t, J = 6.1 Hz, COC**H**CO), 2.63-2.55 (3H, m, CH**H**+ C**H**$_2$).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 207.0 (**C**O), 170.2 (**C**O_2), 148.0 (**C**$_{Ar}$O), 146.7 (**C**$_{Ar}$O), 140.2 (**C**$_{Ar}$), 139.8 (**C**$_{Ar}$), 134.7 (**C**$_{Ar}$), 130.5 (**C**H$_{Ar}$), 130.2 (**C**$_{Ar}$), 129.8 (**C**H$_{Ar}$), 128.6 (**C**H$_{Ar}$), 127.0 (**C**H$_{Ar}$), 109.8 (**C**H$_{Ar}$), 108.6 (**C**H$_{Ar}$), 101.6 (O**C**H$_2$O), 61.6 (CO**C**HCO_2CH_3), 52.8 (O**C**H$_3$), 43.1 (**C**H$_2$), 30.7 (**C**H$_2$), 29.6 (**C**H$_2$).

LRMS(CI) 338 (M^+, 100%), 310 (14%), 250 (18%), 222 (74%), 181 (28%), 165 (60%), 73 (34%) amu.

HRMS(CI) Found M: 338.1149; $C_{20}H_{18}O_5$ requires 338.1154.

6-Oxo-3a,5,6,12c-tetrahydro-*4H,7H*-9,11-dioxa-benzo[*fg*]cyclopenta[*b*]anthracene-6a-carboxylic acid methyl ester (310a)



MP 132-133 °C (ether/petrol)

FT-IR (neat, cm^{-1}): 2950 (w), 2893 (w), 2354 (s), 2339 (s), 1739 (s), 1715 (s), 1497 (s), 1460 (s), 1214 (s), 1034 (s).

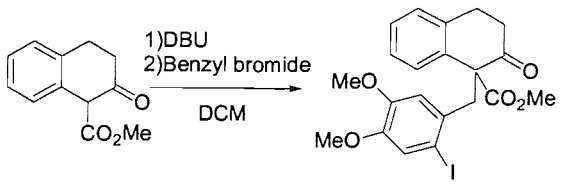
^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.55 (1H, d, J = 8.0 Hz, C**H**$_{Ar}$), 7.36 (1H, t, J = 8.0 Hz, C**H**$_{Ar}$), 7.22 (1H, s, C**H**$_{AR}$), 7.19 (1H, d, J = 8.0 Hz, C**H**$_{AR}$), 6.81 (1H, s, C**H**$_{AR}$), 5.99 (1H, d, J = 2.1 Hz, OC**H**$_2$O), 5.98 (1H, d, J = 2.1 Hz, OC**H**$_2$O), 3.59 (1H, d, J = 15.0 Hz, C**H**HCCO), 3.53 (3H, s, OC**H**$_3$), 3.40 (1H, ddd, J = 16.6, 11.4, 5.4 Hz, C**H**HCO), 3.08 (1H, ddd, J = 16.2, 6.2, 4.0 Hz, C**H**H), 2.95 (1H, d, J = 15.0 Hz, CH**H**CCO), 2.93 (1H, m, CH**H**), 2.65 (1H, ddd, J = 16.4, 11.7, 6.0 Hz, CH**H**CO).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 206.9 (**C**O), 169.7 (**C**O_2), 147.9 (**C**$_{Ar}$O), 147.7 (**C**$_{Ar}$O), 136.8 (**C**$_{Ar}$), 135.1 (**C**$_{Ar}$), 131.1 (**C**$_{Ar}$), 128.9 (**C**H$_{Ar}$), 128.9 (**C**H$_{Ar}$), 128.2 (**C**$_{Ar}$), 127.4 (**C**H$_{Ar}$), 127.1 (**C**$_{Ar}$), 122.6 (**C**H$_{Ar}$), 109.4 (**C**H$_{Ar}$), 104.7 (**C**H$_{AR}$), 101.5 (O**C**H$_2$O), 58.7 (CO**C**CO$_2$CH$_3$), 53.3 (O**C**H$_3$), 37.6 (**C**H$_2$), 35.4 (**C**H$_2$), 28.6 (**C**H$_2$).

LRMS(CI) 354 ([M+NH_4]$^+$, 25%), 337 ([MH]$^+$, 52%), 319 (12%), 277 (100%), 235 (28%), 189 (20%), 59 (22%) amu.

HRMS(ES) Found 2M+Na: 695.1876; $C_{40}H_{32}O_{10}$ requires 695.1888.

1-(2-Iodo-4,5-dimethoxybenzyl)-2-oxo-1,2,3,4-tetrahydro-naphtalene-1-carboxylic acid methyl ester (306b)



mw = 480 g/mol

$C_{21}H_{21}O_5I$

DBU (2.99 mL, 20.00 mmol) was added to a solution of tetralone **305** (3.40 g, 16.66 mmol) in dichloromethane (300 mL). The mixture was stirred for 1 hour then benzyl bromide (7.14 g, 20.00 mmol) was added. After 16 hours, H_2O (50 mL) was added and the aqueous phase extracted with dichloromethane (2 x 20 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, ether/petrol, 10/90) gave the title compound **306b** (5.20 g, 10.83 mmol, 65%) as a white solid.

MP 116-118 °C (ether/petrol)

FT-IR (neat, cm^{-1}): 3002 (w), 2950 (m), 2841 (w), 2259 (w), 1739 (s), 1710 (s), 1502 (s), 1247 (s), 1218 (s), 1162 (s).

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.31-7.11 (4H, m, C**H**$_{Ar}$), 7.08 (1H, s, C**H**$_{Ar}$), 6.13 (1H, s, C**H**$_{Ar}$), 3.93 (1H, d, *J* = 14.0 Hz, C**H**HCCO), 3.79 (3H, s, OC**H**$_3$), 3.68 (3H, s, OC**H**$_3$), 3.51 (1H, d, *J* = 14.3 Hz, CH**H**CCO), 3.46 (3H, s, OC**H**$_3$), 2.81-2.75 (1H, m, CH**H**CO), 2.69-2.58 (1H, m, C**H**HCO), 2.40-2.22 (2H, m, C**HH**).

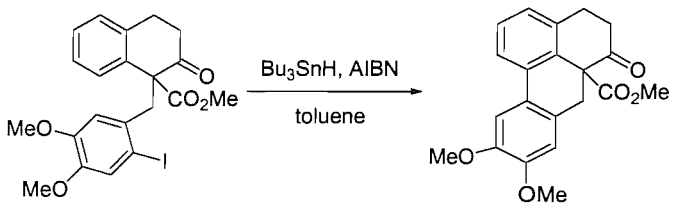
^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 208.4 (**C**O), 171.8 (**C**O$_2$), 148.4 (**C**$_{Ar}$O), 148.2 (**C**$_{Ar}$O), 136.9 (**C**$_{Ar}$), 135.7 (**C**$_{Ar}$), 131.1 (**C**$_{Ar}$), 128.7 (**C**H$_{Ar}$), 128.3 (**C**H$_{Ar}$), 127.9 (**C**H$_{Ar}$), 127.4 (**C**H$_{Ar}$), 121.8 (**C**H$_{Ar}$), 113.3 (**C**H$_{Ar}$), 90.0 (**C**$_{Ar}$I), 64.3

(COCCO), 56.0 (OCH_3), 55.4 (OCH_3), 53.1 (OCH_3), 46.3 (CH_2), 39.2 (CH_2), 27.3 (CH_2).

LRMS(CI) 480 (M^+, 2%), 353 ($[M-I]^+$, 8%), 337 (22%), 277 (100%), 246 (6%), 189 (10%), 151 (60%) amu.

CHN Calculated C 52.52, H 4.41. Found C 52.74.H 4.45.

9,10-Dimethoxy-6-oxo-3a,5,6,11c-tetrahydro-*4H,7H*-benzo[*de*]anthracene-6a-carboxylic acid methyl ester (310b)



mw = 352 g/mol

$C_{19}H_{20}O_5$

To a solution of tetralone **306b** (2.5 g, 5.21 mmol) in toluene (200 mL) under nitrogen was added Bu_3SnH (2.10 mL, 7.81 mmol) and AIBN (86 mg, 0.52 mmol). The mixture was stirred at 80 °C for 16 hours then cooled to room temperature. Aqueous potassium fluoride (10% w/v, 20 mL) was added and the resulting mixture stirred vigorously for 24 hours. The organic phase was washed with brine (2 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 10% ether/toluene) afforded the title compound **310b** (1.11 g, 3.15 mmol, 61%) as a white powder.

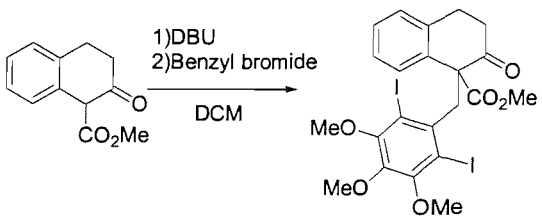
FT-IR (neat, cm^{-1}): 2950 (m), 2845 (w), 2354 (w), 1743 (s), 1706 (s), 1516 (s), 1460 (m), 1346 (m), 1256 (s), 1209 (s), 1152 (s).

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.61 (1H, d, J = 8.5 Hz, C**H**$_{Ar}$), 7.38 (1H, t, J = 8.5 Hz, C**H**$_{Ar}$), 7.24 (1H, s, C**H**$_{AR}$), 7.17 (1H, d, J = 8.5 Hz, C**H**$_{AR}$), 6.85 (1H, s, C**H**$_{AR}$), 3.98 (1H, s, OCH_3), 3.94 (3H, s, O**CH$_3$**), 3.61 (1H, d, J = 17.1 Hz, C**H**HCCO), 3.50 (3H, s, O**CH$_3$**), 3.45-3.31 (1H, m, CH**H**CO), 3.12-2.86 (1H, m, C**H**HCO), 2.98 (1H, d, J = 17.1 Hz, CH**H**CCO), 2.73-2.52 (2H, m, C**HH**).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 206.9 (**C**O), 169.5 (**C**O_2), 149.3 (**C**$_{AR}$O), 148.4 (**C**$_{Ar}$O), 136.7 (**C**$_{Ar}$), 134.8 (**C**$_{Ar}$), 130.7 (**C**$_{Ar}$), 128.5 (**C**H$_{Ar}$), 127.0 (**C**H$_{Ar}$), 126.5 (**C**$_{Ar}$), 125.3 (**C**$_{Ar}$), 122.1 (**C**H$_{Ar}$), 111.6 (**C**H$_{Ar}$), 107.2 (**C**H$_{AR}$), 58.5 (CO**C**CO_2CH_3), 56.1 (O**C**H_3), 56.0 (O**C**H_3), 53.1 (O**C**H_3), 37.4 (**C**H_2), 34.8 (**C**H_2), 28.3 (**C**H_2).

LRMS(CI) 270 ([M+NH_4]$^+$, 12%), 353 ([MH]$^+$, 8%), 335 (10%), 293 (100%), 251 (22%), 207 (8%), 178 (8%), 59 (13%) amu.

1-(2,6-Diiodo-3,4,5-trimethoxybenzyl)-2-oxo-1,2,3,4-tetrahydro-naphtalene-1-carboxylic acid methyl ester (306d)



mw = 636 g/mol

$C_{22}H_{22}O_6I_2$

DBU (0.49 mL, 3.27 mmol) was added to a solution of tetralone **305** (0.55 g, 2.73 mmol) in dichloromethane (52 mL). The mixture was stirred for 1 hour then benzyl bromide **299c** (1.67 g, 3.27 mmol) was added. After 16 hours, H_2O (20 mL) was added and the aqueous

phase extracted with dichloromethane (2 x 20 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, ether/petrol, 10/90) gave the title compound **306d** (0.255 g, 0.40 mmol, 15%) as a white solid.

MP 153-155 °C (ether/petrol)

FT-IR (neat, cm^{-1}): 2931 (m), 2358 (w), 1743 (s), 1455 (s), 1398 (s), 1360 (s), 1214 (s), 1081 (s).

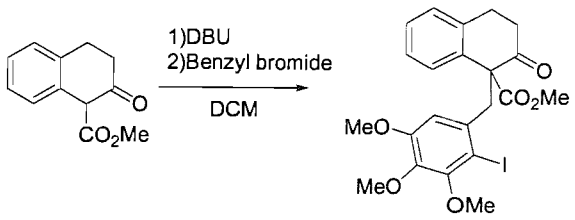
^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.20-7.03 (4H, m, C**H**$_{Ar}$), 4.61 (1H, d, J = 14.7 Hz, C**H**HCCO), 4.46 (1H, d, J = 14.7 Hz, CH**H**CCO), 3.85 (3H, s, OC**H**$_3$), 3.75 (3H, s, OC**H**$_3$), 3.72 (3H, s, OC**H**$_3$), 2.91-2.87 (2H, m, C**HH**CO), 2.85-2.61 (2H, m, C**HH**).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 207.6 (**C**O), 171.6 (**C**O_2), 153.8 (2x**C**$_{Ar}$O), 143.6 (**C**$_{Ar}$O), 139.2(**C**$_{Ar}$), 136.4 (**C**$_{Ar}$), 136.1 (**C**$_{Ar}$), 130.7 (**C**H$_{Ar}$), 128.1 (**C**H$_{Ar}$), 127.6 (**C**H$_{Ar}$), 126.4 (**C**H$_{Ar}$), 95.1 (2x**C**$_{Ar}$I), 63.9 (CO**C**CO), 61.2 (O**C**H$_3$), 60.7 (2xO**C**H$_3$), 53.4 (O**C**H$_3$), 51.8 (**C**H$_2$), 39.3 (**C**H$_2$), 28.6 (**C**H$_2$).

LRMS(CI) 480 (M^+, 2%), 353 ($[M-I]^+$, 8%), 337 (22%), 277 (100%), 246 (6%), 189 (10%), 151 (60%) amu.

CHN Calculated C 52.52, H 4.41. Found C 52.74.H 4.45.

1-(2-Iodo-3,4,5-trimethoxybenzyl)-2-oxo-1,2,3,4-tetrahydro-naphtalene-1-carboxylic acid methyl ester (306c)



mw = 510 g/mol

$C_{22}H_{23}O_6I$

DBU (0.49 mL, 3.27 mmol) was added to a solution of tetralone **305** (0.55 g, 2.73 mmol) in dichloromethane (52 mL). The mixture was stirred for 1 hour then benzyl bromide (1.67 g, 3.27 mmol) was added. After 16 hours, H_2O (20 mL) was added and the aqueous phase extracted with dichloromethane (2 x 20 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, ether/petrol, 10/90) gave the title compound **306c** (0.255 g, 0.40 mmol, 15%) as a white solid.

MP 156-158 °C (ether/petrol)

FT-IR (neat, cm^{-1}): 2992 (w), 2931 (m), 1739 (s), 1710 (s), 1479 (s), 1384 (s), 1233 (s), 1100 (s), 1006 (m).

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.18-7.10 (4H, m, CH_{Ar}), 6.21 (1H, s, CH_{Ar}), 4.02 (1H, d, J = 14.3, CHH), 3.81 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 3.64 (1H, d, J = 14.3 Hz, CHH), 3.51 (3H, s, OCH_3), 2.88-2.78 (1H, m, CHH), 2.69-2.47 (1H, m, CHH), 2.45-2.31 (2H, m, CHH).

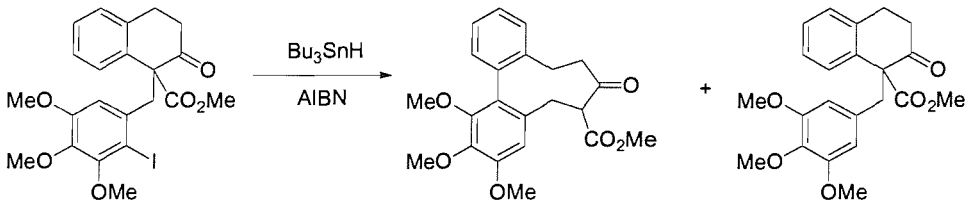
^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 208.4 (CO), 171.8 (CO_2), 153.0 ($C_{Ar}O$), 152.7 ($C_{Ar}O$), 141.1 ($C_{Ar}O$), 136.8(C_{Ar}), 135.5 (C_{Ar}), 134.6 (C_{Ar}), 128.6 (CH_{Ar}), 128.5 (CH_{Ar}), 127.9 (CH_{Ar}), 127.3 (CH_{Ar}), 110.4 (CH_{Ar}), 91.1 ($C_{Ar}I$), 64.4

(COCCO), 61.1 (OCH_3), 60.8 (OCH_3), 55.7 (OCH_3), 53.1 (OCH_3), 46.3 (CH_2), 39.1 (CH_2), 27.3 (CH_2).

LRMS(CI) 384 ($[M-I+H]^+$, 8%), 367 (8%), 307 (100%), 183 (45%), 115 (6%) amu.

HRMS(EI) Found M: 510.0542; $C_{22}H_{23}O_6I$ requires 510.0539.

7-Oxo-6,7,8,9-tetrahydro-5*H*-dibenzo[*a*,*c*]cyclononene-6-carboxylic acid methyl ester (308c) and 2-Oxo-1-(3,4,5-trimethoxy-benzyl)-1,2,3,4-tetrahydro-maphtalene-1-carboxylic methyl ester (309c)



mw = 384 g/mol mw = 384 g/mol

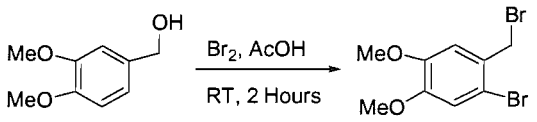
$C_{22}H_{24}O_6$ $C_{22}H_{24}O_6$

To a solution of tetralone **306c** (0.848 g, 1.66 mmol) in toluene (67 mL) under nitrogen was added Bu_3SnH (0.67 mL, 2.50 mmol) and AIBN (27 mg, 0.16 mmol). The mixture was stirred at 80 °C for 16 hours then cooled to room temperature. Aqueous potassium fluoride (10% w/v, 20 mL) was added and the resulting mixture stirred vigorously for 24 hours. The organic phase was washed with brine (2 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The title compounds **308c** (0.22 g, 0.58 mmol, 35%) and **309c** (0.22 g, 0.58 mmol, 35%) could not be separated by column chromatography.

^{1}H NMR δ (300 MHz, $CDCl_3$): 7.29-7.05 (11H, m, 11 x CH_{AR}), 6.60 (1H, s, CH_{AR} of **308c**), 5.75 (2H, s, 2 x CH_{AR} of **309c**), 3.91 (3H, s, OCH_3 of **308c**), 3.90 (3H, s, OCH_3 of **308c**), 3.75 (3H, s, OCH_3 of **309c**), 3.71 (3H, s, OCH_3 of **308c**), 3.70 (3H, s, OCH_3 of **309c**), 3.58 (3H, s, OCH_3 of **308c**), 3.54 (6H, s,

2 x OCH_3 of **309c**), 3.51 (1H, obs d, C**H**H of **309c**), 3.23 (1H, d, J = 13.11 Hz, CH**H** of **309c**), 3.11 (1H, dd, J = 14.3, 3.1 Hz, C**H**CO_2CH_3 of **308c**), 2.99-2.87 (2H, m, CH_2 of **308c**), 2.71-2.61 (6H, m, CH_2 of **309c** and CH_2CH_2CO of **308c**), 2.59-2.26 (1H, m, C**H**H of **309c**), 1.95-1.75 (1H, m, CH**H** of **309c**).

1-(Bromomethyl)-2-bromo-4,5-dimethoxybenzene(297f)



mw = 310 g/mol

$C_9H_{10}Br_2$

To a stirred solution of alcohol (17.64g, 0.104 mol) in glacial acetic acid (31.94 mL) at 0 °C was added bromine (6.46 mL, 0.125 mol) in glacial acetic acid (19.16 mL) dropwise over 30 minutes. After stirring for a further 2 hours at room temperature, the suspended cream solid formed was isolated via suction filtration and washed with water (50 mL). The crude material was recrystallised from petrol to afford the title compound as a pale cream solid (20.02 g, 0.064 mol, 61%).

MP 49-51 °C (petrol)

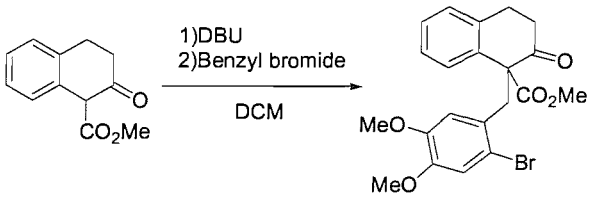
FT-IR (neat, cm^{-1}): 2959 (w), 2836 (w), 1797 (m), 1502 (s), 1441 (s), 1261 (s), 1204 (s), 1166 (s), 859 (m), 797 (m).

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.03 (1H, s, CH_{Ar}), 6.94 (1H, s, CH_{Ar}), 4.60 (2H, s, CH_2), 3.90 (3H, s, OCH_3), 3.89 (3H, s, OCH_3).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 149.9 (**C**$_{Ar}$), 128.9 (**C**$_{Ar}$), 115.7 (**C**H_{Ar}), 115.0 (**C**$_{Ar}$), 113.4 (**C**H_{Ar}), 56.3 (OCH_3), 56.2 (OCH_3), 34.3 (CH_2).

LRMS(CI) 231 (56%), 230 (55%), 153 (100%), 137 (22%), 108 (64%) amu.

1-(2-Bromo-4,5-dimethoxybenzyl)-2-oxo-1,2,3,4-tetrahydro-naphtalene-1-carboxylic acid methyl ester (300f)



mw = 433 g/mol

$C_{21}H_{21}O_5Br$

DBU (6.15 mL, 41.2 mmol) was added to a solution of tetralone (7.00 g, 34.3 mmol) in dichloromethane (500 mL). The mixture was stirred for 1 hour and the benzyl bromide (13.82 g, 44.6 mmol) was added. After 16 hours, H_2O (30 mL) was added and the aqueous phase extracted with dichloromethane (2 x 20 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, ether/petrol, 10/90) gave the title compound **300f** (5.98 g, 13.8 mmol, 40%) as a white solid.

MP 111-113 °C (ether/petrol)

FT-IR (neat, cm^{-1}): 2997 (w), 2954 (m), 2836 (w), 2250 (w), 1739 (s), 1710 (s), 1507 (s), 1214 (s), 1162 (s), 727 (s).

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.28-7.24 (3H, m, 3 x CH_{Ar}), 7.12 (1H, obs d, CH_{Ar}), 6.84 (1H, s, CH_{Ar}), 6.14 (1H, s, CH_{Ar}), 3.96 (1H, d, J = 13.8 Hz, CHH), 3.79 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 3.48 (3H, s, OCH_3), 3.46

(1H, d, J = 13.8 Hz, CH**H**), 2.88-2.78 (1H, m, C**H**H), 2.69-2.47 (1H, m, CH**H**), 2.45-2.31 (2H, m, C**HH**).

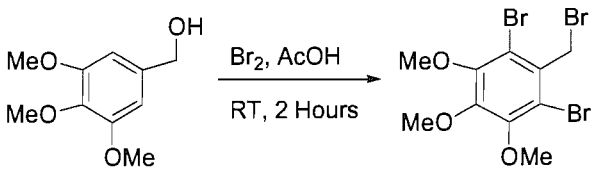
^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 208.5 (**C**O), 171.9 (**C**O_2), 148.3 (**C**$_{Ar}$O), 147.5 (**C**$_{Ar}$O), 136.8 (**C**$_{Ar}$), 135.9(**C**$_{Ar}$), 128.6 (**C**H$_{Ar}$), 128.1 (**C**H$_{Ar}$), 127.8 (**C**H$_{Ar}$), 127.3 (**C**H$_{Ar}$), 127.1 (**C**$_{Ar}$), 115.7 (**C**$_{Ar}$), 115.3 (**C**H$_{Ar}$), 114.2 (**C**H$_{Ar}$), 64.1 (COCCO), 56.0 (O**C**H_3), 55.6 (O**C**H_3), 53.1 (O**C**H_3), 42.2 (**C**H_2), 39.1 (**C**H_2), 27.2 (**C**H_2).

LRMS(CI) 434 ([M^{81}Br]$^+$, 2%), 432 ([M^{79}Br], 2%), 353 ([M-Br]$^+$, 6%), 337 (20%), 293 (8%), 276 (18%), 231 (28%), 202 (26%), 189 (46%), 115 (50%), 59 (100%) amu.

HRMS(ES) Found M+Na: 455.0464; $C_{21}H_{21}O_5BrNa$ requires 455.0464.

CHN Calculated C 58.21, H 4.88. Found C 58.38, H 4.93.

1-(Bromomethyl)-2,6-dibromo-3,4,5-trimethoxybenzene (299b)



mw = 419 g/mol

$C_{10}H_{11}O_3Br_3$

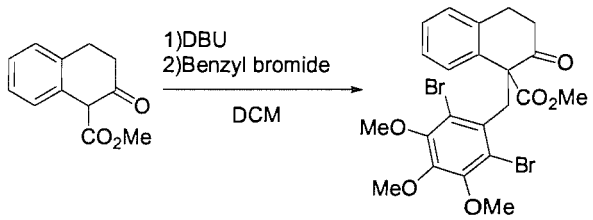
To a stirred solution of alcohol (12.17g, 0.072 mol) in glacial acetic acid (22.0 mL) at 0 °C was added bromine (4.46 mL, 0.086 mol) in glacial acetic acid (13.4 mL) dropwise over 30 minutes. After stirring for a further 16 hours at room temperature, the mixture was extracted with ethyl acetate (2 x 30 mL) and washed with water (50 mL). The crude material was recrystallised from petrol to afford the title compound as a pale cream solid (15.03 g, 0.040 mol, 56%).

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 4.89 (2H, s, CH_2), 3.96 (3H, s, OCH_3), 3.91 (6H, s, 2 x OCH_3).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 151.1 (2 x C_{Ar}), 148.0 (C_{Ar}), 131.8 (C_{Ar}), 116.0 (2 x C_{Ar}), 61.5 (OCH_3), 61.1 (2 x OCH_3), 35.1 (CH_2).

LRMS(CI) 419 ($[M^{81}Br]^+$, 6%), 417 ($[M^{79}Br]^+$, 6%), 340 ($[M-^{79}Br]^+$, 100%), 339 ($[M-^{80}Br]^+$, 86%), 282 (16%), 262 ($[MH-^{79}Br-^{79}Br]^+$, 38%), 260 ($[MH-^{81}Br-^{79}Br]$), 183 (42%), 167 (18%), 91 (16%) amu.

1-(2,6-Dibromo-3,4,5-trimethoxy-benzyl)-2-oxo-1,2,3,4-tetrahydro-naphtalene-1-carboxylic acid methyl ester (300g)



mw = 542 g/mol

$C_{22}H_{22}O_6Br_2$

DBU (0.549 mL, 3.67 mmol) was added to a solution of the tetralone (0.500 g, 2.45 mmol) in dichloromethane (33 mL). The mixture was stirred for 1 hour then benzyl bromide (1.540 g, 3.67 mmol) was added. After 16 hours, H_2O (30 mL) was added and the aqueous phase extracted with dichloromethane (2 x 20 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, ether/petrol, 10/90) gave the title compound (0.743 g, 1.37 mmol, 56%) as a white solid.

MP 161-163 °C (ether/petrol)

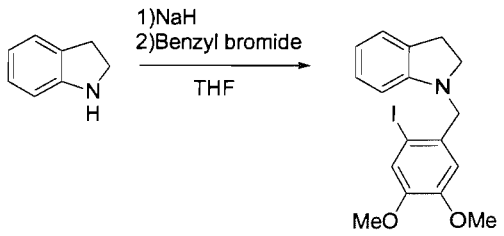
FT-IR (neat, cm^{-1}): 2998 (w), 2938 (w), 2847 (w), 1743 (s), 1463 (s), 1407 (s), 1381 (s), 1219 (s), 1087 (s), 1010 (s), 787 (s).

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.19-7.08 (3H, m, 3 x CH_{Ar}), 7.01 (1H, obs d, CH_{Ar}), 4.38 (1H, d, J = 14.5 Hz, CHH), 4.24 (1H, d, J = 14.5 Hz, CHH), 3.87 (3H, s, OCH_3), 3.74 (6H, s, 2 x OCH_3), 3.72 (3H, s, OCH_3), 2.82-2.66 (4H, m, 2 x CHH).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 208.7 (CO), 171.8 (CO_2), 150.4 (2 x $C_{Ar}O$), 146.5 ($C_{Ar}O$), 136.2 (C_{Ar}), 135.4 (C_{Ar}), 132.9 (C_{Ar}), 130.0 (CH_{Ar}), 128.0 (CH_{Ar}), 127.6 (CH_{Ar}), 126.4 (CH_{Ar}), 117.7 (2 x C_{Ar}), 64.1 (COCCO), 61.5 (OCH_3), 60.9 (2 x OCH_3), 53.3 (OCH_3), 43.1 (CH_2), 39.0 (CH_2), 27.8 (CH_2).

LRMS(CI) 463 ([M-^{79}Br]$^+$, 18%), 461 ([M-^{81}Br]$^+$, 6%), 403 (14%), 386 (24%), 339 (100%), 308 (78%), 293 (24%), 262 (26%), 202 (28%), 178 (32%) amu.

1-(2-Iodo-4,5-dimethoxy-benzyl)-2,3-dihydro-1*H*-indole (362)



mw = 395 g/mol

$C_{17}H_{18}INO$

To a solution of sodium hydroxide (0.115 g, 4.83 mmol) in THF (11 mL) was added indoline (0.500 g, 4.20 mmol, 0.471 mL). The mixture was stirred for 5 minutes and then a solution of benzyl bromide (1.725 g, 4.83 mmol) in THF (4 mL) was added. After 16 hours, H_2O (10 mL) was added and the aqueous phase extracted with dichloromethane (2 x 20 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$)

and concentrated *in vacuo*. Purification by column chromatography (silica gel, ether/petrol, 10/90) gave the title compound (0.757 g, 1.91 mmol, 45%) as a cream powder.

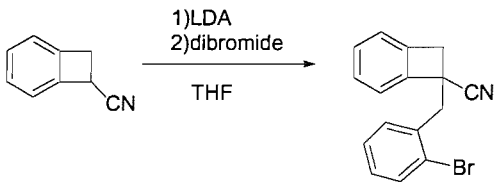
FT-IR (neat, cm^{-1}): 2931 (w), 2837 (w), 1605 (m), 1490 (s), 1461 (m), 1375 (m), 1252 (s), 1205 (s), 1157 (s), 1022 (m), 728 (s).

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.18 (1H, s, C**H**$_{AR}$), 7.05 (2H, dd, J = 13.0, 8.0 Hz, 2 x C**H**$_{AR}$), 6.96 (1H, s, C**H**$_{AR}$), 6.67 (1H, t, J = 8.0 Hz, C**H**$_{AR}$), 6.49 (1H, d, J = 8.0 Hz, C**H**$_{AR}$), 4.12 (2H, s, C**H**$_2$), 3.81 (3H, s, OC**H**$_3$), 3.76 (3H, s, OC**H**$_3$), 3.32 (2H, t, J = 8.0 Hz, C**H**$_2$), 2.98 (2H, t, J = 8.0 Hz, C**H**$_2$).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 152.6 (**C**$_{AR}$), 149.7 (**C**$_{AR}$), 148.8 (**C**$_{AR}$), 132.8 (**C**$_{AR}$), 130.1 (**C**$_{AR}$), 127.5 (**C**H$_{AR}$), 124.7 (**C**H$_{AR}$), 121.7 (**C**H$_{AR}$), 118.2 (**C**H$_{AR}$), 112.2 (**C**H$_{AR}$), 107.6 (**C**H$_{AR}$), 86.9 (**C**$_{AR}$), 58.9 (**C**H$_2$), 56.4 (O**C**H$_3$), 56.2 (O**C**H$_3$), 54.2 (**C**H$_2$), 28.9 (**C**H$_2$).

LRMS (CI) 396 ($[MH]^+$, 60%), 151 ($[M-I]^+$, 70%), 151 (100%), 118 (80%), 91 (30%), 63 (18%) amu.

7-(2-Bromo-benzyl)-bicyclo[4.2.0]octa-1(6),2,4-triene-7-carbonitrile (317c)



mw = 298 g/mol

$C_{16}H_{12}BrN$

A solution of the carbonitrile **316** (1.0 g, 7.75 mmol) in THF (33 mL) was added to LDA, prepared from diisopropylamine (0.94 g, 9.30 mmol, 1.30 mL) and ^{t}BuLi (7.15 mL, 9.30 mmol) in THF (2.5 mL) at -78 °C. After one hour, 2-bromo-benzylbromide (3.294 g, 13.17

mmol) was added and the reaction mixture was stirred at room temperature for 16 hours. H_2O (30 mL) was added and the aqueous phase extracted with ether (3 x 20 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, ether/petrol, 10/90) afforded the title compound **317c** (2.03 g, 6.81 mmol, 88%) as a white powder.

MP 88-90 °C

FT-IR (neat, cm-1): 3066 (w), 2935 (w), 2230 (m), 1565 (w), 1471 (m), 1440 (m), 1027 (m), 771 (s), 728 (s).

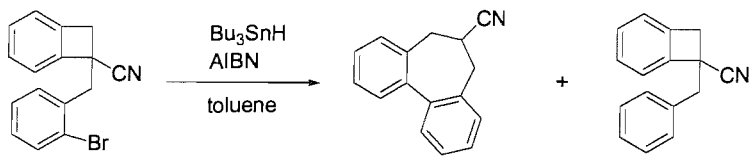
^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.62 (1H, dd, J = 8.1, 1.2 Hz, C**H**$_{AR}$), 7.51 (1H, dd, J = 7.6, 1.5 Hz, C**H**$_{AR}$), 7.37-7.15 (5H, m, 5 x C**H**$_{AR}$), 7.07 (1H, d, J = 7.1 Hz, C**H**$_{AR}$), 3.79 (1H, d, J = 14.3 Hz, C**H**H), 3.58 (1H, d, J = 14.3 Hz, CH**H**), 3.53 (2H, dd, J = 17.6, 14.3 Hz, C**H**$_2$).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 142.9 (**C**$_{AR}$), 141.3 (**C**$_{AR}$), 135.5 (**C**$_{AR}$), 133.4 (**C**H$_{AR}$), 131.2 (**C**H$_{AR}$), 129.9 (**C**H$_{AR}$), 129.2 (**C**H$_{AR}$), 128.2 (**C**H$_{AR}$), 127.7 (**C**H$_{AR}$), 125.5 (**C**$_{AR}$), 124.0 (**C**H$_{AR}$), 122.3 (**C**H$_{AR}$), 121.8 (**C**N), 43.1 (**C**H$_2$), 43.0 (**C**CN), 41.4 (**C**H$_2$).

LRMS (CI) 317 ($[M^{81}(Br)+NH_4]^+$, 40%), 315 ($[M^{79}(Br)+NH_4]^+$, 40%), 299 ($[M^{81}(Br)]^+$, 36%), 297 ($[M^{79}(Br)]^+$, 36%), 219 ($[M\text{-}Br]^+$, 100%), 203 (40%), 189 (24%) amu.

HRMS (CI) Found M: 297.01441; $C_{16}H_{12}N^{79}Br$ requires 297.01531.

7-Benzyl-bicyclo[4.2.0]octa-1,3,5-triene-7-carbonitrile (319c) and 6,7-Dihydro-5*H*-dibenzo[a,c]cyclopheptene-6-carbonitrile (318c)

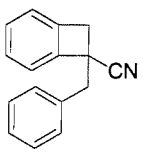


mw = 219 g/mol mw = 219 g/mol

$C_{16}H_{13}N$ $C_{16}H_{13}N$

A solution of nitrile **317c** (1.00 g, 3.35 mmol) in toluene (145 mL) was added Bu_3SnH (0.99 mL, 3.69 mmol) and AIBN (0.11 g, 0.67 mmol). The mixture was heated to 80 °C for 16 hours then cooled to room temperature. Aqueous potassium fluoride (10% w/v, 40 mL) was added and the resulting mixture stirred vigorously for 24 hours. The organic phase was washed with brine (2 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 10% ether/petrol) afforded firstly **319c** (46 mg, 0.21 mmol, 6%) then cycloheptane **318c** (0.576 g, 2.63 mmol, 78%) both as white powders.

7-Benzyl-bicyclo[4.2.0]octa-1,3,5-triene-7-carbonitrile (319c)



MP 67-69 °C

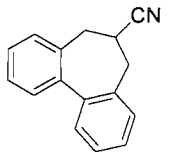
FT-IR (neat, cm^{-1}): 3065 (w), 3030 (w), 2931 (w), 2232 (w), 1496 (m), 1455 (s), 760 (s), 701 (s).

1H NMR δ ppm (300 MHz, CDCl3): 7.85-7.21 (7H, m, 7 x C**H**$_{AR}$), 7.17 (1H, d, J = 8.5 Hz, C**H**$_{AR}$), 6.97 (1H, d, J = 8.5 Hz, C**H**$_{AR}$), 3.80 (1H, d, J = 13.7 Hz, C**H**H), 3.47 (1H, d, J = 13.7 Hz, CH**H**), 3.35 (1H, d, J = 13.7 Hz, C**H**H), 3.18 (1H, d, J = 13.7 Hz, CH**H**).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 143.4 (**C**), 141.3 (**C**), 136.0 (**C**), 129.9 (2 x **C**H$_{AR}$), 129.8 (**C**H$_{AR}$), 128.7 (2 x **C**H$_{AR}$), 128.1 (**C**H$_{AR}$), 127.7 (**C**H$_{AR}$), 124.0 (**C**H$_{AR}$), 122.4 (**C**H$_{AR}$), 121.7 (**C**), 43.9 (**C**CN), 43.1 (2 x **C**H$_2$).

LRMS (CI) 237 ([M+NH$_4$]$^+$, 100%), 219 (M$^+$, 26%), 204 (6%), 165 (4%), 108 (6%), 91 (12%) amu.

6,7-Dihydro-5*H*-dibenzo[a,c]cyclopheptene-6-carbonitrile (318c)



MP 111-113 °C

FT-IR (neat, cm^{-1}): 3025 (w), 2955 (w), 2232 (m), 1482 (m), 1440 (m), 779 (m), 745 (s).

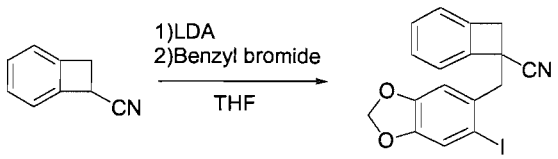
^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.49-7.30 (8H, m, 8 x C**H**$_{AR}$), 3.41 (1H, q, J = 16.0, 8.0 Hz, C**H**CN), 3.01-2.56 (4H, m, 2 x C**H**$_2$).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 140.7 (2 x **C**$_{AR}$), 134.5 (2 x **C**$_{AR}$), 129.3 (2 x **C**H$_{AR}$), 128.7 (2 x **C**H$_{AR}$),128.3 (2 x **C**H$_{AR}$), 128.2 (2 x **C**H$_{AR}$), 121.90 (**C**N), 35.2 (**C**HCN), 34.5 (2 x **C**H$_2$).

LRMS (CI) 237 ($[M+NH_4]^+$, 100%), 219 (M^+, 82%), 192 (32%), 178 (22%), 166 (68%) amu.

HRMS (CI) Found 219.1045; $C_{16}H_{13}N$ requires 219.1048.

7-(6-Iodo-benzo[1,3]dioxol-5-ylmethyl)-bicyclo[4.2.0]octa-1(6)-2,4-triene-7-carbon (317d)



mw = 389 g/mol

$C_{17}H_{12}INO$

A solution of the carbonitrile **316** (0.95 g, 7.36 mmol) in THF (33 mL) was added to LDA, prepared from diisopropylamine (0.89 g, 8.83 mmol, 1.23 mL) and ^{t}BuLi (5.89 mL, 8.83 mmol) in THF (2.5 mL) at -78 °C. After one hour, the benzyl bromide (4.26 g, 12.52 mmol) was added and the reaction mixture was stirred at room temperature for 16 hours. H_2O (30 mL) was added and the aqueous phase extracted with ether (3 x 20 mL), washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, ether/petrol, 10/90) afforded the title compound **317d** (1.10 g, 2.83 mmol, 38%) as a cream powder.

MP 112-114 °C (petrol/AcOEt)

FT-IR (neat, cm^{-1}): 2254 (w), 1503 (m), 1478 (s), 1228 (m), 1039 (m), 905 (s), 727 (s).

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.38-7.26 (2H, m, 2 x CH_{AR}), 7.29 (1H, s, CH_{AR}), 7.17 (1H, d, J = 6.9 Hz, CH_{AR}), 7.07 (1H, d, J = 7.3 Hz, CH_{AR}), 7.01 (1H, s, CH_{AR}), 6.00 (2H, s, OCH_2O), 3.77 (1H, d, J = 14.1 Hz, CHH),

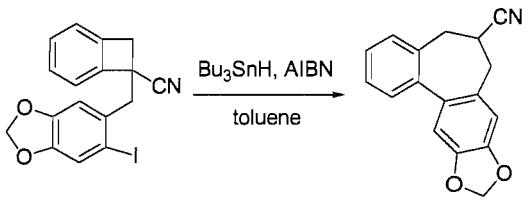
3.55 (1H, d, J = 14.1 Hz, CH**H**), 3.47 (1H, d, J = 14.4 Hz, C**H**H), 3.39 (1H, d, J = 14.4 Hz, CH**H**).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 148.7 (**C**$_{AR}$), 148.0 (**C**$_{AR}$), 142.7 (**C**$_{AR}$), 141.4 (**C**$_{AR}$), 132.1 (**C**$_{AR}$), 130.0 (**CH**$_{AR}$), 128.3 (**CH**$_{AR}$), 124.0 (**CH**$_{AR}$), 122.5 (**CH**$_{AR}$), 121.7 (**C**N), 119.1 (**CH**$_{AR}$), 109.8 (**CH**$_{AR}$), 102.0 (O**C**H$_2$O), 90.1 (**C**$_{AR}$), 46.0 (**C**H$_2$), 43.2 (**C**CN), 43.1 (**C**H$_2$).

LRMS (CI) 407 ([M+NH$_4$]$^+$, 88%), 389 (M$^+$, 92%), 262 ([M-I]$^+$, 100%), 247 (12%), 232 (38%), 204 (58%), 190 (12%), 176 (22%), 152 (8%), 115 (10%) amu.

HRMS (CI) Found M: 388.9915 ; $C_{17}H_{12}INO_2$ requires 388.9912.

6,7-Dihydro-5*H*-9,11-dioxa-benzo[3,4]cyclohepta[1,2-*f*]indene-6-carbonitrile (318d)



mw = 263 g/mol

$C_{17}H_{13}NO_2$

To a solution of nitrile **317d** (2.037 g, 5.23 mmol) in toluene (220 mL) were added Bu_3SnH (1.55 mL, 5.76 mmol) and AIBN (0.172 g, 1.04 mmol). The mixture was heated to 80 °C for 16 hours then cooled to room temperature. Aqueous potassium fluoride (10% w/v, 40 mL) was added and the resulting mixture stirred vigorously for 24 hours. The organic phase was washed with brine (2 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 10% ether/petrol) afforded the cycloheptane **318d** (0.689 g, 2.62 mmol, 55%) as a white powder.

MP 124-126 °C (ether/petrol)

FT-IR (neat, cm^{-1}): 2921 (w), 2221 (w), 1503 (m), 1483 (s), 1262 (m), 1036 (m), 525 (s), 500 (s).

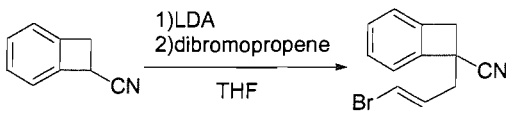
^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.26-7.16 (2H, m, 2 x C**H**$_{AR}$), 7.11 (1H, d, J = 7.1 Hz, C**H**$_{AR}$), 7.05 (1H, s, C**H**$_{AR}$), 6.91 (1H, d, J = 7.1 Hz, C**H**$_{AR}$), 6.84 (1H, s, C**H**$_{AR}$), 6.09 (2H, d, J = 1.9 Hz, OC**H**$_2$O), 3.83-3.80 (1H, m, C**H**CN), 3.39 (1H, dd, J = 14.0, 5.2 Hz, C**H**H), 3.23 (1H, dd, J = 14.0, 7.8 Hz, CH**H**), 3.13 (1H, dd, J = 14.0, 8.3 Hz, C**H**H), 2.94 (1H, dd, J = 14.0, 2.1 Hz, CH**H**).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 151.6 (**C**$_{AR}$), 147.9 (**C**$_{AR}$), 146.4 (**C**$_{AR}$), 143.4 (**C**$_{AR}$), 141.4 (**C**$_{AR}$), 127.8 (**C**H$_{AR}$), 126.9 (**C**H$_{AR}$), 123.3 (**C**H$_{AR}$), 122.3 (**C**H$_{AR}$), 118.4 (**C**$_{AR}$), 111.6 (**C**H$_{AR}$), 110.2 (**C**H$_{AR}$), 104.6 (**C**N), 102.4 (O**C**H$_2$O), 43.6 (**C**HCN), 38.9 (**C**H$_2$), 36.2 (**C**H$_2$).

LRMS (CI) 262 ([M-H]$^+$, 100%), 203 (10%), 94 (4%), 58 (6%) amu.

HRMS (ES) Found M+Na: 286.0840; $C_{17}H_{13}NO_2Na$ requires 286.0888.

7-((*E*)-3-Bromo-allyl)-bicyclo[4.2.0]octa-1(6),2,4-triene-7-carbonitrile (317e)



mw = 248 g/mol

$C_{12}H_{10}BrN$

A solution of the carbonitrile (0.95 g, 7.36 mmol) in THF (33 mL) was added to LDA, prepared from diisopropylamine (0.89 g, 8.83 mmol, 1.23 mL) and ^{t}BuLi (6.31 mL, 8.83 mmol) in THF (2.5 mL) at -78 °C. After one hour, the dibromopropene (2.50 g, 12.52

mmol) was added and the reaction mixture was stirred at room temperature for 16 hours. H_2O (30 mL) was added and the aqueous phase extracted with ether (3 x 20 mL), washed with brine (20 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (silica gel, ether/petrol, 10/90) afforded the title compound (0.54 g, 2.18 mmol, 29%) as a white powder.

FT-IR (neat, cm^{-1}): 3073 (w), 2933 (w), 2233 (w), 1624 (w), 1458 (m), 1425 (w), 1328 (w), 1283 (m), 908 (s), 726 (s), 666 (s).

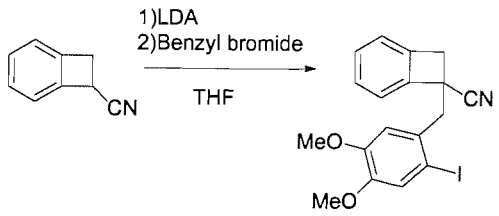
^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.36-7.29 (2H, m, C**H**), 7.24 (1H, d, J = 7.0 Hz, C**H**), 7.18 (1H, d, J = 7.0 Hz, C**H**), 6.45 (1H, dt, J = 7.1, 1.1 Hz, C**H**), 6.30 (1H, dd, J = 14.3, 7.1 Hz, C**H**), 3.74 (1H, d, J = 14.3 Hz, C**H**H), 3.39 (1H, d, J = 14.3 Hz, CH**H**), 2.94 (2H, d, J = 6.9 Hz, C**H$_2$**).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 143.0 (**C**$_{AR}$), 141.4 (**C**$_{AR}$), 130.2 (**C**H$_{AR}$), 128.8 (**C**H$_{AR}$), 128.6 (**C**H$_{AR}$), 124.3 (**C**H$_{AR}$), 121.9 (**C**H), 121.5 (**C**N), 112.5 (**C**H), 42.6 (**C**H$_2$), 41.6 (**C**CN), 37.3 (**C**H$_2$).

LRMS (CI) 267 ($[M^{81}(Br)+NH_4]^+$, 62%), 265 ($[M^{79}(Br)+NH_4]^+$, 78%), 249 ($[M^{81}(Br)]^+$, 54%), 247 ($[M^{79}(Br)]^+$, 66%), 185 (32%), 168 (100%), 153 (94%), 141 (86%), 115 (72%), 89 (22%) amu.

HRMS (CI) Found M: 246.9995; $C_{12}H_{10}N^{79}Br$ requires 246.9997.

7-(6-Iodo-benzo[1,3]dimethoxy-5-ylmethyl)-bicyclo[4.2.0]octa-1(6),2,4-triene-7-carbon (317b)



mw = 405 g/mol

$C_{18}H_{16}INO_2$

A solution of the carbonitrile **316** (0.95 g, 7.36 mmol) in THF (33 mL) was added to LDA, prepared from diisopropylamine (0.89 g, 8.83 mmol, 1.238 mL) and ^{t}BuLi (5.89 mL, 8.83 mmol) in THF (2.5 mL) at -78 °C. After one hour, the benzyl bromide (4.47 g, 12.52 mmol) was added and the reaction mixture was stirred at room temperature for 16 hours. H_2O (30 mL) was added and the aqueous phase extracted with ether (3 x 20 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and the solvent was removed *in vacuo*. Purification by column chromatography (silica gel, ether/petrol, 10/90) afforded the title compound **317b** (1.203 g, 2.97 mmol, 40%) as a white powder.

MP 143-145 °C

FT-IR (neat, cm-1): 2997 (w), 2954 (m), 2926 (w), 2827 (w), 2358 (m), 1587 (s), 1497 (s), 1460 (s), 1431 (s), 1370 (s), 1337 (s), 1256 (s), 1223 (s), 1204 (s), 1162 (s), 1114 (m), 1025 (s), 854 (s), 722 (s).

^{1}H NMR δ ppm (400 MHz, $CDCl_3$): 7.40-7.28 (2H, m, 2 x CH_{AR}), 7.29 (1H, s, CH_{AR}), 7.18 (1H, d, J = 7.5 Hz, CH_{AR}), 7.07 (1H, d, J = 7.0 Hz, CH_{AR}), 7.02 (1H, s, CH_{AR}), 3.91 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.77 (1H, d, J = 14.0 Hz, CHH), 3.56 (1H, d, J = 14.0 Hz, CHH), 3.53 (1H, d, J = 14.5 Hz, CHH), 3.43 (1H, d, J = 14.5 Hz, CHH).

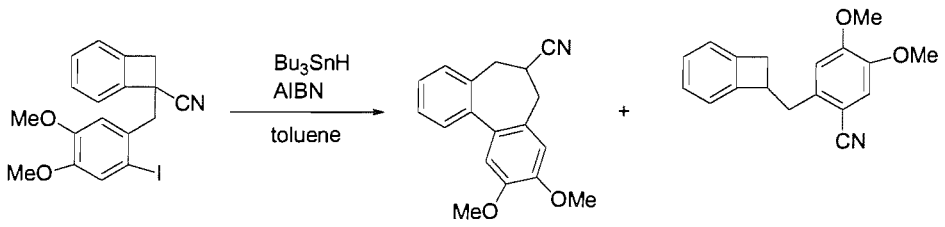
^{13}C NMR δ ppm (100 MHz, $CDCl_3$): 149.9 (C_{AR}), 149.5(C_{AR}), 143.4(C_{AR}), 142.1 (C_{AR}), 131.8 (C_{AR}), 130.5(CH_{AR}), 128.8 (CH_{AR}), 124.6 (CH_{AR}), 123.0

(CH_{AR}), 122.6 (**C**N), 122.5 (CH_{AR}), 113.5 (CH_{AR}), 90.5 ($C_{AR}I$), 56.8 (OCH_3), 56.6 (OCH_3), 46.3 (CH_2), 44.0 (**C**CN), 43.3 (CH_2).

LRMS (CI) 405 (M^+, 100%), 278 (64%), 263 (50%), 247 (34%), 234 (22%), 204 (16%), 190 (22%), 177 (32%), 165 (22%), 139 (8%), 115 (12%) amu.

HRMS (CI) Found M: 405.0229; $C_{18}H_{16}NO_2I$ requires 405.0225.

2,3-Dimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptene-6-carbonitrile (318b) and 2-Bicyclo[4.2.0]octa-1(6),2,4-trien-7-ylmethyl-4,5-dimethoxy-benzonitrile (320b)

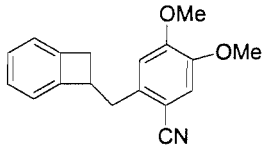


mw = 279 g/mol mw = 279 g/mol

$C_{18}H_{17}NO_2$ $C_{18}H_{17}NO_2$

To a solution of nitrile **317b** (0.995 g, 2.45 mmol) in toluene (102 mL) were added Bu_3SnH (0.73 mL, 2.70 mmol) and AIBN (0.081 g, 0.49 mmol). The mixture was heated to 80 °C for 16 hours then cooled to room temperature. Aqueous potassium fluoride (10% w/v, 40 mL) was added and the resulting mixture stirred vigorously for 24 hours. The organic phase was washed with brine (2 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 10% ether/petrol) afforded the cycloheptane **318b** (0.197 g, 0.70 mmol, 29%) then **320b** (0.374 g, 1.34 mmol, 55%) both as white powders.

2-Bicyclo[4.2.0]octa-1(6),2,4-trien-7-ylmethyl-4,5-dimethoxy-benzonitrile (320b)



MP 155-157 °C (ether/petrol)

FT-IR (neat, cm^{-1}): 3002 (w), 2916 (m), 2845 (w), 2216 (s), 1602 (m), 1512 (s), 1455 (m), 1341 (w), 1266 (s), 1228 (s), 1095 (m), 745 (m).

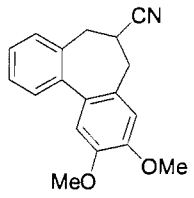
^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.19 (1H, t, J = 7.2 Hz, C**H**$_{AR}$), 7.16 (1H, t, J = 7.2 Hz, C**H**$_{AR}$), 7.10 (1H, d, J = 7.1 Hz, C**H**$_{AR}$), 7.08 (1H, s, C**H**$_{AR}$), 6.87 (1H, d, J = 7.2 Hz, C**H**$_{AR}$), 6.80 (1H, s, C**H**$_{AR}$), 3.92 (3H, s, OC**H**$_3$), 3.90 (3H, s, OC**H**$_3$), 3.88 (1H, m, C**H**CN), 3.40 (1H, dd, J = 13.9, 5.1 Hz, C**H**H), 3.29 (1H, dd, J = 13.9, 7.1 Hz, CH**H**), 3.11 (1H, dd, J = 13.9, 8.6 Hz, C**H**H), 2.93 (1H, dd, J = 13.9, 2.2 Hz, CH**H**).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 152.1 (**C**$_{AR}$), 147.6 (**C**$_{AR}$), 147.3 (**C**$_{AR}$), 143.1 (**C**$_{AR}$), 138.7 (**C**$_{AR}$), 127.3 (**C**H$_{AR}$), 126.3 (**C**H$_{AR}$), 122.9 (**C**H$_{AR}$), 121.8 (**C**H$_{AR}$), 118.2 (**C**$_{AR}$), 113.9 (**C**H$_{AR}$), 112.3 (**C**H$_{AR}$), 103.2 (**C**$_{AR}$), 55.8 (O**C**H$_3$), 55.7 (O**C**H$_3$), 43.2 (**C**HCN), 38.2 (**C**H$_2$), 35.7 (**C**H$_2$).

LRMS (CI) 278 ([M-H]$^+$, 100%), 262 (8%), 234 (10%), 218 (5%), 190 (8%), 164 (4%) amu.

HRMS (CI) Found M: 279.1252; $C_{18}H_{17}NO_2$ requires 279.1259.

2,3-Dimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cycloheptene-6-carbonitrile (318b)



MP 161-163 °C

FT-IR (neat, cm^{-1}): 2950 (s), 2921 (s), 2845 (s), 2235 (w), 1602 (w), 1512 (s), 1450 (s), 1351 (m), 1261 (s), 1242 (s), 1209 (s), 1143 (s), 1043 (m), 1025 (m), 755 (m).

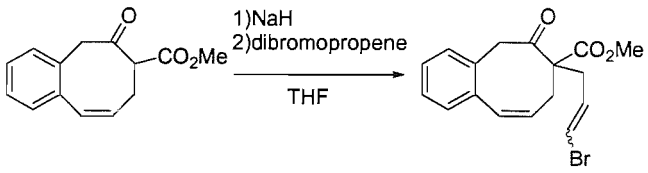
1H NMR δ ppm (300 MHz, CDCl3): 7.26-7.16 (4H, m, 4 x CH_{AR}), 6.79 (1H, s, CH_{AR}), 6.68 (1H, s, CH_{AR}), 3.79 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.23-3.18 (1H, m, $CHCH_2$), 3.67-3.51 (4H, m, 2 x CH_2).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 149.1 (**C**), 149.0 (**C**), 141.1 (**C**), 134.9 (**C**), 133.1 (**C**), 129.6 (CH_{AR}), 128.6 (CH_{AR}), 128.5 (CH_{AR}), 128.0 (CH_{AR}), 127.2 (**C**), 122.2 (**C**), 112.8 (CH_{AR}), 112.4 (CH_{AR}), 56.5 (2 x OCH_3), 35.7 (**C**H), 34.9 (CH_2), 34.4 (CH_2).

LRMS (CI) 297 ($[M+NH_4]^+$, 82%), 279 (M^+, 100%), 253 ($[M-CN]^+$, 10%), 209 (10%), 165 (20%), 152 (15%), 139 (8%), 115 (6%) amu.

HRMS (ES) Found M+Na: 302.1157; $C_{18}H_{17}NO_2Na$ requires 302.1151.

7-((E)-3-Bromo-allyl)-6-oxo-5,6,7,8-tetrahydro-benzocyclooctene-7-carboxylic acid methyl ester (302)



mw = 349 g/mol

$C_{17}H_{17}O_3Br$

To a solution of sodium hydride (0.035 g, 1.46 mmol) in THF (15 mL) was added benzooctanone **301h** (0.306 g, 1.33 mmol). The mixture was stirred for 10 minutes and then dibromopropene (0.146 mL, 1.46 mmol) was added. After 16 hours, H_2O (10 mL) was added and the aqueous phase extracted with dichloromethane (2 x 20 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, ether/petrol, 10/90) gave the 2 stereoisomers of the compound **302** as a colourless oil (0.250 g, 0.72 mmol, 54%). The 2 stereoisomers were not separated.

FT-IR (neat, cm^{-1}): 3063 (w), 3016 (w), 2945 (w), 2841 (w), 1706 (s), 1436 (m), 1233 (m), 1204 (m), 745 (m).

^{1}H NMR δ ppm (300 MHz, $CDCl_3$): 7.50-7.43 (2H, m, 2 x CH_{AR}), 7.28-7.22 (4H, m, 4 x CH_{AR}), 7.15-7.13 (2H, m, 2 x CH_{AR}), 6.77 (2H, 2 x d, J = 11.2 Hz, 2 x CH_{Alkene}), 6.29-6.05 (6H, m, 2 x CH_{Alkene}), 4.03 (2H, d, J = 11.4 Hz, 2 x C**H**H), 3.79 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.55 (1H, d, J = 11.2 Hz, C**H**H), 3.53 (1H, d, J = 11.2 Hz, CH**H**), 2.69-2.32 (6H, m, 3 x C**HH**), 2.07 (2H, dt, J = 14.7, 8.5 Hz, C**HH**).

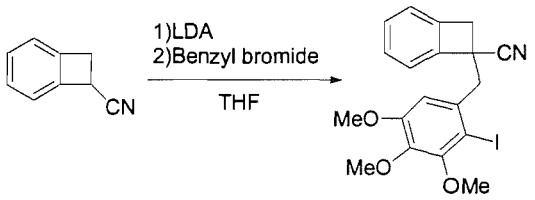
^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 205.1 (CO_2), 204.9 (CO_2), 171.4 (**C**O), 171.2 (**C**O), 136.7 (C_{AR}), 136.6 (C_{AR}), 133.9 (C_{AR}), 133.8 (C_{AR}), 133.0 (**C**H), 132.7 (**C**H), 132.6 (**C**H), 130.4 (**C**H), 130.0 (**C**H), 129.4 (**C**H), 129.2 (**C**H),

128.7 (**C**H), 127.9 (**C**H), 127.8 (**C**H), 127.3 (**C**H), 111.0 (**C**H), 108.0 (**C**H), 57.6 (**C**CO), 57.3 (**C**CO), 52.6 (O**C**H_3), 47.5 (**C**H_2), 47.4 (**C**H_2), 38.9 (**C**H_2), 35.4 (**C**H_2), 32.5 (**C**H_2), 32.2 (**C**H_2).

LRMS (CI) 396 ($[MH]^+$, 60%), 151 ($[M\text{-}I]^+$, 70%), 151 (100%), 118 (80%), 91 (30%), 63 (18%) amu.

HRMS (ES) Found M^{79}Br+ Na: 371.0256; $C_{17}H_{17}O_3{}^{79}BrNa$ requires 371.0253.

7-(2-Iodo-3,4,5-trimethoxy-benzyl)-bicyclo[4.2.0]octa-1,3,5-triene-7-carbonitrile (317a)



mw = 435 g/mol

$C_{19}H_{18}O_3NI$

A solution of the carbonitrile **316** (0.95 g, 7.36 mmol) in THF (33 mL) was added to LDA, prepared from diisopropylamine (0.89 g, 8.83 mmol, 1.238 mL) and ^{t}BuLi (5.89 mL, 8.83 mmol) in THF (2.5 mL) at -78 °C. After one hour, the benzyl bromide (3.70 g, 9.57 mmol) was added and the reaction mixture was stirred at room temperature. H_2O (30 mL) was added and the aqueous phase extracted with ether (3 x 20 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by column chromatography (silica gel, ether/petrol, 10/90) to afford the title compound **317a** (3.20 g, 7.35 mmol, 99 %) as a white powder.

MP 94-96 °C (ether/petrol)

FT-IR (neat, cm^{-1}): 3002 (w), 2932 (w), 2324 (w), 1558 (w), 1477 (m), 1458 (m), 1385 (m), 1244 (m), 1197 (m), 1156 (m), 1102 (s), 991 (s), 845 (w), 765 (s), 723 (s).

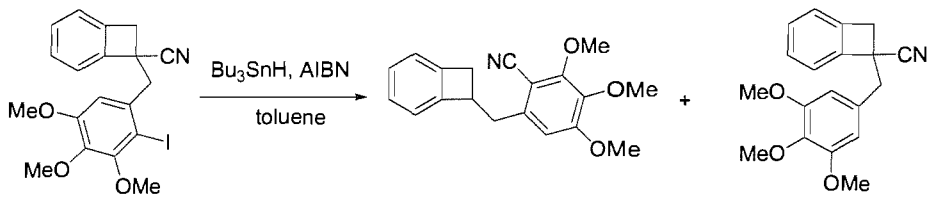
^{1}H NMR δ (300 MHz, $CDCl_3$): 7.33 (1H, t, J = 7.5 Hz, C**H**$_{AR}$), 7.25 (1H, t, J = 7.5 Hz, C**H**$_{AR}$), 7.14 (1H, d, J = 7.3 Hz, C**H**$_{AR}$), 7.01 (1H, d, J = 7.3 Hz, C**H**$_{AR}$), 6.92 (1H, s, C**H**$_{AR}$), 3.89 (3H, s, OC**H**$_3$), 3.87 (3H, s, OC**H**$_3$), 3.84 (3H, s, OC**H**$_3$), 3.73 (1H, d, J = 14.2 Hz, C**H**H), 3.54 (1H, d, J = 12.8 Hz, CH**H**), 3.52 (2H, app s, C**HH**).

^{13}C NMR δ (75 MHz, $CDCl_3$): 153.4 (**C**), 153.2 (**C**), 142.7 (**C**), 141.5 (**C**), 141.3 (**C**), 134.3 (**C**), 129.8 (**C**H$_{AR}$), 128.0 (**C**H$_{AR}$), 123.9 (**C**H$_{AR}$), 122.2 (**C**H$_{AR}$), 121.8 (**C**), 109.5 (**C**H$_{AR}$), 90.2 (**C**$_{AR}$I), 61.0 (O**C**H$_3$), 60.7 (O**C**H$_3$), 56.1 (O**C**H$_3$), 45.9 (**C**H$_2$), 43.1 (**C**CN), 42.8 (**C**H$_2$).

LRMS(CI) 453 ([M+NH_4]$^+$, 60 %), 435 (M^+, 35 %), 327 (5 %), 309 ([M-I]$^+$, 100 %), 293 (26 %), 277 (22 %), 250 (8 %), 207 (8 %), 178 (10 %), 152 (6 %) amu.

HRMS(CI) Found M: 435.03130 calculated 435.03315.

2-Bicyclo[4.2.0]octa-1(6),2,4-trien-7-ylmethyl-3,4,5-dimethoxy-benzonitrile (320a) and 7-(3,4,5-trimethoxy-benzyl)-bicyclo[4.2.0]octa-1,3,5-triene-7-carbonitrile (319a)

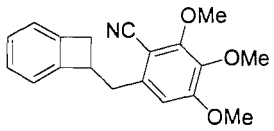


mw = 309 g/mol mw = 309 g/mol

$C_{19}H_{19}O_3N$ $C_{19}H_{19}O_3N$

To a solution of carbonitrile **317a** (1.96 g, 4.50 mmol) in toluene (189 mL) were added Bu_3SnH (1.33 mL, 4.95 mmol) and AIBN (148 mg, 0.90 mmol). The mixture was stirred at 80 °C for 16 hours then cooled to room temperature. Aqueous potassium fluoride (10% w/v, 20 mL) was added and the resulting mixture stirred vigorously for 24 hours. The organic phase was washed with brine (2 x 20 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (silica gel, 20 % ether/petrol) afforded the title compounds **320a** (1.17 g, 3.78 mmol, 84 %) and **319a** (0.069 g, 0.22 mmol, 5 %) each as colourless oils.

Data for (320a)

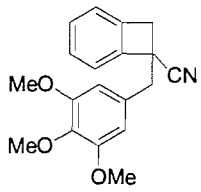


FT-IR (neat, cm^{-1}): 2938 (br), 2221 (w), 1591 (m), 1568 (m), 1495 (m), 1456 (m), 1405 (m), 1339 (m), 1250 (w), 1195 (w), 1123 (s), 1069 (w), 1031 (m), 908 (s), 728 (s).

^{1}H NMR δ (300 MHz, $CDCl_3$): 7.22-7.11 (2H, m, 2 x C**H**$_{AR}$), 7.06 (1H, d, J = 6.9 Hz, C**H**$_{AR}$), 6.87 (1H, d, J = 6.9 Hz, C**H**$_{AR}$), 6.58 (1H, s, C**H**$_{AR}$), 4.05 (3H, s, OC**H**$_3$), 3.86 (6H, s, 2 x OC**H**$_3$), 3.81 (1H, m, C**H**CH$_2$), 3.37 (1H, dd, J = 14.3, 5.1 Hz, CH**H**), 3.20 (1H, dd, J = 13.9, 7.3 Hz, CH**H**), 3.06 (1H, dd, J = 13.9, 8.4 Hz, CH**H**), 2.91 (1H, dd, J = 13.9, 2.3 Hz, CH**H**).

^{13}C NMR δ (75 MHz, $CDCl_3$): 157.2 (**C**), 155.8 (**C**), 147.9 (**C**), 143.4 (**C**), 141.5 (**C**), 140.0 (**C**), 127.6 (**C**H$_{AR}$), 126.6 (**C**H$_{AR}$), 123.2 (**C**H$_{AR}$), 122.1 (**C**H$_{AR}$), 115.7 (**C**), 108.6 (**C**H$_{AR}$), 99.5 (**C**), 61.7 (O**C**H$_3$), 61.1 (O**C**H$_3$), 56.2 (O**C**H$_3$), 43.2 (**C**H), 38.9 (**C**H$_2$), 36.1 (**C**H$_2$).

Data for (319a)



FT-IR (neat, cm^{-1}): 2937 (w), 2838 (w), 2248 (w), 1700 (w), 1589 (m), 1506 (m), 1457 (m), 1421 (m), 1335 (m), 1238 (m), 1122 (s), 1005 (m), 910 (m), 720 (s).

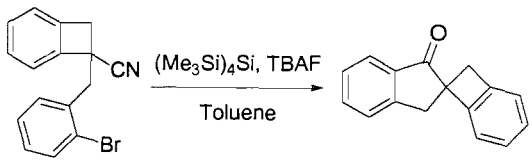
^{1}H NMR δ (300 MHz, $CDCl_3$): 7.33 (1H, obs td, J = 7.8, 1.1 Hz, C**H**$_{AR}$), 7.25 (1H, t, J = 7.5 Hz, C**H**$_{AR}$), 7.15 (1H, d, J = 7.2 Hz, C**H**$_{AR}$), 6.97 (1H, d, J = 7.5 Hz, C**H**$_{AR}$), 6.52 (2H, s, 2 x C**H**$_{AR}$), 3.86 (3H, s, OC**H**$_3$), 3.83 (6H, s, 2 x OC**H**$_3$), 3.74 (1H, d, J = 14.1 Hz, C**H**H), 3.40 (1H, d, J = 14.1 Hz, CH**H**), 3.27 (1H, d, J = 13.6 Hz, C**H**H), 3.05 (1H, d, J = 13.6 Hz, CH**H**).

^{13}C NMR δ (75 MHz, $CDCl_3$): 153.5 (2 x **C**$_{AR}$), 143.7 (**C**$_{AR}$), 141.6 (**C**$_{AR}$), 137.9 (**C**$_{AR}$), 131.8 (**C**$_{AR}$), 130.2 (**C**H$_{AR}$), 128.3 (**C**H$_{AR}$), 124.4 (**C**H$_{AR}$), 122.6 (**C**H$_{AR}$), 122.1 (**C**), 107.3 (2 x **C**H$_{AR}$), 61.3 (O**C**H$_3$), 56.5 (2 x O**C**H$_3$), 44.1 (**C**CN), 43.7 (**C**H$_2$), 43.3 (**C**H$_2$).

LRMS(CI) 327 ($[M+NH_4]^+$, 18 %), 310 ($[MH]^+$, 100 %), 294 (12 %), 234 (5 %), 181 (12 %) amu.

HRMS(CI) Found M: 309.1363; $C_{19}H_{19}NO_3$ requires 309.1364.

Spiro[benzocyclobutane-1,2'-indan-1-one] (356)



mw = 220 g/mol

$C_{16}H_{12}O$

To a solution of carbonitrile **317c** (0.144 g, 0.483 mmol) in toluene (10 mL) was added the tetrakistrimethylsilylsilane (0.310 g, 0.966 mmol) and then tetrabutylammonium fluoride (1.93 mL of a 1M solution in THF). The mixture was stirred at 100 °C for 16 hours and then cooled to room temperature. H_2O (30 mL) was added and the aqueous phase was separated and extracted with ether (3 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, ether/petrol, 5/95) afforded the title compound **356** (0.085 g, 0.386 mmol, 80 %) as a white solid.

MP 84-86 °C (ether/petrol)

FT-IR (neat, cm^{-1}): 3068 (m), 2916 (m), 1706 (s), 1606 (s), 1455 (s), 1270 (s), 1200 (m), 916 (s), 750 (s), 722 (s).

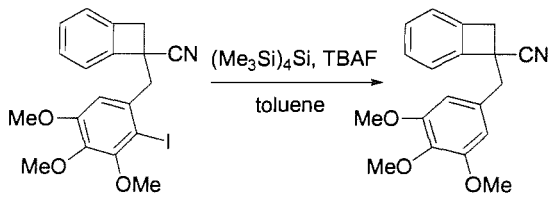
^{1}H NMR δ ppm (300 MHz, CDCl3): 7.87 (1H, d, J = 7.5 Hz, C**H**$_{AR}$), 7.68 (1H, t, J = 7.5 Hz, C**H**$_{AR}$), 7.55 (1H, d, J = 7.5 Hz, C**H**$_{AR}$), 7.46 (1H, t, J = 7.5 Hz, C**H**$_{AR}$), 7.32-7.20 (3H, m, 3 x C**H**$_{AR}$), 6.90 (1H, d, J = 6.7 Hz, C**H**$_{AR}$), 3.68 (1H, d, J = 13.6 Hz, C**H**H), 3.67 (1H, d, J = 17.3 Hz, CH**H**), 3.63 (1H, d, J = 17.3 Hz, C**H**H), 3.28 (1H, d, J = 13.6 Hz, CH**H**).

^{13}C NMR δ ppm (75 MHz, $CDCl_3$): 205.9 (**C**O), 152.4 (**C**$_{AR}$), 146.8 (**C**$_{AR}$), 143.3 (**C**$_{AR}$), 136.2 (**C**$_{AR}$), 135.1 (**C**H$_{AR}$), 128.2 (**C**H$_{AR}$), 127.7 (**C**H$_{AR}$), 127.6 (**C**H$_{AR}$), 126.5 (**C**H$_{AR}$), 124.5 (**C**H$_{AR}$), 123.1 (**C**H$_{AR}$), 120.5 (**C**H$_{AR}$), 58.7 (**C**CO), 41.9 (**C**H$_2$), 38.1 (**C**H$_2$).

LRMS(CI) 221 ($[M+H]^+$, 100%), 191 ($[M-CHO]^+$, 40%), 165 (16%), 115 (7%) amu.

HRMS(EI) Found M: 220.08876 calculated 220.08882.

7-(3,4,5-Trimethoxy-benzyl)-bicyclo[4.2.0]octa-1,3,5-triene-7-carbonitrile (319a)



mw = 309 g/mol

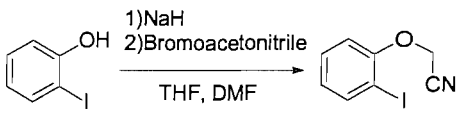
$C_{19}H_{19}O_3N$

To a solution of carbonitrile **317a** (1.360 g, 3.126 mmol) in toluene (65 mL) was added tetrakistrimethylsilylsilane (2.006 g, 6.252 mmol) and tetrabutylammonium fluoride (12.5 mL of a 1M solution in THF, 12.5 mmol). The mixture was stirred at 100 °C for 16 hours and then cooled at room temperature. H_2O (40 mL) was added and the aqueous phase was extracted with ether (3 x 20 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, ether/petrol, 5/95) afforded the title compound **319a** (0.840 g, 2.718 mmol, 87 %) as a white solid.

MP 116-118°C

DATA same as previously reported

(2-Iodo-phenoxy)-acetonitrile (352)



mw = 259 g/mol

C_8H_6OIN

To a solution of bromo-acetonitrile (0.580 mL, 8.33 mmol) in DMF/THF was added NaH (0.220 g, 9.17 mmol) at 0 °C under nitrogen followed after 5 minutes by iodophenol (2.017 g, 9.17 mmol). The reaction mixture was allowed to warm to room temperature and left to stir for 16 hours. The compound was partitioned between ether (40 mL) and water (40 mL). The organic phase was separated, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (10/90 ether/petrol) yielded the title compound **352** (1.57 g, 6.05 mmol, 72%) as a white powder.

FT-IR (neat, cm^{-1}): 2921 (m), 1990 (w), 1561 (w), 1433 (m), 1322 (m), 1196 (m), 1034 (s), 1010 (s), 737 (s).

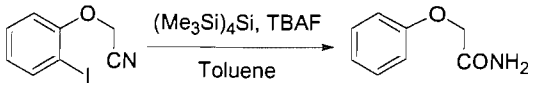
^{1}H NMR δ (300 MHz, $CDCl_3$): 7.85 (1H, d, J = 7.6 Hz, C**H**$_{AR}$), 7.37 (1H, t, J = 7.6 Hz, C**H**$_{AR}$), 6.99 (1H, d, J = 8.0 Hz, C**H**$_{AR}$), 6.88 (1H, t, J = 7.6 Hz, C**H**$_{AR}$), 4.83 (2H, s, C**H**$_2$).

^{13}C NMR δ (75 MHz, $CDCl_3$): 155.4 (**C**$_{AR}$O), 140.2 (**C**H$_{AR}$), 129.8 (**C**H$_{AR}$), 125.2 (**C**H$_{AR}$), 114.7 (**C**N), 113.7 (**C**H$_{AR}$), 86.7 (**C**I), 54.8 (**C**H$_2$CN).

LRMS(CI) 277 ([M+NH_4]$^+$, 18%), 259 (M^+, 100%), 149 (47%), 134(62%), 109 (29%), 92 (24%), 81 (6%), 63 (10%) amu.

HRMS(EI) found M: 258.94972 calculated 258.94942.

2-Phenoxy-acetamide (353)[80]



mw = 151 g/mol

$C_8H_9O_2N$

CAS = 621-88-5

To a solution of **352** (0.500 g, 1.93 mmol) in toluene (40 mL) was added tetrakistrimethylsilylsilane (0.929 g, 2.89 mmol) and tetrabutylammonium fluoride (5.79 mL of a 1M solution in THF, 5.79 mmol). The mixture was stirred at 100 °C for 16 hours then cooled to room temperature. H_2O (30 mL) was added and the aqueous phase was separated and extracted with ether (3 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, ether/petrol, 5/95) afforded the title compound **353** (0.250 g, 1.66 mmol, 86 %) as a yellow solid.

Data for **353** were consistent with literature values.

MP 98-99 °C (petrol/ether) lit[81] 102-104 °C (AcOEt/Hexane)

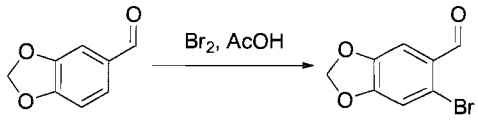
FT-IR (neat, cm^{-1}): 3304 (br), 2921 (m), 1677 (s), 1587 (s), 1493 (s), 1237 (s), 1058 (w), 755 (s), 689 (m).

^{1}H NMR δ (300 MHz, $CDCl_3$): 7.25-7.10 (2H, m, 2 x C**H**$_{AR}$), 6.91 (1H, t, J = 7.3 Hz, C**H**$_{AR}$), 6.84-6.75 (2H, m, 2 x C**H**$_{AR}$), 6.55 (1H, s, N**H**H), 6.17 (1H, s, NH**H**), 4.41 (2H, s, C**H**$_2$).

^{13}C NMR δ (75 MHz, $CDCl_3$): 171.7 (**C**O), 157.1 (**C**$_{AR}$O), 129.8 (2 x **C**H$_{AR}$), 122.2 (**C**H$_{AR}$), 114.6 (2 x **C**H$_{AR}$), 67.0 (**C**H$_2$).

LRMS(CI) 169 ($[M+NH_4]^+$, 100%), 152 ($[MH]^+$, 94%), 133 (8%), 94 (5%), 77 (5%), 60 (11%) amu.

6-Bromo-benzo[1,3]dioxole-5-carbaldehyde (264)[82]



mw = 229 g/mol

$C_8H_5O_3Br$

To a stirred solution of piperonal (3.00 g, 20.0 mmol) in glacial acetic acid (6 mL) at 0 °C was added bromine (1.23 mL, 24.0 mmol), dropwise over 30 minutes. After 2 hours at room temperature, the reaction mixture was partitioned between ethyl acetate (10 mL) and water (15 mL). The organic phase was separated, washed with $NaHSO_3$ (20 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure. Purification by column chromatography (silica gel, ether/ petrol 10/90) afforded 6-bromopiperonal (2.01 g, 8.73mmol, 44 %) as a pale yellow solid.

Data for **264** were consistent with literature values.

MP 128-129 °C (petrol) lit[82] 131-132 °C (aq ethanol)

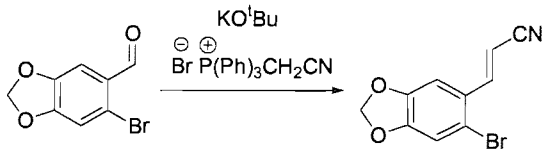
FT-IR 2860 (w), 1677 (s), 1611 (m), 1488 (s), 1408 (m), 1261 (m), 1110 (s), 1034 (m), 925 (s), 835 (m).

^{1}H NMR δ (300 MHz, $CDCl_3$): 10.11 (1H, s, C**H**O), 7.28 (1H, s, C$\mathbf{H}_{AR}$), 6.96 (1H, s, C$\mathbf{H}_{AR}$), 6.01 (2H, s, OC$\mathbf{H}_2$O).

^{13}C NMR δ (75 MHz, $CDCl_3$): 190.3 (**C**O), 153.3 (**C**$_{AR}$), 148.1 (**C**$_{AR}$), 128.0 (**C**$_{AR}$), 121.5 (**C**$_{AR}$), 113.2 (**C**H$_{AR}$), 108.1 (**C**H$_{AR}$), 102.7 (O**C**H$_2$O).

LRMS(CI) 230 ([M^{81}Br]$^+$, 70%), 228 ([M^{79}Br]$^+$, 100%), 201 ([M(^{81}Br)-CHO]$^+$, 28%), 199 ([M(^{79}Br)-CHO]$^+$, 34%), 183 (8%), 143 (24%), 120 (20%), 90 (16%), 62 (74%) amu.

(*E*)-3-(6-Bromo-benzo[1,3]dioxol-5-yl)-acrylonitrile (365)



mw = 252 g/mol

$C_{10}H_6O_2BrN$

Phosphonium bromide (7.34 g, 19.2 mmol) was suspended in THF (133 mL) and cooled at 0 °C. Potassium terbutoxide (2.156 g, 19.2 mmol) was added over 5 minutes and the mixture was allowed to warm to room temperature over 40 minutes. After re-cooling to 0 °C, the aldehyde (4.0 g, 17.4 mmol) was added as a solution in THF (45 mL). After 16 hours the reaction mixture was filtered through celite and concentrated *in vacuo*. Purification by column chromatography (silica gel, ether/petrol 10/90) gave **365** (2.29 g, 9.08 mmol, 52%) as a white solid.

MP 79-81 °C

FT-IR (neat, cm^{-1}): 2924 (m), 2358 (w), 2220 (s), 1613 (m), 1502 (s), 1484 (s), 1414 (m), 1252 (s), 1125 (m), 1035 (s), 959 (m), 922 (m).

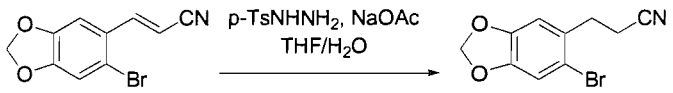
^{1}H NMR δ (300 MHz, $CDCl_3$): 7.72 (1H, d, J = 16.4 Hz, C**H**$_{Alcene}$), 7.07 (1H, s, C**H**$_{AR}$), 6.97 (1H, s, C**H**$_{AR}$), 6.05 (2H, s, OC**H**$_2$O), 5.68 (1H, d, J = 16.4 Hz, C**H**$_{Alcene}$).

^{13}C NMR δ (75 MHz, $CDCl_3$): 150.8 (**C**$_{AR}$), 148.6 (**C**H$_{AR}$), 148.1 (**C**$_{AR}$), 126.7 (**C**$_{AR}$), 117.9 (**C**$_{AR}$), 117.6 (**C**$_{AR}$), 113.2 (**C**H$_{AR}$), 105.5 (**C**H$_{AR}$), 102.5 (O**C**H$_2$O), 96.6 (**C**Br).

LRMS(CI) 253 ([M^{81}Br]$^+$, 96%), 251 ([M^{79}Br]$^+$, 100%), 172 ([M-Br]$^+$, 56%), 114 (60%), 87 (43%), 63 (30%) amu.

HRMS(CI) Found M: 251.9658; $C_{10}H_6O_2Br_1N_1$ requires 251.9655.

3-(6-Bromo-benzo[1,3]dioxol-5-yl)-propionitrile (350)[83]



mw = 254 g/mol

$C_{10}H_8O_2BrN$

CAS = 27452-03-5

A rapidly stirred solution of alkene **365** (0.264 g, 1.047 mmol), *para*-toluenesulfonohydrazide (1.175 g, 9.428 mmol) and sodium acetate (0.773 g, 9.428 mmol) in THF (6.5 mL) and water (6.5 mL) was heated at reflux for 16 hours. On cooling to ambient temperature, potassium carbonate (2.00 g) was added. After 2 hours the reaction mixture was diluted with water (20 mL) and extracted with ether (3 x 15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to a cream solid. Purification by column chromatography (5 % ether in petrol) gave the title compound **350** as a white solid (0.239 g, 0.094 mmol, 90 %).

Data for **350** were consistent with literature values.

MP 81-82 °C (ethanol) lit[83] 79-81 °C (ethanol)

FT-IR (neat, cm^{-1}): 2906 (br), 2245 (w), 2215 (w), 1502 (m), 1476 (s), 1410 (w), 1234 (s), 1158 (w), 1116 (m), 1037 (s), 930 (m).

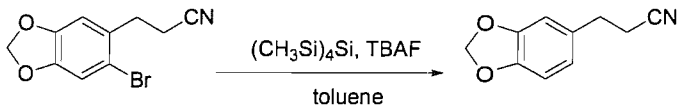
^{1}H NMR δ (300 MHz, $CDCl_3$): 7.02 (1H, s, C**H**$_{AR}$), 6.79 (1H, s, C**H**$_{AR}$), 5.99 (2H, s, OC**H**$_2$O), 3.00 (2H, app t, J = 7.1 Hz, C**H**H), 2.63 (2H, app t, J = 7.1 Hz, CH**H**).

^{13}C NMR δ (75 MHz, $CDCl_3$): 148.6 ($\mathbf{C}_{AR}O$), 147.8 ($\mathbf{C}_{AR}O$), 130.1 ($\mathbf{C}_{AR}$), 118.8 ($\mathbf{C}_{AR}$ or **C**N), 114.3 ($\mathbf{C}_{AR}$ or **C**N), 113.0 ($\mathbf{C}H_{AR}$), 110.3 ($\mathbf{C}H_{AR}$), 101.9 ($O\mathbf{C}H_2O$), 32.0 ($\mathbf{C}H_2$), 17.7 ($\mathbf{C}H_2$).

LRMS(CI) 273 ($[M^{81}(Br)+NH_4]^+$, 14%), 271 ($[M^{79}(Br)+NH_4]^+$, 14%), 255 ($[M^{81}Br]^+$, 84%), 253 ($[M^{79}Br]^+$, 86%), 213 (100%), 175 ($[M\text{-}Br)]^+$, 52%), 157 (6%), 135 (4%), 116 (8%), 76 (18%) amu.

HRMS(CI) Found M: 252.9735; $C_{10}H_8NO_2{}^{79}Br$ requires 252.9738.

3-Benzo[1,3]dioxol-5-yl-propionamide (351)[84]



mw = 175 g/mol

$C_{10}H_9O_2N$

CAS = 5703-61-7

To a solution of nitrile **350** (0.230 g, 0.905 mmol) in toluene (11 mL), was added tetrakistrimethylsilylsilane (0.581 g, 1.81 mmol) and tetrabutylammonium fluoride (3.62 mL of a 1M solution in THF, 3.62 mmol) was added. The mixture was stirred at 100 °C for 16 hours then cooled at room temperature. H_2O (30 mL) was added and the aqueous phase was separated and extracted with ether (3 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, ether/petrol, 5/95) afforded the title compound **351** (0.139 g, 0.724 mmol, 80 %) as a colourless oil.

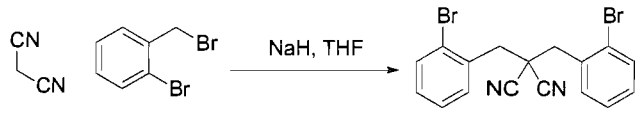
Data for **351** were consistent with literature values.

FT-IR (neat, cm^{-1}): 3583 (br), 2950 (s), 2931 (s), 2793 (m), 2245 (w), 1488 (m), 1441 (m), 1370 (w), 1247 (s), 1181 (m), 1086 (w), 1034 (m), 930 (m).

^{1}H NMR δ (300 MHz, $CDCl_3$): 6.69 (1H, d, J = 7.9 Hz, C**H**$_{Ar}$), 6.62 (1H, s, C**H**$_{AR}$), 6.61 (1H, d, J = 7.9 Hz, C**H**$_{AR}$), 5.86 (2H, s, O**CH$_2$**O), 2.79 (2H, app t, J = 7.5 Hz, C**HH**), 2.49 (2H, app t, J = 7.5 Hz, C**HH**).

LRMS(CI) 193 (M^+, 100%), 175 (56%), 135 (70%), 105 (6%), 77 (5%) amu.

2,2-Bis-(2-bromo-benzyl)-malononitrile (366)



mw = 324 g/mol

$C_{17}H_{12}BrN_2$

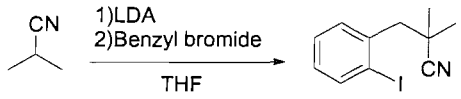
To a solution of malononitrile (1.00 g, 15.14 mmol) in THF (60 mL) was added NaH (0.789 g, 33.30 mmol) at 0 °C under nitrogen. After 30 minutes bromobenzyl bromide (8.323 g, 33.30 mmol) was added. The reaction mixture was allowed to warm to room temperature, stirred for 16 hours then partitioned between ether (30 mL) and water (50 mL). The organic phases were separated, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (10/90 ether/petrol) gave title compound **366** (3.531 g, 10.89 mmol, 72%) as a white powder.

FT-IR (neat, cm^{-1}): 3059 (w), 2993 (w), 2324 (w), 1570 (w), 1471 (s), 1439 (s), 1045 (s), 1021 (m), 755 (s), 724 (s).

^{1}H NMR δ (300 MHz, $CDCl_3$): 7.52 (2H, dd, J = 7.9, 1.1 Hz, 2 x C**H**$_{AR}$), 7.47 (2H, dd, J = 7.5, 1.5 Hz, 2 x C**H**$_{AR}$), 7.25 (2H, td, 7.5, 1.1 Hz, 2 x C**H**$_{AR}$), 7.11 (2H, td, J = 7.9, 1.5 Hz, 2 x C**H**$_{AR}$), 3.47 (4H, s, 2 x C**H$_2$**).

^{13}C NMR δ (75 MHz, $CDCl_3$): 133.6 (2 x CH_{AR}), 131.9 (2 x C_{AR}), 131.8 (2 x CH_{AR}), 130.5 (2 x CH_{AR}), 128.1 (2 x CH_{AR}), 126.0 (2 x C_{AR}), 114.7 (2 x CN), 41.4 (2 x CH_2), 39.4 (CCN).

3-(2-Iodo-phenyl)-2,2-dimethyl-propionitrile (354)



mw = 285 g/mol

$C_{11}H_{12}NI$

A solution of the carbonitrile (1.00 g, 14.47 mmol) in THF (4.6 mL) was added to LDA, prepared from diisopropylamine (1.75 g, 17.36 mmol, 0.024 mL) and ^{t}BuLi (9.65 mL, 17.36 mmol) in THF (61 mL) at –78 °C. After one hour, the 2-iodobenzyl bromide (7.30 g, 24.59 mmol) was added and the reaction mixture was stirred at room temperature. H_2O (30 mL) was added and the aqueous phase was separated and extracted with ether (3 x 20 mL). The organic phases were combined and then washed with brine (40 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, ether/petrol, 10/90) gave the title compound **354** (3.79 g, 13.29 mmol, 92 %) as a white powder.

MP 87-89 °C

FT-IR (neat, cm^{-1}): 2979 (w), 2329 (m), 2020 (w), 1465 (m), 1012 (m), 757 (m).

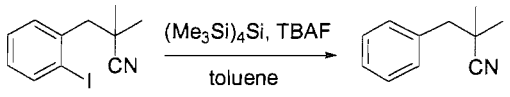
^{1}H NMR δ (300 MHz, $CDCl_3$): 7.81 (1H, dd, J = 7.9, 1.1 Hz, C**H**$_{AR}$), 7.42 (1H, dd, J = 7.5, 1.5 Hz, C**H**$_{AR}$), 7.30 (1H, td, J = 7.5, 1.1 Hz, C**H**$_{AR}$), 6.90 (1H, td, J = 7.9, 1.5 Hz, C**H**$_{AR}$), 3.01 (2H, s, C**H**$_2$), 1.36 (6H, s, 2 x C**H**$_3$).

^{13}C NMR δ (75 MHz, $CDCl_3$): 141.8 (**C**H_{AR}), 140.9 (**C**), 132.6 (**C**H_{AR}), 130.9 (**C**H_{AR}), 130.3 (**C**H_{AR}), 126.5 (**C**N), 104.5 (**C**), 50.7 (**C**H_2), 36.2 (**C**CN), 28.5 (2 x **C**H_3).

LRMS(EI) 285 (M^+, 88 %), 217 (100 %), 143 (12 %), 115 (34 %), 90 (78 %), 77 (12 %), 63 (40 %) amu.

HRMS(I) Found M: 285.0009; $C_{11}H_{12}N_1I_1$ requires 285.0014.

2,2-Dimethyl-3-phenyl-propionitrile (355)[85]



mw = 159 g/mol

$C_{11}H_{13}N$

To a solution of nitrile **354** (1.00 g, 3.50 mmol) in toluene (73 mL) were added tetrakistrimethylsilylsilane (2.25 g, 7.01 mmol) and the tetrabutylammonium fluoride (14.0 mL of a 1M solution in THF, 14.0 mmol). The mixture was stirred at 100 °C for 16 hours then cooled to room temperature. H_2O (30 mL) was added and the aqueous phase extracted with ether (3 x 20 mL). The organic phases were combined, dried ($MgSO_4$) and evaporated *in vacuo*. Purification by column chromatography (silica gel, ether/petrol, 5/95) afforded the title compound **355** (0.496 g, 3.12 mmol, 89 %) as a white solid.

Data for **355** were consistent with literature values.

MP 52-53 °C lit[85] 57 °C

FT-IR (neat, cm^{-1}): 2975 (w), 2230 (w), 1979 (w), 1716 (w), 1602 (w), 1494 (w), 1449 (w), 1369 (w), 1262 (w), 1193 (w), 1071 (w), 1031 (w), 906 (w), 760 (s).

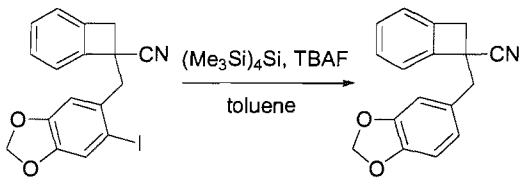
^{1}H NMR δ (300 MHz, $CDCl_3$): 7.40-7.20 (5H, m, 5 x CH_{AR}), 2.90 (2H, s, CH_2), 1.30 (6H, s, 2 x CH_3).

^{13}C NMR δ (75 MHz, $CDCl_3$): 135.6 (**C**), 130.2 (2 x **C**H_{AR}), 128.3 (2 x **C**H_{AR}), 127.3 (**C**H_{AR}), 124.7 (**C**), 46.6 (**C**H_2), 33.4 (**C**CH_3), 26.5 (2 x **C**H_3).

LRMS(CI) 177 ([M+NH_4]$^+$, 94 %), 159 (M^+, 38 %), 133 (14 %), 108 (35 %), 91 (100 %), 65 (18 %) amu.

HRMS(CI) Found M: 159.1049; $C_{11}H_{13}N_1$ requires 159.1048.

7-Benzo[1,3]dioxol-5-ylmethyl-bicyclo[4.2.0]octa-1,3,5-triene-7-carbonitrile (361)



mw = 263 g/mol

$C_{17}H_{13}O_2N$

To a solution of nitrile **317d** (0.8 g, 2.05 mmol) in toluene (43 mL) were added tetrakistrimethylsilylsilane (1.32 g, 4.11 mmol) and tetrabutylammonium fluoride (8.22 mL of a 1M solution in THF, 8.22 mmol). The mixture was stirred at 100 °C for 16 hours then cooled to room temperature. H_2O (30 mL) was added and the aqueous phase were separated and extracted with ether (3 x 20 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, ether/petrol, 5/95) afforded the title compound **361** (0.492 g, 1.87 mmol, 91 %) as a pale orange oil.

^{1}H NMR δ (300 MHz, $CDCl_3$): 7.33-7.20 (2H, m, 2 x C**H**$_{AR}$), 7.13 (1H, d, J = 7.3 Hz, C**H**$_{AR}$), 6.97 (1H, d, J = 7.3 Hz, C**H**$_{AR}$), 6.80 (1H, d, J = 1.5 Hz, C**H**$_{AR}$), 6.78 (1H, d, J = 8.0 Hz, C**H**$_{AR}$), 6.74 (1H, dd, J = 8.0, 1.5 Hz, C**H**$_{AR}$), 5.94 (1H, d, J = 1.5 Hz, OC**H**HO), 5.93 (1H, d, J = 1.5 Hz, OCH**H**O), 3.70 (1H,

d, J = 14.3 Hz, C**H**H), 3.38 (1H, d, J = 14.3 Hz, CH**H**), 3.20 (1H, d, J = 13.9 Hz, C**H**H), 3.03 (1H, d, J = 13.9 Hz, CH**H**).

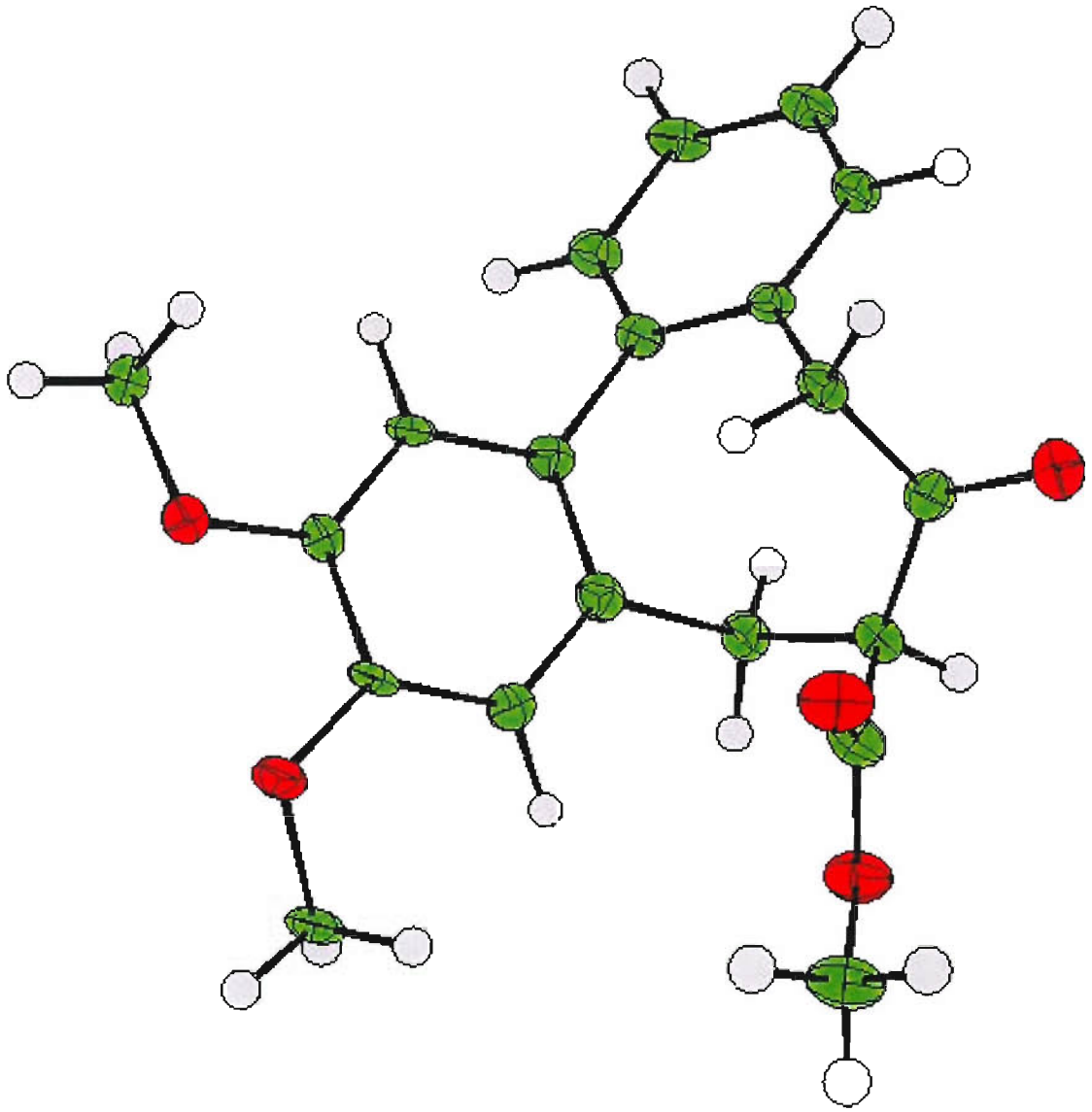
^{13}C NMR δ (75 MHz, $CDCl_3$): 147.7 (**C**), 147.0 (**C**), 143.3 (**C**), 141.1 (**C**), 129.7 (**C**H_{AR}), 129.6 (**C**), 128.0 (**C**H_{AR}), 123.9 (**C**H_{AR}), 123.0 (**C**H_{AR}), 122.2 (**C**H_{AR}), 121.5 (**C**), 110.0 (**C**H_{AR}), 108.3 (**C**H_{AR}), 101.1 (O**C**H_2O), 43.9 (**C**CN), 42.8 (**C**H_2), 42.7 (**C**H_2).

LRMS(CI) 281 ($[M+NH_4]^+$, 96 %), 263 (M^+, 100 %), 248 (10 %), 204 (12 %), 190 (20 %), 176 (10 %), 152 (8 %), 135 (18 %) amu.

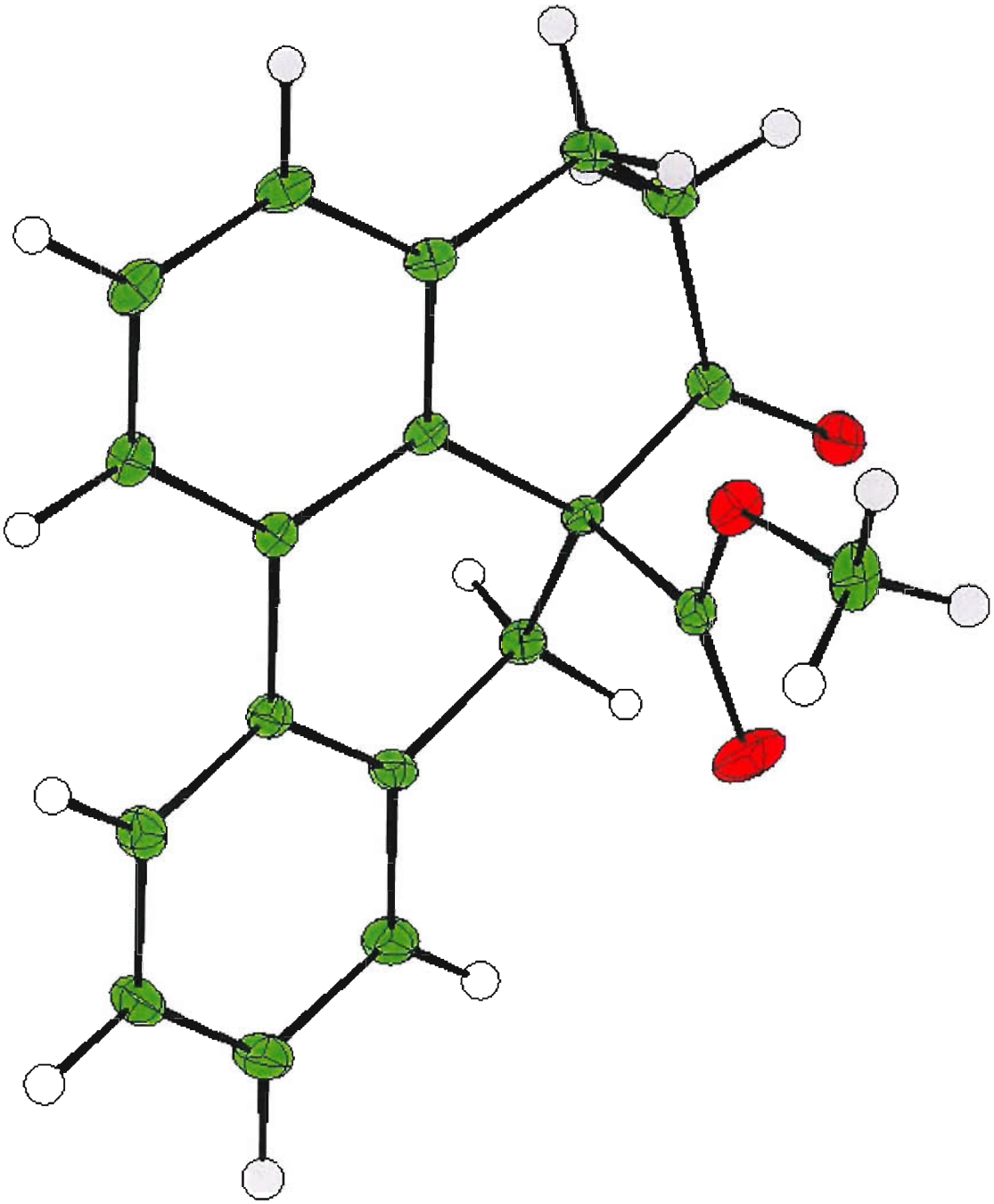
HRMS(CI) Found M: 263.09436; $C_{17}H_{13}NO_3$ requires 263.09463.

Appendix

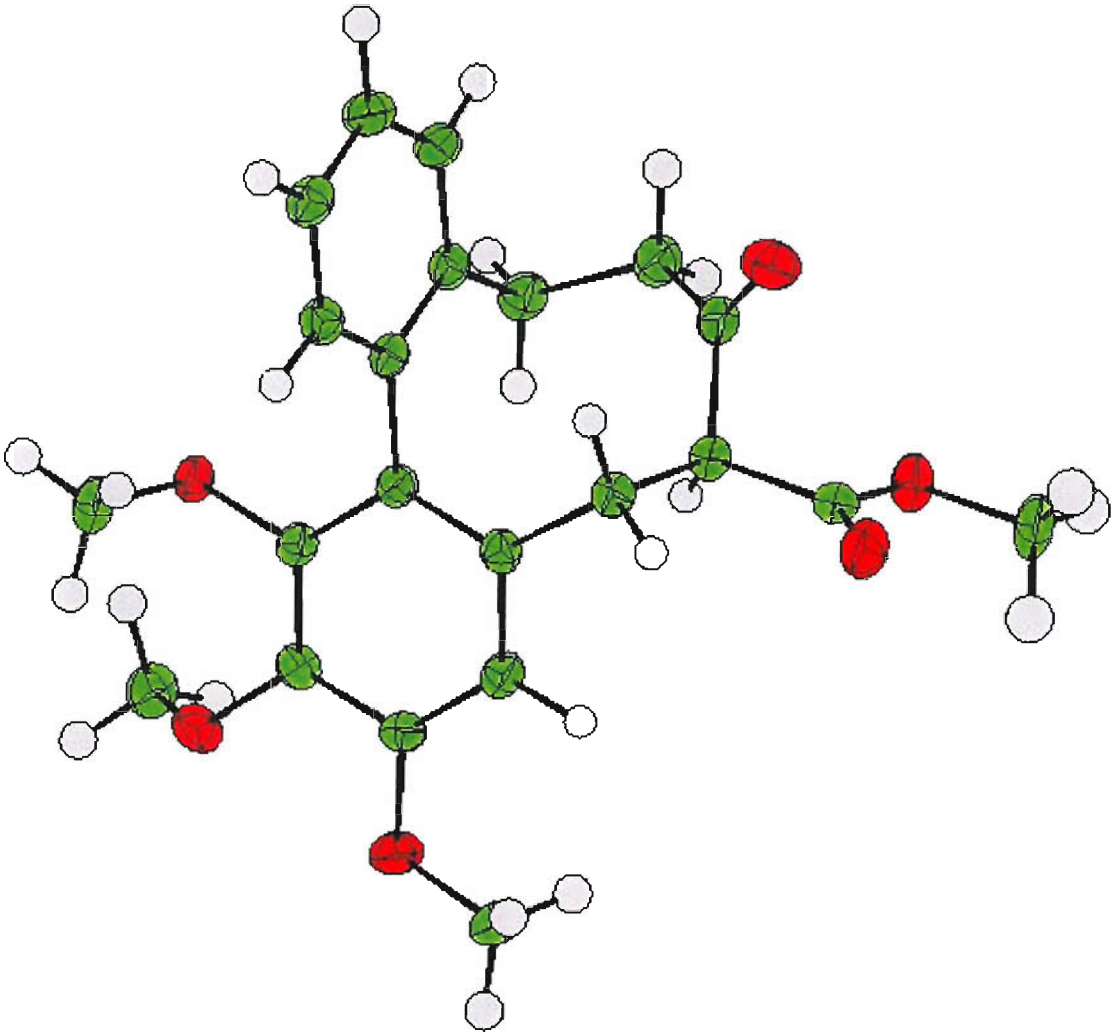
2,3-Dimethoxy-7-oxo-5,6,7,8-tetrahydrodibenzo[a,c]cyclooctene-6-carboxylic acid methyl ester (301b)



6-Oxo-5,6-dihydro-4*H*,7*H*-benzo[*de*]anthracene-6a-carboxylic acid methyl ester (308e)



7-Oxo-6,7,8,9-tetrahydro-5*H*-dibenzo[*a*,*c*]cyclononene-6-carboxylic acid methyl ester (308c)



Chapter 7 References

Chapter 7 References

[1] A. Studer and M. Bossart, *Tetrahedron* **2001**, *57*, 9649.
[2] H. Wieland, *Chem. Ber.* **1911**, *44*, 2550.
[3] W. H. Urry and M. S. Kharasch, *J. Am. Chem. Soc.* **1944**, *66*, 1438.
[4] R. Leardini, D. Nanni, G. F. Pedulli, A. Tundo, G. Zanardi, E. Foresti and P. Palmieri, *J. Am. Chem. Soc.* **1989**, *111*, 7723.
[5] K. A. Parker, D. M. Spero and K. C. Inman, *Tetrahedron Lett.* **1986**, *27*, 2833.
[6] A. N. Abeywickrema and A. L. J. Beckwith, *J. Org. Chem.* **1987**, *52*, 4072.
[7] H. Ishibashi, K. Ohata, M. Niihara, T. Sato and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1* **2000**, 547.
[8] H. Ishibashi, T. Kobayashi, S. Nakashima and O. Tamura, *J. Org. Chem.* **2000**, *65*, 9022.
[9] H. Ishibashi, T. S. So, K. Okochi, T. Sato, N. Nakamura, H. Nakatani and M. Ikeda, *J. Org. Chem.* **1991**, *56*, 95.
[10] N. S. Narasimhan and I. S. Aidhen, *Tetrahedron Lett.* **1988**, *29*, 2987.
[11] S. Winstein, R. Heck, S. Lapporte and R. Baird, *Experientia* **1956**, *12*, 138.
[12] M. Julia and J.-C. Chottard, *Bull. Soc. Chim. Fr.* **1968**, 3691.
[13] H. Senboku, H. Hasegawa, K. Orito and M. Tokuda, *Tetrahedron Lett.* **2000**, *41*, 5699.
[14] H. Ishibashi, N. Nakamura, K. Ito, S. Kitayama and M. Ikeda, *Heterocycles* **1990**, *31*, 1781.
[15] S.-F. Wang, C.-P. Chuang, J.-H. Lee and S.-T. Liu, *Tetrahedron* **1999**, *55*, 2273.
[16] Y.-L. Wu, C.-P. Chuang and P.-Y. Lin, *Tetrahedron* **2000**, *56*, 6209.
[17] J. Aubé, X. Peng, Y. Wang and F. Takusagawa, *J. Am. Chem. Soc.* **1992**, *114*, 5466.
[18] D. S. Black, G. L. Edwards and S. M. Laaman, *Tetrahedron Lett.* **1998**, *39*, 5853.
[19] H. Amii, S. Kondo and K. Uneyama, *J. Chem. Soc., Chem. Commun.* **1998**, 1845.
[20] S. P. Green and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1* **1998**, 193.
[21] P. C. Montevecchi and M. L. Navacchia, *J. Org. Chem.* **1998**, *63*, 537.
[22] W. R. Bowman, E. Mann and J. Parr, *J. Chem. Soc., Perkin Trans. 1* **2000**, 2991.
[23] D. C. Harrowven, M. I. T. Nunn, N. A. Newman and D. R. Fenwick, *Tetrahedron Lett.* **2001**, *42*, 961.
[24] D. C. Harrowven, B. J. Sutton and S. Coulton, *Tetrahedron Lett.* **2001**, *42*, 9061.
[25] D. C. Harrowven, B. J. Sutton and S. Coulton, *Org. Biomol. Chem.* **2003**, *1*, 4047.
[26] J. W. Wilt and C. F. Dockus, *J. Am. Chem. Soc.* **1970**, *92*, 5813.
[27] J. J. Köhler and W. N. Speckamp, *Tetrahedron Lett.* **1977**, 631.
[28] J. J. Köhler and W. N. Speckamp, *Tetrahedron Lett.* **1977**, 635.
[29] D. L. J. Clive and T. L. B. Boivin, *J. Org. Chem.* **1989**, *54*, 1997.
[30] M. L. E. N. da Mata, W. B. Motherwell and F. Ujjainwalla, *Tetrahedron Lett.* **1997**, *38*, 137.
[31] W. B. Motherwell and A. M. K. Pennell, *J. Chem. Soc., Chem. Commun.* **1991**, 877.
[32] L. Capella, P. C. Montevecchi and D. Nanni, *J. Org. Chem.* **1994**, *59*, 3368.
[33] D. C. Harrowven and R. Browne, *Tetrahedron Lett.* **1995**, *36*, 2861.
[34] D. C. Harrowven, *Tetrahedron Lett.* **1993**, *34*, 5653.

[35] A. Ryokawa and H. Togo, *Tetrahedron* **2001**, *57*, 5915.
[36] A. M. Rosa, A. M. Lobo, P. S. Branco, S. Prabhakar and A. M. D. L. Pereira, *Tetrahedron* **1997**, *53*, 269.
[37] A. M. Rosa, A. M. Lobo, P. S. Branco, S. Prabhakar and M. Sá-da-costa, *Tetrahedron* **1997**, *53*, 299.
[38] E. Lee, H. S. Whang and C. K. Chung, *Tetrahedron Lett.* **1995**, *36*, 913.
[39] D. Crich and J.-T. Hwang, *J. Org. Chem.* **1998**, *63*, 2765.
[40] W. R. Bowman, H. Heaney and B. M. Jordan, *Tetrahedron* **1991**, *47*, 10119.
[41] F. Aldabbagh and W. R. Bowman, *Tetrahedron Lett.* **1997**, *38*, 3793.
[42] F. Aldabbagh, W. R. Bowman and E. Mann, *Tetrahedron Lett.* **1997**, *38*, 7937.
[43] L. Benati, P. Spagnolo, A. Tundo and G. Zanardi, *J. Chem. Soc., Chem. Commun.* **1979**, 141.
[44] A. M. Rosa, A. M. Lobo, P. S. Branco and S. Prabhakar, *Tetrahedron* **1997**, *53*, 285.
[45] K. Wakabayashi, H. Yorimitsu, H. Shinokubo and K. Oshima, *Org. Lett.* **2000**, *2*, 1899.
[46] D. L. J. Clive and S. Kang, *Tetrahedron Lett.* **2000**, *41*, 1315.
[47] D. L. J. Clive and S. Kang, *J. Org. Chem.* **2001**, *66*, 6083.
[48] B. Alcaide and A. Rodríguez-Vicente, *Tetrahedron Lett.* **1998**, *39*, 6589.
[49] S. Amrein, M. Bossart, T. Vasella and A. Studer, *J. Org. Chem.* **2000**, *65*, 4281.
[50] A. Studer, M. Bossart and T. Vasella, *Org. Lett.* **2000**, *2*, 985.
[51] W. B. Motherwell and S. Vázquez, *Tetrahedron Lett.* **2000**, *41*, 9667.
[52] A. Studer and M. Bossart, *J. Chem. Soc., Chem. Commun.* **1998**, 2127.
[53] M. Bossart, R. Fässler, J. Schoenberger and A. Studer, *Eur. J. Org. Chem.* **2002**, 2742.
[54] S. Guidotti, L. R.;, D. Nanni, P. Pareschi and G. Zanardi, *Tetrahedron Lett.* **1995**, *36*, 451.
[55] R. Leardini, H. McNab and D. Nanni, *Tetrahedron* **1995**, *51*, 12143.
[56] R. Loven and W. N. Speckamp, *Tetrahedron Lett.* **1972**, 1567.
[57] D. C. Harrowven, M. I. T. Nunn, N. J. Blumire and D. R. Fenwick, *Tetrahedron Lett.* **2000**, *41*, 6681.
[58] D. C. Harrowven and M. I. T. Nunn, *Tetrahedron Lett.* **1998**, *39*, 5875.
[59] R. K. Freidlina and A. B. Terent'ev, *Free Radical Chemistry* **1980**, Ed.; Heyden: London.
[60] Y. Ikeya, H. Taguchi, I. Yosioka and H. Kobayashi, *Chem. Pharm. Bull.* **1979**, *27*, 1383.
[61] M. Tanaka, C. Mukaiyama, H. Mitsuhashi and T. Wakamatsu, *Tetrahedron Lett.* **1992**, *33*, 4165.
[62] M. Taafrout, F. Rouessac and J.-P. Robin, *Tetrahedron Lett.* **1983**, *24*, 2983.
[63] M. D. Drew, N. J. Lawrence, D. Fontaine and L. Sehkri, *Synlett* **1997**, 989.
[64] I. Shibata, T. Yoshiba, A. Baba and H. Matsuda, *Chem. Lett.* **1991**, 307.
[65] D. C. Harrowven, I. L. Guy and M. I. T. Nunn, *Chem. Commun.* **2004**, 1966.
[66] J. Cossy, L. Tresnard and D. G. Pardo, *Eur. J. Org. Chem.* **1934**, 1925.
[67] C. Arth, M. Clemens and W. Meise, *Justus Liebigs Ann. Chem.* **1994**, 259.
[68] A. S. Dey, A. Rosowski and E. J. Modest, *J. Org. Chem.* **1970**, 536.
[69] C. De Luca, A. Inesi and L. Rampazzo, *J. Chem. Soc., Perkin trans. 2* **1983**, 1821.
[70] W. Schroth and W. Treibs, *Justus Liebigs Ann. Chem.* **1961**, 214.
[71] D. F. Taber and R. E. Ruckle, *J. Am. Chem. Soc.* **1986**, 7686.
[72] D. M. Coltard and J. L. Charlton, *Can. J. Chem.* **1996**, 88.

[73] R. Olivera, R. San Martin, E. Dominguez, X. Solans, M. K. Urtiaga and M. I. Arriortua, *J. Org. Chem.* **2000**, 6398.
[74] J. D. Olszewski, M. Marshalla, M. Sabat and R. J. Sundberg, *J. Org. Chem.* **1994**, 4285.
[75] F. E. Ziegler and J. A. Schwartz, *J. Org. Chem.* **1978**, 985.
[76] E. Wenkert, E.-M. Loeser, S. N. Mahapatra, F. Schenker and E. M. Wilson, *J. Org. Chem.* **1964**, 435.
[77] M. V. Sargent, *J. Chem. Soc., Perkin Trans. 1* **1987**, 231.
[78] C. S. Swindell and W. Fan, *J. Org. Chem.* **1996**, 1109.
[79] A. Kouvarakis and H. E. Ketarinopoulos, *Syn. Comm.* **1995**, 3035.
[80] A. Khalafi-Nezhad, B. Mokhtari and M. Rad, *Tetrahedron Lett.* **2003**, 7325.
[81] S. L. Shapiro, V. A. Parrino, E. Rogow and L. Freedman, *J. Am. Chem. Soc.* **1959**, 3726.
[82] P. C. Conrad, P. L. Kwiatkowski and P. L. Fuchs, *J. Org. Chem.* **1987**, 586.
[83] M. E. Jung, P. Y.-S. Lam, M. M. Mansuri and L. M. Speltz, *J. Org. Chem.* **1985**, 1087.
[84] G. Blay, L. Cardona, B. Garcia, L. Lahoz and J. R. Pedro, *Tetrahedron* **1996**, 8611.
[85] A. Costantino, *Bull. Soc. Chim. Fr.* **1970**, 912.