Approaches to the quaternary stereocentre and to the heterocyclic core in diazonamide A using the Heck reaction and related coupling reactions†

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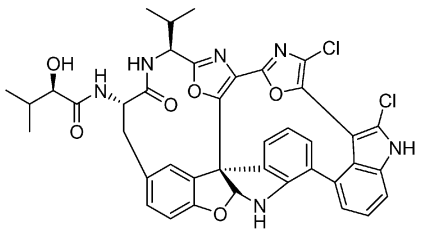
In model studies towards the quaternary centre at the heart of diazonamide A (early structure **2**; revised structure **1**), cyclisations of the alkene-substituted iodoaryls **4**, **13**, **18** and **23**, under Heck reaction conditions, were shown to lead to the corresponding benzodihydrofuran **5**, benzofuranone **14** and the oxindoles **19** and **24** respectively, in 50–80% yield. Further manipulation of the benzodihydrofuran **5** then led to the intermediates **30**, **33** and **39**, which make up parts of the oxazole–indole heterocyclic core in diazonamide A. Attempts to perform a corresponding 13-*exo*-trig Heck cyclisation from the precursor **46a**, prepared from **44** and **45**, leading to **47** were not successful. A similar outcome was obtained during attempts to effect Heck cyclisations from the ester **57** and the related ether **59**. Treatment of the chromene-substituted iodoaryl **62** with $Pd(OAc)_2$, PPh_3 and Ag_2CO_3 led to the spirocycle **64** as a crystalline solid. X-Ray crystal structure analysis established that the quaternary centre in **64** had the same configuration as that present in diazonamide A (**1**).

Introduction

The indole–oxazole-based cyclopeptide diazonamide A (**1**), isolated from the ascidian ("sea squirt") *Diazona angulata*, has been a natural product of intrigue, structural controversy and, above all, synthetic challenge ever since it was reported in the literature in 1991.[1] Diazonamide A displays potent cytotoxicity towards human colon carcinoma and B-16 murine melanoma cells *in vitro*, with $IC_{50} < 15$ ng mL^{-1}.[2] In 1991, diazonamide A was originally assigned as structure **2**.[1] However, almost exactly ten years later, Harran *et al.* synthesised this compound only to find that the assigned structure was incorrect.[3] A reinterpretation of the X-ray and spectroscopic data led to the newly assigned structure **1**.[4] In contemporaneous studies, first Nicolaou,[5] and then Harran[6] and their respective collaborators described elegant solutions to the total synthesis of this intriguing and formidable secondary metabolite.

Since it was first described, diazonamide A has enticed a number of synthetic chemists, challenged by its fascinating and unusual structure.[7] We were one such group, perhaps influenced at the time by our contemporaneous synthetic studies towards other oxazole-based natural products[8] and our interests in applications of transition-metal-mediated sp^2–sp^2 alkene coupling reactions in synthesis.[9] In this paper, we draw together, and describe, some studies we have made to develop a route to the quaternary centre linking the two aryl rings and one of the oxazoles to the aminal-bearing carbon centre in diazonamide A, based specifically on the ubiquitous Heck reaction. We also summarise studies we have made to elaborate the heterocyclic core in diazonamide A using related Pd(0)-mediated alkene coupling reactions.[10]



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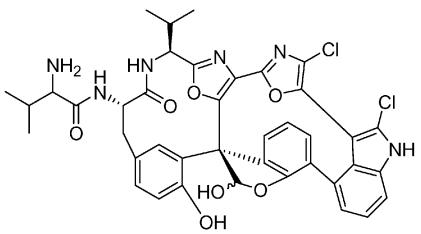

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Results and discussion

Analytical disconnections based on the Heck and related coupling reactions

In other, earlier, studies we developed the scope for cobalt(I)-mediated oxidative carbon-to-carbon bond coupling reactions,[11] and also the Stille reaction, in the synthesis of a range of natural products, *e.g.* thienamycin,[12a] forskolin,[12b] rhizoxin D,[8b] deoxylophotoxin,[12c] anhydropristinamycin,[12d] and amphidinolide A.[12e] We also examined, and compared, the scope for cobalt(I)- and Pd(0)-mediated (*i.e.*, Heck reaction), and the Heck and Stille reactions in sp^2–sp^2 alkene coupling reactions in synthesis, including natural product synthesis.[13] With this background, we felt that a useful approach to both the quaternary centre and to the heterocyclic core in diazonamide A could be developed based on the key

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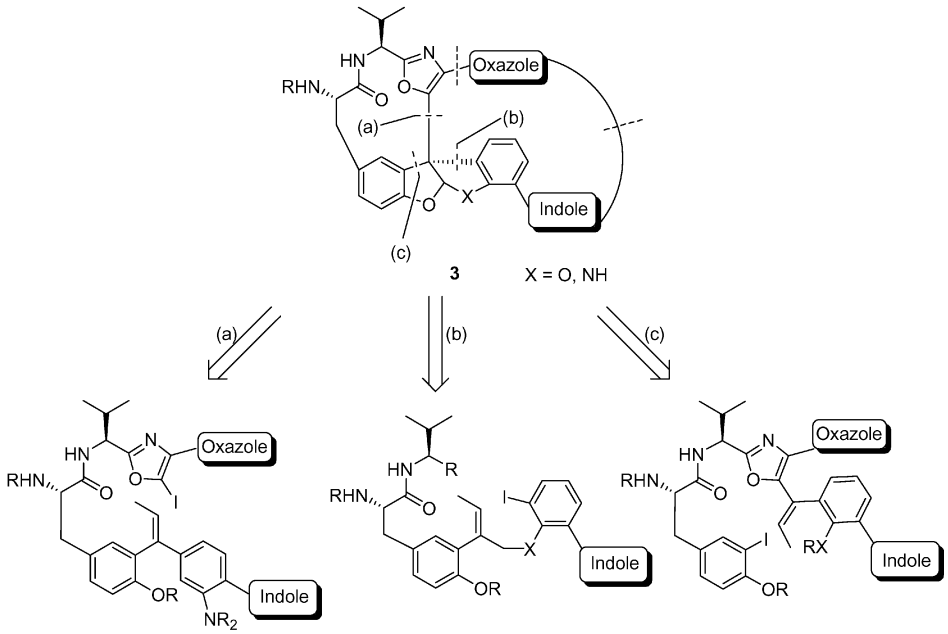
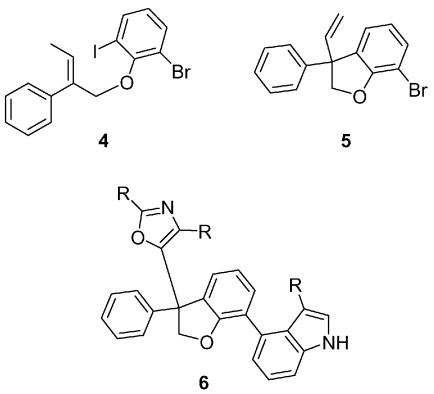


Analytical Disconnections to the Heterocyclic Core **3** in Diazonamide based on the Heck Reaction and related Coupling Reactions

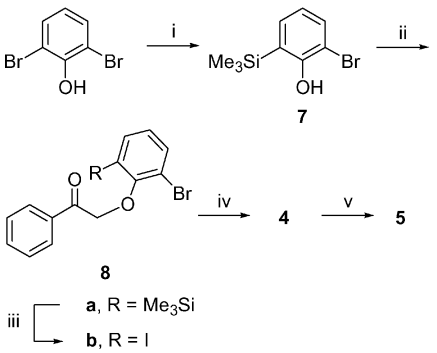
disconnections highlighted on structure **3**.[14] In broad terms, the disconnections focused on the quaternary centre in diazonamide A translate to: (i) two similar Heck reactions, *i.e.*, disconnections (b) and (c) involving aryl rings B or C, and (ii) a Heck, or similar coupling reaction with the oxazole ring A, disconnection (a), and appropriate alkene substrates. The other oxazole/indole/aryl disconnections are more obvious. We have focussed on most of these key disconnections using both structure **2**, the earlier proposed structure for diazonamide A, and the correct structure **1**.

The Pd(0)-mediated coupling reaction of an aryl or vinyl iodide with an alkene, to create a new carbon-to-carbon bond, described by Heck in 1968, has become one of the most revered reactions in contemporary organic synthesis.[15–17] There is no doubt that the pioneering work of Heck[16] laid the platform for other related Pd(0)-mediated coupling reactions, including Stille (organostannanes), Suzuki (organoboronic acids), Hiyama (organosilanes), Kumada (organonickels) and Negishi (organozincs) couplings. The outstanding potential for the Heck reaction is perhaps nowhere better illustrated than its use in an intramolecular fashion in the construction of quaternary carbon centres. Furthermore, this feature of the reaction is nowhere better demonstrated than in the elegant work of Overman and his co-workers,[17] particularly in target natural product synthesis. The regioselectivity of simple, intermolecular Heck reactions is controlled by steric factors, with the new carbon-to-carbon bond being formed at the least-substituted end of the alkene bond.[16] However, in the formation of small rings *via* the Heck reaction, conformational constraints override steric factors and, in the cases of 5-, 6- and 7-ring constructions, *exo*-modes of cyclisation predominate.[15d] With the quaternary centre in diazonamide A as our focus, we have designed a number of substrates and used several Heck reaction conditions to access products from both *exo*- and *endo*-modes of macrocyclisation for further possible elaboration to more advanced precursors to the natural product.



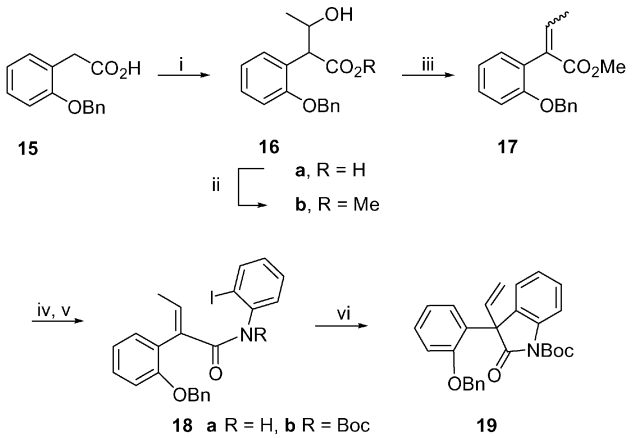
5-*Exo*-trig cyclisations of the substituted iodoaryls 4, 13, 18 and 23, under Heck reaction conditions, leading to to 5, 14, 19 and 24 respectively

In our earliest investigations, with the diazonamide A structure **2** in mind, we examined the intramolecular Heck reaction from the alkene-substituted iodobenzene **4**, *i.e.*, disconnection (b) in structure **3**. We anticipated that this reaction would lead largely to the benzodihydrofuran product **5**, *via* a 5-*exo* mode of cyclisation.[14] Furthermore, we expected to be able to elaborate the alkene unit in **5** to an oxazole, and also carry out sp^2–sp^2 coupling reactions of **5** to 5-substituted indoles, allowing access to an advanced model compound, *i.e.* **6**, towards the diazonamide A structure **2**. We therefore prepared the alkene-substituted iodobenzene **4** from 2,6-dibromophenol in four straightforward steps, shown in Scheme 1. Lithium–bromide exchange in 2,6-dibromophenol, followed by a quench with TMSCl, first gave the arylsilane **7**. Alkylation of **7** with 2-bromoacetophenone in the presence of Na_2CO_3 next gave **8a**, which was then converted into the iodide **8b** using $AgBF_4$ and iodine. Finally, a Wittig reaction between the



Scheme 1 *Reagents and conditions*: i) NaH, $ClSiMe_3$, 0 °C, then *n*BuLi, THF, −78 °C, 99%; ii) $PhCOCH_2Br$, Na_2CO_3, MeCN, 64% (recovered **7**, 27%); iii) $AgBF_4$, I_2, MeOH, 95%; iv) *n*BuLi, $EtP^+Ph_3\ Br^-$, then **8b**, 98% 3 : 1 *E*/*Z*; v) $Pd(OAc)_2$, PPh_3, Ag_2CO_3, 80 °C, 4 days, 72%.

ketone **8b** and the ylide, derived from ethyltriphenylphosphonium bromide, gave the alkene **4** as a 3 : 1 mixture of *Z*- and *E*-isomers. When the iodoalkene **4** was treated with $Pd(OAc)_2$ in DMF at 80 °C, in the presence of Ag_2CO_3 and PPh_3, for 4 days (*i.e.* under Heck conditions)[15] a facile 5-*exo*-trig cyclisation ensued, producing the expected benzodihydrofuran **5** in 72% yield. In a similar manner, the more elaborate tyrosine-substituted substrate **13**, derived from the vinylstannane **10** and the aryl iodide **11** *via* the carboxylic acid **12b** (Scheme 2), underwent an intramolecular 5-*exo*-trig Heck cyclisation, using $Pd_2(dba)_3$ and Ag_3PO_4, leading to the corresponding benzofuranone **14**, albeit in a more modest yield of 49%. Finally, with the correct diazonamide A structure **1** in mind, we showed that the amide analogues **18** and **23** of the ester **13** underwent similar Heck cyclisations leading to the corresponding oxindoles **19** and **24** respectively, in reasonable yields. The amide **18** was prepared from 2-benzyloxyphenylacetic acid **15** following deprotonation and alkylation with acetaldehyde to **16a**, esterification and dehydration to **17** and, finally, coupling with 2-iodoaniline (Scheme 3). The chiral oxazolidine anilide **23** was elaborated from the aryl iodide **21**, prepared from the substituted tyrosine **20b**, following a Stille coupling reaction with methyl *E*-2-(trimethylstannyl)but-2-enoate, leading to **22**, and an amide bond forming reaction with 2-iodoaniline in the presence of trimethylaluminium (Scheme 4). Interestingly, the free amine



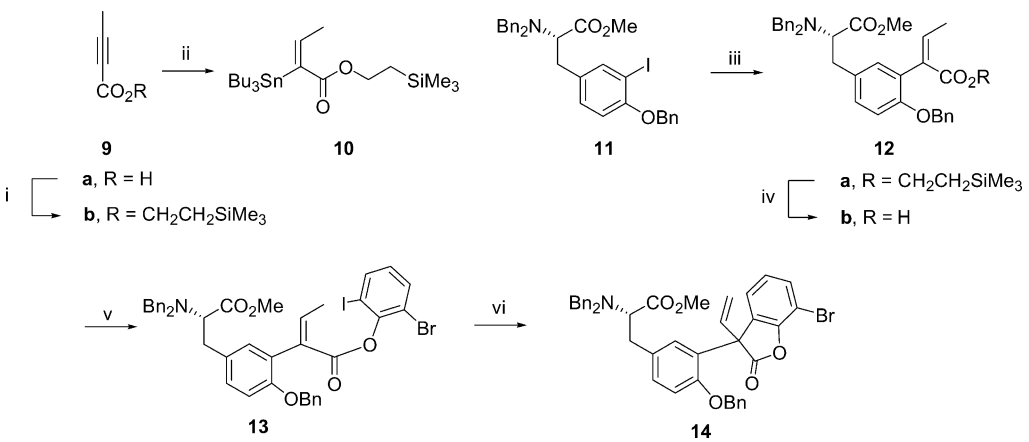
Scheme 3 *Reagents and conditions*: i) LDA, THF, −78 °C, then CH_3CHO, 92%; ii) CH_3COCl, MeOH, 84%; iii) $MeSO_2Cl$, DBU, 97% 2 : 1 *E*/*Z*; iv) $AlMe_3$, 2-iodoaniline, 0–40 °C, 70%; v) $(Boc)_2O$, DMAP, *i*Pr_2NEt, 83%; vi) $Pd_2(dba)_3$, PPh_3, Ag_3PO_4, DMA, 90 °C, 66%.

18a corresponding to **18b** failed to undergo a Heck cyclisation, and only one diastereomer of the oxindole **24** was produced in the cyclisation of **23** (76%).

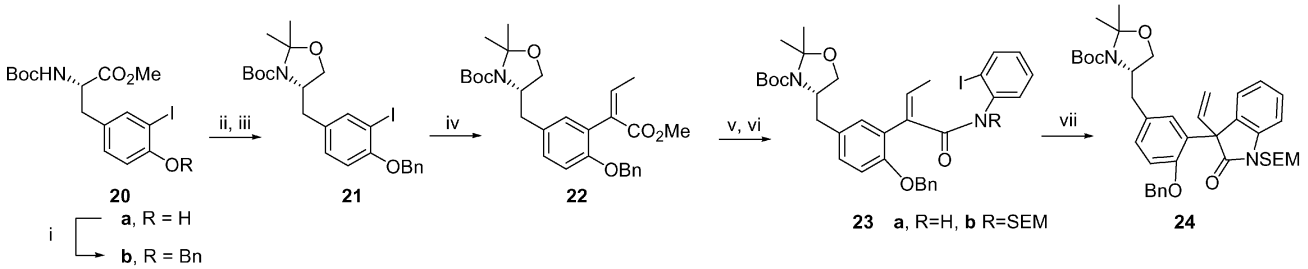
Although we were not able to achieve an enantioselective Heck cyclisation of the substrate **4**,[14] we did separate the enantiomers of the racemic acid **25b**, produced after ozonisation of the alkene **5**. Thus, the racemic acid was converted into a mixture of the corresponding diastereoisomeric α-methylbenzylamides **26**, one of which was obtained as colourless crystals (Scheme 5). X-Ray crystallographic analysis established that the quaternary centre in the more polar, crystalline benzylamide (Fig. 1) had the opposite configuration to that present in diazonamide A. Hydrolysis of the less polar benzylamide **26** gave the *S*-carboxylic acid **27**, having the same configuration present in natural diazonamide A (**1**).

Elaboration of 5 to the heterocyclic units 30, 33 and 39 in diazonamide A

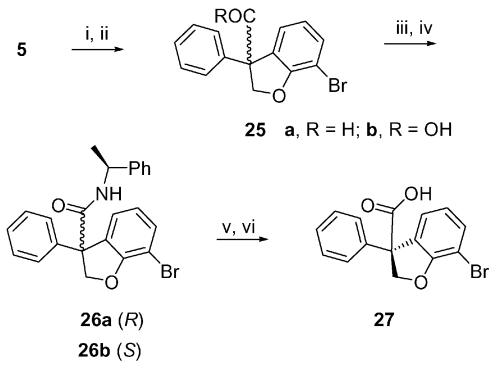
Having secured a satisfactory synthesis of the substituted benzodihydrofuran **5**, the feasibility of converting it into parts of the heterocyclic core, *i.e.* **6**, in the diazonamide A structure **2** was then explored. Thus, we first examined the conversion of **5**



Scheme 2 *Reagents and conditions*: i) $Me_3SiCH_2CH_2OH$, DCC, DMAP; ii) $Pd(OAc)_2$, PPh_3, Bu_3SnH, 85% (over 2 steps); iii) **10**, Ph_3As, CuI, NMP, Pd/C, 55%; iv) TBAF, THF, 0–5 °C, 63%; v) EDCI, then 2-bromo-6-iodophenol, DMAP, 60%; vi) $Pd_2(dba)_3$, dppp, Ag_3PO_4, Bu_4NBr, 90–95 °C, 49%.



Scheme 4 *Reagents and conditions*: i) K_2CO_3, $PhCH_2Br$, DMF, 90%; ii) $LiBH_4$, THF, 93%; iii) $BF_3{\cdot}OEt_2$, $Me_2C(OMe)_2$, 90%; iv) Ph_3As, $Pd_2(dba)_3$, CuI, *E*-MeCH=C($SnBu_3$)CO_2Me, NMP, 76%; v) $AlMe_3$, 2-iodoaniline, CH_2Cl_2, 0–40 °C, 74%; vi) NaHMDS, $Me_3SiCH_2CH_2OCH_2Cl$, THF, 90%; vii) $Pd_2(dba)_3$, PPh_3, Ag_3PO_4, DMA, 90 °C, 77%.



Scheme 5 *Reagents and conditions*: i) O_3, PPh_3, 84%; ii) $NaClO_2$, K_2HPO_4, $Me_2C{=}CHCH_3$, 85%; iii) $SOCl_2$, Δ, 93%; iv) *S*-(−)-α-methylbenzylamine, Et_3N, chromatography, 92% (*S* : *R*, 1 : 1); v) **26b**, *p*TSA, toluene, Δ, 83%; vi) aq. KOH, 84% (70% over two steps).

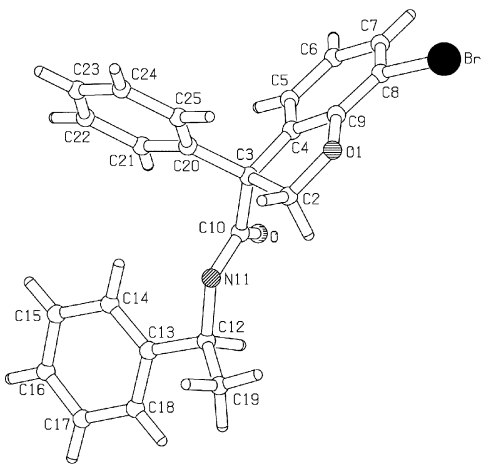
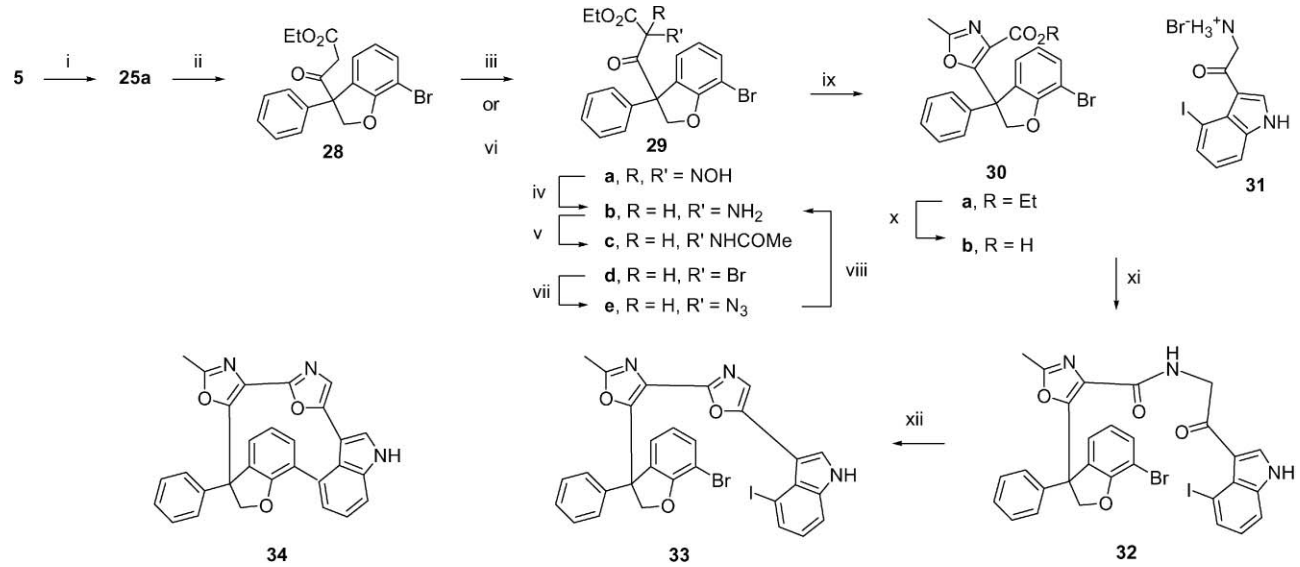


Fig. 1 X-Ray crystal structure of the α-methylbenzylamide **26b**.

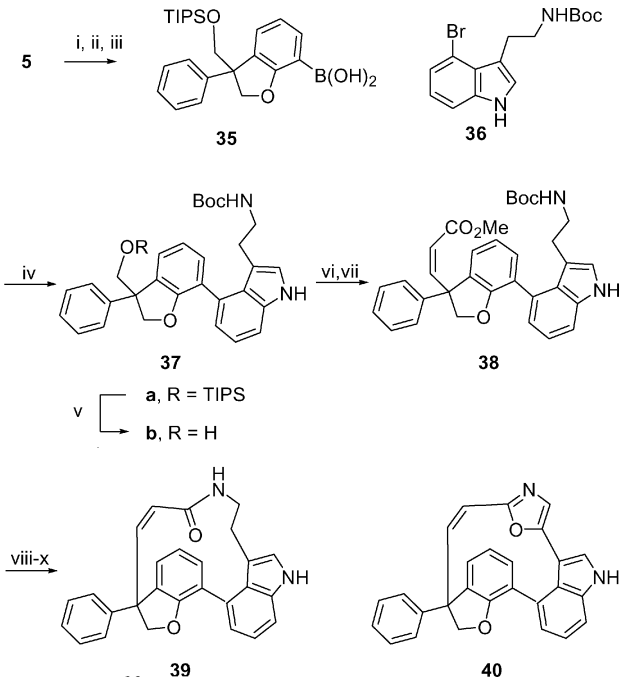
into the oxazole-substituted benzodihydrofuran **30** as a prelude to preparing the macrocyclic bis-oxazole indole **34**. Oxidative cleavage of **5** first gave the aldehyde **25a** which, on treatment with ethyl diazoacetate in the presence of $ZrCl_4$[18] at 0 °C, was converted into the corresponding β-keto ester **28** in 84% yield. In an alternative sequence, the β-keto ester **28** was produced from the carboxylic acid **25b** following reaction of the corresponding imidazolide with magnesium ethoxycarboxylacetate.[19] The β-keto ester **28** was then converted into the oxime **29a** which, on reduction with zinc dust in acetic acid, produced the α-amino β-keto ester derivative **29b**, the precursor to the acetamide **29c**. The same amide **29c** could also be produced from **28**, *via* a more lengthy procedure following: i) deprotonation and bromination, leading to **29d**, followed by ii) azide **29e** formation and reduction to the amine **29b**, using triphenylphosphine, and finally iii) acylation of **29b**, using acetyl chloride. Cyclodehydration of **29c**, using Ph_3P–I_2–NEt_3,[20] then gave the oxazole benzodihydrofuran **30a** in 89% yield. Hydrolysis of **30a** to the corresponding carboxylic acid **30b**, followed by acid chloride formation and reaction with the substituted 5-iodoindole **31**, gave the keto amide **32**. The keto amide **32** was then converted into the benzodihydrofuran–indole-substituted bis-oxazole intermediate **33** by straightforward treatment with Et_3N–Ph_3P in hexachloroethane (Scheme 6). Disappointingly, in spite of a number of attempts we were not able to achieve the intramolecular Ullmann coupling of **33** to the aromatic core **34** of diazonamide A under a range of conditions, *e.g.* Stille, nickel catalysis. Either the starting material or the product of reduction of the carbon-to-iodine bond in the indole ring of **33** was recovered. We therefore turned to the use of the corresponding Suzuki reaction, and found that the coupling reaction of the boronic acid **35**, derived from **5**, with the substituted 5-bromoindole **36**,[21] gave a satisfactory 80% yield of the benzodihydrofuran–indole **37a** (Scheme 7). Cleavage of the TIPS ether group in **37a**, followed by oxidation of the resulting alcohol then gave the corresponding aldehyde. A Still–Gennari olefination[22] reaction between this aldehyde and bis(2,2,2-trifluoroethylmethoxycarbonylmethyl)phosphonate then produced the *Z*-alkenoate **38**. Hydrolysis of the ester group and deprotection of the Boc group in **38**, followed by macrolactamisation of the resulting amino acid in the presence of DPPA–iPr$_2$NEt gave the macrolactam **39**. Frustratingly, however, we were not able to oxidise the benzylic methylene unit in **39** to the corresponding keto amide precursor *en route* to the oxazole–indole **40**.

Examination of the 13-*exo*-trig Heck cyclisation of 46a to the macrolactam 47

Encouraged by the outcome of the aforementioned 5-*exo*-trig Heck cyclisations, leading to the products **5**, **14**, **19** and **24**, we next decided to examine the more ambitious Heck reaction from the precursor **46a** *i.e.* disconnection (c) on structure **3**. In contemporaneous work, Harran *et al.*[23] had studied the Heck cyclisation of the lower homologue **46b** and showed that it gave the product **48b**, resulting from a 13-*endo*-trig cyclisation. However, we felt that the presence of the additional methyl group on the alkene bond in **46a**, in combination with the electronically controlled Heck reaction conditions developed by Cabri *et al.*[24]



Scheme 6 *Reagents and conditions*: i) O_3, PPh_3, 84%; ii) EtO_2CCHN_2, $ZrCl_4$, 84%; iii) $NaNO_2$, HOAc, **28** → **29a**, 94%; iv) Zn, HOAc; v) AcCl, Et_3N, 0 °C → rt, **29a** → **29b** → **29c**, 71%; vi) NaH, Br_2, **28** → **29d**, 99%; vii) NaN_3, DMF, 0 °C, 79%; viii) PPh_3, THF, 75%; ix) Et_3N, PPh_3, I_2, 86%; x) LiOH, MeOH, H_2O, 98%; xi) $(COCl)_2$, then **31**, 60%; xii) Et_3N, PPh_3, 81%.

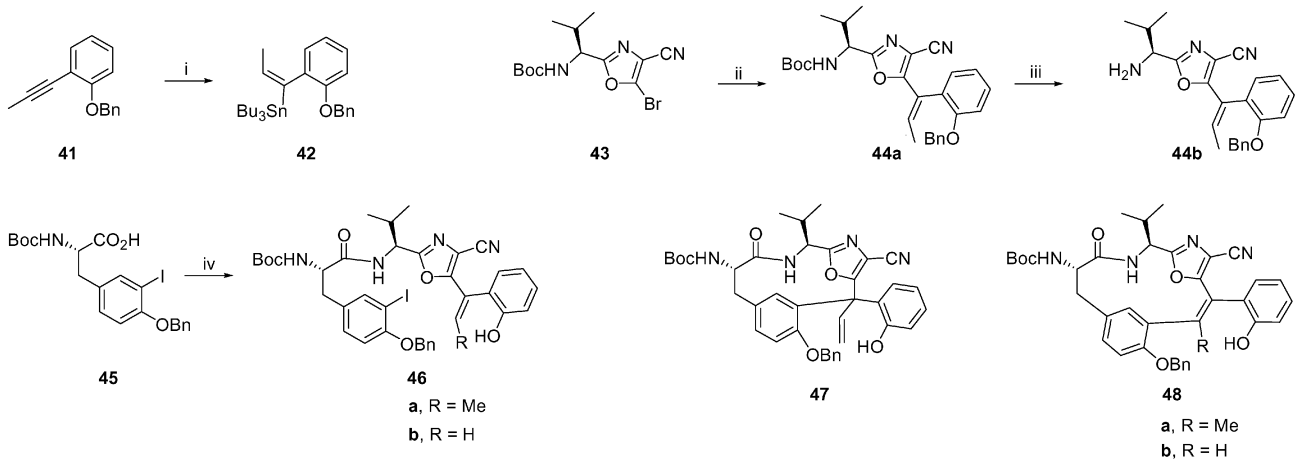


Scheme 7 *Reagents and conditions*: i) O_3, CH_2Cl_2, −78 °C, then O_2–MeOH, then $NaBH_4$, 61%; ii) *i*Pr_3SiCl, Im, DMF, 83%; iii) BuLi, $B(OMe)_3$, THF, 99%; iv) $Pd(PPh_3)_4$, K_2CO_3, **36**, 80%; v) TBAF, THF, rt → 60 °C, 91%; vi) $PySO_3$, Et_3N, DMSO, 82%; vii) $MeO_2CCH_2PO(OCH_2CF_3)_2$, KHMDS, 18-crown-6, THF, −78 °C, 96%; viii) LiOH, DME; ix) TFA, CH_2Cl_2; x) DPPA, *i*Pr_2NEt, CH_2Cl_2, 49% (over 3 steps).

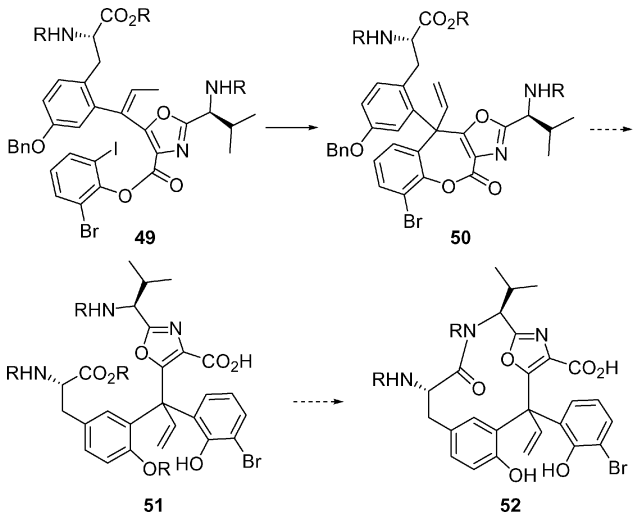
(*i.e.* Pd(dppp), TlOAc, DMF, 80 °C), might promote cyclisation at the more electron-deficient end of the alkene bond in **46a**, leading to the product of *exo*-cyclisation, *i.e.* **47**. We therefore prepared the substrate **46a**, as shown in Scheme 8; this involved an initial Stille coupling reaction between the vinylstannane **42** and the bromooxazole **43**, leading to **44a**, followed by a coupling reaction of the amine **44b** with the carboxylic acid **45**, as the key steps.[23] Treatment of **46a** under the conditions of Cabri *et al.*,[24] however, failed to produce any product resulting from an intramolecular Heck reaction. We tried using a range of alternative conditions and cocktails, including the use of silver phosphate and carbonate, the addition of sodium formate and different temperatures, but all to no avail. However, we were able to repeat the Heck cyclisation of **46b**, described by Harran *et al.*,[23] and obtained the same result, *i.e.* the formation of the product **48b** from a 13-*endo*-trig cyclisation. It therefore seems likely that the additional steric requirements of the bidentate ligand, used in the Cabri conditions, and the additional methyl substitution on the alkene bond in the substrate conspire to inhibit a Heck cyclisation from **46a** in either the 12-*exo* or the 13-*endo* modes.

Synthesis of the tethered Heck reaction precursors 57 and 59, and the chromene 63. Cyclisation of 63 to the spirocycle 64 under Heck conditions

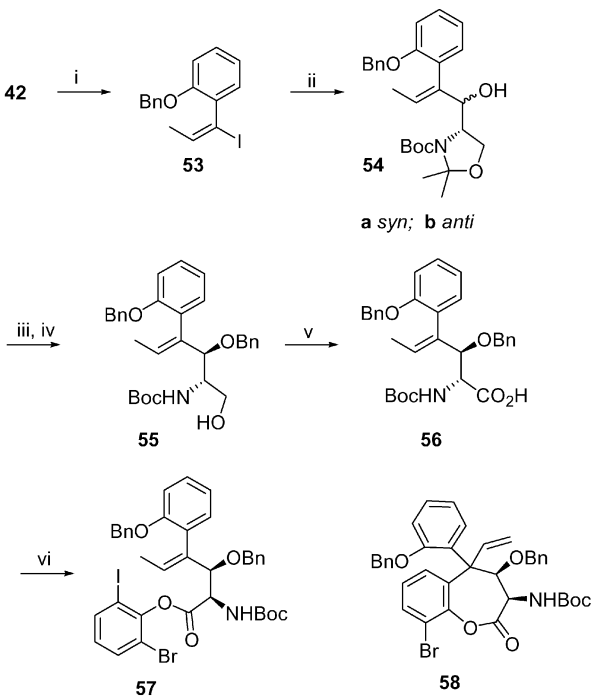
After the disappointment of not being able to achieve an intramolecular Heck cyclisation from the substrate **46a**, we decided to examine corresponding Heck reactions from "tethered" substrates akin to **49**. The idea behind this proposal was that if we could achieve the cyclisation of **49** to **50**, with simultaneous introduction of the correct stereochemistry at the newly introduced quaternary carbon centre, following elaboration *via* **51** we would have a reasonably advanced intermediate, *viz.* **52**, *cf.* **47**, *en route* to diazonamide A. However, before embarking on such an ambitious program, we investigated the feasibility of the overall proposal using the less substituted precursor **57**, synthesised from the vinylstannane **42**[25] as shown in Scheme 9. Thus, conversion of **42** into the vinyl iodide **53**, followed by lithium–iodine exchange, transmetallation with $MgBr_2$[26] and finally reaction with Garner's aldehyde[27] gave the secondary alcohol **54** as a mixture of *syn* and *anti*-diastereoisomers.



Scheme 8 *Reagents and conditions*: i) $(PPh_3)_2PdCl_2$, Bu_3SnH, 73%; ii) **42**, $PdCl_2(MeCN)_2$, DMF, 25 °C, 81%; iii) BBr_3, CH_2Cl_2, −78 °C, 79%; iv) **44b**, DIPEA, TBTU, DMF, 0 °C, 60%.



The diastereomers were separated by chromatography, and the X-ray crystal structure confirmed the *syn*-stereochemistry assigned to **54a** (Fig. 2). Benzylation of the *anti*-diastereomer **54b** followed by cleavage of the oxazolidine in the product, leading to **55**, and functional group manipulation gave the carboxylic acid **56**. Finally, a straightforward esterification of **56** with 2-bromo-6-iodophenol gave the substrate **57** for the attempted Heck cyclisation to **58**. Frustratingly, all attempts to effect a 7-*exo*-trig Heck cyclisation from the alkene **57** met with failure. A similar outcome was obtained with the analogous 'ether'-tethered precursors **59**, produced from the *syn* and *anti*-alcohols **54a** and **54b**.



Scheme 9 *Reagents and conditions*: i) I_2, THF, 0 °C, 81%; ii) *n*BuLi, $MgBr_2$, −78 °C, Garner's aldehyde, 74%; iii) NaH, BnBr, THF, rt → 65 °C, 92%; iv) BF_3–HOAc, 98%; v) $NaHCO_3$, periodinane, then $NaClO_2$, KH_2PO_4, *t*BuOH, 39% over 2 steps; vi) EDC, DMAP, 2-iodo-6-bromophenol, 55%.

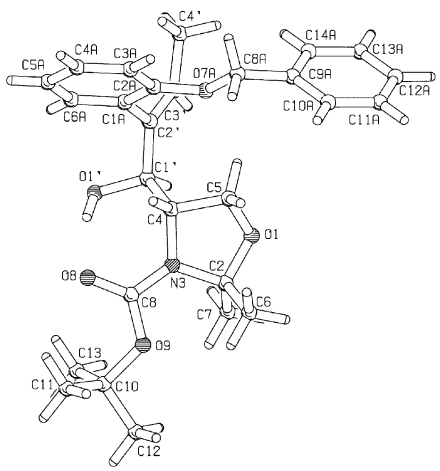


Fig. 2 X-Ray crystal structure of the secondary alcohol **54a**.

Somewhat perplexed by the lack of reactivity of the substrates **57** and **59** towards Heck cyclisations, we examined the X-ray crystal

structures of the *syn*-precursors **54a** and **59a** and, to our surprise, found that the alkene units and the aryl rings to which they are attached are essentially orthogonal; presumably due to the severe steric interactions involving the *ortho* benzyl ether substituent and the methyl groups of the propenyl units (see Fig. 2 and Fig. 3). This structural feature could preclude coordination of the metallated aryl rings in both **57** and **59** to their respective alkene bonds, thereby preventing any attempted Heck reactions with these substrates. In order to add credence to this supposition, we decided to then examine the corresponding Heck reactions with the chromene substrates **62** and **63**, which are devoid of any of the steric interactions present in the benzyl ether-aryl propenyl compounds **57** and **59**.

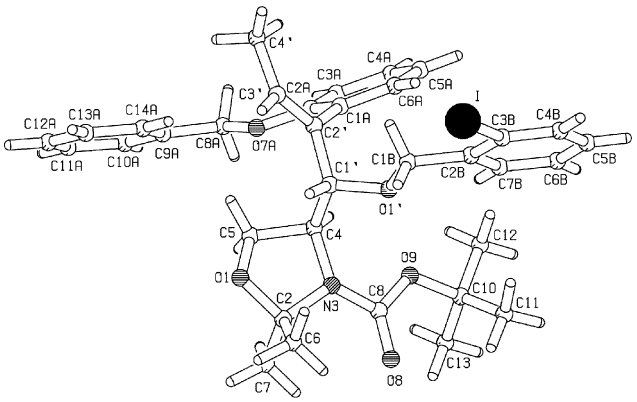
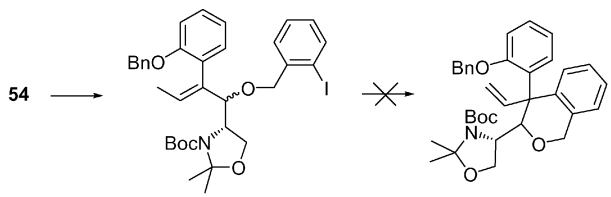


Fig. 3 X-Ray crystal structure of the iodide **59a**.



59 **a** *syn*; **b** *anti*

The substituted chromenes **62** and **63** were prepared starting from the known 4-bromo-2*H*-chromene **60**[28] using the method employed in the synthesis of the analogous benzyl ethers **59** (Scheme 10). Much to our satisfaction, when the *syn*-diastereoisomer **62** was treated with $Pd(OAc)_2$, PPh_3 and Ag_2CO_3 in tetrahydrofuran at 60 °C for 2 days, a single product **64**, resulting from a 6-*exo*-trig cyclisation, was obtained in 42% yield. The product was obtained as a crystalline solid whose X-ray structure (Fig. 4) established that the quaternary centre had the same absolute configuration as the same centre in natural diazonamide A. Interestingly, when the same Heck reaction was carried out in *N*,*N*-dimethylacetamide at higher temperature (85–90 °C), a small amount (~8%) of the corresponding isomeric ether **65**, resulting from a competing 7-*endo*-trig cyclisation, was produced concurrently. A similar outcome was obtained when the *anti*-diastereoisomer **63**, corresponding to **62**, was subjected to Heck cyclisation *i.e.*, the major product was the spiro-chromene **66**.

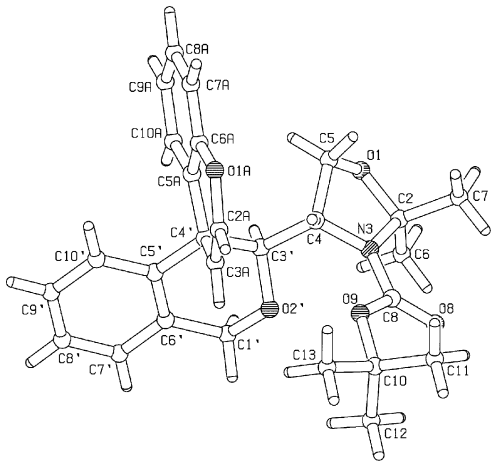
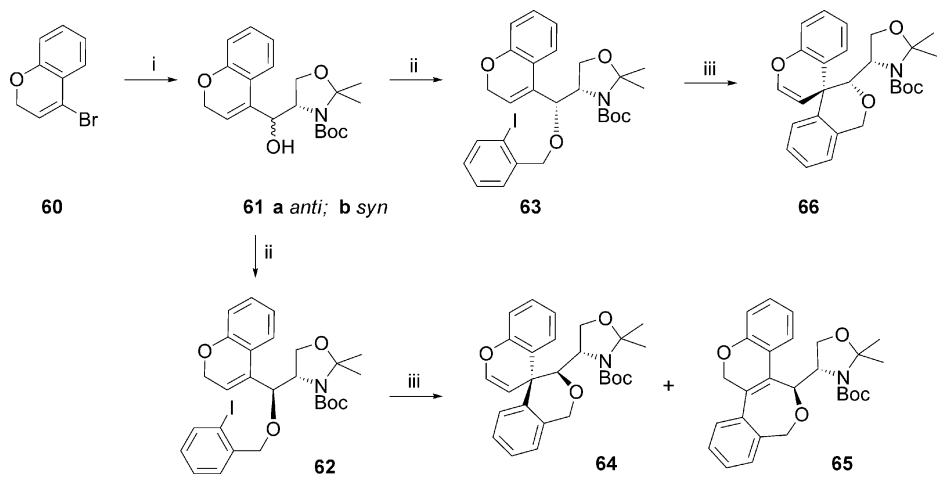


Fig. 4 X-Ray crystal structure of the spirocyclic system **64**.

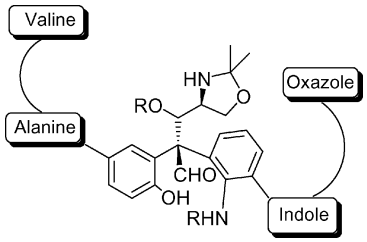
Having eventually achieved a route to the quaternary centre, and investigated routes to the heterocyclic core, *viz.* **6** in diazonamide A (**1**), using the Heck and related Pd(0)-mediated coupling reactions, the spirocyclic system **64** remained a daunting distance from the ultimate synthetic target. Thus, significant manipulations of the structure **64**, including oxidative cleavage of the vinyl ether



60 **61** **a** *anti*; **b** *syn* **63** **66** **62** **64** **65**

Scheme 10 *Reagents and conditions*: i) *n*BuLi, $MgBr_2$, −78 °C, Garner's aldehyde, 65%; ii) NaHMDS, 0 °C, then 2-iodobenzyl bromide, Bu_4NI, 53%; iii) PPh_3, Ag_2CO_3, $Pd(OAc)_2$, 41–54%.

moiety, and insertion of nitrogen at the benzylic ether carbon, would be required to approach a precursor akin to **67**, for further extensive development. Although some of these synthetic conversions were investigated,[29] the re-assignment of the structure of diazonamide A (**2**) mid-way through our studies, together with the decisive synthetic investigations of Harran and Nicolaou and their respective collaborators discouraged us from further pursuing our own particular approach to **2** based broadly on the Heck and related reactions. We therefore abandoned our studies towards a synthesis of diazonamide A at this point.



67

Summary

In summary, our studies of the scope for the Heck and related coupling reactions in forming the quaternary stereocentre and the heterocyclic core in diazonamide A have allowed access to compounds **5**, **14**, **19**, **24**, **64** [*cf.* disconnection (b) on structure **3**] and also to compounds **30**, **33** and **39**. Unfortunately, we were not able to realise a 13-*exo*-trig Heck cyclisation of **46a** to the macrolactam **47** [*cf.* disconnection (c) on structure **3**]. We did not examine cross-coupling reactions involving 2-substituted oxazoles in this particular study [*cf.* disconnection (a) on structure **3**]. Nevertheless, there is ample precedent for this type of chemistry, using a range of substituted oxazoles, in the literature,[30] some of which we have exploited in other research programs in our laboratory involving polyoxazole-based natural products. These other studies will be presented at a later date.

Experimental

General details

All melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Optical rotations were recorded in spectroscopic grade chloroform on a Jasco DIP-370 polarimeter, and $[\alpha]_D$ values were recorded in units of 10^{-1} deg cm^2 g^{-1}. Infrared spectra were obtained on a Perkin–Elmer 1600 series FT-IR instrument as dilute solutions in spectroscopic grade chloroform. Proton NMR spectra were recorded on a Bruker DPX 360 (360 MHz) 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 solvent peaks, and the multiplicity of each signal is designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; sx, sextet; br, broad; m, multiplet; app., apparent. All coupling constants are quoted in Hertz. Carbon-13 NMR spectra were recorded using a Bruker DPX 360 (90 MHz) instrument as dilute solutions in deuterochloroform, unless otherwise stated. Chemical shifts are reported relative to residual solvent peaks using a broad-band decoupled mode, and the multiplicities were determined using a DEPT sequence. When required, ^{1}H–^{1}H COSY spectra were recorded on a Bruker DPX 360 (360 MHz) instrument and standard Bruker software with no modifications. ^{1}H–^{13}C HMQC/HMBC and NOE spectra were recorded on a Bruker AV 400 (400 MHz) spectrometer. Mass spectra were recorded on either a VG Autospec, an MM-701CF, a VG Micromass 7070E or a Micromass LCT spectrometer, using electron ionisation (EI), electrospray (ESI) or fast atom bombardment (FAB) techniques. Microanalytical data were obtained on a Perkin-Elmer 240B elemental analyser. All crystals for crystallography were mounted on dual-stage glass fibres using RS3000 perfluoropolyether oil, and flash-frozen in the cold stream of the diffractometer's low-temperature device.

Flash chromatography was performed using Merck silica gel 60 as the stationary phase and the solvents employed were of analytical grade. "Petrol" used in chromatography refers to light petroleum, bp 60–80 °C. All reactions were monitored by thin layer chromatography using aluminium plates precoated with Merck silica gel 60 F_{254}, which were visualised with ultraviolet light and then with either acidic alcoholic vanillin solution, basic potassium permanganate solution, or acidic anisaldehyde solution.

Dry organic solvents were routinely stored under a nitrogen atmosphere and/or dried over sodium wire. Benzene and dichloromethane were distilled from calcium hydride. Dry tetrahydrofuran was obtained from a solvent drying tower. Other organic solvents and reagent were purified by the accepted literature procedures. Solvent was removed *in vacuo* using a Büchi rotary evaporator. Where necessary, reactions requiring anhydrous conditions were performed in dry solvents in flame-dried or oven-dried apparatus under a dry nitrogen atmosphere.

***E*- and *Z*-1-(2-Bromo-6-iodophenoxy)-2-phenylbut-2-ene (4).** A solution of *n*-butyllithium (1.6 M) in hexanes (56 mL, 90.0 mmol) was added dropwise over 20 min to a stirred suspension of ethyltriphenylphosphonium bromide (33.5 g, 90.0 mmol) in tetrahydrofuran (600 mL) at 0 °C under a nitrogen atmosphere; the mixture was then stirred at 0 °C for 20 min. A solution of the ketone **8b** (31.4 g, 75.0 mmol) in tetrahydrofuran (600 mL) was added dropwise over 15 min, and the mixture was then stirred at room temperature for 3 h. The mixture was quenched with saturated aqueous ammonium chloride (500 mL) and water (300 mL) and then extracted with diethyl ether (3 × 500 mL). The combined organic extracts were dried and concentrated *in vacuo.* Diethyl ether (200 mL) was added to the residue and the solution was then cooled to 0 °C. Pentane (400 mL) was added to the rapidly stirred solution, and the mixture was kept at 0 °C for 30 min. The precipitated solid was removed by filtration, and the filtrate was concentrated *in vacuo.* The residue was purified by chromatography, eluting with 5% ethyl acetate in petroleum ether, to give a 3 : 1 mixture of *Z*- and *E*-isomers of the *olefin* (31.5 g, 98%) as an oil; ν_{max} ($CHCl_3$)/cm^{-1} 1600, 1551; δ_H (270 MHz, $CDCl_3$) 7.71 (1 H, dd, *J* 7.9 and 1.5, *E* Ar*H*), 7.69 (1 H, dd, *J* 7.9 and 1.5, *Z* Ar*H*), 7.57 (2 H, dd, *J* 8.0 and 1.2, *E* Ar*H*), 7.50 (1 H, dd, *J* 7.9 and 1.5, *E* Ar*H*), 7.49 (1 H, dd, *J* 7.9 and 1.5, *Z* Ar*H*), 7.37–7.21 (5 H + 3 H, m, Ar*H*), 6.67 (2 H, t, *J* 7.9, Ar*H*), 6.19 (1 H, q, *J* 6.9, *Z*-C*H*CH$_3$), 6.07 (1 H, q, *J* 7.1, *E*-C*H*CH$_3$), 4.98 (2 H, s, *E*-OCH_2), 4.65 (2 H, s, *Z*-OCH_2), 1.96 (3 H, d, *J* 7.1, *E*-CHCH_3), 1.73 (3 H, d, *J* 6.9, *Z*-CHCH_3); δ_C (67.8 MHz, $CDCl_3$) 155.7 (*E*

s), 155.2 (*Z* s), 141.2 (*E* s), 138.7 (*E* d), 138.6 (*Z* d), 138.0 (*Z* s), 136.6 (*Z* s), 136.2 (*E* s), 133.8 (*E* d), 133.7 (*Z* d), 129.5 (*E* d), 129.0 (d), 127.9 (d), 127.0 (6 × d), 117.1 (s), 92.9 (s), 92.8 (s), 77.0 (*Z* t), 69.8 (*E* t), 14.8 (*E* q), 14.6 (*Z* q); *m*/*z* (FAB) Found: 427.9279 (M^+, 1%, $C_{16}H_{14}BrIO$ requires 427.9275), 349 (1), 285 (1), 91 (91).

(±)-3-Ethenyl-7-bromo-3-phenyl-2,3-dihydrobenzofuran (5). A solution of palladium(II) acetate (210 mg, 0.93 mmol) in DMF (10 mL) was added to a mixture of the bromoiodo olefin **4** (20.0 g, 46.7 mmol), triphenylphosphine (490 mg, 1.89 mmol) and silver carbonate (27.1 g, 98.1 mmol) in DMF (590 mL) at room temperature under a nitrogen atmosphere and the mixture was then heated at 80 °C for 4 days. Additional palladium(II) acetate (105 mg, 0.47 mmol) in a DMF solution (5 mL) was added after the first and third days. The mixture was cooled to room temperature, filtered through Celite®, diluted with water (3000 mL) and then extracted with diethyl ether (3 × 1000 mL). The combined organic extracts were washed with water (1500 mL) then dried and concentrated *in vacuo.* The residue was purified by chromatography, eluting with 10% ethyl acetate in petroleum ether, to give the *dihydrobenzofuran* (10.1 g, 72%) as a colourless oil; ν_{max} ($CHCl_3$)/cm^{-1} 1634, 1598; δ_H (270 MHz, $CDCl_3$) 7.36 (1 H, dd, *J* 7.9 and 1.3, Ar*H*), 7.32–7.22 (5 H, m, Ar*H*), 7.00 (1 H, dd, *J* 7.3 and 1.3, Ar*H*), 6.72 (1 H, t, *J* 7.7, Ar*H*), 6.27 (1 H, dd, *J* 17.2 and 10.6, C*H*=CH_2), 5.31 (1 H, d, *J* 10.6, CH=C*H*H), 5.07 (1 H, d, *J* 17.2, C=CH*H*), 4.86 (1 H, d, *J* 9.2, CH*H*O), 4.72 (1 H, d, *J* 9.2, C*H*HO); δ_C (67.8 MHz, $CDCl_3$) 156.9 (s), 143.4 (s), 140.7 (d), 133.5 (s), 131.8 (d), 128.5 (d), 127.3 (d), 127.1 (d), 124.5 (d), 122.2 (d), 115.5 (t), 103.3 (s), 83.3 (t), 58.4 (s); *m*/*z* (ESI) Found: 300.0173 (M^+, 91%, $C_{16}H_{13}BrO$ requires 300.0150), 221 (46), 205 (13), 194 (95), 178 (21), 118 (6), 77 (28).

(2*E*)-2-[2-(Benzyloxy)phenyl]-*N*-(2-iodophenyl)but-2-enamide (18a). A solution of 2-iodoaniline (1.0 g, 4.5 mmol) in dichloromethane (10 mL) was added dropwise over 10 min to a stirred solution of trimethylaluminium (2 M) in hexane (2.3 mL, 4.5 mmol) at 0 °C under a nitrogen atmosphere. After 10 min, the solution was allowed to warm to room temperature and stirred for 30 min giving a clear red–brown solution. A solution of the unsaturated ester **17** (0.5 g, 1.8 mmol) in dichloromethane (10 mL) was added dropwise over 10 min, and the mixture was then heated at reflux for 20 h. The mixture was cooled to 0 °C, then water (5 mL) was added over 15 min, followed by saturated aqueous Rochelle's solution (10 mL), and the mixture was stirred at room temperature for 15 min. After removal of the solvent *in vacuo*, diethyl ether (20 mL) was added to the residue and the separated aqueous layer was extracted with diethyl ether (3 × 15 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo.* The residue was purified by chromatography, eluting with 10% ethyl acetate in petroleum ether, to give the *anilide* (0.57 g, 70%) as a yellow oil; (Found: C, 58.7; H, 4.4; N, 2.9; $C_{23}H_{20}NO_2I$ requires: C, 58.9; H, 4.3; N, 3.0%); ν_{max} ($CHCl_3$)/cm^{-1} 3697, 3347, 2914, 1682; δ_H (360 MHz, $CDCl_3$) 8.52 (1 H, dd, *J* 8.2 and 1.5, Ar*H*), 7.70 (1 H, br s, N*H*), 7.66 (1 H, dd, *J* 8.2 and 1.5, Ar*H*), 7.41–7.33 (2 H, m, Ar*H* and =C*H*CH_3 obs), 7.32–7.21 (7 H, m, Ar*H*), 7.12–7.07 (2 H, m, Ar*H*), 6.77 (1 H, dt, *J* 7.8 and 1.6, Ar*H*), 5.13 (2 H, s, PhCH_2OAr), 1.74 (3 H, d, *J* 7.1, =CHCH_3); δ_C (90.6 MHz, $CDCl_3$) 165.0 (s), 156.6 (s), 138.9 (s), 138.7 (d), 138.1 (d), 136.7 (s), 134.1 (s), 132.2 (d), 130.3 (d), 129.2 (d), 128.5 (d), 127.7 (d), 127.0 (d), 125.3 (d), 123.8 (s), 121.5 (d), 120.9 (d), 113.1 (d), 88.9 (s), 70.0 (t), 15.5 (q); *m*/*z* (ESI) Found: 492.0478 ([M + Na]$^+$, $C_{23}H_{20}INO_2Na$ requires 492.0436), 470 (62), 380 (6), 337 (12), 310 (22).

***tert*-Butyl-(2*E*)-2-[2-(benzyloxy)phenyl]-*N*-(2-iodophenyl)carbamate (18b).** Di-*tert*-butyl dicarbonate (225 mg, 1.02 mmol) and 4-dimethylaminopyridine (11 mg, 0.09 mmol), followed by diisopropylethylamine (0.15 mL, 0.85 mmol) were added in single portions to a stirred solution of the anilide **18a** (400 mg, 0.85 mmol) in acetonitrile (10 mL). The mixture was stirred at room temperature for 3 h, then water (5 mL) was added and the solvent was removed *in vacuo.* Diethyl ether (20 mL) was added to the residue and the separated aqueous layer was then extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), then dried over $MgSO_4$ and concentrated *in vacuo.* The residue was purified by chromatography, eluting with 5% ethyl acetate in petroleum ether, to give the *carbamate* (400 mg, 83%) as pale yellow crystals; mp 118–120 °C (from petroleum ether (bp 60–80 °C)–acetone); (Found: C, 58.7; H, 4.9; N, 2.2; $C_{28}H_{28}NO_4I$ requires: C, 59.1; H, 5.0; N, 2.2%); ν_{max} ($CHCl_3$)/cm^{-1} 1734, 1688, 1152; δ_H (360 MHz, $CDCl_3$) 7.74 (1 H, d, *J* 7.9, Ar*H*), 7.40 (2 H, d, *J* 7.5, Ar*H*), 7.33 (2 H, dt, *J* 6.9 and 2.0, ArH), 7.29–7.21 (2 H, m, Ar*H* and =C*H*CH_3), 7.15–7.05 (2 H, m, Ar*H*), 6.97–6.81 (5 H, m, Ar*H*), 5.10 (2 H, s, PhCH_2OAr), 1.80 (3 H, d, *J* 7.1, =CHCH_3), 1.26 (9 H, s, COOC(CH_3)$_3$); δ_C (90.6 MHz, $CDCl_3$) 171.2 (s), 156.2 (s), 151.5 (s), 141.8 (s), 139.2 (d), 137.6 (d), 136.9 (s), 136.4 (s), 133.0 (d), 129.8 (d), 129.0 (d), 128.9 (d), 128.5 (d), 128.3 (d), 127.6 (d), 127.1 (d), 124.5 (s), 120.6 (d), 113.3 (d), 99.8 (s), 82.7 (s), 70.8 (t), 27.7 (q), 15.5 (q); *m*/*z* (ESI) Found: 592.0933 ([M + Na]$^+$, $C_{28}H_{28}INO_4Na$ requires 592.0961), 576 (9), 492 (23), 470 (94), 452 (6).

***tert*-Butyl 3-(2-(benzyloxy)phenyl)-2-oxo-3-vinylindoline-1-carboxylate (19).** A mixture of triphenylphosphine (6 mg, 22.0 μmol), silver phosphate (46 mg, 110 μmol) and tris(dibenzylideneacetone)dipalladium(0) (6 mg, 5.50 μmol) in dimethylacetamide (0.5 mL) was stirred at room temperature under a nitrogen atmosphere for 2 h. A solution of the anilide **18b** (31 mg, 55.0 μmol) in dimethylacetamide (1 mL) was added in one portion and the solution was then degassed with nitrogen for 1 h. The solution was heated at 90 °C for 24 h, then cooled to room temperature, filtered through Celite® and washed with diethyl ether (10 mL). Water (5 mL) was added to the filtrate and the separated aqueous layer was then extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with brine (15 mL), then dried over $MgSO_4$ and concentrated *in vacuo.* The residue was purified by chromatography, eluting with 5% ethyl acetate in petroleum ether, to give the *oxindole* (15 mg, 66%) as a colourless oil; ν_{max} ($CHCl_3$)/cm^{-1} 2931, 1791, 1725, 1606; δ_H (360 MHz, $CDCl_3$) 7.72 (1 H, d, *J* 8.1, Ar*H*), 7.51 (1 H, dd, *J* 7.5 and 1.6, Ar*H*), 7.31–7.19 (5 H, m, Ar*H*), 7.10 (1 H, dt, *J* 7.5 and 1.0, Ar*H*), 7.01 (1 H, dt, *J* 7.5 and 1.0, Ar*H*), 6.87–6.80 (4 H, m, Ar*H*), 6.33 (1 H, dd, *J* 17.2 and 10.2, C*H*=CH_2), 5.42 (1 H, d, *J* 10.2, CH=C*H*H), 4.96 (1 H, d, *J* 17.2, CH=CH*H*), 4.84 (1 H, d, *J* 11.7, PhC*H*HOAr), 4.71 (1 H, d, *J* 11.7, PhCH*H*OAr), 1.51 (9 H, s, COOC(CH_3)$_3$); δ_C (90.6 MHz, $CDCl_3$) 175.5 (s), 155.4 (s), 149.5 (s), 140.1 (s), 137.3 (d), 136.0 (s), 129.8 (s), 129.5 (d), 129.2 (d), 128.9 (s), 128.4 (d), 127.9 (d), 127.8 (d), 127.4 (d), 124.6 (d), 123.8 (d), 120.7 (d),

119.0 (t), 115.2 (d), 112.2 (d), 83.6 (s), 70.1 (t), 58.8 (s), 28.1 (q); *m/z* (ESI) Found: 464.1867 ([M + Na]$^+$, $C_{28}H_{27}NO_4Na$ requires 464.1838), 386 (13), 364 (41), 343 (22), 342 (85).

***tert*-Butyl (4*S*)-4-{4-benzyloxy-3-[2-oxo-1-((2-trimethylsilyl)-ethoxy)methyl)-3-vinyl-2,3-dihydro-1*H*-indol-3-yl]benzyl}-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (24).** A mixture of triphenylphosphine (56 mg, 0.21 mmol), silver phosphate (440 mg, 1.10 mmol) and tris(dibenzylideneacetone)dipalladium(0) (55 mg, 0.05 mmol) in dimethylacetamide (1 mL) was stirred at room temperature under a nitrogen atmosphere for 2 h. A solution of the anilide **23b** (430 mg, 0.53 mmol) in dimethylacetamide (7 mL) was added, in one portion, and the mixture was then degassed with nitrogen for 1 h. The solution was heated to 90 °C for 36 h, then cooled to room temperature, filtered through Celite® and washed with diethyl ether (20 mL). Water (20 mL) was added and the separated aqueous layer was then extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with brine (50 mL), then dried over $MgSO_4$ and concentrated *in vacuo.* The residue was purified by chromatography, eluting with 10% ethyl acetate in petroleum ether, to give the *oxindole* (280 mg, 77%) as a pale yellow oil; $[\alpha]_D^{20}$ −19.0 (*c* 1.5 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2955, 1719, 1691; δ_H (360 MHz at 318 K, $CDCl_3$) 7.37–7.21 (5 H, m, Ar*H*), 7.09 (1 H, br s, Ar*H*), 7.00 (1 H, t, *J* 7.5, Ar*H*), 6.89 (2 H, d, *J* 7.5, Ar*H*), 6.84–6.76 (3 H, m, Ar*H*), 6.35 (1 H, dd, *J* 17.2 and 10.2, C*H*=CH$_2$), 5.31 (1 H, d, *J* 10.2, CH=C*H*H), 4.98 (1 H, d, *J* 17.2, CH=CH*H*), 4.92 (1 H, d *J* 11.1, NC*H*HO), 4.69 (1 H, d, *J* 10.6, PhC*H*HOAr), 4.59 (1 H, d, *J* 10.6, PhCH*H*OAr), 4.20–3.95 (1 H, m, NC*H*CH$_2$Ar), 3.89–3.81 (3 H, m, NCH*H*O and NCHC*H*$_2$O), 3.45–3.40 (2 H, m, SiCH$_2$C*H*$_2$O), 3.30–3.08 (1 H, m, ArC*H*HCH), 2.67 (1 H, dd, *J* 12.9, ArCH*H*CH), 1.64–1.51 (15 H, m, COOC(C*H*$_3$)$_3$ and C(C*H*$_3$)$_2$), 0.89–0.74 (2 H, m, (CH$_3$)$_3$SiC*H*$_2$), 0.08 (9 H, s, (C*H*$_3$)$_3$SiCH$_2$); δ_C (90.6 MHz at 318 K, $CDCl_3$) 177.7 (s), 154.6 (s), 151.7 (s), 142.5 (s), 137.7 (d), 137.6 (d), 136.0 (s), 130.6 (d), 130.5 (d), 129.5 (d), 128.4 (d), 128.3 (d), 128.1 (d), 127.6 (d), 124.4 (d), 122.2 (d), 117.8 (t), 112.0 (d), 109.5 (d), 94.1 (s), 79.6 (s), 70.3 (t), 69.0 (t), 66.1 (t), 65.3 (t), 59.4 (d), 58.6 (s), 39.9 (t), 28.6 (q), 26.9 (q), 23.3 (q), 17.7 (t), −1.5 (q); *m/z* (ESI) Found: 707.3516 ([M + Na]$^+$, 27%, $C_{40}H_{52}N_2O_6SiNa$ requires 707.3492), 511 (100), 467 (11), 217 (17).

(*S*)-4-[(*E*),(*R*)-2-(2-Benzyloxyphenyl)-1-hydroxybut-2-enyl]-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (54b) and (*S*)-4-[(*E*)-(*S*)-2-(2-benzyloxyphenyl)-1-hydroxybut-2-enyl]-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (54a). A solution of *tert*-butyllithium (1.5 M) in hexanes (0.66 mL, 0.99 mmol) was added dropwise over 0.25 h to a stirred solution of the vinyl iodide **53** (157 mg, 0.449 mmol) in diethyl ether (5 mL) at −78 °C, and the mixture was then stirred at −78 °C for a further 0.75 h. A solution of $MgBr_2$ (1 M in diethyl ether and benzene, 1.00 mL, 1.00 mmol)[26] was added rapidly using a syringe, and the mixture was then stirred at −78 °C for a further 0.5 h. A solution of Garner's aldehyde (64 mg, 0.28 mmol) in tetrahydrofuran (2 mL) was added over 0.5 h, and the mixture was stirred for 1 h at −78 °C then warmed to room temperature and stirred for a further 16 h. The mixture was quenched with 2 M hydrochloric acid (10 mL) and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with sat. aqueous sodium bicarbonate solution (10 mL) and brine (10 mL), then dried, and concentrated to leave a sticky colourless solid. The solid was purified by chromatography, eluting with ethyl acetate–petrol (16 : 84), to give (i) the *anti-allylic alcohol* **54b** (66 mg, 51%) as colourless crystals; mp 112.5–114.0 °C (from ethyl acetate–petroleum ether); (Found: C, 71.3; H, 7.8; N, 2.9; $C_{27}H_{35}NO_5$ requires: C, 71.5; H, 7.8; N, 3.1%); $[\alpha]_D^{18}$ +16.0 (*c* 1.02 in $CDCl_3$); ν_{max}/cm^{-1} ($CDCl_3$) 3686, 3563, 2936 and 1694; δ_H (250 MHz, d$_6$-DMSO, 353 K) 7.42–7.23 (6 H, m, Ar*H*), 7.06 (1 H, app. d, *J* 7.9, Ar*H*), 6.97–6.92 (2 H, m, Ar*H*), 5.95 (1 H, q, *J* 6.8, [rotamer 1 + rotamer 2] =C*H*CH$_3$), 5.08 (1 H, d, *J* 14.1, ArC*H*HO), 5.03 (1 H, d, *J* 14.1, ArCH*H*O), 4.75 (1 H, br s, C*H*OH), 4.45 (1 H, br s, O*H*), 3.84 (1 H, dd, *J* 8.5 and 3.3, C*H*HO), 3.67–3.64 (1 H, m, C*H*N), 3.56–3.49 (1 H, m, CH*H*O), 1.47 (3 H, s, CC*H*$_3$), 1.39 (3 H, d, *J* 6.8, [rotamer 1 + rotamer 2] =CHC*H*$_3$), 1.36 (3 H, s, CC*H*$_3$), 1.27 (9 H, s, C(C*H*$_3$)$_3$); δ_C (90 MHz, $CDCl_3$, 330 K) 156.0 (s), 152.2 (s), 138.0 (s), 137.2 (s), 131.0 (d), 128.6 (d), 128.1 (s), 127.9 (d), 127.2 (d), 123.5 (d), 121.3 (d), 112.6 (d), 94.3 (s), 79.8 (s), 74.7 (d), 70.5 (t), 63.0 (t), 59.7 (d), 28.4 (q), 26.4 (q), 23.4 (q), 14.2 (q); *m/z* (ESI) Found: 476.2375 ([M + Na]$^+$, $C_{27}H_{35}NO_5Na$ requires 476.2413), 476 ([M + Na]$^+$, 100%), 296 (80); and (ii) the *syn-allylic alcohol* **54a** (32 mg, 23%) as a colourless oil which crystallised on standing at 4 °C for one week; (Found: C, 71.5; H, 7.8; N, 2.5; $C_{27}H_{35}NO_5$ requires: C, 71.5; H, 7.8; N, 3.1%). $[\alpha]_D^{20}$ +21.2 (*c* 1.02 in $CDCl_3$); ν_{max}/cm^{-1} ($CDCl_3$) 3687, 3549, 2957 and 1694; δ_H (360 MHz, $CDCl_3$, 333 K) 7.42–7.26 (6 H, m, Ar*H*), 7.26–7.22 (1 H, m, Ar*H*), 6.99–6.96 (2 H, m, Ar*H*), 5.88 (1 H, q, *J* 6.7, =C*H*CH$_3$), 5.27 (2 H, s, ArC*H*$_2$O), 4.28 (1 H, dd, *J* 9.8 and 5.1, C*H*OH), 3.85 (1 H, app br s, C*H*N), 3.82 (1 H, app d, *J* 9.4, C*H*HO), 3.50 (1 H, dd, *J* 8.8 and 6.0, CH*H*O), 1.61 (3 H, s, CC*H*$_3$), 1.50 (3 H, d, *J* 6.7, =CHC*H*$_3$), 1.43 (9 H, s, C(C*H*$_3$)$_3$); δ_C (90 MHz, $CDCl_3$, 333 K) 156.0 (s), 138.7 (s), 137.2 (s), 132.5 (d), 128.6 (d), 128.5 (d), 128.0 (d), 127.5 (d), 126.5 (s), 124.0 (s), 121.1 (d), 112.1 (d), 94.2 (s), 80.9 (s), 70.5 (t), 65.8 (t), 60.9 (d), 28.4 (q), 27.6 (q), 24.0 (q), 14.5 (q); *m/z* (ESI) Found: 476.2372 ([M + Na]$^+$, $C_{27}H_{35}NO_5Na$ requires 476.2413), 476 ([M + Na]$^+$, 100%).

X-Ray crystal structure for (+)-syn-*allyl alcohol* ***54a***. $C_{27}H_{35}NO_5$, M = 453.56, orthorhombic, a = 9.5722(11), b = 11.5881(13), c = 23.044(3) Å, U = 2556.1(9) Å^3, T = 150(2) K, space group $P2_12_12_1$ (No. 19), Z = 4, D_c = 1.179 g cm^{-3}, μ(Mo-$K\alpha$) = 0.081 mm^{-1}, 22 674 reflections collected, 3463 unique (R_{int} 0.038) which were used in all calculations. Final R_1 [3045 $F > 4\sigma(F)$] = 0.0297 and wR(all F^2) was 0.0787. CCDC reference number 613517. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b609604b

(*S*)-4-[(*E*)-(*S*)-2-(2-Benzyloxyphenyl)-1-(2-iodobenzyloxy)but-2-enyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (59a). Sodium hydride (60% dispersion in oil, 53 mg, 1.33 mmol) was added portion-wise to a stirred solution of the *syn*-allylic alcohol **54a** (500 mg, 1.10 mmol) in tetrahydrofuran (5 mL) at 0 °C, and the mixture was stirred at 0 °C for 15 min. 2-Iodobenzyl bromide (448 mg, 1.43 mmol) was added, the mixture was heated to 55 °C for 20 h and then concentrated *in vacuo.* The residue was quenched with saturated aqueous ammonium chloride (5 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution (5 mL), washed with brine (5 mL) then dried and concentrated *in vacuo.* The residue was purified by

chromatography, eluting with ethyl acetate–petrol (5 : 95 to 20 : 80), to give (i) the *syn-ether* (580 mg, 79%) as colourless crystals; mp 81.5–84.0 °C; (Found: C, 60.6; H, 5.9; N, 1.7; $C_{34}H_{40}NO_5I$ requires: C, 61.0; H, 6.0; N, 2.1; I, 19.0%); $[\alpha]_D^{20}$ +25.6 (*c* 2.33 in $CDCl_3$); ν_{max}/cm^{-1} ($CDCl_3$) 2935 and 1681; δ_H (360 MHz, $CDCl_3$, 333 K) 7.80 (1 H, app d, *J* 6.5, Ar*H*), 7.63 (1 H, app d, *J* 7.6, Ar*H*), 7.40–7.28 (6 H, m, Ar*H*), 7.26–7.18 (2 H, m, Ar*H*), 6.97–6.91 (3 H, m, Ar*H*), 6.03 (1 H, q, *J* 6.8, =C*H*), 5.05 (2 H, s, ArCH_2O), 4.74 (1 H, d, *J* 13.3, ArC*H*HO), 4.46 (1 H, d, *J* 13.3, ArCH*H*O), 4.07 (2 H, app s, C*H*O and C*H*N), 3.82 (1 H, app d, *J* 9.1, C*H*HO), 3.59 (1 H, m, CH*H*O), 1.59 (3 H, d, *J* 6.8, =CHCH_3), 1.53 (3 H, br s, C(CH_3)(CH$_3$)), 1.46 (3 H, s, C(CH$_3$)(CH_3)), 1.32 (9 H, br s, C(CH_3)$_3$); δ_C (90 MHz, $CDCl_3$, 333 K) 156.2 (s), 153.1 (s), 141.5 (s), 138.8 (d), 137.4 (s), 135.0 (s), 131.8 (d), 129.9 (d), 128.7 (d), 128.5 (d), 128.2 (d), 128.0 (d), 127.4 (d), 126.8 (s), 121.0 (d), 112.0 (d), 94.1 (s), 86.2 (d), 79.3 (s), 74.8 (t), 70.5 (t), 65.8 (t), 59.4 (d), 28.5 (q), 28.0 (q), 24.1 (q), 14.8 (q); *m*/*z* (ESI) Found: 692.1841 ([M + Na]$^+$, $C_{34}H_{40}NO_5INa$ requires 692.1849), 692 ([M + Na]$^+$, 100%), 570 (25), 319 (15); (1*S*,7a*S*)-1-{(1*E*)-1-[2-(benzyloxy)phenyl]prop-1-en-1-yl}-5,5-dimethyldihydro-1*H*-[1,3]oxazolo[3,4-*c*][1,3]oxazol-3-one was also obtained as a colourless oil (61 mg, 14.5%); $[\alpha]_D^{20}$ −7.5 (*c* 1.87 in $CDCl_3$); ν_{max}/cm^{-1} ($CDCl_3$) 2938, 1738, 1598, 1578 and 1499; δ_H (360 MHz, $CDCl_3$, 298 K) 7.50–7.29 (6 H, m, Ar*H*), 7.16–7.14 (1 H, m, Ar*H*), 7.03–6.99 (2 H, m, Ar*H*), 6.07 (1 H, q, *J* 6.8, [rotamer 1 + rotamer 2] =C*H*CH$_3$), 5.08 (2 H, s, ArCH_2O), 4.96 (1 H, app d, *J* 6.3, C*H*O), 4.09 (1 H, app dd, *J* 6.3 and 6.5, C*H*N), 3.68 (1 H, dd, *J* 6.5 and 2.1, C*H*HO), 3.45 (1 H, dd, *J* 6.5 and 1.1, CH*H*O), 1.67 (3 H, s, C(CH_3)(CH$_3$)), 1.56 (3 H, d, *J* 6.8, [rotamer 1 + rotamer 2] =CHCH_3), 1.29 (3 H, s, C(CH$_3$)(CH_3)); δ_C (90 MHz, $CDCl_3$, 298 K) 156.8 (s), 155.9 (s), 136.8 (s), 134.2 (s), 131.8 (d), 129.4 (d), 128.6 (d), 128.0 (d), 127.3 (s), 127.0 (d), 124.7 (d), 121.3 (d), 112.3 (d), 94.4 (s), 81.9 (d), 70.1 (t), 67.9 (t), 63.0 (d), 27.2 (q), 23.4 (q), 14.5 (q); *m*/*z* (ESI) Found: 402.1655 ([M + Na]$^+$, $C_{23}H_{25}NO_4Na$ requires 402.1681), 402 ([M + Na]$^+$, 100%).

X-Ray crystal structure of the syn-*ether* ***59a***. $C_{30}H_{40}INO_5$, M = 669.57, monoclinic, a = 11.7081(8), b = 10.0539(7), c = 13.8008(10) Å, β = 97.039(2)°, U = 1612.3(3) Å^3, T = 150(2) K, space group $P2_1$ (No. 4), Z = 2, D_c = 1.379 g cm^{-3}, μ(Mo-$K\alpha$) = 1.033 mm^{-1}, 8763 reflections collected, 6911 unique (R_{int} 0.016) which were used in all calculations. Final R_1 [6129 $F > 4\sigma(F)$] = 0.0286 and wR(all F^2) was 0.0675. The absolute structure parameter refined to −0.043(10). CCDC reference number 613518. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b609604b

(*S*)-4-[(*S*)-(2*H*-1-Benzopyran-4-yl)hydroxymethyl]-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (61a) and (*S*)-4-[(*R*)-(2*H*-1-benzopyran-4-yl)hydroxymethyl]-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (61b). A solution of *n*-butyllithium (2.5 M) in tetrahydrofuran (17.3 mL, 43.3 mmol) was added over 0.5 h to a stirred solution of 4-bromo-2*H*-chromene **60** (9.60 g, 43.3 mmol) in diethyl ether (90 mL) and the mixture was stirred at −40 °C for 10–15 min. A solution of magnesium bromide (1 M in diethyl ether and benzene, 90.0 mL, 90.0 mmol) was added rapidly, and the solution was then stirred at −40 °C for a further 45 min. A solution of Garner's aldehyde (6.20 g, 27.1 mmol) in diethyl ether (20 mL) was added over 0.75 h, and the mixture was then stirred at room temperature for a further 1 h. The mixture was cooled to 0 °C, then quenched with 2 M hydrochloric acid (150 mL) and extracted with diethyl ether (3 × 100 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution (250 mL) and brine (250 mL), dried and concentrated *in vacuo*. The residue was purified by chromatography, eluting with ethyl acetate–petrol (10 : 90 to 30 : 70), to give (i) the *anti-alcohol* **61a** (3.65 g, 37%) as a foam; $[\alpha]_D^{22}$ +17.6 (*c* 0.34 in $CDCl_3$); ν_{max}/cm^{-1} ($CDCl_3$) 3682, 3524 and 1693; δ_H (360 MHz, C_6D_6, 320 K) 7.80 (1 H, br s, Ar*H*), 7.10–7.05 (1 H, m, Ar*H*), 6.97–6.92 (2 H, m, Ar*H*), 5.95 (1 H, t, *J* 3.6, [rotamer 1 + rotamer 2] =C*H*CH$_2$), 5.40 (1 H, br s, C*H*OH), 4.64–4.63 (2 H, d, *J* 3.6, [rotamer 1 + rotamer 2] ArOCH_2), 4.25–4.23 (1 H, m, C*H*N), 4.10 (1 H, dd, *J* 9.2 and 2.8 C*H*HO), 3.53 (1 H, dd, *J* 9.2 and 7.2 CH*H*O), 2.38 (1 H, br s, O*H*), 1.78 (3 H, s, C(CH_3)(CH$_3$)), 1.55 (3 H, s, C(CH$_3$)(CH_3)), 1.52 (9 H, s, C(CH_3)$_3$); δ_C (90 MHz, C_6D_6, 320 K) 154.4 (s), 152.3 (s), 134.2 (s), 128.9 (d), 123.8 (d), 121.55 (s), 121.0 (d), 118.55 (d), 116.1 (d), 94.25 (s), 79.8 (s), 68.4 (d), 65.1 (t), 62.05 (t), 59.6 (d), 28.0 (q), 26.7 (q), 26.2 (q); *m*/*z* (ESI) Found: 384.1750 (M$^+$ + Na, $C_{20}H_{27}NO_5Na$ requires 384.1786), 384 ([M + Na]$^+$, 100%), 285 (80); and (ii) the *syn-alcohol* **61b** (2.75 g, 28%) as a foam; $[\alpha]_D^{20}$ +12.3 (*c* 1.30 in $CDCl_3$); ν_{max}/cm^{-1} ($CDCl_3$) 3680, 3359 (br), 2937, 1731, 1694 and 1604; δ_H (360 MHz, $CDCl_3$, 325 K): 7.58 (1 H, d, *J* 7.7, Ar*H*), 7.12 (1 H, dt, *J* 7.7 and 1.4 Ar*H*), 6.91 (1 H, dt, *J* 7.6 and 1.1 Ar*H*), 6.82 (1 H, dd, *J* 8.0 and 1.1, Ar*H*), 5.92 (1 H, t, *J* 3.9, =C*H*CH$_2$), 4.76 (2 H, d, *J* 3.9, CH_2O), 4.69 1 H, (d, *J* 8.6, C*H*OH), 4.35–4.30 (1 H, m, C*H*N), 3.79–3.75 (2 H, m, OCH_2), 1.58 (3 H, s, C(CH_3)(CH$_3$)), 1.54 (9 H, s, C(CH_3)$_3$), 1.50 (3 H, s, C(CH$_3$)(CH_3)); δ_C (90 MHz, $CDCl_3$, 325 K): 154.4 (s), 134.8 (s), 129.0 (d), 124.3 (d), 122.0 (s), 121.3 (d), 121.2 (d), 116.1 (d), 94.4 (s), 81.6 (s), 76.0 (d), 64.9 (t), 64.8 (t), 62.1 (d), 28.3 (q), 27.0 (q), 24.0 (q); *m*/*z* (ESI) Found: 384.1775 ([M + Na]$^+$, $C_{20}H_{27}NO_5Na$ requires 384.1786), 384 ([M + Na]$^+$, 100%), 285 (73).

(*S*)-4-[(*S*)-(2*H*-1-Benzopyran-4-yl)-(2-iodobenzyloxy)methyl]-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (62). Sodium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 7.60 mL, 7.60 mmol) was added using a syringe, in one portion, to a stirred solution of the *syn*-allylic alcohol **61b** (2.11 g, 5.86 mmol) in tetrahydrofuran (250 mL) at 0 °C, and the mixture was then stirred at 0 °C for 15 min. 2-Iodobenzyl bromide (18.3 g, 58.6 mmol) and tetrabutylammonium iodide (11.0 g, 29.3 mmol) were added, and the mixture was then heated to reflux for 20 h and concentrated *in vacuo*. The residue was quenched with saturated aqueous ammonium chloride and extracted with diethyl ether (3 × 40 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution (40 mL) and brine (40 mL), dried and concentrated *in vacuo*. The residue was purified by chromatography, eluting with diethyl ether–pentane (100 : 0 to 50 : 50), to give the corresponding *iodobenzyl ether* (1.81 g, 53%) as a colourless viscous oil; $[\alpha]_D^{17}$ +7.13 (*c* 3.40 in $CDCl_3$); ν_{max}/cm^{-1} ($CDCl_3$) 2974, 1687 and 1604; δ_H (360 MHz, $CDCl_3$, 325 K) 7.81 (1 H, dd, *J* 7.9 and 1.0, Ar*H*), 7.62 (1 H, d, *J* 7.6, Ar*H*), 7.51–7.47 (1 H, m, Ar*H*), 7.32 (1 H, dd, *J* 7.5 and 1.0, Ar*H*), 7.12 (1 H, dd, *J* 7.7 and 1.4, Ar*H*), 6.95 (1 H, dd, *J* 7.6 and 1.4, Ar*H*), 6.85 (2 H, m, Ar*H*), 6.00 (1 H, t, *J* 3.7, =C*H*), 4.85 (1 H, dd, *J* 15.0 and 3.8, CH*H*O), 4.80 (1 H, dd, *J* 15.0 and 3.8, CH*H*O), 4.72–4.64 (1 H, m, C*H*O), 4.63 (1 H, d, *J* 12.6, ArC*H*HO), 4.50 (1 H, d, *J* 12.6, CH*H*O), 4.50–4.45 (1 H, m, C*H*N), 4.05 (1 H, app t, *J*

11.4 C*H*HO), 3.86 (1 H, dd, *J* 9.5 and 6.0, CH*H*O) 1.51 (9 H, s, C(CH_3)$_3$), 1.48 (3 H, s, C(CH_3)(CH$_3$)), 1.32 (3 H, s, C(CH$_3$)(CH_3)); δ_C (90 MHz, $CDCl_3$, 325 K) 154.6 (s), 153.0 (s), 140.8 (s), 139.2 (d), 132.0 (s), 129.4 (d), 129.2 (d), 128.5 (s), 128.3 (d), 124.7 (d), 122.6 (d), 121.3 (d), 116.3 (d), 97.8 (s), 94.5 (s), 80.1 (s), 75.4 (t), 69.4 (t), 65.3 (t), 64.2 (d), 59.8 (d), 28.6 (q), 26.6 (q), 23.8 (q); *m/z* (ESI) Found: 600.1227 ([M + Na]$^+$, $C_{27}H_{32}NO_5INa$ requires 600.1223), 600 ([M + Na]$^+$, 100%); (1*S*,7a*S*)-1-(2*H*-chromen-4-yl)-5,5-dimethyldihydro-1*H*-[1,3]oxazolo[3,4-*c*][1,3]oxazol-3-one was also obtained: $[\alpha]_D^{20}$ +60.3 (*c* 5.97 in $CDCl_3$); ν_{max}/cm^{-1} ($CDCl_3$) 2939, 2846, 1732, 1660, 1606, 1576 and 1495; δ_H (360 MHz, $CDCl_3$, 298 K) 7.18 (1 H, app dt, *J* 7.7 and 1.4 Ar*H*), 6.94–6.87 (2 H, m, Ar*H*), 6.78 (1 H, dd, *J* 7.6 and 1.5, Ar*H*), 6.05 (1 H, t, *J* 3.8, [rotamer 1 + rotamer 2] =C*H*), 5.21–5.20 (1 H, m, C*H*O), 4.85–4.82 (2 H, m, CH_2O), 4.20 (1 H, dd, *J* 8.0 and 6.4, C*H*HO), 4.11 (1 H, ddd, *J* 7.8, 6.3 and 5.3, C*H*N), 3.84 (1 H, app t, *J* 8.0, CH*H*O), 1.77 (3 H, s, C(CH_3)(CH$_3$)), 1.41 (3 H, s, C(CH$_3$)(CH_3)); δ_C (90 MHz, $CDCl_3$, 330 K) 156.1 (s), 154.8 (s), 131.4 (s), 130.0 (d), 122.0 (d), 121.5 (d), 120.1 (s), 119.1 (d), 116.9 (d), 95.2 (s), 76.2 (d), 68.7 (t), 65.1 (t), 64.0 (d), 27.6 (q), 23.3 (q); *m/z* (ESI) Found: 288.1239 ([M + H]$^+$, $C_{16}H_{18}NO_4$ requires 288.1237), 288 ([M + Na]$^+$, 100%), 244 (85).

(*S*)-4-[(*R*)-(2*H*-1-Benzopyran-4-yl)-(2-iodobenzyloxy)methyl]-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (63). The *anti*-ether was prepared from the *anti*-allylic alcohol **61a** using an identical procedure to that described for the preparation of **62**: $[\alpha]_D^{19}$ −15.6 (*c* 7.60 in $CDCl_3$); ν_{max}/cm^{-1} ($CDCl_3$) 2976, 2279, 1746 and 1682; δ_H (360 MHz, $CDCl_3$, 332 K) 7.82 (1 H, dd, *J* 7.9 and 1.0, Ar*H*), 7.70–7.50 (2 H, m, Ar*H*), 7.36–7.34 (1 H, m, Ar*H*), 7.15–7.12 (1 H, m, Ar*H*), 7.00–6.95 (1 H, m, Ar*H*), 6.83 (2 H, dd, *J* 8.0 and 1.0, Ar*H*), 6.00–5.95 (1 H, m, =C*H*), 5.30–4.95 (1 H, br s, C*H*O), 4.86–4.78 (2 H, m, CH_2O), 4.63 (1 H, d, *J* 12.8, ArC*H*HO), 4.51 (1 H, d, *J* 12.8, ArCH*H*O), 4.27 (1 H, dd, *J* 8.9 and 3.4, C*H*HO), 4.21 (1 H, app qn, *J* 3.4, C*H*N), 3.04 (1 H, dd, *J* 8.9 and 6.0, CH*H*O), 1.62 (3 H, s, C(CH_3)(CH$_3$)), 1.51 (12 H, br s, C(CH$_3$)(CH_3) and C(CH_3)$_3$); δ_C (90 MHz, $CDCl_3$, 332 K) 154.5 (s), 152.9 (s), 140.8 (s), 139.2 (d), 132.0 (s), 129.3 (d), 129.1 (d), 128.3 (d), 124.2 (d), 121.7 (s), 121.4 (s), 116.2 (d), 97.5 (s), 95.0 (s), 80.4 (s), 76.05 (t), 76.0 (d), 65.5 (t), 63.3 (t), 59.4 (d), 28.7 (q), 26.4 (q), 25.1 (q); *m/z* (ESI) Found: 600.1267 ([M + Na]$^+$, $C_{27}H_{32}NO_5INa$ requires 600.1223), 600 ([M + Na]$^+$, 100%); (1*R*,7a*S*)-1-(2*H*-chromen-4-yl)-5,5-dimethyldihydro-1*H*-[1,3]oxazolo[3,4-*c*][1,3]oxazol-3-one (0.27 g, 16%) was also obtained as an oil; δ_H (360 MHz, C_6D_6, 325 K) 7.03–7.00 (1 H, m, Ar*H*), 6.88 (1 H, dd, *J* 8.1 and 1.1, Ar*H*), 6.75 (1 H, dd, *J* 7.6 and 1.2, Ar*H*), 6.49 (1 H, dd, *J* 7.6 and 1.4, Ar*H*), 5.80 (1 H, t, *J* 3.7, [rotamer 1 + rotamer 2] =C*H*), 5.13 (1 H, m, C*H*O), 4.47–4.45 (2 H, m, CH_2O), 4.18 (1 H, app q, *J* 7.6, C*H*N), 3.35 (2 H, d, *J* 7.6, CH_2O), 1.79 (3 H, s, C(CH_3)(CH$_3$)), 1.42 (3 H, s, C(CH$_3$)(CH_3)); δ_C (90 MHz, C_6D_6, 325 K) 155.1 (s), 154.3 (s), 129.7 (d), 129.0 (s), 121.6 (d), 120.8 (d), 119.6 (s), 118.5 (d), 116.5 (d), 94.2 (s), 71.3 (d), 67.7 (2 × CH$_2$), 60.8 (d), 27.4 (q), 22.9 (q); *m/z* (ESI) Found: 288.1211 ([M + H]$^+$, $C_{16}H_{18}NO_4$ requires 288.1237), 288 ([M + H]$^+$, 100%).

***tert*-Butyl (4*S*)-2,2-dimethyl-4-[(3′*S*,4*R*)-1′*H*-spiro[chromene-4,4′-isochromen]-3′-yl]-1,3-oxazolidine-3-carboxylate (64).**

Method 1. A slurry of triphenylphosphine (839 mg, 3.14 mmol), silver carbonate (1.75 g, 6.28 mmol), the 2-iodobenzyl ether **62** (1.81 g, 3.14 mmol) and palladium acetate (178 mg, 0.784 mmol) was heated under reflux in a nitrogen atmosphere in tetrahydrofuran (100 mL) for 2 days, then cooled to room temperature. The mixture was refluxed for 2 days, cooled to room temperature and filtered through Celite®. The filter cake was washed with ethyl acetate portion-wise (5 × 10 mL), and the combined filtrates were washed with brine (50 mL), dried and concentrated *in vacuo.* The residue was purified by chromatography, eluting with diethyl ether–petrol (20 : 80), to give the *spiro-benzpyran* (460 mg, 41%).

Method 2. The procedure already described was followed except that the mixture was heated in DMA at 90 °C for 4 days. The crude product was purified by chromatography on silica, eluting with diethyl ether–petrol (2 : 98 to 20 : 80) to give the *spiro-benzpyran* (340 mg, 54%) as a colourless solid; mp 179–180 °C; (Found: C, 71.2; H, 6.9; N, 3.0; $C_{27}H_{31}NO_5{\cdot}H_2O$ requires: C, 71.2; H, 7.0; N, 3.1%); $[\alpha]_D^{18}$ +101.0 (*c* 1.64 in $CDCl_3$); ν_{max}/cm^{-1} ($CDCl_3$) 2978, 1682 and 1580; δ_H (360 MHz, C_6D_6, 333 K) 7.09–6.99 (5 H, m, Ar*H*), 6.82–6.79 (1 H, m, Ar*H*), 6.76–6.71 (2 H, m, Ar*H*), 6.59 (1 H, d, *J* 6.3, =C*H*O), 5.24 (1 H, d, *J* 6.3, =C*H*), 4.84 (2 H, s, ArCH_2O), 4.67 (1 H, dd, *J* 9.0 and 4.7, C*H*N), 3.81 (1 H, d, *J* 9.0, C*H*O), 3.47 (1 H, dd, *J* 9.0 and 4.8, C*H*HO), 2.72 (1 H, app t, *J* 9.0, CH*H*O), 1.86 (3 H, s, C(CH_3)(CH$_3$)), 1.65 (3 H, s, C(CH$_3$)(CH_3)), 1.62 (9 H, s, C(CH_3)$_3$); δ_C (90 MHz, C_6D_6, 333 K) 152.2 (s), 143.9 (s), 137.8 (d), 133.6 (s), 131.0 (d), 129.6 (d), 128.1 (d), 126.8 (d), 125.9 (d), 123.9 (s), 123.4 (d), 123.2 (d), 116.25 (d), 106.5 (d), 92.95 (s), 82.8 (d), 78.3 (s), 69.1 (t), 66.2 (t), 58.2 (d), 42.4 (s), 28.2 (q), 27.05 (q), 23.8 (q); *m/z* (ESI) Found: 472.2081 ([M + Na]$^+$, $C_{27}H_{31}NO_5Na$ requires 472.2100), 513 ([M + CH_3CN + Na]$^+$, 100%), 472 (65). A small amount (8%) of the 7-ring ether **65** was also isolated; $[\alpha]_D^{17}$ +112.7 (*c* 0.60 in $CDCl_3$); ν_{max}/cm^{-1} ($CDCl_3$) 2934, 1682 and 1600; δ_H (360 MHz, $CDCl_3$, 328 K) 7.53–7.50 (2 H, m, Ar*H*), 7.43–7.36 (2 H, m, Ar*H*), 7.27–7.25 (2 H, m, Ar*H*), 7.20–7.16 (1 H, m, Ar*H*), 6.94–6.90 (1 H, m, Ar*H*), 5.79 (1 H, d, *J* 4.0, C*H*O), 5.19 (1 H, d, *J* 14.1, ArC*H*HO), 4.67 (1 H, d, *J* 12.4, C*H*HO), 4.60 (1 H, d, *J* 14.1, ArCH*H*O), 4.46 (1 H, d, *J* 12.4, CH*H*O), 4.17 (1 H, dd, *J* 7.5 and 4.1, C*H*N), 3.64–3.63 (2 H, m, CHCH_2O), 1.49 (9 H, s, C(CH_3)$_3$), 1.29 (3 H, s, C(CH_3)(CH$_3$)), 0.91 (3 H, s, C(CH$_3$)(CH_3)); δ_C (90 MHz, $CDCl_3$, 328 K) 157.4 (s), 152.9 (s), 141.0 (s), 136.9 (s), 132.3 (s), 132.1 (s), 129.2 (d), 128.5 (d), 128.0 (d), 127.7 (d), 127.6 (d), 125.8 (s), 124.2 (d), 121.8 (d), 116.5 (d), 94.4 (s), 80.1 (s), 78.0 (d), 68.7 (t), 68.5 (t), 64.2 (t), 61.7 (d), 28.7 (q), 25.3 (q) 23.7 (q); *m/z* (ESI) Found: 472.2067 ([M + Na]$^+$, $C_{27}H_{31}NO_5Na$ requires 472.2100), 472 ([M + Na]$^+$, 100%), 350 (75), 336 (31), 257 (18).

*X-Ray crystal structure of the spiro-benzpyran **64**.* $C_{27}H_{31}NO_5$, M = 449.53, monoclinic, a = 9.4857(10), b = 9.8441(10), c = 13.0354(14) Å, β = 100.138(2)°, U = 1198.2(4) Å^3, T = 150(2) K, space group $P2_1$ (No. 4), Z = 2, D_c = 1.246 g cm^{-3}, μ(Mo-$K\alpha$) = 0.080 mm^{-1}, 7124 reflections collected, 2980 unique (R_{int} 0.033) which were used in all calculations. Final R_1 [2238 $F > 4\sigma(F)$] = 0.0376 and wR(all F^2) was 0.0739. CCDC reference number 613519. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b609604b

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