Green, Clive P. (1999) Synthetic studies towards the cytotoxic marine natural product diazonamide A. PhD thesis, University of Nottingham.

Synthetic Studies towards the Cytotoxic Marine Natural Product Diazonamide A

by

Clive P. Green

A Thesis Submitted to the University of Nottingham

for the Degree of Doctor of Philosophy

December 1999

CONTENTS

DECLARATION

I declare that the substance of this thesis has not been submitted, nor is concurrently being submitted in candidature for any other degree. I also declare that the work embodied in this thesis is the result of my own investigations. Where the work of other investigators has been used, this has been fully acknowledged in the text.

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G. Pattenden

ACKNOWLEDGEMENTS

ABSTRACT

The thesis describes synthetic studies towards the marine natural product diazonamide A. This unprecedented compound was recently isolated from a colonial ascidian and displays exceptional levels of cytotoxic activity against human cancer cell lines. The Introduction includes an account of how diazonamide A was isolated and its structure determined. This is followed by a summary of the different natural products which have been isolated from ascidians, and highlights the structural similarities between these compounds and diazonamide A. The Introduction concludes with a review of structurally related natural products which concentrates on compounds containing oxazole rings or biaryl bonds.

The Results and Discussion section of the thesis details our general strategy for a synthesis of the macrocyclic aromatic core of diazonamide A. A synthesis of the two key fragments in this strategy, namely the benzofuran oxazole unit and the iodo indole unit, is then described. This is followed by the elaboration of these units towards the target macrocycle. A detailed discussion is presented throughout this section including a review of the Heck and Ullmann reactions, and methods of oxazole formation. This section culminates by describing our initial synthetic efforts on an alternative approach to the macrocyclic core of diazonamide A.

The third chapter of the thesis is the Experimental section containing full details of the preparative work completed and listing spectroscopic and analytical data for all new compounds synthesised during the study.

The thesis is concluded by a schematic account of the contemporaneous work towards a total synthesis of diazonamide A that has been conducted by four other research groups.

ABBREVIATIONS

Ac	acetyl
AIDS	aquired immunodeficiency syndrome
Ar	aryl
BINAP	2,2'*bis*-(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
Cbz	benzyloxycarbonyl
CSA	10-camphorsulfonic acid
DAST	diethylaminosulfur trifluoride
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexyl carbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPC	diethyl phosphoryl cyanide
de	diastereomeric excess
DIBAL-H	di-*iso*-butylaluminium hydride
DIPEA	di-*iso*-propylethylamine
DMA	*N, N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	ethylene glycol dimethyl ether
DMF	*N, N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
dppe	1,2-(diphenylphosphino)ethane

dppp	1,3-(diphenylphosphino)propane
EDC	1-(3-dimethylaminopropyl)-3-ethyl carbodiimide
ee	enantiomeric excess
Et	ethyl
HIV	human immunodeficiency virus
HMPA	hexamethylphosphoramide
HMTA	hexamethylphosphorous triamide
HOBt	1-hydroxybenzotriazole hydrate
HQ	hydroquinone
HRMS	high resolution mass spectrometry
HRFABMS	high resolution fast atom bombardment mass spectrometry
Im	imidazole
IR	infra red
KHMDS	potassium *bis*-(trimethylsilyl)amide
LDA	lithium di-*iso*-propylamide
LiHMDS	lithium *bis*-(trimethylsilyl)amide
Me	methyl
MOM	methoxymethyl
Ms	methanesulfonyl
NCS	*N*-chlorosuccinimide
NaHMDS	sodium *bis*-(trimethylsilyl)amide
NMP	1-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Ph	phenyl
PMB	*para*-methoxybenzyl
PPA	polyphosphoric acid
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl

PTSA	*para*-toluenesulfonic acid
Py	pyridine
PyBoP	(benzotriazol-1-yloxy-tripyrrolidino)phosphonium hexafluorophosphate
R	general substituent
RNA	ribonucleic acid
SAMP	(*S*)-(-)-1-amino-2-(methoxymethyl)pyrrolidine
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBTU	2-(1*H*-benzotriazole-1yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TC	thiophene-2-carboxylate
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	tri-*iso*-propylsilyl
tlc	thin layer chromatography
TMS	trimethylsilyl
TMEDA	*N, N, N', N'*-tetramethylethylenediamine
TMU	tetramethylurea
tol	tolyl
TPS	*tert*-butyldiphenylsilyl
Ts	*para*-toluenesulfonyl
TTFA	thallium trifluoroacetate
UV	ultraviolet

1. INTRODUCTION

1.1 Isolation and Structure Elucidation of the Diazonamides

During the past twenty-five years marine natural products chemists have discovered many biologically important secondary metabolites which are unprecedented in structure. Two outstanding examples are diazonamides A (**1**) and B (**2**). These highly unusual, cytotoxic marine natural products were described by Fenical *et al*[1] in 1991 following their investigations of the colonial ascidian *Diazona chinensis* (order Phlebobranchia),[2] which was collected from the ceilings of small caves along the Northwest coast of Siquijor Island, Philippines.

1 R_1 = H, R_2 =

2 R_1 = Br, R_2 = H
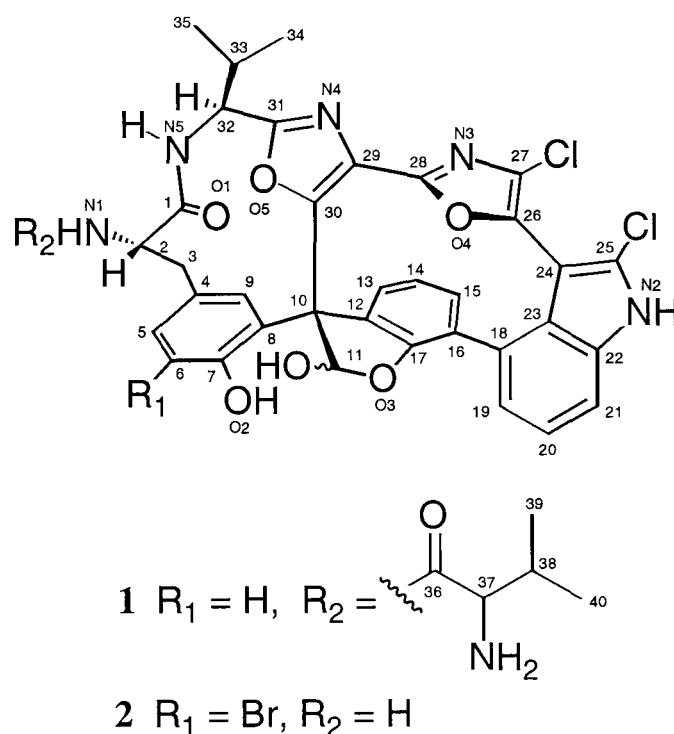
Diazonamides A (**1**) and B (**2**) are two of the structurally most attractive marine natural products isolated in recent years and they represent an entirely new class of halogenated, highly unsaturated cyclic peptides. A simplified structural representation of diazonamides A (**1**) and B (**2**) shows that the molecules contain two fused macrocycles. The northern macrocycle incorporates the peptide portion of the secondary metabolite, comprising a 3,4,5-trisubstituted-L-tyrosine residue and an L-valine residue. The southern macrocycle is particularly intriguing as it contains a variety of interesting structural features in a 3-dimensional array of heterocyclic and

aromatic rings. The centrepiece of this unusual heterocyclic network is a chiral quaternary carbon centre located at C10. This centre links a trisubstituted oxazole to a benzofuran and lies adjacent to a cyclic hemiacetal. The aforementioned trisubstituted oxazole forms part of an impressive *bis*-oxazole segment in which a second oxazole is further subtended to an indole nucleus; both the second oxazole and the indole units also incorporate chloride substituents at C27 and C25 respectively. The southern macrocyclic framework is completed by the inclusion of a biaryl bond connecting the indole to the benzofuran, which entraps the polycyclic biaryl skeleton as a single atropisomer. Diazonamide A (**1**) differs from diazonamide B (**2**) only in the substitution pattern of the northern macrocycle, containing an additional valine residue at N1, whilst lacking bromination at the C6 position of the tyrosine residue.
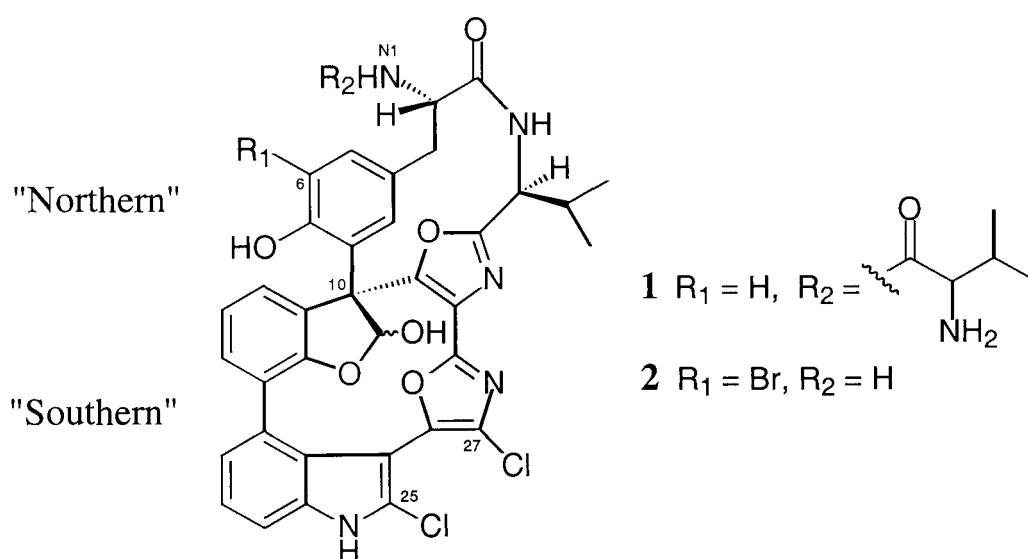
Combination of ^{1}H, ^{13}C NMR and HRFABMS techniques led to the assignment of several structural subunits in the diazonamides. However, the large number of singlet carbons and heteroatoms prevented the use of ^{1}H-^{13}C NMR correlation methods for connecting the fragments into a complete structure. The missing connectivities were established by a single-crystal X-ray diffraction analysis of the *p*-bromobenzamide derivative of diazonamide B (**3**), which was prepared by reacting diazonamide B (**2**) with *p*-bromobenzoyl chloride in pyridine.

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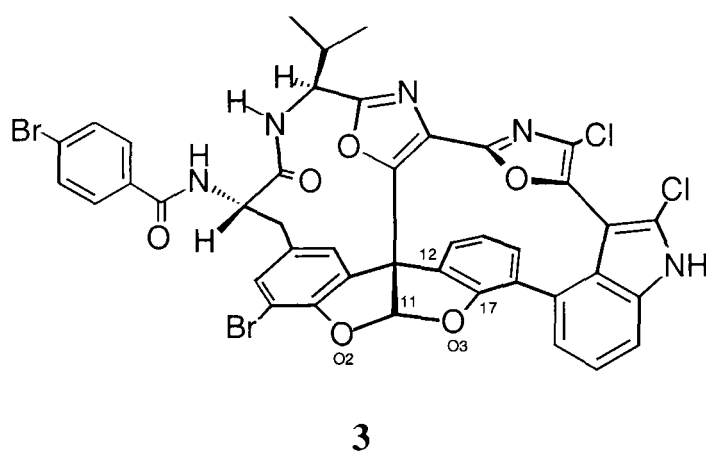
A direct assignment of the absolute stereochemistry of diazonamide B (**2**) was obtained from the crystal structure, with the exception of the stereochemistry at the C11 position. This hemiacetal centre in diazonamide B (**2**) is converted into an acetal on formation of the *p*-bromobenzamide derivative (**3**). Molecular mechanics studies of the hemiacetal (**2**) and its corresponding aldehyde tautomer indicate a small preference (~1kcal/mol) for the *R* configuration at C11 (OH down) in the hemiacetal (**2**) and a small preference (~1kcal/mol) for aldehyde conformations in which the *si* face of the aldehyde faces O3, also leading to an *R* configuration at C11. However, these calculated differences are too small to assign the stereochemistry securely at this centre and it remains unresolved. The absolute stereochemistry of the terminal valine present in diazonamide A (**1**) is also undetermined.

From the crystal structure of diazonamide B *p*-bromobenzamide (**3**) the two oxazole rings are twisted with respect to one another with a dihedral angle of 29°. The chlorooxazole and chloroindole rings have a dihedral angle of 60° and the chloro indole ring has a dihedral angle of 74° with the C12-C17 phenol. Not surprisingly, the UV spectra of diazonamides A (**1**) and B (**2**) show very little indication of their high degree of unsaturation as the strict steric requirements of the bicyclic framework forces the aromatic rings out of conjugation, preventing any significant π-orbital overlap.

Remarkable cytotoxic properties have been recorded for the diazonamides,[1] with diazonamide A (**1**) being the more active metabolite. Diazonamide A (**1**)

demonstrates potent *in vitro* activity against HCT-116 human colon carcinoma and B-16 murine melanoma cancer cell lines, with IC_{50} values of less than 15ng/ml.

1.2 Ascidian Natural Products

Ascidians represent the most highly evolved group of organisms commonly investigated by marine natural products chemists. They are often referred to as sea squirts, because many species expel streams of water through a siphon when disturbed, or as tunicates, because their body is covered by a sack-like case or tunic. By appearance, they may superficially resemble marine sponges. However, the contractions which cause a sea squirt to spray streams of water provide a means to distinguish ascidians from other marine invertebrates.

The discovery of several modified arabino nucleosides from a *Tedania* sponge by Bergmann in 1950,[3] is generally credited as marking the birth of the field of marine natural products. However, it was not until 1974 that Fenical isolated the first ascidian metabolite, geranyl hydroquinone (**4**), an antileukemic and cytotoxic agent from *Aplidium* sp.[4] The occurrence of an anticancer compound in these marine organisms provided a powerful incentive to further expand this area of research and since that time ascidians have been the source of numerous bioactive natural products.[5]
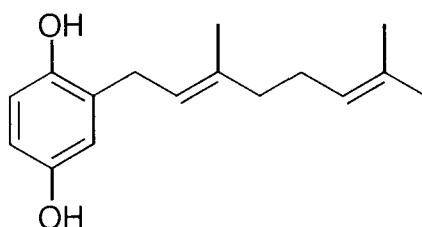
4 Geranyl hydroquinone

Seventeen years after the discovery of **4**, Fenical isolated the diazonamides A (**1**) and B (**2**),[1] which are regarded as perhaps the most unusual ascidian metabolites isolated to date. The diazonamides can be categorised structurally as nitrogen-containing peptide metabolites. Because the ascidians have demonstrated a specialised ability to

biosynthesise amino acid derivatives, this category represents the major structural class within the ascidian family. Perhaps the most significant of the peptide metabolites is the cyclic depsipeptide didemnin B (**5**), which was isolated from the tunicate *Trididemnum solidum* in 1981.[6] This was the first marine natural product to enter clinical trials as a potential anticancer agent.[7] It has also been reported to be exceedingly active as an immunosuppressive agent, in addition to inhibiting herpes simplex virus types I and II and other lethal RNA viruses.[8] Didemnin B (**5**) was first synthesised by Rinehart *et al*[9] and more recently by Jouille *et al*.[10]
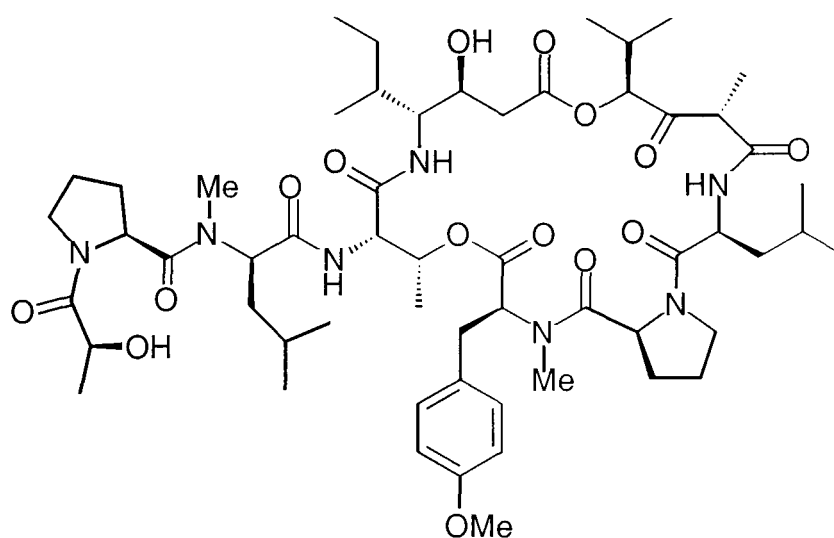
5 Didemnin B

The peptide metabolites are prolific producers of cyclic peptides which contain azole or azoline rings in their heteronuclear framework. The oxazole ring system, which is present in the diazonamides, is the least abundant of these heterocyclic units in members of this structural class. However, a 2,4-disubstituted oxazole ring has been incorporated into the cyclic hexapeptides bistatramides C (**6**) and D (**7**), which were isolated from *Lissoclinum bistratum* in 1992.[11] Bistatramide C (**6**) has been synthesised by Meyers and Aguilar,[12] the oxazole ring being prepared by oxidation of the corresponding oxazoline.[13]
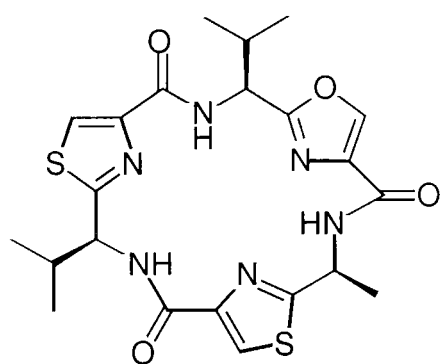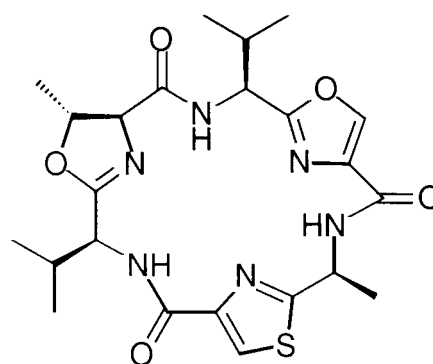
6 Bistatramide C   **7** Bistatramide D

Thiazoles and thiazolines, the sulfur analogues of oxazoles and oxazolines, along with oxazolines themselves, are extremely prevalent within this class of ascidian natural products. The lissoclinamides are one family of peptide metabolites which embrace all of these heterocyclic units. Lissoclinamide 4 (**8**) was isolated from *Lissoclinum patella* in 1989[14] and is one of a group of eight related cyclic heptapeptides which display mild cytotoxic activity. They differ only in the oxidation states of the sulfur-containing rings and the absolute stereochemistries of the amino acid counterparts. The structure of lissoclinamide 4 (**8**) was corrected six years after its isolation, following completion of the total synthesis by Boden and Pattenden.[15]
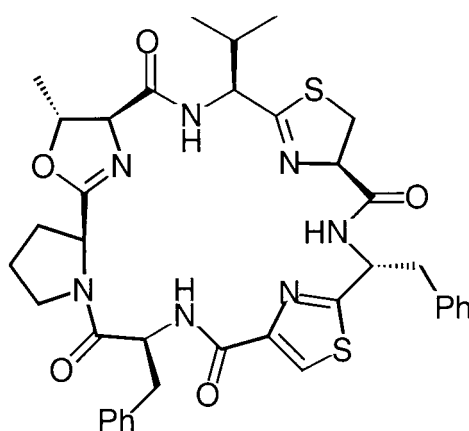
8 Lissoclinamide 4

Not all of the peptide metabolites form cyclic species. Halocyamine A (**9**) was isolated from the blood of the solitary ascidian *Halocynthia roretzi* in 1990.[16] It is an indole-containing linear tetrapeptide, composed of several amino acids which are unusual to ascidian secondary metabolites. Halocyamine A (**9**) possesses antiviral,

7

antimicrobial and cytotoxic activity.[17] Approaches towards the synthesis of halocyamine A (9) have not yet been reported.
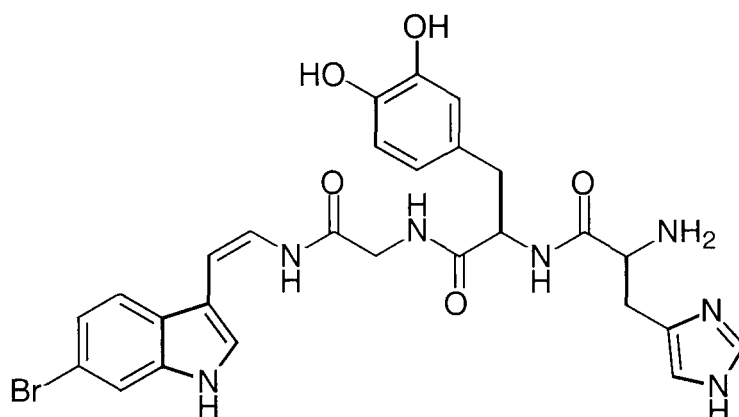
9 Halocyamine A

The remaining families of ascidian metabolites show very few direct structural similarities to the diazonamides. Several interesting tyrosine-derived metabolites called ecteinascidians were described independently by two research groups in 1990 and 1991 from the Caribbean ascidian *Ecteinascidia turbinata*.[18] The most abundant member of this class is ecteinascidin 743 (**10**), an exceedingly potent antitumor agent with a tetrahydro*iso*-quinoline core, the same as that determined for the safracins and saframycins.[19] An elegant total synthesis of ecteinascidin 743 (**10**) was reported recently by Corey *et al.*[20]
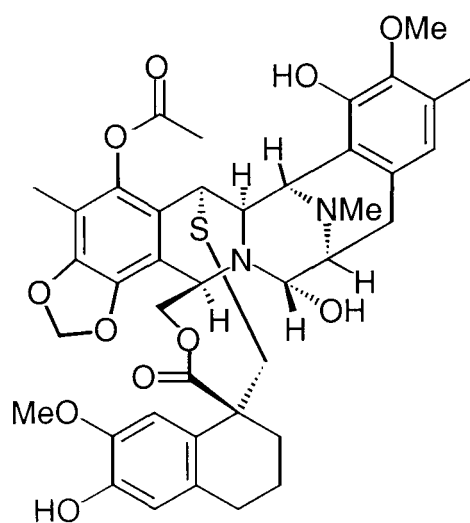
10 Ecteinascidin 743

Two unique dopamine-derived cyclic polysulfide metabolites were isolated from ascidians of the genus *Lissoclinum* in 1991.[21] Varacin (**11**) and lissoclinotoxin A (**12**) were the first examples of naturally occurring benzopentathiepins containing five contiguous sulfur atoms. Both metabolites exhibit antifungal activity, whilst varacin (**11**) is also a cytotoxic agent and lissoclinotoxin A (**12**) displays antimicrobial activity. The total synthesis of varacin (**11**) has been reported by the research groups of Danishefsky,[22] Davidson[23] and Still,[24] whilst the total synthesis of lissoclinotoxin A (**12**) has been described by Davidson *et al.*[25]
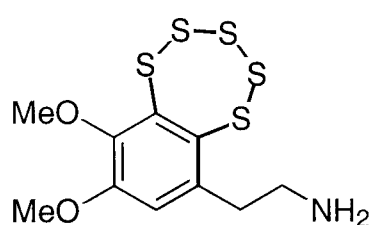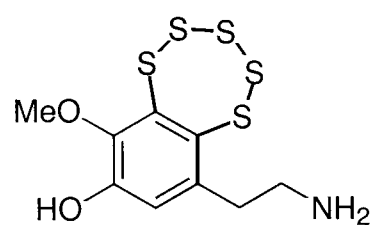
11 Varacin   **12** Lissoclinotoxin A

The ascidian *Eudistoma olivaceum* has been an extraordinarily rich source of tryptophan-derived metabolites. The eudistomins A (**13**) and C (**14**) were isolated in 1984[26] and are examples from the vast eudistomin family. All the metabolites from this class of natural product are derived from tryptophan and one other amino acid. Eudistomins A (**13**) and C (**14**) both exhibit halogenation of the indole ring and possess significant antiviral activity, making them the targets of much research within the synthetic community.[27]
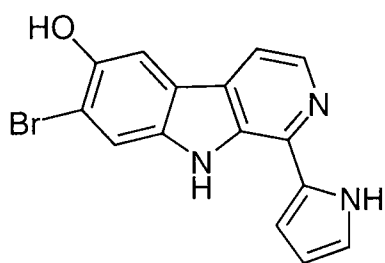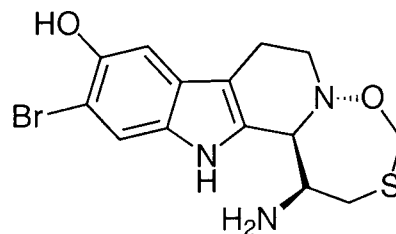
13 Eudistomin A   **14** Eudistomin C

Ascididemin (**15**) and 2-bromoleptoclinidinone (**16**), from *Leptoclinides* sp. and *Didemnum* sp. respectively, formed a new class of structurally related ascidians. the polycyclic aromatic alkaloids, when they were first isolated in the late 1980's.[28] This is perhaps now the fastest growing class of ascidian metabolites. These cytotoxic marine natural products are based on a pyrido[*k,l*]acridine skeleton and exhibit a remarkably high degree of unsaturation. Bracher has synthesised both ascididemin (**15**)[29] and 2-bromoleptoclinidinone (**16**),[30] whilst Rees *et al* have also described a synthesis of ascididemin (**15**).[31]
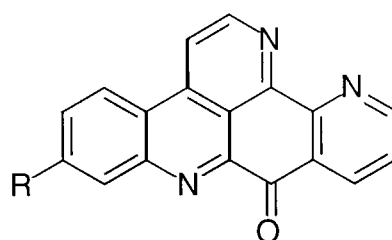
15 R = H; Ascididemin

16 R = Br; 2-bromoleptoclinidinone

Other interesting members of this class of ascidian natural products are the segolines A (**17**) and B (**18**), novel polycyclic alkaloids which were isolated from the Red Sea tunicate *Eudistoma* sp. in 1989.[32] These unique antiviral and antitumor bioactive compounds contain a substituted tetracyclic benzo-3,6-diazaphenanthroline ring system and glutarimide moiety. A total synthesis of the segolines has not yet been reported.
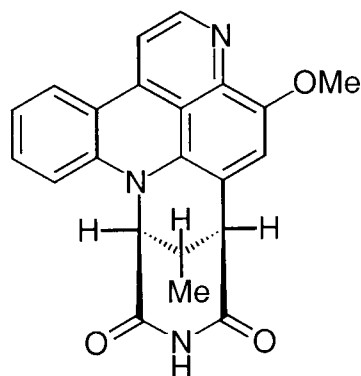
17 Segoline A
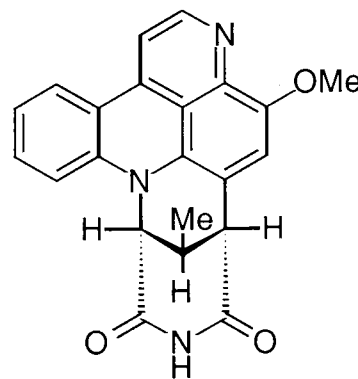
18 Segoline B

The lysine-derived metabolites are composed of three different structural types of alkaloid. The pseudodistomins A (**19**) and B (**20**), isolated from the Okinawan tunicate *Pseudodistoma kanoko* in 1987,[33] were the first piperidine alkaloids to be isolated from a marine source. The tunicate *Clavelina picta* has been the source of both quinolizidine and indolizidine alkaloids. Clavapictine A (**21**), isolated in 1991,[34] is one such quinolizidine alkaloid, whilst piclavine A (**22**), an antifungal and antimicrobial agent isolated in 1992,[35] is an example from the indolizidine alkaloids. Piclavine A (**22**) is the only lysine-derived metabolite to be synthesised, an accomplishment reported recently by Jefford *et al.*[36]
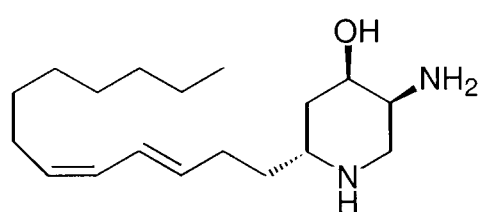
19 Pseudodistomin A
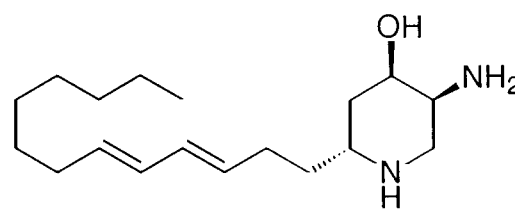
20 Pseudodistomin C
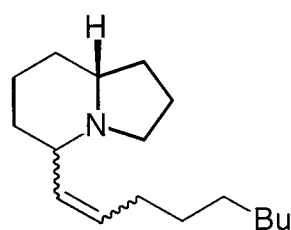
21 Clavapictine A
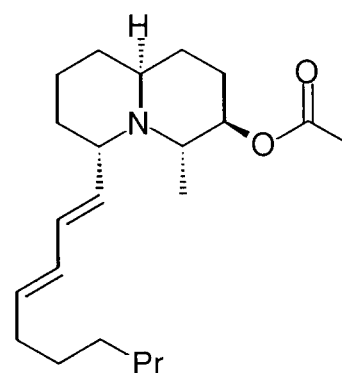
22 Piclavine A

The didemnid tunicates are a particularly rich source of ascidian metabolites which are devoid of nitrogen. Examples of these metabolites include the didemnenones A (**23**) and B (**24**), C_{11}-cyclopentanoid natural products isolated from the Caribbean tunicate *Trididemnum* cf. *cyanophorum* in 1988.[37] Synthetic interest in these compounds was stimulated by their challenging structure and broad-range antimicrobial and antileukemic activity, resulting in the total synthesis of the didemnenones A (**23**) and B (**24**) by the research groups of Forsyth[38] and Takano.[39]
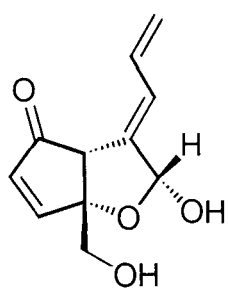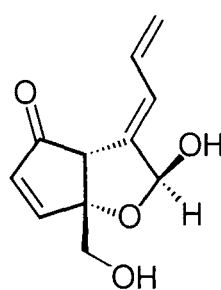
23 Didemnenone A   **24** Didemnenone B

1.3 Oxazole-Containing Natural Products

The oxazole ring is becoming a more prevalent characteristic in recently isolated natural products. The majority of molecules incorporate this 5-membered heteroaromatic motif as an isolated unit within a cyclic or acyclic framework. However, recent interest has been stimulated by natural products which contain contiguously linked *bis-* and *tris*-oxazole arrays. Some of the many oxazole containing natural products to be isolated and synthesised are highlighted here.

Calyculin A (**25**) was isolated from the marine sponge *Discodermi calyx* in 1986.[40] It contains a 2,4-disubstituted oxazole moiety amongst a wide variety of differing functionality, which includes a [5.6]spiroketal and a cyanotetraene. Calyculin A (**25**) has aroused considerable interest due to its ability to inactivate serine/threonine protein phosphatases 1 and 2A.[41] Successful total syntheses of calyculin A (**25**) were reported by the research groups of Evans,[42] Masamune[43] and Smith.[44]
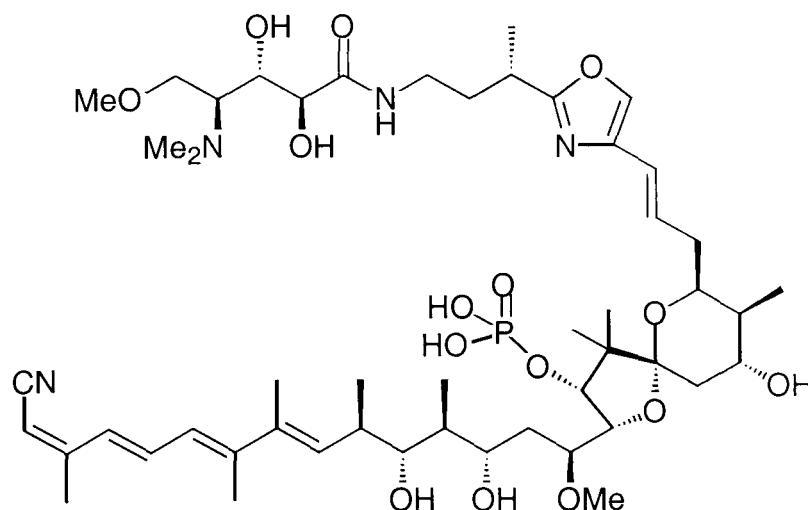
25 Calyculin A

Phorboxazoles A (**26**) and B (**27**) have been isolated from the Indian Ocean marine sponge *Phorbas* sp. in 1995.[45] Their gross structures were shown to encompass an unprecedented molecular architecture of four oxane rings, two 2,4-disubstituted oxazole rings and a 21-membered macrolactone, incorporating fifteen asymmetric centres. They exhibit a broad range of biological activity, showing exciting cytotoxic, cytostatic and antifungal properties. A total synthesis of phorboxazole A (**26**) was completed recently by Forsyth *et al.*[46]
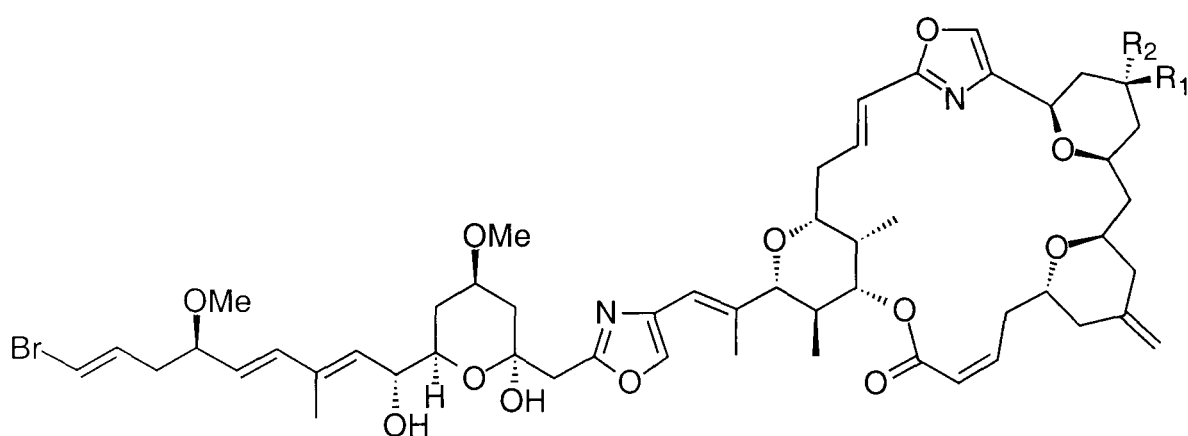
26 R$_1$ = H, R$_2$ = OH; Phorboxazole A

27 R$_1$ = OH, R$_2$ = H; Phorboxazole B

Rhizoxin A (**28**), isolated from *Rhizopus chinensis* Rh-2 in 1984 as the pathogen of rice seedling blight,[47] binds to β-tubulin at the same site as maytansine[48] causing either inhibition of polymerisation or depolymerisation of tubulin. In addition to antifungal activity,[49] it exhibits remarkable antitumor activity. Rhizoxin A (**28**) is a unique oxazole containing compound because the 2,4-disubstituted oxazole moiety resides at the terminus of the side chain. This triene chromophore is fused to a 16-membered macrolide which contains two epoxides and a δ-lactone ring. A total synthesis of rhizoxin A (**28**) was reported by Ohno *et al.*[50]
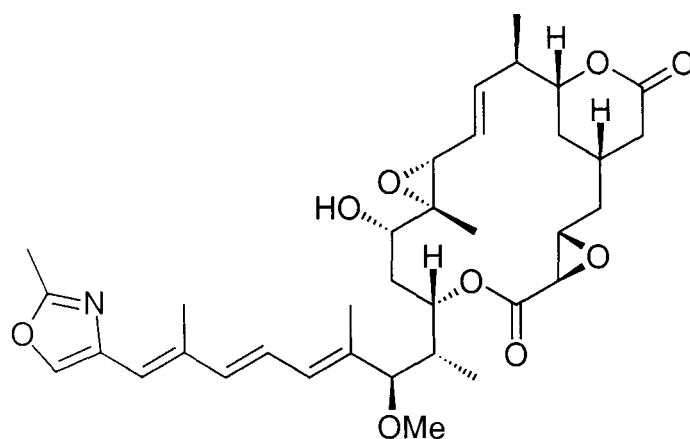
28 Rhizoxin

The group A virginiamycin antibiotics also accommodate a 2,4-disubstituted oxazole. In conjunction with an acrylamide unit, a polyene segment and an amino acid residue, the oxazole ring forms part of a 23-membered macrolactone core. The macrocyclic antibiotic virginiamycin M_2 (**29**) was isolated from *Streptomyces virginiae* in 1966.[51] It has been recognised as a cholecystokinin antagonist for treating panic, anxiety and cancer withdrawal.[52] A total synthesis of virginiamycin M_2 (**29**) was reported recently by Schlessinger *et al.*[53] Ten years after the isolation of virginiamycin M_2 (**29**), the broad spectrum antibiotic madumycin II (**30**) was isolated from a culture of *Streptomyces graminofaciens.*[54] A total synthesis of madumycin II (**30**) was reported by Meyers *et al* .[55] A synthesis of the related antibiotic 14,15-anhydropristinamycin II_B (**31**) was accomplished by Pattenden *et al.*[56]
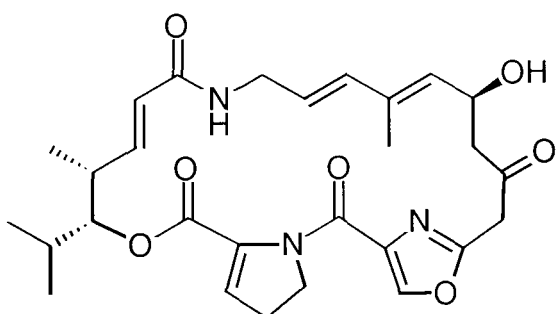
29 Virginiamycin M_2

30 Madumycin II

14
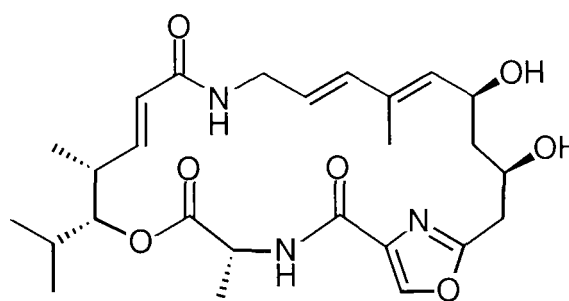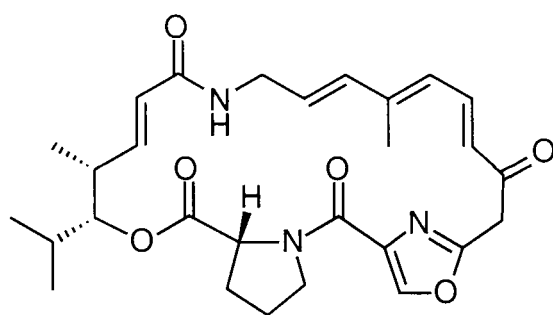
31 14,15-Anhydropristinamycin II_B

The 2,4-disubstituted oxazole ring is a feature of several cyclic peptide natural products. Orbiculamide A (**32**) and keramamide E (**33**), isolated from the marine sponge *Theonella* sp. in 1991[57] and 1995[58] respectively, are of particular interest. These antileukemic metabolites display a conjugated oxazole system within a cyclic array of amino acids, subtended by a 2-halo indole unit similar to that found in the diazonamides. At present, no total syntheses of these compounds have been reported.
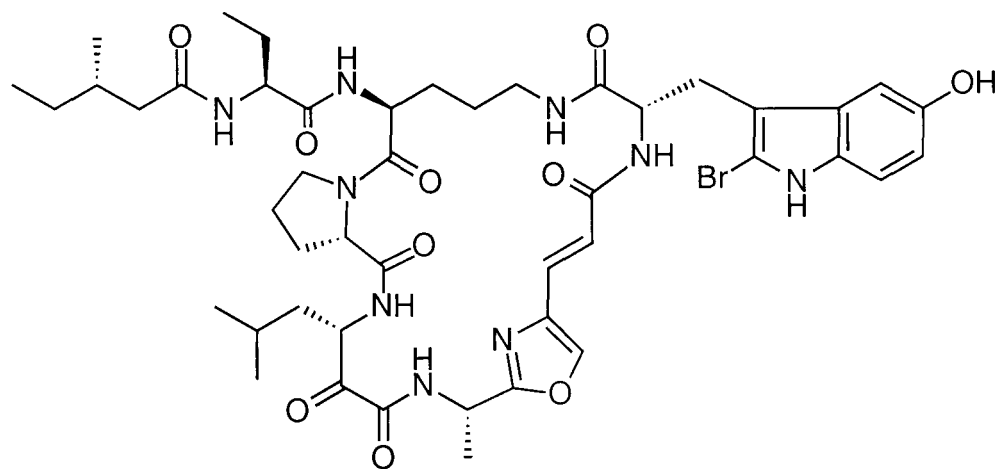
32 Orbiculamide A

33 Keramamide E

15
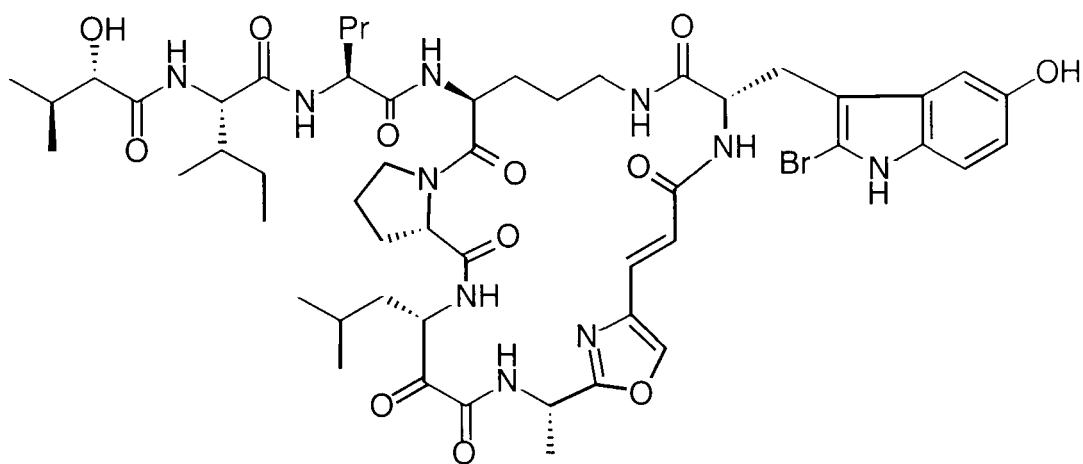
One of the earliest oxazole-containing compounds to be discovered was the antiepileptic alkaloid pimprinine (**34**), which was isolated from the bacterium *Streptomyces pimprina* in 1960.[59] Almost twenty years later, two related alkaloids, pimprinethine (**35**) and pimprinaphine (**36**), were isolated from *Streptomyces cinnamomeus* and *Streptomyces oliverticillium* respectively.[60] These alkaloids differ only in the nature of the substituent at the C2 position of the oxazole ring, whilst all contain an unusual 2,5-disubstituted oxazole fused to the C3 position of an indole, a structural feature also inherent in the diazonamides. Several syntheses of these natural products have been reported.[60,61]
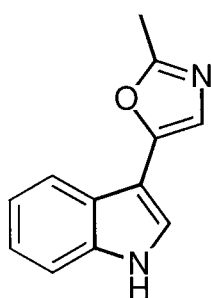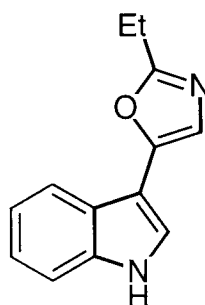
34 Pimprinine   **35** Pimprinethine   **36** Pimprinaphine
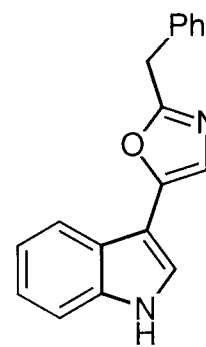
More recently, the indolyl oxazole unit has appeared in the marine alkaloid almazole C (**37**). This alkaloid, which bears the amino acid residue L-phenylalanine at the C2 position of a 2,5-disubstituted oxazole ring, was isolated from a red Senegalese delesseriacean seaweed, of the genus *Haraldiophyllum*, in 1994.[62] A biomimetic synthesis of almazole C (**37**) was reported by Pietra *et al.*[62]
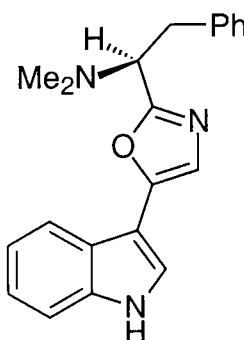
37 Almazole C

Phorbazoles A-D (**38-41**) were isolated from the Indo-Pacific sponge *Phorbas aff clathra* in 1994[63] and they represent further examples of 2,5-disubstituted oxazoles. Phorbazole A (**38**) is a particularly interesting member of this chlorinated phenylpyrrolyloxazole family, as it is the only marine natural product other than the diazonamides to display chlorination at the C4 position of the oxazole ring. A total synthesis of phorbazole A (**38**) has not yet been reported.
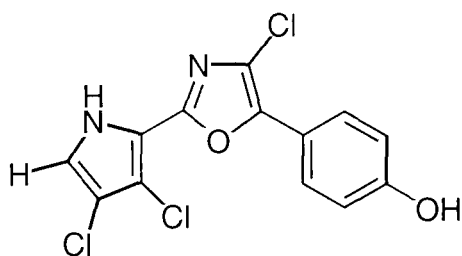
38 Phorbazole A
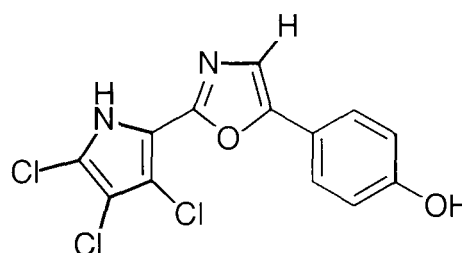
39 Phorbazole B
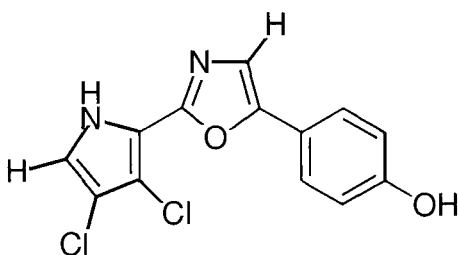
40 Phorbazole C
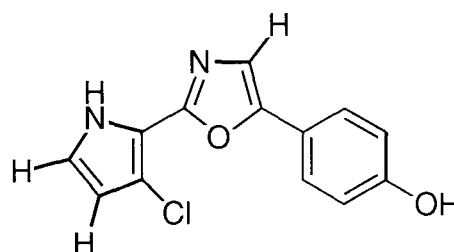
41 Phorbazole D

In contrast to the large number of natural products that contain isolated oxazole rings, significantly fewer compounds with contiguously linked polyoxazoles are known.

The diazonamides are one of only three types of compounds that contain a *bis*-oxazole system, with the hennoxazoles and muscoride A (**42**) completing this intriguing family of natural products. Hennoxazole A (**43**) was isolated from the marine sponge *Polyfibrospongia* sp. in 1991 and was shown to be highly active against herpes simplex virus.[64] This structurally diverse natural product incorporates a pyranoid glycoside and a homoconjugated triene terminus in addition to the *bis*-oxazole unit. A total synthesis of hennoxazole A (**43**) was first reported by Wipf and Lim.[65] In this original synthesis, the first oxazole ring was constructed by cyclodehydration of a hydroxy amide to give an oxazoline ring,[66] which was

subsequently oxidised to the corresponding oxazole.[67] For the preparation of the second oxazole ring these steps were reversed and a hydroxy amide was first oxidised to the corresponding aldehyde,[68] which underwent cyclodehydration to give the oxazole.[69] An alternative synthesis of hennoxazole A (43) was reported recently by Williams et al .[70]
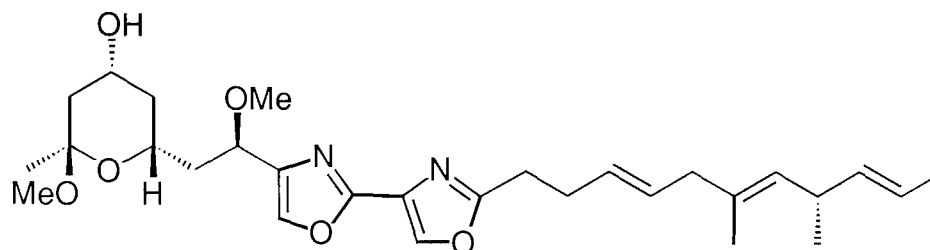
43 Hennoxazole A

Muscoride A (42) was isolated from the freshwater cyanobacterium *Nostoc muscorum* in 1995.[71] The *bis*-oxazole core of muscoride A (42) is formally derived from two threonine residues. This is a rather remarkable characteristic, since even isolated oxazoles derived from threonine are rare. However, it is interesting to note that this leads to the trisubstituted oxazole system which is also found in the diazonamides. This novel *bis*-oxazole core, in conjunction with an *N*-reverse-prenylated amino acid and antibacterial activity, has stimulated the interest of several synthetic research groups. Wipf and Venkatraman published the first total synthesis of muscoride A (42),[72] employing the oxidation-cyclodehydration protocol to construct both heteroaromatic rings.[68,69] An alternative synthesis of muscoride A (42) was reported by Pattenden et al,[73] in which the cyclodehydration-oxidation sequence was used to prepare the *bis*-oxazole system.[74]

42 Muscoride A

tris-Oxazole-containing marine natural products are amongst the most fascinating family of metabolites to be isolated from marine organisms in recent years. These intriguing molecules include the ulapualides,[75] kabiramides,[76] halichondramides,[77] halishigamides[78] and mycalolides.[79] They were first isolated from the egg masses of the marine nudibranche *Hexabranchus sanguineus* in 1986[75] and exhibit a wide range of interesting and unusual biological activity, including antileukemic, antifungal and ichthyotoxic properties.[80] The structures of these metabolites are based around three contiguous oxazole rings which form part of a 23-membered lactone attached to a lipid-like side chain that terminates in an *N*-methyl-*N*-alkenylformamide group. It is not surprising that these extraordinarily interesting, bioactive macrolides have attracted the attention of the synthetic community. Although the stereochemical integrity of ulapualide A (**44**) is in some doubt, Chattopadhyay and Pattenden have recently completed a total synthesis of the entire ulapualide framework.[81] In this approach, the three oxazole rings were constructed by the cyclodehydration-oxidation protocol.[74c,82] Extensive work in this area by Panek *et al* has shown that the *tris*-oxazole system can also be prepared using Hantzsch-type methodology,[83] whilst Yoo has utilised a sequential rhodium(II)-catalysed cycloaddition reaction to furnish the *tris*-oxazole fragment.[84]

44 Ulapualide A

1.4 Biaryl Natural Products

Although the fascinating structures of the diazonamides present many challenges to those embarking on total synthesis studies, perhaps none appears more daunting than the construction of the atropisomeric biaryl axis which connects C16 of the benzofuran ring to C18 of the halo indole system.

This complicating issue of atropisomerism is not unique to the diazonamides. The biaryl axis is the central building block in a very large number of natural products of differing structure, biological activity and biosynthetic origin. These include polyketides, terpenes, lignans, quinones, coumarins, flavonoids, tannins, peptides and alkaloids.[85,86] This section is not intended to be a thorough review of atropisomeric biaryl natural products, but rather serves to highlight some of the many biaryl compounds that have been isolated in Nature and have captured the interest of research groups world-wide because of their fascinating molecular architecture and striking biological activity.

Despite the proliferation of axially chiral biaryl compounds that have been isolated in Nature, very few can challenge the diazonamides for structural complexity. One notable exception is vancomycin (**45**), which was isolated from *Streptomyces orientalis* in 1956[87] and is the prototypical member of a large family of antibiotics which include, for example, ristocetin, avovaricin, synmonicin and teicoplanin. The intriguing structures of these antibiotics consist of an arylglycine-rich heptapeptide aglycon to which are appended an array of sugar residues. Structural diversity within this family of natural products is created by variation in the aglycon amino acid constituents and in the nature, position and number of incorporated sugar residues.[88] The biaryl amino acid, actinoidic acid (**46**), is a common segment in all the antibiotics of the vancomycin family. This structural feature shares a similarity with the biaryl segment of the diazonamides since it is elegantly incorporated in a 12-membered cyclic structure (**47**). Clinical applications of vancomycin (**45**) to the treatment of Gram-positive bacterial infections and its efficacy against methicillin-resistant

Staphylococcus aureus have established vancomycin (**45**) as the antibiotic of last resort against infections of this deadly pathogen.[89] Such striking structural diversity and biological activity have inspired recently two monumental total syntheses of the vancomycin aglycon by Evans *et al*[90] and Nicolaou *et al*.[91]
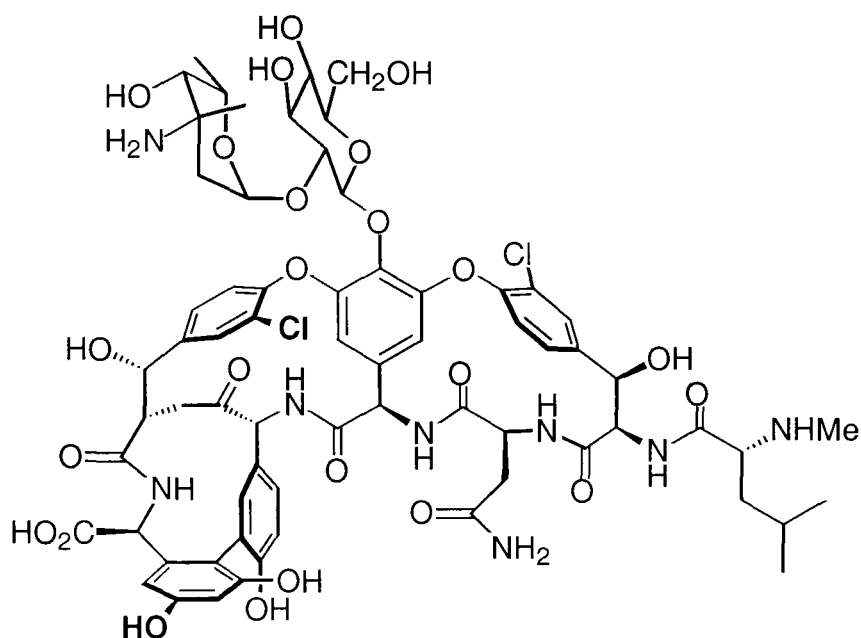
45 Vancomycin
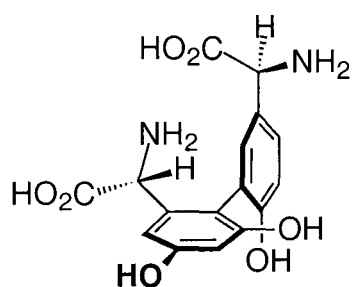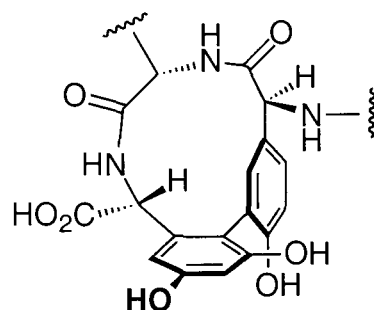
46 Actinoidic acid   **47** Cyclic biaryl segment

Complestatin (**48**) is a unique glycopeptide antibiotic, isolated from the mycelium of *Streptomyces lavendulae* in 1989.[92] Although this polycyclic macropolypeptide is related to the vancomycin antibiotics, many structural differences exist. The most dominant variations are the absence of any sugar residues and the presence of a tryptophan residue instead of a tyrosine ring as one half of the biaryl segment in a 16-membered macrocycle. Complestatin (**48**) also differs from vancomycin (**45**) in its biological activity. It is a poor inhibitor of Gram-positive bacteria, but has a potential utility in AIDS treatment and is a potent inhibitor with anticomplement activity.[93]

21

Although a total synthesis of complestatin (**48**) has not yet been achieved, synthetic approaches to the biaryl system have been reported.[94]
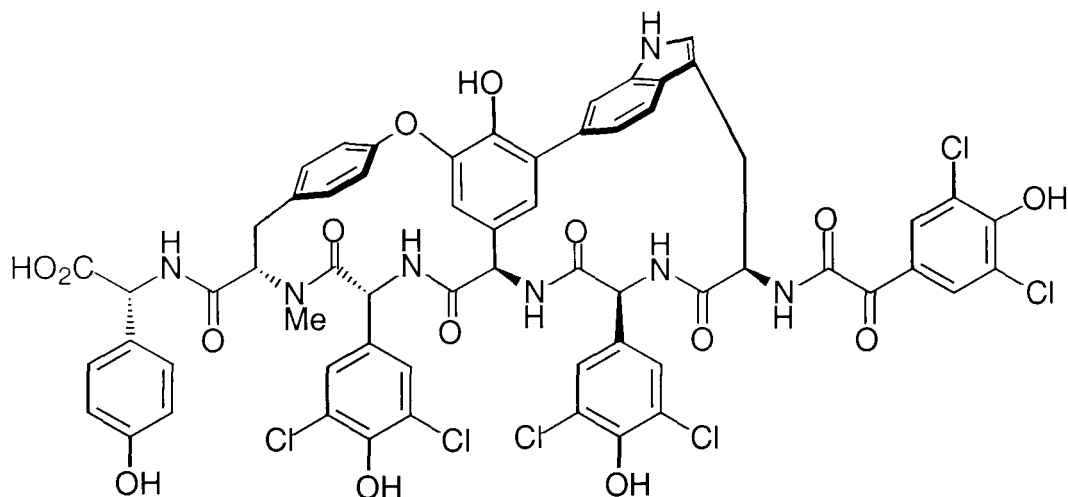
48 Complestatin

Not all macrocyclic biaryl systems are contained within such complex molecular frameworks. Lythranidine (**49**), isolated from *Lythrum anceps* in 1970,[95] is an example of a more structurally simplistic biaryl-containing macrocyclic natural product. This cyclophane alkaloid incorporates the biaryl axis into a 17-membered ring that also encompasses a *trans*-2,6-dialkylpiperidine. Lythranidine (**49**) was synthesised by Fujita *et al*[96] and by Coggins *et al*,[97] but no pharmacological studies have yet been reported.
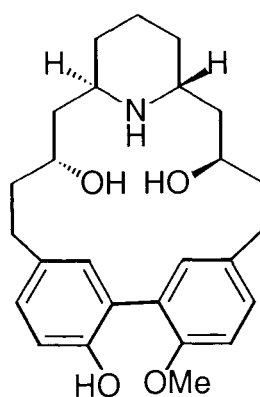
49 Lythranidine

The natural products described previously, all display the biaryl segment within a complex cyclic framework. This structural feature differs distinctly from the majority of biaryl systems in naturally occurring compounds, where the biaryl segment is contained in an acyclic array.

Of all the classes of biaryl acyclic natural products that have been isolated in Nature, the alkaloids stand out as providing perhaps the richest source of examples. Ancistrocladine (50), an optically active cryptophenolic alkaloid, was isolated from the roots of *Ancistrocladus heyneanus* in 1971.[98] Ancistrocladine (50) contains the *iso*-quinoline ring system, a common aromatic partner in biaryl alkaloid natural products, in addition to a highly substituted biphenyl system that is configurationally stable to above 200°C. No pharmacological investigations have yet been carried out with ancistrocladine (50) despite a total synthesis of the alkaloid by Bringmann *et al.*[99]
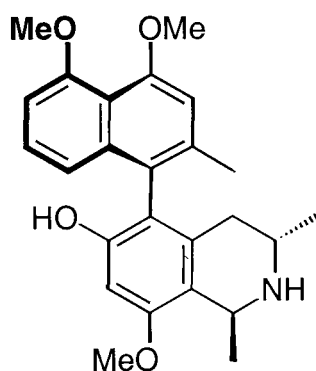
50 Ancistrocladine

Structurally related to ancistrocladine (50), but less sterically congested around the biaryl axis, is the naphthyl*iso*-quinoline alkaloid dioncophylline A (51). This axially chiral biaryl alkaloid was isolated from the West African liana *Triphyophyllum peltatum* in 1990[100] and was found to exhibit fungicidal and antimalarial activity.[101] A successful total synthesis of dioncophylline A (51) was completed by Bringmann *et al.*[102] Relying on the ready availability of this alkaloid on a multigram scale from natural sources, Bringmann *et al* prepared its dimer, jozimine A (52).[103] Jozimine A (52) was the first non-natural dimer of a naturally occurring, monomeric

naphthyl*iso*-quinoline alkaloid to be synthesised. It has aroused much interest since it was found to display antimalarial activity twenty times higher than that of its monomer.[103]
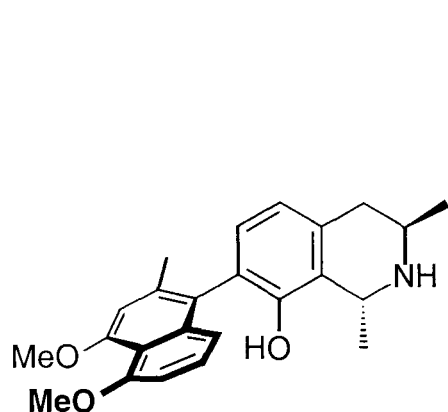
51 Dioncophylline A
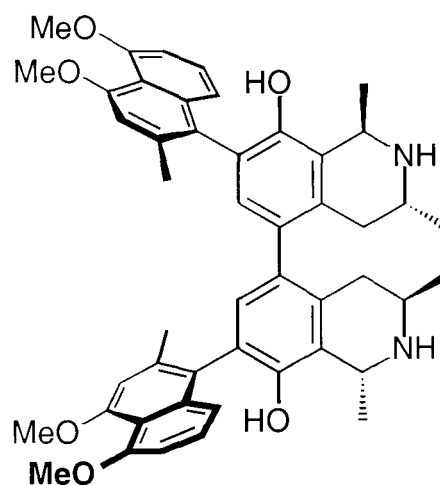
52 Jozimine A

Several alkaloids which possess structural characteristics similar to those of jozimine A (**52**) have been isolated in Nature. Michellamine A (**53**), isolated from *A. korupensis* in 1991,[104] is representative of a unique natural class of biologically important tetra-aryls with activity against human immunodeficiency virus (HIV).[105] Structurally, michellamine A (**53**) is characterised by the presence of six free phenolic hydroxy groups, two secondary amino functions and by the existence of four stereocentres and three axes, two of which are stereogenic due to restricted rotation. This C_2-symmetric dimer was synthesised using an oxidative phenolic coupling of the monomeric naphthyl*iso*-quinoline alkaloid natural product korupensamine A (**54**) by Bringmann *et al*,[106] then subsequently by Kelly *et al*[107] and Hoye *et al*.[108]
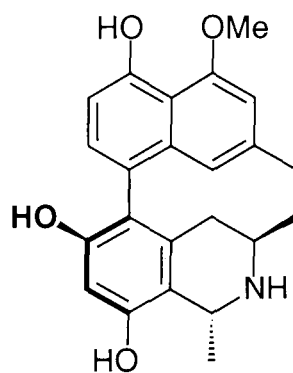
54 Korupensamine A
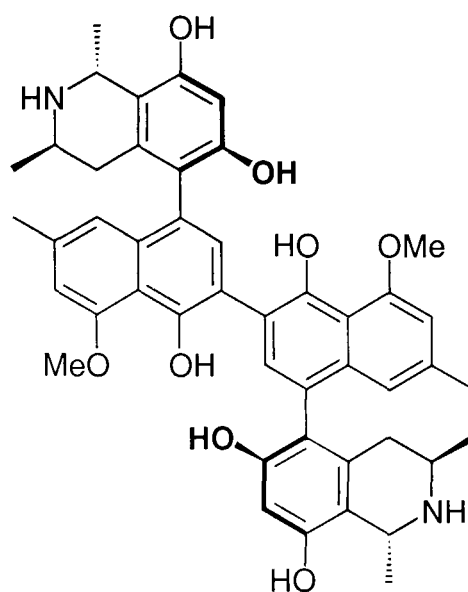
53 Michellamine A

A more complex biaryl alkaloid system is found in vingramine (**55**). This cytotoxic *bis*-indole natural product was isolated from the seeds of *Catharanthus roseus* in 1998.[109] Its structure is exceptional due to the unusual biphenyl linkage and the presence of an *iso*-butyramide group and a tetrahydrofuran ring. No synthetic studies towards vingramine (**55**) have been reported.
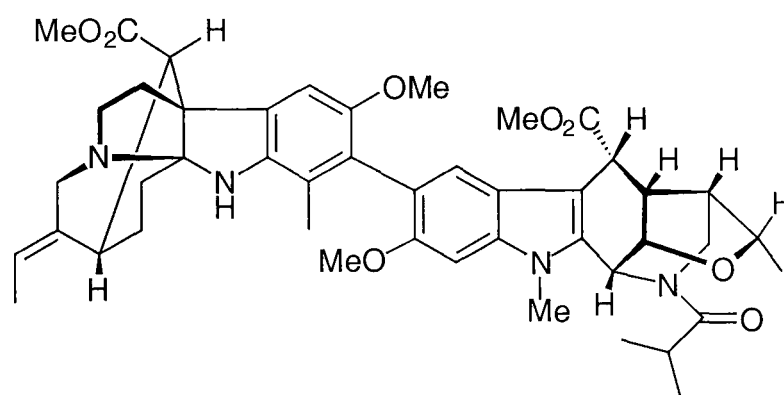
55 Vingramine

Although the peptides and alkaloids provide a plethora of biaryl natural products, many classes of naturally occurring compounds possessing biaryl systems have been reported which are devoid of nitrogen.

Mastigophorene A (**56**), a constitutionally symmetric, dimeric sesquiterpene, was isolated from the primitive Asiatic liverwort *Mastigophora diclados* in 1991.[110] Its

structure is characterised by the presence of two pentasubstituted aromatic rings and two chiral cyclopentyl residues. Mastigophorene A (**56**) exhibits nerve growth and network formation acceleration activity[110] and has been synthesised recently by Meyers *et al*[111] and by Bringmann *et al*.[112]
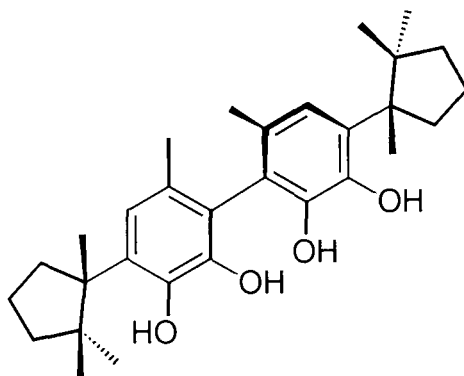
56 Mastigophorene A

Another dimeric sesquiterpene, gossypol, has received much attention since it was first revealed to be active as an antispermatogenic agent.[113] Gossypol has also been shown to be effective against tumour cells, HIV type 1, herpes simplex virus and influenza,[114] since it was isolated from cotton seeds in 1886.[115] An asymmetric total synthesis of (*S*)-(+)-gossypol (**57**) was achieved recently by Meyers and Willemson.[116]
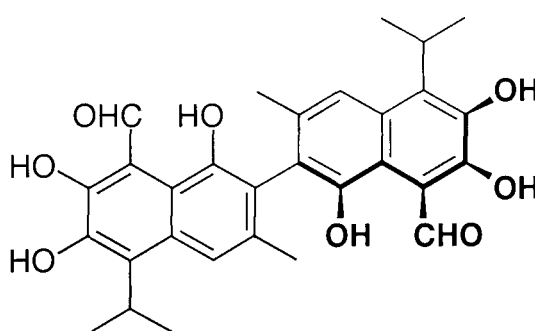
57 (*S*)-(+)-Gossypol

Knipholone (**58**) was first isolated from the sun dried roots of *Kniphofia foliosa* in 1984,[117] a perennial herb widely distributed in the mountainous regions of central and northern Ethiopia, which is used in traditional Ethiopian medicine for the treatment of

abdominal cramps and also displays antimalarial activity. Knipholone (**58**) represents a new type of anthraquinone pigment[118] in which the chrysophanol chromophore is connected to an acylphloroglucinol unit by a chiral biaryl linkage. A total synthesis of knipholone (**58**) has not yet been reported.
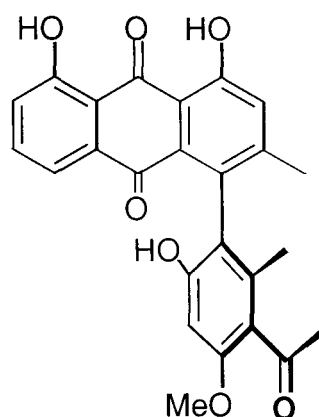
58 Knipholone

Pradimicin A (**59**), from *Actinomadura hibisca*,[119] is yet another biaryl quinone natural product, in which the biaryl axis forms part of a 6-membered ring. This antifungal antibiotic, isolated in 1989, has a unique structure consisting of a 5,6-dihydrobenzo[*a*]naphthacene chromophore substituted with D-alanine and disaccharide residues. A total synthesis of pradimicinone, the pradimicin A (**59**) aglycon, was reported recently by Suzuki *et al.*[120]
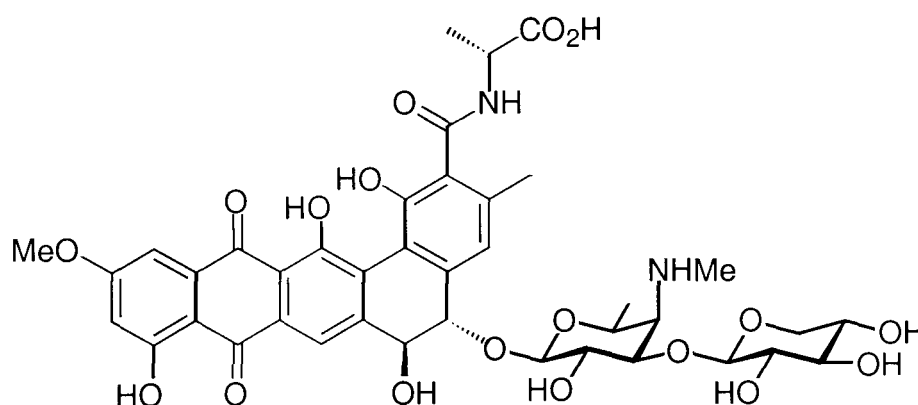
59 Pradimicin A

Steganone (**60**) is one of four *bis*-benzocyclooctadiene lignan lactones isolated from *Steganotaemia araliacea* in 1973.[121] This antileukemic, cytotoxic natural product

contains three stereochemical elements, two of which are on the lactone ring, whilst the third is the asymmetric biaryl bond between the two phenyl rings. Steganone (**60**) has attracted considerable interest within the synthetic community, resulting in eleven reported total syntheses,[122] five of which have been enantioselective.[123]
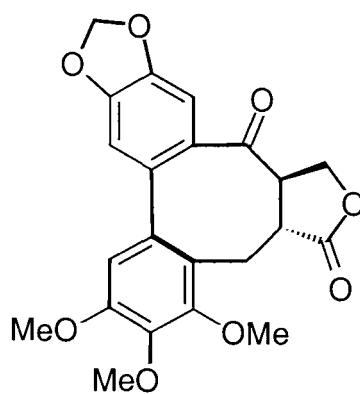
60 Steganone

Chaetocromin A (**61**) was first isolated from *Chaetomium virescens* in 1980.[124] It is one of a closely related family of *bis*-(naphtho-γ-pyrone) metabolites which include, for example, cephalochromin, nigerone, ustilaginoidins and aurasperones.[125] Chaetochromin A (**61**) is the outstanding member of this class due to its pronounced cytotoxic and antitumour activity, but a successful total synthesis has yet to be described.
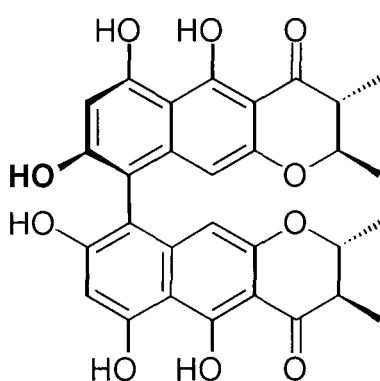
61 Chaetochromin A

Geraniin (**62**) is the main tannin of plants of several *Geranium* species and also Euphorbiaceae. This eligatannin was first isolated from *Geranium thunbergii* in 1975[126] in an attempt to obtain the active principle of this medicinal plant, which is

one of the most popular folk medicines and also is an official antidiarrheic in Japan.[127] Geraniin (**62**) displays an interesting structure in which a cyclohexenetrione moiety is attached to a glucose residue, which is further linked to a chiral biphenyl system.
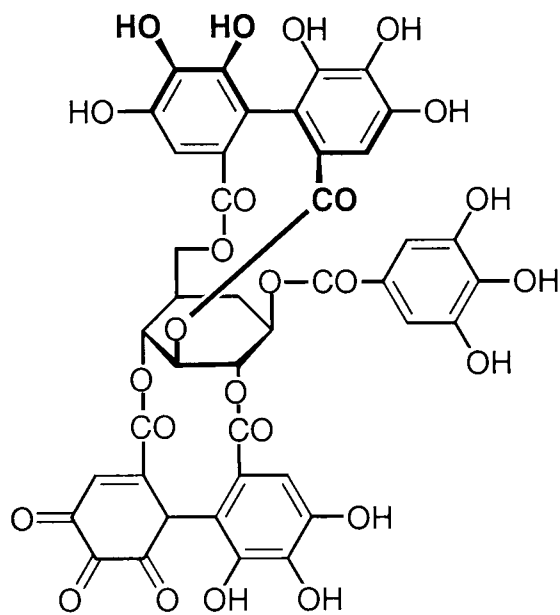
62 Geraniin

2. RESULTS AND DISCUSSION

2.1 General Strategy and Retrosynthesis

The high degree of complexity associated with the macrocyclic aromatic core of diazonamide A (1), prompted us to concentrate our initial efforts towards the construction of the key C-C σ-bonds within this heterocyclic framework. The synthetic endeavors of previous workers in Nottingham on the project,[128] had demonstrated that it was possible to utilise palladium-catalysed sp²-sp² coupling protocols to prepare a benzofuran-oxazole fragment, a benzofuran-indole fragment and an indole-oxazole fragment. The completion of a macrocyclic system containing all four of the aromatic units present in the southern macrocycle of diazonamide A (63) was the next challenge to be confronted. Hence, at the outset of my research, the complex macrocycle (64) became our synthetic target.

63   **64**
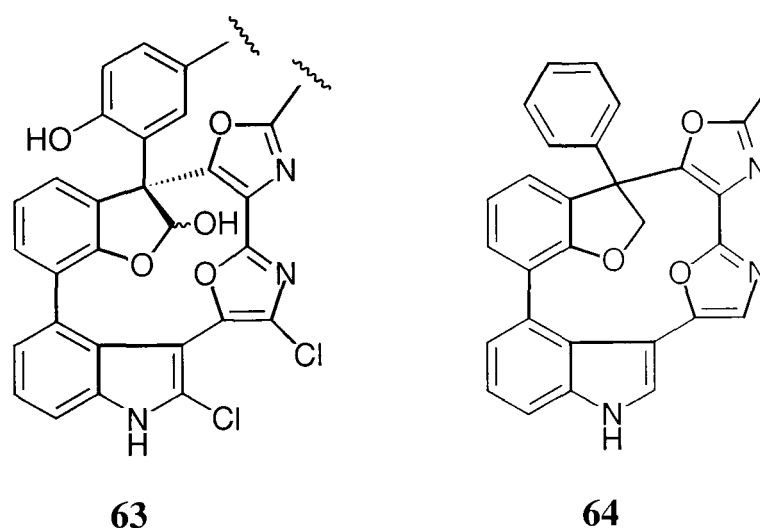
Although the macrocycle (64) represents only the aromatic core of diazonamide A (1), its synthesis is still a significant proposition. The benzofuran in 64 is linked *via* a quaternary carbon centre to a trisubstituted oxazole. This forms part of a *bis*-oxazole segment in which the remaining oxazole is fused to an indole. The atropisomeric biaryl bond linking the indole to the benzofuran in 64 completes the macrocyclic structure.

Following our keen interest in macrocyclic sp²-sp² coupling reactions,[56,129] we devised a retrosynthetic strategy in which the macrocycle (**64**) was first disconnected across the biaryl bond to provide the acyclic system (**65**). The intramolecular union of two aryl halide units in the presence of a suitable transition metal, the Ullmann reaction,[130] would be expected to result in the formation of the desired macrocycle (**64**). The acyclic fragment (**65**) still represents a significant synthetic challenge, as all four of the aromatic units present in the macrocycle remain intact. However, retrosynthetic disassembly of the disubstituted oxazole revealed the amide (**66**). On the basis of precedent,[65,69,72] it was projected that cyclisation of the keto amide function in **66** with triphenylphosphine, iodine or hexachloroethane and a suitable base, would lead to the formation of the macrocyclic precursor (**65**). The amide (**66**) can be dismantled in a convergent fashion by retrosynthetic cleavage of the amide bond to provide the acid (**67**) and the amine (**68**). It was anticipated that activation of the carboxylic acid function in **67** as a mixed anhydride or acid chloride and exposure to the amine (**68**), would result in the formation of the amide (**66**).

64   **65**   **66**   X,Y = Br or I

67   **68**
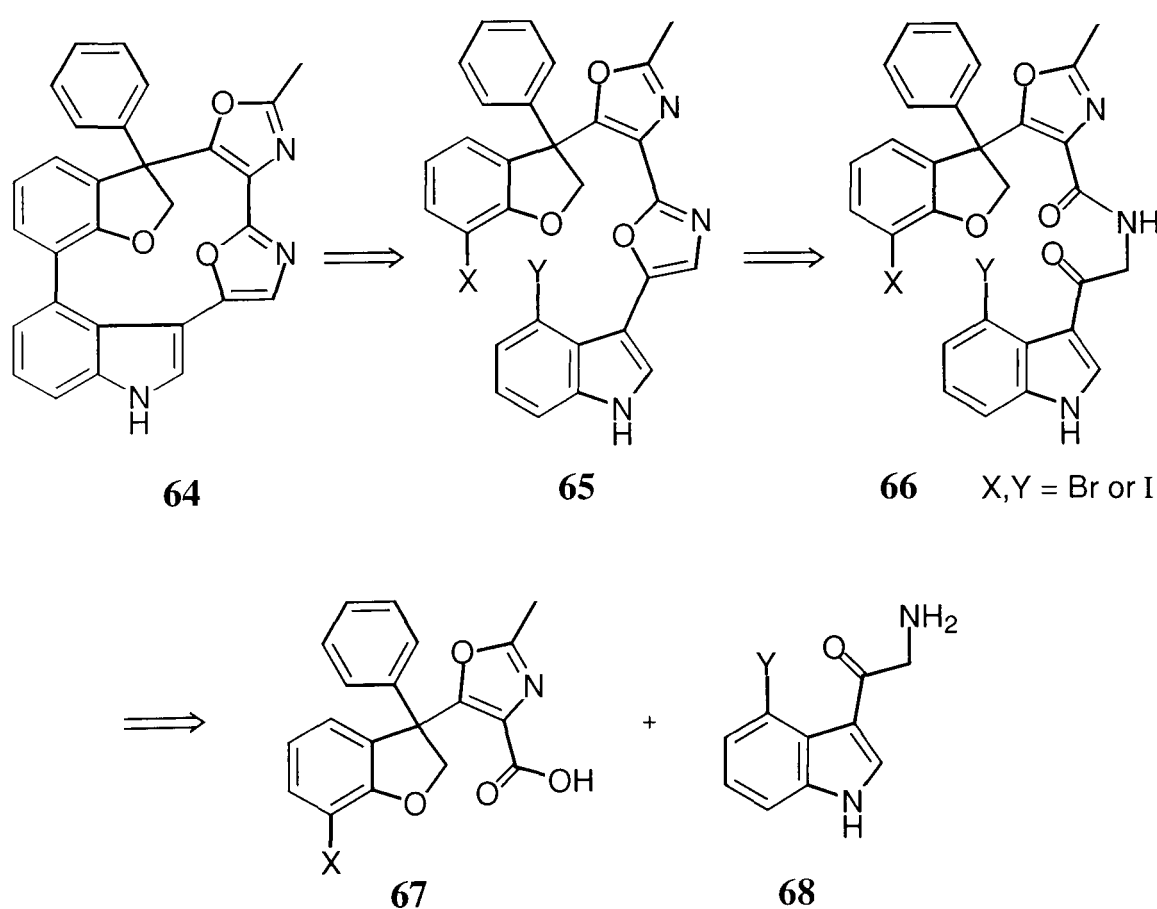
2.2 Synthesis of the Benzofuran Oxazole Acid Fragment (69)

2.2.1 Introduction

The acid fragment (67) is by far the more structurally complex of the two crucial synthetic intermediates derived from the previous retrosynthetic analysis (2.1). It incorporates the quaternary carbon centre at the C2 position of the benzofuran ring which is linked to a phenyl ring and a trisubstituted oxazole. In addition, the halogen substituent at the C7 position of the benzofuran ring is vital for the final macrocyclisation reaction.

2.2.2 Retrosynthetic Analysis

Following a similar retrosynthetic protocol to that described previously for the *bis*-oxazole (65), we envisaged obtaining the target compound (69) from the amide (70) by a cyclodehydration process,[69] then hydrolysis of the ester function. It was anticipated that the amide function of 70 could be introduced into the ketone (71), possibly *via* an azide, oxime or diazo intermediate. The ketone (71) can be traced retrosynthetically to the aldehyde (72) and then to the terminal alkene (73). In the forward sense, oxidative cleavage of the terminal alkene (73) would be expected to provide the aldehyde (72),[132] which could undergo a two carbon homologation with ethyl diazoacetate in the presence of a suitable Lewis acid leading to the ketone (71).[133] The terminal alkene (73) is a crucial intermediate in the synthesis of the acid (69), since it can be derived from the iodide (74). In the synthetic direction, subjecting the iodide (74) to palladium(0) catalysis could lead to the benzofuran framework *via* a Heck reaction.[134] By utilising this powerful tool, we would unite two sp^2-hybridised carbon centres, introduce the quaternary carbon centre at the C2 position of the benzofuran ring and leave a terminal alkene for elaboration to the trisubstituted oxazole (69).

69 **70** **71**

72 **73** **74**
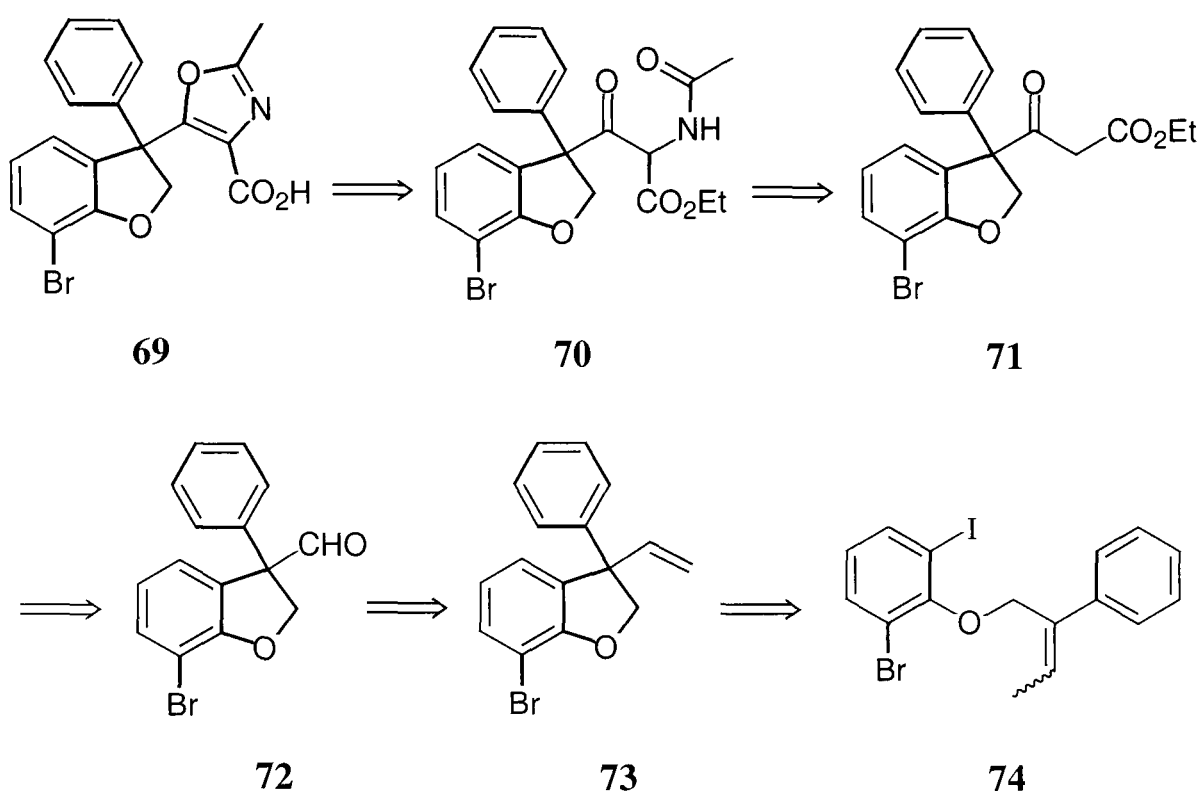
It was envisaged that the trisubstituted alkene (**74**) could be obtained by a Wittig reaction[135] between the ketone (**75**) and (ethyl)triphenylphosphonium bromide in the presence of a suitable base. We anticipated that the introduction of iodine into the ketone (**75**) could be achieved by an *ipso*-substitution of the aryl silane (**76**) with silver tetrafluoroborate and iodine. Logical retrosynthetic disassembly across the phenolic ether linkage next provided the disubstituted phenol (**77**) and 2-bromoacetophenone (**78**), with the disubstituted phenol (**77**) ultimately being obtainable from phenol (**79**), *via* the dibromo derivative (**80**).[136] In the forward sense, it was expected that the reaction of bromine and *t*-butylamine with phenol (**79**) would lead to the *ortho*-dibromo derivative (**80**).[136] Preparation of the trimethylsilyl phenol ether and treatment with *n*-butyllithium could then give the bromo silyl phenol (**77**) *via* a silyl group migration[137] in the intermediate aryl lithium species. Deprotonation of the acidic phenolic hydrogen with an appropriate base and exposure of the resulting phenoxide anion to 2-bromoacetophenone (**78**) would then be expected to provide the desired ketone (**76**).

74   **75**   **76**

78   **77**   **80**   **79**
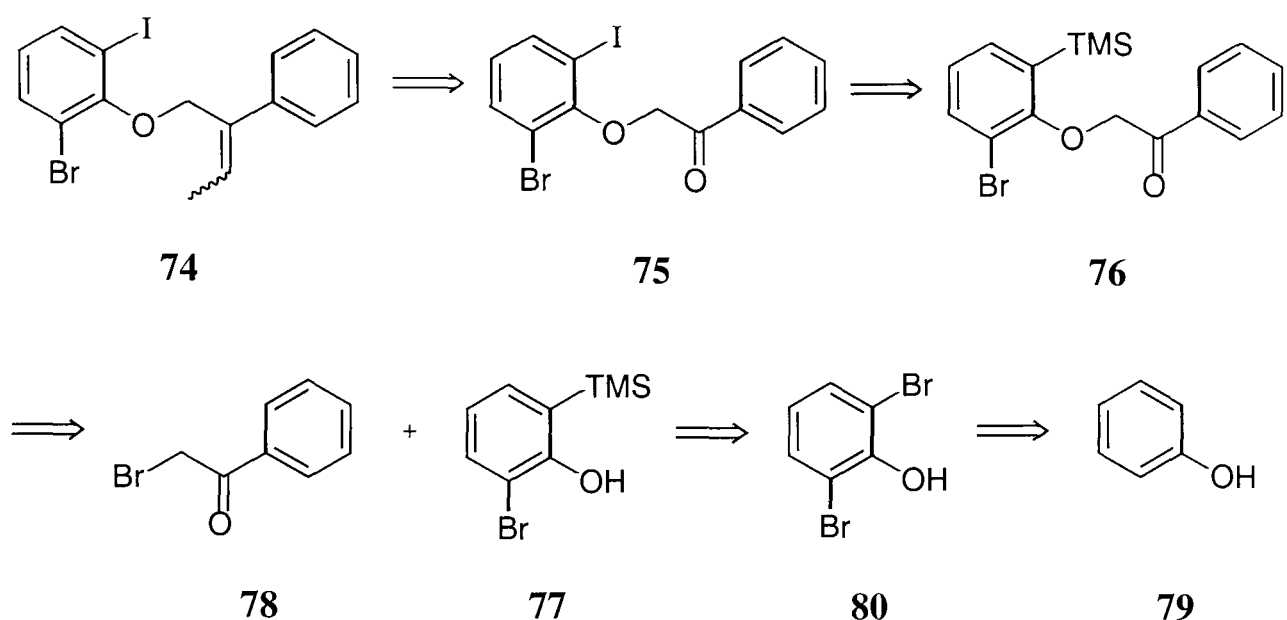
2.2.3 Synthesis of the Aryl Iodo Alkene Fragment (74)

Our synthesis of the iodide (**74**), the precursor for the crucial Heck reaction,[134] followed the retrosynthetic plan outlined previously (**2.2.2**). The synthesis commenced by treatment of phenol (**79**) with *t*-butylamine and bromine at -70°C to give 2,6-dibromophenol (**80**) in 63% yield (**Scheme 1**).[136] The phenol (**80**) was transformed to the trimethylsilyl ether (**81**) using sodium hydride and chlorotrimethylsilane. Treatment of the trimethylsilyl ether (**81**) with *n*-butyllithium at -78°C effected a lithium-bromine exchange reaction, generating the putative aryl lithium species (**82**). This organometallic compound (**82**) then underwent a 1,3-silyl shift,[137] to give the aryl silane (**77**) in an excellent 83% yield for this one pot reaction. Alkylation of the phenolic hydroxyl in **77** to give the ketone (**76**) was achieved in 95% yield on exposure of the aryl silane (**77**) to potassium carbonate and 2-bromoacetophenone (**78**). The silyl function in the ketone (**76**) was next converted into an iodide *via* an *ipso*-substitution reaction, with silver tetrafluoroborate and iodine, to give the aryl iodide (**75**) in 77% yield. This proved an extremely efficient method for introducing iodine into the aromatic system, with the aryl silane acting as a masked aryl iodide. Wittig olefination[135] of the ketone (**75**) using *n*-butyllithium

35

with (ethyl)triphenylphosphonium bromide at 0°C, finally gave the desired trisubstituted alkene (74), as a 2:1 ratio of geometrical isomers in 96% yield.
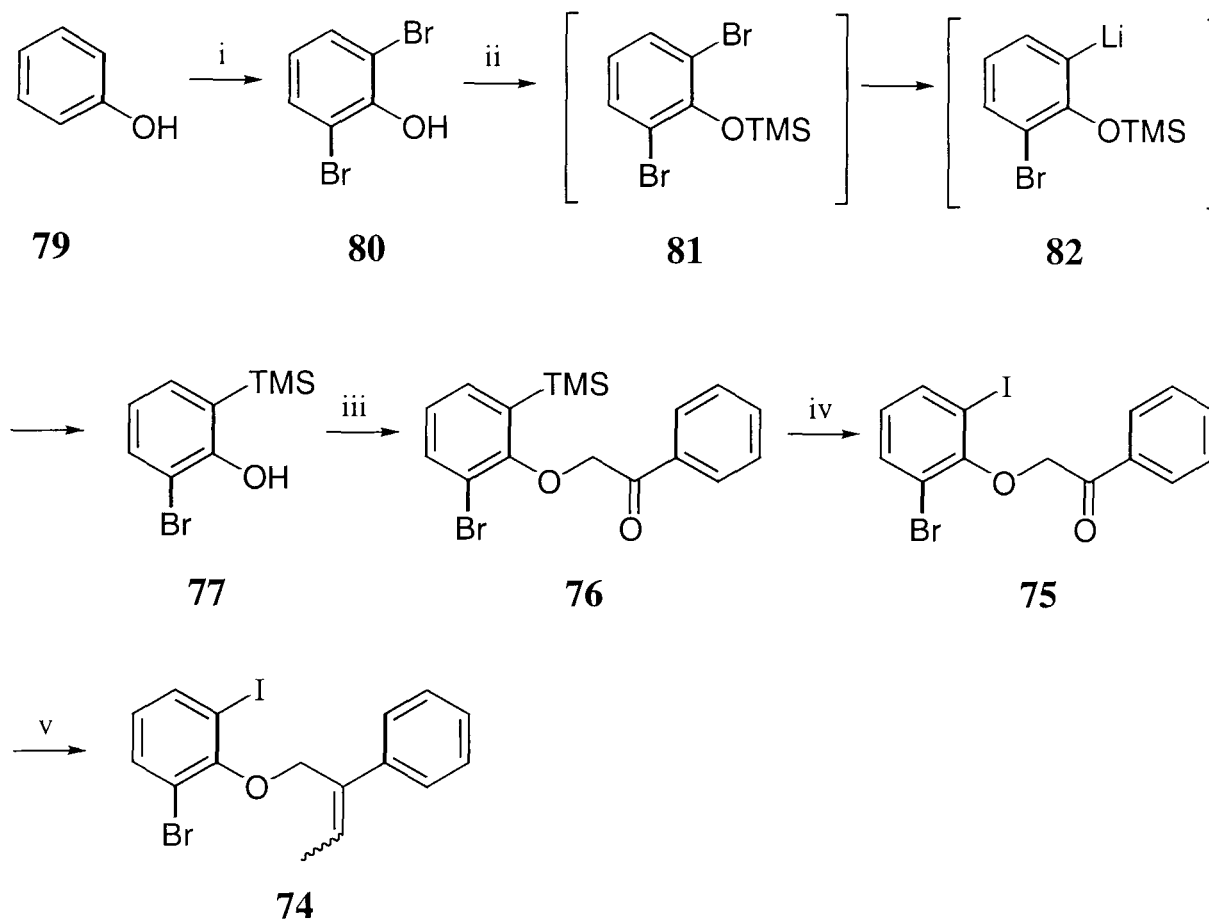
Reagents: i, *t*-BuNH$_2$, Br$_2$, PhMe, CH$_2$Cl$_2$, 63%; ii, NaH, TMSCl, *n*-BuLi, THF, 83%; iii, K$_2$CO$_3$, **78**, MeCN, 95%; iv, I$_2$, AgBF$_4$, EtOH, 77%; v, *n*-BuLi, EtPPh$_3$Br, THF, 96%.

Scheme 1

At this juncture, we thought it appropriate to consider the possibility of utilising the Heck reaction[134] in a system which we could extend to the northern macrocycle of diazonamide A (**1**). In order to implement such a strategy, we required the iodide (**83**), as the relevant Heck precursor. The only structural difference between **83** and the previous iodide (**74**) is the incorporation of a suitably protected tyrosine residue in place of the phenyl ring. We anticipated that we could follow a very similar retrosynthetic pathway for the iodide (**83**) to that described previously for the iodide (**74**). The task now became the synthesis of the bromide (**84**), an analog of 2-bromoacetophenone (**78**) which incorporates the protected tyrosine residue.
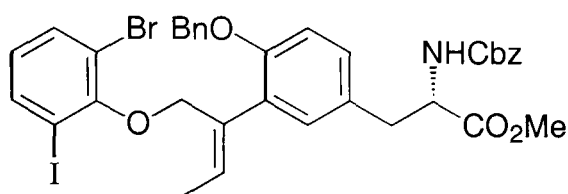
83
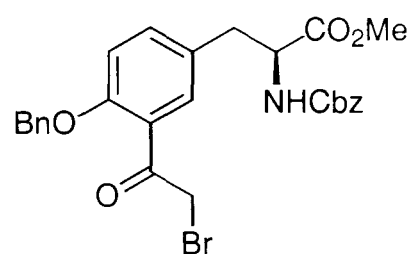
84

Our synthesis of the bromide (**84**) commenced with a Friedel-Crafts acylation reaction of L-tyrosine (**85**) using acetyl chloride and aluminum chloride at 100°C,[138] to give the ketone (**86**) in 67% yield (**Scheme 2**). With the carbonyl function now introduced, we proceeded to protect the three remaining active sites in the ketone (**86**). To this end, esterification of the carboxylic acid function with acetyl chloride and methanol[139] at reflux first provided the methyl ester (**87**) in 95% yield. The amine was next converted into the benzyl carbamate (**88**) under the action of sodium carbonate and benzyl chloroformate at 0°C in 77% yield. Protection of the phenolic hydroxyl function as a benzyl ether proved slightly more difficult due to the low reactivity of the phenoxide anion, which can delocalise its negative charge into the neighbouring ketone function. However, protection of the hydroxyl was finally achieved by treatment of **88** with potassium carbonate, benzyl bromide and three equivalents of DMPU[140] in DMF[141] to give the benzyl ether (**89**) in a modest 34% yield. With all the reactive sites now suitably protected, we could address the question of how to introduce the bromine substituent. We found that bromination was best performed by *in situ* formation of the silyl enol ether (**90**) with lithium *bis*-(trimethylsilyl)amide and chlorotrimethylsilane at -78°C, followed by rapid addition of bromine to give the bromide (**84**) in 78% yield.
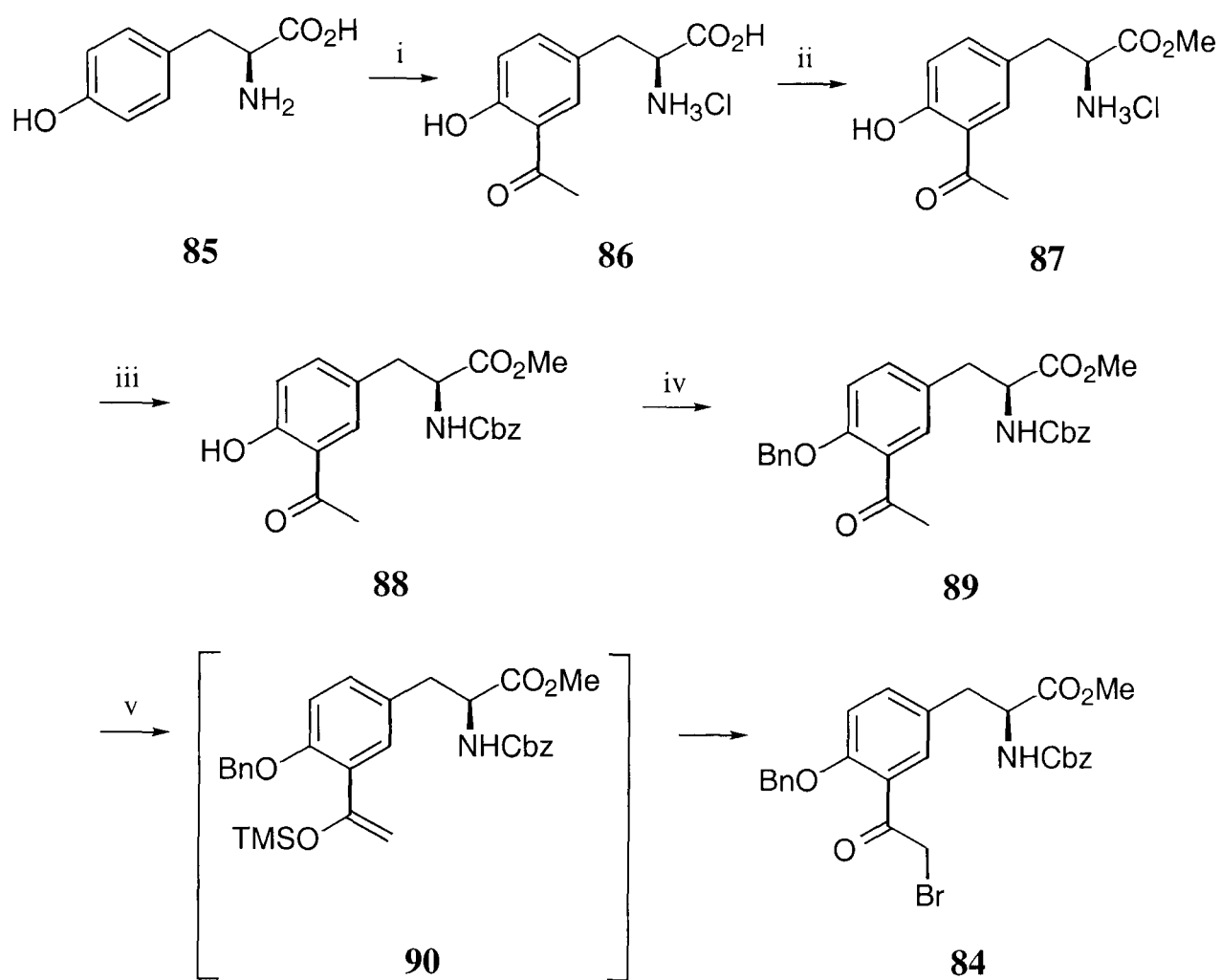
Reagents: i, AcCl, AlCl$_3$, PhNO$_2$, Δ, 67%; ii, AcCl, MeOH, Δ, 95%; iii, Na$_2$CO$_3$, PhCH$_2$OCOCl,

THF, H$_2$O, 77%; iv, K$_2$CO$_3$, BnBr, DMPU, DMF, 34%; v, LiHMDS, TMSCl, Br$_2$, THF,

CH$_2$Cl$_2$, 78%.

Scheme 2

With the bromide (**84**) now in hand, we could follow the previous synthetic steps described in **Scheme 1** for the preparation of the iodide (**74**). Hence, the phenolic hydroxyl in the aryl silane (**77**) underwent alkylation on treatment with potassium carbonate and the bromide (**84**) to give the aryl silane (**91**) in 85% yield (**Scheme 3**). The aryl iodide required for the Heck reaction[134] was again unmasked by an *ipso*-substitution of the aryl silane (**91**) with iodine and silver tetrafluoroborate to give the ketone (**92**) in 99% yield. Exposure of the ketone (**92**) to the Wittig olefination conditions used to prepare the trisubstituted alkene (**74**) (**Scheme 1**), gave only trace amounts of the desired product. Since the remaining starting material could be recovered from the reaction, we believed that the phosphonium ylide derived by

treatment of (ethyl)triphenylphosphonium bromide with *n*-butyllithium, was primarily involved in abstracting an acidic hydrogen adjacent to the ketone function in **92**. This problem was overcome by employing sodium *bis*-(trimethylsilyl)amide as the base at -40°C to give the desired trisubstituted alkene (**83**), the second Heck precursor, in 62% yield.
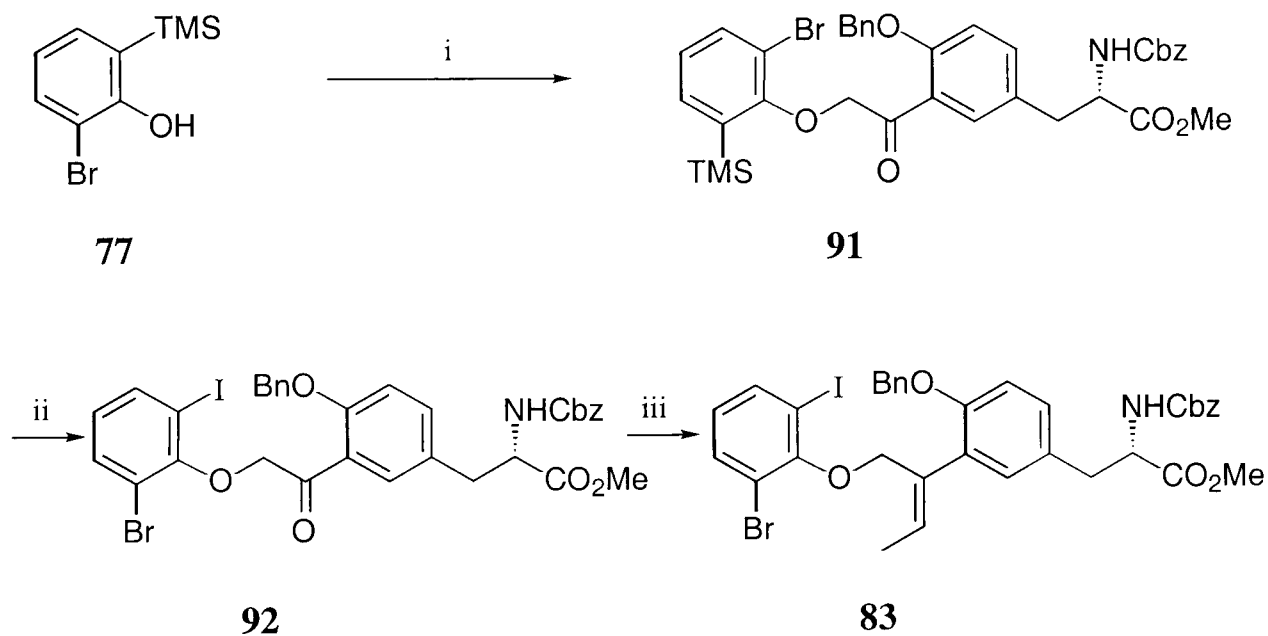
Reagents: i, K_2CO_3, **84**, MeCN, 85%; ii, I_2, $AgBF_4$, EtOH, 99%; iii, NaHMDS, EtPPh$_3$Br, THF, 62%.

Scheme 3

2.2.4 The Heck Reaction

The palladium-catalysed arylation or alkenylation of alkenes is a process known as the Heck reaction.[134] First described by R. F. Heck in the late 1960s,[142] the reaction received little attention in the first decade since its discovery, but has undergone a resurgence in the late 1980s and 1990s. The ability of the reaction to bring about complex structural changes, construct unprecedented molecular frameworks and form quaternary stereogenic centres using only a catalytic amount of palladium(0), has established it as one of the true power tools of modern organic synthesis.

The Heck reaction[134] can be defined as the palladium(0)-catalysed reaction of an alkenyl or aryl halide (**93**) with an alkene (**94**) to create a new C-C σ-bond in the product alkene (**95**), along with the formation of a hydrogen halide as a by-product.

Pd(0), base

93   +   **94**   →   **95**   +   HX
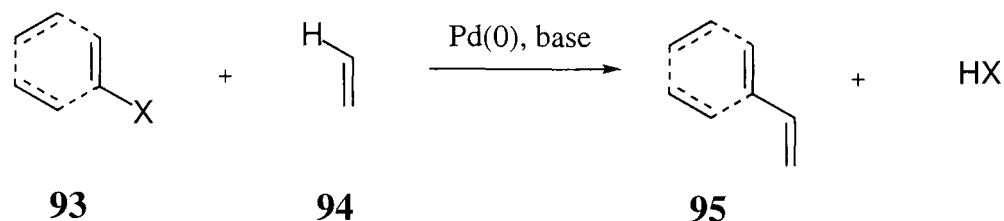
The currently accepted mechanism of the reaction is summarised overleaf. The catalytic active species is believed to be a coordinatively unsaturated 14-electron palladium(0) complex, typically *bis*-(triphenylphosphine)palladium(0) (**96**). This is formed *in situ* by the sequential loss of ligands from the saturated tetra*kis*-(triphenylphosphine)palladium(0). The active species (**96**) initiates the first step in the catalytic cycle by taking part in an oxidative addition reaction with an alkenyl or aryl halide or triflate (R^1-X) to give the 16-electron complex (**97**). Complexation of the reacting alkene to **97** is followed by a *syn* insertion of the alkene into the σ-alkenyl or σ-aryl C-Pd bond, generating the organopalladium species (**98**). The next step in the catalytic cycle involves a simple internal bond rotation to give the organopalladium species (**99**). This event establishes the necessary *syn* relationship between a β-hydrogen atom and the palladium atom. The reaction-terminating *syn* elimination of a β-hydride can now take place to liberate the product alkene (**100**) and the hydridopalladium complex (**101**). Finally, a base-assisted reductive elimination of HX from the hydridopalladium complex (**101**) regenerates the catalytically active 14-electron species (**96**).

Pd(PPh$_3$)$_4$

$\downarrow$ -PPh$_3$

Pd(PPh$_3$)$_3$

$\downarrow$ -PPh$_3$

base.HX

reductive elimination

base

Pd(PPh$_3$)$_2$
96

R^1-X

oxidative addition

H-Pd(PPh$_3$)$_2$-X
101

R^1-Pd(PPh$_3$)$_2$-X
97

syn β-hydride elimination

R^2

alkene insertion

R^1 ⟍ R^2
100

H   Pd(PPh$_3$)$_2$-X
R^1⋯⋯H   ⋯⋯H
H   R^2
99

R^1 Pd(PPh$_3$)$_2$-X
H⋯⋯   ⋯⋯H
H   R^2
98

C-C bond rotation
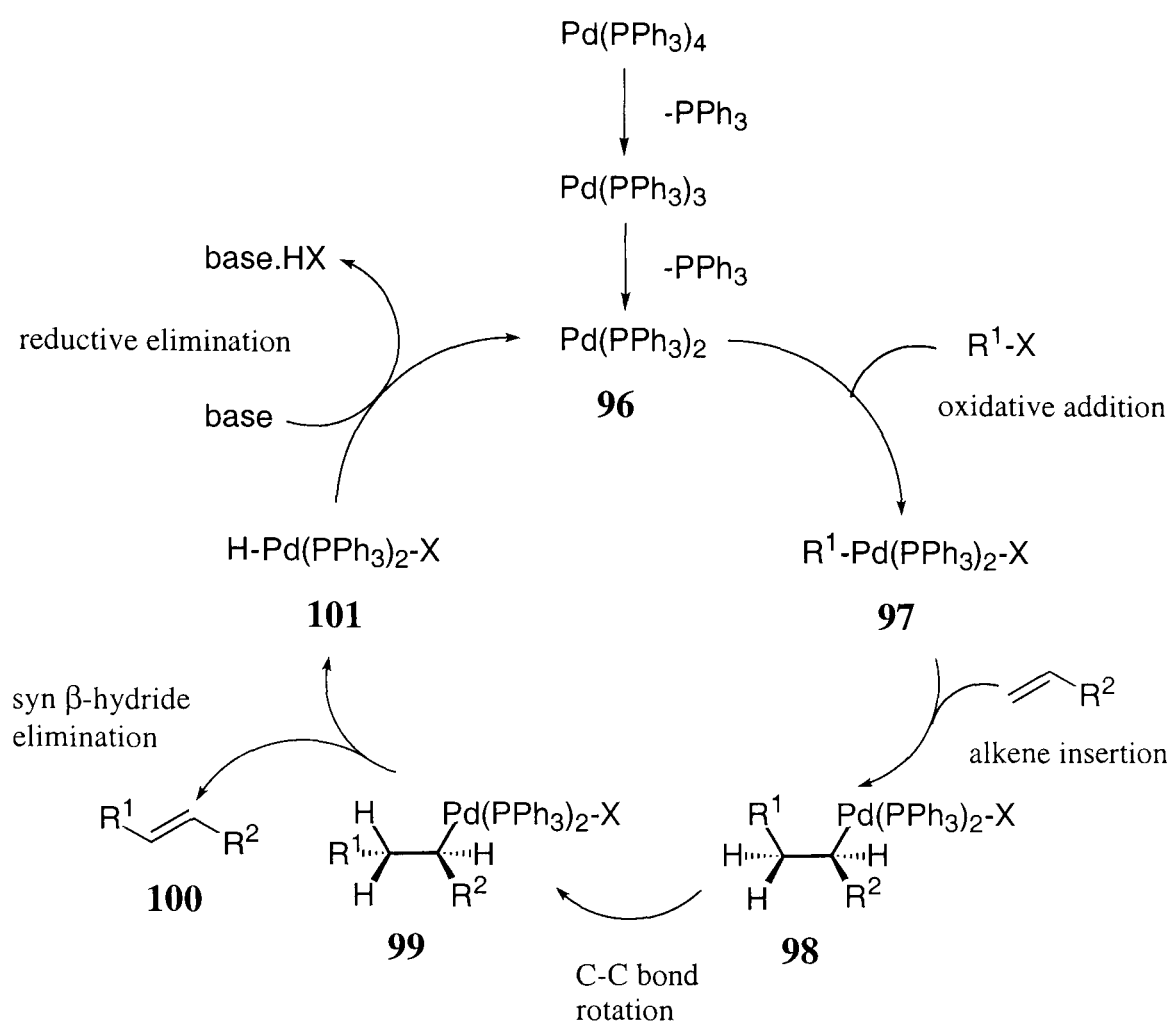
The problem of regioselectivity in the alkene insertion step of the catalytic cycle is one of the most fundamentally important aspects of the Heck reaction. After oxidative addition, the 16-electron complex (**102**) can follow one of the two paths depicted overleaf. The factor determining which path is followed is the nature of the halide, X, in the complex (**102**).[134e,143] If the catalytically active 14-electron palladium(0) species undergoes oxidative addition into an aryl or alkenyl halide bond when X is a halide (usually either bromide or iodide) then the reaction proceeds along Path A. In order for the reacting alkene to form a coordinated complex to the palladium (**103**), then, due to the strong nature of the palladium-halide bond, another ligand must dissociate. This may be a phosphine or a solvent molecule. If, as depicted, a chelating *bis*-phosphine is present, then one of its phosphorus atoms must dissociate before alkene coordination can take place. If X is a triflate then the reaction proceeds along Path B. In this instance, the affinity of the triflate for the palladium is considerably

41

weaker than that of a halide, hence the triflate can readily dissociate to form the cationic complex (**104**) to which the reacting alkene can then coordinate.
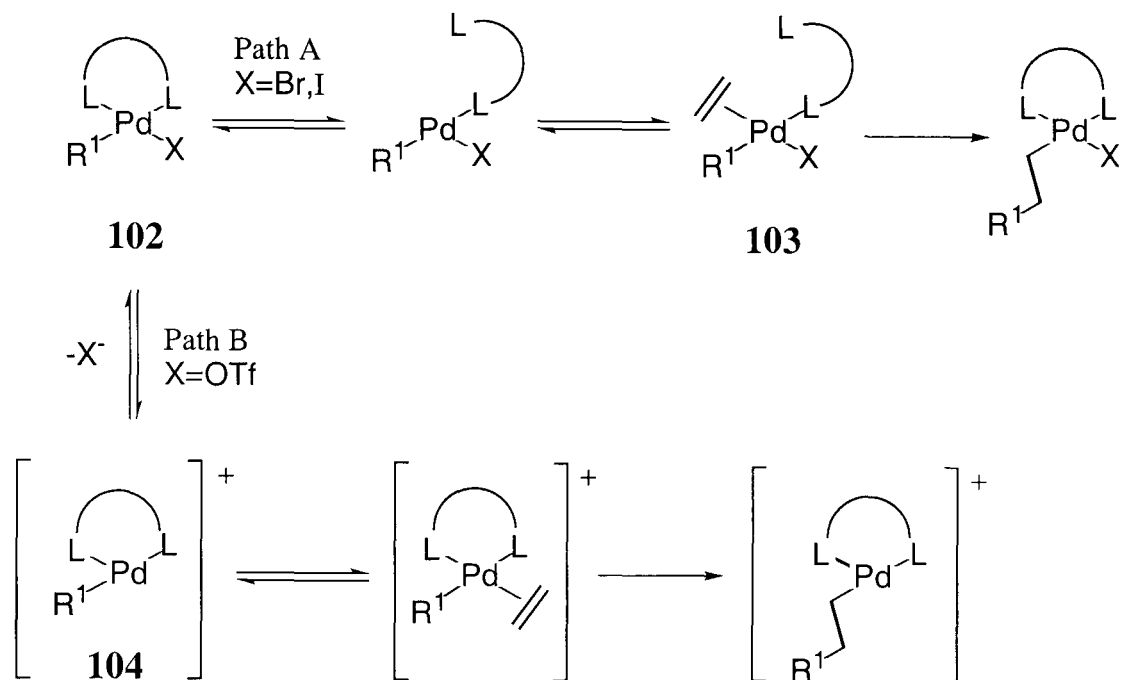
In a simple reaction such as that of an aryl iodide with the α-substituted alkene (**105**), the reaction follows Path A and the alkene coordinates to give a neutral complex similar to **103** shown above. In this case steric considerations dominate and the new C-C bond tends to be formed at the least substituted end of the alkene to give the disubstituted alkene (**106**). In the reaction of an aryl triflate with the α-substituted alkene (**105**) the reaction follows Path B to give a cationic complex similar to **104**. The cationic nature of the palladium species increases the polarisation of the coordinated double bond. Electronic factors now govern the alkene insertion step and the aryl group is transferred to the end of the alkene with the lowest electron density to give the product alkene (**107**).
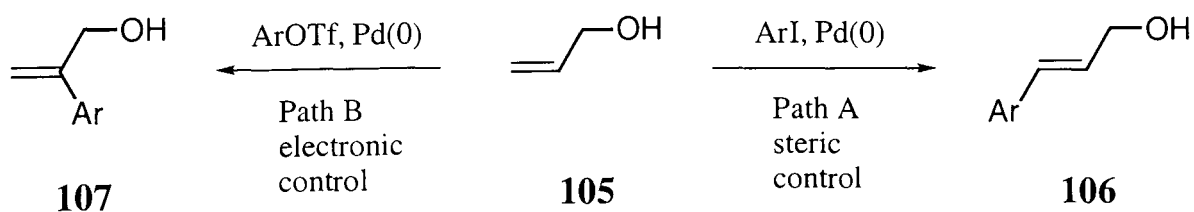
In the intramolecular Heck reaction conformational constraints also exist, in addition to the steric and electronic constraints already discussed. In the alkene insertion step the alkene should ideally adopt a coplanar alignment with the palladium and the carbon atom of the aryl or alkenyl species.[144] This creates the eclipsed conformation depicted in **108** as opposed to the twisted conformation illustrated in **109**.
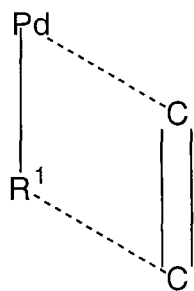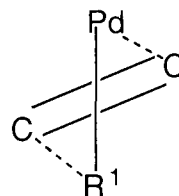
108 Eclipsed   **109** Twisted

Accessing an eclipsed conformation in an intermolecular reaction is not normally a problem and hence the reaction is governed by the steric and/or electronic factors surrounding the orientation of the reacting alkene in the alkene insertion step. However, in an intramolecular reaction the alkene may be constrained to only one eclipsed conformation due to the size and/or shape of the substrate. In this case only one of the possible regioisomers will be observed. For the synthesis of 5-, 6- and 7-membered rings, the reaction almost always occurs *via* the *exo* mode of cyclisation as conformational considerations outweigh any steric or electronic factors in the system.

The well-established intermolecular Heck reaction[134] has proved to be a useful method for extending the carbon framework of a molecule. However, by virtue of its possible application to essentially every type of alkene and tolerance of a variety of functional groups, attention in recent years has centred primarily around the intramolecular variant of the Heck reaction.[134f] Careful choice of substrates and skilful tailoring of reaction conditions has led to a tremendous variety of elegant and highly convergent routes to structurally complex molecules. The intramolecular Heck reaction[134f] is especially suited for the construction of congested polycyclic

frameworks and quaternary stereogenic centres (**110**), which are notoriously difficult to build by conventional means. In these instances, the reacting alkene involved in the cyclisation is geminally substituted.
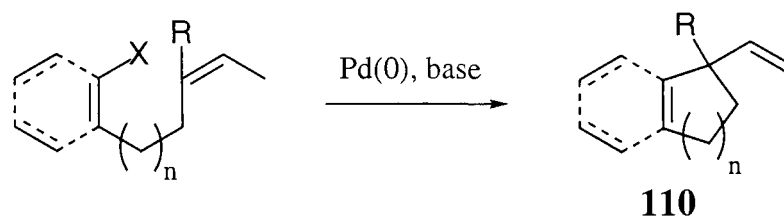
The diverse complexity of molecular architecture that can be constructed utilising the intramolecular Heck reaction[134f] has been amply demonstrated by the research group of Overman. They found that exposure of the aryl iodide (**111**) to a catalytic amount of palladium(0) resulted in the formation of the unsaturated morphinan (**112**) in 60% yield (**Scheme 4**).[145] A new carbocyclic ring and a crucial quaternary stereocentre are formed in this 6-*exo*-trig intramolecular process. Further elaboration of **112** gave the alkaloid (-)-morphine (**113**).
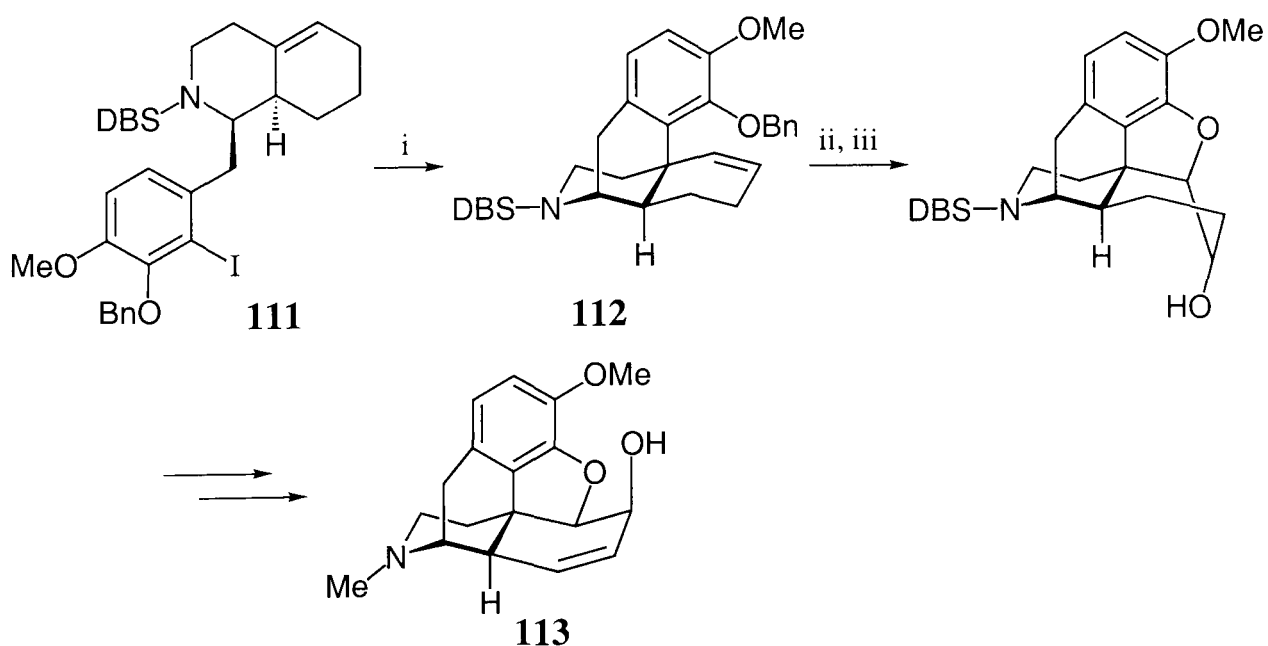
Reagents: i, Pd(OCOCF$_3$)$_2$(PPh$_3$)$_2$, pempidine, PhMe, Δ, 60%; ii, BF$_3$·OEt$_2$, EtSH; iii, ArCO$_3$H, CSA, CH$_2$Cl$_2$.

Scheme 4

When the substrate was modified to include a second alkene (**114**) and subjected to similar reaction conditions, the pentacycle (**115**) was produced in 56% yield.[146] In this transformation, intramolecular Heck insertion proceeded to form the intermediate tetracyclic π-allyl palladium complex (**116**). Intramolecular nucleophilic attack by the free phenolic hydroxyl group on the electrophilic π-allyl palladium complex, then gave the pentacyclic opiate core (**115**), which was also elaborated to (-)-morphine (**113**).

Me

HO   **114**

i

OMe

116
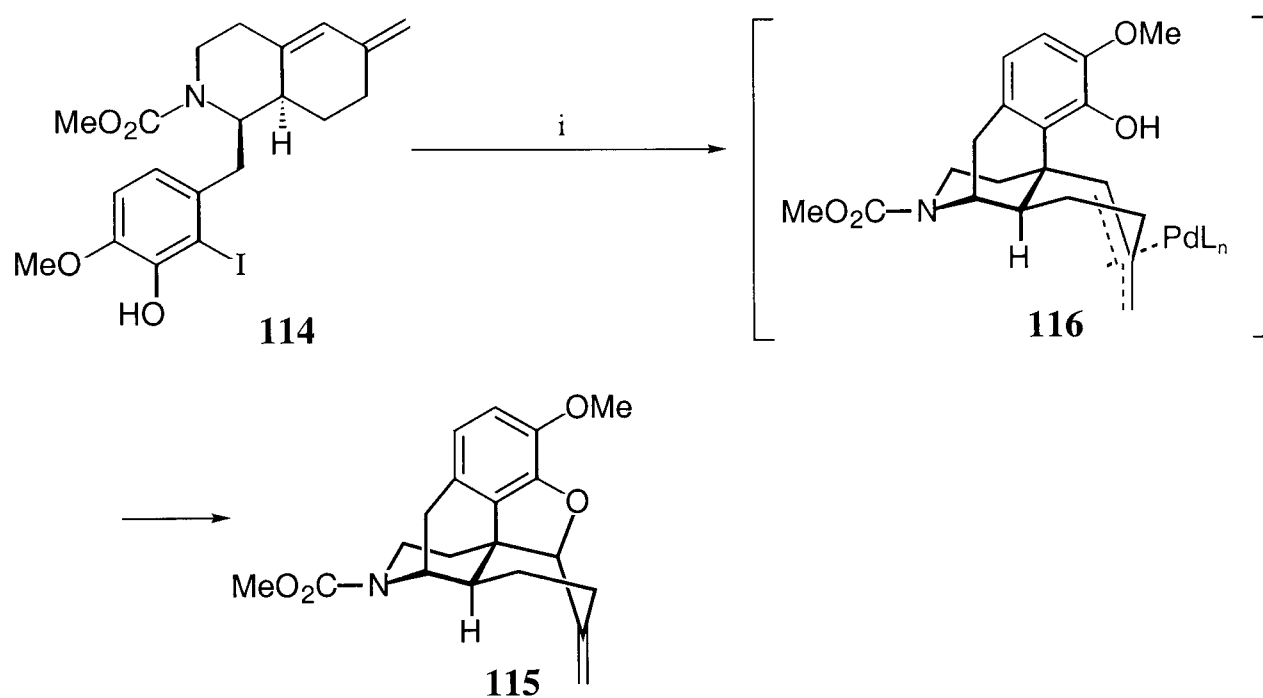
Reagents: i, Pd(OCOCF3)2(PPh3)2, pempidine, PhMe, Δ, 56%.

In systems which lack a β-hydrogen, the *syn* β-hydride elimination pathway in the catalytic cycle is blocked. As a result, the organopalladium species formed after the initial alkene insertion step is available to engage a proximal alkene in the system. This sets in motion a sequence of successive intramolecular Heck reactions from a single substrate which can lead to multiple ring formations and compounds of impressive molecular architecture. A most convincing demonstration of the utility of the tandem intramolecular Heck cyclisation can be found in the first total synthesis of racemic scopadulcic acid A by Overman *et al.*[147] In this concise synthesis, the action of a catalytic amount of palladium(0) on the alkenyl iodide (**117**) results in the formation of the tricycle (**118**) in 83% yield. The sequential Heck insertion reactions

are only possible due to the absence of a β-hydrogen in the organopalladium intermediate (119).

117

119

118
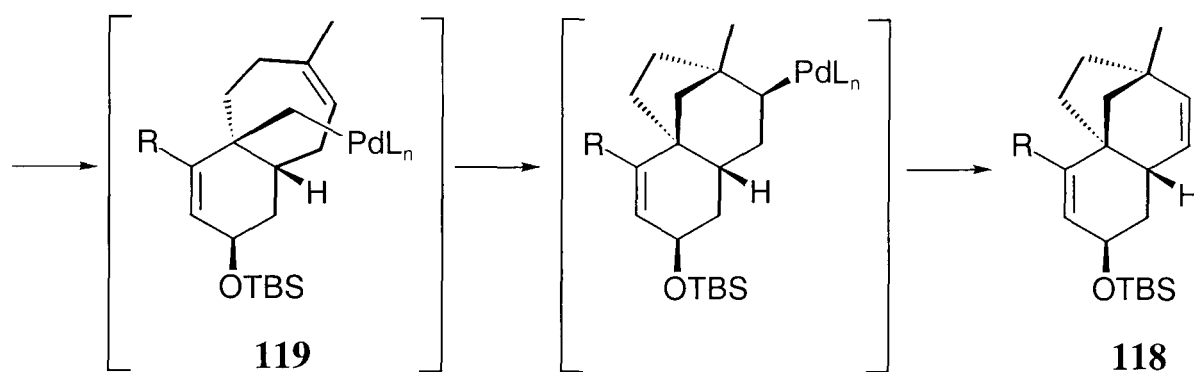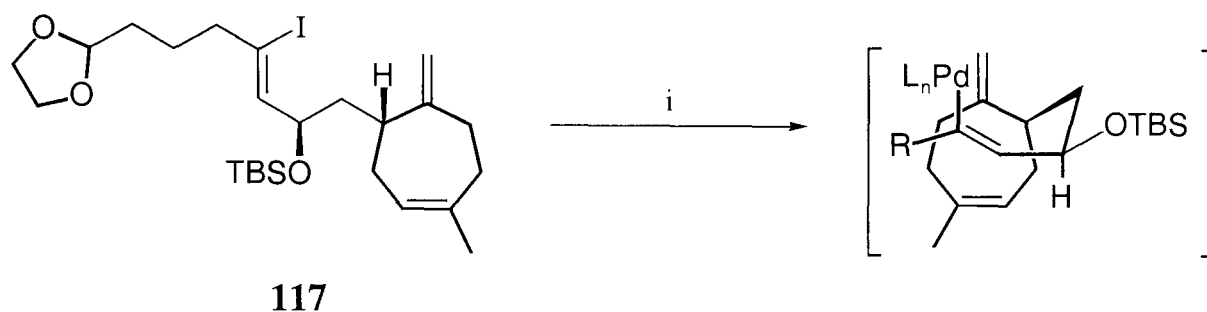
Reagents: i, Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$, THF, Δ, 83%.

The area of cascade Heck cyclisations has been extended far beyond the impressive tandem examples described previously. Negishi *et al* have developed a novel cascade approach to pentacycles which utilises alkynes in the insertion step of the catalytic cycle.[148] In their approach to the pentacycle (120), the alkenyl palladium(II) complex formed by oxidative addition of a catalytic amount of palladium(0) into the alkenyl iodide (121), undergoes a 6-*exo*-dig intramolecular Heck reaction with the proximal alkyne to form a new alkenyl palladium(II) complex (122). This complex can then react with the remaining three alkynes in a similar fashion, with carbonylative intramolecular esterification as the terminating step, to give the pentacycle (120) in 66% yield.
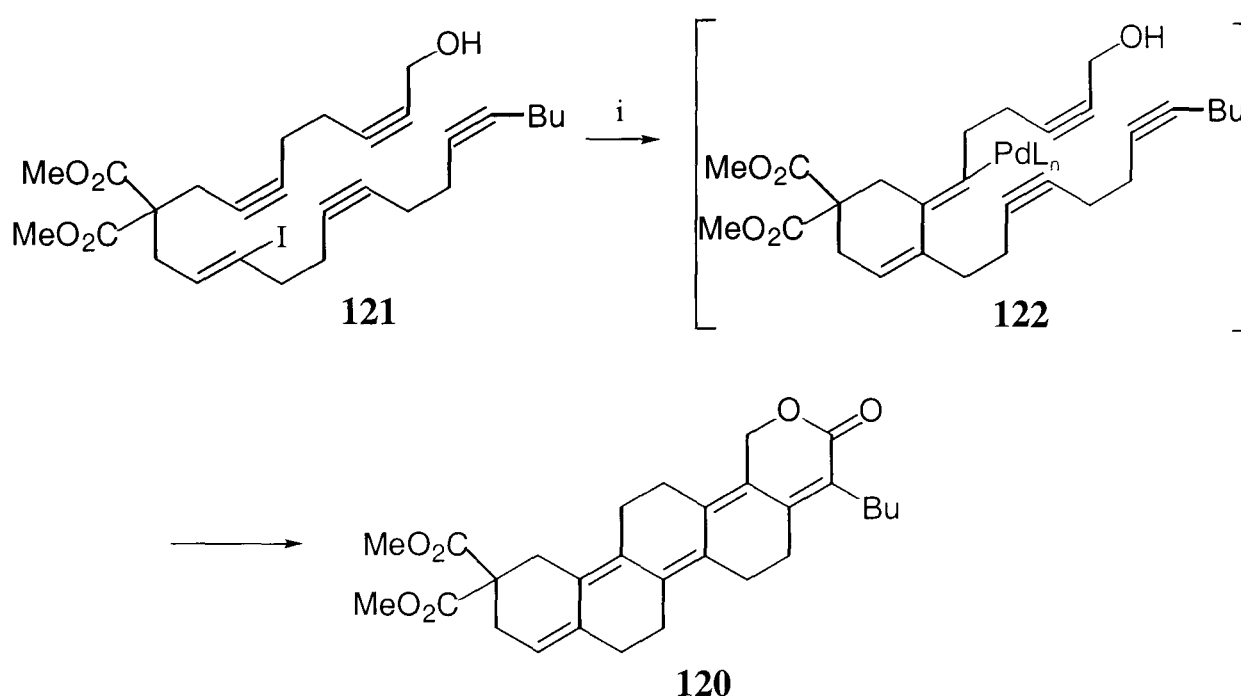
Reagents: i, $Cl_2Pd(PPh_3)_2$, Et_3N, CO, MeOH, Δ, 66%.

All the examples described so far have involved the formation of carbocycles, but it has been demonstrated that the Heck reaction[134] is also a powerful tool in the synthesis of heterocyclic frameworks. The Heck reaction[134] is particularly prevalent in the synthesis of indoles and heterocycles containing the indole skeleton. In 1977 Mori et al described the first intramolecular Heck cyclisation to form the indole system.[149] They found that the aryl bromide (123) could be cyclised to the indole (124) in 43% yield. Under the reported conditions, the initially formed alkene would be exo-cyclic, but this completely isomerises in the reaction mixture to the more stable endo-cyclic position.
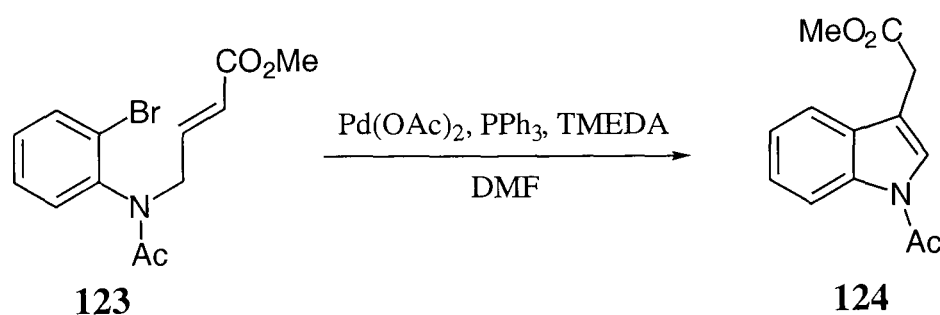
Grigg et al have shown that the Heck reaction can also be employed in the synthesis of lactams.[150] They prepared the lactam (125) by a 6-exo-trig cyclisation of the iodide

47

(**126**), installing the central 6-membered ring and the chiral quaternary carbon centre in 68% yield. This crucial step in the synthesis of the naturally occurring alkaloid (*R,R*)-crinan (**127**) was initially hampered by a proposed palladium(II)-mediated cleavage of the lactam ring. This problem was circumvented by the addition of water to the reaction mixture.
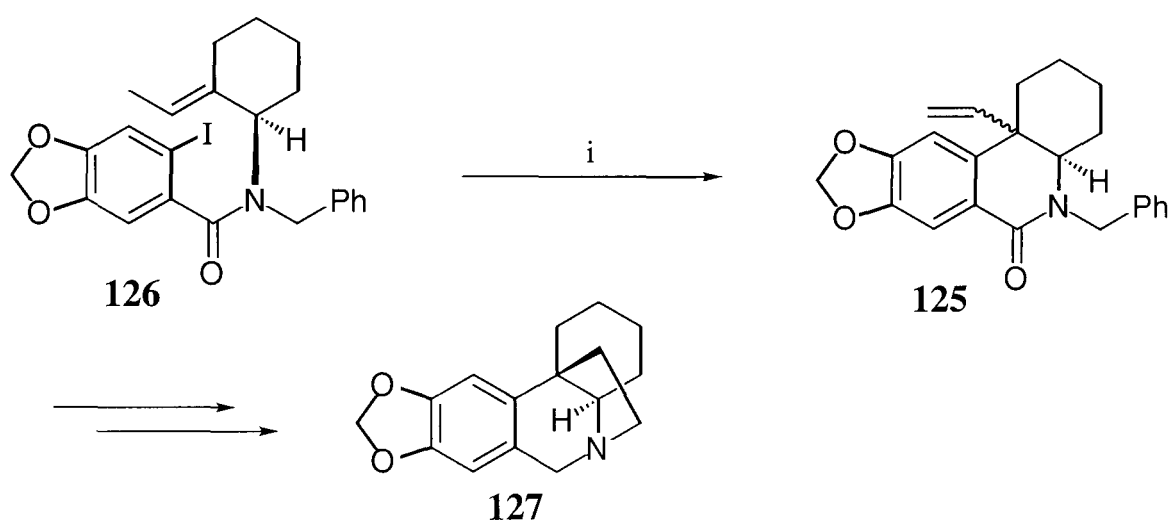
Reagents: i, Pd(OAc)$_2$, P(*o*-tol)$_3$, K$_2$CO$_3$, H$_2$O, MeCN, Δ, 68%.

In a concise synthesis of racemic dehydrotubifoline (**128**), Rawal *et al*[151] accomplished the catalytic palladium(0)-mediated conversion of the alkenyl iodide (**129**) to the natural product (**128**) under the conditions developed by Jeffery[152] in 79% yield. The product of this Heck cyclisation is the enamine (**130**). This substance is a participant in a tautomeric equilibrium with the imine (**128**), which is shifted substantially in favour of the natural product (**128**).
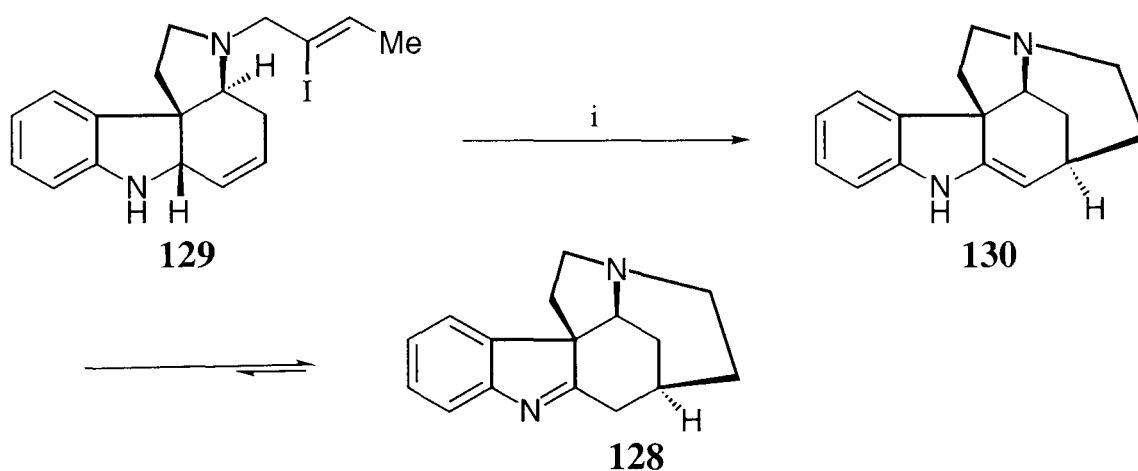
Reagents: i, Pd(OAc)$_2$, K$_2$CO$_3$, *n*-BuN$_4$Cl, DMF, Δ, 79%.

The tolerance of potentially sensitive functional groups to the conditions required for Heck cyclisation is particularly evident in the impressive assembly of the tetracycle (**131**), an advanced intermediate in the synthesis of FR-900482 (**132**) by Danishefsky *et al.*[153] In the crucial C-C bond forming reaction, exposure of the aryl iodide (**133**) to a catalytic amount of palladium(0) effected the desired Heck arylation to afford the tetracycle (**131**) in an excellent 93% yield.

133

131

132
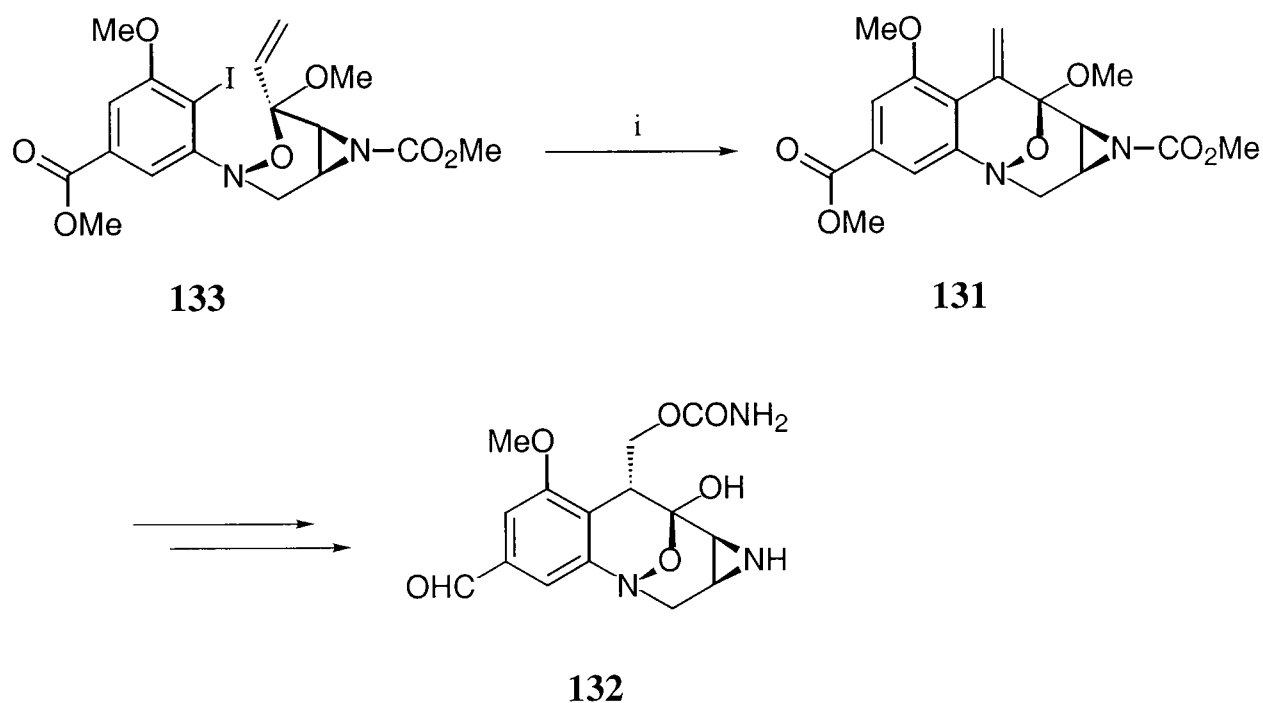
Reagents: i, Pd(PPh₃)₄, Et₃N, MeCN, Δ, 93%.

The intramolecular Heck reaction[134f] is often highly diastereoselective. The use of chiral auxiliaries in providing stereocontrol has received surprisingly little attention. However, Grigg *et al* have shown that amino ethers may be effective chiral auxiliaries for the Heck reaction.[154] Thus, when the acyclic alkene (**134**) bearing the SAMP chiral auxiliary was subjected to standard Heck cyclisation conditions, diastereoselectivities of 95% were achieved in the product alkene (**135**).

134   **135**
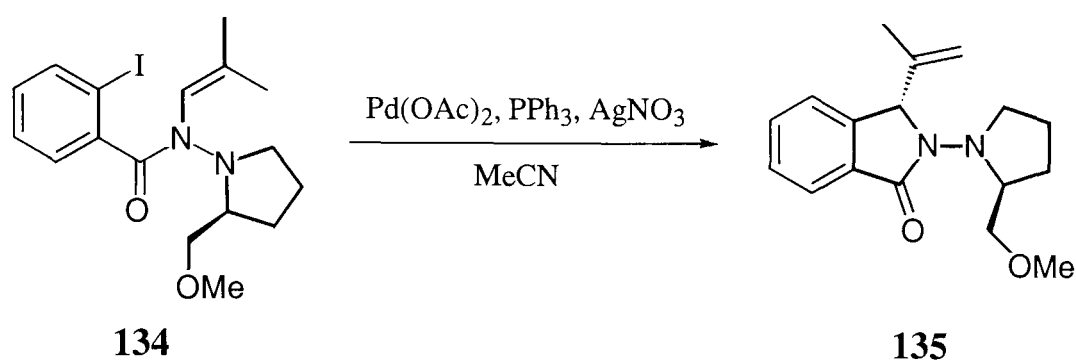
The subtle tailoring of reaction conditions to control the diastereoselectivity of an intramolecular Heck reaction has been described by Overman *et al*[155] in their synthetic efforts towards the hexacyclic indole alkaloid gelsemine (**136**). By altering the nature of the base, the cyclisation could be tuned to favour one of the possible oxindole products, as shown overleaf. Thus, when triethylamine was used as the base in the cyclisation of the aryl bromide (**137**), the reaction gave an 89:11 ratio of stereoisomers in favour of the oxindole (**138**). However, when silver phosphate was employed as the base, a 3:97 ratio of stereoisomers in favour of the oxindole (**139**) was observed. The proposal to account for this reversal in stereoselectivity was founded on the nature of the 16-electron aryl palladium(II) complex formed by oxidative addition of palladium(0) to the aryl bromide (**137**). When triethylamine was used as the base, the neutral aryl palladium(II) complex (**140**) was formed. This complex could coordinate the proximal alkene to give the oxindole (**138**). However, when silver phosphate was employed as the base, the ability of the silver salt to sequester the bromide away from the palladium led to the formation of a cationic palladium intermediate. This cationic species could coordinate both alkenes present in the substrate to form the aryl palladium(II) intermediate (**141**) and ultimately the oxindole (**139**).

50
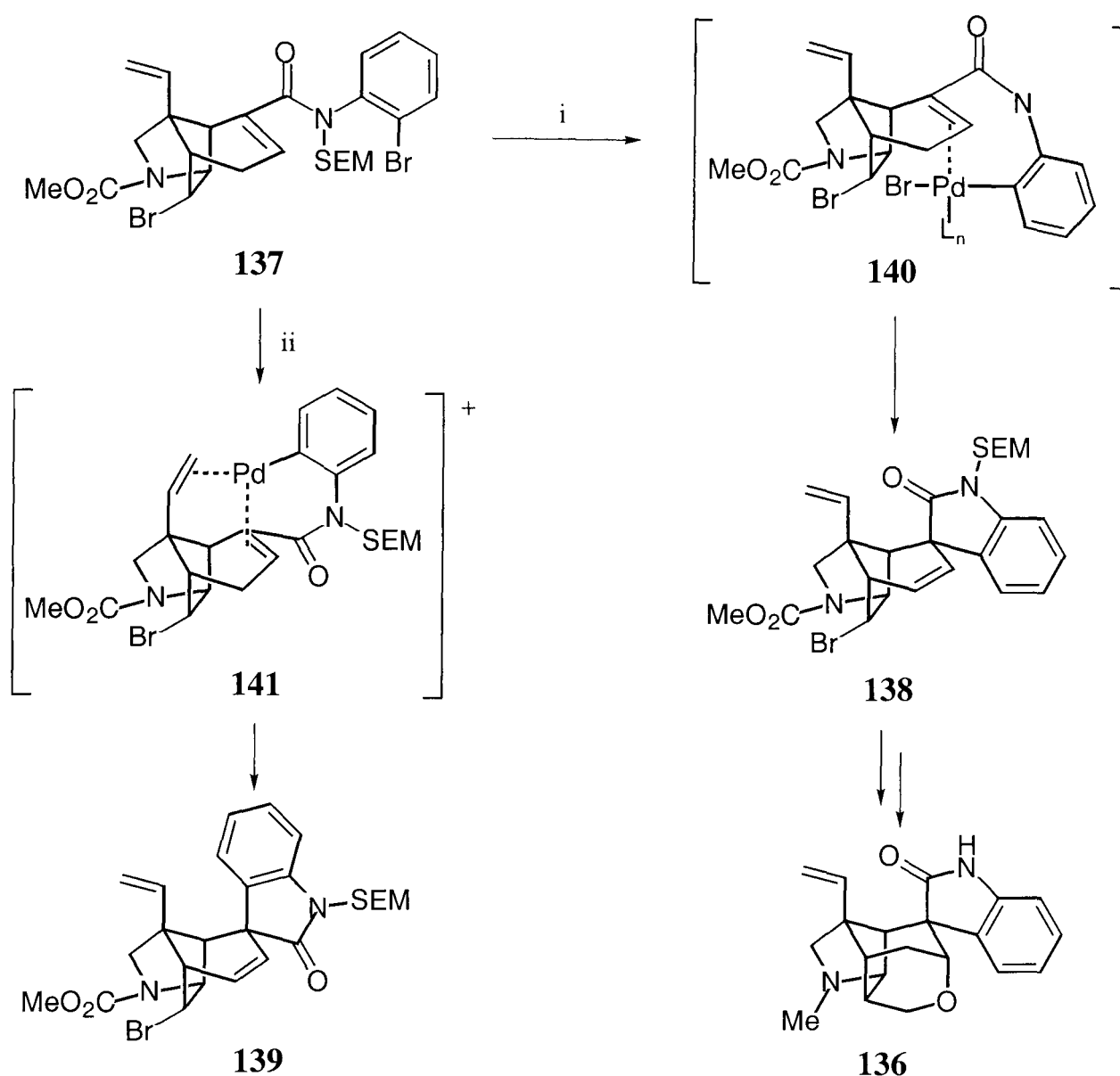
Reagents: i, Pd$_2$(dba)$_3$, Et$_3$N, PhMe, Δ; ii, Pd$_2$(dba)$_3$, Ag$_3$PO$_4$, THF, Δ.

The area of the asymmetric Heck reaction has been explored mainly by the research group of Shibasaki.[134d] They have demonstrated that prochiral aryl and alkenyl iodides and triflates can be cyclised to products of high optical purity. Given the many reports of chiral phosphine ligands dating back to the early 1970s,[156] it is perhaps a little surprising that the phosphine-mediated asymmetric Heck reaction was not attempted until the late 1980s. However, the reaction has since been successfully developed to the point where both tertiary and quaternary stereogenic centres can be generated with a high degree of enantioselectivity. The bulk of the reported examples involve intramolecular ring closure reactions,[134f] which have the advantage of allowing relatively easy control of alkene regiochemistry and geometry in the product, in addition to tolerating less reactive alkene substrates. The chiral

bis-phosphine BINAP has been found to be the most successful ligand for this reaction. The highest degree of influence over the enantioselectivity of the reaction is exerted when both phosphorus atoms are bound to the palladium atom. For this to be the case when the palladium coordinates to the alkene, the reaction must proceed *via* a cationic 16-electron palladium complex. Hence, the use of silver salts is essential for obtaining good enantiocontrol with aryl or alkenyl iodides.[157] With these factors in mind, Shibasaki *et al* have shown that the vinyl iodide (**142**) can be cyclised to the decalin system (**143**) in 67% yield and 87% ee.[158]
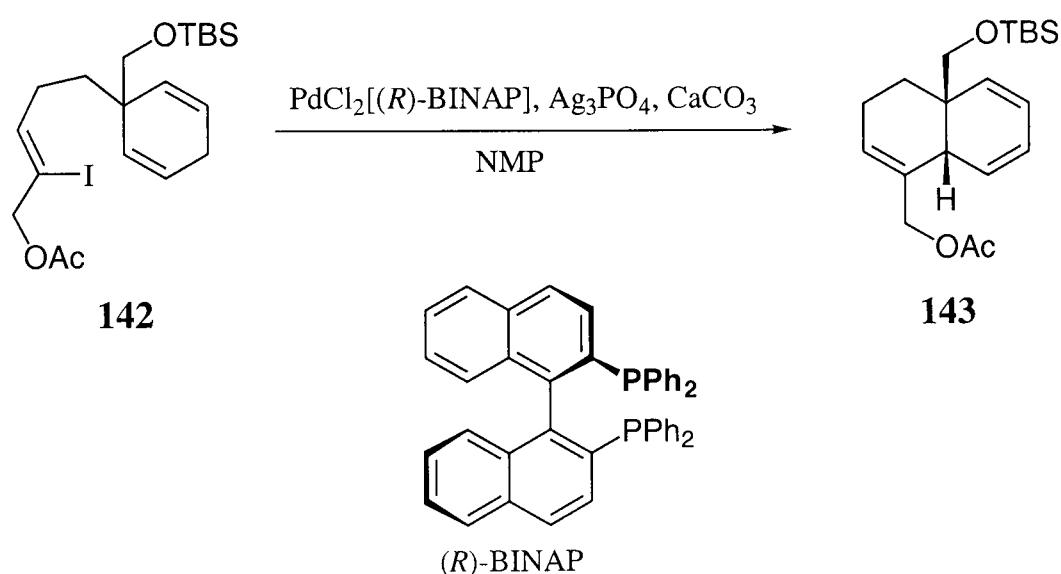
In an extension of this work, the Shibasaki group have prepared the optically active bicyclic diene (**144**) from the alkenyl triflate (**145**).[159] To rationalise this novel transformation, it was proposed that oxidative addition of an asymmetric palladium(0) catalyst first generated the cationic 16-electron palladium complex (**146**). Insertion of the coordinated alkene then gave the transitory π-allyl palladium complex (**147**). This complex is captured in a regio and stereocontrolled fashion by an acetate ion to give the bicycle (**144**) in 89% yield and 80% ee.
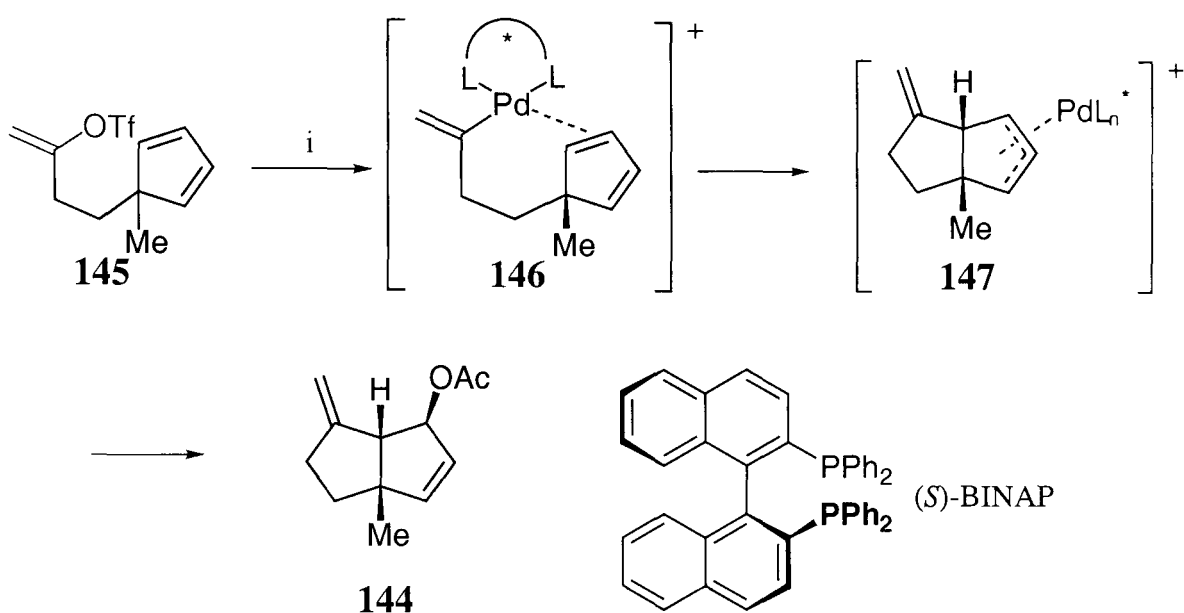
Reagents: i, Pd(OAc)$_2$, (S)-BINAP, n-Bu$_4$NOAc, DMSO, 89%, 80% ee.

By varying the nature of the base, Overman *et al* have shown that it is possible to access either enantiomer of a cyclic indolone using the same enantiomer of the chiral BINAP ligand.[160] Using silver phosphate as the base in the asymmetric Heck reaction of the aryl iodide (148), resulted in the formation of the (S)-indolone (149) in 81% yield and 71% ee. If pempidine is employed as the base, then the (R)-indolone (150) is formed in 77% yield and 66% ee.
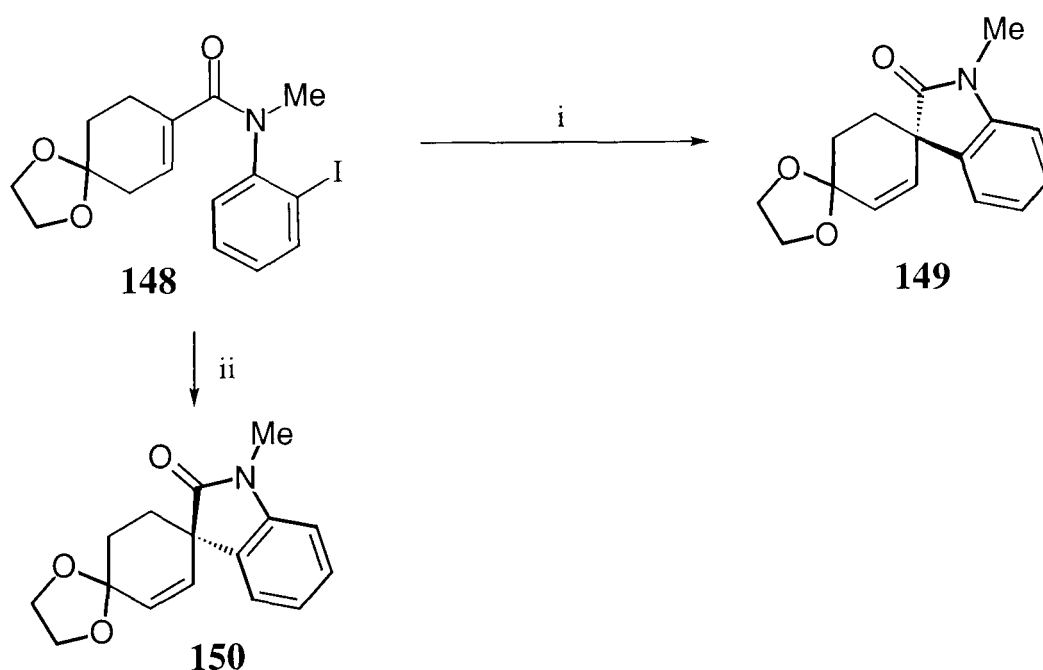
Reagents: i, Pd$_2$(dba)$_3$, (R)-BINAP, Ag$_3$PO$_4$, DMA, Δ, 81%, 77% ee, ii, Pd$_2$(dba)$_3$, (R)-BINAP, pempidine, DMA, Δ, 77%, 66%ee.

53

This brief overview of some of the fascinating synthetic accomplishments that have incorporated the Heck reaction in key steps, has shown that, in the past few years, the Heck reaction has started to reveal its full potential as a powerful tool for the synthetic chemist. The broad spectrum of recent achievements, in particular, the construction of quaternary carbon centres in sensitive heteronuclear frameworks and the advances in diastereo and enantiocontrolled reactions, originally led us to investigate this procedure for the formation of the quaternary carbon centre in the benzofuran-oxazole acid fragment (**69**).

2.2.5 Synthesis of the Benzofuran Amide Fragment (70)

With multigram quantities of the iodide (**74**) in hand, we focused our attention on the preparation of the amide fragment (**70**). Crucial to this phase of the synthesis of the benzofuran oxazole acid fragment (**69**), was the implementation of an intramolecular Heck reaction[134f] to install the quaternary carbon centre. On construction of this centre, the major challenge was to elaborate the resulting terminal alkene to a keto amide function for cyclisation to the trisubstituted oxazole.
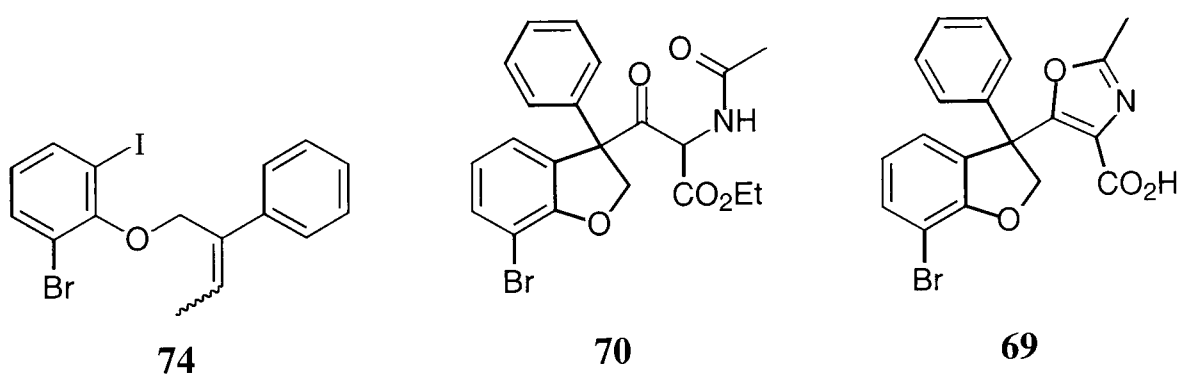
Following an extensive survey of the literature conditions for the Heck reaction and previous work by colleagues on the project,[128] the iodide (**74**) was subjected to the combined action of palladium(II) acetate, triphenylphosphine and silver carbonate in DMF at 80°C to give the terminal alkene (**73**) in a moderate 53% yield.
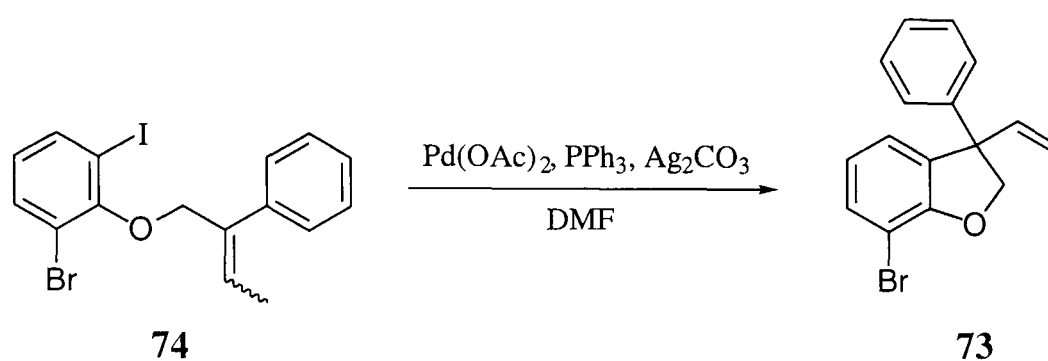
Unfortunately, when the iodide (**83**) was subjected to the Heck reaction conditions, no cyclised product (**150**) was obtained. A vast array of reaction conditions were employed in an effort to effect the 5-*exo*-trig ring closure. These included the use of different dipolar aprotic solvents, amine and inorganic bases, silver[161] and thallium[162] salts as additives, tetrabutylammonium iodide and chloride as phase-transfer agents[152] and a variety of temperatures and reaction times. Although, in every reaction, the substrate was completely consumed, no identifiable products could be isolated. One possible explanation for the failure of this reaction is that the catalytically active palladium(0) species is poisoned by coordination of the carbamate function. Following oxidative addition this process could compete with alkene insertion, hence blocking the catalytic cycle and leading to a variety of unusual by-products. Supporting evidence for this theory is provided by recent studies within the Pattenden group.[163] Exposure of the iodide (**151**), which lacks the carbamate function, to the Heck reaction conditions outlined overleaf, resulted in the formation of the lactone (**152**) in a moderate 52% yield.

151 → **152**
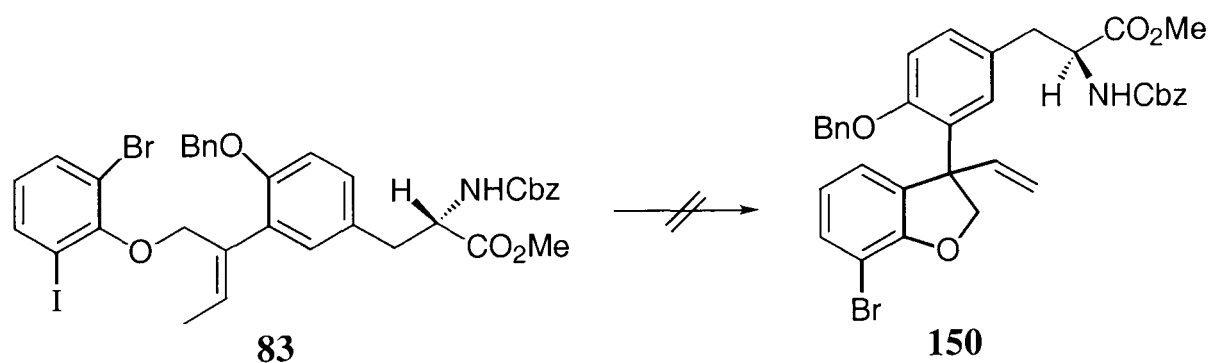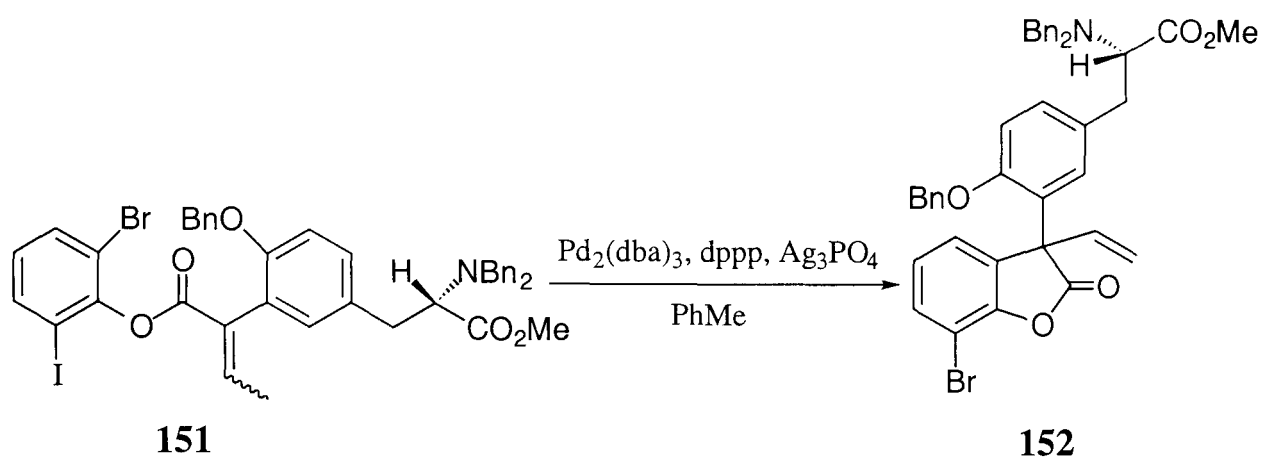
The success of the Heck reaction with the iodide (**74**), led us to concentrate our efforts solely on the formation of the benzofuran oxazole acid (**69**) and advancement to the macrocyclic core of diazonamide A (**64**). Following our retrosynthetic plan, the next target became the ketone (**71**). As part of a study towards the total synthesis of tetronasin,[133] Nomura *et al* recently described the conversion of hindered aldehydes (**153**) to ketones (**154**) using methyl (diazoacetoxy)acetate (**155**) and zirconium chloride. The keto esters (**154**) could be cyclised on treatment with TBAF to provide the γ-unsubstituted α-acyltetronic acids (**156**).

153   **155**   **154**

156
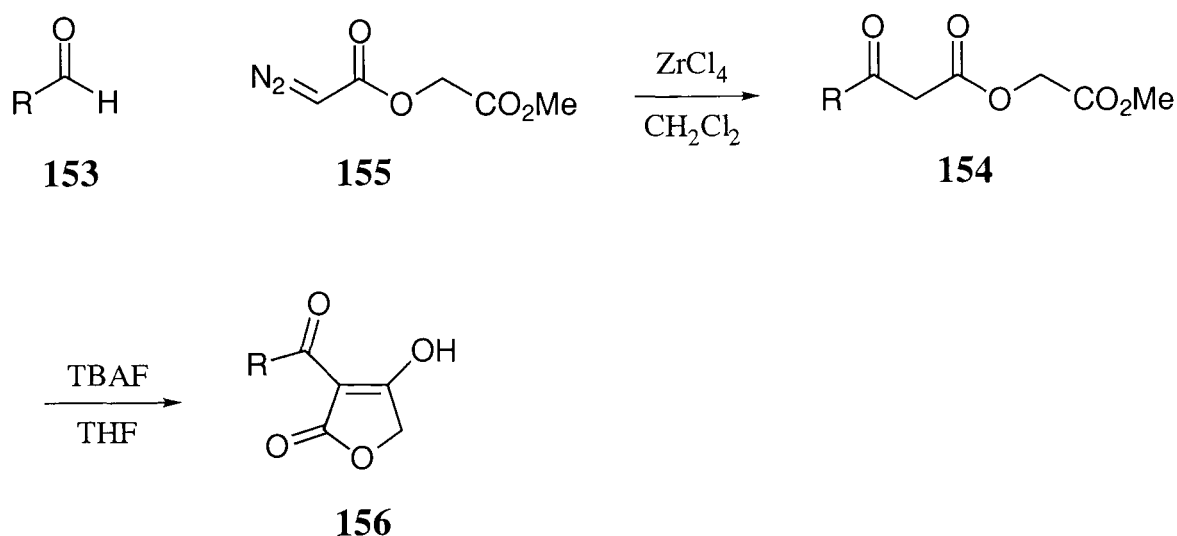
With this precedent in hand, the terminal alkene (**73**) was treated with a catalytic amount of osmium tetroxide and sodium periodate to provide the hindered aldehyde (**72**) in a poor 40% yield (**Scheme 5**).[132b] No improvement in yield could be obtained by carrying out this procedure over two steps, with initial isolation of the intermediate

56

diol, or by treating the terminal alkene (73) with ozone.[132a] However, when the aldehyde (72) was exposed to ethyl diazoacetate and zirconium chloride at 0°C, the two carbon homologation[133] proceeded smoothly to give the ketone (71) in 84% yield.
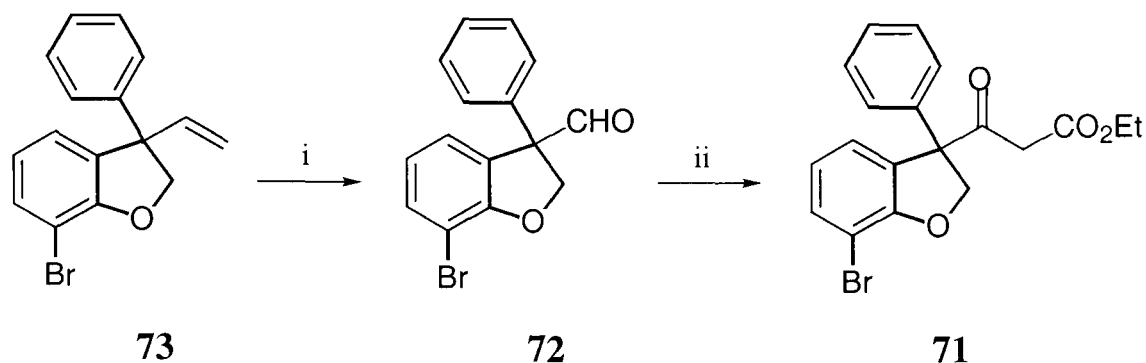
Reagents: i, OsO$_4$, NaIO$_4$, THF, H$_2$O, 40%; ii, ZrCl$_4$, N$_2$CHCO$_2$Et, CH$_2$Cl$_2$, 84%.

Scheme 5

The task now was to introduce an amine function at the position α to both the ketone and ester functions present in the ketone (71), which would ultimately provide the nitrogen atom of the trisubstituted oxazole. It was our initial intention to obtain this amine by the reduction of an azide, which we anticipated we could prepare by nucleophilic displacement of a bromine atom with an azide anion.[164] Hence, the ketone (71) was treated with sodium hydride and bromine at 0°C to give the bromide (157) (**Scheme 6**). When the bromide (157) was then exposed to sodium azide, some nucleophilic substitution was detected to give the azide,[164] which existed in its enol form (158). However, due to the identical polarity of the three substrates, the azide (158) could only be obtained in a mixture which included the ketone (71) and the bromide (157). As a result, all attempts to reduce the azide (158) to the amine (159) using the Staudinger reaction,[165] hydrogenation,[166] or trimethylsilyl iodide,[167] then subsequent acylation, gave only complex mixtures of several unidentifiable products.
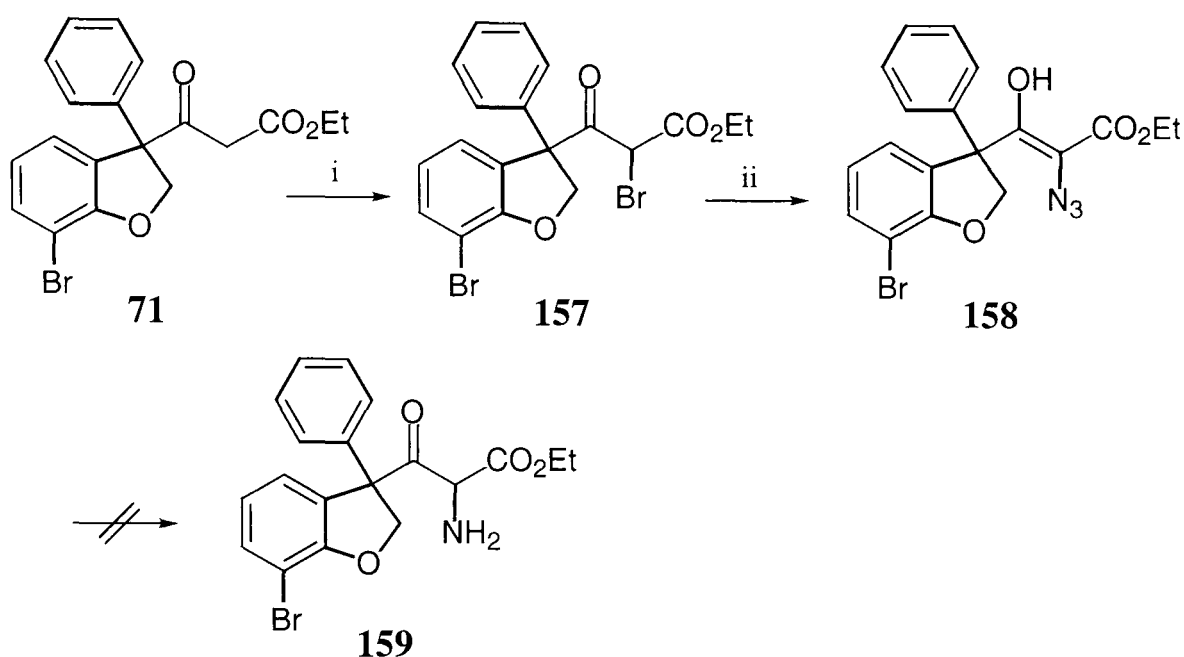
Reagents: i, NaH, Br_2, THF; ii, NaN_3, DMF.

Scheme 6

Having failed in our attempts to prepare and reduce the azide (**158**), we sought an alternative nitrogen-containing functional group which we could elaborate to an amine function. One of the most common methods for preparing α-amino ketones is utilised in the conventional Knorr synthesis of pyrroles.[168] In this classic reaction, nitrosation of the active methylene group in the ketone (**160**) is followed by reduction of the oxime (**161**) to give the amine (**162**) (**Scheme 7**). The amine (**162**) then undergoes condensation with a second ketone (**163**) to give the pyrrole (**164**).
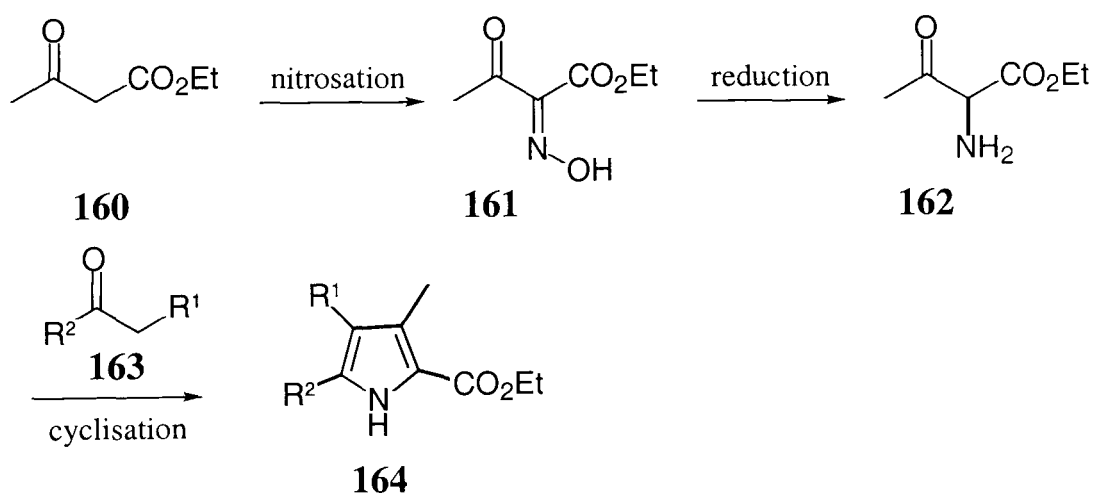
Scheme 7

Application of this methodology to our system began by treatment of the ketone (**71**) with sodium nitrite in aqueous acetic acid (**Scheme 8**).[168] The transitory nitronium ion was captured by the active methylene group to provide a putative nitro species which tautomerised to give the oxime (**165**) as a 2:1 mixture of geometrical isomers in an excellent 94% yield. Reduction of the oxime (**165**) by treatment with activated zinc dust in acetic acid[168] provided the salt (**166**). Since α-amino ketones are known to decompose readily by self-condensation,[169] no attempt was made to purify the salt (**166**). Instead, immediate treatment of **166** with triethylamine liberated the reactive amine function which underwent acylation on exposure to acetyl chloride to give the desired amide (**70**) in 71% overall yield.

Br
71

i →

Br
165

ii →

Br
166

iii →

Br
70
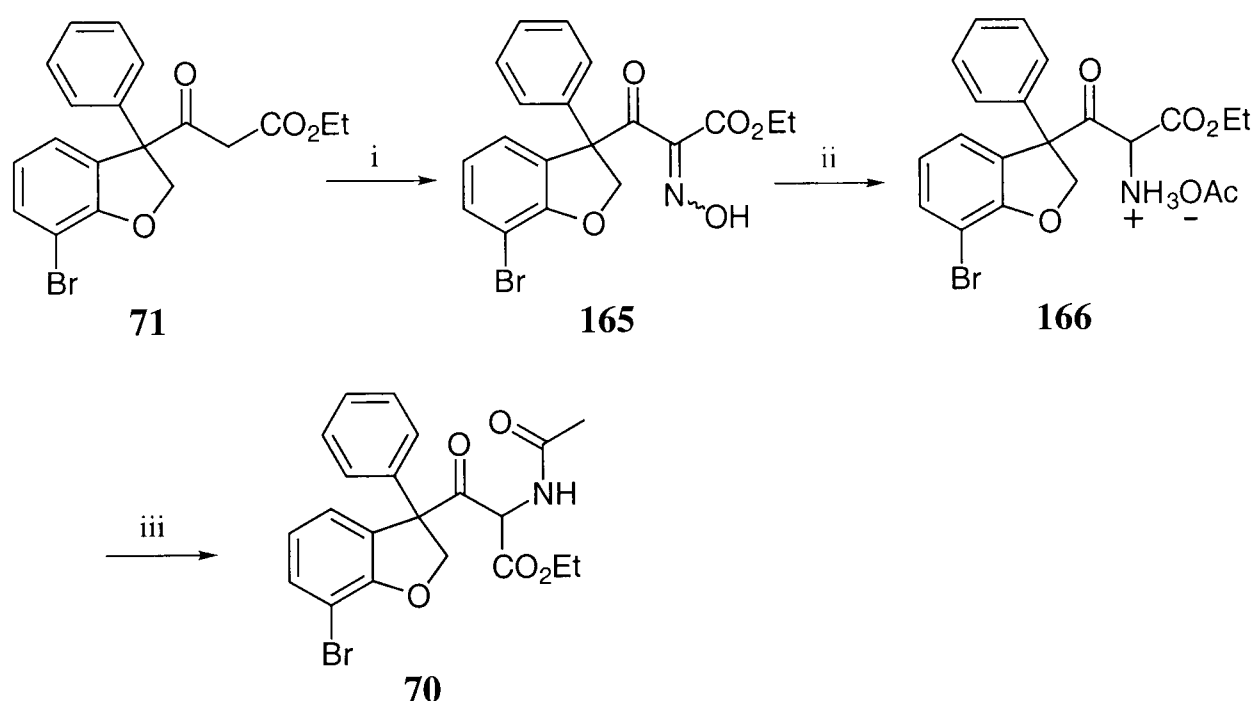
Reagents: i, $NaNO_2$, AcOH, H_2O, 84%; ii, Zn, AcOH, H_2O; iii, Et_3N, AcCl, CH_2Cl_2, 71% (2 steps).

Scheme 8

Although the synthesis described above provided us with an efficient route to the amide (**70**), we also considered an alternative approach, again starting from the ketone (**71**), which avoided the formation of an α-amino ketone intermediate. We were aware of the recent investigations conducted by Moody *et al* into the synthesis of functionalised *mono-* and *bis*-oxazoles.[170] This publication described the rhodium(II)-catalysed reaction of diazocarbonyl compounds in the presence of

primary amides, which resulted in the regioselective insertion of the carbenoid into the amide N-H bond and formation of β-carbonyl amides.

Insertion reactions of metallocarbenoids are widely used in synthesis, although, with the exception of the intramolecular insertion into the N-H bond of a β-lactam developed by Merck as a route to carbapenems and related compounds,[171] the N-H insertion reaction has found little use to date.[172] In a projected synthesis of the natural product phenoxan, Moody *et al* showed that the amide (167) underwent reaction with the rhodium carbenoid derived from the diazomalonate (168) to give the N-H insertion product (169) in 81% yield.
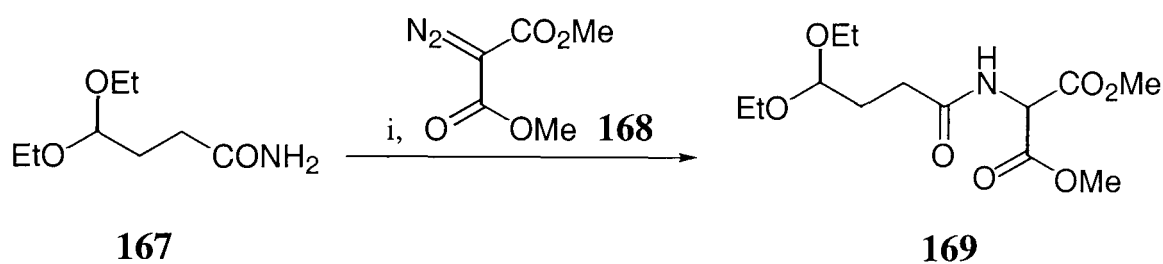
Reagents: i, $Rh_2(OAc)_4$, PhMe, Δ, 81%.

In a bid to effect a rhodium(II)-catalysed N-H insertion reaction to form the amide (70), we initially prepared the diazo compound (170) by treatment of the ketone (71) with triethylamine and 4-acetamidobenzenesulfonyl azide in 99% yield (**Scheme 9**)[173] However, the diazo compound (170) failed to undergo regioselective N-H insertion on treatment with rhodium(II) acetate and acetamide in refluxing chloroform. The only product which could be identified from the complex reaction mixture was the benzofuran (171). A possible mechanistic explanation for production of the benzofuran (171) involves, after initial formation of the rhodium carbenoid (172), a hydride transfer to give the oxonium ion (173), as shown overleaf. Decomplexation of the rhodium species would then be expected to provide the stabilised carbanion (174) which could attack the electrophilic oxonium ion in an intramolecular fashion to give the cyclobutanone (175). A retro-[2+2] reaction to open the strained cyclobutanone ring would finally provide the benzofuran (171).

60
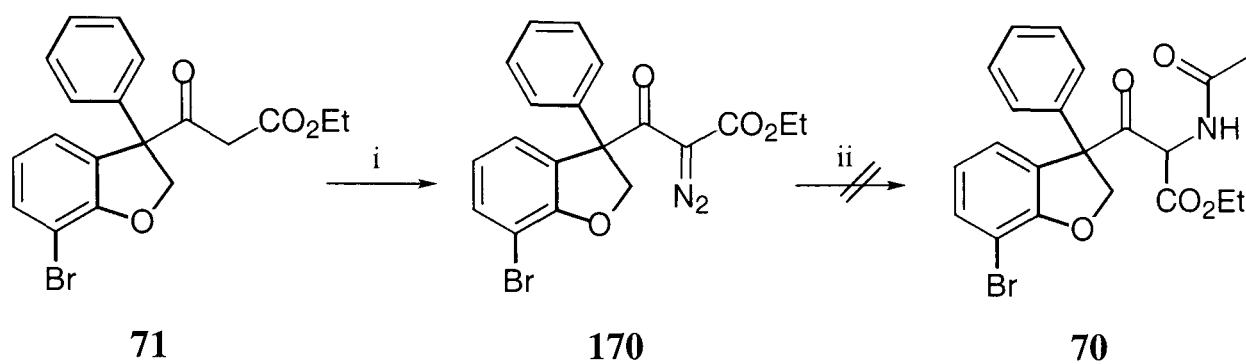
Reagents: i, Et$_3$N, CH$_3$CONHC$_6$H$_4$SO$_2$N$_3$, MeCN, 99%; ii, Rh$_2$(OAc)$_4$, MeCONH$_2$, CHCl$_3$, Δ.

Scheme 9
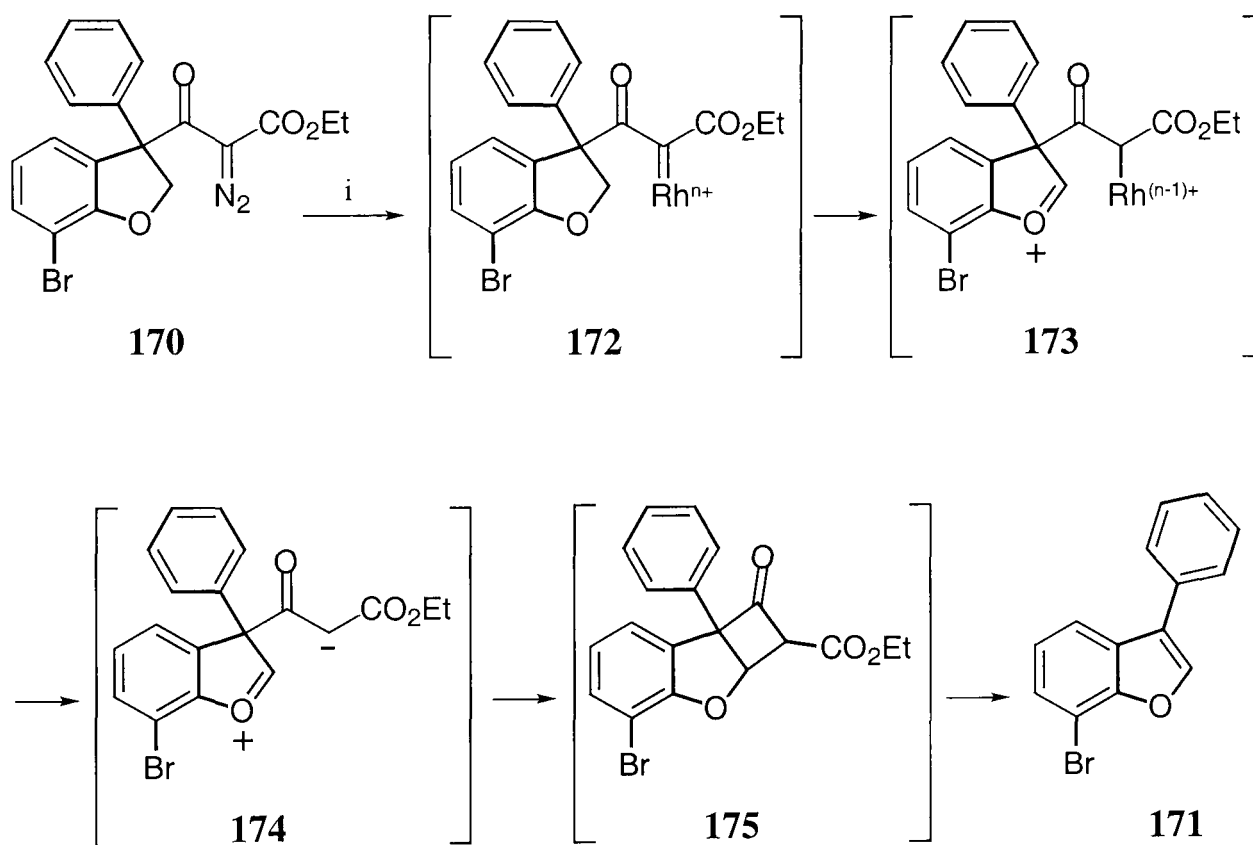
Reagents: i, Rh$_2$(OAc)$_4$, MeCONH$_2$, CHCl$_3$, Δ.

Despite the failure of the carbenoid N-H insertion approach, a successful strategy for the preparation of the amide fragment (**70**), *via* the oxime (**165**), was now in place. The next task to be addressed was the cyclisation of the keto amide function in **70** to a trisubstituted oxazole.

61

2.2.6 Oxazole Formation

The name oxazole was introduced by Hantzsch over a century ago,[174] but the parent ring was not synthesised until some sixty years later. The widespread occurrence, uses and synthesis of oxazole derivatives since that time, have been the subject of extensive reviews.[175] A range of substitution patterns are possible around the oxazole ring, but the 2,4-disubstituted oxazole is by far the most common type found in natural products and the vast majority of research has been towards those compounds possessing a 4-carboxyl substituent. Because of the many roles that these compounds play in natural product and synthetic organic chemistry, many methods have been developed for their efficient construction. With such a plethora of synthetic methods available, only the more relevant examples from the literature will be discussed here.

Early methods for oxazole formation focused on the combination of imidates with amino acids. The procedure of Cornforth,[176] with modifications developed by Meyers,[177] involves initial condensation between ethyl acetimidate hydrochloride (**176**) and glycine ethyl ester hydrochloride to give the imidate (**177**) in 50% yield (**Scheme 10**). Formylation of the imidate (**177**) on treatment with potassium *t*-butoxide and ethyl formate provides the enolate salt (**178**), which can be cyclised to the oxazole (**179**) in refluxing acetic acid in 55% overall yield.
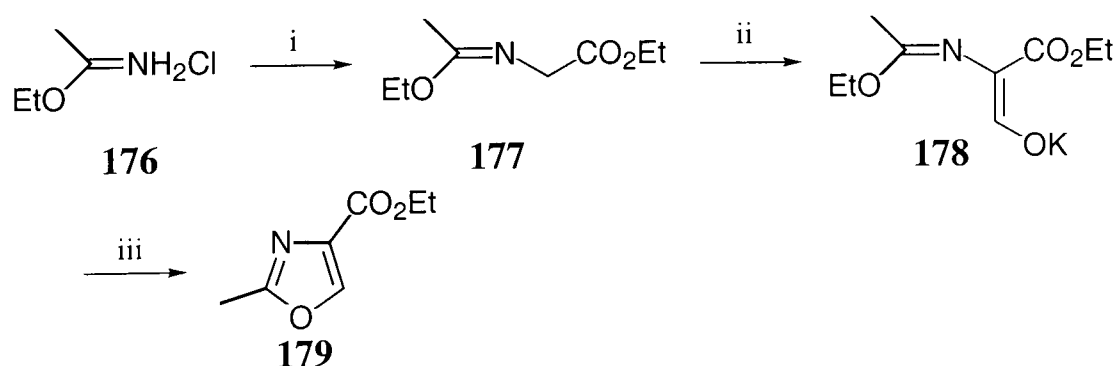
Reagents: i, glycine.OEt.HCl, K_2CO_3, Et_2O, H_2O, 50%; ii, K*t*-BuO, HCO_2Et, THF; iii, AcOH, Δ, 55% (2 steps).

Scheme 10

Alternatively, the combination of an imidate (**180**) with serine methyl ester hydrochloride (**181**) under mild basic conditions gives rise to an oxazoline (**182**), which can be subsequently oxidised to an oxazole (**183**) using conditions developed by Meyers *et al* (**Scheme 11**).[177]
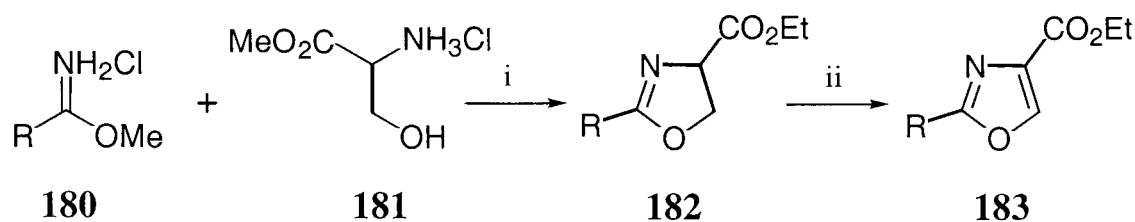
Reagents: i, Et$_3$N, CH$_2$Cl$_2$, 75%; ii, NiO$_2$, hexane, Δ, 53%.

Scheme 11

α-Diazocarbonyl compounds have also been shown to participate in oxazole formation by undergoing 1,3-dipolar cycloaddition reactions with nitriles.[178] In this method, α-diazocarbonyls (**184**) are decomposed thermally, photochemically, or by metal catalysis. The resulting α-carbonyl carbenes (**185**) then undergo a cycloaddition with the nitrile (R^3-CN) to give the oxazole (**186**). This method can provide oxazoles bearing much different, simple functionality, but has not yet been widely applicable towards very complex systems.
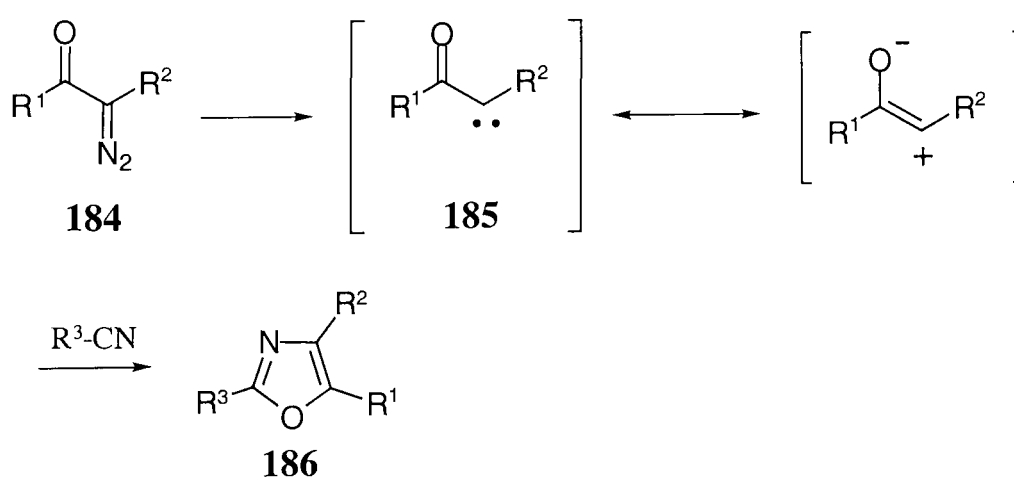
Konopelski *et al* have demonstrated the utility of this reaction in their studies towards diazonamide A (**1**).[173] Treatment of the α-diazo-β-keto ester (**187**) under Lewis acidic conditions in acetonitrile furnished the desired 2-methyl oxazole (**188**) in 64% yield.

This approach is hampered by the need to employ the nitrile as the solvent in order to obtain the best results, thus limiting the functionality that can be incorporated.

187   MeCN   **188**
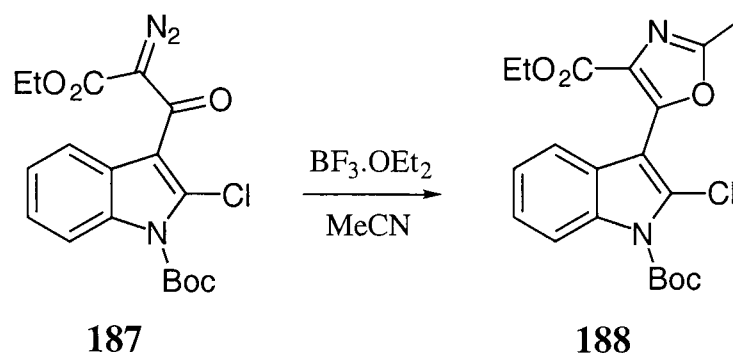
*iso*Cyanides have also been shown to be useful intermediates in oxazole synthesis. Schollkopf *et al* have prepared a wide variety of 2-unsubstituted oxazoles (**189**) in good yields by condensing *iso*cyanides (**190**) with acylating agents (R^1-COX).[179] The reaction proceeds through the intermediacy of the reactive α-*iso*cyano ketones (**191**).

190   **191**   **189**
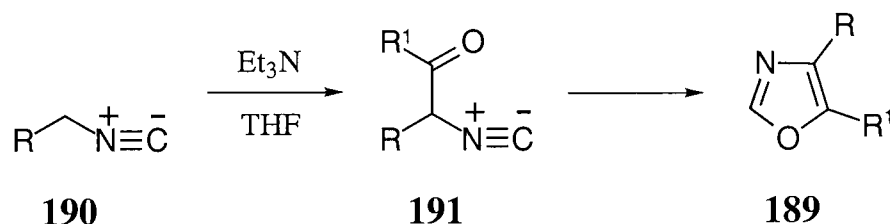
An alternative method for oxazole formation is the Hantzsch synthesis,[180] which has been widely used for the synthesis of thiazoles,[83b] but less so for oxazoles. This method involves condensation of an amide (**192**) with a halo-keto ester (**193**), giving rise to a 2,4-disubstituted oxazole (**194**) after acid-mediated dehydration. The utility of this method has recently been demonstrated by Panek *et al* in a synthesis of the *tris*-oxazole unit of ulapualide A (**44**) (**Scheme 12**).[83a]
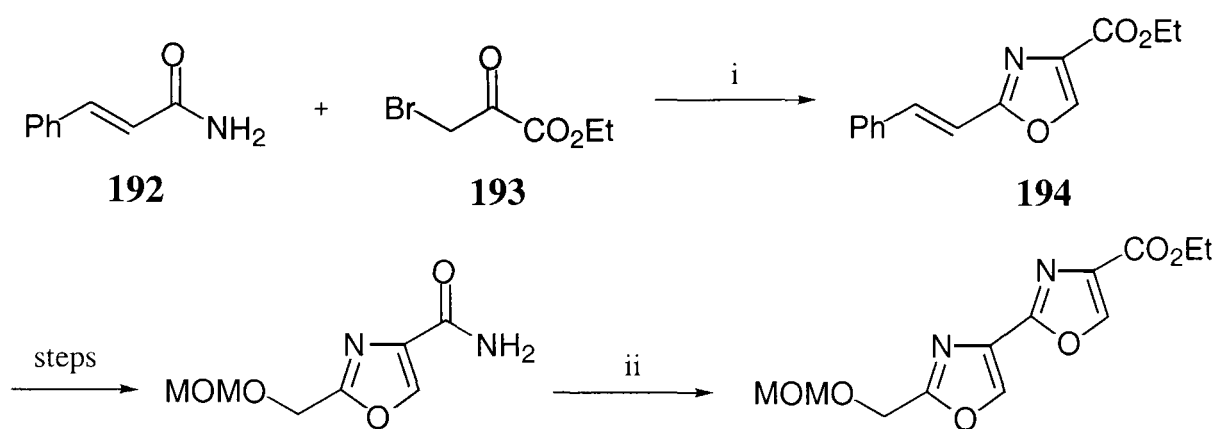
Reagents: i, a) NaHCO₃, Δ; b) TFAA, THF, 83%; ii, a) **193**, NaHCO₃, Δ; b) TFAA, THF. 60%.

Scheme 12

A less common method of oxazole formation requires the cyclisation of a vinyl bromide. In studies towards the thromboxane receptor antagonist BMS 180,291, Das *et al* reported that treatment of the terminal alkene (**195**) with bromine and triethylamine provided the vinyl bromide (**196**) in 92% yield (**Scheme 13**).[181] Cyclisation of the vinyl bromide (**196**) upon exposure to cesium carbonate in dioxane afforded the oxazole (**197**) in 63% yield.
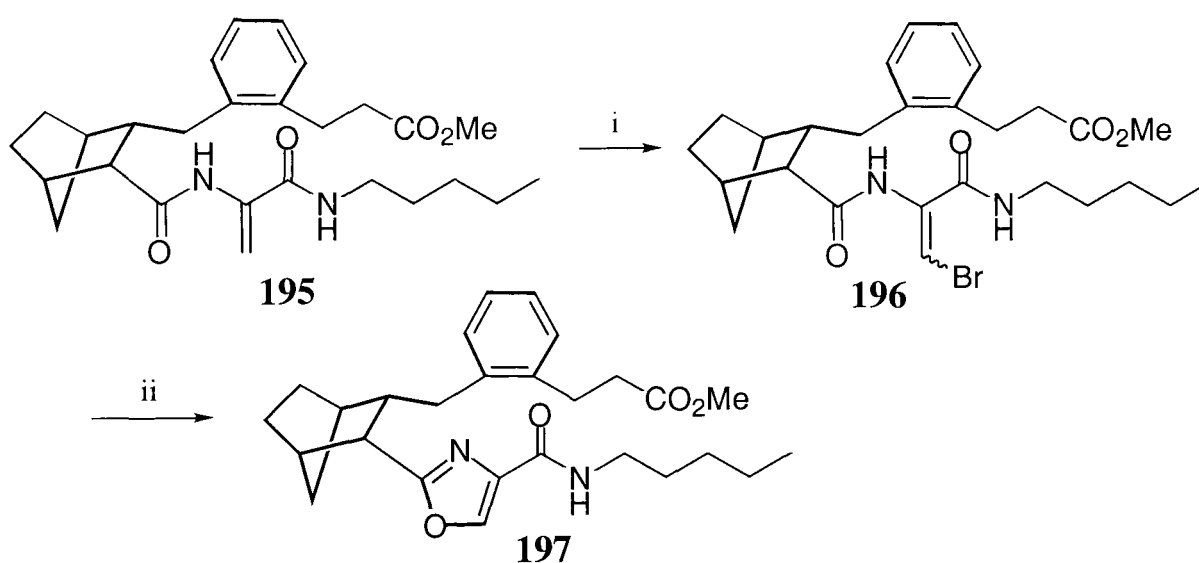
Reagents: i, Br₂, Et₃N, CH₂Cl₂, 92%; ii, Cs₂CO₃, dioxane, 63%.

Scheme 13

Perhaps the most widely used route towards oxazole construction in highly complex natural products involves formation of an amide (**198**) followed by either cyclisation to an oxazoline (**199**) and subsequent oxidation to give the oxazole (**200**), or

65

oxidation to a 1,3-dicarbonyl species (**201**) and cyclodehydration. These methods allow for the formation of oxazoles with high levels of functionality at each position by the union of structurally complex acid (**202**) and amine (**203**) fragments.
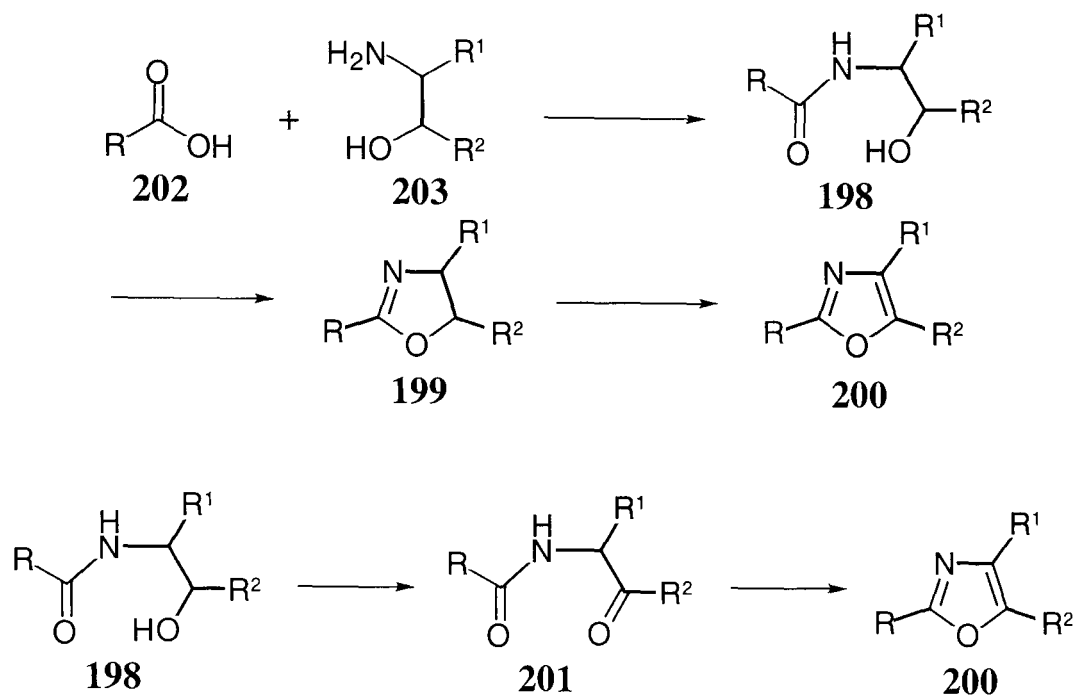
Over recent years many research groups have developed efficient syntheses based on these types of reactions and a whole variety of reagents and conditions are now available to effect these transformations. Initial formation of the oxazoline can be achieved in several ways, but activation of the hydroxy amide function is essential for cyclisation to occur. Activation can be promoted by thionyl chloride, followed by treatment with silver triflate;[182] methanesulfonyl chloride and triethylamine;[183] triphenylphosphine, carbon tetrachloride and DIPEA;[183] under Mitsunobu conditions;[184] phosphorus oxychloride;[185] or the more commonly encountered Burgess' reagent[74c] or DAST.[74b] Careful consideration of substrate reactivity is necessary when choosing a suitable reagent for this transformation, as elimination, aziridine formation or epimerisation may also occur.[66]

The oxidation of an oxazoline to an oxazole has been developed extensively and in general proceeds by either a radical pathway or an addition-elimination sequence. In either case, the need for an enolisable group at the C4 position of the oxazoline ring seems necessary to effect this transformation in good yield. Nickel peroxide has

already been cited as a reliable oxidising agent for this procedure (**Scheme 11**).[177] Other methods that have been examined and shown to be successful include copper(II) bromide and DBU;[67] copper(I) bromide and *t*-butyl peroxybenzoate;[186] formation of 4-seleno-oxazolines, oxidation and elimination;[187] carbon tetrachloride, pyridine and DBU in acetonitrile,[74a] and bromotrichloromethane and DBU.[188] Again, careful choice of reagent is required for oxidation depending on the substrate.

An alternative pathway developed by Wipf has also proven to be extremely useful in oxazole formation *en route* to natural products. Wipf, having encountered problems with the capricious oxidation of oxazolines to oxazoles, pursued a Robinson-Gabriel type cyclisation of a β-keto amide to furnish an oxazole.[69] Thus, oxidation of a β-hydroxy amide with the Dess-Martin reagent,[68] followed by mild cyclodehydration of the intermediate β-keto amide with triphenylphosphine, iodine and triethylamine allowed the rapid synthesis of highly substituted and functionalised oxazoles in good overall yield. Amino aldehydes derived from serine residues were found to cyclise to the oxazole in a much less facile manner. Wipf overcame this problem by changing the reaction conditions, employing the hindered base 2,6-di-*t*-butyl-4-methylpyridine with dibromotetrachloroethane and triphenylphosphine. Under these conditions elimination did not occur spontaneously and required treatment with DBU to furnish the oxazole.[65,189]

The use of both these approaches is described in Wipf's total synthesis of the enantiomer of hennoxazole A (**204**).[65,189] Thus, condensation of the acid (**205**) with serine methyl ester hydrochloride (**181**), *via* the mixed anhydride, gave the β-amido alcohol (**206**) which was cyclised to the oxazoline (**207**) with Burgess' reagent (**Scheme 14**).[74c] Oxidation of **207** with copper(II) bromide and DBU then gave the desired oxazole (**208**) in 37% overall yield.
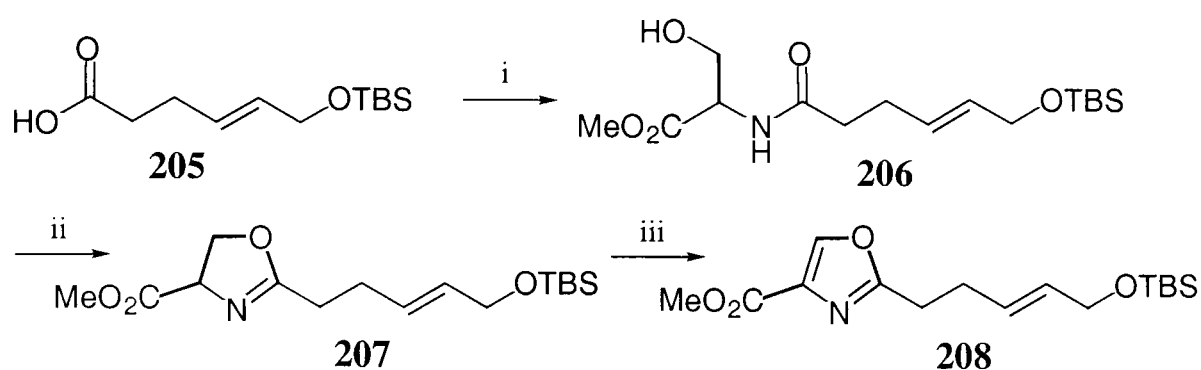
Reagents: i, serine.OMe.HCl, i-BuOCOCl, Et₃N, CH₂Cl₂; ii, Burgess' reagent, THF; iii, CuBr, DBU,

HMTA, CH₂Cl₂, 37% (3 steps).

Scheme 14

Elaboration of the side chain in **208** and hydrolysis of the ester gave the acid (**209**). This was coupled to the amine unit (**210**) to give the β-amido alcohol (**211**) in 63% yield (**Scheme 15**). Oxidation of **211** with Dess-Martin periodinane then gave the intermediate amido aldehyde,[68] which was cyclodehydrated to give the enantiomer of hennoxazole A (**204**) after desilylation with TBAF in 42% overall yield.[65,189]
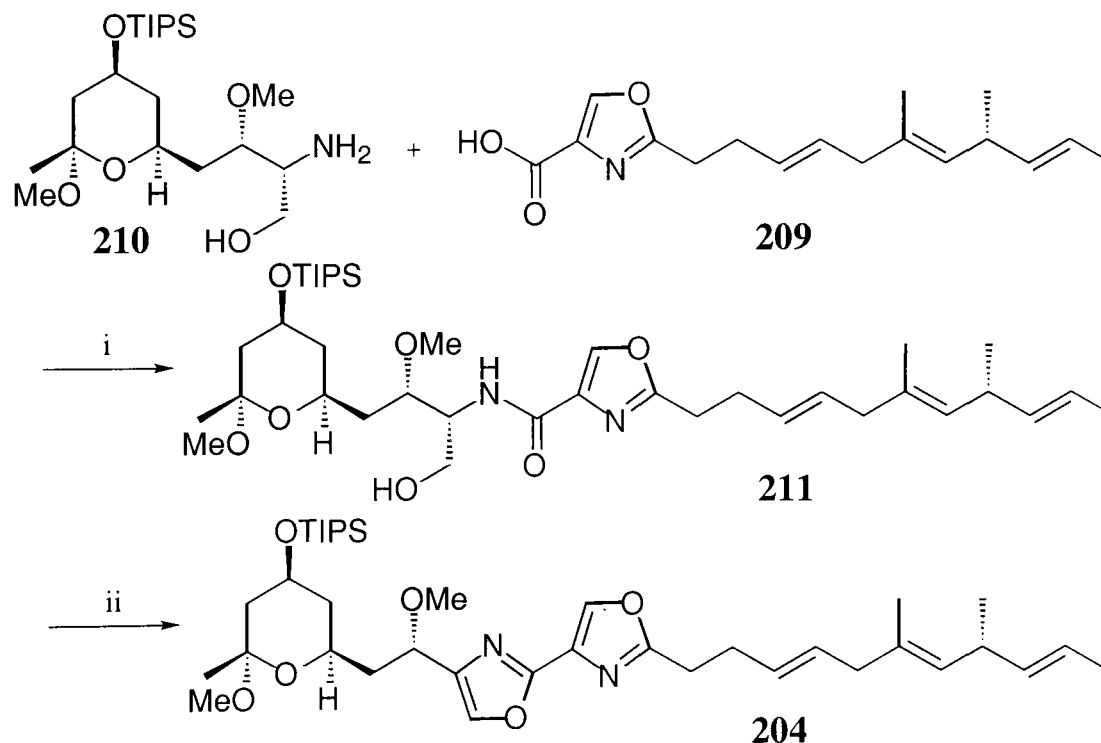
Reagents: i, PyBoP, DIPEA, CH₂Cl₂, 63%; ii, Dess-Martin periodinane, CH₂Cl₂; iii, BrCl₂CCCl₂Br,

PPh₃, 2,6-di-t-butyl-4-methylpyridine, CH₂Cl₂; iv, DBU, MeCN; v, TBAF, THF, 42% (4 steps).

Scheme 15

68

Returning to our own system, we were now in a position to elaborate the β-amido ketone function in the amide (**70**) to the benzofuran oxazole acid fragment (**69**) by cyclisation to form the trisubstituted oxazole and saponification of the ester.

In view of all the literature methods towards oxazole formation, we anticipated that treatment of the amide (**70**) with the mild conditions developed by Wipf[69] would lead to the desired oxazole (**212**). As anticipated, exposure of the amide (**70**) to the action of triphenylphosphine, iodine and triethylamine,[69] rapidly constructed the trisubstituted oxazole framework (**212**) in an excellent 89% yield, as shown below. In this cyclisation, it is proposed that the enol form of the ketone (**70**) is trapped with the highly electrophilic diiodotriphenylphosphorane to form the enol phosphonium salt (**213**).[69] Subsequently, intramolecular addition of the amide onto the vinyl phosphonium species provides the oxazoline (**214**), which can aromatise to the oxazole (**212**) with the expulsion of triphenylphosphine oxide.[69] An alternative mechanism which proceeds *via* the ring closure of an acylimino carbene (**215**), formed by loss of triphenylphosphine oxide from the enol salt (**213**), has also been proposed.[69]
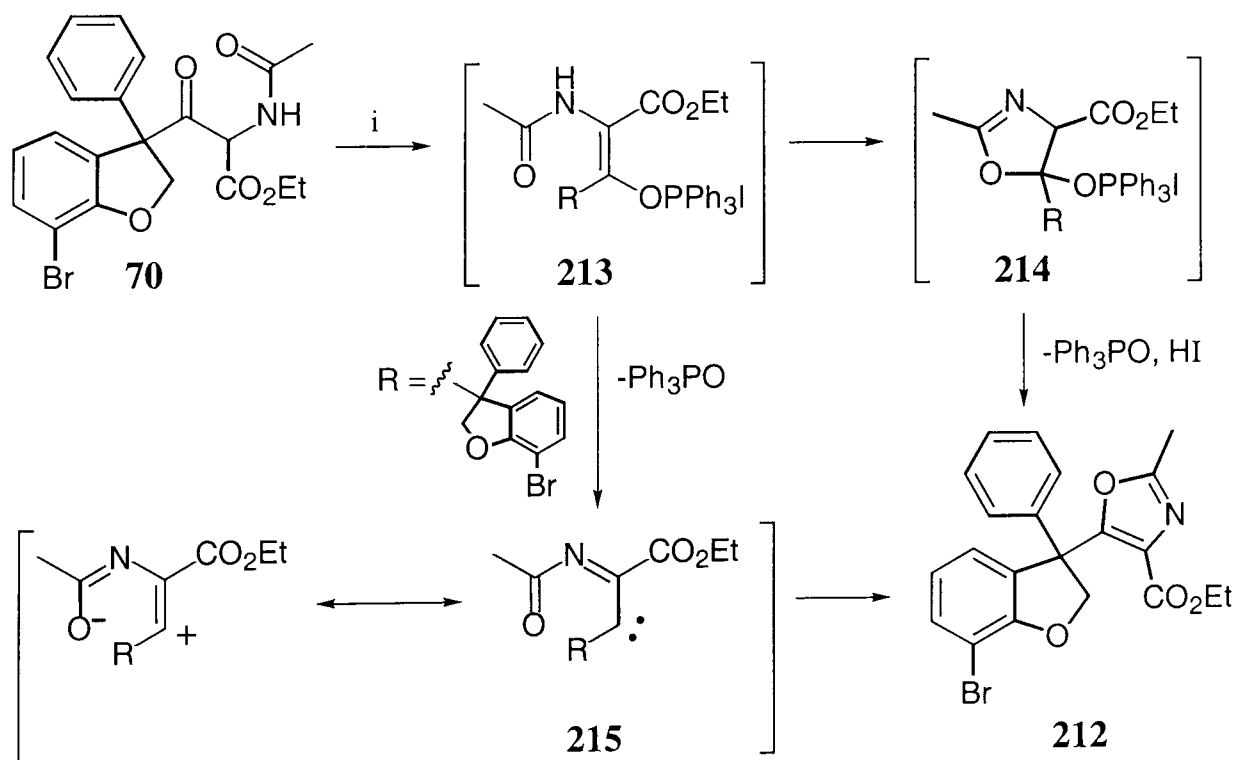
With the carbon framework of the desired benzofuran oxazole fragment now in place, the final saponification step could be addressed. This proceeded uneventfully when the ester (212) was subjected to basic hydrolysis with lithium hydroxide to provide the acid (69) in quantitative yield.
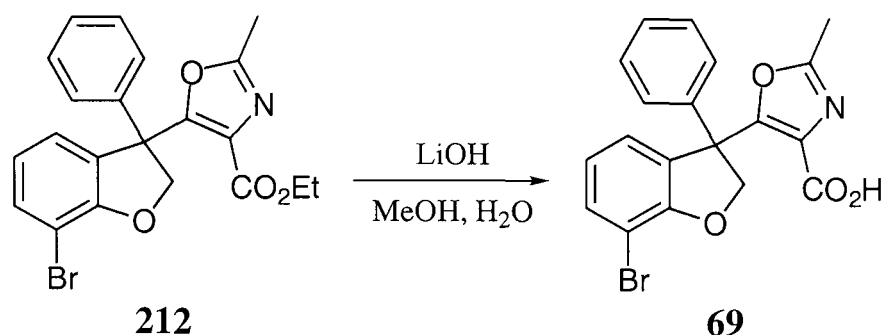
2.2.7 Conclusions

We have demonstrated the use of the intramolecular Heck reaction[134f] as a competent method for the construction of the benzofuran framework *via* a 5-*exo*-trig mode of cyclisation. In addition to the formation of a new C-C bond and quaternary carbon centre, the Heck reaction provided a terminal alkene (73) which could be elaborated efficiently to the central trisubstituted oxazole of diazonamide A. In this reaction sequence we described a facile entry to β-amido ketone functions by oxime formation at an active methylene site, then reduction and acylation.[168] Finally, the application of a mild cyclodehydration protocol[69] for the formation of a trisubstituted oxazole provided us, in excellent yield, with our key synthetic intermediate (69) for advancement towards the macrocyclic core of diazonamide A (64).

2.3 Synthesis of the Indole Fragment (68)

2.3.1 Introduction

Having successfully prepared the benzofuran oxazole acid fragment (69), our attention turned to the synthesis of an indole amine fragment (68) which we could couple to the acid (69) to provide the amide (66). Although the task of synthesising the amine (68) would appear to be less daunting than that posed by the synthesis of the acid (69), two interesting structural features had to be carefully addressed. These surrounded the introduction of a bromine or iodine atom at the C4 position of the indole ring and the incorporation of the ketone functionality in the two carbon side chain. Our strategies for circumventing these synthetic problems are outlined below.

2.3.2 Retrosynthetic Analysis

Whilst contemplating the problems posed by the necessity for the ketone and halogen substituents in the amine (68), it became clear that two alternative pathways for retrosynthetic disassembly could be envisaged. In the first approach, introduction of the ketone function could be anticipated to occur at a late stage in the synthesis, when the halogen substituent on the indole ring was already in place. In the second strategy, this sequence could be reversed and the halogen atom could be incorporated with the ketone function already in place.

When we considered the first approach in greater detail we envisaged the carbamate (216) as a precursor for the desired amine (217). In the forward sense, benzylic oxidation of the indole system would be expected to introduce the required ketone function[190] and acid-induced removal of the carbamate group[191] would provide the target compound (217). We anticipated that the carbamate (216) could be prepared from the nitro compound (218),[128] using a series of functional group manipulations. In an unusual retrosynthetic disconnection, we next envisaged cleaving the central

C-C σ-bond of the side chain to provide the tertiary amine (**219**) and nitromethane. In the synthetic direction, treatment of the amine (**219**) with iodomethane would be expected to form a quaternary ammonium salt. Removal of the silyl group on exposure of the salt to TBAF could then initiate elimination of trimethylamine to give a highly electrophilic ene imine.[192] Trapping of this reactive species with the stabilised carbanion of nitromethane would execute a one carbon homologation and give the nitro compound (**218**).[193] It was anticipated that the bromine atom could be introduced into **219** by a metal-halogen exchange reaction of the amine (**220**), where the nitrogen atom of the tertiary amine function is used to direct the metallation to the C4 position of the indole ring.[194] The bulky TIPS protecting group would prevent any deprotonation by the alkyl lithium base at the C2 position of the indole ring and could be introduced by silylation of commercially available gramine (**221**).[195]

217　　　　**216**　　　　**218**

219　　　　**220**　　　　**221**
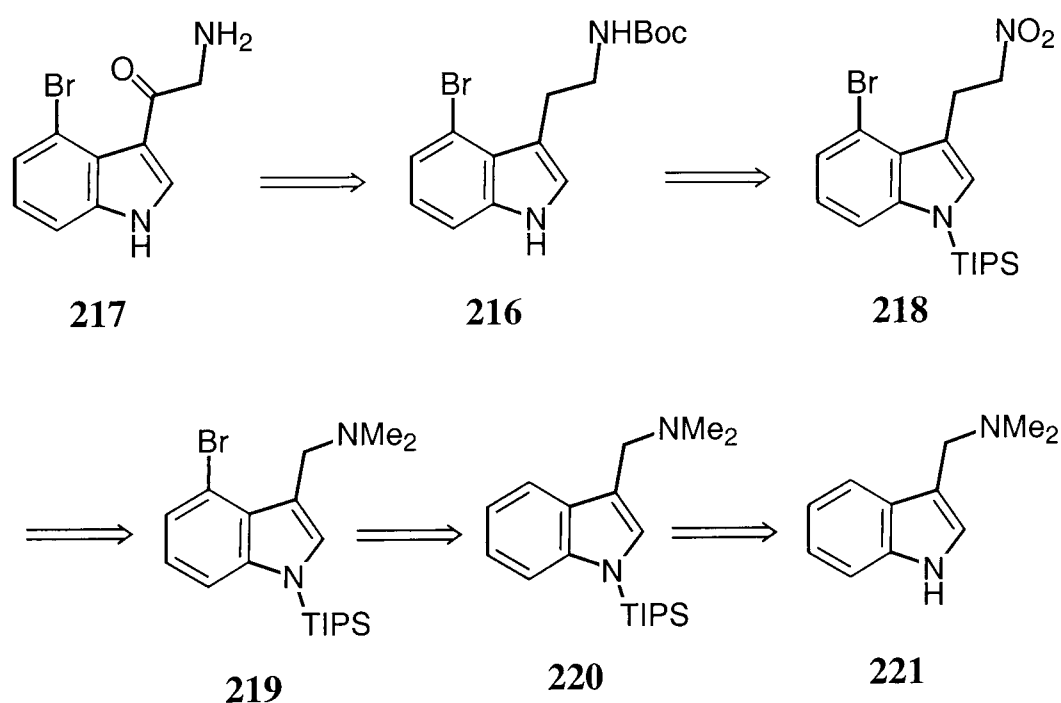
In our alternative approach, we again considered the carbamate (**222**)[196] as a suitable protecting group for the amine (**223**). However, in this strategy we now envisaged the ketone function being present prior to iodination. It was our belief that we could utilise the directing power of the ketone (**224**) to guide thallation to the C4 position of the indole ring,[197] then effect a thallium-iodine exchange to provide the carbamate (**222**).[197a,198] In an effort to devise a short synthetic pathway, we chose to next

disconnect across the C-C bond which fused the indole to the side chain at the C3 position. In the synthetic direction, we anticipated that treatment of indole (**225**) with an alkyl Grignard base would remove the proton from the indole nitrogen, but that the electron density would reside at the C3 position of the indole ring. Acylation of this reactive carbanion with the acid chloride derived from carbobenzyloxyglycine (**226**) would lead to the ketone (**224**) in one step.[199]

223   222   224

225   226
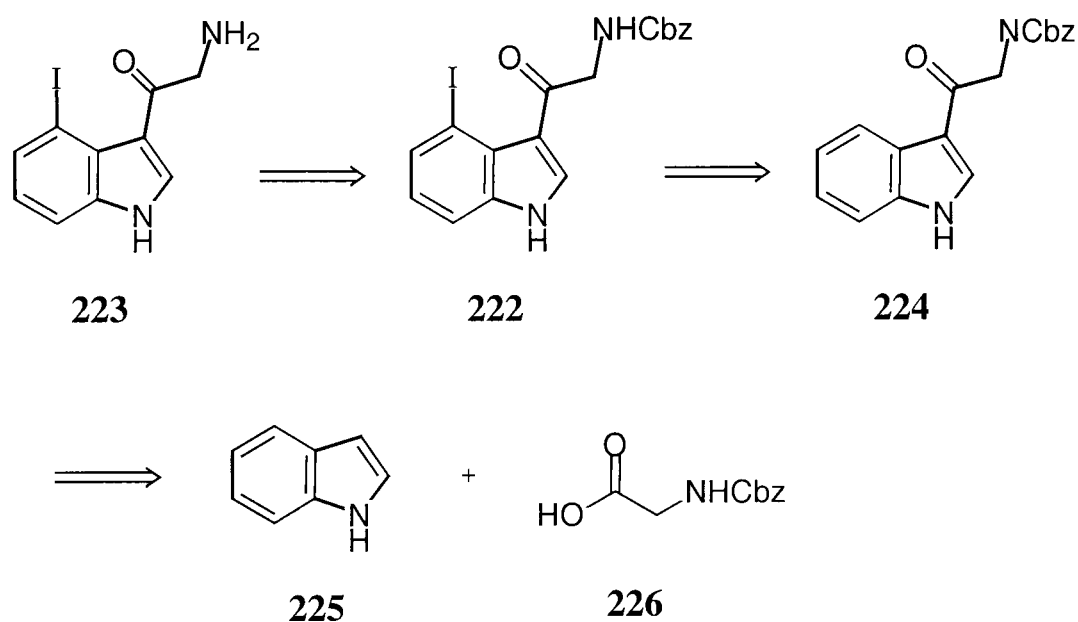
2.3.3 Synthetic Approaches to the Bromo Indole Amine (217)

With our synthetic plans now formulated we began to construct the bromide (**217**) following the first retrosynthetic pathway. Significant quantities of the silylated gramine (**220**) were available from previous studies[128] and this became our starting point. When the protected gramine (**220**) was treated with *t*-butyllithium at 0°C, the pendant tertiary amine directed lithiation to the C4 position of the indole ring to form the putative aryllithium species (**227**) (**Scheme 16**).[194] The bulky TIPS protecting group was effective at blocking any lithiation at the C2 position.[194] The organometallic compound (**227**) was then trapped by bromine at -78°C to provide the bromide (**219**) in 58% yield. Treatment of the bromide (**219**) with iodomethane uneventfully provided the quaternary ammonium salt (**228**). Exposure of the salt (**228**) to the action of TBAF facilitated removal of the silyl function and elimination

of trimethylamine to give the highly reactive ene imine intermediate (**229**).[192] This electrophile was trapped *in situ* by nucleophilic attack of the carbanion derived from nitromethane to effect a one carbon homologation of the side chain and provide the desired nitro compound (**218**) in 80% yield.[193]
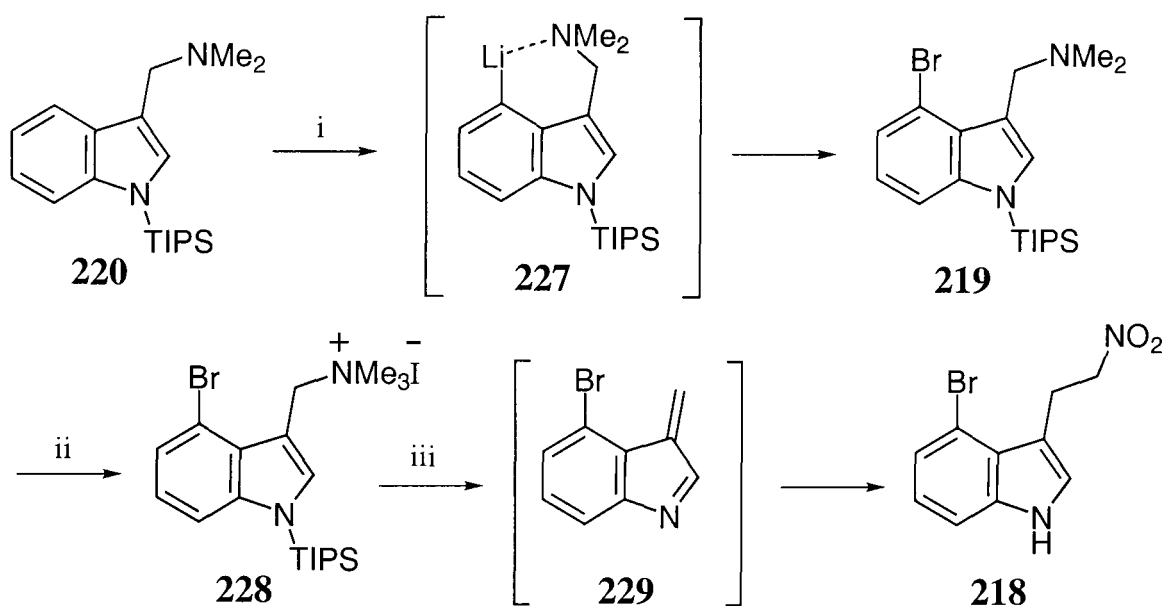
Reagents: i, *t*-BuLi, Br$_2$, Et$_2$O, 58%; ii, MeI, PhH; iii, TBAF, MeNO$_2$, THF, 80% (2 steps).

Scheme 16

The next task was to convert the nitro function to a *t*-butyl carbamate which would act as an acid labile protecting group for an amine function. To accomplish this, the nitro compound (**218**) was subjected to zinc in aqueous acetic acid at 80°C to provide the crude salt (**230**), which was immediately treated with sodium hydroxide and di-*t*-butyl dicarbonate to give the carbamate (**216**) in 85% overall yield (**Scheme 17**).
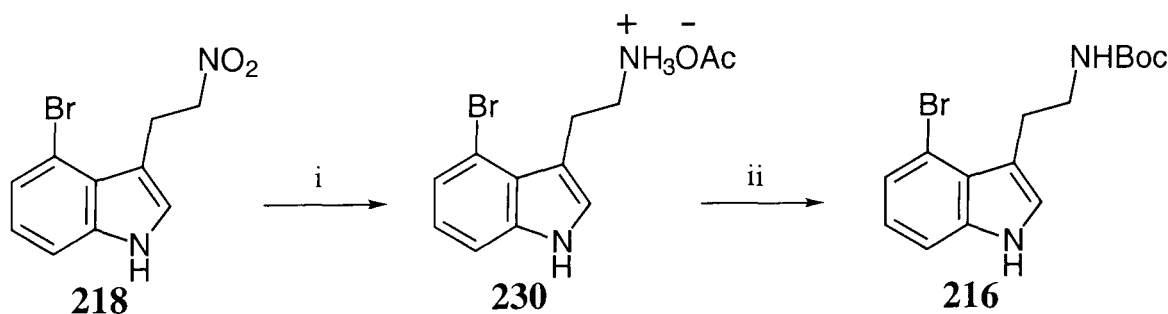
Reagents: i, Zn, AcOH, H$_2$O, Δ; ii, NaOH, (Boc)$_2$O, *t*-BuOH, 85% (2 steps).

Scheme 17

74

With the carbamate (216) now in hand, we were in a position to attempt the benzylic oxidation to introduce the ketone function. Yonemitsu *et al* had previously demonstrated that DDQ was an excellent reagent for the selective oxidation of the side chains at the C3 position of indoles.[190] In a synthesis of the antiepileptic alkaloid pimprinine (34)[59], it was shown that treatment of *N*-acetyltryptamine (231) with DDQ in aqueous THF effected a benzylic oxidation to give the ketone (232) in 73% yield (**Scheme 18**).[190a] This underwent cyclodehydration in refluxing phosphorus oxychloride[185] to provide pimprinine (34)[59] in 82% yield.
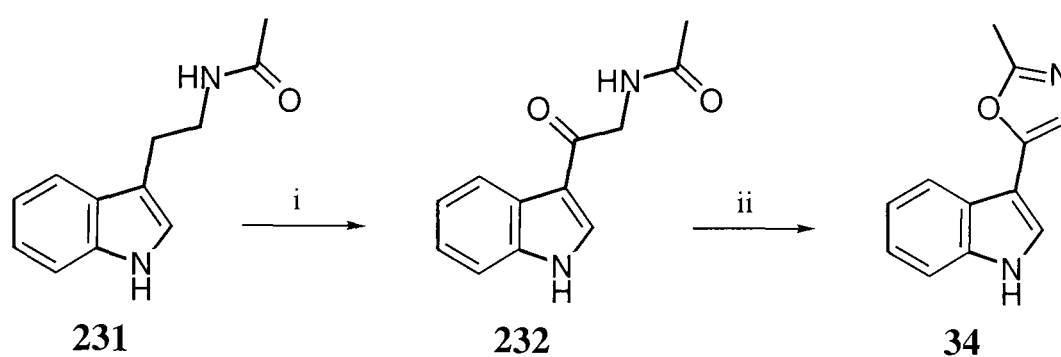
Reagents: i, DDQ, THF, H_2O, 73%; ii, $POCl_3$, Δ, 82%.

Scheme 18

Following the protocol developed by Yonemitsu *et al*,[190] we treated the carbamate (216) with DDQ in aqueous THF. As expected, the major product was oxidation of the benzylic site on the side chain at the C3 position of the indole ring. Unfortunately, the oxidation procedure only provided the secondary alcohol (233) in 75% yield and not the required ketone (234) (**Scheme 19**). Extensive investigations into the further oxidation of the alcohol (233) to the ketone (234) resulted only in the decomposition of the alcohol (233). The failure of the benzylic oxidation is particularly surprising based on the precedent set by Yonemitsu *et al*.[190] In an effort to determine the role of the substrate on the reactivity, we prepared the carbamate (235) by treatment of tryptamine (236) with sodium hydroxide and di-*t*-butyl dicarbonate (**Scheme 20**). The carbamate (235) was subjected, without purification, to the action of DDQ in aqueous THF[190] to provide the ketone (237) in 39% overall yield, with no evidence that the

reaction had stopped at the alcohol. This result suggests the bromine atom at the C4 position of the indole ring is having some bearing on the reactivity of the carbamate (**216**) with DDQ and curtailing the reaction when the alcohol (**233**) is formed. However, the exact influence of this substituent remains unclear.
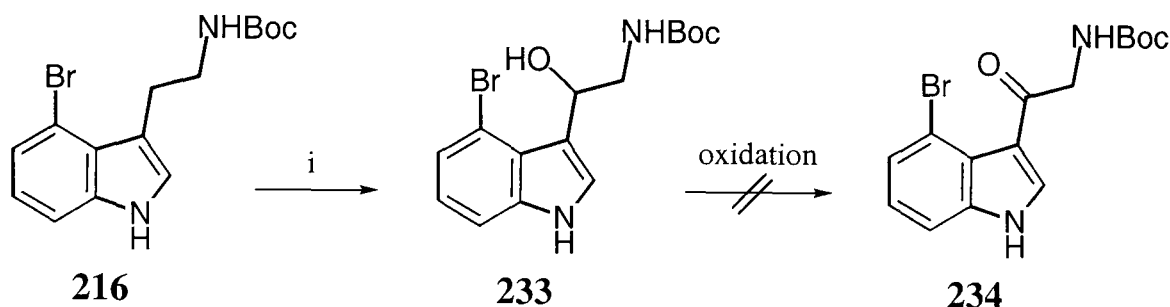
Reagents: i, DDQ, THF, H_2O, 75%.

Scheme 19
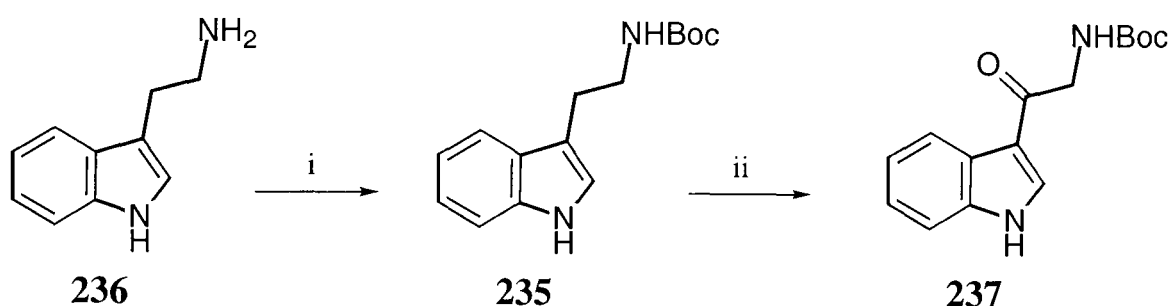
Reagents: i, NaOH, (Boc)$_2$O, dioxane, H_2O; ii, DDQ, THF, H_2O, 39% (2 steps).

Scheme 20

2.3.4 Synthetic Approaches to the Iodo Indole Amine (223)

With the failure of the benzylic oxidation,[190] we concentrated our efforts on preparing the desired amine (**223**) following the second retrosynthetic plan. In this approach the order of the key steps is reversed and the ketone is present prior to incorporation of the halogen substituent.

It was our desire to establish an efficient synthesis of the amine (**223**). To this end, we planned on incorporating the indole side chain in a single step. Treatment of indole (**225**) with ethylmagnesium bromide produced the corresponding indolyl anion (**238**). This anion has essentially covalent rather than ionic character and exposure at 0°C to

76

the acid chloride derived from the *N*-protected glycine (**226**), trapped the anion (**238**) at the C3 position of the indole ring to give the ketone (**224**) in 13% yield.[199] Our efforts to improve the yield of this step by transmetallating the Grignard intermediate with zinc chloride,[200] or activating the acid chloride with aluminum chloride,[201] produced no advancement in yield. Although this method provided us with small amounts of material with which we could investigate the feasibility of future steps, it did not allow us access to large amounts of the ketone (**224**). To obtain multigram quantities of material, we employed the two step approach outlined previously. Hence, tryptamine (**236**) was treated with sodium hydroxide and benzoyl chloride to provide the benzyl carbamate (**239**), which was next treated with DDQ[190] to give the desired ketone (**224**) in 72% overall yield (**Scheme 21**).
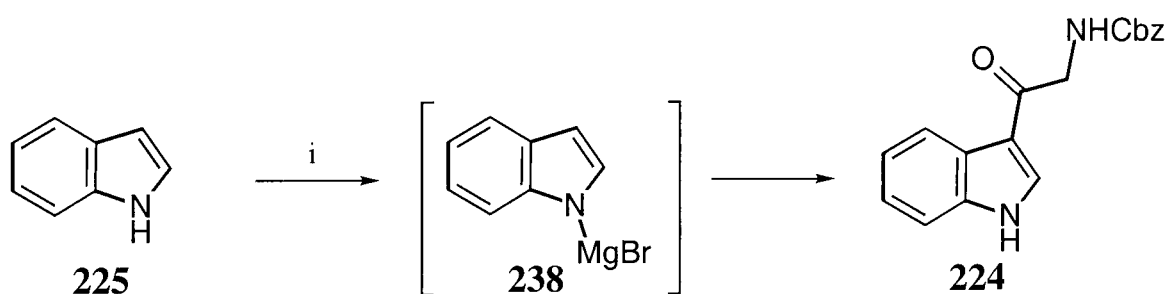
Reagents: i, EtMgBr, ClCOCH2NHCbz, Et2O, 13%.
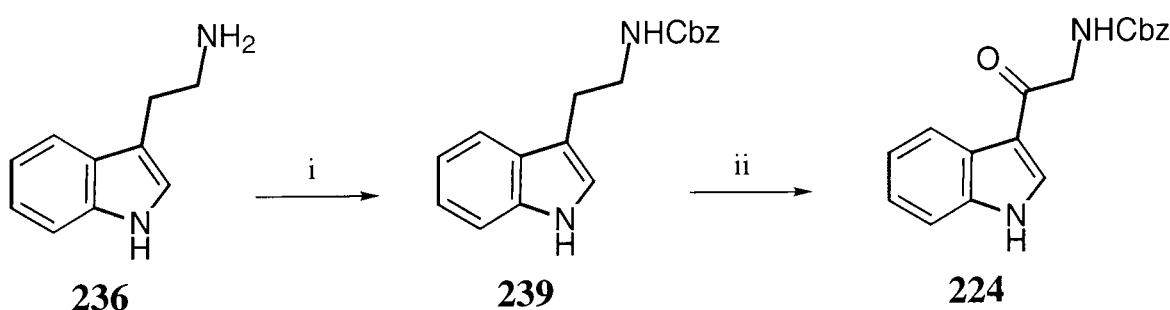
Reagents: i, NaOH, CbzCl, dioxane, H2O; ii, DDQ, THF, H2O, 72% (2 steps).

Scheme 21

McKillop *et al* gave impetus to the study of thallium in organic synthesis when they reported that the electrophilic aromatic metallation of benzenoid compounds (**240**) with thallium trifluoroacetate (TTFA) provided the arylthallium compounds (**241**).[198b] Perhaps more interestingly, they observed that treatment of the arylthallium

compounds (**241**) with aqueous potassium iodide solution resulted in instantaneous precipitation of thallium iodide and formation of the corresponding aromatic iodides (**242**).[198b]
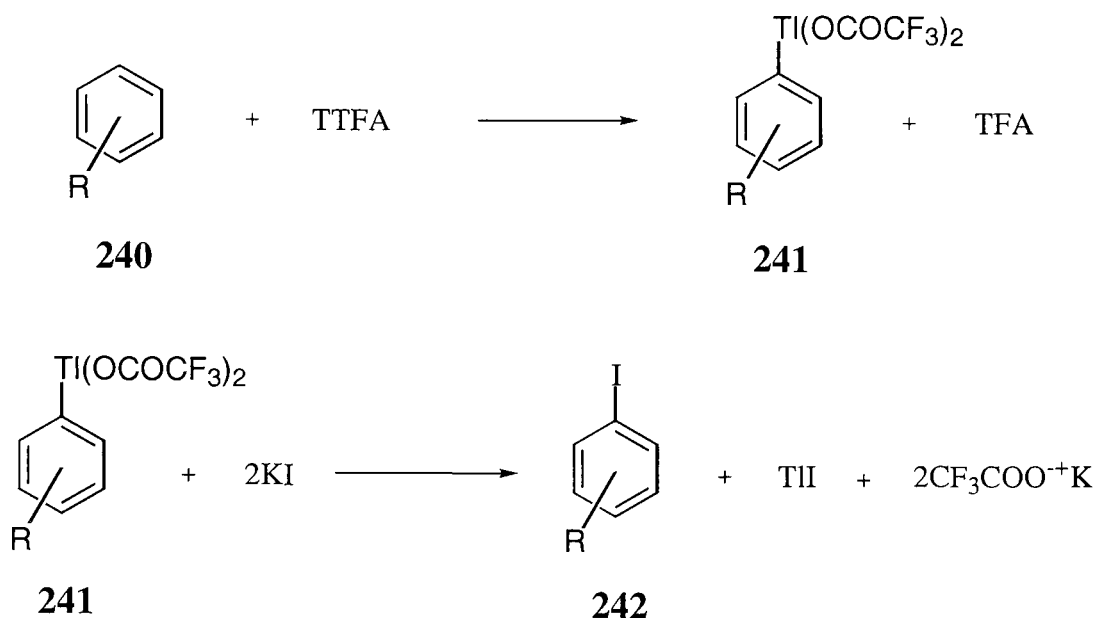
Hollins and Colnago extended this two step thallation-iodination procedure when they investigated its application with heteroaromatic substrates.[198a] They found that exposure of pyrrole aldehyde (**243**) to thallium trifluoroacetate provided the aryl thallium intermediate (**244**), which then gave the diiodide (**245**) upon exposure to aqueous potassium iodide. More importantly however, they showed that treatment of the indole aldehyde (**246**) under identical reaction conditions provided the iodide (**247**) *via* the thallium intermediate (**248**). Preferential thallation at the C4 position of the indole ring was rationalized by assuming that thallium coordinates with the carbonyl group of the side chain and also that the C4 position is less deactivated than the C2 position.[198a]

246   248   247
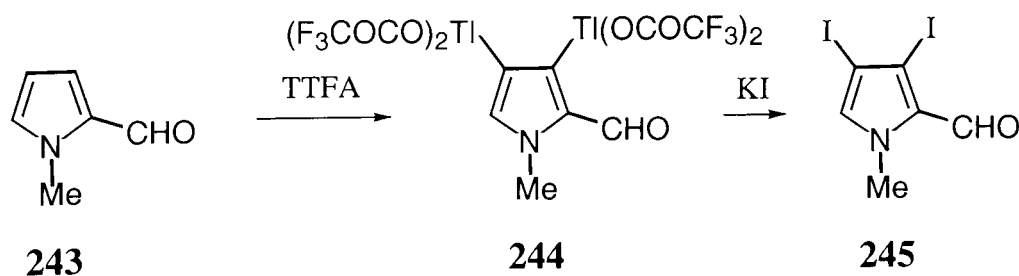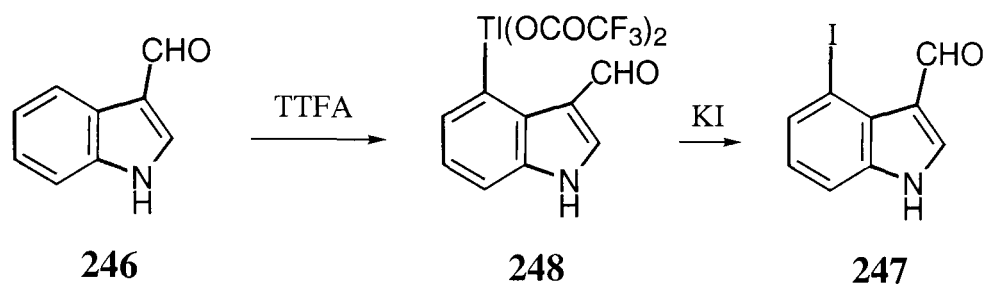
In recent years the most significant developments in this procedure have been attributable to the work of Somei. Following investigations into the regioselective synthesis of 4-substituted indoles,[197] Somei *et al* developed a one pot synthetic method for conversion of the aldehyde (246) to the iodide (247).[197a] This procedure avoided isolation of the toxic thallium intermediate (248) and used a combination of molecular iodine and copper(I) iodide in DMF to effect the thallium-iodine exchange with an improved yield.

With considerable amounts of our indole carbonyl substrate (224) now available, we turned to the improved conditions of Somei[197a] for incorporation of the iodine substituent. Treatment of the ketone (224) with thallium trifluoroacetate at 30°C effected regioselective electrophilic metallation at the C4 position of the indole ring to give the organothallium intermediate (249) (Scheme 22). Removal of the solvent and exposure of the crude reaction mixture to molecular iodine, copper(I) iodide and DMF prompted a thallium-iodine exchange reaction to give the carbamate (222)[196] in 58% overall yield. Initial attempts to liberate the reactive amine function by hydrogenolysis were unsuccessful and no reaction was observed. However, the benzyl carbamate protecting group could be removed by treatment of the carbamate (222) with hydrogen bromide in acetic acid[191,196] to finally provide our desired indole fragment as the salt (250) in 99% yield.
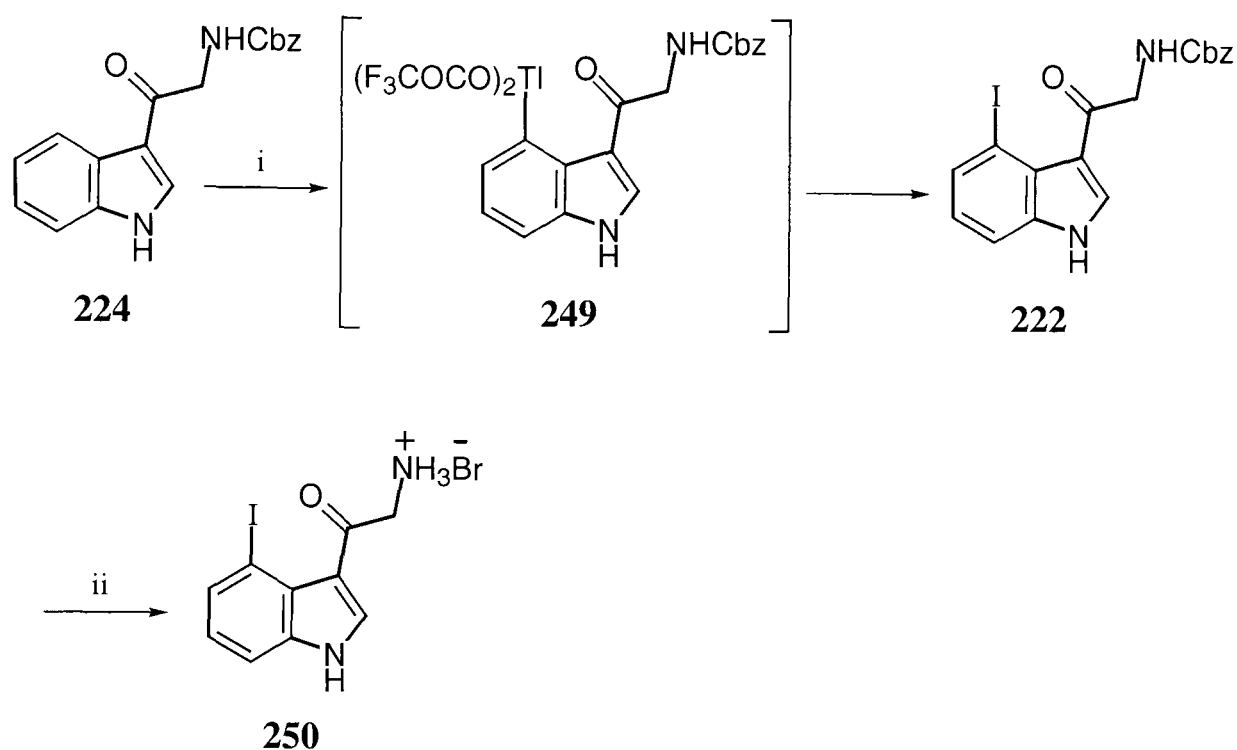
Reagents: i, a) TTFA, TFA; b) CuI, I_2, DMF, 58%; ii, HBr, AcOH, 99%.

Scheme 22

2.3.5 Conclusions

Although we were unsuccessful in utilising a benzylic oxidation[190] to form the desired ketone function in the bromide (**216**), this approach demonstrated the efficiency of the amine-directed metallation-halogenation strategy for the synthesis of a 4-substituted bromo indole (**219**).[194]

Despite earlier failings, we were successful in accessing the salt (**250**). In constructing this fragment we employed a one step procedure for acylation at the C3 position of an indole ring using ethylmagnesium bromide as the base.[199] However, due to the unacceptably low yield of this process, we returned to a two step procedure involving a benzylic oxidation[190] to gain access to multigram quantities of material. This material could be transformed to the salt (**250**) using a carbonyl-directed thallation-iodination protocol[197a] for the regioselective introduction of an iodine substituent at the C4 position of the indole ring and subsequent deprotection.[191]

2.4 Studies towards the Macrocyclic Core of Diazonamide A

2.4.1 Introduction

Having successfully completed the synthesis of the acid (**69**) and the salt (**250**) we were now in a position to consider the union of these two fragments. Once achieved, the entire carbon framework for the macrocyclic core of diazonamide A (**1**) would be in place. In elaborating this framework to the macrocycle (**64**) we faced the considerable synthetic challenges of cyclising another keto amide function, this time to prepare the more complex *bis*-oxazole unit,[64,71] then effecting an intramolecular Ullmann reaction.[130]

69	**250**	**64**
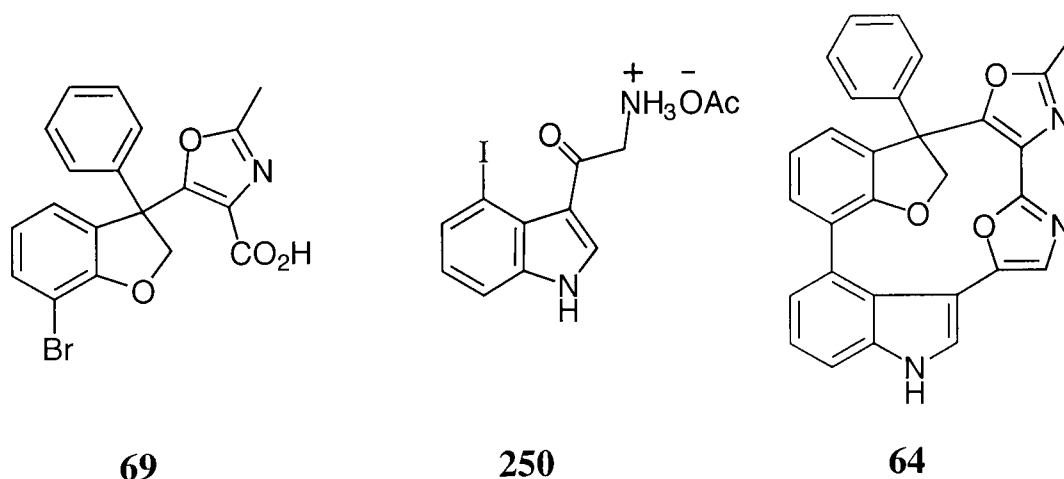
2.4.2 The Ullmann Reaction

The coupling of two aromatic sp^2-hybridised centres to give biaryl compounds is a transformation that has a long history. Like many organic reactions, it has been developed considerably over the past decades to encompass the subtleties of modern chemistry. Before turning our attention to one of the oldest biaryl forming processes, the Ullmann reaction,[130] we will begin by highlighting the main alternative synthetic methods for the construction of biaryl bonds.

The palladium(0)-catalysed Suzuki reaction is perhaps the most favoured method for the formation of biaryl systems.[202] In this process, an arylboronic acid, borate ester or borane (Ar^1-BY_2) is coupled to an aryl halide or triflate (Ar-X) in the presence of an inorganic base (*e.g.* NaOH) and a catalytic amount of palladium(0).

$$\blacksquare \xrightarrow[]{Pd(0)} \text{Ar-Ar}^1 \ + \ \text{HO-BY}_2 \ + \ \text{NaX}$$
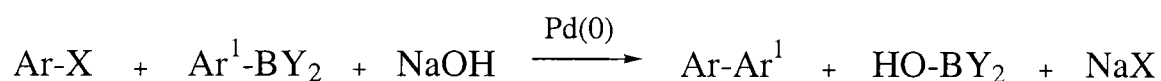
Snieckus has combined the Suzuki reaction with his work on *ortho*-metallation to form a powerful method of converting simple arenes into more complex biaryl systems.[203] One example is in the synthesis of the fluorenone dengibsinin (**251**),[203a] where the amide and isopropoxy groups in the arene (**252**) directed lithiation to the *ortho*-position (**Scheme 23**). The aryllithium species was trapped with tributyl borate to give the borate ester (**253**), which underwent a Suzuki coupling reaction with the iodide (**254**) to provide the biaryl compound (**255**).
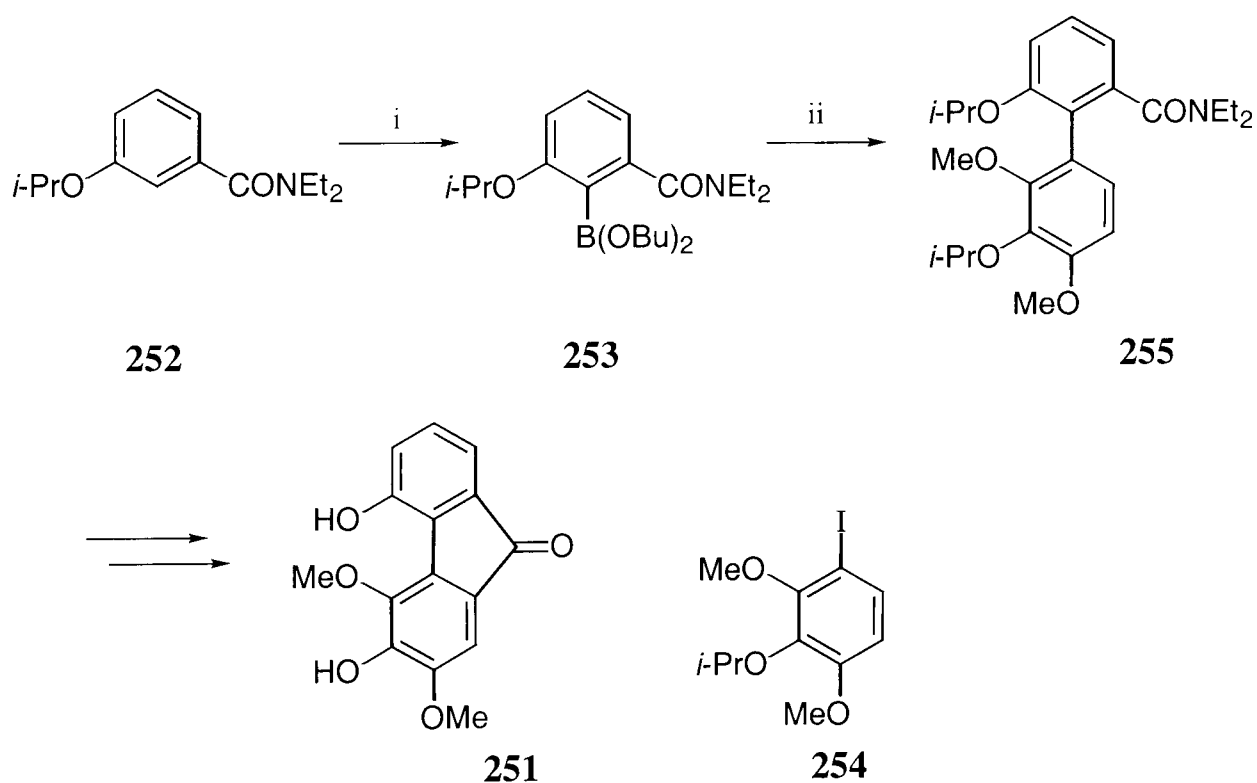
Scheme 23

A closely related coupling process is the Stille reaction,[204] in which the organoboron species in the Suzuki reaction[202] is replaced by an organotin compound. This stannane (Ar^1-SnR$_3$) can be coupled to an aryl halide (Ar-X) in the presence of an inorganic base (*e.g.* K$_2$CO$_3$) to provide the biaryl product.

$$\blacksquare \xrightarrow{\blacksquare} Ar\text{-}Ar^1 \quad + \quad X\text{-}SnR_3$$
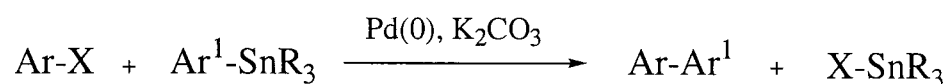
A macrocyclic biaryl Stille reaction has been used by Kilburn *et al* to prepare the possible dipeptide host (256).[205] Despite exchanging the tin and bromine substituents in the precursor (257) to try and increase the reactivity, the macrocycle could never be obtained in greater than 15% yield.

257   256
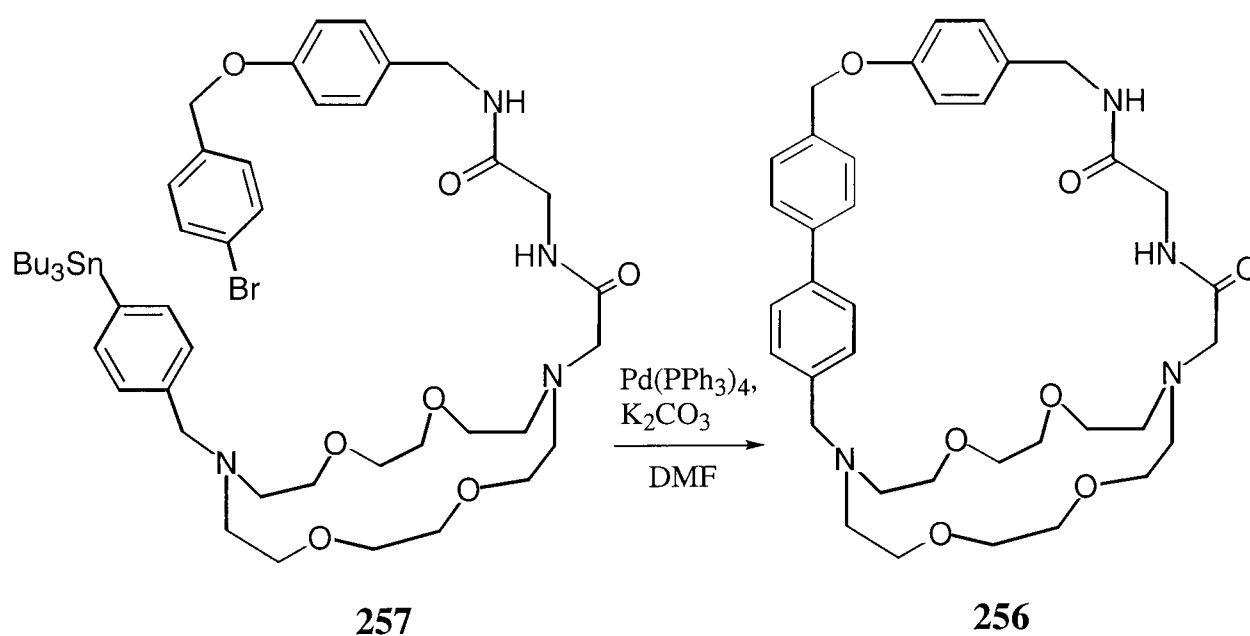
A tandem palladium-catalysed stannylation-biaryl coupling reaction has been developed by the research group of Kelly.[206] The two step process couples two aryl halides and starts with the palladium-catalysed transfer of a trialkyltin unit from hexabutyl or hexamethylditin to one of the aromatic rings to provide an intermediate organostannane. The reactive tin species then undergoes an intramolecular Stille reaction[204] to provide the desired biaryl compound. This tandem process was used by Kelly *et al* in their synthesis of the chiral B-ring unit of pradimicine A (59).[119] In this

efficient synthetic sequence, the diiodide (**258**) was converted into the stannane (**259**) and then the biaryl (**260**) in a single step and 87% yield.[206]
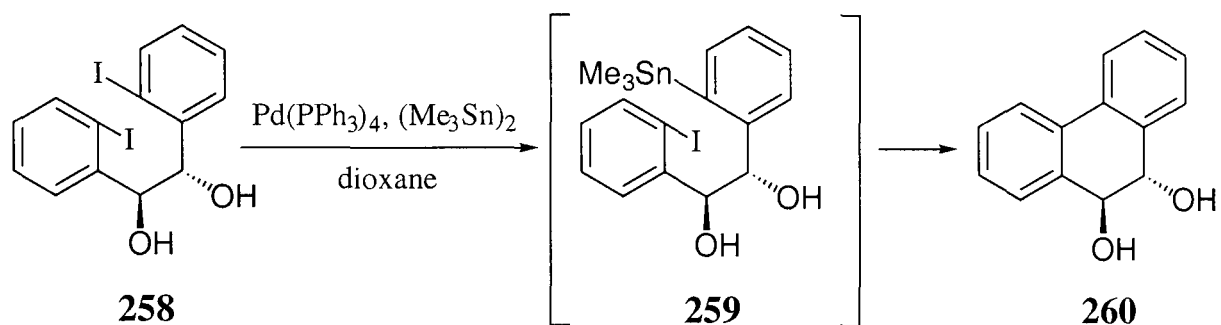
A class of biaryl reactions developed by Somei,[207] has found particular application in the construction of aryl substituted indoles. The reactions involve the palladium(0)-catalysed coupling of organothallium compounds (**261**) with either stannanes (*e.g.* **262**) or boronic acids. They can be interpreted as variations of the Stille and Suzuki couplings,[202,204] with the arylthallium species replacing the aryl halide.
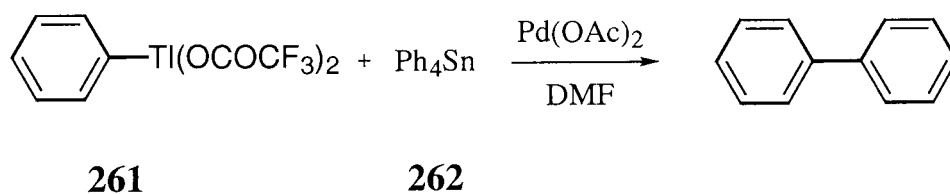
Indole 4-carboxaldehyde derivatives are readily and regiospecifically thallated, so the Somei method is especially suited to the formation of aryl indoles. Konopelski *et al* applied this methodology to form a biaryl bond in their model studies towards diazonamide A.[173] They described the preparation of the organothallium species (**263**), which on treatment with the stannane (**264**), in the presence of a catalytic amount of palladium(0), afforded the coupled product (**265**).

263   264   265
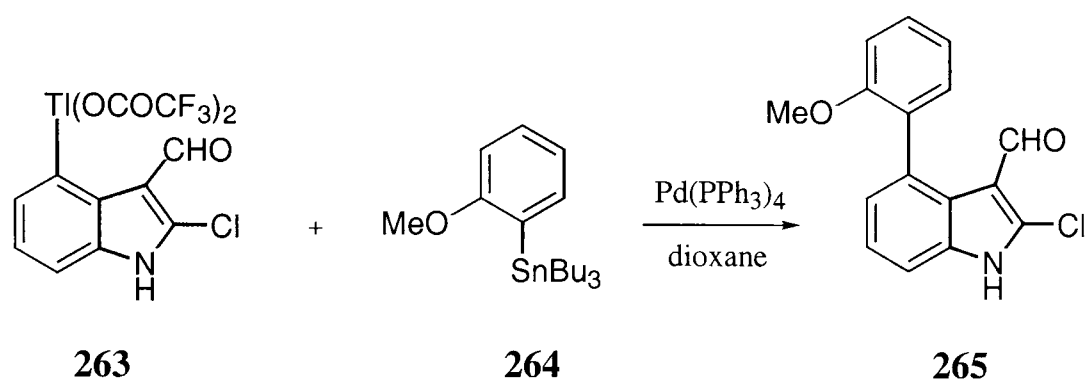
The classical Ullmann synthesis of biaryls comprises the reaction in which two aryl halides are condensed in the presence of finely divided copper to form a new biaryl bond with the elimination of copper halide.[130a,c] Temperatures as high as 250°C are often employed to effect the coupling, but despite these harsh conditions the reaction is often high yielding and tolerates a range of functionality including nitro, aldehyde, ester and alkoxy groups. However, the reaction is greatly inhibited by the presence of substituents which can provide an alternative path for reaction of the aryl halide, such as amino, hydroxy, or free carboxy groups. Bulky groups in the *ortho* position may inhibit the reaction by steric hindrance. However, for simple systems, such as the aryl chloride (266),[208] with little steric crowding, it remains the method of choice.

266
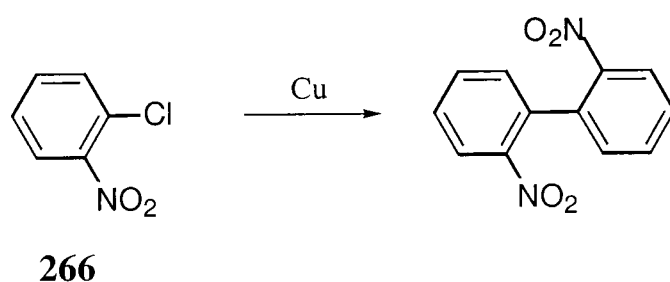
In recent years the Ullmann reaction has been developed extensively by the work of Meyers,[130a] who has shown the potential of the reaction in contemporary synthesis. An example is the asymmetric construction of the biaryl bond in the total synthesis of the natural product mastigophorene A (56)[110] in which a chiral oxazoline auxiliary on the aryl bromide (267) controls the atropisomerism in the coupling reaction to provide the biaryl compound (268) in 85% yield.[111]

267   **268**
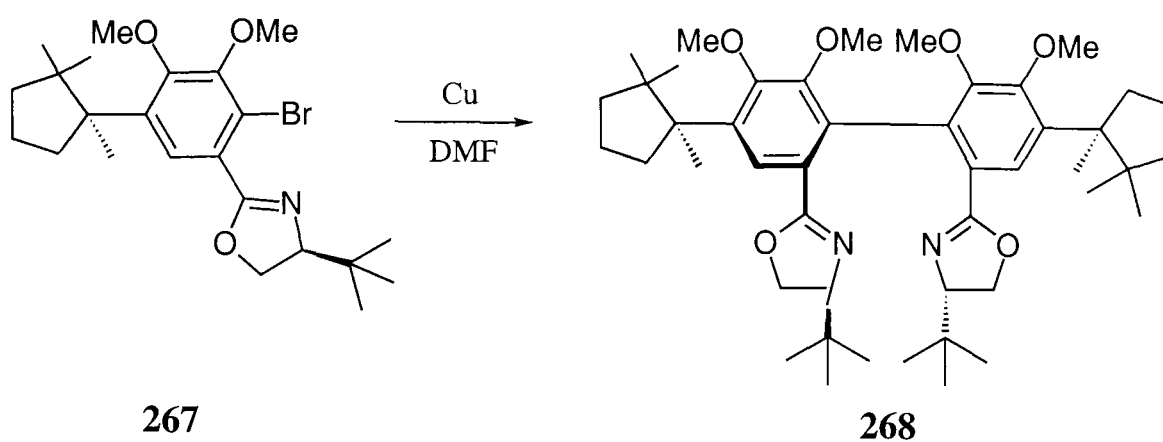
The use of the Ullmann reaction for intramolecular couplings has also been demonstrated. Newman and Logue described the closure of a 7-membered diphenic anhydride ring on refluxing the benzoic anhydride (**269**) with copper bronze in DMF to provide the biaryl anhydride (**270**) in an excellent 90% yield.[209]

269   **270**
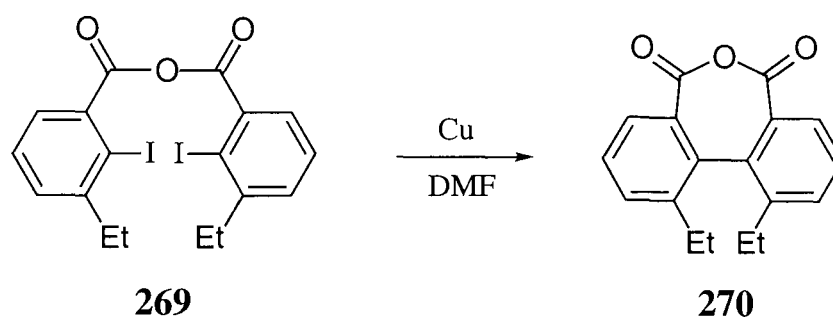
Several modifications to the classical Ullmann coupling conditions have been reported. These have tended to emphasise the use of lower reaction temperatures in an effort to make the reaction applicable to more sensitive substrates. Liebeskind reported that copper(I) thiophene-2-carboxylate promotes efficient reductive coupling of a range of aromatic compounds, incorporating a wide variety of functionality, at ambient temperature in NMP.[210] In one particularly interesting example, it was reported that the diiodide (**271**) underwent an intramolecular Ullmann coupling at ambient temperature to form the biaryl compound (**272**) in 88% yield.

271   CuTC / NMP →   **272**
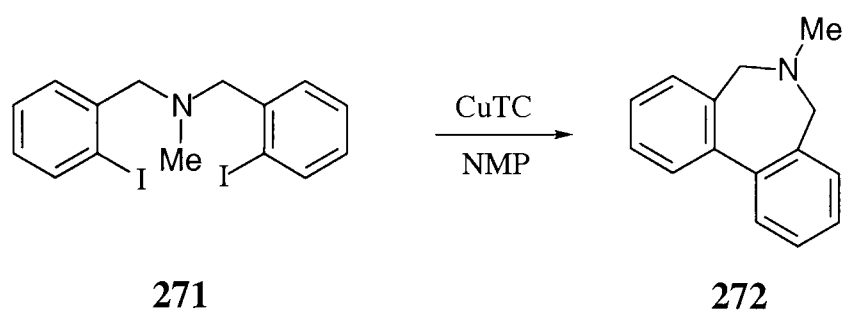
Semmelhack has also developed a lower temperature variant of the classical Ullmann reaction which, instead of copper, uses a zero valent nickel complex.[211] Originally, these were *bis*-(1,5-cyclooctadiene)nickel or tetra*kis*-(triphenylphosphine)nickel, but it has since been demonstrated that reduction of *bis*-(triphenylphosphine)nickel(II) chloride with zinc and then complexation of triphenylphosphine provides an *in situ* method for formation of a highly active nickel(0) reagent.[212] In general, the reactions can be carried out at 50-80°C in dipolar aprotic solvents such as DMF or NMP.

This methodology was employed by Percec *et al* in an intermolecular nickel-catalysed homocoupling of the aryl mesylate (**273**) to give the biphenyl (**274**) in 65% yield.[213] Jutand and Mosleh also described the nickel-catalysed synthesis of a range of symmetrical biaryls (**275**), this time using aryl triflates (**276**) as the starting materials.[214]

273 $Cl_2Ni(PPh_3)_2$, Zn, PPh_3, Et_4NI / THF →   **274**

276 $Cl_2Ni(dppe)$, Zn, KI / DMF →   **275**
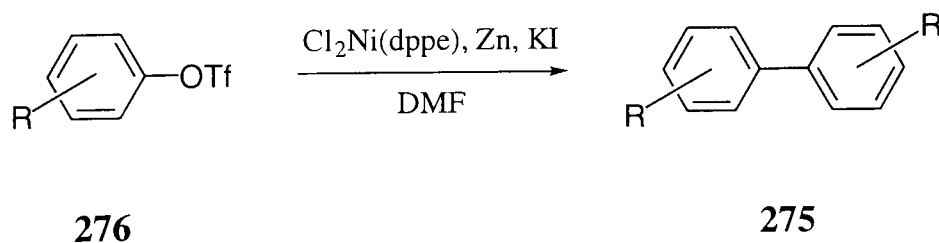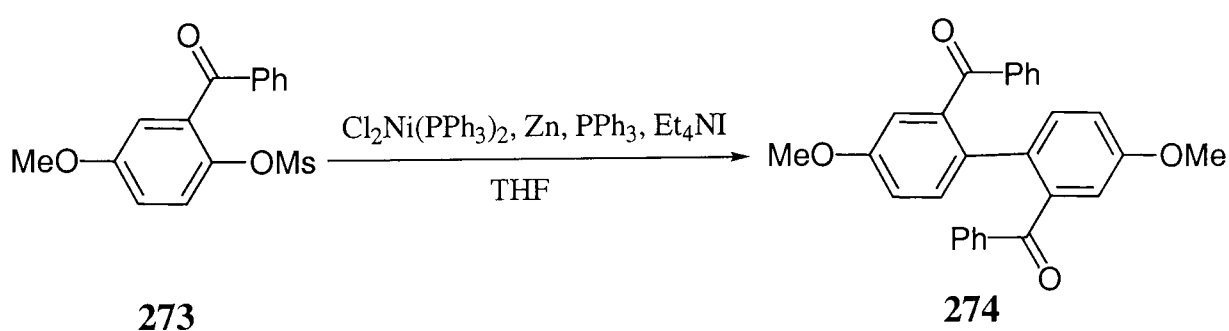
Despite these accomplishments it is the area of intramolecular coupling reactions which have witnessed the greatest applications of this modified Ullmann protocol. Semmelhack *et al* were the first to describe the nickel-promoted intramolecular coupling of two aryl iodides in a total synthesis of the natural product alnusone.[211] They showed that treatment of the diiodide (**277**) with tetra*kis*-(triphenylphosphine)nickel(0) in DMF at 50°C gave the biaryl species (**278**) in 46% yield.

277   **278**
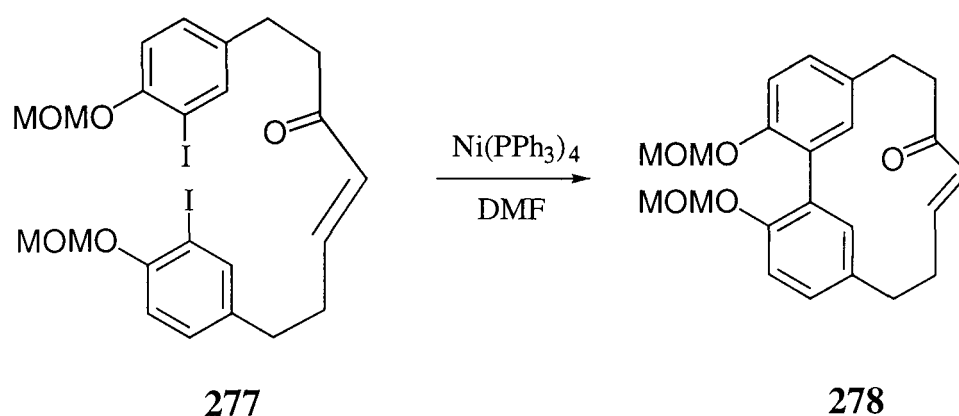
Carruthers *et al* have used this methodology in the key step of a total synthesis of the lythranidine alkaloid (**49**).[95] They utilised the *in situ* reduction of a nickel(II) complex with zinc to provide the active nickel(0) species, which reacted with the diiodide (**279**) to form the 17-membered macrocycle (**280**) in 55% yield.[97]

279   **280**
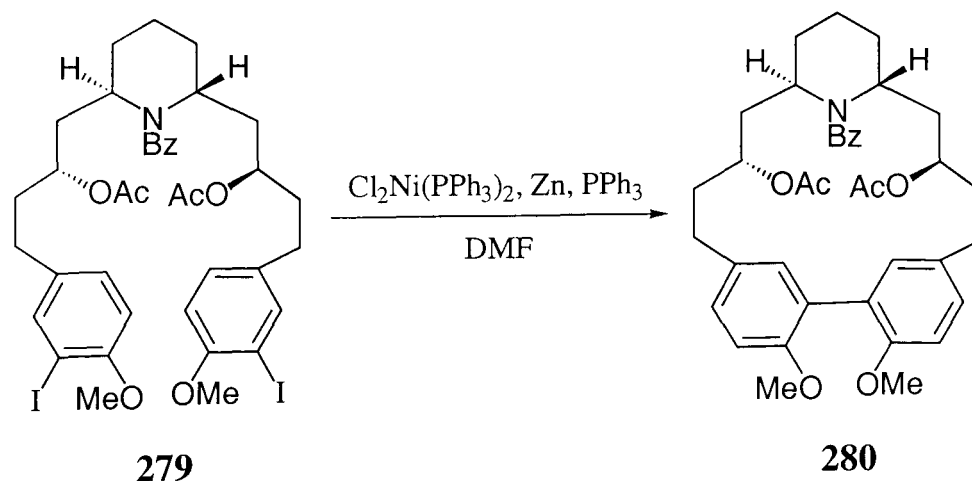
Renewed interest in the biaryl portion of the vancomycin antibiotics has sparked a resurgence in the Ullmann cyclisation,[130] with the recent synthetic studies

concentrating on a nickel-mediated coupling approach.[130b,211,212] If it is assumed that the mechanism of the Ullmann reaction involves the formation of an organonickel intermediate,[130b] then the lower polarisation of the C-Ni bond, in comparison to other organometallic species, allows for greater compatibility of the reaction with common polar functional groups such as alcohols, amines and carbonyl functions. Nicolaou *et al* have demonstrated the tolerance of sensitive functionality to these reaction conditions in their approach to the rigid 12-membered biaryl ring system of the vancomycin antibiotics.[215] It was reported that treatment of the diiodide (**281**), which contains amide, carbamate and ketone functions, with *in situ* generated nickel(0), resulted in the formation of the biaryl system (**282**) in 26% yield. Less sterically encumbered substrates which contained the same functionality could be cyclised in greater yield.

281   **282**
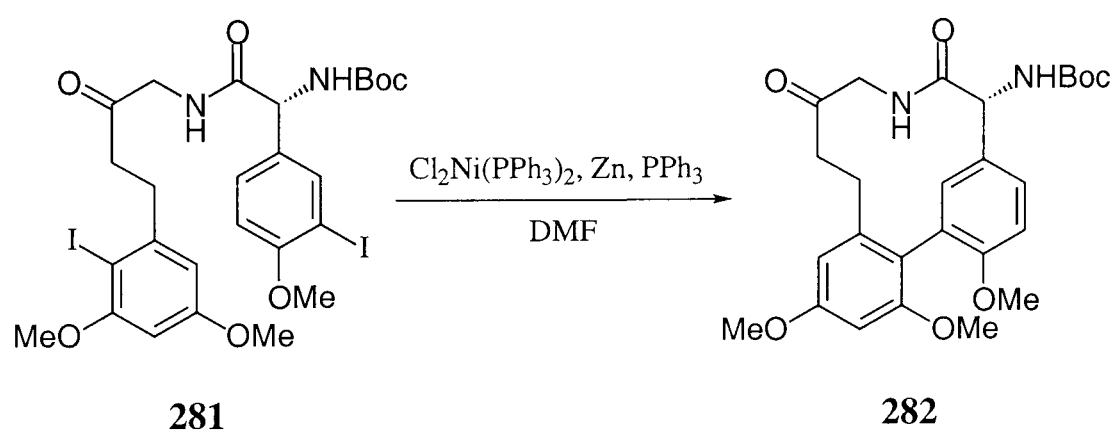
Lipshutz *et al* have applied very similar methodology to prepare the nonracemic biaryl portion of vancomycin (**45**).[216] In this strategy, the diiodide (**283**) is treated with a nickel(II) complex and *n*-butyllithium as the reducing agent to effect the closure of an 8-membered ring and give the model biaryl species (**284**) in 50% yield. A tartrate-derived tether was used to induce the chirality and allow preferential access to only one atropisomer (**284**).

283   **284**
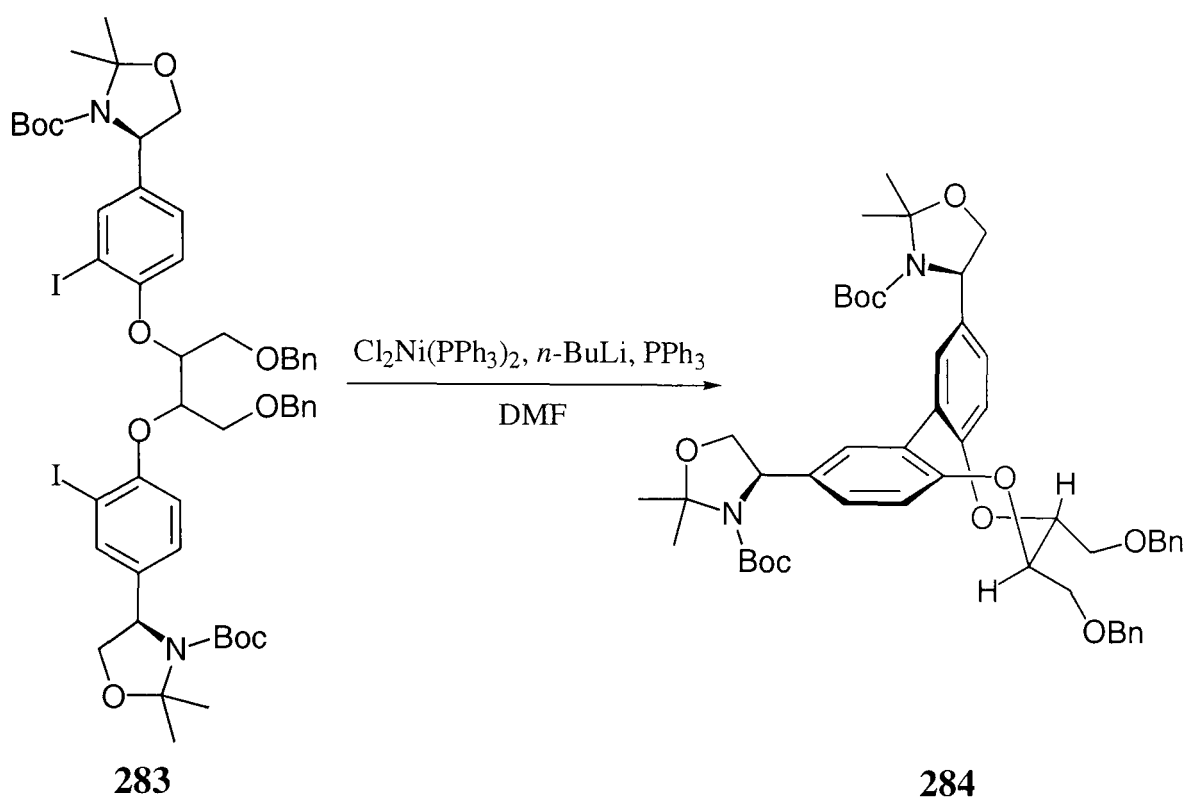
The research group of Roussi has demonstrated the utility of the nickel(0)-based coupling reaction for the formation of a new C-C σ-bond between an indole and a conventional phenyl ring.[217] As well as the application of this protocol to intramolecular cross-couplings which involve heteroaromatic units, it should be noted that this reaction proceeds by the union of two, less reactive, aromatic bromides. Hence, the dibromide (**285**) is cyclised under the standard conditions to give the 17-membered ring macrocycle (**286**) in 17% yield, which is a model compound of the eastern substructure of the natural products kistamycin and chloropeptin II.

285   **286**
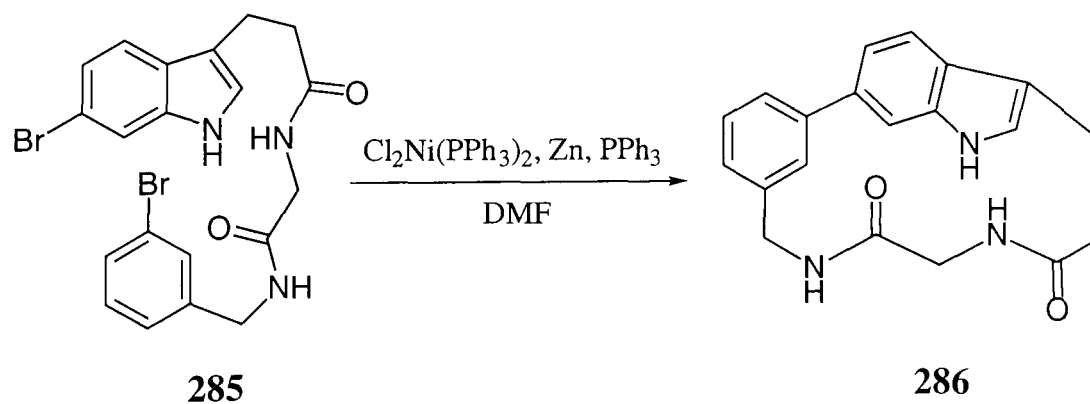
The advent of the nickel(0)-mediated Ullmann coupling reaction[97,211,213-7] meant that the harsh conditions required for the copper-mediated couplings were no longer necessary. However, this effective process suffers because of the need for stoichiometric amounts of the nickel reagent.[212] Thus, the search has continued over recent years for a catalytically active varient to the nickel complexes which also avoids the demanding conditions of the classical copper-promoted coupling.[111,130a,208,209]

Rawal *et al* described recently a novel palladium-catalysed Ullmann coupling reaction.[218] These authors reported the homocoupling of substituted aryl iodides and bromides (**287**) using a catalytic equimolar ratio of palladium acetate and tri-*o*-tolylarsine under basic conditions in the presence of hydroquinone, as a homogenous reductant, in DMA at 75°C. Excellent yields of the coupled products (**288**), generally in excess of 80%, have been achieved.

$$\text{Pd(OAc)}_2,\ \text{As}(o\text{-tol})_3,\ \text{HQ},\ \text{Cs}_2\text{CO}_3$$
$$\text{DMA}$$

287　　　　　　　　　　　　　　　　　　**288**
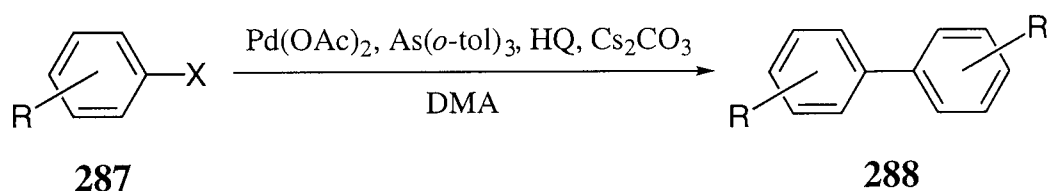
Even more impressive is the extension of this methodology to the formation of 7-membered heterocyclic and carbocyclic rings.[218] Although this intramolecular process has only been applied to the formation of symmetrical macrocyclic systems, it should not be long before this novel transformation is used for the construction of challenging biaryl frameworks in natural products synthesis.
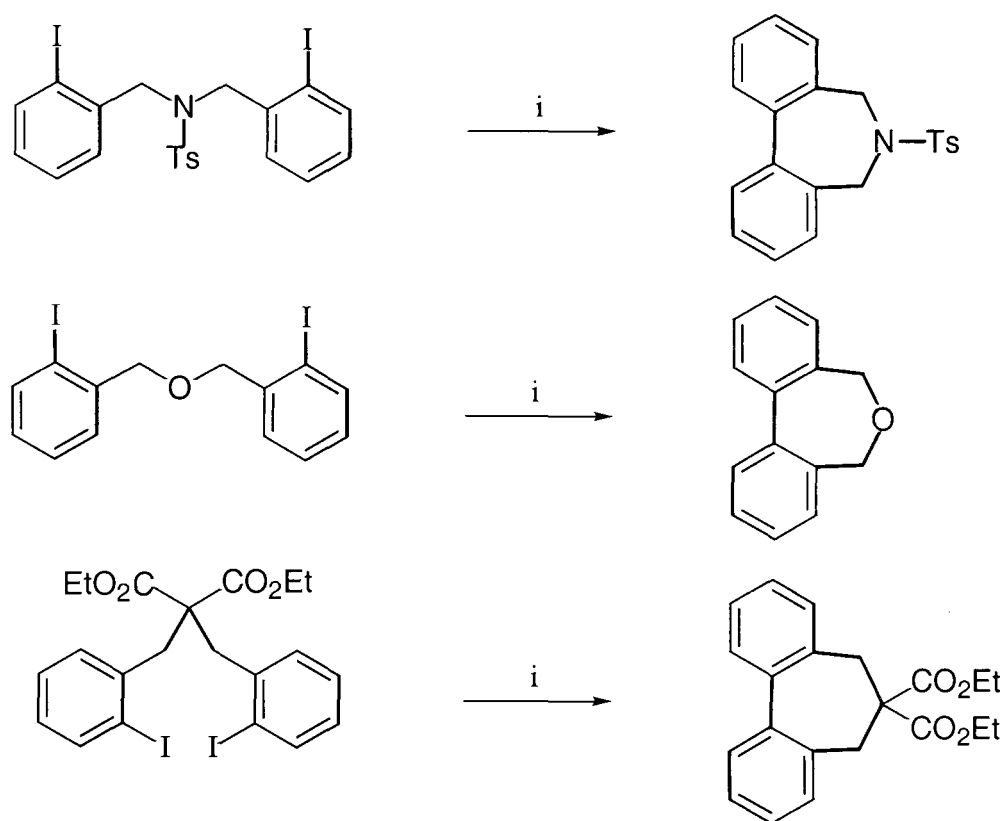
Reagent: i, Pd(OAc)$_2$, As(o-tol)$_3$, hydroquinone, Cs$_2$CO$_3$, DMA, Δ.

This section of the thesis has provided a brief overview of the principle methods available for the formation of biaryl bonds. Particular attention has been paid to the Ullmann coupling reaction[130] and several examples of successful intramolecular variants have been highlighted.[97,209-11,215-18] The succeeding pages will report how these methodologies have been applied to our strategy for construction of the macrocyclic core of diazonamide A (**1**).

2.4.3 A First Generation Approach to the Macrocycle (64)

As mentioned previously, our first task was to unite the benzofuran oxazole acid fragment (**69**) and the salt (**250**) to provide the amide (**289**) which contained the relevant keto amide function for preparation of the *bis*-oxazole unit. Our initial attempts to construct the amide bond used the standard peptide coupling conditions of EDC and HOBt in basic media,[131] which gave the amide (**289**) in a poor 40% yield. In an effort to increase the yield, we turned our attention to the formation of an acid chloride as the reactive electrophilic species. Thus, the acid (**69**) was treated with

92

oxalyl chloride to provide the acid chloride (**290**) (**Scheme 24**). Exposure of the salt (**250**) to triethylamine at 0°C liberated the nucleophilic amine which was trapped with the acid chloride (**290**) to give the amide (**289**) in 60% yield. The amide (**289**) proved to be exceptionally sensitive to the conditions developed by Wipf for oxazole formation.[69] However, after considerable experimentation, we found that careful addition of triethylamine, triphenylphosphine and hexachloroethane to the amide (**289**) induced cyclisation to provide the *bis*-oxazole (**291**) in 81% yield. With the *bis*-oxazole unit now installed we had successfully prepared a system which incorporated all the aromatic units of the southern macrocycle of diazonamide A (**1**). In conjunction, we had the necessary substitution on the aromatic rings for the implementation of our macrocyclisation strategy.
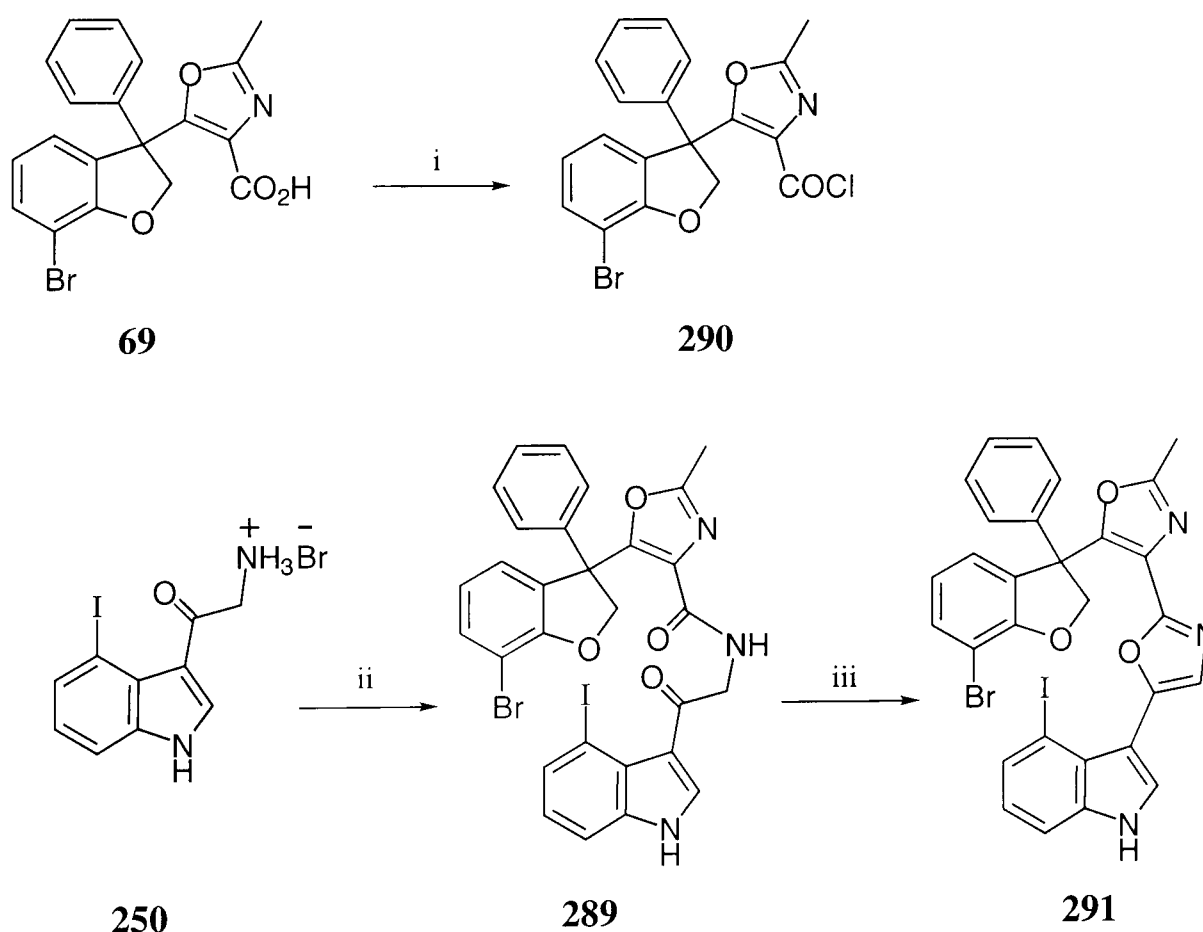
Reagents: i, (COCl)$_2$; ii, Et$_3$N, **290**, CH$_2$Cl$_2$, 60% (2 steps); iii, Et$_3$N, PPh$_3$, Cl$_3$CCCl$_3$,

CH$_2$Cl$_2$, 81%.

Scheme 24

In light of the successful examples of nickel-mediated intramolecular Ullmann couplings described previously,[97,211,213-7] we first focussed our attention on these conditions for carrying out the macrocyclisation in our system. Unfortunately, all attempts to cyclise the *bis*-oxazole (**291**) using nickel reagents, or subsequent reactions under the classical copper-mediated conditions,[111,130a,208,209] failed to provide any of the desired biaryl product (**64**). The major products to be recovered and identified from the reaction mixtures were unreacted starting material (**291**) and the bromide (**292**). Formation of the bromide (**292**) suggested that the aryl iodide unit was obviously reactive, since it presumably underwent oxidative addition of a nickel(0) species to give an organonickel intermediate which was quenched on a proton source.[130b] However, the aryl bromide unit, which remained intact, was either an unreactive site or too far away from the indole ring to engage the organonickel intermediate.

291   i   **292**
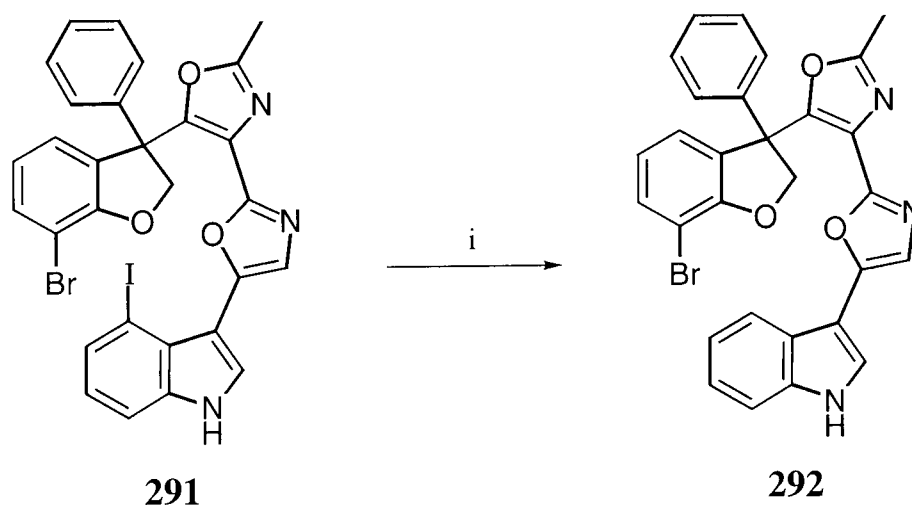
Reagents: i, Cl$_2$Ni(PPh$_3$)$_2$, Zn, PPh$_3$, DMF, Δ; or Cu, Py, Δ.

In an alternative to the Ullmann coupling,[130] the one pot palladium(0)-catalysed stannylation-intramolecular Stille coupling was attempted using tetra*kis*-(triphenylphosphine)palladium(0) and hexabutylditin.[206] It was hoped that this method would form an intermediate stannane in which the tributyltin group resided on the indole ring. Surprisingly, the iodide (**291**) proved unreactive under these conditions. In a final attempt to unite the two aromatic halides we decided to

remove any internal proton source by protecting the indole nitrogen with a TIPS group. We hoped that this would extend the lifetime of the intermediate organonickel species and that cross coupling would then occur, but, again, no biaryl product could be isolated using the nickel(0)-mediated conditions.[212]

2.4.4 A Second Generation Approach to the Macrocycle (64)

Having considered a variety of conditions to effect ring closure in the acyclic precursor (291) without success, we began to analyse the substrate structure and considered subtle changes in a bid to increase the reactivity. From our experiences we had learnt that the ideal substrate for an intramolecular Ullmann coupling using the modified nickel(0) conditions would contain two aryl iodides at the reacting sites.[97,211,213-6] Therefore, we decided to construct the analog of the *bis*-oxazole (291), in which the bromine atom was replaced with an iodine atom.

Following analysis of the intermediates *en route* to the macrocyclic precursor (291), we believed that the alkene (73) represented the most efficient point at which to exchange the bromine atom for an iodine atom. Considerable quantities of the bromide (73) were still available and, in the absence of any sensitive functionality, we anticipated that treatment of the bromide (73) with an alkyllithium base, then exposure of the resulting organolithium species to iodine would provide the desired iodide (293). After extensive experimentation, we found that reaction of *n*-butyllithium with the bromide (73) at -78°C gave the putative aryllithium species (294). Rapid addition of a concentrated solution of iodine in THF trapped the organolithium species (294) and gave the desired iodide (293) in 86% yield.

95
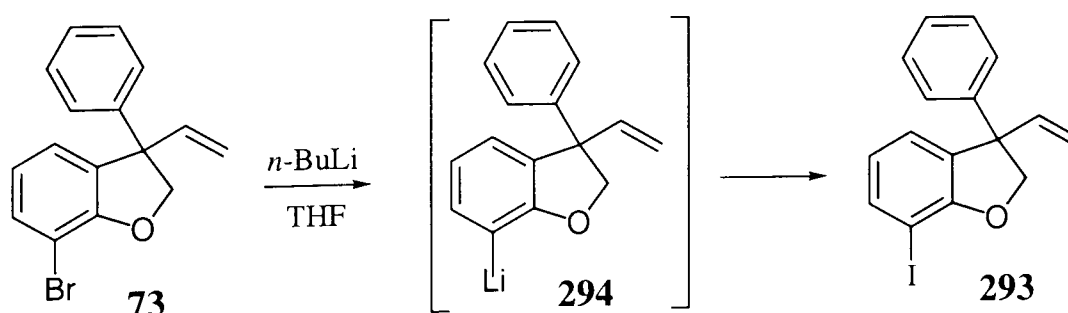
With the iodine substituent on the benzofuran ring now in place, we were in a position to follow the previous synthetic sequence and prepare a modified macrocyclic precursor. Towards this end, the terminal alkene (**293**) was oxidatively cleaved with osmium tetroxide and sodium periodate to give the aldehyde (**295**) in 84% yield (**Scheme 25**).[132b] A two carbon homologation was successfully performed by exposure of the aldehyde (**295**) to ethyl diazoacetate in the presence of zirconium chloride[133] at 0°C to next provide the ketone (**296**) in 50% yield. Treatment of the ketone (**296**) with sodium nitrite in aqueous acetic acid then gave the oxime (**297**) as a 2:1 mixture of geometrical isomers in 89% yield.
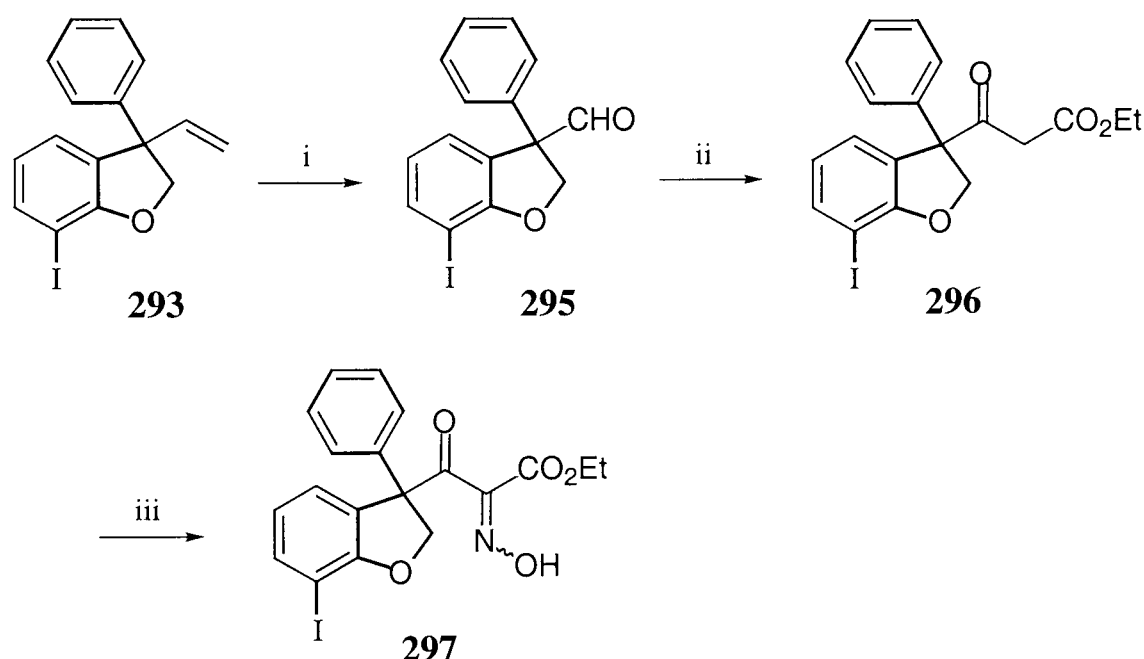
Reagents: i, OsO_4, $NaIO_4$, THF, H_2O, 84%; ii, $ZrCl_4$, N_2CHCO_2Et, CH_2Cl_2, 50%; iii, $NaNO_2$,

$AcOH$, H_2O, 89%.

Scheme 25

With the oxime (**297**) in hand, we were in a position to prepare the oxazole (**298**) using our established reduction, acylation and cyclisation protocol. Treatment of the oxime (**297**) with zinc in aqueous acetic acid effected a smooth reduction of the oxime function to provide the salt (**299**). However, partial reduction of the iodide was also observed, presumably by zinc insertion into the C-I bond and trapping of the organozinc species with a proton from the solvent. This gave the desired salt (**299**) in

a 6:1 ratio with the de-iodinated salt (**300**). All attempts to remove the de-iodinated material (**300**) by chromatography were unsuccessful, both at this stage and in all future synthetic steps. Partial reduction of the C-I bond is not surprising since it has been demonstrated that zinc insertion into aryl halide bonds is more facile for iodides than for bromides.[219] This has led to the use of *o*-bromophenyl iodide (**301**) as the synthetic equivalent of *o*-phenylene-1-anion-2-cation. Takagi *et al* illustrated the synthetic utility of this process in their synthesis of the aromatic compound (**302**).[220] In this example, treatment of *o*-bromophenyl iodide (**301**) with zinc in TMU at 70°C provided the organozinc intermediate (**303**), by preferential zinc insertion into the C-I bond (**Scheme 26**). A Negishi coupling of **303** with 3-iodo-benzoic acid methyl ester, in the presence of tetra*kis*-(triphenylphosphine)palladium(0), next gave the biaryl compound (**304**).[221] A second Negishi coupling using the organozinc species derived from *o*-chlorophenyl iodide and the bromide (**304**) constructed another biaryl bond and the aromatic compound (**302**).[221]
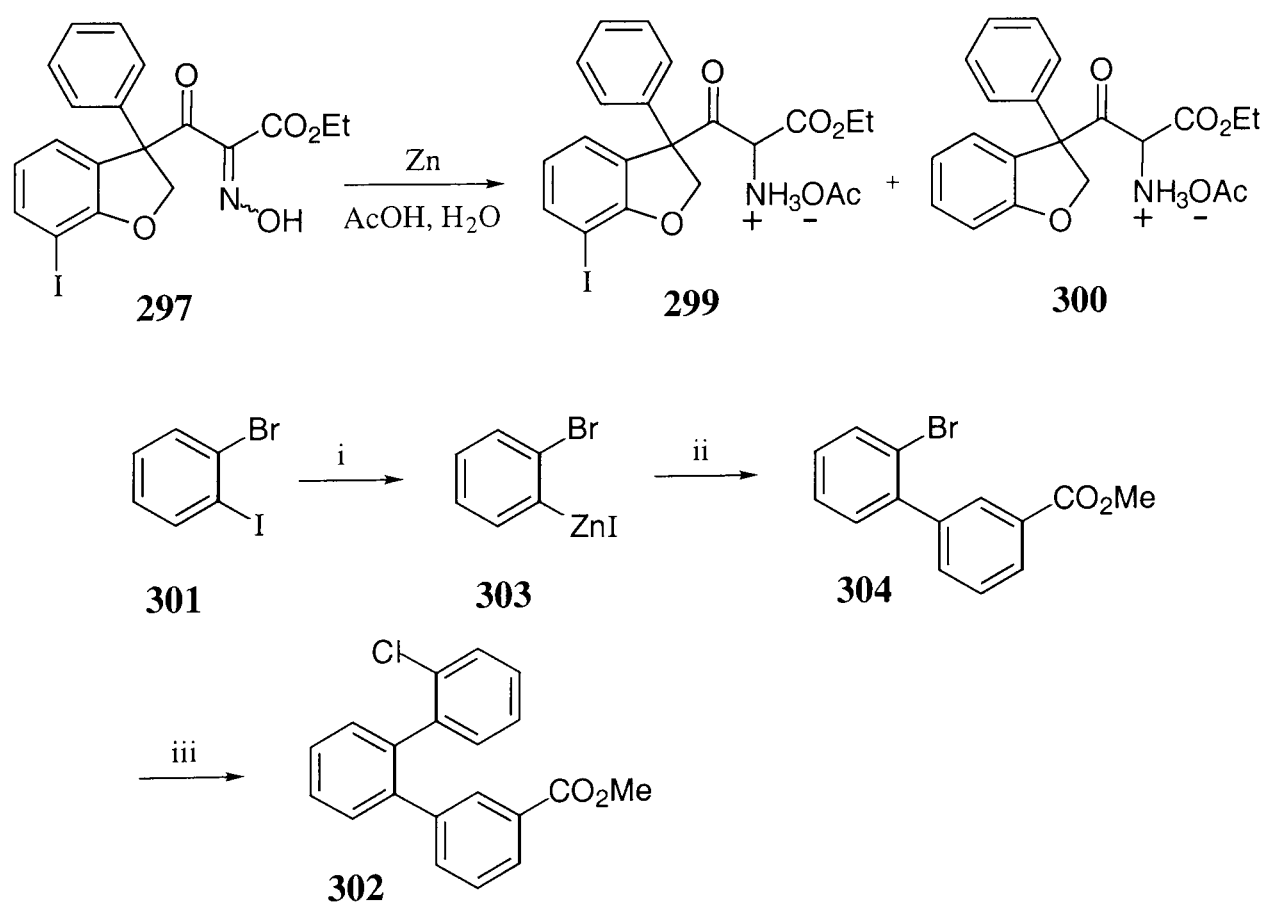
Reagents: i, Zn, TMU, Δ, 95%; ii, Pd(PPh3)4, IC6H4CO2Me; iii, ClC6H4ZnI, TMU, Δ, 88% (2 steps).

Scheme 26

97

The mixture of the salts (**299** and **300**) underwent acylation when treated with acetic anhydride in pyridine to give the amide (**305**) (for clarity, only the iodinated product is now shown) in 53% yield (**Scheme 27**). Exposure of the amide (**305**) to triethylamine, triphenylphosphine and iodine provided the trisubstituted oxazole (**298**) in 89% yield.[69] Finally, basic hydrolysis of the ester (**298**) with lithium hydroxide gave the modified benzofuran oxazole acid fragment (**306**) in quantitative yield.
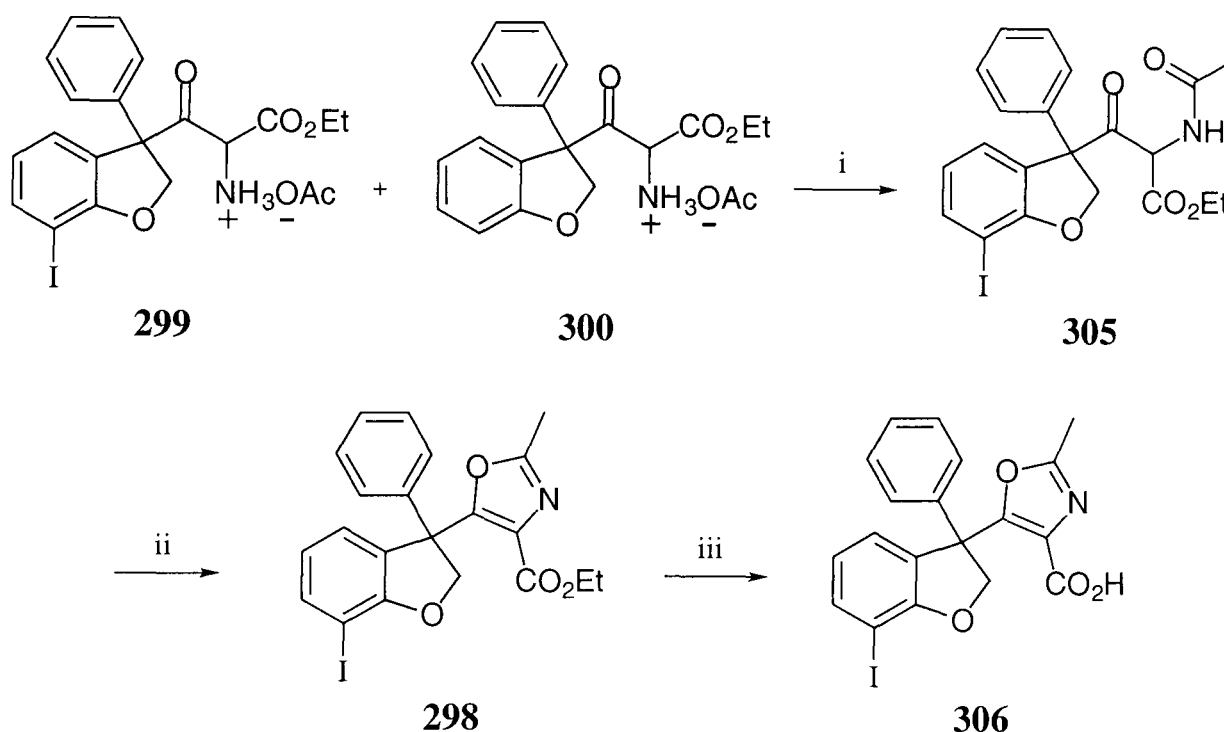
Reagents: i, Ac$_2$O, Py, 53%; ii, Et$_3$N, PPh$_3$, I$_2$, CH$_2$Cl$_2$, 89%; iii, LiOH, MeOH, H$_2$O, 100%.

Scheme 27

Finally, we could consider the union of the two iodide fragments (**306** and **250**). Thus, the acid fragment (**306**) was first converted into the corresponding acid chloride (**307**) by treatment with oxalyl chloride (**Scheme 28**). The salt (**250**) was again treated with triethylamine to liberate the free amine function which was trapped by the acid chloride (**307**) to give the amide (**308**) in a poor 25% yield. Attempts to form the amide bond using standard peptide coupling conditions[131] led to only a 5% recovery of the desired product (**308**). At this juncture we decided to investigate the nickel(0)-mediated Ullmann coupling of the amide (**308**).[97,211,213-7] It was our belief that allowing the disubstituted oxazole to exist in its open keto amide form would

convey greater conformational freedom on the system and possibly bring together the reacting centres. We were very disappointed therefore, when treatment of the amide (**308**) with an active nickel(0) complex[212] gave the reduced compound (**309**) as the only new product in 40% yield.
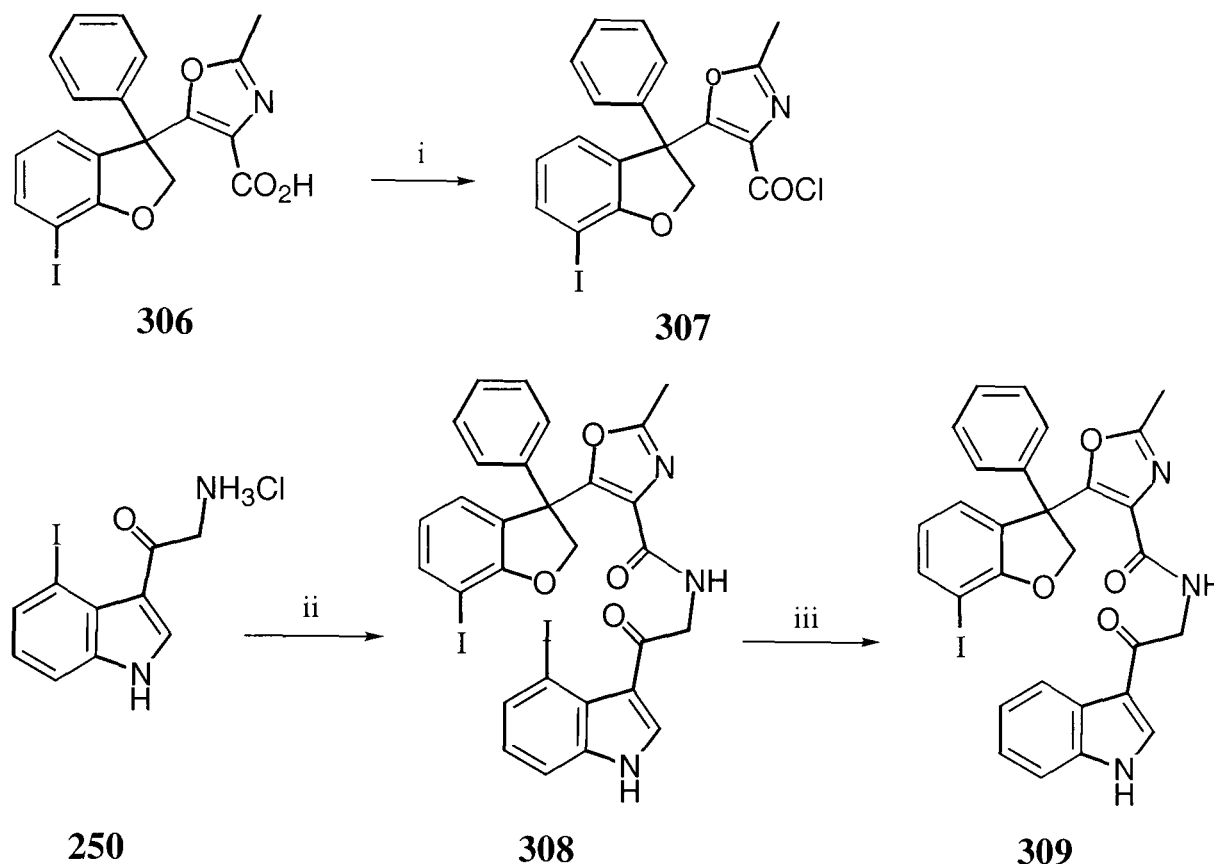
Reagents: i, (COCl)$_2$; ii, Et$_3$N, **307**, CH$_2$Cl$_2$, 25% (2 steps); iii, Cl$_2$Ni(PPh$_3$)$_2$, Zn, PPh$_3$,

DMF, Δ, 40%.

Scheme 28

Following this setback we next treated the amide (**308**) with triethylamine, triphenylphosphine and hexachloroethane to provide the *bis*-oxazole (**310**) in 56% yield (**Scheme 29**).[69] In our final macrocyclisation attempt we treated the *bis*-oxazole (**310**) with an *in situ* generated nickel(0) complex.[212] The reaction was far more complex than that of the amide (**308**), but from the HRMS of the crude reaction mixture it was impossible to detect any of the cyclised product, although it was possible to identify some unreacted starting material and products in which either one or both of the iodine atoms had been removed.
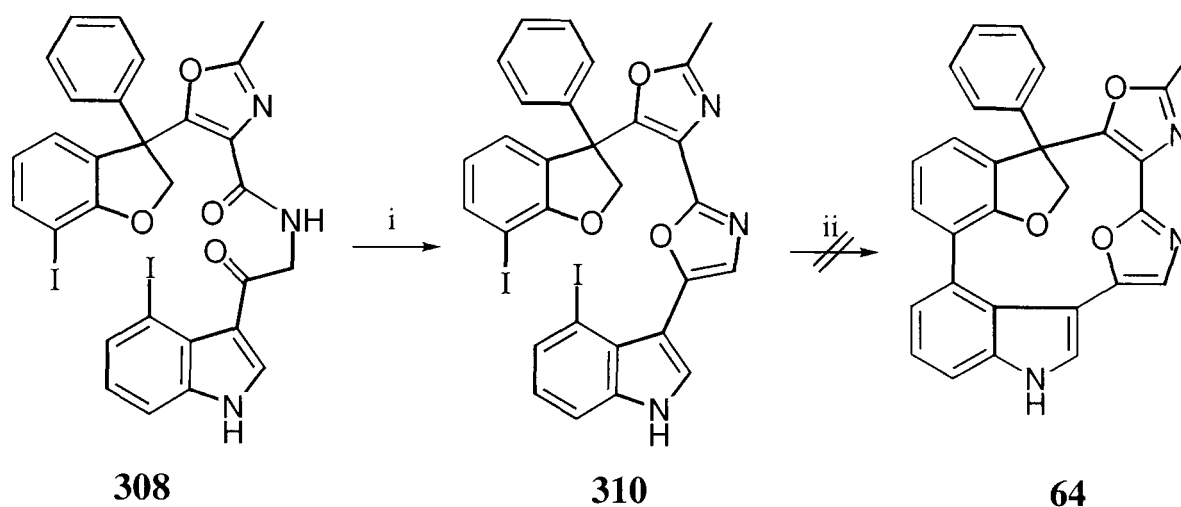
Reagents: i, Et₃N, PPh₃, Cl₃CCCl₃, CH₂Cl₂, 56%; ii, Cl₂Ni(PPh₃)₂, Zn, PPh₃, DMF, Δ.

Scheme 29

2.4.5 An Alternative Approach to the Macrocycle (64)

In light of the problems we encountered in constructing the biaryl bond between the benzofuran ring and the indole ring in the final macrocyclisation step of our synthesis, we began to consider alternative approaches to the macrocyclic aromatic core of diazonamide A (**1**). In planning an alternative strategy, we wanted to make use of the extensive research we had already conducted, whilst simplifying the problem of biaryl bond construction. Our answer to this dilemma is outlined in the retrosynthetic analysis shown overleaf.

In this approach, initial retrosynthetic disassembly now cleaved the disubstituted oxazole of the macrocycle (**64**) to the carbamate (**311**). In the forward sense, we anticipated that removal of the benzyl carbamate protecting group[191] would liberate an amine which could be condensed with a carboxylic acid, exposed following saponification of the ester group, to give an amide.[131] Completion of the macrocyclic core (**64**) would then take place *via* a cyclodehydration reaction to form the *bis*-oxazole unit. Dissection of the remaining oxazole next gave the trisubstituted alkene (**312**).[69] We envisaged utilising the unusual cyclisation of an amide function onto an internal vinyl bromide (**2.2.6**), prepared by treatment of the alkene (**312**) with bromine and triethylamine, to construct the trisubstituted oxazole framework.[181] The

alkene (**312**) incorporates the quaternary carbon centre on the benzofuran ring with a pendant vinyl group. This familiar arrangement could be derived from the iodide (**313**) by an intramolecular 5-*exo*-trig Heck reaction.[134f] This retrosynthetic maneouver greatly simplified the task of disconnecting the alkene (**312**), since the iodide (**313**) can now be cleaved across the phenolic ether linkage to provide the phenol (**314**) and the mesylate (**315**). In the synthetic direction, exposure of the phenol (**314**) to the action of a suitable base was expected to result in the formation of a reactive phenoxide anion which could be trapped by the mesylate (**315**) to provide the Heck precursor (**313**) after exchange of the TMS group for an iodine atom. Construction of the simplified biaryl substrate (**314**) could now take place in an intermolecular fashion by uniting the boronic acid or stannane (**316**) with the iodide (**317**) using a Suzuki or Stille reaction respectively.[202,204]

314 **316** **317** X = B(OH)$_2$ or SnR$_3$
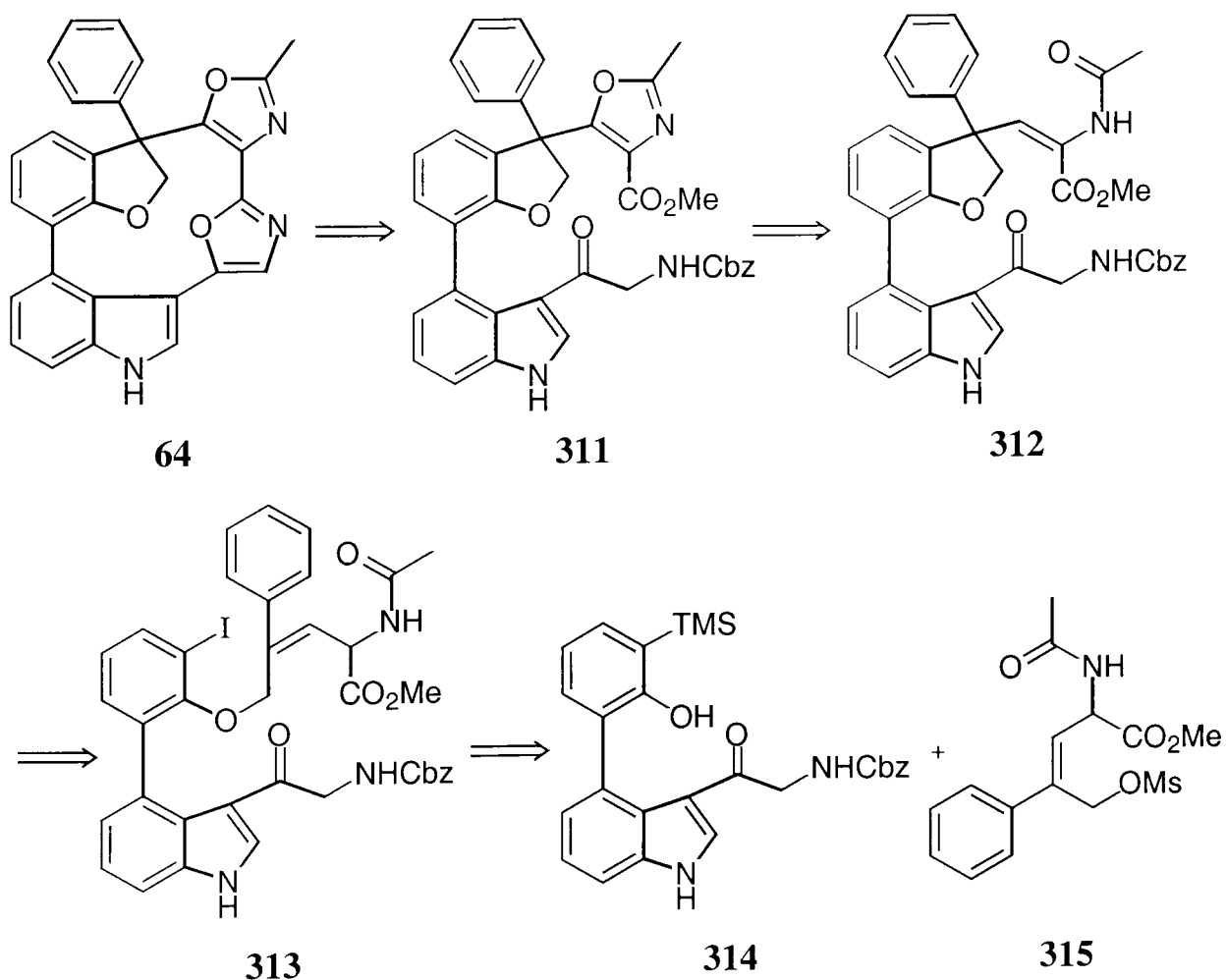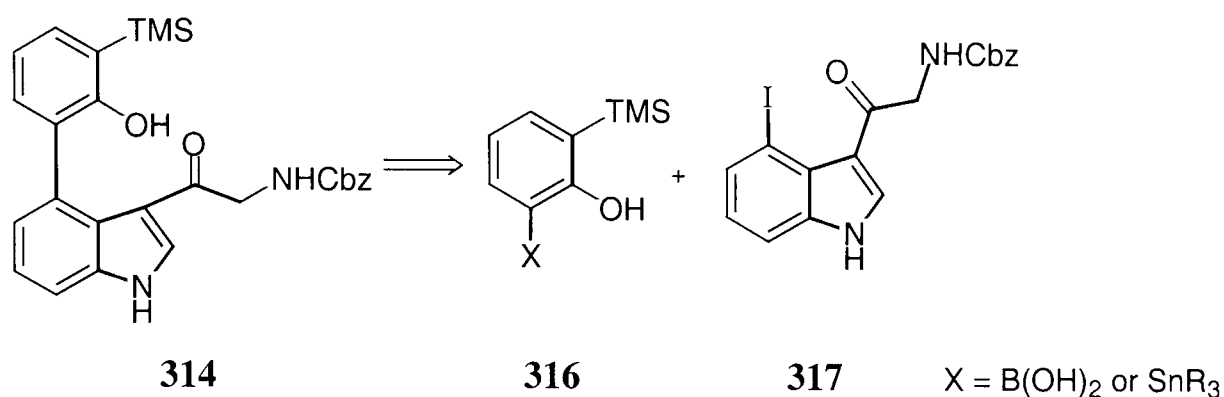
Our initial task on this approach was to prepare a suitable mesylate for coupling with a phenol derivative. We envisaged constructing the trisubstituted alkene using a Wadsworth-Emmons olefination[222] of a phosphonate with Garner aldehyde (**318**).[223] To prepare the required phosphonate we utilised the copper(I) salt-mediated arylation of phosphinyl stabilised carbanions developed by Minami *et al.*[224] Hence, triethyl phosphonoacetate (**319**) was treated with sodium hydride and iodobenzene in the presence of copper(I) iodide at 100°C to provide the phosphonate (**320**) in 71% yield (**Scheme 30**). The phosphonate (**320**) then participated in a Wadsworth-Emmons olefination reaction[222] with Garner aldehyde (**318**),[223] using sodium hydride as the base, to provide the trisubstituted alkene (**321**) in 58% yield. The ester function in **321** was reduced by treatment with DIBAL-H at -78°C to give the alcohol (**322**) in 75% yield. Finally, exposure of the alcohol (**322**) to methanesulfonyl chloride and triethylamine at 0°C gave the crude mesylate (**323**).

In order to determine if this approach offered a viable route for formation of the benzofuran and oxazole rings we chose to first use 2-iodophenol (**324**) instead of a more complex biaryl phenol derivative. Thus, treatment of 2-iodophenol (**324**) with potassium carbonate and the mesylate (**323**) resulted in the formation of the phenolic ether (**325**) (**Scheme 31**). Acid-induced removal of the *t*-butyl carbamate and acetonide protecting groups in **325**, followed by acylation of the crude salt (**326**) with acetic anhydride and DMAP in pyridine, next gave the amide (**327**) in 81% overall yield. Protection of the primary hydroxyl group in **327**, by treatment with

t-butyldimethylsilyl chloride, DMAP and triethylamine, finally provided the silyl ether (**328**), another precursor for the Heck reaction,[134] in 69% yield.
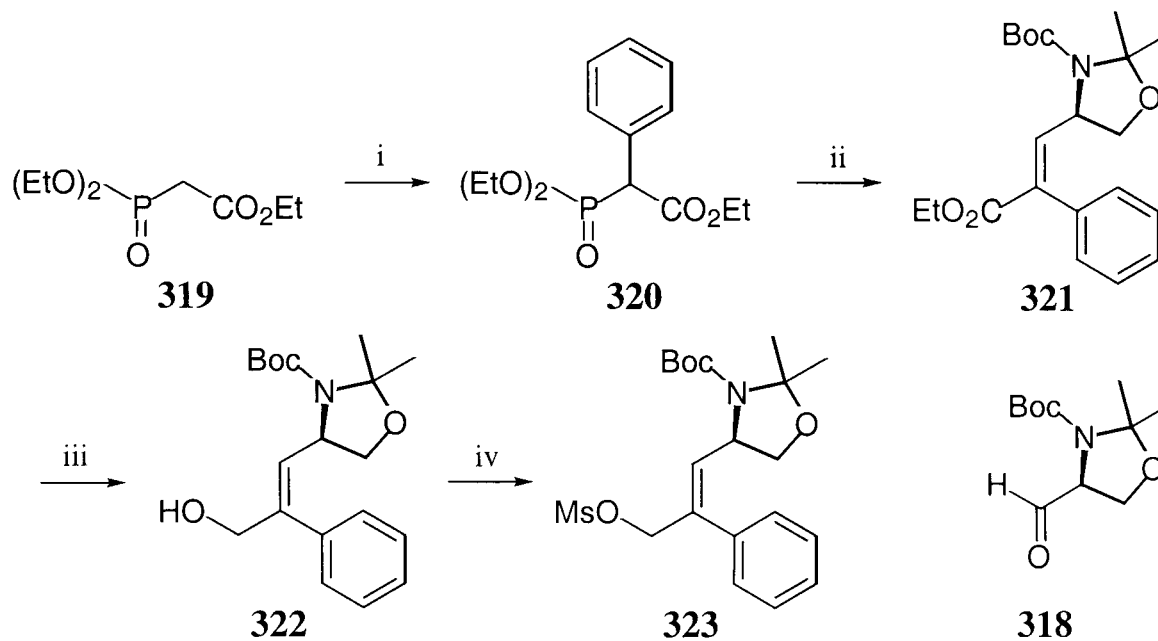
Reagents: i, NaH, CuI, PhI, DMF, Δ, 71%; ii, NaH, **318**, THF, 58%; iii, DIBAL-H, PhMe, 75%; iv,

Et$_3$N, MsCl, CH$_2$Cl$_2$.

Scheme 30
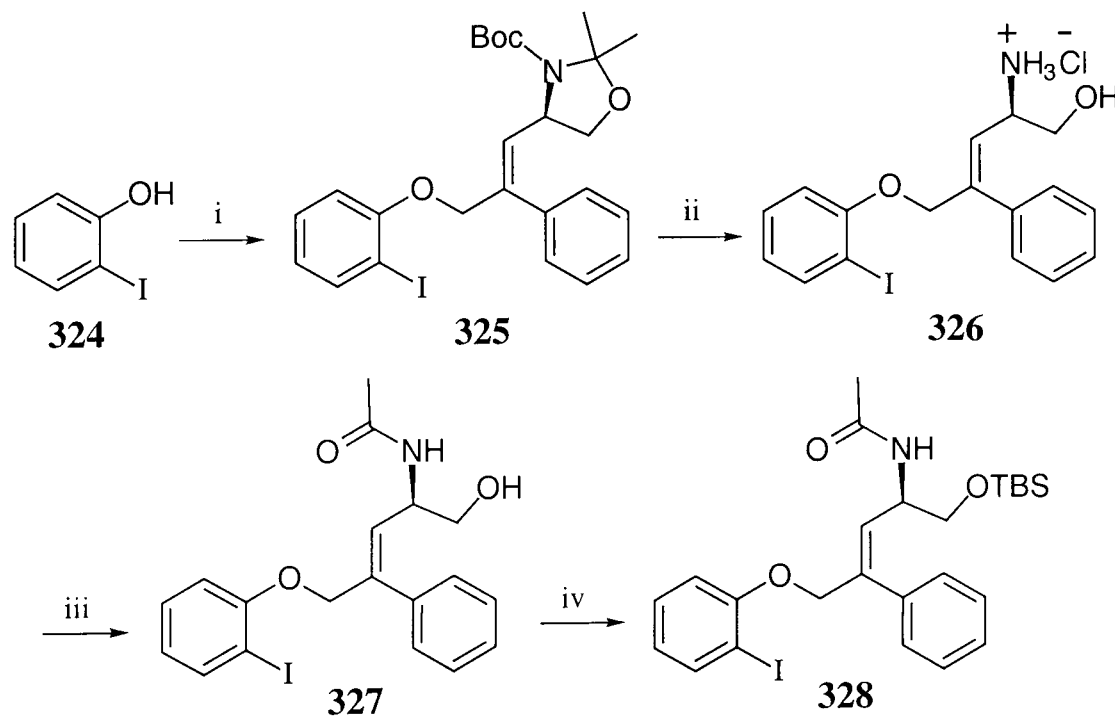
Reagents: i, K$_2$CO$_3$, **323**, DMPU, MeCN, 75%; ii, HCl, dioxane; iii, Ac$_2$O, DMAP, Py, 81% (2 steps);

iv, TBSCl, Et$_3$N, DMAP, CH$_2$Cl$_2$, 69%.

Scheme 31

103

We were now in a position to investigate the intramolecular Heck reaction[134f] of the iodide (**328**). Hence, **328** was treated with *tris*-(dibenzylideneacetone)dipalladium, a bidentate phopshine ligand, a silver salt and a phase-transfer agent in DMF at 80°C, as outlined below. This cocktail provided a complex crude reaction mixture which, after exposure to TBAF in THF, gave one major product. It was not possible to conclusively prove that this product was the alcohol (**329**) as there was insufficient material for ^{13}C NMR studies. However, early indications suggest that this approach might offer an alternative to that described previously and this strategy is currently being pursued within the group. One possible modification of the substrate which could lead to a more favourable Heck reaction involves conversion of the silyl ether (**328**) to the ester (**330**). This alteration should facilitate β-hydride elimination, since the β-hydrogen would be more acidic and the product alkene would exist in conjugation with the carbonyl group. The synthesis of this substrate is also under investigation.
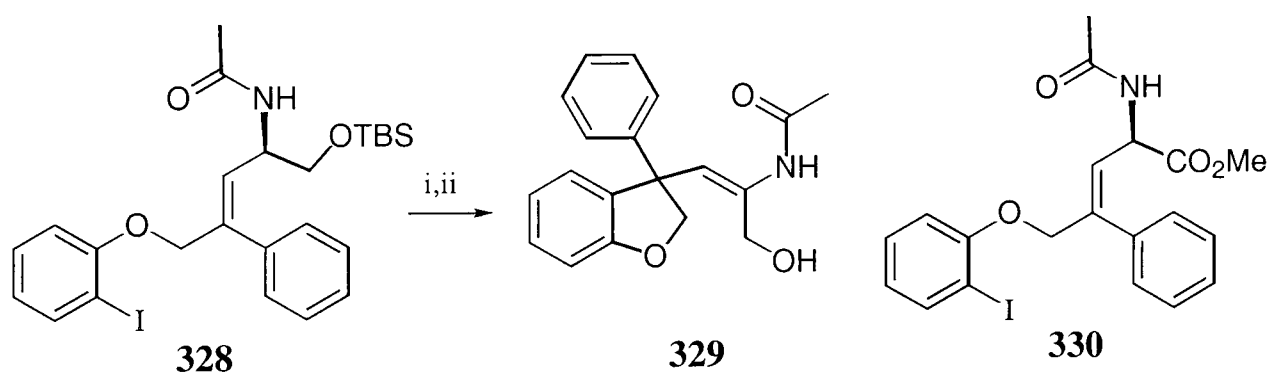
Reagents: i, Pd$_2$(dba)$_3$, dppp, Ag$_3$PO$_4$, *n*-Bu$_4$NBr, DMF, Δ; ii, TBAF, THF.

2.4.6 Conclusions

Ultimately, we were unsuccessful in uniting two aryl halides by an intramolecular Ullmann cyclisation reaction[97,209-11,215-8] to form the biaryl bond and the macrocyclic aromatic core of diazonamide A (**1**). However, we have described an efficient route to suitably substituted precursors for the macrocyclisation reaction which could lead to the desired product (**64**) when treated under modified reaction conditions.[218] Our

approach to these precursors utilised the convergent union of the acids (**69** and **306**) with the amine derived from the salt (**250**) to provide the amides (**289** and **308**).[131] The keto amide function inherent in the amides (**289** and **308**) was then cyclised to construct the intriguing *bis*-oxazole unit.[69]

Our initial investigations into an alternative approach for the synthesis of the macrocycle (**64**), involving another intramolecular Heck reaction[134f] and allowing for intermolecular biaryl bond formation,[202,204] has also been reported.

2.5 Research Summary

The main emphasis throughout this period of research has been towards the efficient construction of the macrocyclic aromatic core of diazonamide A (**1**). Our disconnection strategy simplified this problem to the synthesis of two subunits (**67** and **68**). We applied Heck methodology[134] to form the benzofuran ring in the more complex acid fragment (**67**) *via* an intramolecular 5-*exo*-trig reaction of the iodide (**74**). Our success with this substrate led us to prepare the analog (**83**) which incorporated a protected tyrosine residue for elaboration into the northern substructure of diazonamide A (**1**). However, all attempts to effect ring closure with this substrate met with failure and our synthetic efforts were then concentrated solely towards a model compound of the southern macrocycle. The product alkene (**73**) was next manipulated so that oxazole formation could be investigated. An efficient five step procedure provided the amide (**70**), which encompassed a keto amide function that could be cyclodehydrated under conditions described recently by Wipf[69] to construct the desired trisubstituted oxazole framework in an excellent yield.

The indole fragment (**68**) provided the next challenge *en route* to the macrocycle (**64**). Our initial strategy for the synthesis of this fragment was based on the early inclusion of a bromine substituent and the late introduction of the ketone function. An amine-directed metallation-bromination sequence successfully provided the bromine derivative (**219**).[194] The side chain was elaborated to the carbamate (**216**), but exposure of this compound to the action of DDQ[190] gave only the secondary alcohol (**233**) and none of the desired ketone (**234**). It was possible to introduce the ketone function either in a single step, by acylation of indole (**225**),[199] or in a two step sequence involving the protection and benzylic oxidation of tryptamine (**236**).[190] The carbonyl function in the ketone (**224**) then directed thallation to the C4 position of the indole ring and a thallium-iodine exchange reaction[197a,198] finally provided a suitably substituted indole fragment (**250**).

The two subunits could be combined to give the amide (**289**) by prior activation of the carboxylic acid (**69**) as the acid chloride (**290**). The amide (**289**) included a keto amide function which was again cyclodehydrated under the conditions developed by Wipf[69] to provide the unusual *bis*-oxazole ring system (**291**). This reaction gave our first precursor for an intramolecular Ullmann coupling reaction[97,210,211,215-8] which we hoped would unite the two aromatic halides and form the crucial biaryl bond. However, exposure of the *bis*-oxazole (**291**) to an *in situ* generated nickel(0) complex[212] resulted principally in reduction of the C-I bond. In an effort to increase the reactivity of the benzofuran portion, we decided to synthesise the diiodide precursors (**309** and **310**). To achieve this, we first effected a bromine-iodine exchange reaction of the bromide (**73**), *via* the aryl lithium intermediate (**294**), to provide the iodide (**293**). With the iodide (**293**) now in hand, we next utilised the previous synthetic pathway to prepare two more precursors for the Ullmann reaction.[130] We were hugely disappointed when treatment of the amide (**309**), under Ullmann coupling conditions,[212] again resulted solely in deiodination of the indole portion. The *bis*-oxazole (**310**) also failed to provide any of the desired macrocycle (**64**) under analogous reaction conditions,[212] but there was evidence in this reaction for insertion of the nickel(0) complex into the C-I bond on the benzofuran ring.

Finally, we have described an alternative approach to the macrocycle (**64**) which we hope will simplify the problem of biaryl bond formation. In this strategy we anticipated forming the biaryl bond at an early stage in the synthesis by an intermolecular coupling process.[202,204] Our initial synthetic efforts have focused on preparing a model Heck precursor (**328**). Early indications have shown that this substrate may well participate in the desired 5-*exo*-trig intramolecular coupling process[134f] and this work is ongoing in our laboratories.

3. EXPERIMENTAL

3.0 General Details

All melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were recorded in spectroscopic grade chloroform or methanol on a Jasco DIP-370 polarimeter, $[\alpha]_D$ values are recorded in units of 10^{-1} deg cm^2 g^{-1}. Ultraviolet spectra were recorded on a Philips PU 8700 spectrophotometer as solutions in either deionised water, or spectroscopic grade methanol or ethanol, ε values are recorded in units of dm^3 mol^{-1} cm^{-1}. Infrared spectra were obtained using a Perkin-Elmer 1600 series FT-IR instrument or a Nicolet Magna 550 instrument either in a KBr disc, as a nujol mull, or dilute solutions in spectroscopic grade chloroform. Proton nmr spectra were recorded on either a Bruker DPX 360 (360MHz), or a Varian Unity 300 (300MHz) spectrometer as dilute solutions in deuterochloroform at ambient temperature, unless otherwise stated. The chemical shifts are quoted in parts per million (ppm) relative to residual chloroform as internal standard (δ 7.27) and the multiplicity of each signal is designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; sep., septet; br, broad; m, multiplet; app., apparent. All coupling constants are quoted in Hertz. Carbon-13 nmr spectra were recorded on either a Bruker DPX 360 (at 90.6MHz), a Varian Unity 300 (at 75MHz), or a Jeol EX-270 (at 67.8MHz) instrument as dilute solutions in deuterochloroform, unless otherwise stated. Chemical shifts are reported relative to internal chloroform standard (δ 77.0) on a broad band decoupled mode, and the multiplicities determined using a DEPT sequence. Where required, H-H COSY, H-C COSY and NOE spectra were recorded on a Bruker DPX 360 (360MHz) instrument using standard Bruker software with no modifications. Mass spectra were recorded on a VG Autospec, a MM-701CF, a VG Micromass 7070E or a Micromass LCT spectrometer using electron ionisation (EI), electrospray (ES), or fast atom bombardment (FAB) techniques. Microanalytical data were obtained on a Perkin-Elmer 240B elemental analyser.

Flash chromatography[225] was performed on Merck silica gel 60 as the stationary phase and the solvents employed were either of analytical grade or were distilled before use. All reactions were monitored by tlc using Merck silica gel 60 F_{254} precoated aluminium backed plates which were visualised with ultraviolet light and then with either acidic alcoholic vanillin solution, basic potassium permanganate solution, or acidic anisaldehyde solution.

Routinely, dry organic solvents were stored under nitrogen and/or over sodium wire. Other organic solvents were dried by distillation from the following: THF and benzene (potassium benzophenone ketyl), dichloromethane (calcium hydride) and methanol (magnesium methoxide). Other organic solvents and reagents were purified by the accepted literature procedures.[226] All organic extracts were dried with magnesium sulfate unless otherwise stated. Solvent was removed on a Büchi rotary evaporator. Where necessary, reactions requiring anhydrous conditions were performed in a flame or oven dried apparatus under a nitrogen or argon atmosphere as stated.

3.1 Synthetic Studies towards the Benzofuran Oxazole Unit (69)

2-Bromo-6-(trimethylsilanyl)-phenol (77)
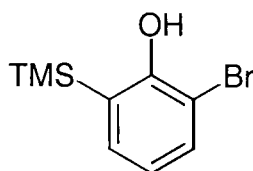
Sodium hydride (3.34g, 60% dispersion in mineral oil, 83.6mmol) was added to a stirred solution of the dibromide (**80**) (10.5g, 41.8mmol) in THF (150ml) at ambient temperature, under an atmosphere of nitrogen. The solution was stirred at ambient temperature for 1 h, then chlorotrimethylsilane (5.3ml, 41.8mmol) was added dropwise over 2 min. The solution was stirred at ambient temperature for 3 h, then cooled to -78°C and n-butyllithium (26.1ml, 1.6M solution in hexanes, 41.8mmol) was added dropwise over 8 min. The mixture was warmed to ambient temperature and a saturated aqueous solution of ammonium chloride (150ml) was added. The mixture was concentrated *in vacuo* to leave an aqueous residue which was extracted with diethyl ether (3 x 150ml). The combined organic extracts were dried (MgSO₄) and concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with petroleum ether (b.p. 40-60°C), to give the aryl silane (8.53g, 83%) as a yellow liquid; υ_{max} (soln., CHCl₃) 3517, 2954, 1324, 1244, 1080, 841cm^{-1}; δ_H (360MHz) 7.50 (1H, dd, J 7.9 and 1.5, phenol H3), 7.35 (1H, dd, J 7.3 and 1.5, phenol H5), 6.83 (1H, app. t, J 7.5, phenol H4), 5.76 (1H, s, OH), 0.37 (9H, s, SiC(CH_3)₃); δ_C (67.8MHz) 157.2 (s), 135.7 (d), 134.1 (d), 128.2 (s), 122.7 (d), 111.6 (s), 0.00 (q); m/z (EI) Found: 243.9910 (M$^+$ C₉H₁₃BrOSi requires 243.9919).

2-[2-Bromo-6-(trimethylsilanyl)-phenoxy]-1-phenylethanone (76)
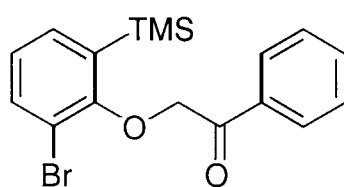
Potassium carbonate (14.0g, 102mmol) and then 2-bromoacetophenone (**78**) (8.89g, 44.7mmol) were added portionwise to a stirred solution of the aryl silane (**77**) (10.0g, 40.6mmol) in acetonitrile (400ml) at ambient temperature, under an atmosphere of nitrogen. The solution was stirred at ambient temperature for 3 h, then filtered and concentrated *in vacuo*. The residue was diluted with ethyl acetate (200ml) and washed with water (200ml), then dried (MgSO$_4$) and concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 5% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the aryl ether (14.0g, 95%) as a pale yellow oil; υ_{max} (soln., CHCl$_3$) 2956, 2901, 1705, 1598, 1579, 1450, 1404, 1091cm^{-1}; δ_H (300MHz) 7.91 (2H, app. dd, J 7.9 and 1.5, phenyl H2 and phenyl H6), 7.51 (1H, app. tt, J 7.0 and 1.5, phenyl H4), 7.49 (1H, dd, J 7.5 and 1.5, phenoxy H3), 7.40 (2H, app. t, J 7.9, phenyl H3 and phenyl H5), 7.31 (1H, dd, J 7.5 and 1.7, phenoxy H5), 6.95 (1H, t, J 7.5, phenoxy H4), 5.27 (2H, s, CH_2), 0.22 (9H, s, SiC(CH_3)$_3$); δ_C (75MHz) 193.8 (s), 160.0 (s), 136.2 (s), 135.7 (d), 135.0 (d), 134.1 (s), 129.2 (d), 128.3 (d), 126.3 (d x 2), 116.7 (s), 75.6 (t), 0.00 (q); *m/z* (EI) Found: 362.0338 (M$^+$ C$_{17}$H$_{19}$BrO$_2$Si requires 362.0336); Found: C, 56.4; H, 5.2; Br, 22.2%, C$_{17}$H$_{19}$BrO$_2$Si requires C, 56.2; H, 5.3; Br, 22.0%.

2-(2-Bromo-6-iodophenoxy)-1-phenylethanone (75)
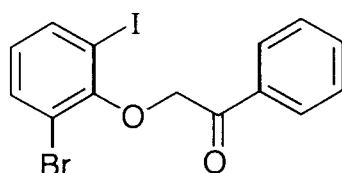
Silver tetrafluoroborate (0.29g, 1.51mmol) was added in a single portion to a stirred solution of the aryl ether (**76**) (0.50g, 1.37mmol) in methanol (14ml) at ambient temperature, under an atmosphere of nitrogen. The solution was cooled to 0°C and iodine (0.38g, 1.51mmol) was added portionwise. The mixture was warmed to ambient temperature and stirred at ambient temperature for 1.5 h, then diluted with diethyl ether (20ml) and filtered. The filtrate was washed with a 20% aqueous solution of sodium thiosulfate (2 x 40ml), then dried (MgSO$_4$) and concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 5% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the iodide (0.44g, 77%) as a pale yellow solid; m.p. 97-99°C, [Lit. m.p. 96-97°C][227]; υ_{max} (soln., CHCl$_3$) 2902, 1706cm^{-1}; δ_H (300MHz) 7.91 (2H, app. d, *J* 7.5, phenyl H2 and phenyl H6), 7.75 (1H, dd, *J* 7.9 and 1.1, Ar), 7.62 (1H, t, *J* 7.5, phenyl H4), 7.56 (1H, dd, *J* 7.9 and 1.1, Ar), 7.50 (2H, app. t, *J* 7.5, phenyl H3 and phenyl H5), 6.77 (1H, t, *J* 7.9, phenoxy H4), 5.27 (2H, s, C*H*$_2$), 0.22 (9H, s, SiC(C*H*$_3$)$_3$); δ_C (75MHz) 193.0 (s), 155.2 (s), 139.3 (d), 134.8 (s), 134.3 (d), 134.2 (d), 129.2 (d), 128.5 (d), 128.2 (d), 92.7 (s), 89.9 (s), 74.8 (t); *m/z* (EI) Found: 415.8909 (M$^+$ C$_{14}$H$_{10}$BrIO$_2$ requires 415.8920); Found: C, 40.1; H, 2.4; I, 30.6%, C$_{14}$H$_{10}$BrIO$_2$ requires C, 40.3; H, 2.4; I, 30.4%.

(*E/Z*)-1-(2-Bromo-6-iodophenoxy)-2-phenylbut-2-ene (74)
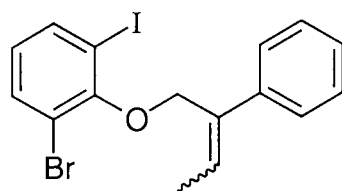
n-Butyllithium (15.5ml, 1.6M in hexanes, 24.8mmol) was added dropwise over 5 min to a stirred solution of (ethyl)triphenylphosphonium bromide (9.19g, 24.8mmol) in THF (125ml) at 0°C, under an atmosphere of nitrogen. The solution was stirred at 0°C for 20 min, then a solution of the iodide (**75**) (7.37g, 17.7mmol) in THF (90ml) was added dropwise over 10 min. The solution was warmed to ambient temperature and

stirred at ambient temperature for 3 h, then a saturated aqueous solution of ammonium chloride (100ml) was added. The mixture was extracted with diethyl ether (3 x 250ml), then the combined organic extracts were dried (MgSO$_4$) and concentrated *in vacuo*. The residue was diluted with diethyl ether (40ml) and cooled to 0°C, then pentane (40ml) was added to the rapidly stirred solution and the mixture was stirred at 0°C for 30min. The mixture was filtered and the filtrate was concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 5% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the alkene (7.34g, 96%), in a 2:1 ratio of *Z:E* geometrical isomers, as a yellow oil; υ_{max} (soln., CHCl$_3$) 2961, 1434, 1368cm^{-1}; δ_H (300MHz, *Z* isomer) 7.78 (1H, dd, *J* 7.9 and 1.5, Ar), 7.58 (1H, dd, *J* 7.9 and 1.5, Ar), 7.52-7.36 (5H, m, phenyl), 6.73 (1H, app. t, *J* 7.5, phenoxy H4), 6.32 (1H, q, *J* 7.2, C*H*CH$_3$), 4.77 (2H, s, CH$_2$), 1.86 (3H, d, *J* 7.2, CH$_3$); δ_C (75MHz) 155.9 (s), 139.3 (d), 138.7 (s), 137.2 (s), 134.4 (d), 134.3 (d), 129.7 (d), 128.6 (d), 127.6 (d), 127.5 (d), 117.8 (s), 93.5 (s), 77.7 (t), 15.3 (q); *m/z* (EI) Found: 427.9273 (M$^+$ C$_{16}$H$_{14}$BrIO requires 427.9274).

(*S*)-2-(3-Acetyl-4-hydroxyphenyl)-1-carboxyethylammonium chloride (86)
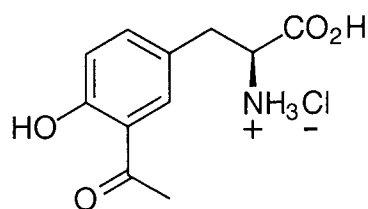
Aluminium chloride (29.0g, 215mmol) was added portionwise to a stirred suspension of L-tyrosine (85) (10.0g, 55.2mmol) in nitrobenzene (150ml) at ambient temperature. Acetyl chloride (4.7ml, 66.2mmol) was added dropwise over 3 min and the mixture was heated at 100°C for 16 h, then cooled to ambient temperature and poured onto a mixture of ice (300g) and concentrated hydrochloric acid (55ml). The aqueous solution was washed with ethyl acetate (2 x 300ml), then concentrated *in vacuo* to leave a residue which was stored at 0°C overnight. The precipitate was

removed by filtration to leave the ketone (9.0g, 67%) as a white solid; m.p. 227-229°C dec. (5M HCl), [Lit. m.p. 221-225°C][228]; δ_H (D$_2$O, 360MHz) 7.53 (1H, d, J 2.0, phenol H2), 7.23 (1H, dd, J 8.1 and 2.0, phenol H6), 6.70 (1H, d, J 8.1, phenol H5), 4.14 (1H, t, J 6.6, C*H*CH$_2$), 3.08 (1H, dd, J 14.5 and 6.0, CHC*H*$_2$), 2.99 (1H, dd, J 14.5 and 7.1, CHC*H*$_2$), 2.40 (3H, s, C*H*$_3$); δ_C (D$_2$O, 67.8MHz) 207.7 (s), 172.2 (s), 160.4 (s), 138.5 (d), 133.2 (d), 125.9 (s), 120.3 (s), 119.1 (d), 54.8 (d), 35.3 (t), 27.2 (q); m/z (FAB) Found: 224.0936 ([M-HCl]$^+$ C$_{11}$H$_{13}$NO$_4$ requires 224.0925).

(S)-2-(3-Acetyl-4-hydroxyphenyl)-1-methoxycarbonylethylammonium chloride (87)
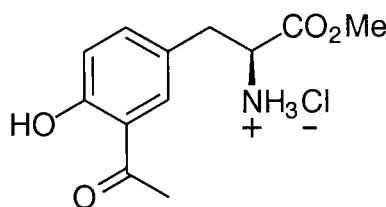
Acetyl chloride (0.9ml, 12.9mmol) was added dropwise over 5 min to methanol (20ml) at 0°C with stirring. The solution was stirred at 0°C for 10 min, then the ketone (86) (1.12g, 4.30mmol) was added portionwise at 0°C and the mixture was warmed to ambient temperature. The mixture was heated at reflux for 3 h, then cooled to ambient temperature and concentrated *in vacuo* to leave the ester (1.12g, 95%) as a white solid, m.p. 187-189°C (MeOH/Et$_2$O), [Lit. m.p. 180-183°C][229]; $[\alpha]_D$ = +7.2 (c = 1.0, MeOH), [Lit. $[\alpha]_D$ = -3.3 (c = 1.0, MeOH)][229]; υ_{max} (KBr) 3410, 1752, 1637, 1490, 1446, 1362, 1252, 1232, 1060cm^{-1}; δ_H (CD$_3$OD, 360MHz) 7.84 (1H, s, phenol H2), 7.44 (1H, dd, J 8.6 and 2.3, phenol H6), 6.99 (1H, d, J 8.6, phenol H5), 4.40 (1H, t, J 6.6, C*H*CH$_2$), 3.88 (3H, s, OC*H*$_3$), 3.29 (1H, dd, J 14.6 and 6.0, CHC*H*$_2$), 3.21 (1H, dd, J 14.6 and 7.3, CHC*H*$_2$), 2.70 (3H, s, COC*H*$_3$); δ_C (CD$_3$OD, 67.8MHz) 206.2 (s), 170.3 (s), 162.8 (s), 138.4 (d), 133.4 (d), 125.8 (s), 121.1 (s), 119.7 (d), 55.1 (d), 53.7 (q), 36.3 (t), 27.2 (q); m/z (EI) Found: 238.1074 ([M-HCl]$^+$ C$_{12}$H$_{15}$NO$_4$ requires 238.1079).

(S)-Methyl-3-(3-acetyl-4-hydroxyphenyl)-2-benzyloxycarbonylaminopropionate (88)
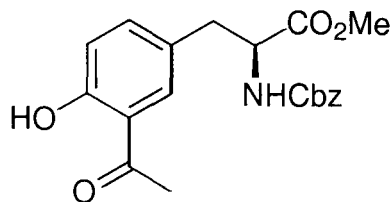
Sodium carbonate (8.97g, 84.6mmol) was added in a single portion to a stirred solution of the ester (**87**) (11.0g, 40.3mmol) in THF (135ml) and water (135ml) at 0°C. Benzyl chloroformate (6.3ml, 44.3mmol) was added dropwise over 1 min at 0°C and the solution was warmed to ambient temperature and stirred at ambient temperature for 2 h. The solution was concentrated *in vacuo* to leave a residue which was diluted with ethyl acetate (30ml). The aqueous layer was separated, then washed with ethyl acetate (30ml). The combined organic extracts were dried (MgSO$_4$) and concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 35% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the carbamate (11.6g, 77%) as a clear oil which solidified on standing; m.p. 91-93°C, [Lit. m.p. 94-96°C][229]; $[\alpha]_D$ = -9.0 (c = 1.0, MeOH), [Lit. $[\alpha]_D$ = -4.9 (c = 1.0, MeOH)][229]; υ_{max} (soln., CHCl$_3$) 3429, 1714, 1644, 1620, 1353cm^{-1}; δ_H (360MHz) 7.45 (1H, s, phenol H2), 7.33 (5H, m, Ar), 7.21 (1H, dd, *J* 8.5 and 2.2, phenol H6), 6.87 (1H, d, *J* 8.5, phenol H5), 5.45 (1H, d, *J* 8.1, N*H*), 5.14 (1H, d, *J* 12.2, C*H*$_2$O), 5.05 (1H, d, *J* 12.2, C*H*$_2$O), 4.68-4.63 (1H, m, C*H*CH$_2$), 3.73 (3H, s, OC*H*$_3$), 3.14 (1H, dd, *J* 14.1 and 5.6, CHC*H*$_2$), 3.01 (1H, dd, *J* 14.1 and 6.4, CHC*H*$_2$), 2.52 (3H, s, COC*H*$_3$); δ_C (67.8MHz) 204.2 (s), 171.7 (s), 161.3 (s), 155.5 (s), 137.3 (d), 136.0 (s), 131.1 (d), 128.4 (d), 128.2 (d), 128.0 (d), 127.4 (d), 126.8 (d), 126.1 (s), 119.4 (s), 118.5 (d), 66.9 (t), 54.6 (d), 52.3 (q), 37.3 (t), 26.5 (q); *m/z* (EI) Found: 371.1359 (M$^+$ C$_{20}$H$_{21}$NO$_6$ requires 371.1369).

(S)-Methyl-3-(3-acetyl-4-benzyloxyphenyl)-2-benzyloxycarbonylamino propionate(89)
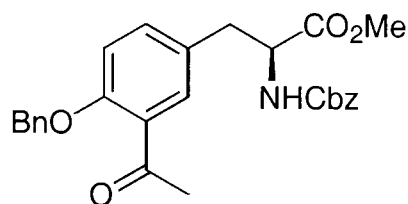
Potassium carbonate (6.70g, 48.5mmol), benzyl bromide (2.1ml, 17.8mmol) and then DMPU (5.9ml, 48.5mmol) were added to a stirred solution of the carbamate (**88**) (6.00g, 16.2mmol) in DMF (80ml) at ambient temperature, under an atmosphere of nitrogen. The solution was stirred at ambient temperature for 22 h, then poured onto water (100ml) and acidified with hydrochloric acid (2M). The aqueous solution was extracted with ethyl acetate (3 x 150ml), then the combined organic extracts were washed with water (300ml) and dried (MgSO$_4$), then concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 35% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the benzyl ether (2.46g, 34%) as a colourless oil which solidified on standing; m.p. 80-82°C, [Lit. m.p. 83-85°C][229]; $[\alpha]_D$ = -6.6 (c = 1.0, MeOH), [Lit. $[\alpha]_D$ = -3.1 (c = 1.0, MeOH)][229]; υ_{max} (soln., CHCl$_3$) 3429, 1714, 1672, 1353cm^{-1}; δ_H (360MHz) 7.56 (1H, d, J 2.3, phenyl H2), 7.45-7.30 (10H, m, Ar), 7.21 (1H, dd, J 8.4 and 2.3, phenyl H6), 6.94 (1H, d, J 8.4, phenyl H5), 5.46 (1H, d, J 7.8, NH), 5.13 (2H, s, ArCH_2OAr), 5.10 (2H, s, CO$_2$CH_2Ar), 4.69-4.62 (1H, m, CHCH$_2$), 3.75 (3H, s, OCH_3), 3.12 (1H, dd, J 13.9 and 5.3, CHCH_2), 3.04 (1H, dd, J 13.9 and 6.2, CHCH_2), 2.59 (3H, s, COCH_3); δ_C (67.8MHz) 199.2 (s), 171.7 (s), 157.1 (s), 155.5 (s), 136.1 (s), 135.9 (s), 134.2 (d), 131.1 (d), 128.5 (d), 128.3 (d), 128.2 (s), 128.1 (d), 128.0 (d), 127.9 (d), 127.8 (s), 127.4 (d), 112.9 (d), 70.5 (t), 66.8 (t), 54.7 (d), 52.3 (q), 36.9 (t), 32.0 (q); m/z (FAB) Found: 462.1925 ([MH]$^+$ C$_{27}$H$_{28}$NO$_6$ requires 462.1917).

(S)-Methyl-3-(4-benzyloxy-3-bromoacetylphenyl)-2-benzyloxycarbonylamino propionate (84)
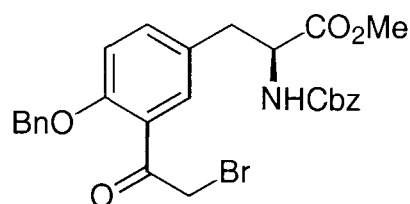
Lithium *bis*-(trimethylsilyl)amide (9.8ml, 1.0M in THF, 9.75mmol) was added dropwise to a stirred solution of the benzyl ether (**89**) (1.50g, 3.25mmol) in THF (35ml) at -78°C, under an atmosphere of nitrogen. The solution was stirred at -78°C for 15 min, then chlorotrimethylsilane (1.4ml, 11.4mmol) was added dropwise over 1 min at -78°C. The solution was warmed to 0°C for 10 min, then cooled to -78°C. A solution of bromine (6.5ml, 3.25mmol) in dichloromethane (20ml) was added dropwise at -78°C and the solution was stirred at -78°C for 1 min, then poured onto a saturated aqueous solution of sodium hydrogencarbonate (10ml). The aqueous phase was separated and extracted with dichloromethane (2 x 10ml). The combined organic extracts were dried (MgSO$_4$), then concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 35% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *bromide* (1.38g, 78%) as a white solid; m.p. 98-99°C; [α]$_D$ = +49.8 (c = 2.9, CHCl$_3$); υ$_{max}$ (soln., CHCl$_3$) 3429, 1714, 1351cm^{-1}; δ$_H$ (360MHz) 7.59 (1H, d, *J* 2.0, phenyl H2), 7.44-7.30 (10H, m, Ar), 7.25 (1H, dd, *J* 8.4 and 2.0, phenyl H6), 6.95 (1H, d, *J* 8.4, phenyl H5), 5.40 (1H, d, *J* 8.0, N*H*), 5.14 (2H, s, ArC*H*$_2$OAr), 5.09 (2H, s, CO$_2$C*H*$_2$Ar), 4.66-4.61 (1H, m, C*H*CH$_2$), 4.50 (2H, s, C*H*$_2$Br), 3.74 (3H, s, C*H*$_3$), 3.09 (1H, dd, *J* 13.9 and 5.3, CHC*H*$_2$), 3.04 (1H, dd, *J* 13.9 and 6.0, CHC*H*$_2$); δ$_C$ (67.8MHz) 192.2 (s), 171.6 (s), 156.9 (s), 155.5 (s), 136.1 (s), 135.4 (s), 135.4 (d), 132.1 (d), 128.7 (s), 128.7 (d), 128.4 (d x 2), 128.2 (d), 128.0 (d), 127.9 (d), 124.9 (s), 112.9 (d), 71.0 (t), 66.8 (t), 54.7 (d), 52.4 (q), 37.4 (t), 36.9 (t); *m/z* (FAB) Found: 540.0986 ([MH]$^+$ C$_{27}$H$_{27}$BrNO$_6$ requires 540.1022).

(S)-Methyl-3-(4-benzyloxy-3-{[2-bromo-6-(trimethylsilanyl)-phenoxy]-acetyl}-phenyl)-2-benzyloxycarbonylaminopropionate (91)
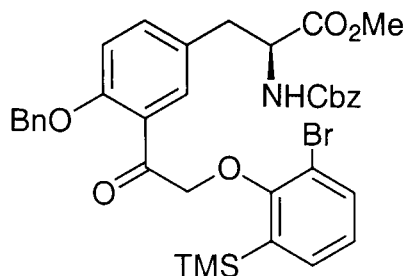
Potassium carbonate (0.77g, 5.55mmol) and then the bromide (**84**) (0.60g, 1.11mmol) were added to a stirred solution of the aryl silane (**77**) (1.09g, 4.44mmol) in acetonitrile (10ml) at ambient temperature, under an atmosphere of nitrogen. The solution was stirred at ambient temperature for 19 h, then filtered and concentrated *in vacuo*. The residue was diluted with ethyl acetate (10ml), then washed with water (10ml) and dried (MgSO$_4$), then concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 35% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *aryl ether* (0.67g, 85%) as a yellow oil; $[\alpha]_D = +38.2$ (c = 1.8, CHCl$_3$); υ_{max} (soln., CHCl$_3$) 3622, 3429, 1718, 1352, 1061, 841cm^{-1}; δ_H (360MHz) 7.82 (1H, d, *J* 2.1, phenyl H2), 7.53 (1H, dd, *J* 8.5 and 2.1, phenyl H6), 7.37-7.22 (12H, m, Ar), 7.02 (1H, t, *J* 7.4, phenoxy H4), 6.95 (1H, d, *J* 8.5, phenyl H5), 5.33 (1H, d, *J* 7.9, N*H*), 5.26 (1H, d, *J* 18.0, COC*H*$_2$OAr), 5.20 (1H, d, *J* 18.0, COC*H*$_2$OAr), 5.12 (2H, s, ArC*H*$_2$OAr), 5.10 (2H, s, CO$_2$C*H*$_2$Ar), 4.70-4.64 (1H, m, C*H*CH$_2$), 3.78 (3H, s, OC*H*$_3$), 3.18 (1H, dd, *J* 13.9 and 5.3, CHC*H*$_2$), 3.11 (1H, dd, *J* 13.9 and 5.8, CHC*H*$_2$), 0.24 (9H, s, SiC(C*H*$_3$)$_3$); δ_C (67.8MHz) 193.8 (s), 172.2 (s), 160.3 (s), 158.0 (s), 156.0 (s), 136.6 (s), 136.0 (s), 135.8 (s), 135.7 (d), 135.5 (d), 134.8 (d), 132.1 (d), 129.1 (d), 129.0 (d), 128.8 (d), 128.6 (d), 128.5 (d), 128.2 (s), 128.1 (d), 125.8 (d), 125.4 (s), 116.8 (s), 113.4 (d), 79.6 (t), 71.4 (t), 67.5 (t), 55.2 (d), 53.0 (q), 37.6 (t), 0.00 (q); *m/z* (FAB) Found: 704.1671 ([MH]$^+$ C$_{36}$H$_{39}$BrNO$_7$Si requires 704.1679).

(*S*)-Methyl-3-(4-benzyloxy-3-{[2-bromo-6-iodophenoxy]-acetyl}-phenyl)-2-benzyloxycarbonylaminopropionate (92)
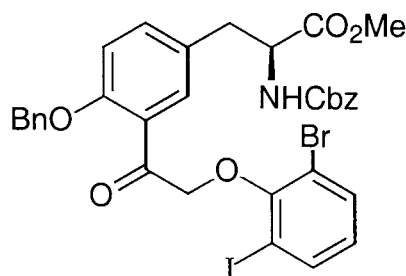
Silver tetrafluoroborate (0.15g, 0.79mmol) was added to a stirred solution of the aryl ether (**91**) (0.40g, 0.56mmol) in ethanol (6ml) at ambient temperature, under an atmosphere of nitrogen. The solution was cooled to 0°C and iodine (0.21g, 0.84mmol) was added in a single portion. The solution was warmed to ambient temperature and stirred at ambient temperature for 19 h, then diluted with diethyl ether (10ml) and filtered. The filtrate was concentrated *in vacuo* to leave a residue which was diluted with water (10ml), then extracted with ethyl acetate (3 x 10ml). The combined organic extracts were washed with hydrochloric acid (30ml, 2M) and brine (30ml), then dried (MgSO$_4$) and concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 35% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *iodide* (0.46g, 99%) as a yellow oil; [α]$_D$ = +36.2 (c = 2.8, CHCl$_3$); υ_{max} (soln., CHCl$_3$) 3429, 1714, 1609cm^{-1}; δ_H (360MHz) 7.83 (1H, d, *J* 2.2, phenyl H2), 7.68 (1H, dd, *J* 7.5 and 0.9, Ar), 7.47 (1H, dd, *J* 7.5 and 0.9, Ar), 7.33-7.23 (11H, m, Ar), 6.94 (1H, d, *J* 8.5, Ar), 6.70 (1H, t, *J* 7.9, phenoxy H4), 5.40 (1H, d, *J* 8.0, N*H*), 5.14-5.13 (2H, m, COC*H*$_2$OAr), 5.09 (4H, s, ArC*H*$_2$OAr and CO$_2$C*H*$_2$Ar), 4.68-4.62 (1H, m, C*H*CH$_2$), 3.76 (3H, s, C*H*$_3$), 3.17 (1H, dd, *J* 13.8 and 5.1, CHC*H*$_2$), 3.08 (1H, dd, *J* 13.8 and 6.0, CHC*H*$_2$); δ_C (67.8MHz) 192.5 (s), 171.7 (s), 157.6 (s), 155.0 (s), 154.7 (s), 138.6 (d), 135.7 (s), 135.4 (s), 135.4 (d), 133.7 (d), 131.7 (d), 128.7 (s), 128.6 (d), 128.5 (d), 128.3 (d), 128.1 (d x 2), 127.7 (d), 127.2 (d), 124.7 (s), 116.5 (s), 113.0 (d), 92.4 (s), 78.2 (t), 71.1 (t), 67.0 (t), 54.8 (d), 52.5 (q), 37.1 (t); *m/z* (FAB) Found: 758.0247 ([MH]$^+$ C$_{33}$H$_{30}$BrINO$_7$ requires 758.0250).

(Z)-(S)-Methyl-3-{4-benzyloxy-3-[1-(2-bromo-6-iodophenoxymethyl)-propenyl]-phenyl}-2-benzyloxycarbonylaminopropionate (83)
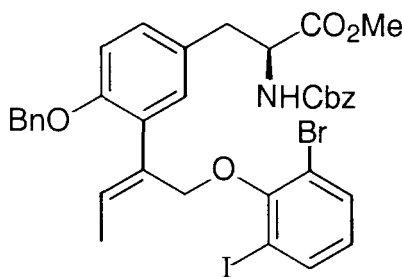
Sodium *bis*-(trimethylsilyl)amide (0.56ml, 1.0M in THF, 0.56mmol) was added dropwise over 1 min to a stirred solution of (ethyl)triphenylphosphonium bromide (0.22g, 0.60mmol) in THF (2ml) at -40°C, under an atmosphere of nitrogen. The solution was stirred at -40°C for 20 min, then a solution of the iodide (**92**) (0.14g, 0.18mmol) in THF (2ml) was added dropwise over 1 min. The solution was stirred at -40°C for 1 h, then poured onto a saturated aqueous solution of ammonium chloride (10ml). The mixture was extracted with diethyl ether (3 x 15ml), then the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 25% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *alkene* (86mg, 62%) as a colourless oil; $[\alpha]_D$ = +16.7 (c = 3.8, $CHCl_3$); υ_{max} (soln., $CHCl_3$) 3430, 1714, 1606, 1349cm^{-1}; δ_H (360MHz) 7.67 (1H, dd, *J* 7.9 and 1.3, Ar), 7.47 (1H, dd, *J* 7.9 and 1.3, Ar), 7.41-7.27 (10H, m, Ar), 7.05-6.97 (2H, m, Ar), 6.87 (1H, d, *J* 8.3, Ar), 6.66 (1H, t, *J* 7.9, phenoxy H4), 6.22 (1H, q, *J* 6.8, C*H*CH₃), 5.31 (1H, d, *J* 2.6, N*H*), 5.07 (4H, s, ArC*H₂*OAr and CO₂C*H₂*Ar), 4.66 (2H, s, ArCC*H₂*OAr), 4.19-4.15 (1H, m, C*H*CH₂), 3.72 (3H, s, OC*H₃*), 3.10 (2H, d, *J* 5.4, CHC*H₂*), 1.62 (3H, d, *J* 6.8, CHC*H₃*); δ_C (67.8MHz) 172.0 (s), 155.6 (s), 155.5 (s), 155.3 (s), 138.6 (d), 137.2 (s), 136.2 (s), 134.2 (s), 133.7 (d), 132.9 (d), 129.2 (s), 129.2 (d), 128.4 (d), 128.1 (d), 128.0 (d), 127.9 (d), 127.6 (d), 127.3 (s), 127.1 (d), 126.8 (d), 117.2 (s), 112.5 (d), 92.9 (s), 76.2 (t), 70.2 (t), 66.8 (t), 61.4 (d), 54.8 (t), 52.3 (q), 37.2 (t), 14.7 (q); *m/z* (ES) Found: 792.0493 ([MNa]⁺ $C_{35}H_{33}BrINO_6Na$ requires 792.0434).

7-Bromo-3-phenyl-3-vinyl-2,3-dihydrobenzofuran (73)
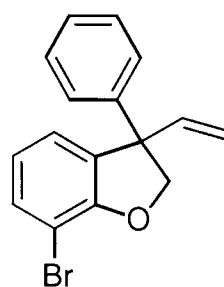
A solution of the alkene (**74**) (2.50g, 5.83mmol) in DMF (20ml) was added dropwise over 3 min to a stirred solution of silver carbonate (3.54g, 12.8mmol) and triphenylphosphine (0.15g, 0.58mmol) in DMF (40ml) at ambient temperature, under an atmosphere of nitrogen. Palladium(II) acetate (65mg, 0.29mmol) was added in a single portion and the solution was heated at 80°C for 92 h, then cooled to ambient temperature and filtered through cellite. The filtrate was diluted with water (500ml) and extracted with diethyl ether (3 x 500ml). The combined organic extracts were dried (MgSO$_4$) and concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 25% dichloromethane in petroleum ether (b.p. 40-60°C), to give the dihydrobenzofuran (0.92g, 53%) as a colourless oil; υ_{max} (soln., CHCl$_3$) 1636, 990cm^{-1}; δ_H (300MHz) 7.36 (1H, dd, J 8.1 and 1.1, Ar), 7.33-7.22 (5H, m, Ar), 7.00 (1H, dd, J 7.5 and 1.1, Ar), 6.82 (1H, t, J 7.5, dihydrobenzofuran H5), 6.27 (1H, dd, J 17.4 and 10.6, C*H*CH$_2$), 5.32 (1H, d, J 10.6, CHC*H*$_2$), 5.08 (1H, d, J 17.4, CHC*H*$_2$), 4.80 (1H, d, J 9.1, C*H*$_2$OAr), 4.73 (1H, d, J 9.1, C*H*$_2$OAr); δ_C (75MHz) 157.4 (s), 143.8 (s), 141.1 (d), 133.9 (s), 132.2 (d), 129.0 (d), 127.8 (d), 127.6 (d), 125.0 (d), 122.7 (d), 116.0 (t), 103.8 (s), 83.7 (t), 58.9 (s); *m/z* (EI) Found: 300.0162 (M$^+$ C$_{16}$H$_{13}$BrO requires 300.0150).

7-Bromo-3-phenyl-2,3-dihydrobenzofuran-3-carbaldehyde (72)
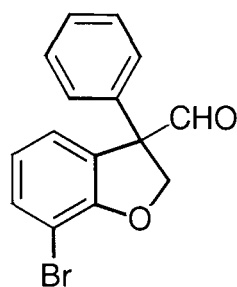
Osmium tetroxide (0.11g, 2.5wt.% solution in 2-methyl-2-propanol, 11μmol) and then sodium periodate (0.54g, 2.50mmol) were added to a stirred solution of the dihydrobenzofuran (73) (0.30g, 1.00mmol) in THF (5ml) and water (5ml) at 0°C, under an atmosphere of nitrogen. The solution was warmed to ambient temperature and stirred at ambient temperature for 16 h. A saturated aqueous solution of ammonium chloride (10ml) was then added and the mixture was extracted with ethyl acetate (3 x 20ml). The combined organic extracts were dried (MgSO$_4$) and concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 10% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the aldehyde (0.12g, 40%) as a colourless oil; υ_{max} (soln., CHCl$_3$) 2821, 1726cm^{-1}; δ_H (360MHz) 9.68 (1H, d, *J* 1.2, C*H*O), 7.49 (1H, dd, *J* 8.0 and 1.1, Ar), 7.45-7.36 (3H, m, Ar), 7.25 (1H, dd, *J* 7.5 and 1.1, Ar), 7.17-7.13 (2H, m, Ar), 6.93 (1H, t, *J* 7.7, dihydrobenzofuran H5), 5.57 (1H, d, *J* 9.2, C*H*$_2$), 4.41 (1H, dd, *J* 9.2 and 1.2, C*H*$_2$); δ_C (90.6MHz) 192.7 (d), 158.1 (s), 137.2 (s), 133.4 (d), 129.5 (d), 128.5 (d), 127.4 (d), 125.5 (s), 124.7 (d), 122.4 (d), 103.9 (s), 77.1 (t), 67.2 (s); *m/z* (EI) Found: 301.9944 (M$^+$ C$_{15}$H$_{11}$BrO$_2$ requires 301.9942).

Ethyl-3-(7-bromo-3-phenyl-2,3-dihydrobenzofuran-3-yl)-3-oxopropionate (71)
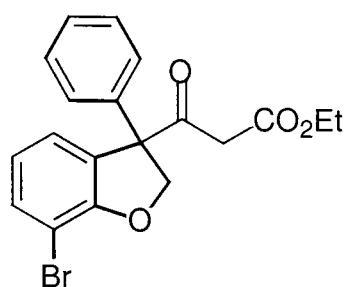
Solutions of ethyl diazoacetate (1.2ml, 10.9mmol) in dichloromethane (8ml) and then the aldehyde (**72**) (1.11g, 3.64mmol) in dichloromethane (8ml) were added dropwise to a stirred solution of zirconium chloride (0.85g, 3.64mmol) in dichloromethane (15ml) at -10°C, under an atmosphere of nitrogen. The solution was warmed to 0°C and stirred at 0°C for 2 h, then warmed to ambient temperature and poured onto brine (30ml). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 30ml). The combined organic extracts were dried (Na$_2$SO$_4$), then concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 10% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the ketone (1.19g, 84%) as a pale red oil; υ_{max} (soln., CHCl$_3$) 2983, 2940, 1744, 1716, 1464, 1448, 1369, 1314, 1120cm^{-1}; δ_H (360MHz) 7.46 (1H, d, *J* 8.0, Ar), 7.42-7.32 (4H, m, Ar), 7.22-7.20 (2H, m, Ar), 6.91 (1H, t, *J* 7.8, dihydrobenzofuran H5), 5.64 (1H, d, *J* 9.1, C*H*$_2$OAr), 4.28 (1H, d, *J* 9.1, C*H*$_2$OAr), 4.05 (2H, qd, *J* 7.1 and 1.9, C*H*$_2$CH$_3$), 3.54 (2H, d, *J* 2.6, C*H*$_2$CO), 1.17 (3H, t, *J* 7.1, C*H*$_3$); δ_C (90.6MHz) 197.1 (s), 166.3 (s), 158.3 (s), 137.8 (s), 133.2 (d), 129.4 (d), 128.3 (d), 126.7 (d), 126.1 (s), 125.2 (d), 122.2 (d), 104.0 (s), 79.0 (t), 69.3 (s), 61.2 (t), 44.6 (t), 13.8 (q); *m/z* (EI) Found: 388.0323 ([MH]$^+$ C$_{19}$H$_{18}$BrO$_4$ requires 388.0310).

Ethyl-3-(7-bromo-3-phenyl-2,3-dihydrobenzofuran-3-yl)-2-diazo-3-oxo propionate (170)
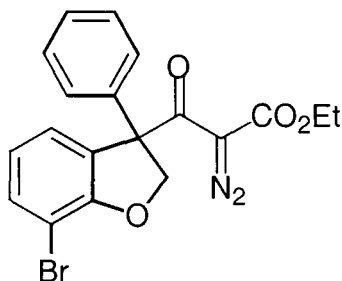
Triethylamine (80μl, 0.66mmol) was added dropwise to a stirred solution of the ketone (**71**) (0.20g, 0.52mmol) in acetonitrile (5ml) at ambient temperature, under an atmosphere of nitrogen. The solution was cooled to 0°C and 4-acetamidobenzenesulfonyl azide (0.15g, 0.62mmol) was added in a single portion. The solution was warmed to ambient temperature and stirred at ambient temperature for 5.5 h, then concentrated *in vacuo* to leave a residue which was diluted with water (20ml). The aqueous solution was extracted with ethyl acetate (3 x 20ml) and the combined organic extracts were dried (Na_2SO_4), then concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 20% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *diazoketone* (0.22g, 99%) as a pale yellow oil; υ_{max} (soln., $CHCl_3$) 2148, 1722, 1644, 1314cm^{-1}; δ_H (360MHz) 7.38-7.34 (3H, m, Ar), 7.29-7.25 (3H, m, Ar), 7.19 (1H, dd, *J* 7.6 and 1.2, Ar), 6.78 (1H, t, *J* 7.8, dihydrobenzofuran H5), 5.23 (1H, d, *J* 10.5, C*H₂*OAr), 5.17 (1H, d, *J* 10.5, C*H₂*OAr), 4.09 (2H, qd, *J* 7.1 and 1.2, C*H₂*CH₃), 1.15 (3H, t, *J* 7.1, C*H₃*); δ_C (90.6MHz) 188.9 (s), 159.6 (s), 156.4 (s), 140.5 (s), 133.2 (d), 129.5 (s), 129.0 (d), 127.3 (d), 126.7 (d), 125.1 (d), 122.0 (d), 103.2 (s), 79.3 (t), 77.2 (s), 67.3 (s), 61.9 (t), 13.9 (q); *m/z* (EI) Found: 386.0145 ([M-N₂]$^+$ $C_{19}H_{15}BrO_4$ requires 386.0154).

(*E/Z*)-Ethyl-3-(7-bromo-3-phenyl-2,3-dihydrobenzofuran-3-yl)-2-hydroxyimino-3-oxo-propionate (165)
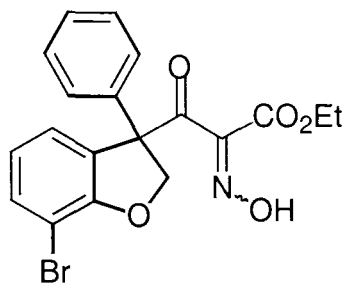
A solution of sodium nitrite (1.69g, 23.8mmol) in water (5ml) was added dropwise over 3 min to a stirred solution of the ketone (**71**) (1.16g, 2.97mmol) in acetic acid (5ml) at ambient temperature. The mixture was stirred at ambient temperature for 2 h, then diluted with water (20ml) and extracted with ethyl acetate (3 x 30ml). The combined organic extracts were washed with water (70ml), a saturated aqueous solution of sodium hydrogencarbonate (70ml) and finally water (70ml), then dried (MgSO$_4$) and concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 30% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *oxime* (1.17g, 94%), in a 2:1 ratio of geometrical isomers, as a yellow oil; υ_{max} (soln., CHCl$_3$, major isomer) 3536, 1630cm^{-1}; δ_H (360MHz) 9.24 (1H, s, O*H*), 7.41 (1H, dd, *J* 6.9 and 1.1, Ar), 7.39 (1H, dd, *J* 7.2 and 1.1, Ar), 7.35-7.30 (2H, m, Ar), 7.25 (1H, tt, *J* 7.1 and 2.2, phenyl H4), 7.19-7.16 (2H, m, Ar), 6.84 (1H, t, *J* 7.7, dihydrobenzofuran H5), 5.37 (1H, d, *J* 9.7, C*H$_2$*OAr), 4.77 (1H, d, *J* 9.7, C*H$_2$*OAr), 4.34 (2H, q, *J* 7.1, C*H$_2$*CH$_3$), 1.33 (3H, t, *J* 7.1, C*H$_3$*); δ_C (90.6MHz) 190.8 (s), 160.8 (s), 157.3 (s), 148.3 (s), 140.8 (s), 132.8 (d), 129.2 (d), 127.6 (d), 127.5 (s), 127.2 (d), 125.6 (d), 122.4 (d), 103.4 (s), 79.4 (t), 67.1 (s), 60.8 (t), 13.9 (q); *m/z* (EI) Found: 399.0114 ([M-H$_2$O]$^+$ C$_{19}$H$_{14}$BrNO$_4$ requires 399.0106).

Ethyl-2-acetylamino-3-(7-bromo-3-phenyl-2,3-dihydrobenzofuran-3-yl)-3-oxopropionate (70)
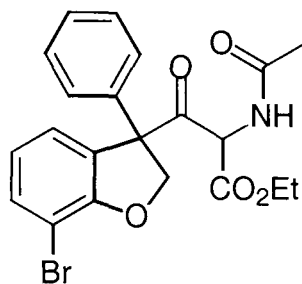
Zinc dust (21mg, 0.32mmol) was added in a single portion to a stirred solution of the oxime (**165**) (68mg, 0.16mmol) in 80% aqueous acetic acid (2ml) at ambient temperature. The solution was stirred at ambient temperature for 3.5 h, with more zinc dust (21mg, 0.32mmol) added after 2.5 h. The precipitate was removed by filtration and washed with acetic acid, then the filtrate was concentrated *in vacuo* to leave the crude *salt* (74mg, 100%) as a pale yellow solid, which was used immediately without characterisation. A solution of acetyl chloride (40μl, 0.48mmol) in dichloromethane (2ml) was added dropwise over 1 min to a stirred solution of the salt (**166**) (74mg, 0.16mmol) and triethylamine (70μl, 0.48mmol) in dichloromethane (3ml) at 0°C, under an atmosphere of nitrogen. The solution was warmed to ambient temperature over 1 h and stirred at ambient temperature for 9.5 h, then diluted with dichloromethane (15ml) and washed with water (20ml). The organic phase was dried (MgSO$_4$) and concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 50% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *amide* (51mg, 71%), in a 2:1 ratio of diastereoisomers, as a pale yellow oil; υ$_{max}$ (soln., CHCl$_3$) 3427, 1749, 1717, 1682, 1314, 1114cm^{-1}; δ$_H$ (360MHz) 7.79 (1H, dd, *J* 7.6 and 1.1, Ar), 7.58 (1H, dd, *J* 7.6 and 1.1, Ar), 7.49-7.44 (2H, m, Ar), 7.40-7.30 (6H, m, Ar), 7.23-7.19 (4H, m, Ar), 6.97 (1H, t, *J* 7.8, dihydrobenzofuran H5), 6.92 (1H, t, *J* 7.8, dihydrobenzofuran H5), 6.68 (1H, d, *J* 7.2, N*H*), 6.55 (1H, d, *J* 8.8, N*H*), 5.81 (1H, d, *J* 8.8, C*H*N), 5.64 (1H, d, *J* 9.2, C*H*$_2$OAr), 5.61 (1H, d, *J* 7.2, C*H*N), 5.54 (1H, d, *J* 9.4, C*H*$_2$OAr), 4.54 (1H, d, *J* 9.4, C*H*$_2$OAr),

4.29 (1H, d, *J* 9.2, C*H₂*OAr), 3.93-3.78 (2H, m, C*H₂*CH₃), 3.44 (2H, dq, *J* 10.7 and 7.2, C*H₂*CH₃), 1.92 (3H, s, C*H₃*CO), 1.89 (3H, s, C*H₃*CO), 1.03 (3H, t, *J* 7.2, CH₂C*H₃*), 1.03 (3H, t, *J* 7.2, CH₂C*H₃*); δ$_C$ (90.6MHz) 199.4 (s), 197.0 (s), 169.5 (s), 169.0 (s), 166.3 (s), 166.1 (s), 158.4 (s), 158.2 (s), 137.2 (s), 137.1 (s), 133.5 (d), 133.2 (d), 129.2 (d), 129.1 (d), 128.4 (d), 128.3 (d), 126.7 (d), 126.6 (d), 126.4 (d), 126.3 (d), 125.6 (s), 122.7 (d), 122.5 (d), 104.1 (s), 103.7 (s), 79.9 (t), 79.2 (t), 69.0 (s), 68.8 (s), 62.4 (t), 62.3 (t), 57.7 (d), 56.6 (d), 22.5 (q), 13.5 (q x 2); *m/z* (ES) Found: 446.0599 ([MH]⁺ C₂₁H₂₁BrNO₅ requires 446.0603).

Ethyl-5-(7-bromo-3-phenyl-2,3-dihydrobenzofuran-3-yl)-2-methyloxazole-4-carboxylate (212)
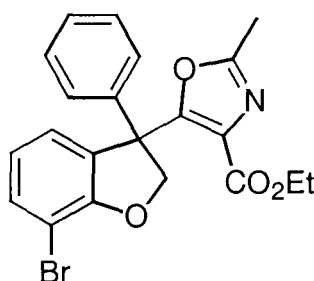
Triethylamine (0.17ml, 1.20mmol) and then a solution of the amide (**70**) (0.13g, 0.30mmol) in dichloromethane (3ml) were added dropwise to a stirred solution of triphenylphosphine (0.16g, 0.60mmol) and iodine (0.15g, 0.60mmol) in dichloromethane (6ml) at ambient temperature, under an atmosphere of nitrogen. The solution was stirred at ambient temperature for 12 h, then concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 50% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the oxazole (0.11g, 86%) as a pale yellow oil; υ$_{max}$ (soln., CHCl₃) 1722, 1123, 1091cm⁻¹; δ$_H$ (360MHz) 7.40 (1H, dd, *J* 8.0 and 1.1, Ar), 7.38 (1H, dd, *J* 7.6 and 1.1, Ar), 7.31-7.24 (3H, m, Ar), 7.14-7.11 (2H, m, Ar), 6.83 (1H, t, *J* 7.7, dihydrobenzofuran H5), 5.29 (1H, d, *J* 9.9, C*H₂*OAr), 5.19 (1H, d, *J* 9.9, C*H₂*OAr), 4.24 (1H, dq, *J* 10.9 and 7.2, C*H₂*CH₃), 4.17 (1H, dq, *J* 10.9 and 7.2, C*H₂*CH₃), 2.50 (3H, s, ArC*H₃*), 1.20 (3H, t, *J* 7.2, CH₂C*H₃*);

δ_C (90.6MHz) 161.2 (s), 159.9 (s), 158.5 (s), 156.8 (s), 143.0 (s), 132.5 (d), 131.2 (s), 128.7 (d), 128.2 (s), 127.4 (d), 126.2 (d), 125.7 (d), 122.5 (d), 103.4 (s), 83.7 (t), 61.3 (t), 56.5 (s), 14.0 (q), 13.9 (q); m/z (EI) Found: 428.0493 ([MH]$^+$ $C_{21}H_{19}BrNO_4$ requires 428.0497).

5-(7-Bromo-3-phenyl-2,3-dihydrobenzofuran-3-yl)-2-methyloxazole-4-carboxylic acid (69)
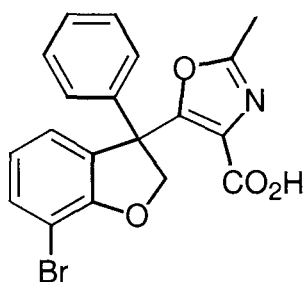
Lithium hydroxide (29mg, 0.70mmol) was added in a single portion to a stirred solution of the oxazole (212) (30mg, 70μmol) in methanol (1.5ml) and water (0.5ml) at ambient temperature. The solution was stirred at ambient temperature for 8 h, then acidified with a 10% aqueous solution of citric acid (2ml) and extracted with ethyl acetate (3 x 5ml). The combined organic extracts were dried (MgSO$_4$) and concentrated in $vacuo$ to leave the acid (28mg, 100%) as a white solid; m.p. 194-196°C (hexane), [Lit. m.p. 192-193°C][227]; λ_{max} (EtOH) 291 (1.85 x 10^4), 284 (1.80 x 10^4), 211nm (1.08 x 10^5); υ_{max} (soln., CHCl$_3$) 3494, 3241 (br), 1762, 1702, 1077cm^{-1}; δ_H (360MHz) 7.44-7.41 (2H, m, Ar), 7.31-7.24 (3H, m, Ar), 7.13-7.10 (2H, m, Ar), 6.86 (1H, t, J 7.8, dihydrobenzofuran H5), 5.41 (1H, d, J 10.0, CH_2), 5.14 (1H, d, J 10.0, CH_2), 2.53 (3H, s, CH_3); δ_C (90.6MHz) 162.9 (s), 160.3 (s), 159.3 (s), 157.0 (s), 142.3 (s), 132.7 (d), 130.7 (s), 128.8 (d), 127.6 (d), 126.3 (d), 125.9 (d), 122.5 (d), 103.5 (s), 83.3 (t), 56.5 (s), 13.7 (q); m/z (ES) Found: 463.0269 ([MNaMeCN]$^+$ $C_{21}H_{17}BrN_2O_4Na$ requires 463.0309).

129

3.2 Synthetic Studies towards the Indole Unit (68)

[4-Bromo-1-(tri-*iso*-propylsilanyl)-1*H*-indol-3-ylmethyl]-dimethylamine (219)
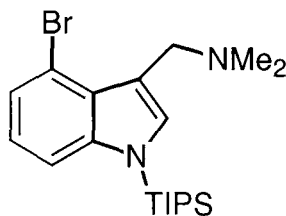
t-Butyllithium (9.4ml, 1.7M solution in pentane, 16.0mmol) was added dropwise over 6min to a stirred solution of dimethyl-[1-(tri-*iso*-propylsilanyl)-1*H*-indol-3-ylmethyl]-amine (**220**) (2.50g, 7.61mmol) in diethyl ether (38ml) at 0°C, under an atmosphere of nitrogen. The solution was stirred at 0°C for 1 h, then cooled to -78°C and bromine (0.51ml, 9.89mmol) was added dropwise over 1 min. The solution was warmed to 0°C over 4 h, then poured onto a 20% aqueous solution of sodium thiosulfate (40ml). The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 x 40ml). The combined organic extracts were washed with a 20% aqueous solution of sodium thiosulfate (150ml) and brine (150ml), then dried (MgSO$_4$) and concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 50% ethyl acetate in petroleum ether (b.p. 40-60°C), increasing to ethyl acetate, to give the bromide (1.80g, 58%) as a brown oil; υ_{max} (soln., CHCl$_3$) 2947, 2869, 2814, 2774, 1600, 1546, 1456cm^{-1}; δ_H (360MHz) 7.45 (1H, d, *J* 8.3, Ar), 7.31 (1H, d, *J* 7.6, Ar), 7.22 (1H, s, indole H2), 6.97 (1H, app. t, *J* 7.9, indole H6), 3.87 (2H, s, C*H$_2$*), 2.36 (6H, s, N(C*H$_3$*)$_2$), 1.71 (3H, sep., *J* 7.6, Si(C*H*(CH$_3$)$_2$)$_3$), 1.16 (18H, d, *J* 7.6, Si(CH(C*H$_3$*)$_2$)$_3$); δ_C (90.6MHz) 142.7 (s), 132.2 (d), 128.7 (s), 124.3 (d), 121.9 (d), 115.9 (s), 113.9 (s), 112.9 (d), 55.0 (t), 45.1 (d), 17.9 (q), 12.6 (q); *m/z* (EI) Found: 408.1602 (M$^+$ C$_{20}$H$_{33}$BrN$_2$Si requires 408.1600).

4-Bromo-3-(2-nitroethyl)-1*H*-indole (218)
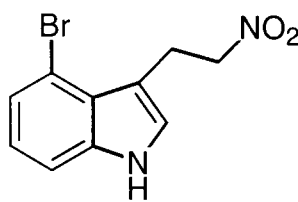
Iodomethane (3.8ml, 61.1mmol) was added dropwise over 3 min to a stirred solution of the bromide (**219**) (2.50g, 6.11mmol) in benzene (25ml) at ambient temperature, under an atmosphere of nitrogen. The solution was stirred at ambient temperature for 16 h, then concentrated *in vacuo* to leave the crude salt (3.20g, 100%) as an off-white solid, which was used immediately without characterisation. Tetrabutylammonium fluoride hydrate (2.89g, 9.16mmol) was added in a single portion to a stirred solution of the salt (**228**) (3.20g, 6.11mmol) and nitromethane (3.3ml, 61.1mmol) in THF (30ml) at ambient temperature, under an atmosphere of nitrogen. The solution was stirred at ambient temperature for 2 h, then concentrated *in vacuo*. The residue was diluted with water (40ml), then extracted with diethyl ether (3 x 40ml). The combined organic extracts were dried (MgSO$_4$) and concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 20% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the nitroindole (2.36g, 80%) as a pale yellow oil; υ_{max} (soln., CHCl$_3$) 3473, 2939, 1557, 1379cm^{-1}; δ_H (360MHz) 8.26 (1H, br s, N*H*), 7.32-7.30 (2H, m, Ar), 7.07-7.02 (2H, m, Ar), 4.78 (2H, t, *J* 6.9, C*H*$_2$N), 3.71 (2H, t, *J* 6.9, C*H*$_2$Ar); δ_C (90.6MHz) 137.5 (s), 125.0 (d), 124.7 (s), 124.1 (d), 123.2 (d), 113.6 (s), 110.9 (d), 110.5 (s), 77.2 (t), 24.3 (t); *m/z* (EI) Found: 267.9859 (M$^+$) C$_{10}$H$_9$BrN$_2$O$_2$ requires 267.9847).

tert-Butyl-[2-(4-bromo-1_H_-indol-3-yl)-ethyl]-carbamate (216)
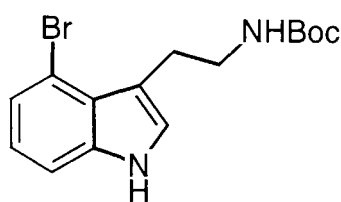
Zinc dust (0.30g, 4.64mmol) was added in a single portion to a stirred solution of the nitroindole **(218)** (0.11g, 0.39mmol) in 80% aqueous acetic acid (14ml) at 75°C. The mixture was heated at 80°C for 4.5 h, then cooled to ambient temperature and filtered. The precipitate was washed with 80% aqueous acetic acid, then dried _in vacuo_ (1mmHg) to give the crude salt (0.10g, 100%) as a pale yellow solid, which was used immediately without characterisation. Di-_tert_-butyl dicarbonate (0.33g, 1.44mmol) was added in a single portion to a stirred solution of the salt **(230)** (0.10g, 0.39mmol) and an aqueous solution of sodium hydroxide (4ml, 2M) in 2-methyl-2-propanol (10ml) at ambient temperature. The mixture was stirred at ambient temperature for 16 h, then concentrated _in vacuo_. The residue was diluted with brine (20ml) and extracted with dichloromethane (3 x 20ml). The combined organic extracts were dried (MgSO$_4$) and concentrated _in vacuo_ to leave a residue which was purified by chromatography on silica, eluting with 35% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the carbamate (0.11g, 85%) as an off-white solid; υ_{max} (soln., CHCl$_3$) 3475, 3306, 2978, 2930, 1703, 1456, 1392, 1367cm^{-1}; δ_H (360MHz) 8.73 (1H, s, indole N_H_), 7.31 (1H, d, _J_ 8.1, Ar), 7.27 (1H, d, _J_ 7.5, Ar), 7.02 (1H, s, indole H2), 7.00 (1H, app. t, _J_ 7.8, indole H6), 4.77 (1H, s, N_H_CO), 3.51 (2H, app. q, _J_ 6.5, C_H_$_2$N), 3.20 (2H, t, _J_ 6.5, C_H_$_2$Ar), 1.47 (9H, s, C(C_H_$_3$)$_3$); δ_C (90.6MHz) 156.2 (s), 137.8 (s), 125.3 (s), 124.1 (d), 123.8 (d), 122.7 (d), 114.1 (s), 113.6 (s), 110.7 (d), 79.2 (s), 42.1 (t), 28.4 (q), 26.6 (t); _m/z_ (EI) Found: 338.0641 (M$^+$ C$_{15}$H$_{19}$BrN$_2$O$_2$ requires 338.0630).

tert-Butyl-[2-(4-bromo-1_H_-indol-3-yl)-2-hydroxyethyl]-carbamate (233)
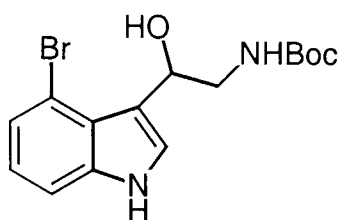
2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (0.33g, 1.47mmol) was added in a single portion to a stirred solution of the carbamate (**216**) (0.25g, 0.74mmol) in THF (8ml) and water (0.9ml) at 0°C, under an atmosphere of nitrogen. The solution was warmed to ambient temperature over 2 h, then stirred at ambient temperature for 2 h. The solution was diluted with diethyl ether (20ml) and washed with an aqueous solution of sodium hydroxide (20ml, 0.1M), then dried (MgSO$_4$) and concentrated _in vacuo_ to leave a residue which was purified by chromatography on silica, eluting with 50% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the _alcohol_ (0.20g, 75%) as a red oil; υ_{max} (soln., CHCl$_3$) 3598, 3471, 1698, 1103cm^{-1}; δ_H (360MHz) 8.86 (1H, s, indole N_H_), 7.31 (1H, dd, _J_ 8.1 and 0.8, Ar), 7.29-7.25 (2H, m, Ar and indole H2), 7.01 (1H, app. t, _J_ 7.9, indole H6), 5.70 (1H, br d, _J_ 5.9, O_H_), 5.15 (1H, br s, N_H_CO), 3.75-3.74 (1H, m, C_H$_2$_), 3.55-3.48 (2H, m, C_H$_2$_, C_H_OH), 1.48 (9H, s, C(C_H$_3$_)$_3$); δ_C (90.6MHz) 157.4 (s), 137.7 (s), 124.5 (s), 124.1 (d), 123.4 (d), 122.9 (d), 117.7 (s), 113.3 (s), 110.8 (d), 79.9 (s), 67.4 (d), 47.5 (t), 28.4 (q); _m/z_ (ES) Found: 377.0487 ([MNa]$^+$ C$_{15}$H$_{19}$BrN$_2$O$_3$Na requires 377.0477).

tert-Butyl-[2-(1_H_-indol-3-yl)-2-oxoethyl]-carbamate (237)
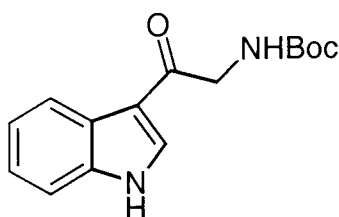
A solution of sodium hydroxide (0.26g, 6.55mmol) in water (3ml) was added dropwise over 1 min to a stirred solution of tryptamine (**236**) (0.50g, 3.12mmol) in dioxane (15ml) at 0°C, under an atmosphere of nitrogen. The solution was stirred at 0°C for 10 min, then di-*tert*-butyl dicarbonate (0.72g, 3.28mmol) was added and the solution was warmed to ambient temperature. The solution was stirred at ambient temperature for 1 h, then concentrated *in vacuo*. The residue was diluted with diethyl ether (20ml) and washed with water (20ml), hydrochloric acid (20ml, 0.1M) and brine (20ml), then dried (MgSO$_4$) and concentrated *in vacuo* to leave the crude carbamate (0.81g, 99%) as a pale red oil, which was used immediately without characterisation. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (0.35g, 1.54mmol) was added in a single portion to a stirred solution of the carbamate (**235**) (0.20g, 0.77mmol) in THF (4ml) and water (0.5ml) at 0°C, under an atmosphere of nitrogen. The solution was warmed to ambient temperature and stirred at ambient temperature for 1.5 h, then concentrated *in vacuo* to leave a residue which was diluted with dichloromethane (5ml). The precipitate was removed by filtration and washed with dichloromethane (5 x 10ml) and diethyl ether (5 x 10ml), then dried *in vacuo* (1mmHg) to give the *ketone* (82mg, 39%) as a white solid; m.p. 230-231°C (EtOH); λ_{max} (MeOH) 296 (1.10 x 10^4), 240 (1.11 x 10^4), 210nm (2.57 x 10^4); υ_{max} (soln., CHCl$_3$) 3459, 1705, 1660, 1492, 1456, 1368, 1055cm^{-1}; δ_H ((CD$_3$)$_2$SO, 360MHz) 8.42 (1H, d, *J* 3.0, indole H2), 8.17 (1H, d, *J* 7.1, Ar), 7.49 (1H, d, *J* 7.0, Ar), 7.26-7.18 (2H, m, indole H5 and indole H6), 7.02 (1H, t, *J* 5.9, N*H*CO), 4.32 (2H, d, *J* 5.9, C*H$_2$*), 1.43 (9H, s, C(C*H$_3$*)$_3$); δ_C ((CD$_3$)$_2$SO, 90.6MHz) 191.7 (s), 156.9 (s), 137.3 (s), 134.3 (d), 126.3 (s), 123.8 (d), 122.7 (d), 122.1 (d), 114.9 (s), 113.1 (d), 78.8 (s), 47.8 (t), 29.2 (q); *m/z* (FAB) Found: 275.1392 ([MH]$^+$ C$_{15}$H$_{19}$N$_2$O$_3$ requires 275.1396); Found: C, 65.4; H, 6.6; N, 10.0%, C$_{15}$H$_{18}$N$_2$O$_3$ requires C, 65.7; H, 6.6; N, 10.2%.

Benzyl-[2-(1*H*-indol-3-yl)-2-oxoethyl]-carbamate (224)
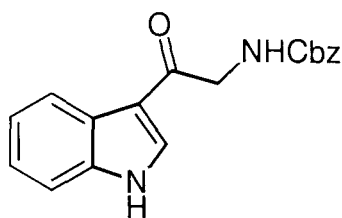
Oxalyl chloride (10.3ml, 50.3mmol) was added dropwise over 5 min to a stirred suspension of benzyloxycarbonylglycine (**226**) (10.0g, 47.8mmol) in diethyl ether (100ml) at ambient temperature, under an atmosphere of nitrogen. The solution was stirred at ambient temperature for 18 h, then filtered and diluted with benzene, then concentrated *in vacuo* to leave the crude acid chloride (10.9g, 100%) as a pale yellow oil, which was used immediately without characterisation. A solution of indole (**225**) (5.90g, 50.3mmol) in diethyl ether (200ml) was added dropwise over 15 min to a stirred solution of ethylmagnesium bromide (16.8ml, 3M in diethyl ether, 50.4mmol) in diethyl ether (500ml) at ambient temperature, under an atmosphere of nitrogen. The solution was stirred at ambient temperature for 10 min, then cooled to 0°C and a solution of the acid chloride (10.9g, 47.8mmol) in diethyl ether (200ml) was added rapidly. The mixture was stirred at 0°C for 30 min, then a saturated aqueous solution of ammonium chloride (300ml) was added and the mixture was warmed to ambient temperature over 2 h. The precipitate was removed by filtration and washed with water (150ml) and diethyl ether (150ml), to leave the ketone (1.90g, 13%) as a pale brown solid; m.p. 214-216°C (EtOH), [Lit. m.p. 215-220°C][199]; λ_{max} (EtOH) 298 (1.23 x 10^4), 241 (1.42 x 10^4), 209nm (3.65 x 10^4); υ_{max} (soln., CHCl$_3$) 3457, 1714, 1661, 1455cm^{-1}; δ_H ((CD$_3$)$_2$SO, 360MHz) 8.45 (1H, d, *J* 2.6, indole N*H*), 8.19-8.16 (1H, m, Ar), 7.54-7.49 (2H, m, Ar), 7.41-7.33 (4H, m, Ar), 7.26-7.21 (3H, m, Ar), 5.09 (2H, s, C*H$_2$*Ar), 4.41 (2H, d, *J* 6.1, C*H$_2$*N); δ_C ((CD$_3$)$_2$SO, 90.6MHz) 191.4 (s), 157.6 (s), 138.1 (s), 137.3 (s), 134.4 (d), 129.3 (d), 128.7 (d x 2), 126.3 (s), 123.8 (d), 122.8 (d), 122.1 (d), 114.8 (s), 113.1 (d), 66.3 (t), 48.0 (t); *m/z* (ES) Found: 331.1069

([MNa]$^+$ $C_{18}H_{16}N_2O_3Na$ requires 331.1059); Found: C, 70.0; H, 5.2; N, 9.1%.

$C_{18}H_{16}N_2O_3$ requires C, 70.1; H, 5.2; N, 9.1%.

Benzyl-[2-(4-iodo-1*H*-indol-3-yl)-2-oxoethyl]-carbamate (222)
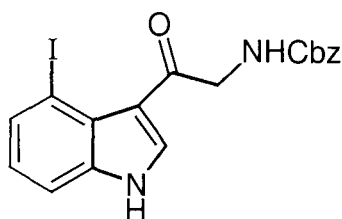
The carbamate (**224**) (20mg, 60μmol) was added in a single portion to a stirred solution of thallium trifluoroacetate (44mg, 80μmol) in trifluoroacetic acid (0.1ml) at ambient temperature, under an atmosphere of nitrogen. The solution was heated at 30°C for 2 h, then cooled to ambient temperature and concentrated *in vacuo*. Iodine (48mg, 0.19mmol), copper iodide (50mg, 0.26mmol) and then DMF (0.44ml) were added to the residue at ambient temperature, under an atmosphere of nitrogen. The solution was heated at 25°C for 2 h, then cooled to ambient temperature and diluted with a solution of methanol (2ml) in dichloromethane (40ml). The mixture was filtered through celite® and the filtrate was washed with brine (40ml) and water (40ml), then dried (MgSO$_4$) and concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 65% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the iodide (15mg, 58%) as a yellow oil which solidified on standing; m.p. 170-172°C; λ_{max} (MeOH) 257 (1.46 x 10^4), 217 (3.88 x 10^4), 194nm (3.99 x 10^4); υ_{max} (soln., CHCl$_3$) 3454, 1716, 1673, 1048cm^{-1}; δ_H (360MHz) 9.25 (1H, br s, indole N*H*), 7.83 (1H, d, *J* 7.6, Ar), 7.80 (1H, m, Ar), 7.42-7.32 (6H, m, Ar), 6.96 (1H, app. t, *J* 7.9, indole H6), 5.93 (1H, s, N*H*CO), 5.17 (2H, s, C*H*$_2$Ar), 4.52 (2H, d, *J* 4.7, C*H*$_2$N); δ_C (CD$_3$OD, 90.6MHz) 193.0 (s), 160.0 (s), 140.3 (s), 139.1 (s), 136.9 (d), 135.5 (d), 130.7 (s), 130.3 (d), 129.8 (d), 129.7 (d), 126.4 (d), 118.0 (s), 114.0 (d), 86.4 (s), 68.6 (t), 51.2 (t); *m/z* (ES) Found: 457.0055 ([MNa]$^+$

$C_{18}H_{15}IN_2O_3Na$ requires 457.0025); Found: C, 49.7; H, 3.4; N, 6.1; I, 29.1%, $C_{18}H_{15}IN_2O_3$ requires C, 49.8; H, 3.5; N, 6.5; I, 29.2%.

2-(4-Iodo-1*H*-indol-3-yl)-2-oxoethylammonium bromide (250)
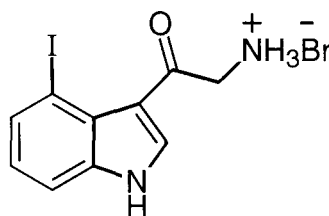
The iodide (**222**) (19mg, 40μmol) was added in a single portion to a stirred solution of hydrogen bromide in acetic acid (1.2ml, 30wt.%) at ambient temperature, under an atmosphere of nitrogen. The solution was stirred at ambient temperature for 1.5 h, then diluted with diethyl ether (5ml). The precipitate was removed by filtration and dried *in vacuo* (1mmHg) to leave the salt (17mg, 99%) as a pale brown solid; m.p. 210-212°C (MeOH); λ_{max} (H_2O) 305 (6.3 x 10^3), 253 (9.2 x 10^3), 216nm (2.09 x 10^4); υ_{max} (KBr) 3407, 3103, 2924, 1654, 1498, 1406, 1096cm^{-1}; δ_H (D_2O, 360MHz) 7.94 (1H, s, indole H2), 7.61 (1H, d, *J* 7.4, Ar), 7.30 (1H, d, *J* 8.1, Ar), 6.80 (1H, app. t, *J* 7.7, indole H6), 4.25 (2H, s, C*H*₂); δ_C (D_2O, 90.6MHz) 186.5 (s), 137.7 (s), 136.0 (d), 135.4 (d), 127.4 (s), 125.1 (d), 113.2 (s), 112.6 (d), 83.5 (s), 45.6 (t); *m/z* (ES) Found: 342.0106 ([MHMeCN-HBr]$^+$ $C_{11}H_{13}IN_3O$ requires 342.0103).

3.3 Synthetic Studies towards the Macrocycle (64)

5-(7-Bromo-3-phenyl-2,3-dihydrobenzofuran-3-yl)-2-methyloxazole-4-carboxylic acid [2-(4-iodo-1*H*-indol-3-yl)-2-oxoethyl]-amide (289)
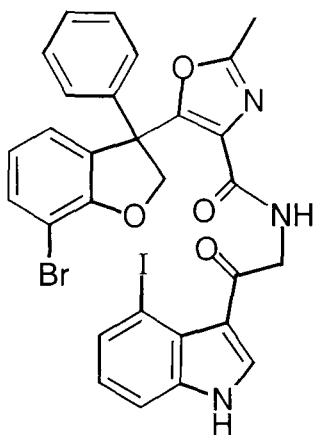
A solution of the acid (**69**) (0.13g, 0.32mmol) in oxalyl chloride (4ml) was stirred at ambient temperature for 3 h. The solution was concentrated *in vacuo* to leave the crude acid chloride (0.13g, 100%) as a yellow oil, which was used immediately without characterisation. Triethylamine (0.45ml, 3.20mmol) was added dropwise over 1 min to a stirred suspension of the salt (**250**) (0.46g, 1.22mmol) in dichloromethane (6ml) at 0°C, under an atmosphere of nitrogen. The solution was stirred at 0°C for 15 min, then a solution of the acid chloride (**290**) (0.13g, 0.32mmol) in dichloromethane (3ml) was added dropwise over 1 min. The solution was warmed to ambient temperature and stirred at ambient temperature for 16 h, then diluted with dichloromethane (10ml) and washed with water (10ml). The aqueous phase was extracted with dichloromethane (2 x 10ml), then the combined organic extracts were dried (MgSO$_4$) and concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 65% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *amide* (0.13g, 60%) as a yellow solid; m.p. 139-142°C; λ_{max} (EtOH) 290 (1.55 x 10^4), 203nm (6.35 x 10^4); υ_{max} (soln., CHCl$_3$) 3454, 3391, 2926, 2855, 1659, 1610, 1459, 1105cm^{-1}; δ_H (360MHz) 9.59 (1H, br s, indole N*H*), 8.14 (1H, t, *J* 4.9, N*H*CO), 7.78 (1H, d, *J* 7.0, Ar), 7.73 (1H, d, *J* 3.0, indole H2), 7.44 (1H,

dd, J 7.6 and 1.1, Ar), 7.41 (1H, dd, J 8.0 and 1.1, Ar), 7.28-7.14 (6H, m, Ar), 6.89 (1H, app. t, J 7.8, Ar), 6.85 (1H, app. t, J 7.8, Ar), 5.56 (1H, d, J 10.0, CH_2OAr), 5.22 (1H, d, J 10.0, CH_2OAr), 4.61 (2H, d, J 4.9 CH_2N), 2.47 (3H, s, CH_3); δ_C (90.6MHz) 187.7 (s), 161.2 (s), 159.2 (s), 157.0 (s), 155.5 (s), 143.3 (s), 137.6 (s), 135.5 (d), 132.5 (d), 132.3 (d), 131.4 (s), 129.9 (s), 128.7 (d), 128.2 (s), 127.4 (d), 126.5 (d), 126.0 (d), 124.9 (d), 122.4 (d), 115.9 (s), 112.1 (d), 103.3 (s), 84.3 (s), 84.1 (t), 56.3 (s), 47.7 (t), 13.8 (q); m/z (ES) Found: 703.9727 ([MNa]$^+$ $C_{29}H_{21}BrIN_3O_4Na$ requires 703.9658).

3-[5'-(7-Bromo-3-phenyl-2,3-dihydrobenzofuran-3-yl)-2'-methyl-[2,4']-bioxazolyl-5-yl]-4-iodo-1H-indole (291)
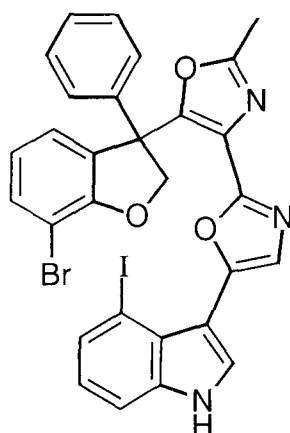
Triethylamine (30μl, 0.23mmol) and then a solution of the amide (**289**) (40mg, 60μmol) in dichloromethane (1ml) were added dropwise to a stirred solution of triphenylphosphine (31mg, 0.12mmol) and hexachloroethane (28mg, 0.12mmol) in dichloromethane (1ml) at 0°C, under an atmosphere of nitrogen. The solution was warmed to ambient temperature and stirred at ambient temperature for 5 h, with more triphenylphosphine (31mg, 0.12mmol), hexachloroethane (28mg, 0.12mmol) and triethylamine (30μl, 0.23mmol) added after 3 h. The solution was diluted with dichloromethane (10ml), then washed with water (10ml). The aqueous phase was extracted with dichloromethane (2 x 10ml), then the combined organic extracts were dried (MgSO$_4$) and concentrated *in vacuo* to leave a residue which was purified by

chromatography on silica, eluting with 65% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *bis-oxazole* (32mg, 81%) as a yellow oil; λ_{max} (EtOH) 284 (2.51 x 10^4), 202nm (7.71 x 10^4); υ_{max} (soln., CHCl$_3$) 3467, 1640, 1595, 1115, 1064cm^{-1}; δ_H (360MHz) 9.18 (1H, br s, indole NH), 7.58 (1H, d, J 7.5, Ar), 7.53 (1H, dd, J 7.6 and 1.1, Ar), 7.41 (1H, dd, J 6.7 and 1.1, Ar), 7.39 (1H, dd, J 6.0 and 1.1, Ar), 7.28-7.20 (6H, m, Ar), 7.14 (1H, s, oxazole H4), 6.90 (1H, app. t, J 7.9, Ar), 6.87 (1H, app. t, J 7.9, Ar), 5.69 (1H, d, J 9.9, CH_2), 5.12 (1H, d, J 9.9, CH_2), 2.53 (3H, s, CH_3); δ_C (90.6MHz) 160.7 (s), 157.1 (s), 154.3 (s), 151.8 (s), 144.1 (s), 142.6 (s), 135.7 (s), 132.7 (d), 132.0 (d), 131.4 (s), 129.2 (d), 128.7 (d), 128.5 (s), 127.9 (d), 127.4 (d), 126.6 (d), 126.4 (d), 126.3 (s), 123.9 (d), 122.5 (d), 111.6 (d), 105.0 (s), 103.4 (s), 84.9 (s), 83.3 (t), 56.4 (s), 13.9 (q); m/z (ES) Found: 663.9786 ([MH]$^+$ C$_{29}$H$_{20}$BrIN$_3$O$_3$ requires 663.9734).

7-Iodo-3-phenyl-3-vinyl-2,3-dihydrobenzofuran (293)
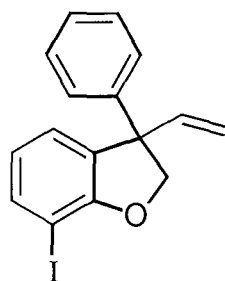
n-Butyllithium (0.16ml, 2.5M solution in hexanes, 0.40mmol) was added dropwise over 1 min to a stirred solution of the aryl bromide (73) (55mg, 0.18mmol) in THF (0.7ml) at -78°C, under an atmosphere of nitrogen. The solution was stirred at -78°C for 1 h, then a solution of iodine (0.37g, 1.46mmol) in THF (0.4ml) was added rapidly and the solution was warmed to ambient temperature over 2 h. The solution was stirred at ambient temperature for 14 h, then poured onto a saturated aqueous solution of sodium thiosulfate (5ml) and stirred at ambient temperature for 30 min. The aqueous solution was extracted with diethyl ether (3 x 10ml), then the combined organic extracts were dried (MgSO$_4$) and concentrated *in vacuo* to leave a residue

which was purified by chromatography on silica, eluting with 2% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *aryl iodide* (54mg, 86%) as a brown oil; υ_{max} (soln., CHCl$_3$) 1636, 1493, 990cm^{-1}; δ_H (360MHz) 7.62 (1H, dd, *J* 7.8 and 1.1, Ar), 7.41-7.27 (5H, m, Ar), 7.09 (1H, dd, *J* 7.4 and 1.1, Ar), 6.76 (1H, app. t, *J* 7.6, dihydrobenzofuran H5), 6.32 (1H, dd, *J* 17.3 and 10.5, C*H*CH$_2$), 5.38 (1H, d, *J* 10.5, CHC*H*$_2$), 5.14 (1H, d, *J* 17.3, CHC*H*$_2$), 4.91 (1H, d, *J* 9.1, C*H*$_2$OAr), 4.77 (1H, d, *J* 9.1, C*H*$_2$OAr); δ_C (90.6MHz) 160.0 (s), 143.4 (s), 140.7 (d), 137.3 (d), 132.0 (s), 128.4 (d), 127.2 (d), 127.0 (d), 125.4 (d), 122.7 (d), 115.4 (t), 82.7 (t), 74.6 (s), 58.6 (s); *m/z* (EI) Found: 348.0008 (M$^+$ C$_{16}$H$_{13}$IO requires 348.0011); Found: C, 55.4; H, 3.6%, C$_{16}$H$_{13}$IO requires C, 55.4; H, 3.5%.

7-Iodo-3-phenyl-2,3-dihydrobenzofuran-3-carbaldehyde (295)
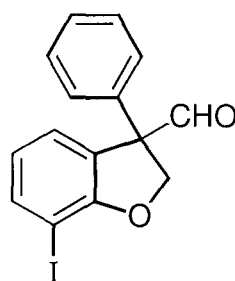
Osmium tetroxide (0.11g, 2.5wt.% solution in 2-methyl-2-propanol, 11μmol) and then sodium periodate (51mg, 0.24mmol) were added to a stirred solution of the aryl iodide (293) (33mg, 0.10mmol) in THF (1ml) and water (1ml) at 0°C, under an atmosphere of nitrogen. The solution was warmed to ambient temperature and stirred at ambient temperature for 18 h, then poured onto a saturated aqueous solution of sodium thiosulfate (5ml) and stirred at ambient temperature for 30 min. The mixture was extracted with ethyl acetate (3 x 10ml), then the combined organic extracts were dried (MgSO$_4$) and concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 15% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *aldehyde* (28mg, 84%) as a colourless oil; υ_{max} (soln., CHCl$_3$) 2821, 2710, 1729cm^{-1}; δ_H (360MHz) 9.68 (1H, d, *J* 1.2, C*H*O), 7.68 (1H, dd, *J* 8.0

141

and 1.1, Ar), 7.45-7.35 (3H, m, Ar), 7.27 (1H, dd, J 7.5 and 1.1, Ar), 7.17-7.14 (2H, m, Ar), 6.80 (1H, app. t, J 7.8, dihydrobenzofuran H5), 5.55 (1H, d, J 9.2, CH_2), 4.40 (1H, dd, J 9.2 and 1.2, CH_2); δ_C (90.6MHz) 192.8 (d), 161.2 (s), 139.1 (d), 137.4 (s), 129.5 (d), 128.5 (d), 127.4 (d), 125.7 (d), 124.1 (s), 122.9 (d), 76.5 (t), 75.0 (s), 67.5 (s); m/z (EI) Found: 349.9799 (M^+ $C_{15}H_{11}IO_2$ requires 349.9804).

Ethyl-3-(7-iodo-3-phenyl-2,3-dihydrobenzofuran-3-yl)-3-oxopropionate (296)
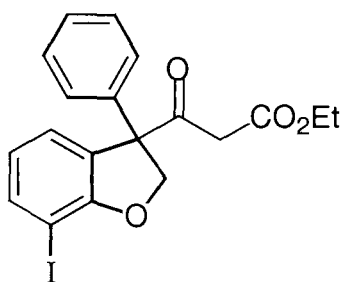
Solutions of the aldehyde (295) (1.03g, 2.94mmol) in dichloromethane (8ml) and ethyl diazoacetate (0.93ml, 8.82mmol) in dichloromethane (8ml) were added dropwise to a stirred solution of zirconium chloride (0.75g, 3.23mmol) in dichloromethane (15ml) at -10°C, under an atmosphere of nitrogen. The solution was warmed to 0°C and stirred at 0°C for 2 h, then warmed to ambient temperature and diluted with water (30ml). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 30ml). The combined organic extracts were dried ($MgSO_4$), then concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 15% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *ketone* (0.64g, 50%) as a pale yellow oil; υ_{max} (soln., $CHCl_3$) 1744, 1716, 1369, 1312, 1114cm^{-1}; δ_H (360MHz) 7.63 (1H, dd, J 7.9 and 1.0, Ar), 7.40-7.19 (6H, m, Ar), 6.77 (1H, app. t, J 7.7, dihydrobenzofuran H5), 5.61 (1H, d, J 9.1, CH_2OAr), 4.25 (1H, d, J 9.1, CH_2OAr), 4.04 (2H, qd, J 7.2 and 2.1, CH_2CH$_3$), 3.53 (2H, d, J 3.6, CH_2CO), 1.15 (3H, t, J 7.2, CH_3); δ_C (90.6MHz) 197.1 (s), 166.2 (s), 161.2 (s), 138.9 (d), 137.8 (s), 129.3 (d), 128.1 (d), 126.7 (d), 126.0 (d), 124.6 (s),

122.6 (d), 78.3 (t), 75.3 (s), 69.3 (s), 61.1 (t), 44.5 (t), 13.8 (q); m/z (EI) Found: 436.0170 (M^+ $C_{19}H_{17}IO_4$ requires 436.0172).

(*E/Z*)-Ethyl-3-(7-iodo-3-phenyl-2,3-dihydrobenzofuran-3-yl)-2-hydroxyimino-3-oxopropionate (297)
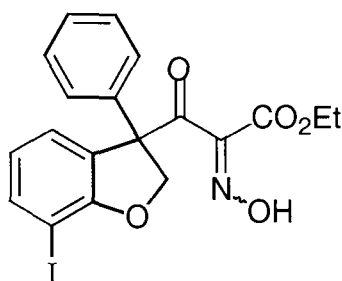
A solution of sodium nitrite (0.26g, 3.67mmol) in water (0.6ml) was added dropwise over 1 min to a stirred solution of the ketone (**296**) (0.20g, 0.46mmol) in acetic acid (5ml) at ambient temperature. The mixture was stirred at ambient temperature for 3 h, then diluted with water (15ml) and extracted with ethyl acetate (3 x 30ml). The combined organic extracts were washed with water (80ml), a saturated aqueous solution of sodium hydrogencarbonate (80ml) and finally water (80ml), then dried (MgSO$_4$) and concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 25% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *oxime* (0.19g, 89%), in a 2:1 ratio of geometrical isomers, as a pale yellow oil; υ_{max} (soln., CHCl$_3$, major isomer) 3534, 3269, 1632cm^{-1}; δ_H (360MHz) 9.72 (1H, s, O*H*), 7.57 (1H, dd, *J* 7.9 and 1.1, Ar), 7.44 (1H, dd, *J* 7.6 and 1.1, Ar), 7.33-7.21 (3H, m, Ar), 7.18-7.16 (2H, m, Ar), 6.70 (1H, app. t, *J* 7.7, dihydrobenzofuran H5), 5.33 (1H, d, *J* 9.7, C*H$_2$*OAr), 4.75 (1H, d, *J* 9.7, C*H$_2$*OAr), 4.32 (2H, q, *J* 7.1, C*H$_2$*CH$_3$), 1.32 (3H, t, *J* 7.1, C*H$_3$*); δ_C (90.6MHz) 191.0 (s), 161.0 (s), 160.1 (s), 148.2 (s), 141.0 (s), 138.4 (d), 129.1 (d), 128.2 (d), 127.5 (d), 126.2 (s), 125.5 (d), 122.9 (d), 78.7 (t), 74.6 (s), 67.3 (s), 62.6 (t), 13.9 (q); m/z (EI) Found: 465.0086 (M^+ $C_{19}H_{16}INO_5$ requires 465.0073).

Ethyl-2-acetylamino-3-(7-iodo-3-phenyl-2,3-dihydrobenzofuran-3-yl)-3-oxopropionate (305)
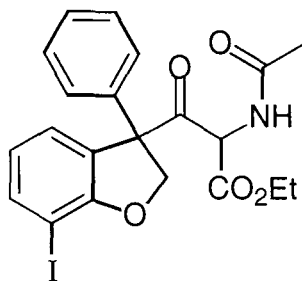
Zinc dust (23mg, 0.35mmol) was added in a single portion to a stirred solution of the oxime (**297**) (0.31g, 0.70mmol) in 80% aqueous acetic acid (7ml) at ambient temperature. The solution was stirred at ambient temperature for 8 h, with more zinc dust (69mg, 1.05mmol) added portionwise over 6 h. The precipitate was removed by filtration and washed with acetic acid, then the filtrate was concentrated *in vacuo* to leave the crude *salt* (0.36g, 100%) as a pale yellow solid, which was used immediately without characterisation. Acetic anhydride (90µl, 0.98mmol) was added dropwise over 1 min to a stirred solution of the salt (**299**) (0.36g, 0.70mmol) in pyridine (7ml) at 0°C, under an atmosphere of nitrogen. The solution was stirred at 0°C for 1 h, then 4-dimethylaminopyridine (36mg, 0.29mmol) was added in a single portion and the solution was warmed to ambient temperature. The solution was stirred at ambient temperature for 9 h, then diluted with ethyl acetate (50ml) and washed with hydrochloric acid (50ml, 2M), water (50ml) and brine (50ml), then dried (MgSO$_4$) and concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 50% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *amide* (0.18g, 53%), in a 2:1 ratio of diastereoisomers, as a pale yellow oil; υ_{max} (soln., CHCl$_3$) 3427, 1748, 1716, 1682, 1313, 1111cm^{-1}; δ_H (360MHz) 7.79 (1H, dd, *J* 7.6 and 1.1, Ar), 7.65 (1H, dd, *J* 7.2 and 1.1, Ar), 7.63 (1H, dd, *J* 6.5 and 1.1, Ar), 7.59 (1H, dd, *J* 7.6 and 1.1, Ar), 7.35-7.29 (6H, m, Ar), 7.24-7.19 (4H, m, Ar), 6.84 (1H, app. t, *J* 7.7, dihydrobenzofuran H5), 6.79 (1H, app. t, *J* 7.7, dihydrobenzofuran H5), 6.72 (1H, d, *J* 7.4, N*H*), 6.63 (1H, d, *J* 8.9, N*H*), 5.81

(1H, d, *J* 8.9, C*H*N), 5.62 (1H, d, *J* 9.3, C*H*$_2$OAr), 5.61 (1H, d, *J* 7.4, C*H*N), 5.51 (1H, d, *J* 9.4, C*H*$_2$OAr), 4.52 (1H, d, *J* 9.4, C*H*$_2$OAr), 4.27 (1H, d, *J* 9.3, C*H*$_2$OAr), 3.92-3.78 (2H, m, C*H*$_2$CH$_3$), 3.45 (2H, dq, *J* 7.5 and 7.2, C*H*$_2$CH$_3$), 1.91 (3H, s, C*H*$_3$CO), 1.87 (3H, s, C*H*$_3$CO), 1.03 (3H, t, *J* 7.2, CH$_2$C*H*$_3$), 1.02 (3H, t, *J* 7.2, CH$_2$C*H*$_3$); δ$_C$ (90.6MHz) 199.4 (s), 197.0 (s), 169.5 (s), 169.0 (s), 166.3 (s), 166.1 (s), 161.3 (s), 161.1 (s), 139.2 (d), 138.9 (d), 137.3 (s), 137.2 (s), 129.1 (d), 129.0 (d), 128.3 (d), 128.2 (d), 127.3 (d), 127.2 (d), 126.7 (d), 126.6 (d), 125.1 (s), 124.2 (s), 123.2 (d), 122.9 (d), 79.2 (t), 79.0 (t), 75.3 (s), 74.8 (s), 69.3 (s), 69.1 (s), 62.3 (t), 57.7 (d), 56.6 (d), 22.4 (q), 13.6 (q), 13.5 (q); *m/z* (FAB) Found: 494.0477 ([MH]$^+$ C$_{21}$H$_{21}$INO$_5$ requires 494.0465).

Ethyl-5-(7-iodo-3-phenyl-2,3-dihydrobenzofuran-3-yl)-2-methyloxazole-4-carboxylate (298)
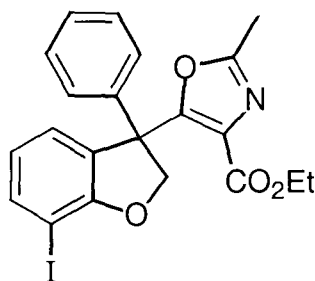
Triethylamine (0.67ml, 4.80mmol) and then a solution of the amide (**305**) (0.59g, 1.20mmol) in dichloromethane (8ml) were added dropwise to a stirred solution of triphenylphosphine (0.63g, 2.40mmol) and iodine (0.61g, 2.40mmol) in dichloromethane (4ml) at ambient temperature, under an atmosphere of nitrogen. The solution was stirred at ambient temperature for 8 h, then concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 50% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *oxazole* (0.51g, 89%) as a colourless oil; υ$_{max}$ (soln., CHCl$_3$) 1722, 1117, 1088cm^{-1}; δ$_H$ (360MHz) 7.57 (1H, dd, *J* 7.8 and 1.0, Ar), 7.38 (1H, dd, *J* 7.7 and 1.0, Ar), 7.28-7.19 (3H, m, Ar), 7.13-7.10 (2H, m, Ar), 6.69 (1H, app. t, *J* 7.7, dihydrobenzofuran H5), 5.26 (1H, d, *J* 9.9,

CH_2OAr), 5.16 (1H, d, J 9.9, CH_2OAr), 4.22 (1H, dq, J 10.8 and 7.1, CH_2CH$_3$), 4.15 (1H, dq, J 10.8 and 7.1, CH_2CH$_3$), 2.48 (3H, s, ArCH_3), 1.18 (3H, t, J 7.1, CH$_2$CH_3); δ_C (90.6MHz) 161.1 (s), 159.8 (s), 159.6 (s), 158.5 (s), 143.0 (s), 138.1 (d), 129.7 (s), 128.6 (d), 127.3 (d), 127.0 (d), 125.6 (s), 126.5 (d), 122.9 (d), 83.0 (t), 74.4 (s), 61.2 (t), 56.7 (s), 13.9 (q), 13.7 (q); m/z (EI) Found: 475.0293 (M$^+$ C$_{21}$H$_{18}$INO$_4$ requires 475.0281).

5-(7-Iodo-3-phenyl-2,3-dihydrobenzofuran-3-yl)-2-methyloxazole-4-carboxylic acid (306)
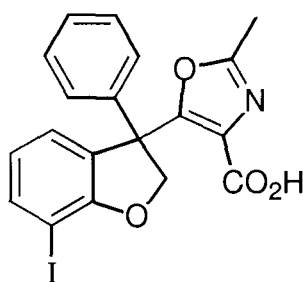
Lithium hydroxide (0.23g, 5.47mmol) was added in a single portion to a stirred solution of the oxazole (298) (0.26g, 0.55mmol) in methanol (6ml) and water (2ml) at ambient temperature. The solution was stirred at ambient temperature for 90 min, then acidified with a 10% aqueous solution of citric acid (15ml) and extracted with ethyl acetate (3 x 25ml). The combined organic extracts were dried (MgSO$_4$) and concentrated *in vacuo* to leave the *acid* (0.25g, 100%) as a colourless oil; υ_{max} (soln., CHCl$_3$) 3466 (br), 3200 (br), 1738, 1015cm^{-1}; δ_H (360MHz) 7.62 (1H, dd, J 7.9 and 1.2, Ar), 7.46 (1H, dd, J 7.6 and 1.2, Ar), 7.31-7.25 (3H, m, Ar), 7.14-7.10 (2H, m, Ar), 6.74 (1H, app. t, J 7.7, dihydrobenzofuran H5), 5.42 (1H, d, J 10.0, CH_2), 5.11 (1H, d, J 10.0, CH_2), 2.50 (3H, s, CH_3); δ_C (CD$_3$OD, 90.6MHz) 164.5 (s), 162.8 (s), 161.7 (s), 160.9 (s), 145.4 (s), 140.2 (d), 131.9 (s), 130.5 (d), 129.8 (s), 129.1 (d), 127.4 (d), 127.3 (d), 124.8 (d), 84.6 (t), 75.7 (s), 58.6 (s), 14.3 (q); m/z (ES) Found: 446.9976 (M$^+$ C$_{19}$H$_{14}$INO$_4$ requires 446.9968).

5-(7-Iodo-3-phenyl-2,3-dihydrobenzofuran-3-yl)-2-methyloxazole-4-carboxylic acid [2-(4-iodo-1*H*-indol-3-yl)-2-oxoethyl]-amide (308)
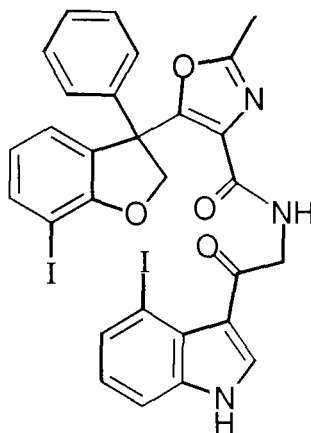
A solution of the acid (**306**) (0.12g, 0.28mmol) in oxalyl chloride (3ml) was heated at reflux for 90 min. The solution was cooled to ambient temperature and concentrated *in vacuo* to leave the crude *acid chloride* (0.13g, 100%) as a yellow oil, which was used immediately without characterisation. Triethylamine (0.31ml, 2.24mmol) was added dropwise over 1 min to a stirred suspension of the salt (**250**) (0.32g, 0.84mmol) in dichloromethane (3ml) at 0°C, under an atmosphere of nitrogen. The solution was stirred at 0°C for 15 min, then a solution of the acid chloride (**307**) (0.13g, 0.28mmol) in dichloromethane (3ml) was added dropwise over 3 min. The solution was warmed to ambient temperature and stirred at ambient temperature for 16 h, then diluted with dichloromethane (20ml) and washed with water (20ml). The aqueous phase was extracted with dichloromethane (2 x 20ml), then the combined organic extracts were dried (MgSO$_4$) and concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 65% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *amide* (50mg, 25%) as a yellow solid; m.p. 139-142°C; υ_{max} (soln., CHCl$_3$) 3454, 2927, 1659, 1609, 1456, 1104cm^{-1}; δ_H (360MHz) 10.09 (1H, br s, indole N*H*), 8.15 (1H, br t, *J* 4.8, N*H*CO), 7.73 (1H, d, *J* 7.6, Ar), 7.65 (1H, d, *J* 3.2, Ar), 7.59 (1H, dd, *J* 7.9 and 1.2, Ar), 7.45 (1H, dd, *J* 7.6 and 1.2, Ar), 7.24-7.12 (6H, m, Ar), 6.82 (1H, app. t, *J* 7.8, Ar), 6.72 (1H, app. t, *J* 7.8, Ar), 5.55 (1H, d, *J* 10.0, C*H*$_2$OAr), 5.18 (1H, d, *J* 10.0, C*H*$_2$OAr), 4.56 (2H, d, *J* 4.8 C*H*$_2$N), 2.45 (3H, s, C*H*$_3$);

δ_C (90.6MHz) 187.8 (s), 160.9 (s), 159.7 (s), 159.1 (s), 155.5 (s), 143.1 (s), 138.0 (s), 137.9 (d), 135.0 (d), 133.3 (s), 129.7 (s), 129.6 (s), 128.4 (d), 128.3 (d), 127.3 (d), 127.0 (d), 125.7 (d), 124.4 (d), 122.6 (d), 115.3 (s), 111.9 (d), 84.5 (s), 83.2 (t), 74.0 (s), 56.4 (s), 47.3 (t), 13.3 (q); m/z (FAB) Found: 729.9740 ([MH]$^+$ $C_{29}H_{22}I_2N_3O_4$ requires 729.9700).

5-(7-Iodo-3-phenyl-2,3-dihydrobenzofuran-3-yl)-2-methyloxazole-4-carboxylic acid [2-(1H-indol-3-yl)-2-oxoethyl]-amide (309)
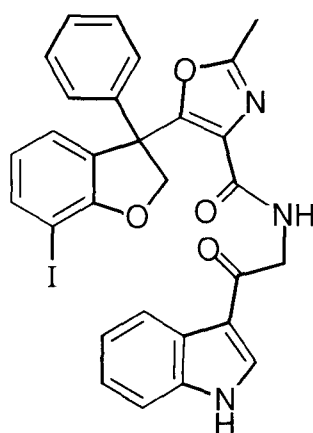
DMF (1ml) was added to *bis*-(triphenylphosphine)nickel(II) chloride (48mg, 70µmol), zinc dust (5mg, 70µmol) and triphenylphosphine (39mg, 0.15mmol) at ambient temperature, under an atmosphere of argon and the solution was heated at 50°C for 1 h. A solution of the amide (308) (30mg, 40µmol) in DMF (7ml) was added dropwise over 5 min to the stirred solution at 50°C and the solution was heated at 50°C for 1 h, then cooled to ambient temperature. The solution was concentrated *in vacuo* to leave a residue which was diluted with ethyl acetate (30ml) and washed with water (30ml). The organic phase was dried (MgSO$_4$) and concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 60% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *amide* (10mg, 40%) as a yellow oil; υ_{max} (soln., CHCl$_3$) 3458, 3391, 2928, 1651, 1609, 1495, 1456, 1119cm^{-1};

δ_H (360MHz) 9.32 (1H, br s, indole NH), 8.34-8.31 (1H, m, Ar), 8.18 (1H, br t, J 4.8, NHCO), 7.83 (1H, d, J 3.2, Ar), 7.61 (1H, dd, J 7.9 and 1.2, Ar), 7.43 (1H, dd, J 7.9

and 1.2, Ar), 7.32-7.15 (8H, m, Ar), 6.73 (1H, app. t, J 7.7, dihydrobenzofuran H5), 5.56 (1H, d, J 10.1, CH_2OAr), 5.21 (1H, d, J 10.1, CH_2OAr), 4.68 (2H, dd, J 4.8 and 1.1, CH_2N), 2.47 (3H, s, CH_3); δ_C (90.6MHz) 188.5 (s), 161.0 (s), 160.1 (s), 159.1 (s), 155.5 (s), 143.4 (s), 138.2 (d), 136.1 (s), 131.0 (d), 130.0 (s), 128.7 (d), 127.6 (d), 127.3 (d), 126.1 (d), 125.2 (s), 124.0 (d), 123.0 (d), 122.8 (d), 122.0 (d), 115.2 (s), 111.7 (d), 83.5 (t), 74.5 (s), 56.7 (s), 46.0 (t), 29.7 (s), 13.8 (q); m/z (FAB) Found: 604.0738 ([MH]$^+$ $C_{29}H_{23}IN_3O_4$ requires 604.0733).

3-[5'-(7-Iodo-3-phenyl-2,3-dihydrobenzofuran-3-yl)-2'-methyl-[2,4']-bioxazolyl-5-yl]-4-iodo-1H-indole (310)
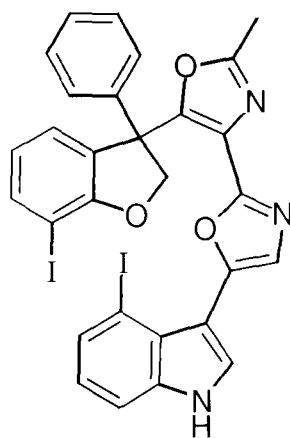
Triethylamine (30μl, 0.18mmol) and then a solution of the amide (**308**) (33mg, 50μmol) in dichloromethane (1ml) were added dropwise to a stirred solution of triphenylphosphine (24mg, 90μmol) and hexachloroethane (21mg, 90μmol) in dichloromethane (1ml) at 0°C, under an atmosphere of nitrogen. The solution was warmed to ambient temperature and stirred at ambiemt temperature for 18 h, with more triphenylphosphine (24mg, 90μmol), hexachloroethane (21mg, 90μmol) and triethylamine (15μl, 90μmol) added after 4 h and 15 h. The solution was diluted with dichloromethane (10ml), then washed with water (10ml). The aqueous phase was extracted with dichloromethane (2 x 10ml), then the combined organic extracts were dried (MgSO$_4$) and concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 65% ethyl acetate in petroleum ether (b.p.

40-60°C), to give the *bis-oxazole* (18mg, 56%) as a yellow oil; υ_{max} (soln., CHCl$_3$) 3467, 1640, 1594, 1114, 1049cm^{-1}; δ_H (360MHz) 9.48 (1H, br s, indole N*H*), 7.61 (1H, dd, *J* 7.9 and 1.0, Ar), 7.57 (1H, d, *J* 7.4, Ar), 7.38 (1H, d, *J* 8.1, Ar), 7.26-7.21 (7H, m, Ar), 7.12 (1H, s, oxazole H4), 6.88 (1H, app. t, *J* 7.8, Ar), 6.75 (1H, app. t, *J* 7.7, Ar), 5.69 (1H, d, *J* 9.9, C*H$_2$*), 5.12 (1H, d, *J* 9.9, C*H$_2$*), 2.54 (3H, s, C*H$_3$*); δ_C (90.6MHz) 160.7 (s), 160.1 (s), 154.2 (s), 151.9 (s), 144.2 (s), 142.7 (s), 138.2 (d), 135.7 (s), 131.9 (d), 130.0 (s), 129.2 (d), 128.7 (d), 128.5 (s), 128.0 (d), 127.4 (d), 127.3 (d), 126.6 (d), 123.8 (d), 123.0 (d), 111.7 (d), 104.8 (s), 84.8 (s), 82.6 (t), 74.6 (s), 56.8 (s), 29.7 (s), 13.9 (q); *m/z* (FAB) Found: 711.9585 ([MH]$^+$ C$_{29}$H$_{20}$I$_2$N$_3$O$_3$ requires 711.9594).

3.4 An Alternative Approach to the Macrocycle (64)

Ethyl-(diethoxyphosphoryl)-phenylacetate (320)
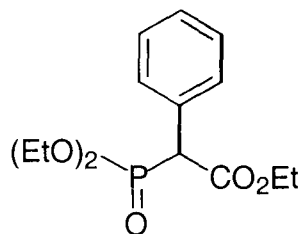
A solution of triethyl phosphonoacetate (**319**) (8.0ml, 40.0mmol) in DMF (6ml) was added dropwise over 10 min to a stirred suspension of sodium hydride (1.60g, 40.0mmol) in DMF (8ml) at ambient temperature under an atmosphere of nitrogen. The solution was stirred at ambient temperature for 10 min, then iodobenzene (2.2ml, 20.0mmol) and copper iodide (3.80g, 20.0mmol) were added in single portions. The solution was heated at 100°C for 7 h, then cooled to ambient temperature and diluted with hydrochloric acid (15ml, 2M). The mixture was filtered through celite$^®$ and diluted with water (50 ml), then the filtrate was extracted with ethyl acetate (3 x 100ml). The combined organic extracts were dried (MgSO$_4$), then concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with

65% ethyl acetate in chloroform, to give the phosphonate (4.24g, 71%) as a pale yellow oil; υ_{max} (soln., CHCl$_3$) 1731, 1601, 1496, 1054cm^{-1}; δ_H (360MHz) 7.52-7.48 (2H, m, Ar), 7.41-7.26 (3H, m, Ar), 4.31-3.92 (7H, m, CH_2, PCH), 1.33-1.14 (9H, m, CH_3); δ_C (90.6MHz) 167.5 (s), 130.9 (s), 129.5 (d), 128.4 (d), 127.8 (d), 63.3 (t), 63.0 (t), 61.7 (t), 52.9 (d), 16.2 (q x 2), 13.9 (q); m/z (ES) Found: 623.2101 ([M$_2$Na]$^+$ C$_{28}$H$_{42}$P$_2$O$_{10}$Na requires 623.2151).

(*E*)-(*S*)-*tert*-Butyl-4-(2-ethoxycarbonyl-2-phenylvinyl)-2,2-dimethyloxazolidine-3-carboxylate (321)
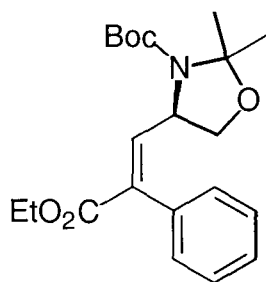
A solution of the phosphonate (**320**) (80mg, 0.27mmol) in THF (1ml) was added dropwise over 1 min to a stirred suspension of sodium hydride (11mg, 60% dispersion in mineral oil, 0.27mmol) in THF (1ml) at ambient temperature, under an atmosphere of nitrogen. The solution was stirred at ambient temperature for 10 min, then a solution of the aldehyde (**318**) (0.12g, 0.53mmol) in THF (1ml) was added dropwise over 1 min. The solution was stirred at ambient temperature for 5 h, then poured onto a saturated aqueous solution of ammonium chloride (5ml). The mixture was extracted with ethyl acetate (3 x 10ml), then the combined organic extracts were dried (MgSO$_4$) and concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 10% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *alkene* (59mg, 58%) as a colourless oil; [α]$_D$ = -41.9 (c = 1.1, CHCl$_3$); υ_{max} (soln., CHCl$_3$) 1694, 1389 1090cm^{-1}; δ_H (C$_6$D$_6$, 360MHz, T 340K) 7.45-7.42 (2H, m, Ar), 7.24-7.13 (3H, m, Ar), 6.37 (1H, d, *J* 8.2, CHCHCH$_2$), 5.29 (1H, br s, CHN), 4.31-4.24 (1H, m, CH_2O), 4.13-4.05 (2H, m, CH_2O), 3.95-3.91 (1H,

m, CH_2O), 1.77 (3H, br s, CCH_3), 1.65 (3H, br s, CCH_3), 1.50 (9H, s, C(CH_3)$_3$), 1.04-0.99 (3H, m, CH$_2$CH_3); δ_C (C$_6$D$_6$, 90.6MHz, T 340K) 167.3 (s), 152.5 (s), 143.9 (d), 138.7 (s), 135.6 (s), 130.5 (d), 128.6 (d), 128.1 (d), 95.1 (s), 80.0 (s), 69.7 (t), 61.1 (t), 57.8 (d), 28.9 (q), 27.4 (q), 24.9 (q), 14.4 (q); m/z (ES) Found: 439.2209 ([MNaMeCN]$^+$ C$_{23}$H$_{32}$N$_2$O$_5$Na requires 439.2209).

(*E*)-(*S*)-*tert*-Butyl-4-(3-hydroxy-2-phenylpropenyl)-2,2-dimethyloxazolidine-3-carboxylate (322)
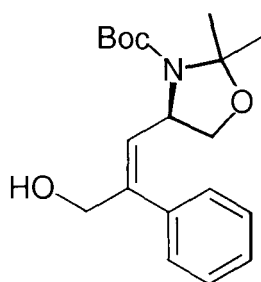
Di-*iso*-butylaluminium hydride (0.31ml, 1.5M in toluene, 0.46mmol) was added dropwise over 1 min to a stirred solution of the alkene (**321**) (69mg, 0.18mmol) in toluene (2ml) at -78°C, under an atmosphere of nitrogen. The solution was warmed to ambient temperature over 3 h, then methanol (1ml) was added dropwise. The solution was poured onto a saturated aqueous solution of potassium sodium tartrate (5ml) with rapid stirring and the mixture was stirred at ambient temperature for 2 h. The mixture was extracted with ethyl acetate (4 x 10ml) and the combined organic extracts were dried (MgSO$_4$), then concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 35% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *alcohol* (45mg, 75%) as a colourless oil which solidified on standing; m.p. 52-54°C; [α]$_D$ = -6.6 (c = 1.0, CHCl$_3$); υ_{max} (soln., CHCl$_3$) 3415, 1290, 1061cm^{-1}; δ_H (360MHz) 7.59 (2H, app. d, *J* 7.4, phenyl H2 and phenyl H6), 7.36 (2H, app. t, *J* 7.3, phenyl H3 and phenyl H5), 7.29 (1H, app. t, *J* 7.2, phenyl H4), 5.85 (1H, d, *J* 10.4, C*H*CHCH$_2$), 5.00 (1H, dd, *J* 10.4 and 5.3, C*H*N), 4.86-4.82 (2H, m, C*H$_2$*OH), 4.17 (1H, dd, *J* 9.0 and 5.8, CHC*H$_2$*), 3.85 (1H, dd, *J* 9.0 and 1.1, CHC*H$_2$*),

152

1.63 (3H, s, CC*H*₃), 1.55 (3H, s, CC*H*₃), 1.49 (9H, s, C(C*H₃*)₃); δ$_C$ (90.6MHz) 152.2 (s), 141.5 (s), 141.1 (s), 128.2 (d), 127.9 (d), 127.3 (d), 126.1 (d), 93.4 (s), 81.0 (s), 67.9 (t), 59.9 (t), 55.0 (d), 28.2 (q), 27.5 (q), 24.5 (q); *m/z* (ES) Found: 356.1858 ([MNa]$^+$ C₁₉H₂₇NO₄Na requires 356.1838).

(*E*)-(*S*)-*tert*-Butyl-4-[3-(2-iodophenoxy)-2-phenylpropenyl]-2,2-dimethyl oxazolidine-3-carboxylate (325)
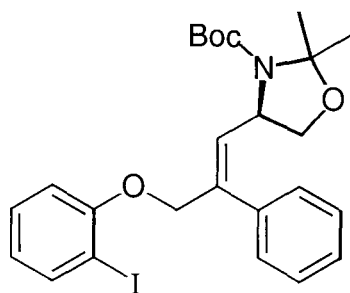
Methanesulfonyl chloride (30μl, 0.37mmol) was added dropwise over 1 min to a stirred solution of the alcohol (322) (0.10g, 0.31mmol) and triethylamine (60μl, 0.46mmol) in dichloromethane (2ml) at 0°C, under an atmosphere of nitrogen. The solution was stirred at 0°C for 80 min, then diluted with diethyl ether (5ml) and washed with a 50% saturated aqueous solution of sodium chloride (5ml) containing hydrochloric acid (1ml, 2M), then a saturated aqueous solution of sodium hydrogencarbonate (5ml). The organic phase was dried (MgSO₄) and concentrated *in vacuo* to leave the *mesylate* (0.13g, 100%) as a colourless oil, which was used immediately without characterisation. 2-Iodophenol (324) (68mg, 0.31mmol) and then potassium carbonate (65mg, 0.47mmol) were added to a stirred solution of the mesylate (323) (0.13g, 0.31mmol) in DMPU (0.2ml) and acetonitrile (3ml) at ambient temperature, under an atmosphere of nitrogen. The solution was stirred at ambient temperature for 19 h, then heated at reflux for 5 h. The solution was cooled to ambient temperature and diluted with ethyl acetate (10ml), then washed with water (10ml). The aqueous phase was extracted with ethyl acetate (10ml), then the combined organic extracts were dried (MgSO₄) and concentrated *in vacuo* to leave a

residue which was purified by chromatography on silica, eluting with 10% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *iodide* (0.12g, 75%) as a colourless oil; $[\alpha]_D$ = +8.2 (c = 1.0, CHCl$_3$); υ_{max} (soln., CHCl$_3$) 1582, 1570, 1275, 1060cm^{-1}; δ_H (C$_6$D$_6$, 360MHz, T 340K) 7.63 (1H, d, *J* 7.4, phenoxy H3), 7.39 (2H, app. d, *J* 7.0, Ar), 7.15-7.07 (3H, m, Ar), 6.94 (1H, t, *J* 7.4, phenoxy H5), 6.62 (1H, br d, *J* 7.4, phenoxy H6), 6.39 (1H, t, *J* 7.4, phenoxy H4), 6.08 (1H, d, *J* 9.8, C*H*CHCH$_2$), 5.16 (1H, br s, C*H*N), 4.76 (1H, br s, C*H*$_2$O), 4.65 (1H, d, *J* 10.9, C*H*$_2$O), 4.02-3.98 (1H, m, C*H*$_2$O), 3.78 (1H, dd, *J* 9.1 and 3.0, C*H*$_2$O), 1.69 (3H, s, CC*H*$_3$), 1.54 (3H, s, CC*H*$_3$), 1.39 (9H, s, C(C*H*$_3$)$_3$); δ_C (C$_6$D$_6$, 90.6MHz, T 340K) 158.7 (s), 152.8 (s), 142.3 (s), 140.7 (d), 130.7 (d), 129.3 (d), 128.9 (d), 128.6 (s), 128.4 (d), 127.5 (d), 123.7 (d), 113.9 (d), 94.9 (s), 87.8 (s), 80.2 (s), 69.7 (t), 68.4 (t), 56.6 (d), 29.2 (q), 28.1 (q), 25.4 (q); *m/z* (ES) Found: 558.1093 ([MNa]$^+$ C$_{25}$H$_{30}$INO$_4$Na requires 558.1117).

(*E*)-(*S*)-2-Acetamido-5-(2-iodophenoxy)-4-phenyl-3-penten-1-ol (327)
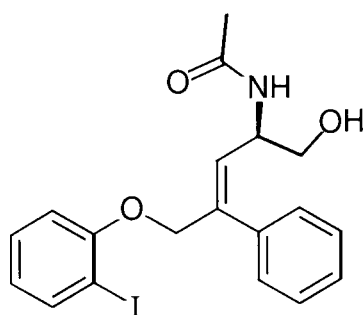
A solution of the iodide (325) (60mg, 0.11mmol) in hydrogen chloride (1ml, 4.0M solution in 1,4-dioxane) was stirred at ambient temperature for 1.5 h, under an atmosphere of nitrogen. The solution was concentrated *in vacuo* (1mmHg) to leave the crude *salt* (67mg, 100%) as a white solid, which was used immediately without characterisation. Acetic anhydride (10µl, 0.13mmol) was added dropwise over 1 min to a stirred solution of the salt (326) (67mg, 0.11mmol) in pyridine (1ml) at ambient temperature, under an atmosphere of nitrogen. The solution was stirred at ambient temperature for 1 h, then 4-dimethylaminopyridine (9mg, 70µmol) was added in a

154

single portion and the solution was stirred at ambient temperature for 18 h. with more acetic anhydride (10µl, 0.13mmol) added after 2 h. The solution was diluted with ethyl acetate (5ml) and washed with hydrochloric acid (5ml, 2M), water (5ml) and brine (5ml), then dried (MgSO$_4$) and concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 2% methanol in ethyl acetate, to give the *acetate* (39mg, 81%) as a white oil; $[\alpha]_D$ = -2.5 (c = 1.1, CHCl$_3$); υ_{max} (soln., CHCl$_3$) 3625, 3436, 1667, 1468, 1372, 1275, 1048cm^{-1}; δ_H (360MHz) 7.76 (1H, dd, *J* 7.8 and 1.4, phenoxy H3), 7.48-7.45 (2H, m, Ar), 7.36-7.27 (4H, m, Ar), 6.93 (1H, d, *J* 7.6, phenoxy H6), 6.73 (1H, app. td, *J* 7.4 and 0.9, phenoxy H4), 6.27 (1H, d, *J* 7.1, N*H*), 6.02 (1H, d, *J* 9.5, C*H*CHCH$_2$), 5.13 (1H, d, *J* 10.5, C*H$_2$*OAr), 4.92-4.86 (1H, m, C*H*N), 4.85 (1H, d, *J* 10.5, C*H$_2$*OAr), 3.84-3.77 (2H, m, C*H$_2$*OH), 3.21 (1H, br s, O*H*), 1.94 (3H, s, C*H$_3$*); δ_C (90.6MHz) 170.6 (s), 157.0 (s), 140.5 (s), 139.4 (d), 138.6 (s), 130.8 (d), 129.6 (d), 128.4 (d), 127.8 (d), 126.4 (d), 123.0 (d), 112.5 (d), 86.4 (s), 67.0 (t), 65.5 (t), 50.4 (d), 23.3 (q); *m/z* (ES) Found: 460.0374 ([MHNa]$^+$ C$_{19}$H$_{21}$INO$_3$Na requires 460.0387).

(*E*)-(*S*)-*N*-[1-(*tert*-Butyldimethylsilanyloxymethyl)-4-(2-iodophenoxy)-3-phenylbut-2-enyl]-acetamide (328)
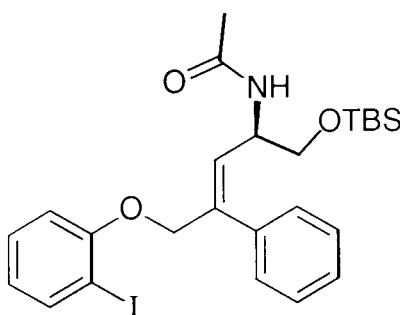
tert-Butyldimethylsilyl chloride (17mg, 0.11mmol) and then 4-dimethylaminopyridine (1mg, 10µmol) were added in single portions to a stirred solution of the acetate (327) (39mg, 90µmol) in dichloromethane (1ml) at 0°C. under an atmosphere of nitrogen. The solution was stirred at 0°C for 10 min. then triethylamine (20µl, 0.14mmol) was added dropwise at 0°C. The solution was

warmed to ambient temperature and stirred at ambient temperature for 20 h, then a saturated aqueous solution of ammonium chloride (3ml) was added. The aqueous phase was separated and extracted with diethyl ether (2 x 5ml), then the combined organic extracts were dried (MgSO$_4$) and concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with 35% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *silyl ether* (34mg, 69%) as a colourless oil: $[\alpha]_D$ = -2.6 (c = 1.0, CHCl$_3$); υ_{max} (soln., CHCl$_3$) 1097, 888, 839cm^{-1}; δ_H (360MHz) 7.76 (1H, dd, *J* 7.7 and 1.5, phenoxy H3), 7.48-7.45 (2H, m, Ar), 7.37-7.27 (4H, m, Ar), 6.95 (1H, dd, *J* 8.3 and 1.2, phenoxy H6), 6.72 (1H, app. td, *J* 7.6 and 1.2, phenoxy H4), 6.09-6.07 (1H, m, N*H*), 6.08 (1H, d, *J* 9.2, C*H*CHCH$_2$), 5.26 (1H, d, *J* 10.6, C*H*$_2$OAr), 4.93-4.86 (1H, m, C*H*N), 4.84 (1H, d, *J* 10.6, C*H*$_2$OAr), 3.83 (2H, d, *J* 3.8, C*H*$_2$OSi), 1.96 (3H, s, COC*H*$_3$), 0.92 (9H, s, SiC(C*H*$_3$)$_3$), 0.08 (3H, s, SiC*H*$_3$), 0.07 (3H, s, SiC*H*$_3$); δ_C (90.6MHz) 169.3 (s), 157.2 (s), 140.8 (s), 139.3 (d), 137.6 (s), 131.8 (d), 129.5 (d), 128.3 (d), 127.5 (d), 126.4 (d), 122.7 (d), 112.6 (d), 86.5 (s), 67.1 (t), 65.5 (t), 49.0 (d), 25.9 (q), 23.3 (q), 18.3 (s), -5.3 (q); *m/z* (ES) Found: 552.1428 ([MH]$^+$ C$_{25}$H$_{35}$INO$_3$Si requires 552.1431).

4. APPENDIX

4.1 Contemporaneous Studies

During the course of this research, four other groups have published their efforts towards a total synthesis of diazonamide A (**1**).[173,196,230] The synthesis of the most relevant and advanced intermediates in each of these approaches has been summarised below.

The research group of Moody were the first to disclose their strategy for a synthesis of diazonamide A (**1**).[230b,230c] The model benzofuranone unit (**331**) was prepared using an intramolecular rhodium carbenoid aromatic C-H insertion reaction. Thus, 2-bromophenol (**332**) was first converted into the diazo ester (**333**), which next underwent rhodium(II)-catalysed decomposition in the presence of rhodium(II) perfluorobutyramide to afford the benzofuranone (**334**) (**Scheme 32**). Subsequent *C*-acylation using ethyl chloroformate then gave the ester (**331**).[231]
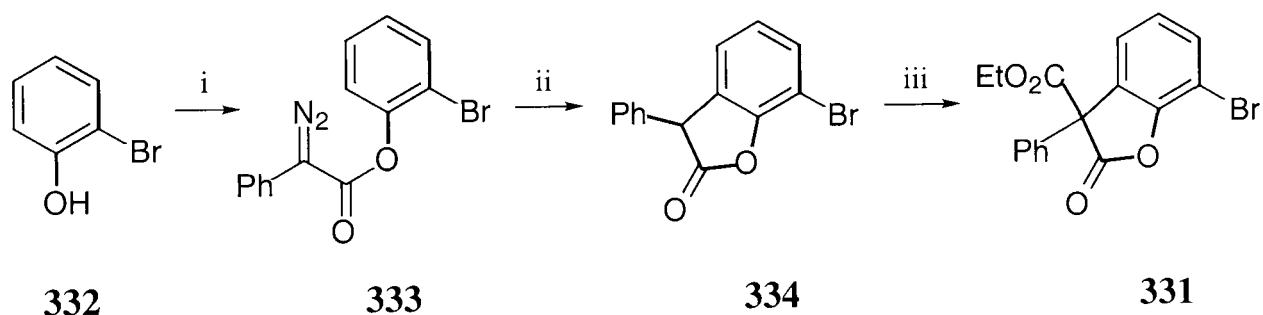
Reagents: i, PhCOCO$_2$H, DCC, TsNHNH$_2$, Et$_3$N, 47%; ii, Rh$_2$(NHCOC$_3$F$_7$)$_4$, CH$_2$Cl$_2$, Δ, 20%; iii, ClCO$_2$Et, Et$_3$N, DMAP, CH$_2$Cl$_2$, 96%.

Scheme 32

Unfortunately, the bromides (**331** and **334**) failed to undergo Suzuki or Stille reactions[202,204] with simple phenyl derivatives. As a result, the more robust 3-arylbenzofuran (**171**) was prepared as the coupling partner. Alkylation of the phenoxide anion of 2-bromophenol (**332**) with 2-bromoacetophenone (**78**), followed by acid-induced cyclisation of the intermediate ketone, provided the benzofuran framework (**171**) (**Scheme 33**). Conversion of the bromide (**171**) to the corresponding boronic acid was followed by a Suzuki reaction[202] with bromobenzene to give the

biaryl compound (**335**). A suitable indole coupling partner was prepared by acylation of 4-bromo indole (**336**)[232] under Vilsmeier conditions[233] and subsequent protection of the indole nitrogen as the *t*-butyl carbamate (**337**) (**Scheme 34**).

332   **171**   **335**
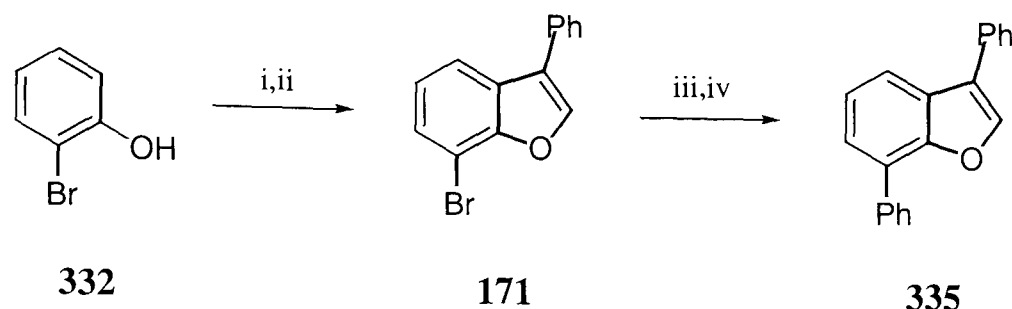
Reagents: i, PhCOCH₂Br, K₂CO₃, acetone, 92%; ii, PPA, Δ, 80%; iii, *n*-BuLi. B(OMe)₃, 80%; iv,

PhBr, Pd(PPh₃)₄, Na₂CO₃, DME, H₂O, 67%.

Scheme 33

336   **337**
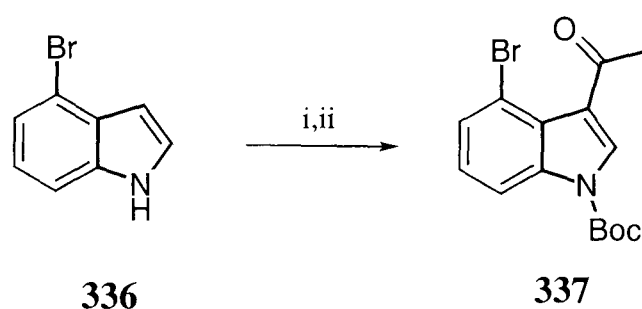
Reagents: i, Me₂NCOCH₃, POCl₃, 70%; ii, (Boc)₂O, DMAP, MeCN, 94%.

Scheme 34

A successful Suzuki reaction[202] between the boronic acid (**338**) and the 4-bromo indole (**337**)[232] gave the biaryl compound (**339**), which underwent diazo-transfer under the conditions developed by Danheiser[234] to give the diazo ketone (**340**) (**Scheme 35**). The attempted rhodium(II)-catalysed decomposition of **340** in the presence of acetonitrile failed to provide any of the desired oxazole (**341**). The major product from this reaction was the 3,4-bridged indole (**342**), the result of a formal intramolecular C-H insertion reaction at the C6 position of the benzofuran ring.[235]
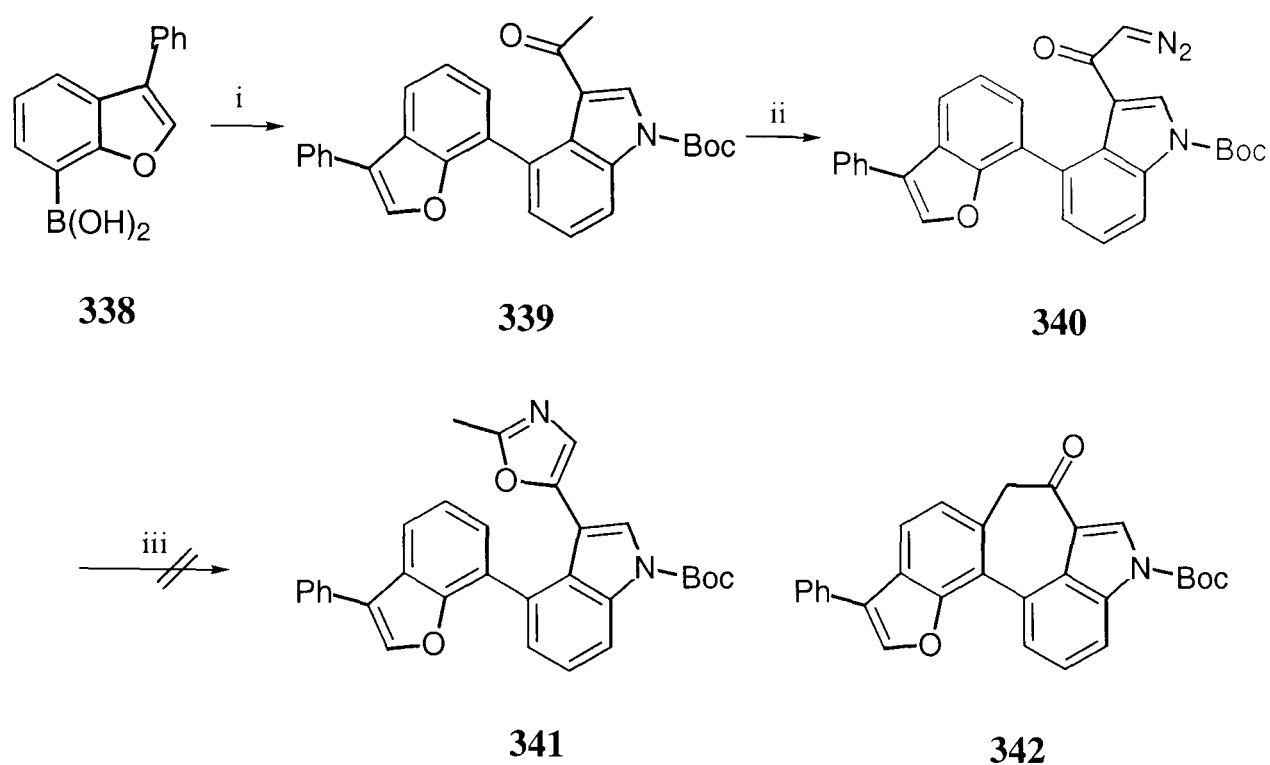
Reagents: i, Pd(PPh$_3$)$_4$, **337**, Na$_2$CO$_3$, DME, H$_2$O, 80%; ii, LiHMDS, CF$_3$CO$_2$CH$_2$CF$_3$, MsN$_3$,

Et$_3$N, 82%; iii, Rh$_2$(NHCOC$_3$F$_7$)$_4$, MeCN, 24%.

Scheme 35

Konopelski *et al* used the copper(I)-promoted reaction of 2,6-dibromophenol (**80**) with dimethyl malonate (**343**) to construct the benzofuranone skeleton (**344**).[173] An intermolecular arylation of the ester (**344**) with the aryllead triacetate reagent (**345**) then gave the benzofuranone (**346**).[236]

344 + **345** → **346**
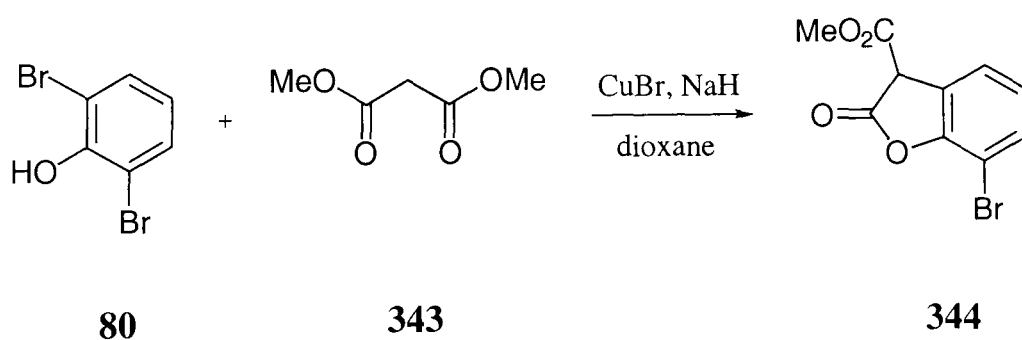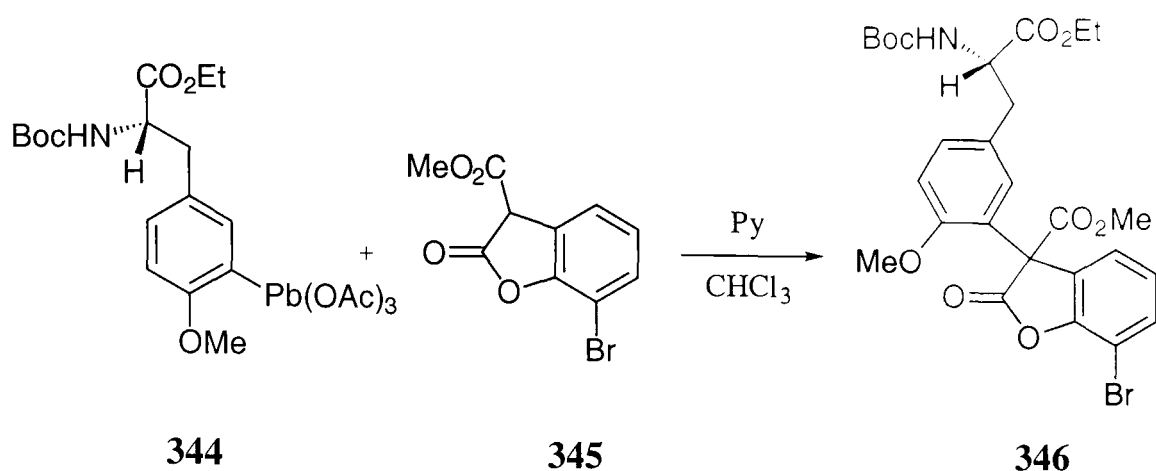
In an effort to prepare a suitable indole coupling partner for an intermolecular Somei reaction[207] to construct the biaryl bond of diazonamide A (**1**), oxindole (**347**) was first converted to the aldehyde (**348**) using a Vilsmeier reaction (**Scheme 36**).[233] Efficient thallation at the C4 position of the indole nucleus was achieved upon exposure of the aldehyde (**348**) to thallium trifluoroacetate.[197a,198a] The organothallium compound (**263**) was then coupled directly to the stannane (**264**) under Stille reaction conditions[204] to provide the biaryl compound (**265**).
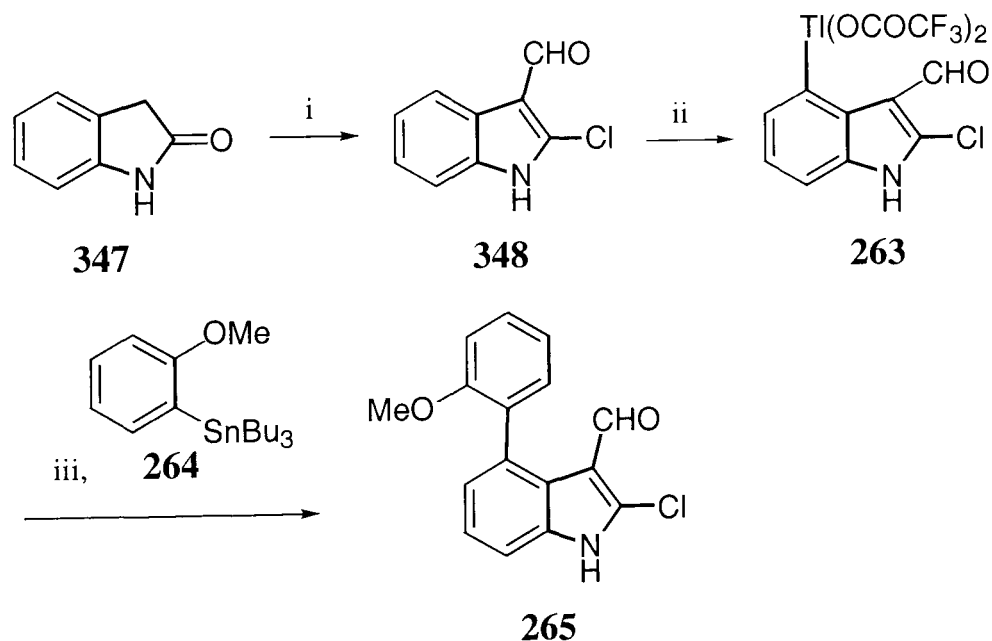
Reagents: i, POCl$_3$, DMF, Py, 73%; ii, TTFA, TFA; iii, Pd(PPh$_3$)$_4$, dioxane, Δ, 21%.

Scheme 36

161

The aldehyde function at the C2 position of the indole ring was elaborated to form the indolyl oxazole fragment of diazonamide A (1). Hence, the carbamate (349) underwent a C2 homologation with ethyl diazoacetate and boron trifluoride diethyl etherate, according to the Roskamp procedure,[237] to give the ketone (350) (**Scheme 37**). Treatment of the ketone (350) with 4-acetamidobenzenesulfonyl azide produced the desired α-diazo-β-keto ester which was converted to the oxazole (188) with acetonitrile in the presence of boron trifluoride diethyl etherate.

349   **350**   **188**
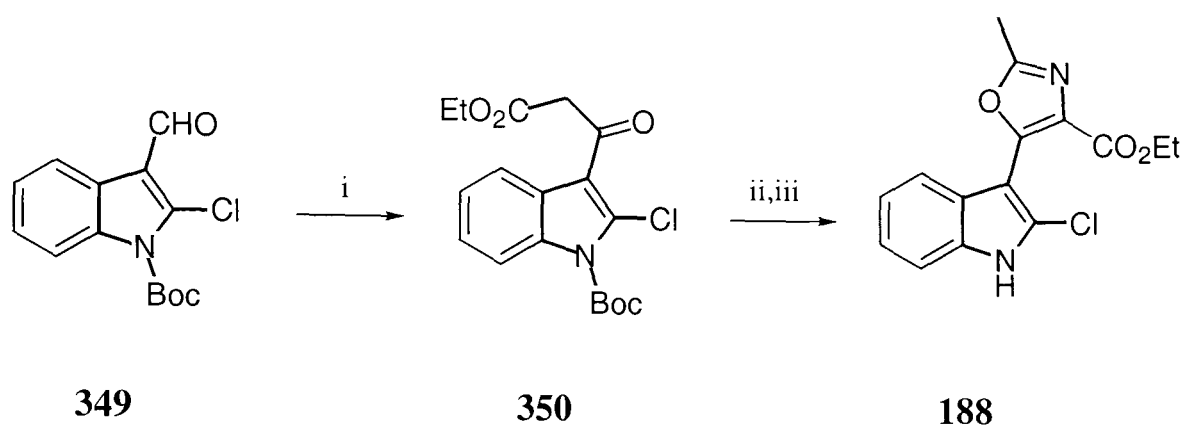
Reagents: i, N$_2$CHCO$_2$Et, BF$_3$.OEt$_2$, CH$_2$Cl$_2$, 85%; ii, CH$_3$CONHC$_6$H$_4$SO$_2$N$_3$, DBU, CH$_2$Cl$_2$,

61%; iii, MeCN, BF$_3$.OEt$_2$, Δ, 64%.

Scheme 37

Wipf *et al* recently published a synthesis of the benzofuranone indolyl oxazole unit of diazonamide A (1).[196] They began by constructing the indolyl oxazole segment (351), starting from the carbamate (222). Removal of the benzyl carbamate protecting group and coupling of the resultant salt with *O*-protected glycolic acid in the presence of diethylphosphoryl cyanide[238] afforded the amide (352) (**Scheme 38**). Cyclodehydration[69] of 352 followed by protection of the indole nitrogen as an ethyl carbamate gave the indolyl oxazole (351). Palladium(0)-catalysed Stille coupling[204] between the indolyl oxazole (351) and the aryl stannane (353), with copper(I) iodide as a co-catalyst,[239] next gave the biaryl species (354). Removal of the methoxy methyl protecting group and acid condensation gave the ester (355) (**Scheme 39**).

162

which underwent an intramolecular Heck reaction[134f] in the presence of (*R*)-BINAP

to give the terminal olefin (**356**) with a poor 14% ee.

222 → **352** → **351**
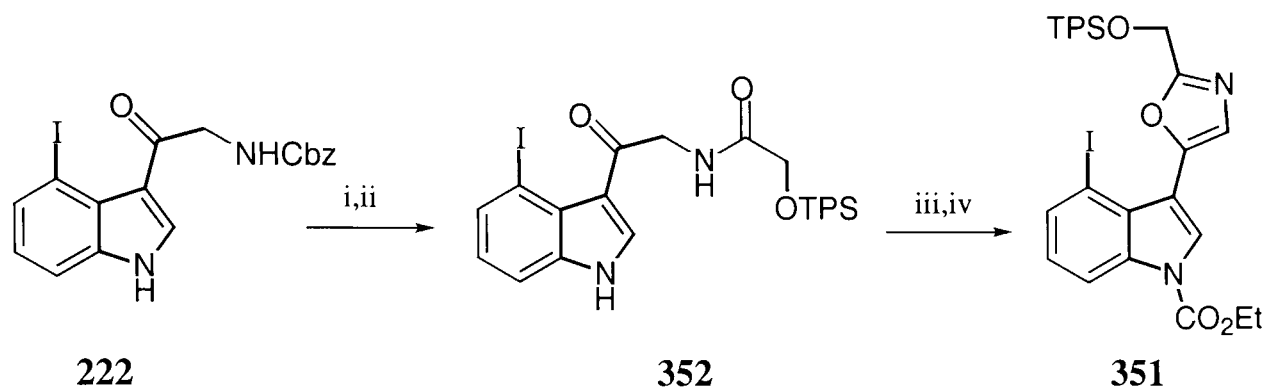
Reagents: i, HBr, AcOH; ii, HO$_2$CCH$_2$OTPS, DEPC, Et$_3$N, THF, 82% (2 steps); iii, PPh$_3$, Cl$_3$CCCl$_3$,

Et$_3$N, CH$_2$Cl$_2$; iv, ClCO$_2$Et, Et$_3$N, DMAP, CH$_2$Cl$_2$, 78% (2 steps).

Scheme 38

351 + **353** →(i) **354**

355 →(iii) **356**
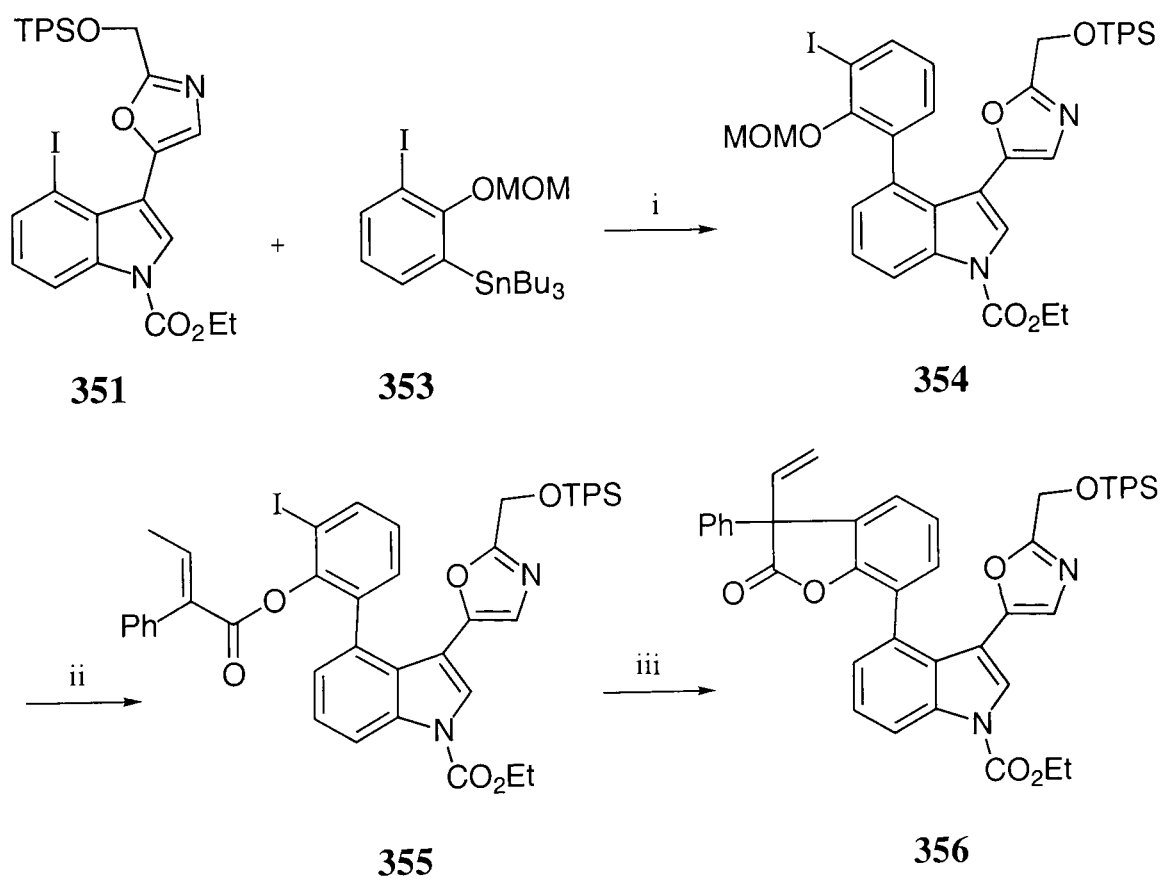
Reagents: i, Pd$_2$(dba)$_3$.CHCl$_3$, CuI, AsPh$_3$, NMP; ii, a) HCl, Et$_2$O, MeOH, CH$_2$Cl$_2$, 39% (2 steps); b)

CH$_3$CHCPhCO$_2$H, EDC, DMAP, CH$_2$Cl$_2$, 96%; iii, Pd$_2$(dba)$_3$, (*R*)-BINAP, Ag$_3$PO$_4$, DMA, Δ. 74%.

Scheme 39

Preliminary studies also showed that chlorination of the indolyl oxazole (351) could be achieved with N-chlorosuccinimide and benzoyl peroxide.

351

NCS, (PhCO)$_2$O$_2$
CCl$_4$
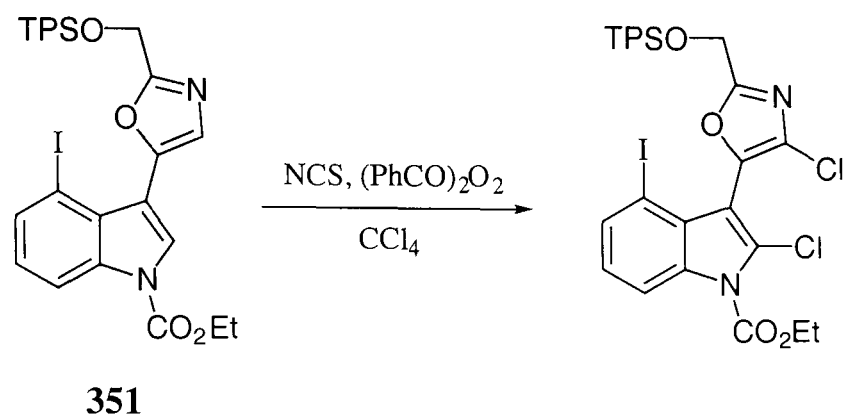
The work of Harran *et al* has concentrated on the synthesis of the northern macrocycle of diazonamide A (1).[230a] In this approach, the N-protected valine residue (357) was treated with aminomalononitrile *p*-toluenesulfonate and EDC to provide the amino oxazole (358), which was converted directly to the bromide (359) (**Scheme 40**).

357   **358**   **359**
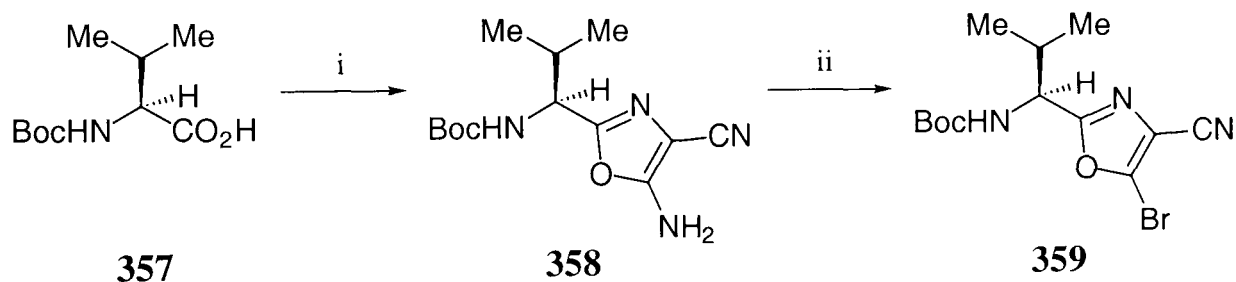
Reagents: i, aminomalononitrile *p*-toluenesulfonate, EDC, Py, 64%; ii, *t*-BuONO, CuBr$_2$, MeCN, 50%.

Scheme 40

The bromide (359) underwent a Stille reaction[204] with the alkenyl stannane (360) to provide the amine (361) after removal of the protecting groups (**Scheme 41**). Peptide coupling between the amine (361) and the tyrosine derivative (362) next gave the iodide (363), which participated in an intramolecular Heck cyclisation[134f] to give the macrocycle (364).
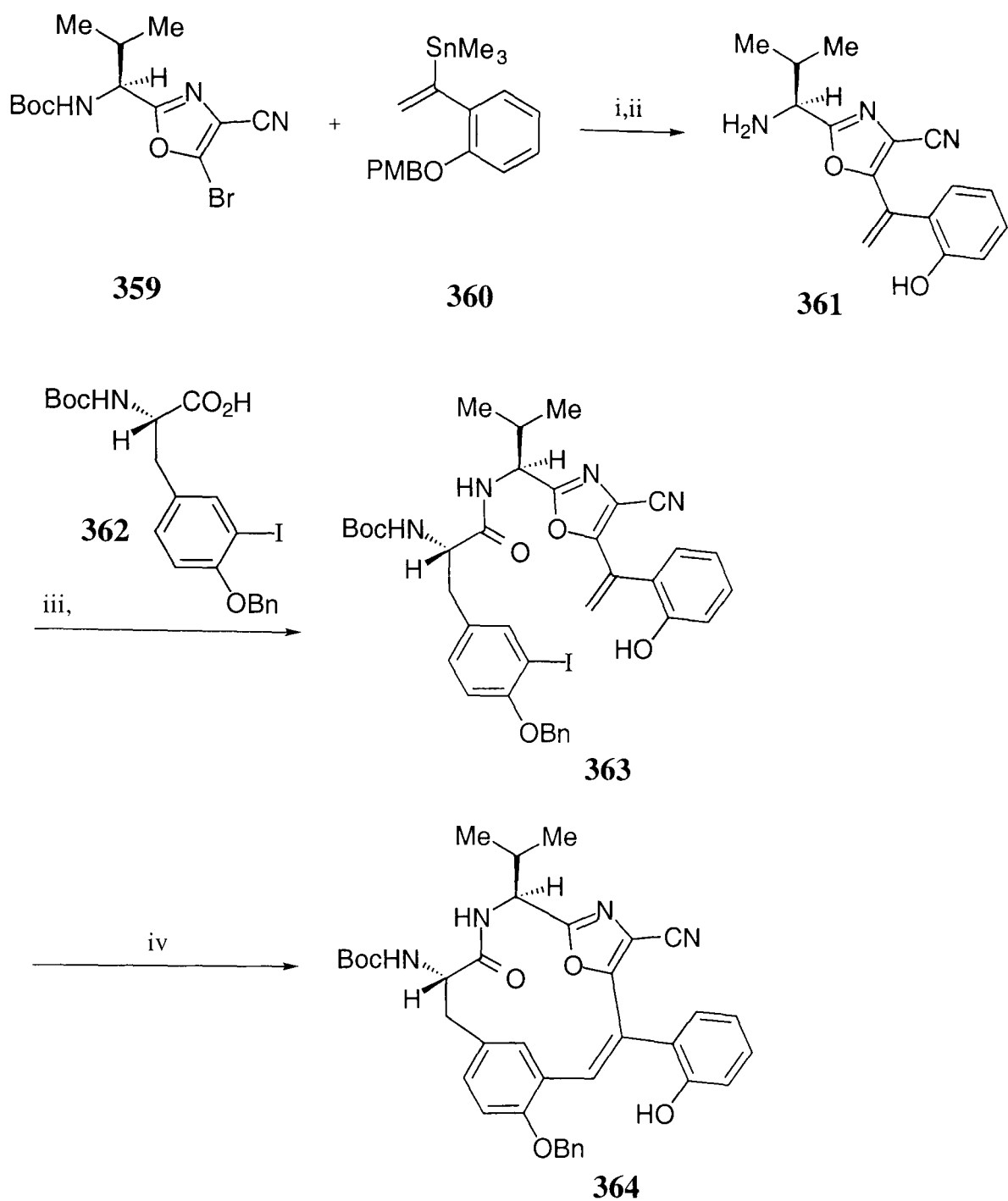
Reagents: i, PdCl$_2$(CH$_3$CN)$_2$, DMF, 94%; ii, BBr$_3$, CH$_2$Cl$_2$, 91%; iii, TBTU, DIPEA, MeCN, 89%;

iv, Pd$_2$(dba)$_3$, Ag$_3$PO$_4$, THF, Δ, 41%.

Scheme 41

165

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