A chemoenzymatic synthesis of the carbobicyclic core associated with CP-225,917 and CP-263,114 (phomoidrides A and B)

Martin G. Banwell,* Kenneth J. McRae and Anthony C. Willis

Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 0200, Australia. E-mail: mgb@rsc.anu.edu.au

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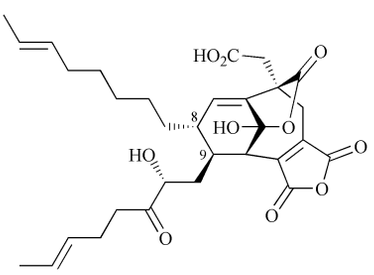
The bromobenzene-derived and enantiopure *cis*-1,2-dihydrocatechol **3** has been converted, *via* a reaction sequence involving Diels–Alder cycloaddition, anionic oxy-Cope rearrangement and Wolff ring-contraction steps, into compound **4** and epimer **24**, which embody key structural elements associated with the nonadride-type natural products CP-225,917 (**1**) and CP-263,114 (**2**).

Introduction

In 1997 Kaneko *et al*. at Pfizer Central Research (USA) detailed the isolation of CP-225,917 (**1**) and CP-263,114 (**2**) from an unidentified fungus.[1] The same group reported[2] that compounds **1** and **2** inhibit Ras farnesyl transferase (from rat's brains) with IC_{50} values of 20 and 6 μM, respectively. The latter compound also inhibits squalene synthase (SQS) with an IC_{50} of 43 μM.[2] These natural products are probably biogenetically related to the nonadrides[2] and, by virtue of their structural complexity and biological activities, have been described as "milestone compounds".[3]



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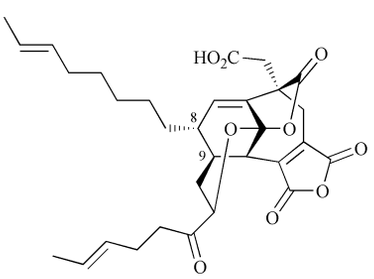

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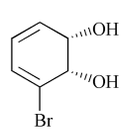
Not surprisingly CP-225,917 and CP-263,114 have attracted significant attention as targets for synthesis. Various approaches,[3,4] including a biomimetic one,[5] have been reported with total syntheses having recently been achieved by Nicolaou,[6a,b] Shair,[6c] Danishefsky[6d] and Fukuyama.[6e] The last[6e] and related studies[7] have allowed the assignment of the absolute stereochemistries of the title compounds which are opposite to those implied by structures **1** and **2**. It is against this background that we now report on the conversion of the *cis*-1,2-dihydrocatechol **3**, which is obtained in large quantity and in enantiopure form by microbial *cis*-dihydroxylation of bromobenzene,[8] into the highly functionalised and monochiral bicyclo[4.3.1]dec-6(7)-ene **4** (phomoidride core numbering shown[4m]). The chemistry detailed herein was commenced before the absolute stereochemistries of compounds **1** and **2** had been established and, for convenience, we chose to use the readily available diol **3** as starting material. However, the enantiomer of compound **3** (*viz*. *ent*-**3**) is known[9] so the work described herein can be employed for the preparation of *ent*-**4** and related systems possessing the same absolute stereochemistry as CP-225,917 and CP-263,114. Compound **4** embodies key structural elements associated with the carbobicyclic core of the title natural products and the strategy used to obtain this material is sufficiently flexible that it should serve as a means for making useful analogues of compounds **1** and **2** and, perhaps, the natural products themselves.



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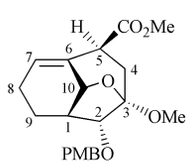

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A central objective associated with the present work was to capitalise on our earlier experience with converting, *via* Diels–Alder cycloaddition and anionic oxy-Cope rearrangement steps, a *cis*-1,2-dihydrocatechol into the AB-ring substructure (a bicyclo[5.3.1]undec-7(8)-ene) associated with taxoids.[10] It was anticipated that through application of Wolff ring-contraction techniques, such a ring system could be converted into the required bicyclo[4.3.1]dec-6(7)-ene-5-carboxylic acid.

Results and discussion

The early stages of the reaction sequence leading, *via* the above-mentioned strategy, from compound **3** to target **4** are shown in Scheme 1. Thus, the readily available and epimerically pure benzylidene acetal of diol **3** was subjected to Diels–Alder reaction with α-chloroacryloyl chloride[11] (which serves as a ketene equivalent).[12] The resulting epimeric mixture of acid chlorides was immediately treated with sodium azide and the ensuing α-chlorinated acyl azides underwent smooth Curtius rearrangement and subsequent hydrolysis to afford ketone **5** (70% from compound **3**). The $\Delta^{5,6}$-double bond associated with

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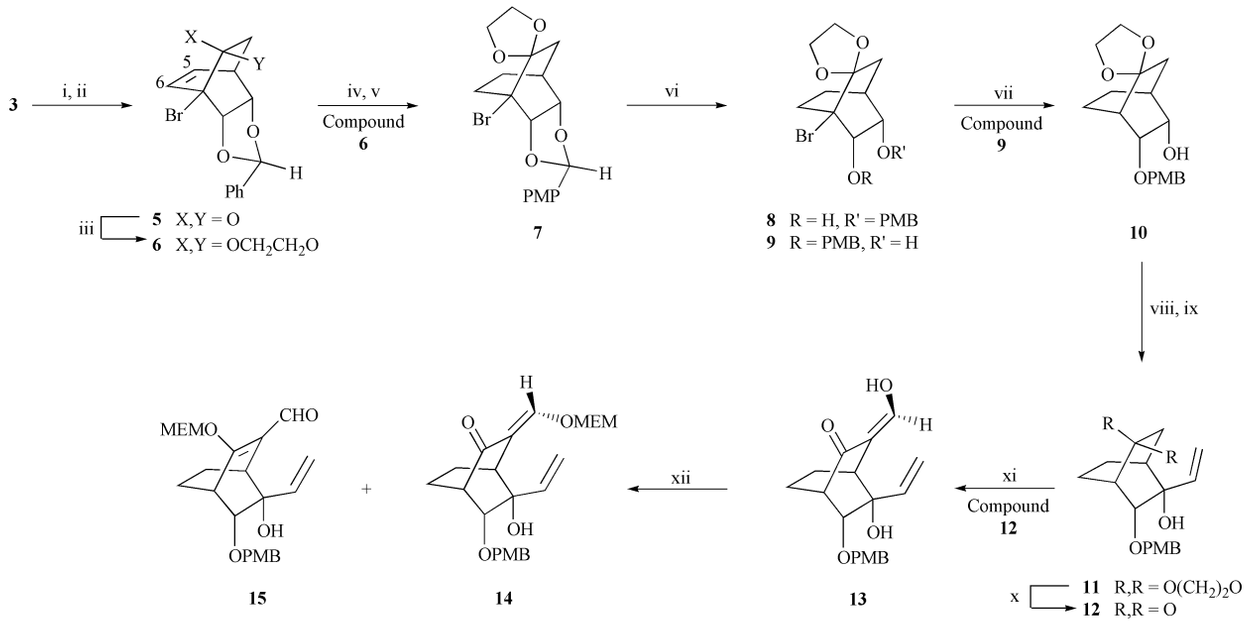
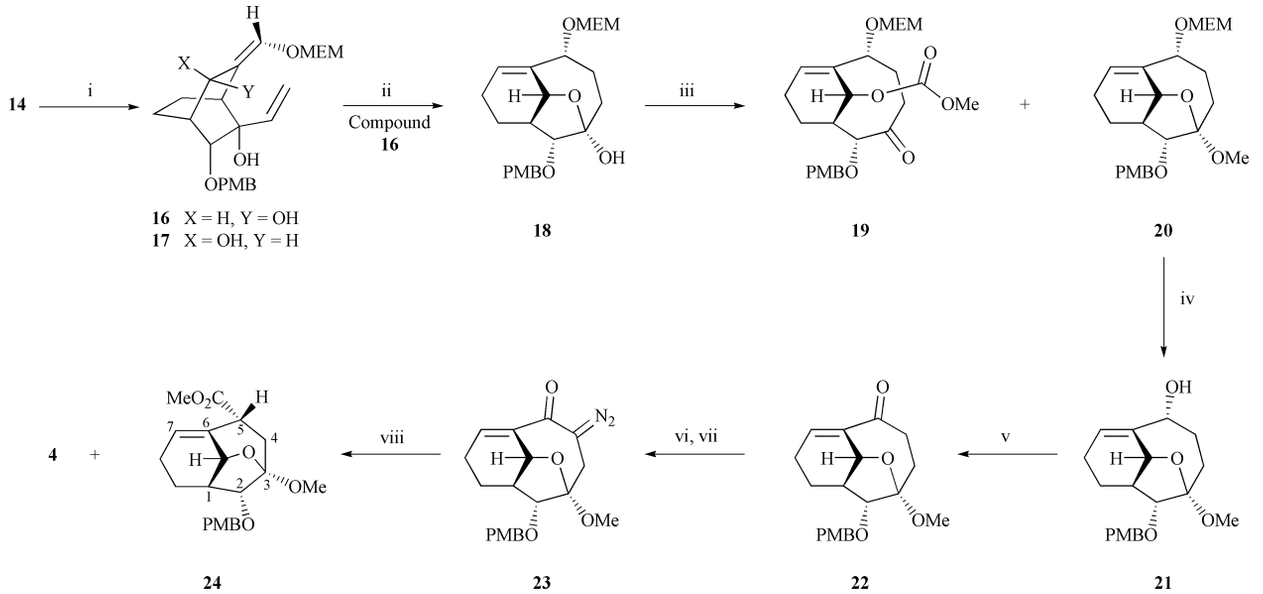


Scheme 1 *Reagents and conditions*: i, benzaldehyde dimethyl acetal (BDMA), (+)-CSA·H_2O, CH_2Cl_2, −20 to −10 °C, 1 h; ii, a. α-chloroacryloyl chloride, K_2CO_3, benzene, 70 °C, 16 h; b. NaN_3, DME, 18 °C, 3 h; c. DME, reflux, 3 h; d. 5% v/v AcOH–H_2O, 0 °C, 0.5 h; iii, $(TMSOCH_2)_2$, TMSOTf, CH_2Cl_2, 18 °C, 24 h; iv, Pd/C, H_2, THF, 18 °C, 26 h; v, PMBDMA, (+)-CSA·H_2O, CH_2Cl_2, −20 °C, 3 h; vi, DIBAL-H, CH_2Cl_2, −50 to 0 °C, 10 h; vii, *n*-Bu_3SnH, AIBN, benzene, *hv*, 18 °C, 6 h; viii, oxalyl chloride, DMSO, CH_2Cl_2, −78 °C, 4 h then NEt_3, −78 °C, 0.5 h then −78 to 18 °C, 0.5 h; ix, $(H_2C{=}CH)MgBr$, THF, −40 °C, 3 h; x, PPTS, 95% v/v acetone–H_2O, reflux, 24 h; xi, NaH, ethyl formate, THF, 0 to 18 °C, 2.5 h; xii, DBU, MEM-Cl, DMF, −55 to −20 °C, 5.66 h (PMP = *p*-methoxyphenyl).

compounds such as **5** and **6** corresponds to the sites of attachment of the side chains at C-8 and C-9 in targets **1** and **2**. It is our intention, in future studies (*vide infra*), to exploit this double bond as a platform for the regio- and diastereo-selective introduction of these moieties. However, for the purposes of the present work, the primary focus of which was to establish the feasibility of the above-mentioned anionic oxy-Cope–Wolff rearrangement sequence, this double bond was deleted. Thus, the readily obtained ethylene acetal derivative, **6** (91%), of ketone **5** was converted into the corresponding saturated diol (97%) upon treatment with dihydrogen in the presence of palladium on carbon, before transformation into the *p*-methoxybenzylidene acetal **7** (97%). In principle, this *p*-methoxybenzylidene acetal moiety could have been introduced at the beginning of the reaction sequence, thereby avoiding the protecting group interconversion described here. However, attempts to prepare such an acetal by reaction of diol **3** with *p*-methoxybenzaldehyde dimethyl acetal (PMBDMA) in the presence of appropriate acid catalysts invariably led to epimeric mixtures of the target compounds. Since, in contrast, the corresponding reaction leading to the simple benzylidene acetal always afforded a single epimeric product the reaction sequence just described proved the more serviceable. Reductive cleavage of acetal **7** could be achieved in a regioselective manner using DIBAL-H and a 2 : 7 mixture of the *p*-methoxybenzyl (PMB) mono-ethers **8** (21%) and **9** (70%), respectively, was obtained. The required regioisomer **9** was subjected to reductive debromination with tri-*n*-butyltin hydride and the single product **10** (70%) thereby obtained was submitted to oxidation with the Dess–Martin periodinane.[13] The ensuing ketone (96%) reacted in a diastereofacially selective fashion with vinylmagnesium bromide to give compound **11** (85%) which was then subjected to acetal hydrolysis using pyridinium toluene-*p*-sulfonate (PPTS) as catalyst. The ketone **12** (90%) thus obtained was subjected to a Claisen condensation reaction with ethyl formate to provide the hydroxymethylenated product **13** (75%) with the *Z*-configuration about the newly introduced double bond, such that the vinylogous acid residue can engage in intramolecular hydrogen-bonding. Reaction of compound **13** with (2-methoxyethoxy)methyl chloride (MEM-Cl) in the presence of DBU at low temperature produced an 8 : 1 mixture of the expected ether **14** (80%) and the isomeric aldehyde **15** (5%) resulting from electrophilic attack of MEM-Cl at the alternate end of the ambident anion derived from the conjugate acid **13**. The illustrated *E*-configuration about the enol ether moiety within compound **14** follows from an X-ray crystallographic study on a derivative (*vide infra*).

All attempts to engage compound **14** in an anionic oxy-Cope rearrangement process failed and in each instance the hydrolysis product **13** was the only characterisable reaction product. On the basis that suppression of the hydrolysis process, which presumably involves a nucleophilic addition–elimination sequence, would allow for the desired arrangement to occur, enone **14** was subjected to modified Luche reduction conditions[14] (Scheme 2) and in this manner an 8 : 1 mixture of unstable allylic alcohols **16** (85%) and **17** (5%) was obtained. The illustrated stereochemistries at the newly installed stereogenic centre within these products follow from the subsequent chemistry. Thus, the major product, **16**, underwent smooth anionic oxy-Cope rearrangement on treatment with potassium hydride and 18-crown-6 (18-C-6) at 60 °C and, after work-up with aqueous ammonium chloride, the lactol **18** (83%) was obtained. Subjection of this last compound to Purdie–Irvine methylation conditions resulted in the formation of the desired acetal **20** (92%) together with small amounts of the crystalline by-product **19** (<5%), the structure of which was determined by single-crystal X-ray analysis (Fig. 1). This X-ray study effectively serves to confirm the structures of all the compounds described to this point. By-product **19** is presumed to result from contamination of the silver oxide used in the methylation process by silver carbonate which serves as the source of the carbon dioxide residue incorporated during the conversion **18** ⟶ **19**. Support for this proposition follows from the observation that when freshly prepared, and presumably carbonate-free, silver oxide is used in the *O*-methylation process then acetal **20** is the exclusive product of reaction.

With the acquisition of compound **20** the introduction of functionality necessary for carrying out the key Wolff ring-contraction step was pursued. To these ends the MEM ether moiety within substrate **20** was cleaved under conditions



Scheme 2 *Reagents and conditions*: i, $NaBH_4$, $CeCl_3$, 2,6-lutidine, EtOH, 0 °C, 1 h; ii, KH, 18-C-6, DME, 60 °C, 2 h then 5% aqueous HCl, 0 °C, 5 min; iii, CH_3I, Ag_2O, DMF, reflux, 30 min; iv, PPTS, *tert*-BuOH, reflux, 4 h; v, Dess–Martin periodinane, CH_2Cl_2, 0 °C, 3 h; vi, NaH, ethyl formate, THF, 0 to 18 °C, 1.5 h; vii, *p*-nitrobenzenesulfonyl azide, NEt_3, CH_2Cl_2, 0 °C, 45 min; viii, MeOH, *hv*, 18 °C, 45 min.

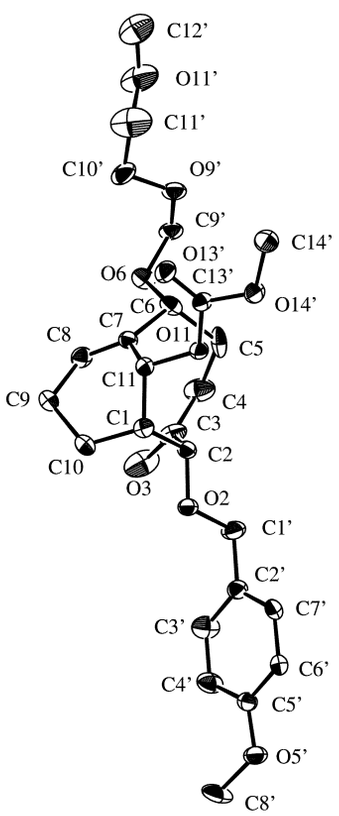


Fig. 1 ORTEP derived from single-crystal X-ray analysis of carbonate **19**.

defined by Monti *et al.*[15] and the ensuing 2°-alcohol **21** (85%) was oxidised to the corresponding ketone **22** (96%) using the Dess–Martin periodinane. In anticipation of a diazo-transfer reaction,[16] α-formylation of this last compound was achieved under standard conditions and the product of this reaction was immediately treated with *p*-nitrobenzenesulfonyl azide.[17] In this fashion the yellow-coloured α-diazoketone **23** (70% from **22**) was obtained and irradiation of a methanolic solution of this compound, using a medium pressure mercury lamp fitted with a Pyrex filter, then afforded a chromatographically separable mixture of the Wolff rearrangement [18] product **4** (25%) and its C-5-epimer **24** (42%). The stereochemistries associated with C-5 in each of epimers **4** and **24** were readily discerned by ^{1}H NMR spectroscopic methods. In particular, in the spectrum of the minor epimer the geminally-related and diastereotopic protons at C-4 show mutual coupling (J_{gem} = 13.7 Hz) but only one of them shows vicinal coupling (J = 7.8 Hz) to the adjacent methine proton, H-5, which resonates, as a doublet, at δ 3.04. In contrast, in the analogous spectrum of the major isomer the equivalent methylene protons are not only coupled to one another (J_{gem} = 13.3 Hz) but each are now also coupled to H-5 (J = 11.1 and 7.4 Hz). Inspection of molecular models and consideration of the relationship between coupling constants and dihedral angle suggest that such observations are best accommodated by the illustrated stereochemical assignments for compounds **4** and **24**.

The lack of any significant level of diastereoselection in the Wolff ring-contraction of diazoketone **23** is likely to be of little consequence because upon deprotonation each of products **4** and **24** would lead to a common ester enolate that will be used to introduce the acetic acid side-chain required at C-5.

Conclusion

Application of the strategy detailed herein to the total synthesis of the title compounds as well as various analogues is now underway in these laboratories. As noted earlier, the double-bond within Diels–Alder adducts such as **5** and **6** could serve as a means by which to introduce the C-8 and C-9 side-chains associated with targets **1** and **2**. A possible scenario is shown in Fig. 2 and relies on conversion of acetal **6**, *via* standard functional group interconversions (FGIs), into the *Se*-phenyl-selenocarbonate **25**. Reaction of such a species with tri-*n*-butyltin hydride under conditions defined by Bachi and Bosch [19] should result in formation of radical **26** which might be expected to engage in a 5-*exo*-*trig* cyclisation onto the proximate double bond more rapidly than it would engage in decarboxylation.[19] If so, then the newly formed alkyl radical, **27**, would be expected to engage in a diastereofacially selective radical allylation reaction with, for example, an allyl sulfone [20] such that compound **28** would be obtained. Reduction of this lactone to the corresponding lactol and subjection of the latter to Wittig-type olefination would enable ready introduction of the C-8 side chain associated with the phomoidrides. Similarly, the allyl residue could be exploited in establishing the C-9

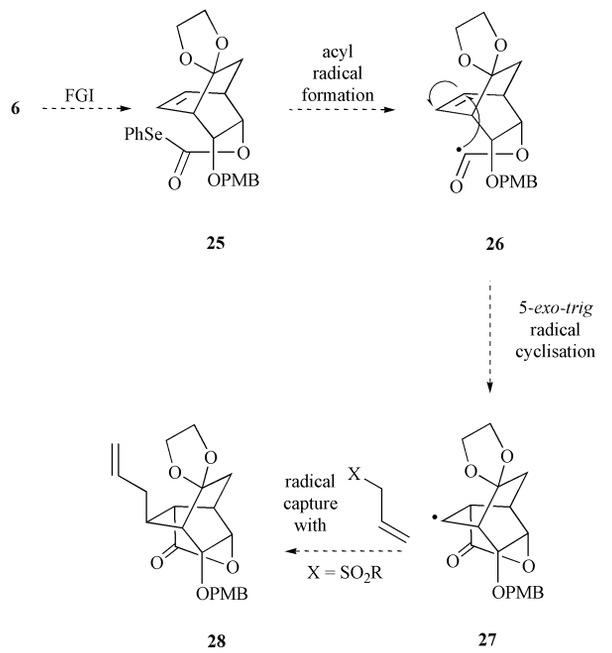


Fig. 2 Possible strategy for the regio- and diastereo-selective incorporation of the phomoidride side-chain synthons into a bicyclo[2.2.2]-octanyl precursor.

side-chain, while the bicyclo[2.2.2]octane moiety could be elaborated to the phomoidride core by the anionic oxy-Cope and Wolff rearrangement chemistries detailed above. Work by others[2–4] has demonstrated that the so-called maleic anhydride moiety associated with targets **1** and **2** can be installed rather easily. Work aimed at amalgamating and implementing these chemistries is currently underway in these laboratories. Results will be reported in due course.

Experimental

Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Varian Gemini 300 or a Varian Mercury 300 spectrometer operating at 300 MHz for proton and 75 MHz for carbon nuclei. Chemical shifts were recorded as δ values in parts per million (ppm). Spectra were acquired in deuteriochloroform ($CDCl_3$) at 20 °C unless otherwise stated. For ^{1}H NMR spectra recorded in $CDCl_3$, the peak due to residual $CHCl_3$ (δ_H 7.26) was used as the internal reference. ^{1}H NMR data are recorded as follows: chemical shift (δ_H) [multiplicity, coupling constant(s) *J*/Hz, relative integral, assignment (where possible)] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. The central peak (δ 77.0) of the $CDCl_3$ triplet was used as the reference for proton-decoupled ^{13}C NMR spectra. For ^{13}C NMR spectra, the data are given as: chemical shift (δ_C) (protonicity), where protonicity is defined as: C = quaternary; CH = methine; CH_2 = methylene; CH_3 = methyl; C or CH_2 = quaternary or methylene; CH or CH_3 = methine or methyl. The assignments of signals observed in various NMR spectra were often assisted by conducting attached proton test (APT), homonuclear (^{1}H–^{1}H) correlation spectroscopy (COSY), nuclear Overhauser effect (NOE), and/or ^{1}H–^{13}C correlation spectroscopy (HETCOR) experiments. Infrared spectra (ν_{max}) were recorded on either a Perkin-Elmer 1800 Fourier Transform infrared spectrophotometer or a Perkin-Elmer Spectrum *One* instrument. Samples were analysed as KBr discs (for solids) or as thin films on KBr plates (for liquids/oils). Low and high resolution mass spectra were recorded on a VG Fisons AutoSpec three sector (E/B/E) double focussing mass spectrometer, using positive-ion electron impact techniques (unless otherwise specified) at the voltages indicated. Mass spectral data are listed as: mass-to-charge ratio (*m*/*z*); assignment (where possible); intensity relative to the base peak. Optical rotations were measured with a Perkin-Elmer 241 polarimeter at the sodium D-line (589 nm) using the spectroscopic grade solvents specified at 20 °C and at the concentrations (*c*) (g 100 mL^{-1}) indicated. The measurements were carried out in a cell with a path length of 1 dm. Specific rotations ($[\alpha]_D^{20}$) were calculated using the equation $[\alpha]_D = (100\alpha)/(cl)$ and are given in 10^{-1} deg cm^2 g^{-1}. Melting points were recorded on a Reichert hot-stage apparatus and are uncorrected except where otherwise stated. Elemental analyses were performed by the Australian National University Microanalytical Services Unit based in the Research School of Chemistry, The Australian National University, Canberra, Australia. Analytical thin layer chromatography (TLC) was conducted on aluminium-backed 0.2 mm thick silica gel 60 F_{254} plates (Merck) and the chromatograms were visualised under a 254 nm UV lamp and/or by treatment with an anisaldehyde–sulfuric acid–ethanol (3 mL : 4.5 mL : 200 mL) dip or, occasionally, with a phosphomolybdic acid–ceric sulfate–sulfuric acid–water (37.5 g : 7.5 g : 37.5 mL : 720 mL) dip, followed by heating. The retention factor (R_f) quoted is rounded to the nearest 0.1. Flash chromatography was conducted according to the method of Still and co-workers[21] using silica gel 60 (mesh size 0.040–0.063 mm) as the stationary phase and the analytical reagent (AR) grade solvents indicated. Many starting materials and reagents were available from the Aldrich Chemical Company or EGA-Chemie and were used as supplied or simply distilled. Drying agents and other inorganic salts were purchased from AJAX or BDH Chemicals. Reactions employing air- and/or moisture-sensitive reagents and intermediates were carried out under an atmosphere of dry, oxygen-free nitrogen in flame-dried apparatus. Room temperature is assumed to be *ca*. 18 °C. Tetrahydrofuran (THF) and diethyl ether were dried using sodium metal and then distilled, as required, from sodium benzophenone ketyl. Methanol was distilled from magnesium methoxide. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Ethylene glycol dimethyl ether (DME) was refluxed over calcium hydride then distilled, as required, from sodium benzophenone ketyl. *N*,*N*-Dimethylformamide (DMF) was heated at reflux over calcium hydride for 16 h then distilled and stored over 3 Å molecular sieves. Organic solutions obtained from work-up of reaction mixtures were dried with magnesium sulfate ($MgSO_4$). Petrol refers to petroleum spirits boiling in the range 40–60 °C unless otherwise specified. Organic solutions were concentrated under reduced pressure on a rotary evaporator with the water bath generally not exceeding 40 °C.

(2*S*,3a*R*,7a*S*)-4-Bromo-3a,7a-dihydro-2-phenyl-1,3-benzodioxole

Benzaldehyde dimethyl acetal (BDMA) (7.50 mL, 0.05 mol) was added, dropwise, to a magnetically stirred suspension of compound **3** (9.50 g, 0.05 mol) and (1*S*)-(+)-camphor-10-sulfonic acid monohydrate ($CSA{\cdot}H_2O$) (260 mg, 1 mmol) in anhydrous CH_2Cl_2 (400 mL) maintained at −20 °C under a nitrogen atmosphere. The reaction mixture was allowed to warm to 10 °C over 1 h then treated with NaOH (300 mL of a 1 M aqueous solution). The separated aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL) and the combined organic phases were washed with brine (1 × 400 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the *title acetal* (*ca*. 14.1 g) as a white solid. This material proved somewhat unstable and was therefore subjected, without purification, to the next step of the reaction sequence. δ_H 7.49 (2H, m), 7.38 (3H, m), 6.41 (1H, d, *J* 6.0), 6.04 (1H, dd, *J* 9.6 and 3.2), 5.93 (1H, dd, *J* 9.6 and 6.0), 5.76 (1H, s), 4.79 (2H, m); δ_C 135.9 (C), 129.6 (CH), 128.2 (CH), 127.0 (CH), 126.0 (CH), 124.2 (CH), 123.3 (CH), 122.9 (C), 99.4 (CH), 76.0 (CH), 73.4 (CH).

(2*S*,3a*S*,4*R*,7*R*,7a*R*)-7-Bromo-3a,4,7,7a-tetrahydro-2-phenyl-4,7-ethano-1,3-benzodioxol-8-one (5)

(2*S*,3a*R*,7a*S*)-4-Bromo-3a,7a-dihydro-2-phenyl-1,3-benzodioxole (10.0 g, 35.83 mmol) was added to a magnetically stirred mixture of α-chloroacryloyl chloride (11.2 g, 89.56 mmol) and potassium carbonate (495 mg, 3.58 mmol) in anhydrous benzene (143 mL) maintained at room temperature under a nitrogen atmosphere. The reaction mixture was then heated to 70 °C for 16 h, cooled to room temperature and concentrated under reduced pressure. The residue thus obtained was immediately dissolved in DME and the resulting solution treated with sodium azide (9.3 g, 143.3 mmol) while being maintained under an atmosphere of nitrogen. The resulting suspension was stirred at 18 °C for 3 h after which time the remaining solids were removed by filtration. The filtrate was heated at reflux for 3 h then cooled to 0 °C and treated with cold (0 °C) acetic acid (20 mL of a 5% v/v aqueous solution). After 0.5 h at 0 °C, the solution was extracted with diethyl ether (3 × 200 mL) and the combined organic phases washed with NaOH (2 × 300 mL of a 1 M aqueous solution) and brine (1 × 300 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale yellow semi-solid (*ca*. 10 g). Subjection of this material to flash chromatography (silica, 15% v/v ethyl acetate–petrol elution) provided, after concentration of the appropriate fractions (R_f 0.4 in 25% v/v ethyl acetate–petrol), the *title* compound **5** (8.0 g, 70% from compound **3**) as a white solid. Recrystallisation (ethyl acetate–petrol) of a portion of this material afforded an analytically pure sample of the title compound as fine white crystals, mp 160–162 °C, $[\alpha]_D$ +312 (*c* 0.3, $CHCl_3$) (Found: C, 56.00; H, 3.93; Br, 24.74%. $C_{15}H_{13}BrO_3$ requires C, 56.10; H, 4.08; Br, 24.88%); ν_{max}/cm^{-1} 1743, 1460, 1405, 1106, 1094, 983, 760, 702; δ_H 7.71–7.36 (3H, complex m), 7.52 (2H, m), 6.42 (1H, m), 6.26 (1H, m), 5.85 (1H, s), 4.62 (1H, m), 4.53 (1H, m), 3.44 (1H, m), 2.44 (1H, dd, *J* 18.8 and 3.8), 2.15 (1H, dd, *J* 18.8 and 1.9); δ_C 199.8 (C=O), 135.6 (CH), 134.8 (CH), 132.3 (CH), 130.7 (CH), 129.0 (CH), 128.0 (CH), 105.8 (CH), 81.9 (CH), 80.2 (CH), 71.5 (C), 35.4 (CH), 34.2 (CH_2); *m*/*z* 322 and 320 ($M^{+\bullet}$, 28 and 29%), 216 and 214 [$(M - C_7H_6O)^{+\bullet}$, 74 and 78], 174 and 172 [$(M - C_9H_8O_2)^{+\bullet}$, 90 and 93], 77 ($C_6H_5^+$, 100). Found (HRMS): $M^{+\bullet}$, 320.0049. $C_{15}H_{13}{}^{79}BrO_3$ $M^{+\bullet}$ requires 320.0048.

(2*S*,3a*S*,4*R*,7*R*,7a*S*)-7-Bromo-3a,4,7,7a-tetrahydro-2-phenyl-4,7-ethano-1,3-benzodioxol-8-one ethylene acetal (6)

1,2-Bis(trimethylsilyoxy)ethane (20.2 mL, 82.7 mmol) was added, dropwise, to a magnetically stirred solution of ketone **5** (8.85 g, 27.55 mmol) in anhydrous CH_2Cl_2 containing TMSOTf (0.21 mL, 1.1 mmol) maintained at 18 °C and under a nitrogen atmosphere. After 24 h the reaction mixture was treated with pyridine (1 mL) then $NaHCO_3$ (100 mL of a saturated aqueous solution). The resulting mixture was extracted with diethyl ether (3 × 100 mL) and the combined organic phases were washed with NaOH (1 × 100 mL of a 1 M aqueous solution) and brine (1 × 200 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale yellow oil. Subjection of this material to flash chromatography (silica, 20% v/v ethyl acetate–petrol elution) provided, after concentration of the appropriate fractions (R_f 0.5 in 25% v/v ethyl acetate–petrol), the *title compound* **6** (9.15 g, 91%) as a white solid which was contaminated with trace amounts (<10%) of the epimeric acetal. This material could be used, without further purification, in the next step of the reaction sequence. Recrystallisation (chloroform–petrol) of a portion of this material afforded an analytically pure sample of compound **6** as white crystalline masses, mp 146–149 °C, $[\alpha]_D$ +140 (*c* 1.0, $CHCl_3$) (Found: C, 55.58; H, 4.56; Br, 21.97%. $C_{17}H_{17}BrO_4$ requires C, 55.91; H, 4.69; Br, 21.88%); ν_{max}/cm^{-1} 2923, 2886, 1458, 1404, 1150, 1091, 1068, 978, 760; δ_H 7.49 (2H, m), 7.34 (3H, m), 6.35 (1H, d, *J* 8.7), 6.23 (1H, dd, *J* 8.7 and *ca*. 6), 5.74 (1H, s), 4.77 (1H, d, *J ca*. 7.5), 4.47 (1H, dd, *J ca*. 7.5 and 3.2), 4.27–4.20 (2H, complex m), 4.03–3.96 (2H, complex m), 3.10 (1H, m), 1.94 (1H, dd, *J* 13.8 and 3.8), 1.84 (1H, dd, *J* 13.8 and 2.2); δ_C 135.5 (C), 133.7 (CH), 132.0 (CH), 129.5 (CH), 128.0 (CH), 127.3 (CH), 110.7 (C), 103.7 (CH), 81.0 (CH), 79.1 (CH), 69.2 (C), 66.0 (CH_2), 65.6 (CH_2), 38.1 (CH_2), 34.8 (CH); *m*/*z* 365 and 363 [$(M - H^{\bullet})^+$, 2 and 2%], 285 [$(M - Br^{\bullet})^+$, 2], 86 ($C_4H_6O_2^{+\bullet}$, 100). Found (HRMS): $(M - H^{\bullet})^+$, 363.0240. $C_{17}H_{17}{}^{79}BrO_4$ $(M - H^{\bullet})^+$ requires 363.0232.

(1*R*,4*S*,5*S*,6*S*)-1-Bromo-5,6-dihydroxybicyclo[2.2.2]octan-2-one ethylene acetal

A magnetically stirred mixture of compound **6** (7.35 g, 20.13 mmol) and 10% Pd/C (1.2 g) in THF (100 mL), maintained at 18 °C, was placed under an atmosphere of hydrogen for 26 h. After this time, the reaction mixture was filtered through a short pad of Celite™ which was subsequently washed with ethyl acetate (200 mL). The combined filtrates were concentrated under reduced pressure to afford a pale yellow oil (*ca*. 7.4 g) which was subjected to flash chromatography (silica, 50–80% v/v ethyl acetate–petrol elution). Concentration of the appropriate fractions (R_f 0.4 in 60% v/v ethyl acetate–petrol), then provided the *title compound* (5.45 g, 97%) as a clear, colourless and viscous oil, $[\alpha]_D$ +1 (*c* 1.5, $CHCl_3$) (Found: C, 42.49; H, 5.44; Br, 28.35%. $C_{10}H_{15}BrO_4$ requires C, 43.03; H, 5.42; Br, 28.63%); ν_{max}/cm^{-1} 3400, 2950, 1325, 1155, 1089, 1027, 984; δ_H 4.25 (1H, ddd, *J* 8.3, 3.4 and 1.7), 4.20–4.03 (3H, complex m), 4.02–3.90 (2H, complex m), 3.35 (1H, d, *J* 4.6), 2.85 (1H, d, *J* 3.4), 2.35 (1H, m), 2.21–2.10 (1H, complex m), 2.08–1.90 (4H, m), 1.53–1.45 (1H, m); δ_C 108.9 (C), 76.6 (C), 69.3 (CH), 68.4 (CH), 65.5 (CH_2), 65.4 (CH_2), 41.1 (CH_2), 32.3 (CH), 26.2 (CH_2), 20.7 (CH_2); *m*/*z* 280 and 278 ($M^{+\bullet}$, 6 and 6%), 263 and 261 [$(M - HO^{\bullet})^+$, 35 and 36], 199 [$(M - Br^{\bullet})^+$, 40], 181 [$(M - H_2O - Br^{\bullet})^{+\bullet}$, 100]. Found (HRMS): $M^{+\bullet}$, 278.0153. $C_{10}H_{15}{}^{79}BrO_4$ requires $M^{+\bullet}$, 278.0154.

(2*S*,3a*S*,4*R*,7*R*,7a*S*)-7-Bromo-3a,4,7,7a-tetrahydro-2-(4′-methoxyphenyl)-4,7-ethano-1,3-benzodioxol-8-one ethylene acetal (7)

p-Methoxybenzaldehyde dimethyl acetal (PMBDMA) (8.77 mL, 46.67 mmol) was added, dropwise, to a magnetically stirred solution of the above-mentioned diol (10.86 g, 38.91 mmol) and (+)-CSA·H_2O (452 mg, 1.95 mmol) in anhydrous CH_2Cl_2 (450 mL) maintained at −20 °C under a nitrogen atmosphere. After 3 h at −20 °C the reaction mixture was treated with NaOH (200 mL of a 1 M aqueous solution). The separated aqueous layer was extracted with CH_2Cl_2 (3 × 250mL) and the combined organic phases were washed with brine (1 × 400 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a white solid. Subjection of this material to flash chromatography (silica, 30% v/v ethyl acetate–petrol elution) provided, after concentration of the appropriate fractions (R_f 0.7 in 40% v/v ethyl acetate–petrol), the *title compound* (14.9 g, 97%) as a white solid. Recrystallisation (ethyl acetate–petrol) of a portion of this material afforded an analytically pure sample of acetal **7** as clear, colourless platelets, mp 150–152 °C; $[\alpha]_D$ +80 (*c* 0.5, $CHCl_3$) (Found: C, 54.38; H, 5.25; Br, 20.01%. $C_{18}H_{21}BrO_5$ requires C, 54.42; H, 5.33; Br, 20.11%); ν_{max}/cm^{-1} 1614, 1516, 1398, 1245, 1081, 1065, 1030; δ_H 7.51 (2H, d, *J* 8.7), 6.93 (2H, d, *J* 8.7), 5.82 (1H, s), 4.62 (1H, dd, *J* 8.4 and 1.6), 4.32 (1H, dd, *J* 8.4 and 1.7), 4.20 (2H, m), 4.04 (2H, m), 3.82 (3H, s), 2.53 (1H, m), 2.28–2.12 (4H, complex m), 1.98 (1H, m), 1.55 (1H, m); δ_C 160.5 (C), 128.2 (CH), 127.9 (C), 113.6 (CH), 108.7 (C), 103.4 (CH), 78.3 (CH), 77.2 (CH), 70.6 (C), 65.7 (CH_2), 65.6 (CH_2), 55.1 (CH_3), 40.8 (CH_2), 30.0 (CH), 25.9 (CH_2), 20.9 (CH_2); *m*/*z* 398 and 396 ($M^{+\bullet}$, 9 and 9%), 397 and 395 [$(M - H)^{+\bullet}$, 14 and 12], 262 and 260 [$(M - C_8H_8O_2)^{+\bullet}$, 31 and 33], 261 and 259 [$(M - C_8H_8O_2 - H^{\bullet})^+$, 32 and 30], 181 [$(M - C_8H_8O_2 - Br^{\bullet})^+$, 100].

Found (HRMS): $M^{+\bullet}$, 396.0562. $C_{18}H_{21}{}^{79}BrO_5$ requires $M^{+\bullet}$, 396.0572.

(1*R*,4*R*,5*S*,6*S*)-1-Bromo-6-hydroxy-5-[(4′-methoxyphenyl)-methoxy]bicyclo[2.2.2]octan-2-one ethylene acetal (8) and (1*R*,4*R*,5*S*,6*S*)-1-bromo-5-hydroxy-6-[(4′-methoxyphenyl)-methoxy]bicyclo[2.2.2]octan-2-one ethylene acetal (9)

DIBAL-H (150.0 mL of a 1 M solution in hexane, 150.0 mmol) was added, dropwise over 1 h, to a magnetically stirred solution of acetal **7** (14.9 g, 37.5 mmol) in CH_2Cl_2 (200 mL) maintained at −50 °C under a nitrogen atmosphere. The resulting mixture was allowed to warm to 0 °C over 10 h, then treated with tartaric acid (500 mL of a 1 M aqueous solution). The mixture thus obtained was partitioned between diethyl ether (300 mL) and brine (200 mL). The separated aqueous layer was extracted with diethyl ether (3 × 400 mL) and the combined organic phases were washed with brine (1 × 500 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a clear, colourless oil. Subjection of this material to flash chromatography (silica, 1 : 1.5 : 7.5 v/v/v ethyl acetate–CH_2Cl_2–petrol elution) provided two fractions, **A** (R_f 0.3) and **B** (R_f 0.2).

Concentration of fraction **A** afforded the *title compound* **8** (3.16 g, 21%) as a clear, colourless oil, $[a]_D$ +1 (*c* 0.6, $CHCl_3$); ν_{max}/cm^{-1} 3494, 1612, 1585, 1514, 1249, 1088, 1030; δ_H 7.27 (2H, d, *J* 8.5), 6.89 (2H, d, *J* 8.5), 4.55 (2H, s), 4.28 (1H, m), 4.18 (2H, m), 3.96 (2H, m), 3.83 (1H, partially obscured m), 3.82 (3H, s), 3.46 (1H, d, *J* 4.2), 2.36 (1H, m), 2.13–1.86 (5H, complex m), 1.48 (1H, m); δ_C 159.3 (C), 129.3 (CH), 129.2 (C), 113.8 (CH), 108.8 (C), 75.4 (CH), 74.9 (C or CH_2), 72.1 (C or CH_2), 69.0 (CH), 65.5 (2 × CH_2, coincident), 55.1 (CH_3), 41.1 (CH_2), 30.0 (CH), 26.1 (CH_2), 21.2 (CH_2); *m*/*z* 400 and 398 ($M^{+\bullet}$, 3 and 3%), 319 [$(M - Br^{\bullet})^+$, <1], 121 (p-$CH_3OC_6H_4CH_2^+$, 100). Found (HRMS): $M^{+\bullet}$, 398.0733. $C_{18}H_{23}{}^{79}BrO_5$ requires $M^{+\bullet}$, 398.0729.

Concentration of fraction **B** afforded the *title compound* **9** (9.90 g, 70%) as a clear, colourless oil, $[a]_D$ −9 (*c* 0.5, $CHCl_3$); ν_{max}/cm^{-1} 3494, 1612, 1585, 1514, 1249, 1086, 1028, 823; δ_H 7.37 (2H, d, *J* 8.6), 6.90 (2H, d, *J* 8.6), 4.93 (1H, d, *J* 10.4), 4.60 (1H, d, *J* 10.4), 4.21–4.11 (3H, complex m), 4.02–3.97 (3H, complex m), 3.82 (3H, s), 3.47 (1H, d, *J* 6.5), 2.38 (1H, m), 2.18 (1H, m), 2.04–1.86 (4H, complex m), 1.46 (1H, m); δ_C 159.4 (C), 129.8 (CH), 129.5 (C), 113.8 (CH), 108.9 (C), 77.9 (CH), 76.0 (CH_2), 74.4 (C), 68.3 (CH), 65.5 (CH_2), 65.4 (CH_2), 55.1 (CH_3), 41.0 (CH_2), 32.7 (CH), 26.8 (CH_2), 20.6 (CH_2); *m*/*z* 400 and 398 ($M^{+\bullet}$, 8 and 8%), 263 and 261 [$(M - p$-$CH_3OC_6H_4CH_2O^{\bullet})^+$, 19 and 20], 138 [$(p$-$CH_3OC_6H_4CH_2OH)^{+\bullet}$, 75], 121 ($p$-$CH_3OC_6H_4$-$CH_2^+$, 100). Found (HRMS): $M^{+\bullet}$, 398.0730. $C_{18}H_{23}{}^{79}BrO_5$, $M^{+\bullet}$ requires 398.0729.

(1*S*,4*S*,5*S*,6*R*)-5-Hydroxy-6-[(4′-methoxyphenyl)methoxy]-bicyclo[2.2.2]octan-2-one ethylene acetal (10)

n-Bu_3SnH (3.9 mL, 13.0 mmol) was added, dropwise, to a magnetically stirred solution of compound **9** (4.0 g, 10.0 mmol) and azoisobutyronitrile (AIBN) (33 mg, 0.2 mmol) in degassed benzene (10 mL) maintained at room temperature under an atmosphere of nitrogen. The reaction mixture was then subjected to irradiation, using a medium-pressure mercury-vapour lamp (125 W) contained within a water-cooled quartz jacket, for 6 h during which time (after 3 h) a second equivalent of AIBN (33 mg, 0.2 mmol) was added. The solvents were then removed under reduced pressure and the residue thus obtained was subjected to flash chromatography (silica, 20–50% v/v ethyl acetate–petrol elution). Concentration of the appropriate fractions (R_f 0.2 in 20% v/v ethyl acetate–petrol) then afforded the *title compound* **10** (2.24 g, 70%) as a clear, colourless oil, $[a]_D$ −20 (*c* 1.6, $CHCl_3$); ν_{max}/cm^{-1} 3508, 2932, 1612, 1514, 1250, 1079, 1032, 1020; δ_H 7.27 (2H, d, *J* 8.5), 6.89 (2H, d, *J* 8.5), 4.50 (2H, ABq, *J* 11.4), 3.97–3.82 (6H, complex m), 3.81 (3H, s), 2.97 (1H, br s), 1.96–1.87 (2H, complex m), 1.86–1.71 (4H, complex m), 1.56 (1H, m), 1.32 (1H, m); δ_C 159.2 (C), 129.7 (C), 129.3 (CH), 113.7 (CH), 106.6 (C), 71.9 (CH_2), 71.8 (CH), 66.7 (CH), 63.8 (CH_2), 63.6 (CH_2), 55.1 (CH_3), 38.3 (CH_2), 36.7 (CH), 33.1 (CH), 17.0 (CH_2), 14.4 (CH_2); *m*/*z* 320 ($M^{+\bullet}$, 7%), 302 [$(M - H_2O)^{+\bullet}$, 4], 183 [$(M - p$-$CH_3OC_6H_4CH_2O^{\bullet})^+$, 30], 138 [$(p$-$CH_3OC_6H_4CH_2OH)^{+\bullet}$, 53], 121 ($p$-$CH_3OC_6H_4CH_2^+$, 100). Found (HRMS): $M^{+\bullet}$, 320.1626. $C_{18}H_{24}O_5$ requires $M^{+\bullet}$, 320.1624.

(1*S*,3*R*,4*S*)-3-[(4′-Methoxyphenyl)methoxy]bicyclo[2.2.2]-octane-2,5-dione 5-(ethylene acetal)

Dimethyl sulfoxide (10.1 mL, 143 mmol) was added, dropwise, to a magnetically stirred solution of oxalyl chloride (6.1 mL, 69 mmol) in dry CH_2Cl_2 (88 mL) maintained at −78 °C under an atmosphere of nitrogen. After 20 min, a solution of compound **10** (7.05 g, 22.0 mmol) in dry CH_2Cl_2 (88 mL) was added, dropwise and *via* cannula, to the reaction mixture. After a further 4 h, triethylamine (20 mL, 143 mmol) was added, dropwise, and the resulting homogeneous solution was stirred at −78 °C for 30 min and for a further 30 min while warming to 18 °C. The reaction mixture was then diluted with CH_2Cl_2 (500 mL) and $NaHCO_3$ (200 mL of a saturated aqueous solution). The separated organic phase was washed with water (1 × 200 mL) and brine (1 × 200 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale yellow oil. Subjection of this material to flash chromatography (silica, 1 : 9 : 10 v/v/v ethyl acetate–CH_2Cl_2–petrol elution) provided, after concentration of the appropriate fractions (R_f 0.2 in 20% v/v ethyl acetate–petrol), the *title compound* (6.72 g, 96%) as a clear, colourless oil, $[a]_D$ +72 (*c* 1.8, $CHCl_3$); ν_{max}/cm^{-1} 2951, 1733, 1612, 1585, 1512, 1464, 1356, 1301, 1247, 1092, 824, 758; δ_H 7.30 (2H, d, *J* 8.7), 6.88 (2H, d, *J* 8.7), 4.83 (1H, d, *J* 11.5), 4.62 (1H, d, *J* 11.5), 4.00–3.81 (5H, complex m), 3.80 (3H, s), 2.42 (1H, m), 2.25 (1H, m), 2.05 (2H, m), 1.83 (4H, m); δ_C 214.3 (C=O), 159.1 (C), 129.9 (C), 129.4 (CH), 113.6 (CH), 108.3 (C), 77.5 (CH), 72.4 (CH_2), 64.1 (CH_2), 63.9 (CH_2), 55.1 (CH_3), 44.0 (CH), 41.9 (CH), 37.7 (CH_2), 23.6 (CH_2), 14.9 (CH_2); *m*/*z* 318 ($M^{+\bullet}$, <1%), 197 [$(M - p$-$CH_3OC_6H_4CH_2O^{\bullet})^+$, 23], 182 [$(M - p$-$CH_3OC_6H_4$-$CHO)^{+\bullet}$, 33], 121 ($p$-$CH_3OC_6H_4CH_2^+$, 100). Found (HRMS): $M^{+\bullet}$, 318.1466. $C_{18}H_{22}O_5$ requires $M^{+\bullet}$, 318.1467.

(1*S*,4*S*,5*S*,6*R*)-5-Ethenyl-5-hydroxy-6-[(4′-methoxyphenyl)-methoxy]bicyclo[2.2.2]octan-2-one ethylene acetal (11)

Vinylmagnesium bromide (31.8 mL of a 1 M solution in THF, 31.8 mmol) was added, dropwise, to a magnetically stirred solution of the above-mentioned ketone (5.05 g, 15.9 mmol) in THF (159 mL) maintained at −40 °C under a nitrogen atmosphere. The reaction mixture was held at −40 °C for 3 h, then treated with NH_4Cl (100 mL of a saturated aqueous solution). The mixture thus obtained was partitioned between diethyl ether (300 mL) and brine (200 mL). The separated aqueous layer was extracted with diethyl ether (3 × 200 mL) and the combined organic phases were washed with brine (1 × 300 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale yellow oil. Subjection of this material to flash chromatography (silica, 40% v/v ethyl acetate–petrol elution) provided, after concentration of the appropriate fractions (R_f 0.5), the *title compound* **11** (4.68 g, 85%) as a clear, colourless oil, $[a]_D$ +23 (*c* 1.2, $CHCl_3$); ν_{max}/cm^{-1} 3513, 2932, 1612, 1514, 1251, 1079; δ_H 7.23 (2H, d, *J* 8.7), 6.88 (2H, d, *J* 8.7), 6.05 (1H, dd, *J* 17.2 and 10.7), 5.33 (1H, dd, *J* 17.2 and 1.6), 5.07 (1H, dd, *J* 10.7 and 1.6), 4.50 (2H, s), 3.99–3.82 (4H, complex m), 3.81 (3H, s), 3.73 (1H, app t, *J* 2.0), 2.08–1.98 (1H, complex m), 1.94–1.87 (2H, complex m), 1.85–1.70 (3H, m), 1.56 (1H, m), 1.30 (1H, m) [signal due to OH not observed]; δ_C 159.3 (C), 143.5 (CH), 129.8 (C), 129.4 (CH), 113.7 (CH), 112.3 (CH_2), 109.7 (C), 75.8 (CH), 72.3 (CH_2), 71.3 (C), 63.8 (CH_2), 63.6 (CH_2), 55.1 (CH_3), 38.0 (CH), 37.6 (CH), 37.2

(CH_2), 19.4 (CH_2), 13.9 (CH_2); *m/z* 346 ($M^{+\bullet}$, <1%), 319 [$(M - C_2H_3^{\bullet})^+$, <1], 225 [$(M - p\text{-}CH_3OC_6H_4CH_2^{\bullet})^+$, 37], 121 ($p\text{-}CH_3OC_6H_4CH_2^+$, 100). Found (HRMS): $M^{+\bullet}$, 346.1780. $C_{20}H_{26}O_5$ requires $M^{+\bullet}$, 346.1780.

(1*S*,4*S*,5*S*,6*R*)-5-Ethenyl-5-hydroxy-6-[(4′-methoxyphenyl)-methoxy]bicyclo[2.2.2]octan-2-one (12)

Pyridinium toluene-*p*-sulfonate (PPTS) (1.13 g, 4.50 mmol) was added to a magnetically stirred solution of ketal **11** (5.2 g, 15.0 mmol) in acetone (156 mL of a 95% v/v aqueous solution) maintained at ambient temperature. The reaction mixture was heated at reflux for 24 h then cooled to 18 °C and partitioned between diethyl ether (400 mL) and $NaHCO_3$ (100 mL of a saturated aqueous solution). The separated aqueous layer was extracted with diethyl ether (3 × 100 mL) and the combined organic phases were washed with brine (1 × 300 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a white solid. Subjection of this material to flash chromatography (silica, 20% v/v ethyl acetate–petrol elution) provided, after concentration of the appropriate fractions (R_f 0.5), the *title compound* **12** (1.22 g, 90%) as a white solid. Recrystallisation (diethyl ether) of a portion of this material afforded an analytically pure sample of ketone **12** as colourless prisms, mp 102–103 °C; $[a]_D$ +11 (*c* 0.9, $CHCl_3$) (Found: C, 71.48; H, 7.50%. $C_{18}H_{22}O_4$ requires C, 71.50; H, 7.33%); ν_{max}/cm^{-1} 3552, 1717, 1611, 1516, 1243, 1101, 1030, 995, 921, 821; δ_H 7.23 (2H, d, *J* 8.7), 6.87 (2H, d, *J* 8.7), 5.91 (1H, dd, *J* 17.2 and 10.7), 5.27 (1H, br d, *J* 17.2), 5.13 (1H, dd, *J* 10.7 and 1.3), 4.57 (1H, d, *J* 11.3), 4.47 (1H, d, *J* 11.3), 3.81 (3H, s), 3.68 (1H, br s), 3.59 (1H, m), 2.62 (1H, app q, *J ca.* 2.6), 2.36–2.13 (5H, complex m), 1.56 (1H, m), 1.38 (1H, m); δ_C 213.9 (C), 159.4 (C), 142.3 (CH), 129.4 (CH), 128.7 (C), 113.7 (CH), 113.2 (CH_2), 74.4 (CH), 72.0 (CH_2), 71.2 (C), 55.0 (CH_3), 47.9 (CH), 41.2 (CH_2), 38.4 (CH), 19.8 (CH_2), 15.4 (CH_2); *m/z* 302 ($M^{+\bullet}$, <1%), 284 [$(M - H_2O)^{+\bullet}$, 2], 181 [$(M - p\text{-}CH_3OC_6H_4CH_2^{\bullet})^+$, 18], 121 ($p\text{-}CH_3OC_6H_4CH_2^+$, 100). Found (HRMS): $(M - H_2O)^{+\bullet}$, 284.1410. $C_{18}H_{22}O_4$ requires $(M - H_2O)^{+\bullet}$, 284.1412.

(1*S*,3*Z*,4*S*,5*S*,6*R*)-5-Ethenyl-5-hydroxy-3-(hydroxymethylene)-6-[(4′-methoxyphenyl)methoxy]bicyclo[2.2.2]octan-2-one (13)

A solution of compound **12** (2.92 g, 9.66 mmol) in THF (50 mL) was added, dropwise, to a magnetically stirred suspension of NaH (966 mg, *ca.* 60% dispersion in mineral oil, 24.1 mmol) in THF (46 mL) maintained at 0 °C under an atmosphere of nitrogen. After 30 min, ethyl formate (7.12 mL, 96.6 mmol) was added, dropwise, and the reaction mixture was allowed to warm to 18 °C over 2 h before being treated with H_2SO_4 (50 mL of a 2 M aqueous solution). The resulting mixture was extracted with diethyl ether (3 × 100 mL) and the combined organic phases were washed with brine (1 × 200 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the *title compound* **13** (2.39 g, 75%) as a white solid. This material could be used, without purification, in the next step of the reaction sequence. Recrystallisation (DME–petrol) of a portion of this material afforded an analytically pure sample of the vinylogous acid **13** as pale pink crystals, mp 114–115 °C; $[a]_D$ −25 (*c* 1.1, $CHCl_3$) (Found: C, 69.03; H, 6.61%. $C_{19}H_{22}O_5$ requires C, 69.07; H, 6.71%); ν_{max}/cm^{-1} 3522, 1672, 1611, 1517, 1246, 1091, 831, 823; δ_H 7.22 (2H, d, *J* 8.7), 7.15 (1H, s), 6.88 (2H, d, *J* 8.7), 5.82 (1H, dd, *J* 17.0 and 10.5), 5.30 (1H, dd, *J* 17.0 and 1.6), 5.04 (1H, br d, *J* 10.5), 4.55 (1H, d, *J* 11.2), 4.47 (1H, d, *J* 11.2), 3.81 (3H, s), 3.65 (1H, br s), 3.44 (1H, br s), 2.72 (1H, app q, *J ca.* 2.6), 2.45 (1H, app t, *J ca.* 2.8), 2.36 (1H, m), 2.08 (1H, m), 1.46 (1H, m), 1.33 (1H, m) [signal due to enolic OH not observed]; δ_C 203.7 (C), 162.2 (CH), 159.6 (C), 143.4 (CH), 129.6 (CH), 128.8 (C), 114.1 (C or CH_2), 113.9 (CH), 112.5 (C or CH_2), 76.2 (CH), 72.6 (CH_2), 71.2 (C), 55.2 (CH_3), 46.6 (CH), 41.5 (CH), 21.0 (CH_2), 14.7 (CH_2); *m/z* 330 ($M^{+\bullet}$, <1%), 312 [$(M - H_2O)^{+\bullet}$, 1], 209 [$(M - p\text{-}CH_3OC_6H_4CH_2^{\bullet})^+$, 8), 121 ($p\text{-}CH_3OC_6H_4CH_2^+$, 100). Found (HRMS): $M^{+\bullet}$, 330.1468. $C_{19}H_{22}O_5$ requires $M^{+\bullet}$, 330.1467.

(1*S*,3*E*,4*S*,5*S*,6*R*)-5-Ethenyl-5-hydroxy-3-(2′-methoxyethoxymethoxymethylene)-6-[(4′-methoxyphenyl)methoxy]bicyclo-[2.2.2]octan-2-one (14) and (1*S*,4*S*,5*R*,6*S*)-6-ethenyl-6-hydroxy-3-(2′-methoxyethoxymethoxy)-5-[(4′-methoxyphenyl)methoxy]-bicyclo[2.2.2]oct-2-ene-2-carbaldehyde (15)

DBU (2.08 mL, 13.94 mmol) was added, dropwise, to a magnetically stirred solution of compound **13** (3.07 g, 9.29 mmol) in DMF (93 mL), maintained at 0 °C under an atmosphere of nitrogen. After 10 min, the reaction mixture was cooled to −55 °C and a solution of MEM-Cl (2.12 mL, 18.58 mmol) in DMF (93 mL) was added dropwise over 40 min. The reaction mixture thus obtained was allowed to warm to −20 °C over 5 h, then treated with NH_4Cl (100 mL of a saturated aqueous solution) and water (50 mL). The separated aqueous layer was extracted with diethyl ether (3 × 200 mL) and the combined organic phases were washed with water (3 × 100) and brine (1 × 300 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale yellow oil. Subjection of this material to flash chromatography (silica, 30% v/v ethyl acetate–petrol elution) provided two fractions, **A** (R_f 0.2) and **B** (R_f 0.1).

Concentration of fraction **A** afforded the *title compound* **14** (3.11 g, 80%) as a clear, colourless oil, $[a]_D$ +14 (*c* 1.4, $CHCl_3$); ν_{max}/cm^{-1} 3500, 1703, 1624, 1514, 1302, 1249, 1078, 960, 832; δ_H 7.44 (1H, s), 7.22 (2H, d, *J* 8.6), 6.86 (2H, d, *J* 8.6), 5.80 (1H, dd, *J* 17.0 and 10.6), 5.33 (1H, dd, *J* 17.0 and 1.6), 5.08 (2H, s), 4.96 (1H, dd, *J* 10.6 and 1.6), 4.53 (1H, d, *J* 11.2), 4.45 (1H, d, *J* 11.2), 3.81 (3H, s), 3.71 (3H, m), 3.51 (3H, m), 3.38 (3H, s), 3.05 (1H, m), 2.64 (1H, m), 2.30 (1H, m), 2.09 (1H, m), 1.54 (1H, m), 1.34 (1H, m); δ_C 201.4 (C), 159.4 (C), 150.7 (CH), 143.2 (CH), 129.5 (CH), 128.9 (C), 118.6 (C or CH_2), 113.8 (CH), 111.9 (C or CH_2), 97.1 (CH_2), 76.1 (CH), 72.3 (C or CH_2), 71.3 (C or CH_2), 71.2 (C or CH_2), 68.2 (C or CH_2), 59.0 (CH_3), 55.2 (CH_3), 47.9 (CH), 38.6 (CH), 19.7 (CH_2), 15.2 (CH_2); *m/z* 419 [$(M + H)^+$, <1%], 312 [$(M - C_4H_{10}O_3^{\bullet})^+$, 37], 121 ($p\text{-}CH_3OC_6H_4CH_2^+$, 100). Found (HRMS): $(M + H)^+$, 419.2072. $C_{23}H_{30}O_7$ requires $(M + H)^+$, 419.2070.

Concentration of fraction **B** afforded the *title compound* **15** (194 mg, 5%) as a clear, colourless oil, ν_{max}/cm^{-1} 3498, 2935, 1703, 1654, 1615, 1514, 1248, 1102, 978, 838; δ_H 9.97 (1H, s), 7.25 (2H, d, *J ca.* 8.5), 6.89 (2H, d, *J ca.* 8.5), 5.65 (1H, dd, *J* 17.0 and 10.6), 5.26 (1H, dd, *J* 17.0 and 1.6), 5.24 (1H, d, *J* 7.0), 5.12 (1H, d, *J* 7.0), 4.92 (1H, dd, *J* 10.6 and 1.6), 4.54 (2H, m), 3.81 (3H, s), 3.78 (2H, m), 3.51 (2H, m), 3.42 (1H, m), 3.34 (3H, s), 3.19 (2H, m), 2.20 (1H, m), 2.02 (1H, m), 1.31 (1H, m), 1.06 (1H, m) [signal due to OH not observed]; δ_C 184.5 (CH), 170.6 (C), 159.5 (C), 144.1 (CH), 129.6 (CH), 129.2 (C), 121.4 (C), 113.9 (CH), 111.9 (CH_2), 92.2 (CH_2), 77.5 (CH), 72.7 (C or CH_2), 71.3 (C or CH_2), 70.4 (C or CH_2), 68.5 (C or CH_2), 58.9 (CH_3), 55.3 (CH_3), 36.8 (CH), 36.1 (CH), 20.3 (CH_2), 16.5 (CH_2); *m/z* 418 ($M^{+\bullet}$, <1%), 312 [$(M - C_4H_{10}O_3^{\bullet})^+$, 6], 121 ($p\text{-}CH_3OC_6H_4CH_2^+$, 100). Found (HRMS): $M^{+\bullet}$, 418.1993. $C_{23}H_{30}O_7$ requires $M^{+\bullet}$, 418.1992.

(1*S*,2*S*,3*R*,4*R*,5*R*,6*E*)-2-Ethenyl-6-(2′-methoxyethoxymethoxymethylene)-3-[(4′-methoxyphenyl)methoxy]bicyclo[2.2.2]octane-2,5-diol (16) and (1*S*,2*S*,3*R*,4*R*,5*S*,6*E*)-2-ethenyl-6-(2′-methoxyethoxymethoxymethylene)-3-[(4′-methoxyphenyl)methoxy]-bicyclo[2.2.2]octane-2,5-diol (17)

Sodium borohydride (90 mg, 2.38 mmol) was added to a magnetically stirred suspension of cerium(III) chloride (586 mg, 2.38 mmol) in EtOH (25 mL) maintained at 0 °C under a nitrogen atmosphere. After 30 min, a solution of compound **14** (500 mg, 1.19 mmol) in ethanol (12 mL) containing 2,6-lutidine (2.4 mL) was added, dropwise, to the reaction mixture. After

1 h at 0 °C the reaction mixture was diluted with water (30 mL) and the resulting solution was extracted with diethyl ether (3 × 50 mL). The combined organic phases were washed with brine (1 × 100 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale yellow oil which was immediately subjected to flash chromatography (silica, 30% v/v ethyl acetate–petrol containing 1% triethylamine elution). In this way two fractions, **A** (R_f 0.5 in 60% v/v ethyl acetate–petrol) and **B** (R_f 0.4 in 60% v/v ethyl acetate–petrol) were obtained.

Concentration of fraction **A** afforded the *title compound* **16** (425 mg, 85%) as a clear, colourless oil, $[\alpha]_D$ −35 (*c* 1.4, $CHCl_3$). ν_{max}/cm^{-1} 3480, 2937, 1684, 1612, 1514, 1463, 1248, 1182, 1091, 1055, 992, 921, 831; δ_H 7.24 (2H, d, *J* 8.6), 6.86 (2H, d, *J* 8.6), 6.46 (1H, s), 6.05 (1H, dd, *J* 17.1 and 10.6), 5.40 (1H, dd, *J* 17.1 and 2.0), 4.98 (1H, dd, *J* 10.6 and 2.0), 4.90 (2H, s), 4.51 (2H, s), 4.39 (1H, br s), 3.80 (3H, s), 3.78 (1H, s), 3.76–3.65 (3H, complex m), 3.53 (2H, m), 3.38 (3H, s), 2.80 (1H, m), 2.15–2.01 (2H, m), 1.91 (1H, m), 1.29–1.14 (2H, m) [signal due to OH not observed]; δ_C 159.2 (C), 144.1 (CH), 141.7 (CH), 129.8 (C), 129.4 (CH), 121.3 (C), 113.7 (CH), 111.1 (CH_2), 95.4 (CH_2), 75.5 (CH), 72.5 (C or CH_2), 71.8 (C or CH_2), 71.4 (C or CH_2), 69.2 (CH), 67.2 (CH_2), 58.9 (CH_3), 55.2 (CH_3), 38.9 (CH), 37.5 (CH), 19.0 (CH_2), 16.0 (CH_2); *m*/*z* 344 [$(M - C_3H_8O_2)^{+\bullet}$, 3%], 121 ($p$-$CH_3OC_6H_4CH_2^+$, 100). Found (HRMS): $(M - C_3H_8O_2)^{+\bullet}$, 344.1625. $C_{23}H_{32}O_7$ requires $(M\text{-}C_3H_8O_2)^{+\bullet}$, 344.1624.

Concentration of fraction **B** afforded the *title compound* **17** (25 mg, 5%) as a clear, colourless oil, ν_{max}/cm^{-1} 3480, 2938, 1682, 1612, 1514, 1249, 1052; δ_H 7.23 (2H, d, *J* 8.6), 6.87 (2H, d, *J* 8.6), 6.46 (1H, s), 5.84 (1H, dd, *J* 17.0 and 10.6), 5.35 (1H, dd, *J* 17.0 and 1.8), 4.95 (1H, dd, *J* 10.6 and 1.8), 4.89 (2H, ABq, *J* 6.7), 4.50 (2H, s), 4.18 (1H, m), 3.81 (3H, s), 3.80–3.53 (5H, complex m), 3.39 (3H, s), 3.17 (1H, br s), 2.77 (1H, m), 2.15–2.10 (2H, complex m), 1.75–1.59 (3H, complex m), 1.37–1.33 (1H, complex m); δ_C 159.4 (C), 144.1 (CH), 143.2 (CH), 129.5 (C), 129.4 (CH), 121.1 (C), 113.8 (CH), 111.4 (CH_2), 95.5 (CH_2), 77.3 (CH), 72.2 (C or CH_2), 71.5 (C or CH_2), 71.4 (C or CH_2), 68.2 (CH), 67.4 (C or CH_2), 59.0 (CH_3), 55.3 (CH_3), 37.5 (CH), 36.7 (CH), 19.4 (CH_2), 11.9 (CH_2); *m*/*z* 420 ($M^{+\bullet}$, 2%), 344 [$(M - C_3H_8O_2)^{+\bullet}$, 5], 223 (40), 193 (100). Found (HRMS): $M^{+\bullet}$, 420.2138.

(2*R*,5*R*,9*S*,9a*R*,10*R*)-2,3,4,5,7,8,9,9a-Octahydro-5-(2′-methoxyethoxymethoxy)-10-[(4′-methoxyphenyl)methoxy]-2,9-methano-1-benzoxepin-2-ol (18)

Potassium hydride (95 mg, 2.37 mmol) was added, in portions, to a magnetically stirred solution of compound **16** (200 mg, 0.48 mmol) and 18-crown-6 (253 mg, 0.95 mmol) in DME (16 mL) maintained at 0 °C under an atmosphere of nitrogen. The resulting pale orange solution was heated to 60 °C for 2 h then cooled to 0 °C and treated with HCl (15 mL of a 5% v/v aqueous solution). The resulting solution was extracted with diethyl ether (3 × 50 mL) and the combined organic phases were washed with brine (1 × 50 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale yellow oil. Subjection of this material to flash chromatography (silica, 60% v/v ethyl acetate–petrol elution) provided, after concentration of the appropriate fractions (R_f 0.4 in 80% v/v ethyl acetate–petrol), the *title compound* **18** (168 mg, 83%) as a clear, colourless oil, $[\alpha]_D$ +90 (*c* 1.1, $CHCl_3$); ν_{max}/cm^{-1} 3388, 1611, 1513, 1456, 1247, 1033; δ_H 7.20 (2H, d, *J* 8.7), 6.85 (2H, d, *J* 8.7), 5.86 (1H, m), 4.73 (2H, m), 4.63 (1H, m), 4.50 (2H, ABq, *J* 11.5), 4.37 (1H, m), 3.83 (2H, m), 3.79 (3H, s), 3.66–3.54 (3H, complex m), 3.39 (3H, s), 2.80 (1H, m), 2.70 (1H, s), 2.23–2.11 (3H, complex m), 2.01 (1H, m), 1.79–1.57 (4H, complex m); δ_C 158.9 (C), 142.0 (C), 130.3 (C), 128.6 (CH), 120.8 (CH), 113.6 (CH), 109.2 (C), 93.5 (CH_2), 87.0 (CH), 76.0 (CH), 73.2 (CH_2), 73.2 (CH), 71.7 (CH_2), 66.8 (CH_2), 58.9 (CH_3), 55.2 (CH_3), 40.6 (CH), 34.4 (CH_2), 33.3 (CH_2), 22.4 (CH_2), 18.5 (CH_2); *m*/*z* 402 [$(M\text{-}H_2O)^{+\bullet}$, <1%], 314 (5), 121 ($p$-$CH_3OC_6H_4CH_2^+$, 100). Found (HRMS): $(M - H_2O)^{+\bullet}$, 402.2042. $C_{23}H_{32}O_7$ requires $(M - H_2O)^{+\bullet}$, 402.2042.

(1*S*,2*R*,6*R*,11*R*)-6-(2′-Methoxyethoxymethoxy)-2-[(4′-methoxyphenyl)methoxy]-3-oxobicyclo[5.3.1]undec-7(8)-en-11-yl methyl carbonate (19) and (2*R*,5*R*,9*S*,9a*R*,10*R*)-2,3,4,5,7,8,9,9a-octahydro-2-methoxy-5-(2′-methoxyethoxymethoxy)-10-[(4′-methoxyphenyl)methoxy]-2,9-methano-1-benzoxepine (20)

A magnetically stirred suspension of compound **18** (42 mg, 0.1 mmol) in DMF (2 mL) and iodomethane (2 mL) containing silver(I) oxide (231 mg, 1.0 mmol) was heated at reflux (*ca*. 43 °C) while being maintained under a nitrogen atmosphere. After 30 min, the reaction mixture was cooled to 18 °C and filtered through a short (2 cm) plug of Celite™ which was washed with ethyl acetate (5 mL). The combined filtrates were concentrated under reduced pressure to afford a pale yellow oil which was immediately subjected to flash chromatography (silica, 30% v/v ethyl acetate–petrol elution) and which provided two fractions, **A** (R_f 0.1) and **B** (R_f 0.2).

Concentration of fraction **A** afforded the *title compound* **19** (2.5 mg, <5%) as a colourless solid. Recrystallisation (diethyl ether–hexane) of this material afforded an analytically pure sample of carbonate **19** as colourless needles, mp 99–100 °C; $[\alpha]_D$ +61(*c* 1.1, $CHCl_3$); ν_{max}/cm^{-1} 1754, 1697, 1613, 1517, 1270, 1253, 1033; δ_H 7.22 (2H, d, *J* 8.7), 6.83 (2H, d, *J* 8.7), 5.81 (1H, m), 5.31 (1H, m), 4.63 (2H, s), 4.38 (1H, partially obscured m), 4.36 (2H, ABq, *J* 11.2), 4.31 (1H, d, *J* 4.7), 3.85 (3H, s), 3.79 (3H, s), 3.73 (1H, m), 3.61–3.48 (3H, complex m), 3.38 (3H, s), 2.91 (1H, m), 2.38–1.71 (8H, complex m); δ_C 211.9 (C=O), 159.3 (C), 154.8 (C), 136.8 (C), 129.7 (C), 129.5 (CH), 127.4 (CH), 113.7 (CH), 93.5 (CH_2), 79.6 (CH), 75.4 (CH), 71.7 (CH_2), 71.2 (CH), 70.8 (CH_2), 67.0 (CH_2), 59.0 (CH_3), 55.2 (CH_3), 55.1 (CH_3), 44.2 (CH), 38.5 (CH_2), 33.1 (CH_2), 20.5 (CH_2), 17.0 (CH_2); *m*/*z* 434 [$(M - C_2H_4O^{\bullet})^+$, <1%], 372 (13), 121 ($p$-$CH_3OC_6H_4CH_2^+$, 100). Found (HRMS): $(M - C_2H_4O^{\bullet})^+$, 434.1938. $C_{25}H_{34}O_9$ requires $(M - C_2H_4O^{\bullet})^+$, 434.1941.

Concentration of fraction **B** afforded the *title compound* **20** (40 mg, 92%) as a clear, colourless oil, $[\alpha]_D$ +80 (*c* 1.1, $CHCl_3$); ν_{max}/cm^{-1} 1612, 1514, 1248, 1110, 1037; δ_H 7.18 (2H, d, *J* 8.6), 6.85 (2H, d, *J* 8.6), 5.85 (1H, m), 4.71 (2H, s), 4.64 (1H, m), 4.45 (2H, ABq, *J* 11.5), 4.41 (1H, partially obscured m), 3.91 (1H, d, *J* 9.3), 3.83–3.76 (1H, partially obscured m), 3.80 (3H, s), 3.67–3.54 (3H, complex m), 3.39 (3H, s), 3.30 (3H, s), 2.70 (1H, m), 2.19–2.00 (3H, complex m), 1.93–1.59 (5H, complex m); δ_C 158.9 (C), 142.1 (C), 130.2 (C), 128.6 (CH), 120.6 (CH), 113.6 (CH), 112.1 (C), 93.5 (CH_2), 83.0 (CH), 75.7 (CH), 73.2 (CH), 73.1 (CH_2), 71.7 (CH_2), 66.8 (CH_2), 58.9 (CH_3), 55.1 (CH_3), 49.2 (CH_3), 41.0 (CH), 33.4 (CH_2), 31.4 (CH_2), 22.4 (CH_2), 18.5 (CH_2); *m*/*z* 358 (<1%), 345 (<1), 328 [$(M - C_4H_{10}O_3)^{+\bullet}$, 10], 121 ($p$-$CH_3OC_6H_4CH_2^+$, 100). Found (HRMS): $(M - C_4H_{10}O_3)^{+\bullet}$, 328.1672. $C_{24}H_{34}O_7$ requires $(M - C_4H_{10}O_3)^{+\bullet}$, 328.1674.

(2*R*,5*R*,9*S*,9a*R*,10*R*)-2,3,4,5,7,8,9,9a-Octahydro-2-methoxy-10-[(4′-methoxyphenyl)methoxy]-2,9-methano-1-benzoxepin-5-ol (21)

A solution of compound **20** (204 mg, 0.47 mmol) in *t*-BuOH (4.7 mL) containing pyridinium toluene-*p*-sulfonate (586 mg, 2.35 mmol) was heated at reflux under an atmosphere of nitrogen for 4 h. The cooled reaction mixture was then diluted with water (20 mL) and the resulting solution extracted with diethyl ether (3 × 30 mL). The combined organic phases were washed with brine (1 × 50 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale yellow oil. Subjection of this material to flash chromatography (silica, 30% v/v ethyl acetate–petrol elution) provided, after concentration of the appropriate fractions (R_f 0.7 in 45% ethyl acetate–petrol), the *title compound* **21** (138 mg, 85%) as a clear,

colourless oil, $[\alpha]_D$ +20 (*c* 1.3, $CHCl_3$) (Found: C, 69.21; H, 7.49%. $C_{20}H_{26}O_5$ requires C, 69.34; H, 7.56%); ν_{max}/cm^{-1} 3438, 1612, 1585, 1513, 1247, 1111, 1091, 1062, 1034; δ_H 7.21 (2H, d, *J* 8.7), 6.85 (2H, d, *J* 8.7), 5.91 (1H, m), 4.67 (1H, br d, *J ca*. 8), 4.48 (2H, ABq, *J* 11.5), 4.44 (1H, br d, *J ca*. 8), 3.93 (1H, d, *J* 9.2), 3.80 (3H, s), 3.30 (3H, s), 2.86 (1H, m), 2.18–1.59 (8H, complex m); δ_C 158.9 (C), 145.4 (C), 130.2 (C), 128.7 (CH), 119.2 (CH), 113.6 (CH), 112.4 (C), 82.6 (CH), 75.8 (CH), 73.2 (CH_2), 69.2 (CH), 55.2 (CH_3), 49.1 (CH_3), 41.2 (CH), 35.5 (CH_2), 31.9 (CH_2), 22.4 (CH_2), 18.6 (CH_2) [signal due to OH not observed]; *m*/*z* 346 ($M^{+\bullet}$, <1%), 328 [$(M - H_2O)^{+\bullet}$, 5], 121 (p-$CH_3OC_6H_4CH_2^+$, 100). Found (HRMS): $M^{+\bullet}$, 346.1774. $C_{20}H_{26}O_5$ requires $M^{+\bullet}$, 346.1780.

(2*R*,9*S*,9a*R*,10*R*)-2,3,4,5,7,8,9,9a-Octahydro-2-methoxy-10-[(4′-methoxyphenyl)methoxy]-2,9-methano-1-benzoxepin-5-one (22)

Dess–Martin periodinane (327 mg, 0.80 mmol) was added, in portions, to a magnetically stirred solution of alcohol **21** (138 mg, 0.40 mmol) in CH_2Cl_2 (5 mL) maintained at 0 °C under an atmosphere of nitrogen. After 3 h the reaction mixture was diluted with CH_2Cl_2 (10 mL) then treated with sodium thiosulfate (5mL of a 1 M aqueous solution) and sodium bicarbonate (5 mL of a saturated aqueous solution). After being stirred vigorously for 15 min, the reaction mixture was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic phases were washed with brine (1 × 50 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale yellow oil. Subjection of this material to flash chromatography (silica, 30% v/v ethyl acetate–petrol elution) provided, after concentration of the appropriate fractions (R_f 0.8 in 50% v/v ethyl acetate–petrol), the *title compound* **22** (132 mg, 96%) as a clear, colourless oil, $[\alpha]_D$ −123 (*c* 1.2, $CHCl_3$); ν_{max}/cm^{-1} 1687, 1612, 1513, 1248, 1116, 1035; δ_H 7.21 (2H, d, *J* 8.6), 6.84 (2H, d, *J* 8.6), 6.48 (1H, m), 4.48 (1H, partially obscured m), 4.45 (2H, ABq, *J* 11.4), 4.04 (1H, d, *J* 10.5), 3.77 (3H, s), 3.36 (3H, s), 2.92–2.74 (2H, complex m), 2.45 (1H, br d, *J ca*. 15), 2.38–2.25 (2H, complex m), 1.87 (1H, m), 1.77–1.59 (3H, complex m); δ_C 204.3 (C=O), 159.0 (C), 143.8 (C), 136.1 (CH), 129.9 (C), 128.8 (CH), 113.6 (CH), 108.6 (C), 80.3 (CH), 72.7 (CH), 71.7 (CH_2), 55.1 (CH_3), 49.7 (CH_3), 39.0 (CH), 38.0 (CH_2), 27.3 (CH_2), 23.6 (CH_2), 20.3 (CH_2); *m*/*z* 344 ($M^{+\bullet}$, 1%), 121 (p-$CH_3OC_6H_4CH_2^+$, 100). Found (HRMS): $M^{+\bullet}$, 344.1624. $C_{20}H_{24}O_5$ requires $M^{+\bullet}$, 344.1624.

(2*R*,9*S*,9a*R*,10*R*)-4-Diazo-2,3,4,5,7,8,9,9a-octahydro-2-methoxy-10-[(4′-methoxyphenyl)methoxy]-2,9-methano-1-benzoxepin-5-one (23)

A solution of ketone **22** (60 mg, 0.17 mmol) in THF (1 mL) was added, dropwise, to a magnetically stirred suspension of NaH (36 mg, *ca*. 60% dispersion in mineral oil, 0.87 mmol) in THF (1 mL) maintained at 0 °C under an atmosphere of nitrogen. After 30 min, ethyl formate (0.28 mL, 3.48 mmol) was added, dropwise. The resulting mixture was allowed to warm to 18 °C over 1.5 h, and was then treated with HCl (2 mL of a 1 M aqueous solution). The resulting mixture was extracted with diethyl ether (3 × 10 mL) and the combined organic phases were washed with brine (1 × 15 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale yellow oil. This material was immediately dissolved in CH_2Cl_2 (3 mL) and the resulting solution cooled to 0 °C then treated with triethylamine (49 μL, 0.35 mmol) and *p*-nitrobenzenesulfonyl azide (45 mg, 0.21 mmol) while being maintained under an atmosphere of nitrogen. After 45 min, the reaction mixture was partitioned between diethyl ether (10 mL) and water (5 mL). The separated aqueous layer was extracted with diethyl ether (3 × 10 mL) and the combined organic phases were washed with brine (1 × 20 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a yellow oil. Subjection of this material to flash chromatography (silica, 1 : 29 : 70 v/v/v triethylamine–ethyl acetate–petrol elution) provided, after concentration of the appropriate fractions (R_f 0.4), the *title compound* **23** (45 mg, 70%) as a clear, yellow oil, ν_{max}/cm^{-1} 2077, 1626, 1514, 1337, 1248, 1109, 1030; δ_H 7.25 (2H, d, *J* 8.5), 6.88 (2H, d, *J* 8.5), 6.42 (1H, m), 4.56 (1H, partially obscured m), 4.50 (2H, ABq, *J* 11.5), 4.07 (1H, d, *J* 10.3), 3.81 (3H, s), 3.39 (1H, d, *J* 16.7), 3.38 (3H, s), 2.92 (1H, m), 2.60 (1H, d, *J* 16.7), 2.30 (1H, m), 1.80–1.61 (3H, complex m); δ_C 190.7 (C), 159.3 (C), 142.1 (C), 133.7 (CH), 129.8 (C), 129.0 (CH), 113.8 (CH), 107.3 (C), 80.6 (CH), 72.8 (CH), 72.3 (CH_2), 62.0 (C), 55.3 (CH_3), 50.4 (CH_3), 38.7 (CH), 29.7 (CH_2), 23.4 (CH_2), 20.5 (CH_2); *m*/*z* 342 [$(M - N_2)^{+\bullet}$, 2%], 121 (p-$CH_3OC_6H_4CH_2^+$, 100). Found (HRMS): $(M - N_2)^{+\bullet}$, 342.1463. $C_{20}H_{22}N_2O_5$ requires, $(M - N_2)^{+\bullet}$, 342.1467.

Methyl (2*R*,4*R*,8*S*,8a*R*,9*R*)-3,4,6,7,8,8a-hexahydro-2-methoxy-9-[(4′-methoxyphenyl)methoxy]-2,8-methano-2*H*-1-benzopyran-4-carboxylate (24) and methyl (2*R*,4*S*,8*S*,8a*R*,9*R*)-3,4,6,7,8,8a-hexahydro-2-methoxy-9-[(4′-methoxyphenyl)methoxy]-2,8-methano-2*H*-1-benzopyran-4-carboxylate (4)

A solution of compound **23** (35 mg, 0.09 mmol) in anhydrous methanol (7 mL) (contained in a Pyrex round-bottom flask) maintained at 18 °C under a nitrogen atmosphere was subjected to external irradiation using a medium-pressure mercury vapour lamp (125 W) contained within a water-cooled quartz jacket. After 45 min the solution became colourless and irradiation was discontinued. The solvent was removed under reduced pressure and the clear, colourless oil thus obtained was subjected to flash chromatography (silica, 20% v/v ethyl acetate–toluene elution) which afforded two fractions, **A** (R_f 0.6) and **B** (R_f 0.5).

Concentration of fraction **A** afforded the *title compound* **24** (15 mg, 42%) as a clear, colourless oil, $[\alpha]_D$ +17 (*c* 0.9, $CHCl_3$); ν_{max}/cm^{-1} 1737, 1612, 1513, 1437, 1246, 1116, 1035, 755; δ_H 7.24 (2H, d, *J* 8.6), 6.85 (2H, d, *J* 8.6), 5.64 (1H, m), 4.55 (2H, ABq, *J* 11.8), 4.36 (1H, m), 3.80 (3H, s), 3.79 (1H, obscured m), 3.75 (3H, s), 3.56 (1H, m), 3.36 (3H, s), 2.63 (1H, m), 2.48 (1H, dd, *J* 13.3 and 11.1), 2.20 (1H, dd, *J* 13.3 and 7.4), 2.09 (1H, m), 1.72–1.57 (3H, complex m); δ_C 173.0 (C=O), 159.0 (C), 138.6 (C), 130.1 (C), 129.0 (CH), 122.5 (CH), 113.6 (CH), 109.3 (C), 79.6 (CH), 75.2 (CH), 71.3 (CH_2), 55.2 (CH_3), 51.8 (CH_3), 50.1 (CH_3), 40.5 (CH), 38.9 (CH), 31.4 (CH_2), 22.1 (CH_2), 18.9 (CH_2); *m*/*z* 374 ($M^{+\bullet}$, <1%), 253 (2), 193 (7), 133 (5), 121 (p-$CH_3OC_6H_4CH_2^+$, 100). Found (HRMS): $M^{+\bullet}$, 374.1730. $C_{21}H_{26}O_6$ requires $M^{+\bullet}$, 374.1729.

Concentration of fraction **B** afforded the *title compound* **4** (9 mg, 25%) as a clear, colourless oil, ν_{max}/cm^{-1} 2947, 1734, 1612, 1514, 1247, 1127, 1033; δ_H 7.23 (2H, d, *J* 8.7), 6.87 (2H, d, *J* 8.7), 5.82 (1H, m), 4.50 (2H, ABq, *J* 11.7), 4.42 (1H, m), 3.80 (3H, s), 3.74 (3H, s), 3.72 (1H, m), 3.39 (3H, s), 3.04 (1H, d, *J* 7.8), 2.83 (1H, d, *J* 13.7), 2.67 (1H, m), 2.26 (1H, dd, *J* 13.7 and 7.8), 2.07 (1H, m), 1.76–1.62 (3H, complex m); δ_C 174.4 (C), 159.1 (C), 138.7 (C), 130.2 (C), 128.9 (CH), 125.9 (CH), 113.7 (CH), 109.5 (C), 82.2 (CH), 75.9 (CH), 71.6 (CH_2), 55.2 (CH_3), 52.3 (CH_3), 50.6 (CH_3), 42.6 (CH), 38.3 (CH), 30.8 (CH_2), 22.4 (CH_2), 19.1 (CH_2); *m*/*z* 374 ($M^{+\bullet}$, 4%), 253 [$(M - C_8H_9O^{\bullet})^+$, 44], 193 (100). Found (HRMS): $M^{+\bullet}$, 374.1724. $C_{21}H_{26}O_6$ requires $M^{+\bullet}$, 374.1729.

X-Ray crystallographic analysis of compound 19

Crystal data: $C_{25}H_{34}O_9$, $M = 478.54$, $T = 193(1)$ K, monoclinic space group $P2_1$, $a = 9.968(2)$, $b = 10.083(2)$, $c = 12.633(1)$ Å, $\beta = 105.15(1)°$, $U = 1225.6(4)$ Å^3, D_c ($Z = 2$) = 1.297 g cm^{-3}, $F(000) = 512.0$, μ(Cu-Kα) = 8.19 cm^{-1}, analytical absorption correction; 1948 unique data ($2\theta_{max} = 120°$), 1909 with $I > 2\sigma(I)$; $R = 0.053$, $wR = 0.044$, GOF = 2.94. CCDC reference number 166070. See http://www.rsc.org/suppdata/p1/b1/b105376k/ for crystallographic files in .cif or other electronic format.

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