Cascade radical-mediated cyclisations with conjugated ynone electrophores. An approach to the synthesis of steroids and other novel ring-fused polycyclic carbocycles†

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A cascade radical-mediated Diels–Alder reaction with the iododienynone **16b** produced the tricyclic ketone **17** (22%). By contrast, treatment of the substituted furans **36** and **47** with Bu_3SnH–AIBN, instead led to the tetracycles **44** and **58** respectively, rather than the anticipated oestranes, *i.e.* **38** and **48**. In a separate study, attempted cascade radical-mediated cyclisations from the *ortho*-aryl substituted iododienynones **72** and **73**, leading to the ring-D aromatic steroid **7**, instead gave the macrocyclic ketone **76** or the novel bridged tricycles **77**/**82**, respectively, depending on whether benzene or heptane was used as solvent in the reactions.

Introduction

Applications of cascade radical-mediated cyclisation reactions towards the construction of a wide array of ring-fused polycyclic carbo- and heterocycles abound in the literature.[1] Over more than a decade, our research group has explored a number of complementary radical-mediated macrocyclisation–transannulation and sequential cascade ring forming reactions to elaborate a plethora of linear, angular, and other ring-fused systems found amongst natural products,[2] including terpenoids, taxoids[3] and steroids.[4] Within these studies we have used alkyl, allyl, vinyl, acyl and oxy-centred radical intermediates, and implicated a number of substituted alkene and alkyne electrophores, *i.e.* radical acceptors. In several investigations we have demonstrated that a terminal conjugated ynone electrophore has particular advantages in cascade reactions involving substrates which incorporate additional alkene unsaturation, *e.g.* the cascade 12-*endo*-dig, 6-*exo*-trig cyclisation of the precursor **1** to the tricyclic 6,8,6-ring fused 'taxane' system **2**.[3,5] In a continuation of our studies of the use of the ynone electrophore in the elaboration of interesting ring-fused systems, we have now examined their scope in two new approaches to steroid synthesis. Thus, in one study we have examined an oestrane ring synthesis of **5** based on a macrocyclisation from a substrate, *viz* **3**, which includes an ynone electrophore and a 1,3-diene unit, leading to **4**, followed by radical-like transannular Diels–Alder cycloaddition (Scheme 1). In a second study, we have explored an approach to ring-D aromatic steroids, such as nicandrenone **8**, based on the cascade of 14-*endo*-dig, 6-*exo*-trig and 6-*exo*/*endo*-trig radical cyclisations between **6** and **7**, shown in Scheme 1.

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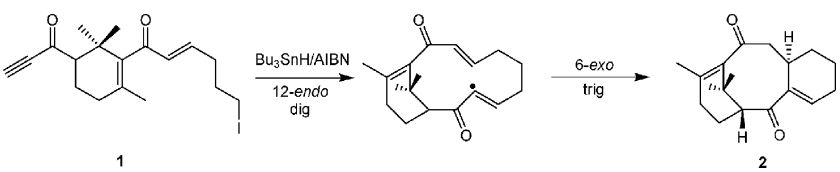
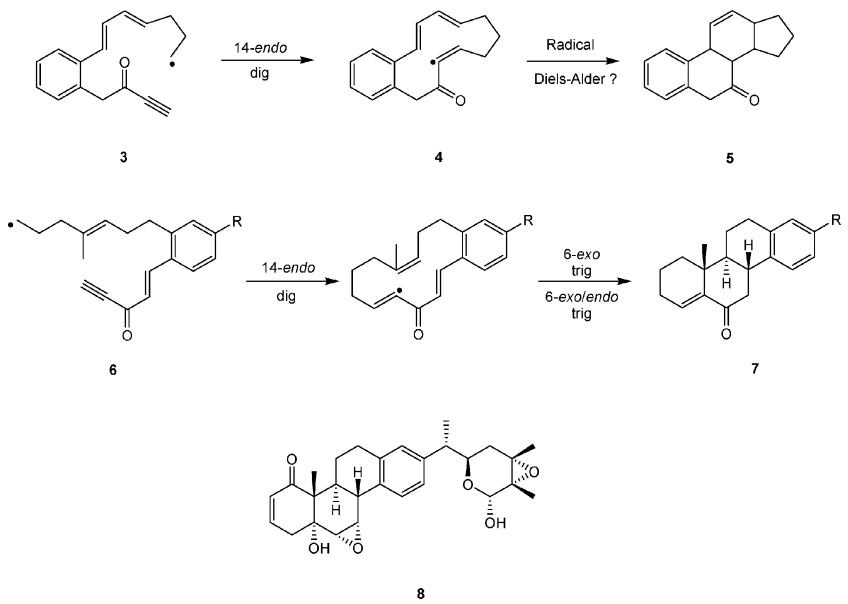
Results and discussion

A radical-mediated Diels–Alder approach to the synthesis of oestranes

A wealth of ingenious methods have been developed to synthesise oestranes and other steroids. Methods based on biogenetic-type electrophilic cyclisations of polyene precursors,[6] Diels–Alder reactions,[7] and transition metal-catalysed cyclisations of enynes and triynes,[8] are particularly prominent. Cascade radical-mediated processes to synthesise steroids have also been examined by several authors,[9] including ourselves.[10] In addition, Deslongchamps *et al.*[11] have described some useful examples of transannular Diels–Alder reactions in steroid ring constructions, and Malacria and Journet[12] have used radical-based intramolecular Diels–Alder reactions in oestrane synthesis.

To demonstrate credence for the proposed radical-mediated Diels–Alder approach to oestranes, presented in Scheme 1, we first examined the less elaborate ω-iodo-1,3-diene ynone system **16b**.[13] The ynone **16b** was elaborated *via* a Suzuki coupling reaction between the known *E*-vinyl iodide **11**[14] and the *E*-vinylboronic acid **10** derived from the known acetylene **9**,[15] in the presence of $Pd(PPh_3)_4$ and aqueous LiOH (Scheme 2). This coupling reaction led to the conjugated *E*,*E*-diene **12a** which, using a sequence of functional group transformations, *i.e.* **12a** → **12b** → **13a** → **13b** → **14**, was next converted into the aldehyde **14**. Treatment of

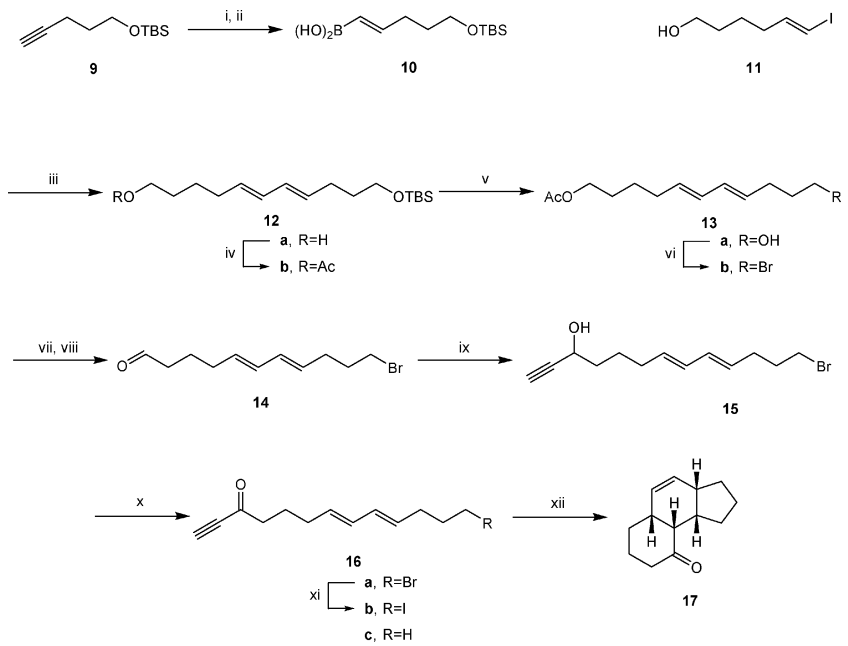




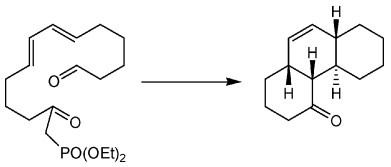
Scheme 1

the aldehyde **14** with acetylenemagnesium bromide led to the corresponding *sec*-alcohol **15**, which was then oxidised to the ynone **16a** using Dess–Martin periodinane. Finally, exchange of bromide for iodide under Finkelstein conditions gave the ω-iodo-1,3-dieneynone system **16b.**

When a solution of **16b** in benzene was treated with Bu_3SnH–AIBN at 80 °C for 8 h, work-up and chromatography gave a single diastereoisomer of the expected tricyclic enone **17**, but in a modest yield of 22%; the only other product characterised was the dienynone **16c** resulting from reduction of the carbon-to-iodide bond in the starting material **16a**. The structure of the tricyclic enone **17** followed from comparison of its spectroscopic data with those of similar compounds prepared earlier by Roush *et al.*,[16] who used a sequence based on an intramolecular Wadsworth–Emmons olefination from an appropriate ketophosphonate precursor, *viz* **18** → **19**, followed by an *in situ* intramolecular Diels–Alder reaction. The *cis*, *syn*, *cis* stereochemistry assigned to **17** was based on detailed NOE studies together with molecular modelling and



Scheme 2 *Reagents and conditions:* (i) catecholborane, THF, 67 °C, 14 h, 77%; (ii) H_2O, 4 h, 87%; (iii) $Pd(OAc)_2$, PPh_3, **11**, THF, aq. LiOH, 40 °C, 16 h, 82%; (iv) Ac_2O, NEt_3, DMAP, DCM, 0 °C, 4 h, 91%; (v) TBAF, THF, 2 h, 79%; (vi) CBr_4, PPh_3, DCM, 0 °C, 30 min, 89%; (vii) K_2CO_3, MeOH, 2 h, 97%; (viii) Dess–Martin periodinane, DCM, 30 min, 89%; (ix) ≡–MgBr, THF, 0 °C → rt, 30 min, 98%; (x) Dess–Martin periodinane, DCM, 30 min, 82%; (xi) NaI, acetone, 16 h, quant.; (xii) Bu_3SnH, AIBN, benzene, 80 °C, 8 h, **16c** = 6%, **17** = 22%.



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comparison of vicinal coupling data in its ^{1}H NMR spectrum, with those of similar compounds described by Roush *et al.*[16] The formation of exclusively the *cis*, *syn*, *cis*-diastereoisomer **17** from **16b** is interesting and most likely implicates a pathway involving a 13-*endo*-dig radical macrocyclisation, leading to **20**, followed by *in situ* H$^\bullet$ quench to the *E*,*E*,*Z*-trienone intermediate **22** and Diels–Alder transannulation through an "*endo*-like" transition state (Scheme 3). It is conceivable that a tandem 6-*exo*-trig, 5-*exo*-trig radical cyclisation from the *E*,*E*,*E*-trienone intermediate **21**, *via* **23**,[17] would also produce **17**, but this pathway would also be expected to lead to a mixture of diastereoisomers of the tricyclic enone.

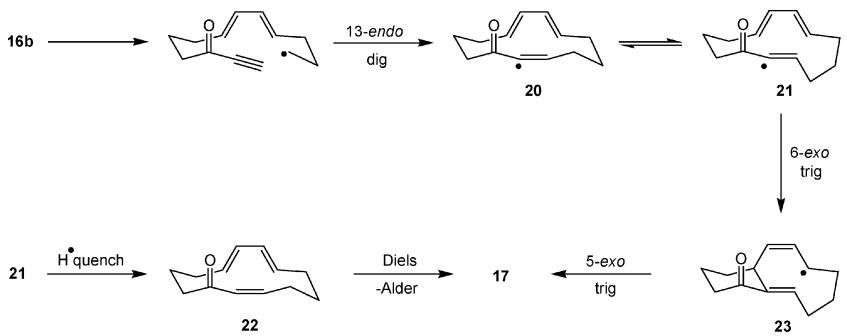
We next decided to examine a cascade radical cyclisation from the corresponding ω-iodoynone **24** where the 1,3-diene unit is accommodated within a furan ring. Furans are well known to act as excellent dienes in Diels–Alder cycloadditions,[18] and the proposed sequence **24** → **25** → **26**, would simultaneously introduce an ether bridge in the adduct **26** permitting further elaboration, as required.

The furyliodoynone **24** was prepared in a straightforward manner, starting from the known substituted propanols **27a**[19] and **28a**[20] (Scheme 4). Thus, protection of **27a** as its TBDPS ether **27b**, followed by conversion into the corresponding 5-furyllithium species **30a** using BuLi, and quenching with Bu_3SnCl first gave the relatively unstable furylstannane **30b**.[21] Without isolation and purification, the stannane **30b** was reacted immediately with the *E*-vinyl iodide **29**, in the presence of $Pd(PPh_3)_2Cl_2$, leading to the substituted vinylfuran **31a** which was characterised as the alcohol **31b**. The *E*-vinyl iodide **29** was prepared from the alcohol **28a** after oxidation to **28b** followed by a Wittig olefination reaction with $ICH_2^+PPh_3I^-$ in the presence of KO^tBu. Hydrogenation of **31b** next gave **32** which by successive functional group interconversions was then converted into the aldehyde **34b**. Treatment of this aldehyde **34b** with acetylenemagnesium bromide led to the propargylic alcohol **34c** which, after oxidation to the corresponding ketone **35a** and exchange of bromide for iodide, gave the furyliodoynone **24**.

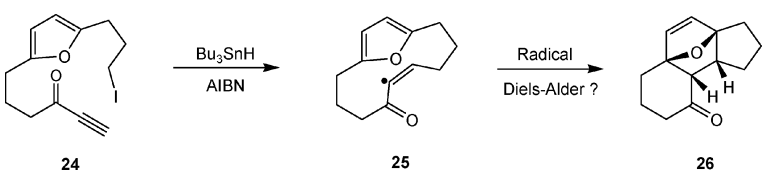
Much to our disappointment, the furyliodoynone **24** was unstable in hot benzene, and treatment of solutions in benzene with Bu_3SnH–AIBN under a range of temperatures led largely to polymeric material. Only in one case, using Bu_3SnH in the presence of Et_3B at 0 °C,[22] were we able to generate a radical centre from the substrate **24**, but this was immediately quenched by H$^\bullet$ producing **35b** in 37% yield. Unperturbed, we reasoned that the corresponding *ortho* benzene-substituted furyliodoynone analogue **36** of **24** would be more robust to heat, and allow us to realise a cascade radical-mediated macrocyclisation–transannulation Diels–Alder sequence, *via* **37**, producing the oestrane **38**.

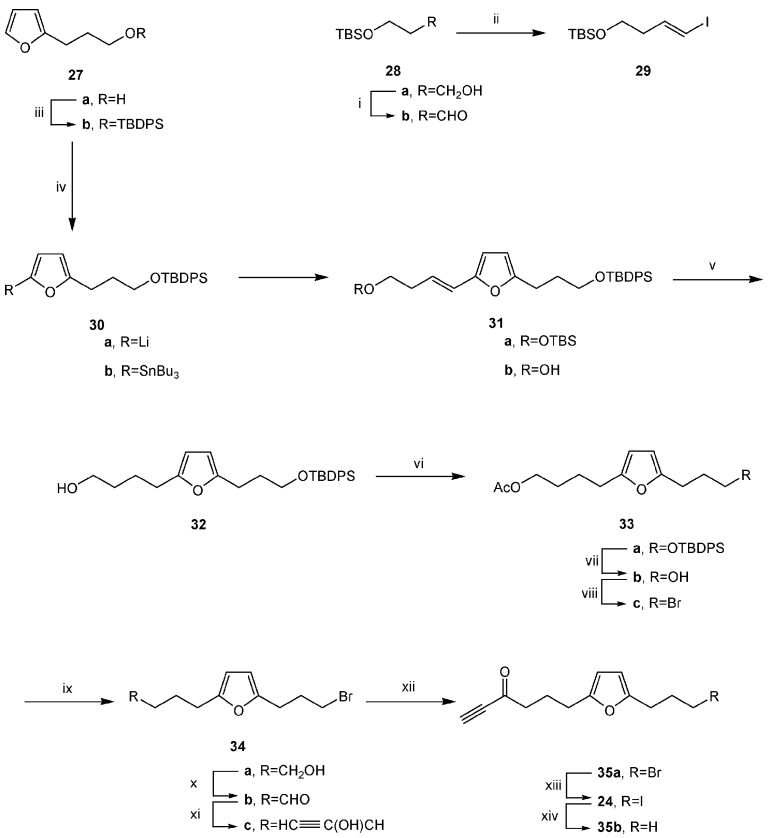
The arylfuran iodoynone **36** was rapidly accessed *via* the adduct **39a** resulting from a Stille coupling reaction between the previously synthesised furylstannane **30b** and 2-iodobenzeneacetonitrile (Scheme 5). The arylfuran **39a** was next elaborated to the aldehyde **40b** in three straightforward synthetic steps, which was then converted into the iodoynone **36** using chemistry developed earlier in the synthesis of the analogue **24**.

When a dilute solution of the arylfuran iodoynone **36** in refluxing benzene was treated with Bu_3SnH–AIBN, a single tetracyclic product was isolated in 45% yield (69% based on recovered starting material). The NMR spectroscopic data recorded for the tetracycle were not consistent with the expected oestrane ring system **38**. Instead, the data, *i.e.* the presence of three olefinic protons, one of which, absorbing at δ_H 5.89 correlated with a carbon resonance at δ_C 89.8 ppm next to oxygen, were consistent with the alternative tetracyclic [6,8,6,5] ring-fused dihydrofuran structure **44**. The tetracyclic ether **44** is produced from **36** *via* initial 13-*endo*-dig macrocyclisation of the alkyl radical intermediate **43** leading to the vinyl radical species **37** which equilibrates with the geometrical isomer **46** (Scheme 6). A 6-*exo*-trig cyclisation at C-2 of the furan ring in **46**, accompanied by allylic migration then produces the benzylic radical intermediate **45** which is quenched by H-abstraction leading to **44**.

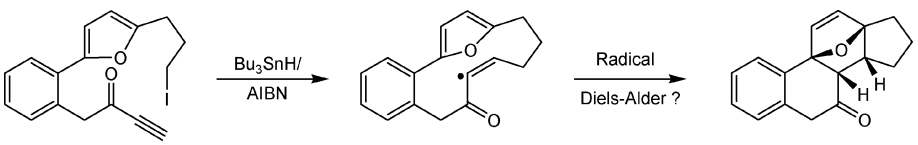


Scheme 3





Scheme 4 *Reagents and conditions:* (i) PCC, silica, DCM, 4 h, 60%; (ii) $ICH_2^+PPh_3I^-$, KO^tBu, THF, −60 → −40 °C, 2 h, 97%; (iii) TBDPSCl, NEt_3, DMAP, DCM, 16 h, 97%; (iv) (a) ^{t}-BuLi, THF, −78 → −20 °C, 3 h, then Bu_3SnCl, −20 °C → rt, 3 h, then **29**, $Pd(PPh_3)_2Cl_2$, THF, 67 °C, 16 h, (b) PPTS, MeOH, 24 h, 40%; (v) $Pd(OH)_2$, H_2, MeOH, 6 h, 96%; (vi) Ac_2O, NEt_3, DMAP, DCM, 0 °C, 6 h, 74%; (vii) TBAF, THF, 2h, 96%; (viii) CBr_4, PPh_3, DCM, 0 °C, 20 min, 95%; (ix) K_2CO_3, MeOH, 4 h, 98%; (x) Dess–Martin periodinane, DCM, 20 min, 70%; (xi) ≡–MgBr, THF, 0 °C → rt, 30 min, 84%; (xii) Dess–Martin periodinane, DCM, 30 min, 88%; (xiii) NaI, K_2CO_3, acetone, 14 h, quant.; (xiv) Et_3B, Bu_3SnH, Tol, 0 °C, 48 h, 37%.

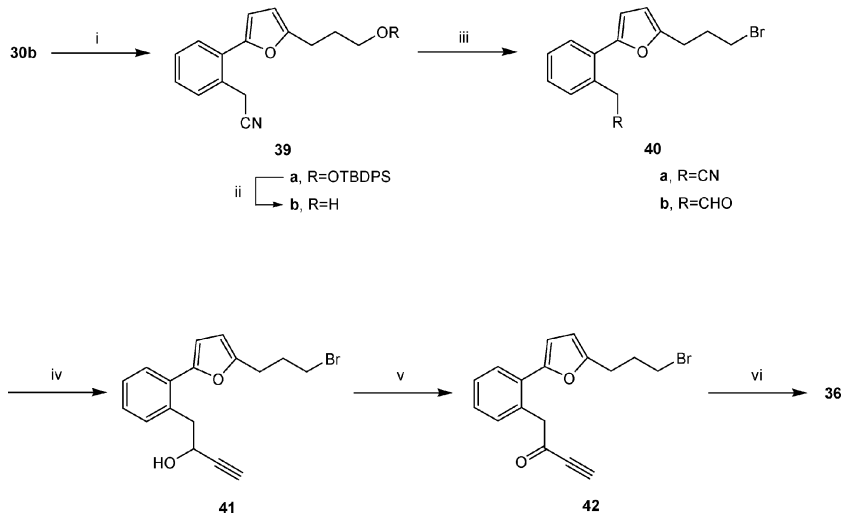


36 **37** **38**

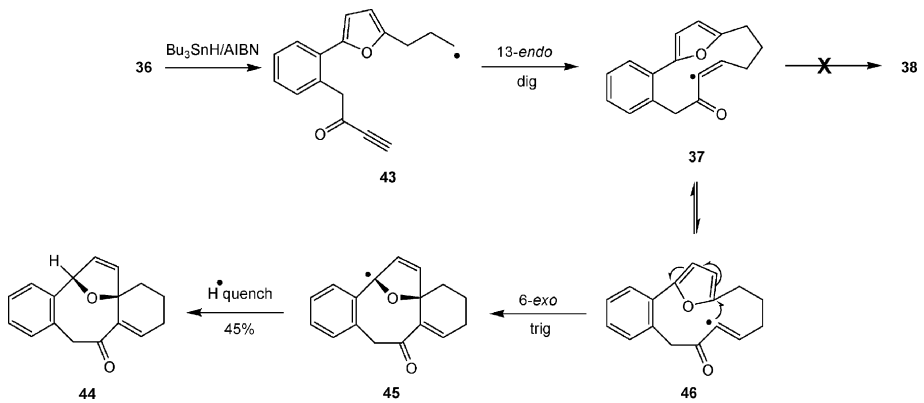
We surmised that the driving force for the formation of **44** from **36** not only had its origins in the relative stabilisation and reactivity of the equilibrating vinyl radical intermediates **37** and **46**,[17] but also in the stabilisation of the product radical centre in **45**, by the neighbouring benzene ring and adjacent oxygen centre. To overcome the latter stabilisation, we therefore finally decided to examine a radical cascade from the cyclohexene analogue of **36**, *i.e.* **47**, in anticipation of synthesising the modified steroidal ring system **48**.

The substituted cyclohexene **47** was synthesised *via* a Stille coupling reaction between the furylstannane **30b** and the vinyl-triflate **51** derived in two straightforward steps from the known hemiaminal **49**,[23] which gave the furanylcyclohexene **52a** in 85% yield (Scheme 7). A series of functional group manipulations allowed the conversion of **52a** into the substituted aldehyde **53c** which was then converted into the ω-iodoynone **47** using synthetic methods and procedures already developed in the synthesis of the related compounds **16b**, **24** and **36**.

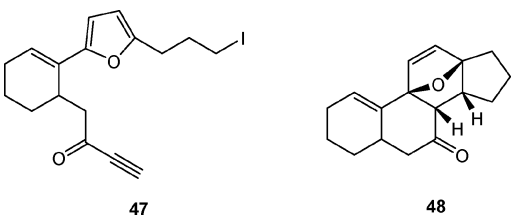
When a solution of the ω-iodoynone **47** in benzene was treated with Bu_3SnH–AIBN, work-up and chromatography gave a single diketone product, as colourless crystals, in 40% yield. Detailed analysis of the ^1H and ^{13}C NMR spectroscopic data failed to resolve the structure of the product, and suitable crystals for X-ray analysis could not be grown. We therefore treated the diketonic product with DIBAL-H which led to a crystalline diol, *viz* **59** suitable for X-ray analysis. The X-ray crystal structure of the diol (Fig. 1)[24] demonstrated that the diketone product resulting from treatment of the ω-iodoynone **47** has the novel and unusual tetracyclic diene dione structure **58**. The formation of **58** presumably results from an initial 13-*endo*-dig macrocyclisation from the radical intermediate **54** leading to **55**, which then undergoes 6-*exo*-trig transannular cyclisation leading to the new radical intermediate **56** (Scheme 8). Instead of being quenched by H-abstraction, leading to a structure similar to **44**, the radical **56** then undergoes a precedented fragmentation[25] to the enedione species **57**. A final 5-*exo*-trig radical cyclisation, involving the



Scheme 5 *Reagents and conditions:* (i) 2-iodobenzeneacetonitrile, $Pd(PPh_3)_2Cl_2$, THF, 67 °C, 16 h, 89%; (ii) TBAF, *p*TSA, THF, 12 h, 75%; (iii) CBr_4, PPh_3, DCM, 0 °C, 30 min, 85%; (iv) (a) DIBAL-H, Tol, −78 → 0 °C, 4.5 h, (b) ≡–MgBr, THF, −78 °C → rt, 2h, 60%; (v) Dess–Martin periodinane, DCM, 2 h, 50%; (vi) NaI, K_2CO_3, acetone, 14 h, 77%.



Scheme 6



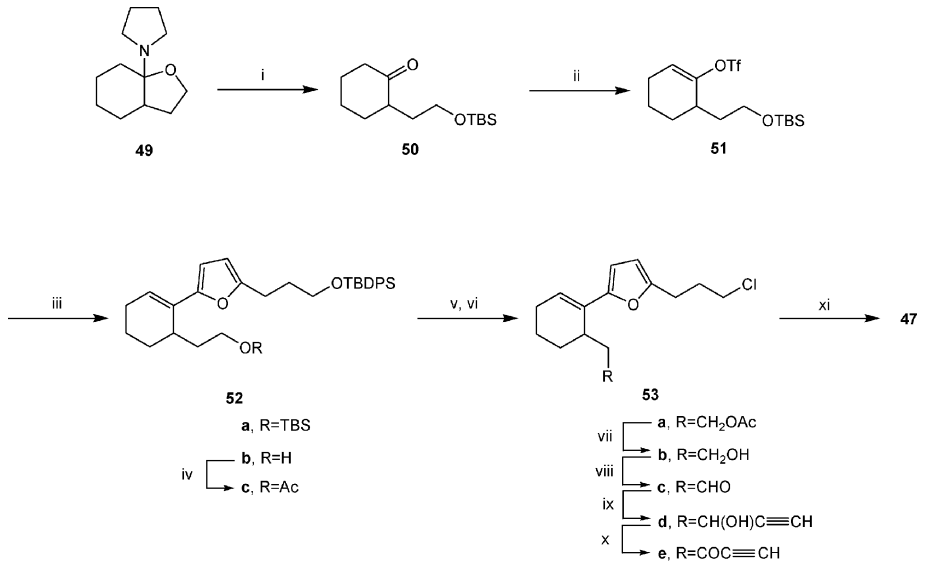
cyclohexene double bond in **57** then leads to the tetracyclic diene dione **58**.

A radical-mediated cyclisation approach to ring-D aromatic steroids

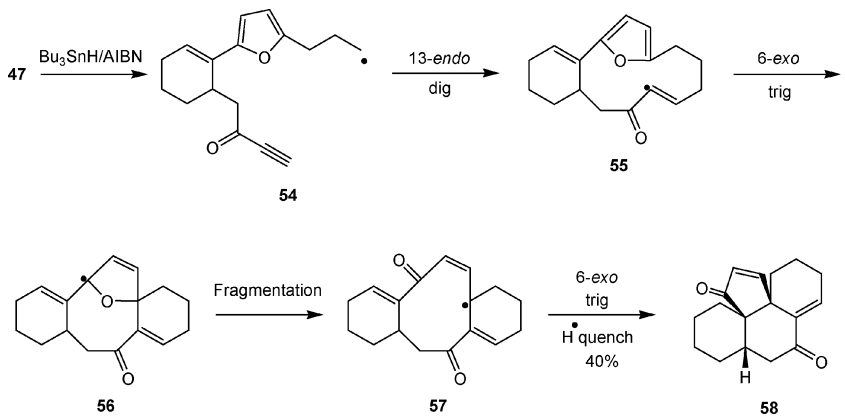
The family of insect antifeedant compounds known as nicandrenones, *e.g.* **8**, isolated from the Peruvian "shoofly" plant *Nicandra physaloides* is probably the best-known group of naturally occurring ring-D aromatic steroids.[26] Although some detailed studies have been made of the possible origin of the aromatic rings in these compounds,[27] relatively little attention has been given to their total synthesis.[28]

In an earlier study, which resulted in a synthesis of *epi*-oestrone **62**, we showed that treatment of the iododienynone **60** with Bu_3SnH–AIBN led to the polycyclic enone **63** in 40% yield, *via* a cascade of 13-*endo*-dig (to **61**), 5-*exo*-trig and 6-*exo*–*endo*-trig radical cyclisations (Scheme 9).[29] As an approach to ring-D aromatic steroids we reasoned that, by analogy, the iododienynone **64**, which contains a trisubstituted, rather than a disubstituted, double bond, and one more methylene carbon in its side-chain compared to **60**, should undergo a similar cascade of radical cyclisations leading to the polycycle **7**, as a possible progenitor to nicandrenones, *e.g.* **8**.[30]

In order to establish proof of principle, we first prepared both the *E*- and *Z*-isomers of the trisubstituted double bonds in **64** where R = H and OMe, *i.e.* **72a**, **73a**, **72b** and **73b** (Scheme 10). These syntheses were carried out in a fairly straightforward manner starting from readily available starting materials. Thus, separate Julia olefination reactions between the benzothiazole sulfone **66**, derived in two steps from the secondary alcohol **65b**,[31] and the previously synthesised aldehydes **67a** and **67b**,[29] using NaHMDS as base, first led to 3 : 2 mixtures of *E*- and *Z*-isomers of the corresponding trisubstituted alkene products **68a** and **68c** respectively. The *E*- and *Z*-isomers were easily separated following deprotection to the corresponding alcohols **68b/d** and chromatography. The pure *E*- and *Z*-isomers of **68b**



Scheme 7 *Reagents and conditions:* (i) (a) HCl, reflux, 5h, (b) TBSCl, NEt_3, DMAP, 16 h, 65%; (ii) (a) LDA, THF, −78 °C → rt, 2 h, (b) $PhNTf_2$, THF, −78 → 0 °C, 3 h, 99%; (iii) (a) **30b**, $Pd(PPh_3)_2Cl_2$, THF, 67 °C, 5 h, (b) PPTS, MeOH, 48 h, 85%; (iv) Ac_2O, NEt_3, DMAP, DCM, 0 °C, 6 h, 96%; (v) TBAF, THF, 1.5 h, 98%; (vi) NCS, PPh_3, K_2CO_3, DCM, 0 °C, 30 min, 94%; (vii) K_2CO_3, MeOH, 16 h, 94%; (viii) Dess–Martin periodinane, DCM, 0 °C, 30 min, 76%; (ix) ≡–MgBr, THF, 0 °C → rt, 30 min, 94%; (x) Dess–Martin periodinane, DCM, 30 min, 87%; (xi) NaI, K_2CO_3, 2-butanone, 80 °C, 10 h, 66%.



Scheme 8

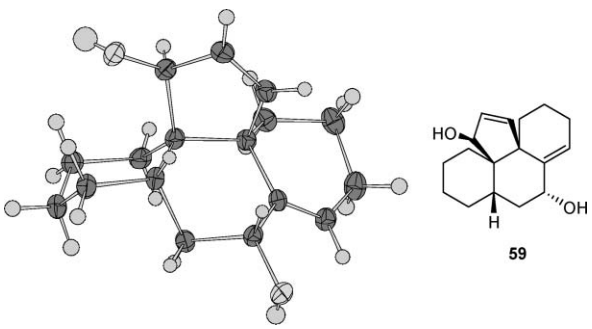
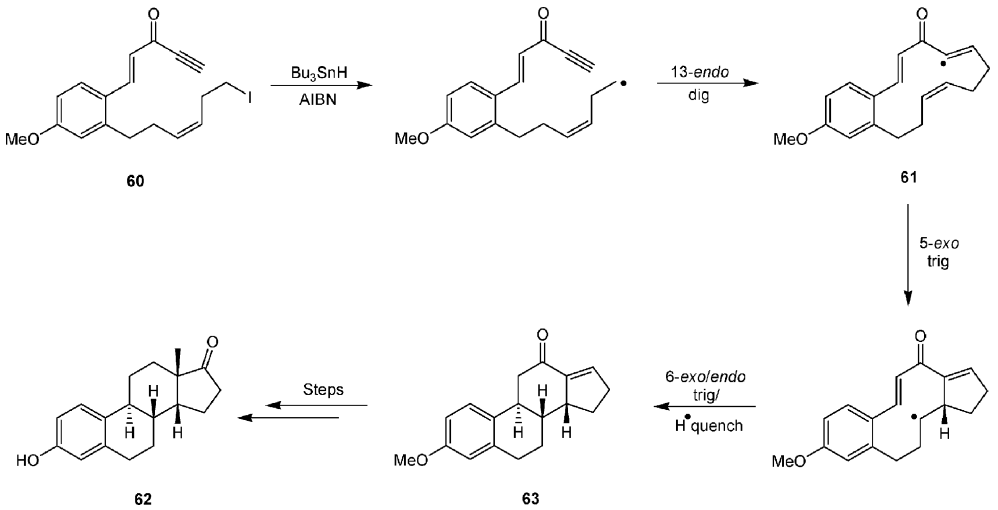


Fig. 1 X-Ray crystal structure of the diol **59**.

and **68d** were then converted separately into the *E*- and *Z*-isomeric iododienynones **72** and **73** respectively, following chlorination to **69a/c**, reduction and oxidation to **69b/d**, addition of acetylene (leading to **70**), oxidation to **71**, and, finally, chloride–iodide exchange (Scheme 10) using essentially the same reagents and procedures to those used earlier in the elaborations of **24**, **36** and **47**.

Addition of Bu_3SnH–AIBN, over 8 hours, to a refluxing solution of the *Z*-iododienynone **73a** in benzene, followed by further heating for 12 hours, resulted in the formation of a single product in 35% yield. Analysis of ^1H and ^{13}C NMR spectroscopic data showed clearly that the product had the macrocyclic structure **76a** (Scheme 11), resulting from a straightforward 14-*endo*-dig cyclisation from the alkyl radical intermediate **74a** produced from **73a**, followed by H-quench of the resulting vinyl radical **75a**. The analogous macrocyclic ketone **76b** was produced (40%) when the corresponding *Z*-iododienynone **73b** was treated likewise with Bu_3SnH–AIBN. The *E*-geometry of the newly incorporated alkene bond in **76** followed conclusively from the magnitude of the observed couplings between the vicinal olefinic hydrogen atoms, *i.e.* *J* 15 Hz, in the ^1H NMR spectrum.

We assume that the different outcome following treatment of **73** with Bu_3SnH–AIBN, compared to **60**, has its origins in the



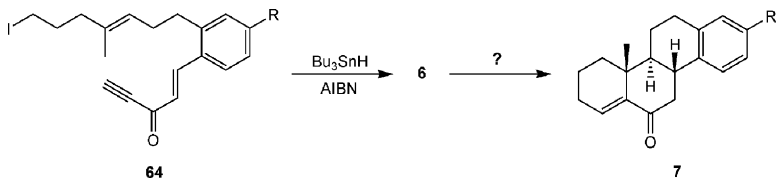
preferred conformation of the first-formed macrocyclic radical intermediate **75**. Thus, a favourable conformation in **75** could facilitate rapid H-abstraction processes, perhaps involving the methyl group hydrogens on the adjacent trisubstituted double bond, to the exclusion of transannular-radical C–C bond forming reactions found with the corresponding macrocyclic radical intermediate **61** produced from **60**. We examined a range of alternative reaction conditions, designed to promote a cascade of radical cyclisations producing the ring-D aromatic steroid **7** from **73**, but to no avail, instead only the macrocyclic ketone **76** was obtained. We also attempted to produce **7** by treatment of the macrocyclic ketone **76** with SmI_2 in THF, but only starting material was recovered.

We next studied the outcome of treatment of the corresponding *E*-iododienynones **72a** and **72b** with Bu_3SnH–AIBN, and this was even more interesting and surprising! Thus, treatment of the methoxyaryl-substituted iododienynone **72b** with Bu_3SnH–AIBN in refluxing benzene, followed by work-up and chromatography gave a 2 : 1 mixture of two diastereoisomers of an oily, chemically homogenous, polycyclic product in approximately 30% yield. The separation, and hence identification of these methoxyaryl-substituted cyclic products proved problematic. The mixture of diastereoisomers was therefore demethylated, using BBr_3 in CH_2Cl_2 at −78 °C, which led to a 2 : 1 mixture of diastereoisomers of the corresponding phenols, isolated as a viscous liquid solid. Crystallisation of the mixture from diethyl ether–pentane gave a homogenous sample of the major diastereoisomer, as colourless crystals, suitable for X-ray analysis.

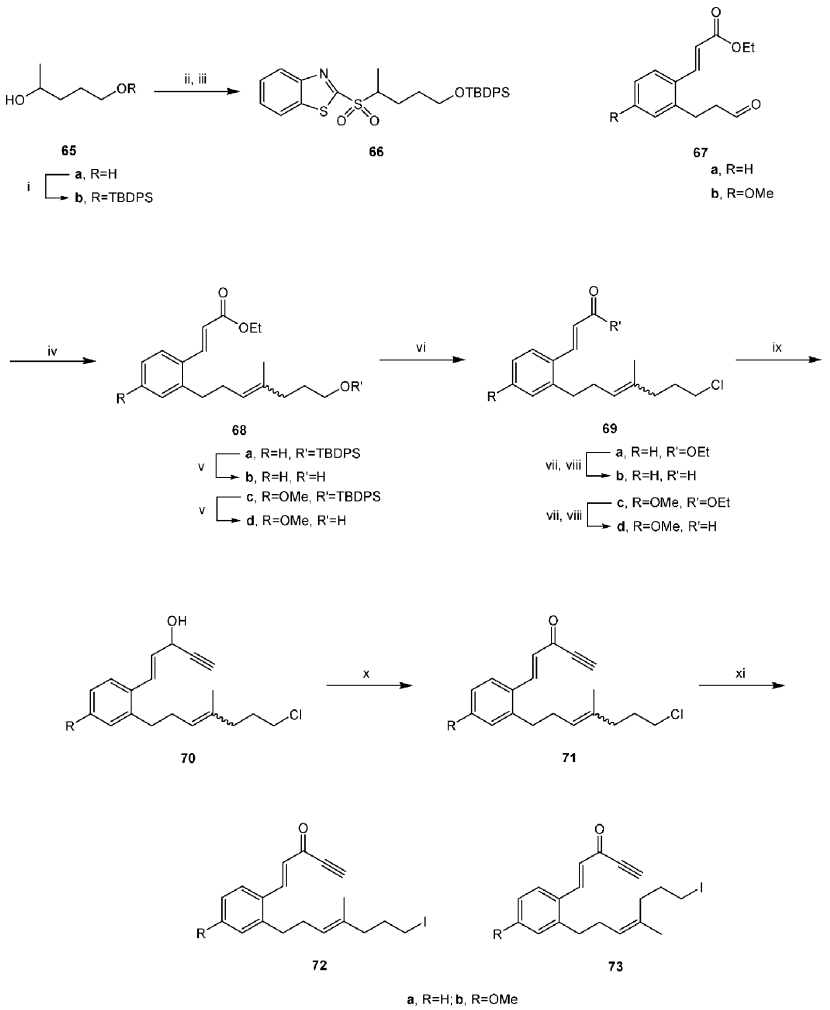
To our surprise, the X-ray crystal structure[32] showed that we had produced the unusual angular 6,6,6-ring fused substituted aromatic structure **77** as the major product following treatment of the iododienynone **72b** with Bu_3SnH–AIBN in refluxing benzene. A similar 2 : 1 mixture of diastereoisomers, with **77a** as the major isomer, was produced when the corresponding des-methoxy iododienynone **72a** was treated with Bu_3SnH–AIBN in refluxing benzene.

The formation of the bridged tricycle **77** from **72** requires three intramolecular carbon-to-carbon bond-forming processes involving C-1 and C-11; C-5 and C-10; and C-4 and C-13; in addition to an intermolecular radical coupling reaction between C-14 and the benzene used as solvent. It is likely that **77** is produced from **72** by initial 11-*endo*-trig cyclisation of the radical precursor **78** leading first to the benzylic radical intermediate **79**. Sequential 6-*exo*-trig (to **80**) and 6-*exo*-dig radical cyclisations, next lead to the vinyl radical intermediate **81**. The radical **81** is then quenched by coupling to the solvent benzene, producing the benzylidene substituted tricycle **77**, together with a diastereoisomer (Scheme 12).

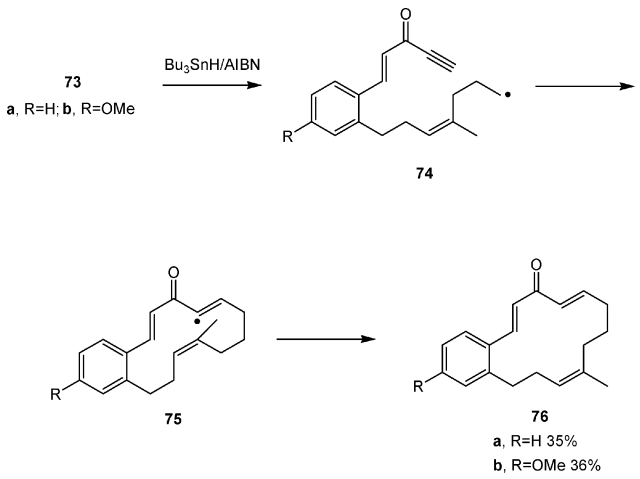
The differing reactivity of **72** and **73** reflects the importance of the geometry of the trisubstituted double bonds in these substrates, permitting 14-*endo*-trig macrocycliation to **75** with the *Z*-isomer **73** and, by contrast, favouring an unforeseen 11-*endo*-trig cyclisation (to **79**) with the *E*-isomer **72**. Whereas the 14-ring radical **75** suffers straightforward H-quench producing the macrocyclic trienone **76**, the favoured stereoelectronics present in the 11-ring radical **79** permit the subsequent radical cyclisations, leading to **81** *via* **80** (Scheme 11). Although the addition of carbon centered radicals to, and the formation of radicals from, benzene and other aryls is precedented,[33] we were somewhat surprised to encounter this phenomenon in the case leading to **77** from **81**. We therefore investigated the outcome of treatment of the iododienynone **72b** with Bu_3SnH–AIBN in refluxing heptane at 98 °C, in place of benzene. To our satisfaction, we found that the only product was a 2 : 1 mixture of diastereoisomers of the angular ring-fused enone **82**, analogous to **77b**, resulting from hydrogen, instead of benzene, quench of the presumed vinyl radical



Scheme 9



Scheme 10 *Reagents and conditions:* (i) TBDPSCl, NaH, THF, 2 h, 98%; (ii) 2-mercaptobenzothiazole, PPh_3, DEAD, THF, 24 h, 99%; (iii) *m*-CPBA, $NaHCO_3$, DCM, −40 °C → rt, 12 h, 93%; (iv) NaHMDS, **66**, THF, −78 °C → rt, 12 h, 38–55%; (v) TBAF, THF, 3 h, 25–52%; (vi) NCS, PPh_3, K_2CO_3, DCM, 1 h, 85–98%; (vii) DIBAL-H, DCM, −78 °C, 4 h, 85–92%; (viii) MnO_2, DCM, 20 h, 81–89%; (ix) ≡–MgBr, THF, −78 °C → rt, 22 h, 93–99%; (x) MnO_2, DCM, 18 h, 81–88%; (xi) NaI, K_2CO_3, 2-butanone, 80 °C, 24 h, 87–95%.

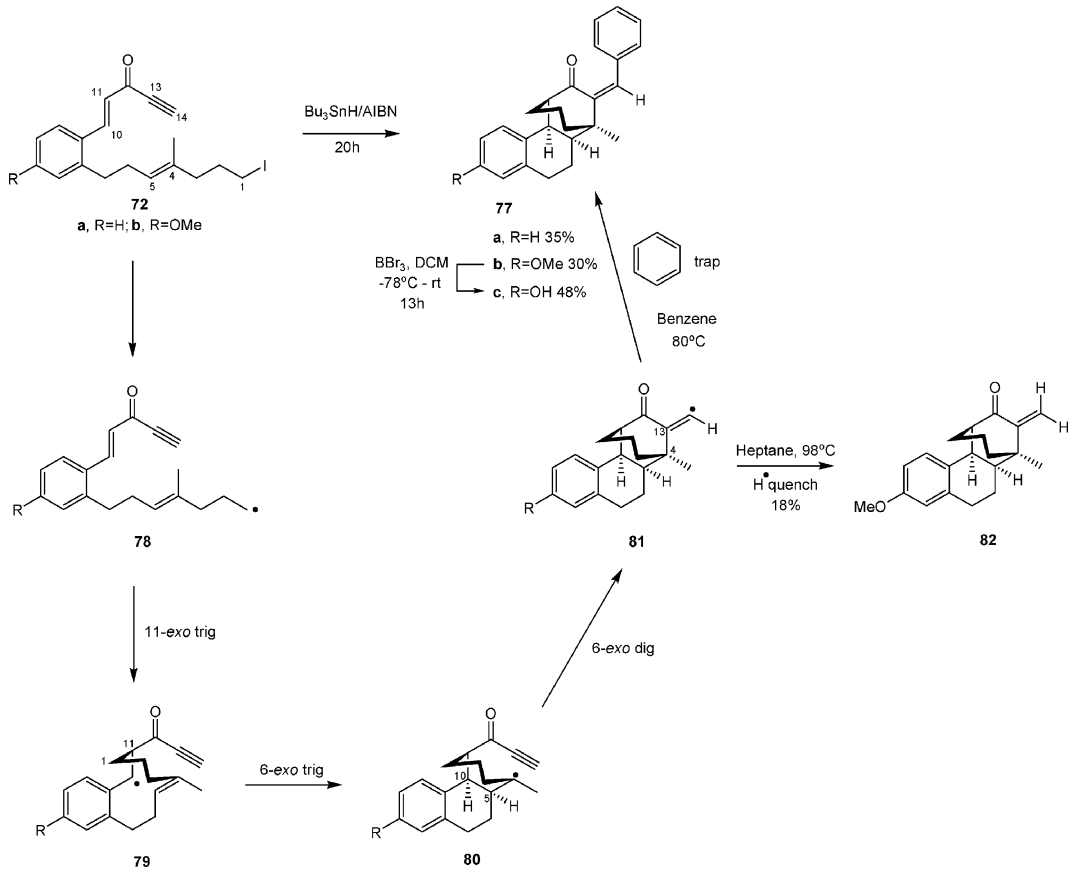


Scheme 11

intermediate **81**. Although X-ray crystallography and comparative NMR spectroscopic data established that structures **77** and **82** represent the stereochemistries of the major diastereoisomers of the angular ring-fused compounds resulting from treatment of **72** with Bu_3SnH–AIBN, we have no reliable data, or intelligence, with which to assign a stereochemistry to the minor diastereoisomers of **77**/**81** produced simultaneously in these reactions.

Summary

We have evaluated the scope for two radical-based cascade reactions involving ynone electrophores towards oestranes and ring-D aromatic steroids (Scheme 1). Our attempts to carry out radical-mediated Diels–Alder reactions with the substrates **36** and **47**, leading to **38** and **48** respectively, instead led to the unexpected tetracyclic structures **44** and **58**. Likewise, treatment of the isomeric iododienynones **72** and **73** with Bu_3SnH–AIBN led to either the macrocycle **76** or to the novel bridged tricycles **77** and **81** (depending on whether benzene or heptane was used as solvent), rather than to the anticipated ring-D steroid system **7**. Not for the first time, therefore, these studies have demonstrated how interesting and unpredictable some radical reactions can be. This



Scheme 12

is particularly so when a range of alternative reaction pathways are presented to radical intermediates by neighbouring functionality in a constrained environment, as found in the substrates **47** and **73**, in particular. Nevertheless, these same radical reactions frequently offer the opportunity to elaborate novel and unusual structures and ring systems not available by more conventional synthetic methods, *e.g.* the polycycles **58** and **77**.

Experimental

General details

All melting points were determined using a Kofler hot-stage or Bibby Stuart Scientific SMP3 apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 1600 series FT-IR instrument as liquid films or as dilute solutions in spectroscopic grade chloroform. Proton NMR spectra were recorded on a Bruker WM 250 (250 MHz), Joel EX 270 (270 MHz), Bruker DPX 360 (360 MHz), Bruker AM 400 (400 MHz) or Bruker DRX500 (500 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 Joel EX 270 (68 MHz), Bruker DPX 360 (91 MHz), Bruker AM 400 (101 MHz) or Bruker DRX500 (126 MHz) instrument as dilute solutions in deuterochloroform, unless otherwise stated. Chemical shifts are reported relative to residual solvent peaks using a broadband decoupled mode, and the multiplicities were determined using a DEPT sequence. When required, 1H–1H COSY spectra were recorded on a Bruker AM 400 (400 MHz) instrument and standard Bruker software with no modifications. 1H–13C HMQC–HMBC and NOE spectra were recorded on a Bruker AM 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. 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 40–60 °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. Dichloromethane was distilled from calcium hydride. Dry tetrahydrofuran and benzene were distilled from sodium and benzophenone. Other organic solvents and reagents were purified

by the accepted literature procedures. Solvents were removed *in vacuo* at approx. 20 mm Hg 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.

2-Oxo-tricyclo[7,4,01,6,09,13]trideca-7-ene 17. A solution of tri-*n*-butyltin hydride (0.18 ml, 0.68 mmol), and 2,2′-azobis(isobutyronitrile) (4.5 mg, 0.03 mmol) in dry benzene (10 ml) was added dropwise over 6 h to a stirred, refluxing solution of the iodide **16b** (0.18 g, 0.57 mmol) and 2,2′-azobis(isobutyronitrile) (4.5 mg, 0.03 mmol) in dry, degassed benzene (180 ml), under an argon atmosphere. The mixture was held at reflux for a further 2 h, then cooled and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with 10% ether in light petroleum (bp 40–60 °C), to give (i) the ynone **16c** (7 mg, 6%) (eluted first) as a colourless oil, ν_{max}(film)/cm^{-1} 1682, 1456, 988; δ_H (360 MHz, $CHCl_3$) 0.90 (3H, t, *J* 7.4 Hz, C*H*$_3$), 1.33–1.46 (2H, m, C*H*$_2$), 1.76–1.81 (2H, m, C*H*$_2$), 2.01–2.13 (4H, m, 2 × C*H*$_2$), 2.61 (2H, t, *J* 7.4 Hz, C*H*$_2$CO), 3.22 (1H, s, ≡C–H), 5.47–5.64 (2H, m, 2 × =C*H*), 5.96–6.06 (2H, m, 2 × =C*H*); δ_C (68 MHz, $CHCl_3$) 14.1 (q), 22.9 (t), 23.8 (t), 32.0 (t), 35.1 (t), 45.1 (t), 78.8 (d), 81.9 (s), 130.6 (d), 130.7 (d), 132.1 (d), 133.5 (d), 187.7 (s); *m*/*z* (EI) 190.1351 (M$^+$, $C_{13}H_{18}O$ requires 190.1358); and (ii) the tricycle **17** (25 mg, 22%) (eluted second) as a colourless oil, ν_{max}(film)/cm^{-1} 1702, 1168, 896; δ_H (500 MHz, $CHCl_3$) 1.44–1.94 (9H, m), 2.03–2.09 (1H, m, O=CCH$_2$C*H*$_a$H$_b$), 2.21–2.32 (2H, m, O=CC*H*$_a$H$_b$ + O=CCHC*H*CHCH$_2$), 2.46–2.51 (2H, m, O=CCH$_a$*H*$_b$ + O=CCHC*H*CH=), 2.60–2.63 (1H, m, O=CCHCHC*H*CH$_2$), 2.85 (1H, app t, *J* 6.0 Hz, O=CC*H*), 5.48 (1H, d, *J* 10.1 Hz, O=CCHCHCHC*H*=), 5.56 (1H, dt, *J* 10.1 and 3.6 Hz, O=CCHCHC*H*=); δ_C (100 MHz, $CHCl_3$) 23.8 (t), 24.5 (t), 28.1 (t), 29.5 (t), 31.3 (t), 36.4 (d), 39.5 (d), 40.6 (d), 41.3 (t), 48.8 (d), 127.7 (d), 131.5 (d), 214.9 (s).

5,6-Benzo-14-oxa-8-oxo-tricyclo[7,4,11,4,01,9]trideca-2,9-diene 44. A solution of tri-*n*-butyltin hydride (65 µl, 0.24 mmol), and 2,2′-azobis(isobutyronitrile) (1.6 mg, 0.01 mmol) in dry benzene (5 ml) was added dropwise over 2 min to a stirred, refluxing solution of the iodide **36** (76 mg, 0.20 mmol) and 2,2′-azobis(isobutyronitrile) (1.6 mg, 0.01 mmol) in dry, degassed benzene (66 ml), under an argon atmosphere. The mixture was held at reflux for a further 4 h, and then cooled and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with a gradient of 10 to 30% ether in light petroleum (bp 40–60 °C), to give (i) *recovered starting material* (26 mg, 34%) (eluted first) as a colourless oil, and (ii) the dihydrofuran **44** (23 mg, 45%) (eluted second) as a colourless oil, which crystallised upon standing at 0 °C; ν_{max}(film)/cm^{-1} 1682, 1632, 751, 736; δ_H (250 MHz, $CHCl_3$) 1.69–2.00 (4H, m, =CHCC*H*$_2$C*H*$_2$), 2.12–2.33 (2H, m, O=CC=CHC*H*$_2$), 3.33 (1H, d, *J* 11.7 Hz, O=CC*H*$_a$H$_b$), 4.66 (1H, d, *J* 11.7 Hz, O=CH$_a$*H*$_b$), 5.89 (1H, app t, *J* 2.1 Hz, ArC*H*), 5.95 (1H, dd, *J* 5.9 and 1.8 Hz, ArCHCH=C*H*), 6.31 (1H, dd, *J* 5.9 and 2.1 Hz, ArCHC*H*=), 6.44 (1H, t, *J* 3.6 Hz, O=CC=C*H*), 7.19–7.29 (4H, m, 4 × Ar*H*); δ_C (100 MHz, $CHCl_3$) 20.7 (t), 25.3 (t), 36.7 (t), 46.1 (t), 89.5 (s), 89.8 (d), 126.5 (d), 127.3 (d), 127.8 (s), 128.9 (d), 129.1 (d), 133.3 (d), 133.6 (d), 134.9 (d), 138.3 (s), 143.7 (s), 202.2 (s); *m*/*z* (EI) 252.1156 (M$^+$, $C_{17}H_{16}O_2$ requires 252.1150).

8,17-Dioxo-tetracyclo[12,3,01,6,09,14]heptadeca-9,15-diene 58. A solution of tri-*n*-butyltin hydride (32 µl, 0.12 mmol), and 2,2′-azobis(isobutyronitrile) (1 mg, 0.005 mmol) in dry benzene (3 ml) was added dropwise over 30 min to a stirred, refluxing solution of the iodide **47** (37 mg, 0.10 mmol) and 2,2′-azobis(isobutyronitrile) (1 mg, 0.005 mmol) in dry, degassed benzene (30 ml), under an argon atmosphere. The mixture was held at reflux for a further 2 h, then cooled and concentrated *in vacuo* to leave a yellow oil. The oil was purified by chromatography on silica, eluting with a gradient of 10 to 50% ether in light petroleum (bp 40–60 °C), to give the tetracyclic dione **58** (10 mg, 40%) as a colourless solid, mp 106–108 °C (acetone); ν_{max}(film)/cm^{-1} 1694, 1614; δ_H (500 MHz, $CHCl_3$) 1.15–1.25 (2H, m, O=CCH$_2$CHC*H*$_2$), 1.33–1.44 (2H, m, O=CCC*H*$_a$H$_b$ + O=CCCC*H*$_a$H$_b$), 1.50–1.54 (1H, m, O=CCH$_2$CHCH$_2$C*H*$_a$H$_b$), 1.63–1.89 (6H, m, O=CCCH$_a$*H*$_b$ + O=CCCH$_2$C*H*$_a$H$_b$ + O=CCH$_2$CHCH$_2$CH$_a$*H*$_b$ + O=CCCCH$_a$*H*$_b$ + O=CCCCH$_2$C*H*$_2$), 2.05 (1H, app dq, *J* 13.1 and 3.8 Hz, O=CCH$_2$C*H*), 2.12–2.13 (2H, m, O=CC*H*$_2$), 2.21 (1H, td, *J* 17.1 and 4.1 Hz, O=CCCH$_2$CH$_a$*H*$_b$), 2.30–2.38 (1H, m, O=CC=CHC*H*$_a$H$_b$), 2.44 (1H, dtt, *J* 20.3, 5.3 and 1.5 Hz, O=CC=CHCH$_a$*H*$_b$), 6.26 (1H, d, *J* 5.7 Hz, O=CC*H*=), 7.10 (1H, dd, *J* 5.3 and 2.8 Hz, O=CC=C*H*), 7.61 (1H, d, *J* 5.7 Hz, O=CCH=C*H*); δ_C (91 MHz, $CHCl_3$) 18.6 (t), 23.5 (t), 25.3 (t), 25.7 (t), 29.3 (t), 29.4 (t), 31.1 (t), 37.6 (d), 42.0 (t), 50.1 (s), 54.3 (s), 131.0 (d), 136.6 (s), 139.1 (d), 169.8 (d), 198.4 (s), 214.0 (s); *m*/*z* (EI) 256.1455 (M$^+$, $C_{17}H_{20}O_2$ requires 256.1463).

8α,17β-Dihydroxy-tetracyclo[12,3,01,6,09,14]heptadeca-9,15-diene 59. A solution of di-iso-butylaluminium hydride (100 µl) in dichloromethane (1 M, 0.10 mmol) was added dropwise over 2 min to a stirred solution of the tetracyclic dione **58** (10 mg, 0.04 mmol) in dry dichloromethane (1 ml), at −78 °C, under a nitrogen atmosphere. The mixture was allowed to warm to 0 °C over 2 h and then dichloromethane (5 ml) and water (5 ml) were added. The organic layer was separated and the aqueous layer was then re-extracted with dichloromethane (2 × 5 ml). The combined organic extracts were dried and concentrated *in vacuo* to leave a yellow solid, which was purified by chromatography on silica, eluting with 50% ether in light petroleum (40–60 °C), to give the diol **59** (5 mg, 50%) as colourless crystals, mp 127–130 °C (ether); ν_{max}(film)/cm^{-1} 3390, 1698, 1634, 734; δ_H (360 MHz, $CHCl_3$) 1.23–1.82 (13H, m), 2.00–2.07 (2H, m, HOCHC=CHC*H*$_2$), 2.10–2.18 (1H, m), 2.25–2.37 (1H, m), 3.98–4.03 (1H, m, HOC*H*C=), 4.85–4.86 (1H, m, HOC*H*CH=), 5.60 (1H, dd, *J* 5.8 and 2.2 Hz, HOCHCH=C*H*), 5.81 (1H, dd, *J* 5.5 and 3.4 Hz, HOCHC=C*H*), 5.87 (1H, dd, *J* 5.8 and 2.2 Hz, HOCHC*H*=); δ_C (91 MHz, $CHCl_3$) 20.1 (t), 21.1 (t), 24.7 (t), 25.0 (t), 29.7 (t), 31.0 (t), 32.1 (d), 33.3 (t), 39.7 (t), 54.9 (s), 56.1 (s), 70.9 (d), 86.6 (d), 117.8 (d), 132.8 (d), 141.4 (s), 142.4 (d); *m*/*z* (EI) 260.1771 (M +, $C_{17}H_{24}O_2$ requires 260.1776).

(5*E*,8*E*,13*Z*)-11,12,15,16-Tetrahydro-13-methylbenzo[14]annulen-7(10*H*)-one 76a. A solution of tri-*n*-butyltin hydride (110 µl, 0.41 mmol) and 2,2′-azobis(isobutyronitrile) (32 mg, 0.19 mmol) in degassed benzene (13 ml) was added dropwise, over 8 h, *via* syringe pump to a stirred solution of the iodide **73a** (127 mg, 0.32 mmol) and 2,2′-azobis(isobutyronitrile) (16 mg, 0.10 mmol) in degassed benzene (130 ml) at 80 °C under an argon atmosphere. The mixture was heated under reflux for a further 12 h, then cooled to room temperature and concentrated *in vacuo*. The residue was purified

by flash column chromatography (5–10% Et_2O, 95–90% petrol) on silica gel to leave the macrocycle **76a** (30 mg, 35%) as a colourless oil, ν_{max}(sol $CHCl_3$)/cm^{-1}, 1644, 1623; δ_H (400 MHz, $CDCl_3$), 1.63–1.76 (2H, m, CH=CHCH_2CH_2), 1.76 (3H, s, CH=CCH_3), 2.12–2.20 (4H, m, ArCH_2CH_2 + CH=CHCH_2CH_2CH_2), 2.37 (2H, dtd, *J* 7.0, 4.5 and 1.5 Hz, CH=CHCH_2), 2.66 (1H, app dd, *J* 5.0 and 4.0 Hz, ArCH_aH$_b$), 2.67 (1H, app d, *J* 12.0 Hz, ArCH$_a$$H_b$), 5.37 (1H, t, *J* 8.0 Hz, C*H*=CCH$_3$), 6.21 (1H, dt, *J* 16.0 and 1.5 Hz, O=CC*H*=CH), 6.58 (1H, dt, *J* 16.0 and 4.5 Hz, O=CCH=C*H*), 6.73 (1H, d, *J* 16.5 Hz, ArCH=C*H*), 6.97–7.34 (3H, m, 3 × Ar*H*), 7.70 (1H, dd, *J* 7.5 and 1.5 Hz, Ar*H*), 7.86 (1H, d, *J* 16.5Hz, ArC*H*=CH); δ_C (100 MHz, $CDCl_3$), 23.2 (q), 28.1 (t), 30.1 (t), 31.3 (t), 32.1 (t), 35.3 (t), 123.4 (d), 125.7 (d), 126.9 (d), 127.7 (d), 130.5 (d), 130.6 (d), 130.7 (d), 132.3 (s), 137.7 (s), 142.2 (s), 142.7 (d), 147.7 (d), 197.0 (s); *m*/*z* (ES) 289.1566 (M + Na^+, $C_{19}H_{22}ONa$ requires 289.1568).

(5*E*,8*E*)-11,12,13,14,15,16-Hexahydro-2-methoxy-13-methylbenzo[14]annulen-7(10*H*)-one 76b. A solution of tri-*n*-butyltin hydride (85 µl, 0.32 mmol) and 2,2′-azobis(isobutyronitrile) (26 mg, 0.16 mmol) in degassed benzene (11 ml) was added dropwise, over 8 h, *via* syringe pump to a stirred solution of the iodide **73b** (110 mg, 0.26 mmol) and 2,2′-azobis(isobutyronitrile) (13 mg, 0.08 mmol) in degassed benzene (110 ml) at 80 °C under an argon atmosphere. The mixture was heated under reflux for a further 12 h, then cooled to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography (5–10% Et_2O, 95–90% pentane) on silica gel to leave the macrocycle **76b** (28 mg, 36%) as a yellow oil, ν_{max}(sol $CHCl_3$)/cm^{-1}, 1640, 1602; δ_H (400 MHz, $CDCl_3$), 1.63–1.80 (2H, m, CH=CHCH_2CH_2), 1.82 (3H, s, CH=CCH_3), 2.10–2.19 (4H, m, ArCH_2CH_2 + CH=CHCH_2CH_2CH_2), 2.39 (2H, dtd, *J* 7.0, 4.0 and 1.0 Hz, CH=CHCH_2), 2.66 (2H, app t, *J* 6.0 Hz, ArCH_2), 3.84 (3H, s, OCH_3), 5.38 (1H, t, *J* 7.5 Hz, C*H*=CCH$_3$), 6.20 (1H, dt, *J* 15.5 and 1.0 Hz, O=CC*H*=CH), 6.58 (1H, dt, *J* 15.5 and 4.0 Hz, O=CCH=C*H*), 6.75 (1H, d, *J* 16.0 Hz, ArCH=C*H*), 6.79 (1H, d, *J* 1.5 Hz, CH$_3$OCC*H*C), 6.84 (1H, dd, *J* 7.0 and 1.5 Hz, CH$_3$OCC*H*CH), 7.55 (1H, d, *J* 7.0 Hz, CH$_3$OCCHC*H*), 7.88 (1H, d, *J* 16.0 Hz, ArC*H*=CH); δ_C (100 MHz, $CDCl_3$), 23.0 (q), 29.0 (t), 30.1 (t), 31.5 (t), 32.1 (t), 35.5 (t), 55.4 (q), 123.3 (d), 125.7 (d), 127.0 (d), 127.7 (d), 130.4 (d), 130.3 (d), 130.8 (d), 132.3 (s), 137.9 (s), 142.1 (s), 142.7 (d), 147.6 (d), 198.3 (s); *m*/*z* (ES) 297.1864 (M + H^+, $C_{20}H_{25}O_2$ requires 297.1854).

Benzylidene substituted bridged tricycle 77a. A solution of tri-*n*-butyltin hydride (107 µl, 0.4 mmol) and 2,2′-azobis(isobutyronitrile) (32 mg, 0.2 mmol) in degassed benzene (13 ml), was added dropwise, over 8 h, *via* syringe pump to a stirred solution of the iodide **72a** (130 mg, 0.33 mmol) and 2,2′-azobis(isobutyronitrile) (16 mg, 0.10 mmol) in degassed benzene (130 ml), at 80 °C under an argon atmosphere. The mixture was heated under reflux for 12 h, then cooled to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica (5–10% Et_2O, 95–90% petrol) to give the bridged tricyclic ketone **77a** (38 mg, 35%) as a colourless oil (inseparable mixture of diastereoisomers in a 2 : 1 ratio); ν_{max}(sol $CHCl_3$)/cm^{-1}, 1694, 1614; δ_H (400 MHz, $CDCl_3$), (major diastereoisomer) 1.40 (3H, s, CH_3), 1.48–1.89 (6H, m), 1.98–2.24 (3H, m), 2.68 (1H, app td, *J* 15.5 and 2.5 Hz, ArCH_aH$_b$), 2.94 (1H, app dt, *J* 15.5 and 3.5 Hz, ArCH$_a$$H_b$), 3.28 (1H, app dt, *J* 8.0 and 3.0 Hz, O=CC*H*), 3.38 (1H, dd, *J* 10.0 and 3.0 Hz, ArC*H*), 6.89 (1H, s, PhC*H*), 7.08–7.43 (9H, m, 9 × Ar*H*); (minor diastereoisomer) 1.27 (3H, s, CH_3), 1.48–1.89 (6H, m), 1.98–2.24 (3H, m), 2.86 (1H, app d, *J* 10.5 and 1.5 Hz, O=CC*H*), 3.02 (2H, m, ArCH_2), 3.34 (1H, dd, *J* 10.5 and 1.5 Hz, ArC*H*), 6.71 (1H, s, PhC*H*), 7.08–7.43 (9H, m, 9 × Ar*H*); δ_C (100 MHz, $CDCl_3$) (major diastereoisomer) 21.4 (t), 24.7 (t), 25.0 (t), 27.6 (q), 30.9 (t), 36.8 (d), 37.1 (t), 43.5 (s), 45.7 (d), 52.4 (d), 125.7 (d), 126.4 (d), 127.5 (d), 127.9 (2C d), 128.0 (d), 129.0 (2C d), 129.1 (d), 135.4 (d), 136.8 (s), 137.0 (s), 139.6 (s), 144.1 (s), 205.7 (s); (minor diastereoisomer) 21.8 (t), 24.0 (t), 24.3 (q), 25.8 (t), 28.7 (t), 40.7 (s), 43.6 (d), 46.0 (t), 46.5 (d), 47.2 (d), 123.3 (d), 125.4 (d), 126.2 (d), 127.8 (2C d), 128.6 (2C d), 128.9 (d), 129.1 (d), 135.1 (d), 136.6 (s), 137.4 (s), 139.5 (s), 142.6 (s), 206.1 (s); *m*/*z* (ES) 343.2053 (M + H^+, $C_{25}H_{27}O$ requires 343.2056).

Benzylidene substituted methoxy bridged tricycle 77b. A solution of tri-*n*-butyltin hydride (170 µl, 0.61 mmol) and 2,2′-azobis(isobutyronitrile) (25 mg, 0.15 mmol) in degassed benzene (20 ml), was added dropwise over 8 h *via* syringe pump, to a stirred solution of the iodide **72b** (200 mg, 0.51 mmol) and 2,2′-azobis(isobutyronitrile) (50 mg, 0.30 mmol) in degassed benzene (200 ml), at 80 °C under an argon atmosphere. The mixture was heated under reflux for a further 12 h, then allowed to cool to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica (2–10% Et_2O, 98–90% petrol) to give the bridged tricyclic ketone **77b** (45 mg, 30%) as an inseparable mixture of diastereoisomers in a 2 : 1 ratio, as a colourless oil, ν_{max}(sol $CHCl_3$)/cm^{-1}, 1693, 1612; δ_H (400 MHz, $CDCl_3$) (major diastereoisomer) 1.39 (3H, s, CH_3), 1.47–1.63 (3H, m), 1.69–1.85 (3H, m), 2.01–2.19 (3H, m), 2.67 (1H, app td, *J* 15.5 and 3.0 Hz, ArCH_aH$_b$), 2.89 (1H, app dt, *J* 15.5 and 3.5 Hz, ArCH$_a$$H_b$), 3.21 (1H, ddd, *J* 8.0 and 3.0 Hz, and 2.5 Hz, O=CC*H*), 3.32 (1H, dd, *J* 10.0 and 3.0 Hz, ArC*H*), 3.80 (3H, s, OCH_3), 6.69 (1H, d, *J* 2.5 Hz, CH$_3$OCC*H*C), 6.77 (1H, dd, *J* 8.5 and 2.5 Hz, CH$_3$OCC*H*CH), 6.87 (1H, s, PhC*H*=), 7.17 (1H, d, *J* 8.5 Hz, CH$_3$OCCHC*H*), 7.26–7.44 (5H, m, 5 × Ph*H*); (minor diastereoisomer) 1.27 (3H, s, CH_3), 1.51–1.82 (6H, m), 1.96–2.19 (3H, m), 2.81 (1H, app d, *J* 8.5 Hz, O=CC*H*), 3.00 (2H, app t, *J* 8.5 Hz, ArCH_2), 3.29 (1H, dd, *J* 8.5 and 1.5 Hz, ArC*H*), 3.79 (3H, s, OCH_3), 6.68 (1H, d, *J* 3.0 Hz, CH$_3$OCC*H*C), 6.71 (1H, s, PhC*H*=), 6.78 (1H, dd, *J* 8.5 and 3.0 Hz, CH$_3$OCC*H*CH), 7.00 (1H, d, *J* 8.5 Hz, CH$_3$OCCHC*H*), 7.26–7.38 (5H, m, 5 × Ph*H*); δ_C (100 MHz, $CDCl_3$) (major diastereoisomer) 21.4 (t), 24.7 (t), 24.8 (t), 27.6 (q), 31.2 (t), 36.1 (d), 36.9 (t), 43.4 (s), 45.7 (d), 52.6 (d), 55.2 (q), 112.4 (d), 113.3 (d), 127.8 (2C d), 127.9 (d), 128.5 (d), 128.7 (s), 129.0 (2C d), 135.3 (d), 136.9 (s), 140.7 (s), 144.0 (s), 157.4 (s), 205.8 (s); (minor diastereoisomer) 21.8 (t), 23.7 (t), 24.2 (q), 25.9 (t), 29.1 (t), 40.7 (s), 42.9 (d), 46.0 (t), 46.7 (d), 47.3 (d), 55.2 (q), 110.6 (d), 114.4 (d), 124.2 (d), 127.7 (2C d), 127.8 (d), 129.0 (2C d), 131.6 (s), 135.0 (d), 136.6 (s), 138.7 (s), 142.6 (s), 158.0 (s), 206.1 (s); *m*/*z* (ES) 373.2155 (M + H^+, $C_{26}H_{29}O_2$ requires 373.2162).

Phenolic bridged tricycle 77c. Boron tribromide (50 µl, 0.53 mmol) was added dropwise, to a stirred solution of the tricycle **77b** (50 mg, 0.13 mmol) in dichloromethane (10 ml) at −78 °C, under a nitrogen atmosphere. The solution was warmed to room temperature slowly over 13 h, and then quenched with water (50 ml). The separated aqueous phase was extracted with

dichloromethane (3 × 50 ml) and the combined organic extracts were dried and concentrated *in vacuo*. The residue was purified by flash column chromatography, (10% Et_2O, 90% petrol) to give a 2 : 1 mixture of diastereoisomers of the phenol **77c** (23 mg, 48%) as a viscous liquid solid. Crystallisation from diethyl ether and pentane gave the major diastereoisomer as colourless crystals, mp 195–196 °C; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3597, 1693, 1608; δ_H (400 MHz, $CDCl_3$) (major diastereoisomer) 1.39 (3H, s, CH_3), 1.46–1.62 (3H, m), 1.69–1.85 (3H, m), 2.01–2.20 (3H, m), 2.63 (1H, app td, *J* 15.5 and 3.5 Hz, ArCH_aH$_b$), 2.85 (1H, app dt, *J* 15.5 and 3.0 Hz, ArCH$_a$$H_b$), 3.19 (1H, app d, *J* 10.0 Hz, O=CC*H*), 3.31 (1H, dd, *J* 10.0 and 3.0 Hz, ArC*H*), 4.71 (1H, br s, O*H*), 6.62 (1H, d, *J* 2.5 Hz, HOCC*H*C), 6.66 (1H, dd, *J* 8.5 and 2.5 Hz, HOCC*H*CH), 6.89 (1H, s, PhC*H*=), 7.11 (1H, d, *J* 8.5 Hz, HOCCHC*H*), 7.27–7.36 (3H, m, 3 × Ph*H*), 7.42 (2H, app d, *J* 7.5 Hz, 2 × Ph*H*); (minor diastereoisomer) 1.26 (3H, s, CH_3), 1.47–1.81 (6H, m), 1.95–2.13 (3H, m), 2.79 (1H, app d, *J* 10.0 Hz, O=CC*H*), 2.93–2.99 (2H, m, ArCH_2), 3.30 (1H, dd, *J* 10.0 and 2.0 Hz, ArC*H*), 5.25 (1H, br s, O*H*), 6.59 (1H, d, *J* 2.5 Hz, HOCC*H*C), 6.65 (1H, dd, *J* 8.5 and 2.5 Hz, HOCC*H*CH), 6.71 (1H, s, PhC*H*=), 6.92 (1H, d, *J* 8.5 Hz, HOCCHC*H*), 7.25–7.39 (5H, m, 5 × Ph*H*); δ_C (100 MHz, $CDCl_3$) (major diastereoisomer) 21.4 (t), 24.7 (t), 24.9 (t), 27.6 (q), 31.0 (t), 36.1 (d), 37.0 (t), 43.5 (s), 45.7 (d), 52.6 (d), 113.7 (d), 114.8 (d), 127.8 (2C d), 127.9 (d), 128.7 (d), 128.8 (s), 129.0 (2C d), 135.4 (d), 137.0 (s), 141.0 (s), 144.0 (s), 153.3 (s), 205.9 (s); (minor diastereoisomer) 21.8 (t), 23.8 (t), 24.3 (q), 25.9 (t), 28.9 (t), 40.7 (s), 43.0 (d), 46.0 (t), 46.8 (d), 47.3 (d), 112.3 (d), 115.7 (d), 127.7 (s), 127.8 (2C d), 128.0 (d), 128.7 (d), 128.9 (2C d), 135.3 (d), 138.1 (s), 139.3 (s), 144.5 (s), 154.1 (s), 206.7 (s); *m*/*z* (ES) 359.1999 (M + H$^+$, $C_{25}H_{27}O_2$ requires 359.2006).

Methylidene substituted methoxy bridged tricycle 82. A solution of tri-*n*-butyltin hydride (107 µl, 0.40 mmol) and 2,2′-azobis(isobutyronitrile) (6 mg, 0.04 mmol) in degassed heptane (14 ml), was added dropwise over 8 h *via* syringe pump, to a stirred solution of the iodide **72b** (140 mg, 0.33 mmol) and 2,2′-azobis(isobutyronitrile) (35 mg, 0.21 mmol) in degassed heptane (140 ml), at 90 °C under an argon atmosphere. The mixture was heated under reflux for a further 12 h, then allowed to cool to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica (2–10% Et_2O, 98–90% petrol) to give the bridged tricyclic ketone **82** (18 mg, 18%) as an inseparable mixture of diastereoisomers in a 2 : 1 ratio, as a colourless oil, ν_{max}(sol $CHCl_3$)/cm^{-1}, 1695, 1611; δ_H (400 MHz, $CDCl_3$), (major diastereoisomer) 1.31 (3H, s, CH_3), 1.50–1.83 (6H, m), 1.98–2.14 (3H, m), 2.62 (1H, app td, *J* 14.5 and 3.0 Hz, ArCH_aH$_b$), 2.86 (1H, app dt, *J* 14.5 and 3.5 Hz, ArCH$_a$$H_b$), 3.21 (1H, app dd, *J* 9.0 and 3.0 Hz, and 2.5 Hz, O=CC*H*), 3.32 (1H, dd, *J* 10.5 and 3.0 Hz, ArC*H*), 3.79 (3H, s, OCH_3), 5.43 (1H, d, *J* 1.0 Hz, =CH_aH$_b$), 6.23 (1H, d, *J* 1.0 Hz, =CH$_a$$H_b$), 6.69 (1H, d, *J* 2.5 Hz, CH_3OCC*H*C), 6.75 (1H, dd, *J* 8.5 and 2.5 Hz, CH_3OCC*H*CH), 7.16 (1H, d, *J* 8.5 Hz, CH_3OCCHC*H*); (minor diastereoisomer) 1.20 (3H, s, CH_3), 1.55–1.95 (6H, m), 1.98–2.18 (3H, m), 2.52 (1H, app d, *J* 9.0 Hz, O=CC*H*), 2.95 (2H, app t, *J* 8.5 Hz, ArCH_2), 3.26 (1H, dd, *J* 9.0 and 1.5 Hz, ArC*H*), 3.78 (3H, s, OCH_3), 5.33 (1H, d, *J* 1.0 Hz, =CH_aH$_b$), 6.19 (1H, d, *J* 1.0 Hz, =CH$_a$$H_b$), 6.68 (1H, d, *J* 3.0 Hz, CH_3OCC*H*C), 6.76 (1H, dd, *J* 8.0 and 3.0 Hz, CH_3OCC*H*CH), 6.98 (1H, d, *J* 8.0 Hz, CH_3OCCHC*H*); δ_C (100 MHz, $CDCl_3$) (major diastereoisomer) 21.5 (t), 23.4 (t), 24.8 (t), 27.0 (q), 31.1 (t), 36.2 (d), 37.0 (t), 43.4 (s), 44.3 (d), 51.2 (d), 55.2 (q), 112.3 (d), 113.3 (d), 119.0 (t), 128.3 (d), 128.6 (s), 140.9 (s), 148.5 (s), 157.4 (s), 205.2 (s); (minor diastereoisomer) 21.8 (t), 22.3 (t), 24.4 (q), 25.9 (t), 29.1 (t), 40.1 (s), 41.7 (d), 44.7 (t), 46.1 (d), 46.5 (d), 55.3 (q), 110.6 (d), 114.4 (d), 119.7 (t), 127.8 (d), 131.6 (s), 138.7 (s), 146.2 (s), 158.0 (s), 205.3 (s); *m*/*z* (ES) 319.1669 (M + Na$^+$, $C_{20}H_{24}O_2Na$ requires 319.1674).

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