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# Taxane Diterpene Synthesis Studies. Part 1: Chemoenzymatic and Enantiodivergent Routes to AB-ring Substructures of Taxoids and *ent*-Taxoids*

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The microbially derived *cis*-1,2-dihydrocatechol **2** has been converted, via reaction sequences including Diels–Alder cycloaddition and anionic oxy-Cope rearrangement steps, into enantiopure bicyclo[5.3.1]undecenes **21** and **34**, which correspond to AB-ring substructures of *ent*-taxoids and taxoids, respectively.

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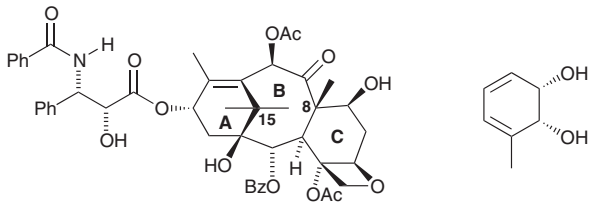
## Introduction

The taxane diterpenes have attracted enormous attention from synthesis chemists because of their challenging molecular architectures and because certain members of this class of compound, most notably Taxol (paclitaxel, **1**, Diagram 1), display clinically useful anti-tumour properties.[1] Many elegant approaches to and several total syntheses of taxoid natural products have been developed in recent years.[2,3] Martin and co-workers have demonstrated,[4] using racemic materials, that anionic oxy-Cope rearrangement[5] of 2-alkenyl-6-methylenebicyclo[2.2.2]octan-2-ols provides an especially attractive means for preparing the bicyclo[5.3.1]undecenyl- or AB-ring system associated with taxoids. However, this approach is limited by a paucity of monochiral bicyclo-[2.2.2]octanyl systems[6] which would allow for the synthesis of enantiopure bicyclo[5.3.1]undecenes. Since monochiral *cis*-1,2-dihydrocatechols[7] such as **2** (Diagram 1) engage, as the 4π-component, in diastereofacially selective Diels–Alder cycloaddition reactions with the resultant formation of bicyclo[2.2.2]octenes,[7,8] we have investigated the possibility of converting these adducts into enantiomerically pure bicyclo[5.3.1]undecenones via anionic oxy-Cope rearrangement chemistry. We now report that by such means the *cis*-1,2-dihydrocatechol **2**, which is available in quantity via microbial oxidation of toluene,[7] can be readily elaborated to the AB-ring system associated with EITHER taxoids OR *ent*-taxoids.

The retrosynthetic analysis employed in the present work is shown in Fig. 1 and hinges on the idea that the target bicyclo[5.3.1]undecenes **3** and *ent*-**3** could be generated via anionic oxy-Cope rearrangement of the corresponding




**1** **2**

**Diagram 1.**

2-alkenyl-6-methylenebicyclo[5.3.1]undecenes **4** and *ent*-**4**, respectively. As the labelling implies, each of these pairs of compounds is enantiomerically related if they possess the mirror-image stereochemistry at the hydroxy-bearing centre, namely C2 in **3**/*ent*-**3** and C3 in **4**/*ent*-**4**, and pseudo-enantiomerically related if they possess the same configuration at these stereogenic centres. Compounds **4** and *ent*-**4** should be accessible from a COMMON precursor **5** through appropriate manipulation of either the diol or alkenyl moieties as well as methylenation of the ketone carbonyl. Compound **5** could, in a formal sense at least, be generated via a Diels–Alder reaction between diene **2** and a ketene equivalent. The successful implementation of these ideas is detailed below.

## Results and Discussion

Initial efforts were focussed, for reasons of simplicity, on that route leading to an AB-ring substructure of *ent*-taxoids as exemplified by the *O*-benzyl derivative of *ent*-**3**. The reaction sequence (Scheme 1) begins with a Diels–Alder reaction between α-chloroacrylonitrile, a well known ketene

*Certain aspects of this work have been reported in preliminary form: M. G. Banwell, P. Darmos, M. D. McLeod, D. C. R. Hockless, *Synlett* **1998**, 897. doi:10.1055/S-1998-1801

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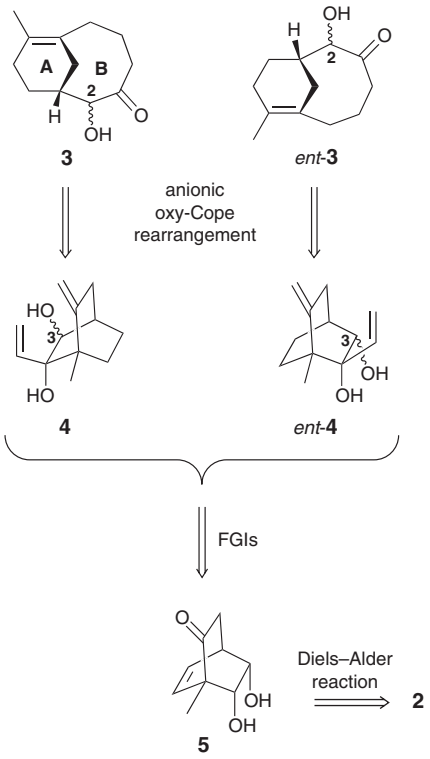
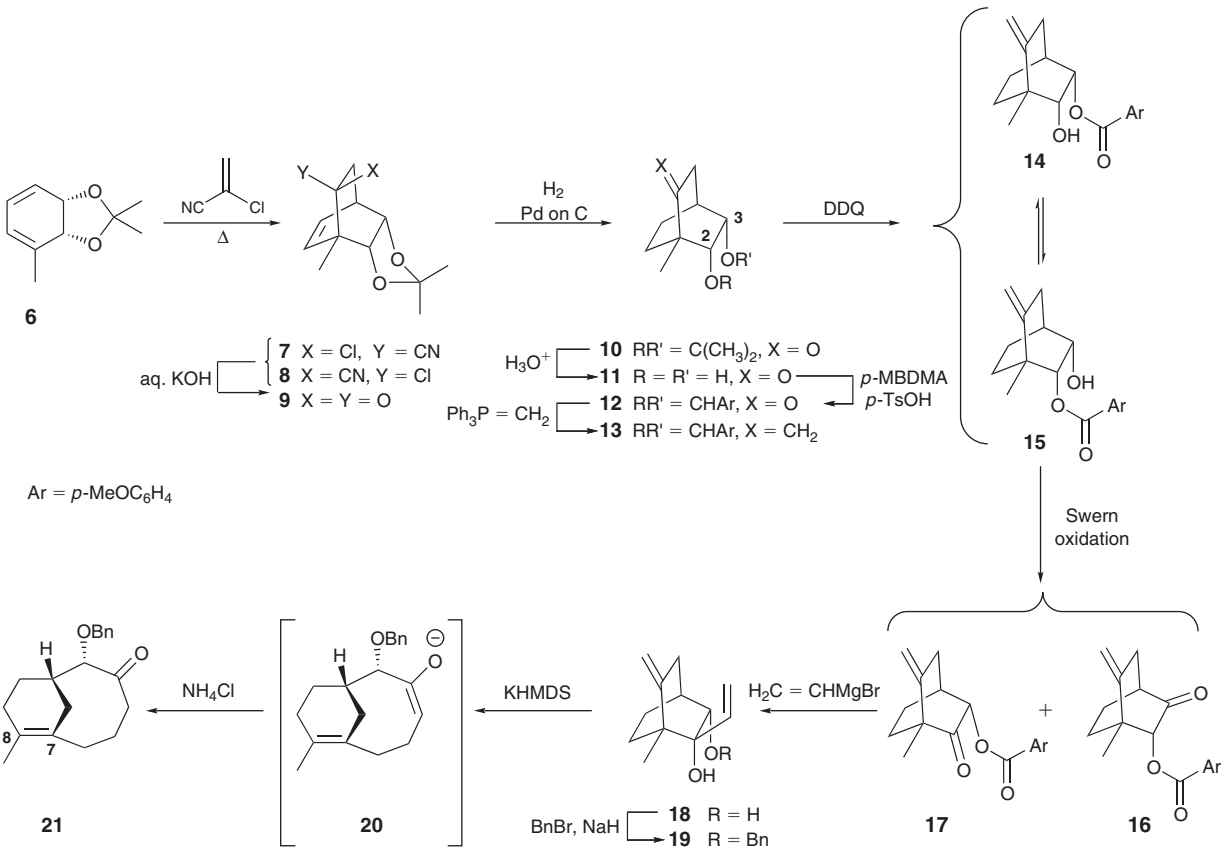



**Fig. 1.**

equivalent used in such cycloaddition processes, and the acetonide derivative, **6**,[8b] of diol **2** (the use of a diol protecting group was required because of the lack of participation of compound **2** itself in the equivalent Diels–Alder reaction with α-chloroacrylonitrile under conventional conditions). By such means a chromatographically separable mixture of the epimeric adducts **7** (70%) and **8** (18%) was obtained and the structure of the latter was established by single-crystal X-ray analysis (see Fig. 2 and Experimental section). Reaction of the mixture of compounds **7** and **8** with aqueous KOH provided ketone **9** (81%) which was converted into its saturated analogue **10** (96%) under standard hydrogenation conditions. Acid-catalyzed hydrolysis of the acetonide group within this latter compound provided the corresponding diol **11** (67% at 86% conversion) which, because of a need to protect the C3 hydroxy whilst leaving its counterpart free for oxidation, was re-protected as its *p*-methoxybenzylidene acetal **12** (100%) by reaction with *p*-methoxybenzaldehyde dimethylacetal (*p*-MBDMA) in the presence of catalytic amounts of *p*-toluenesulfonic acid (*p*-TsOH). Compound **12**, representing a protected and saturated form of intermediate **5** associated with the retrosynthetic analysis (Fig. 2), was obtained as a single diastereoisomer in which the *p*-methoxyphenyl residue assumes the *endo*-configuration (as determined by nuclear Overhauser effect (nOe) NMR experiments) at the acetal carbon atom, presumably by virtue of the producing reaction proceeding under conditions of kinetic control.[9] It should also be noted that the need to effect




**Scheme 1.**

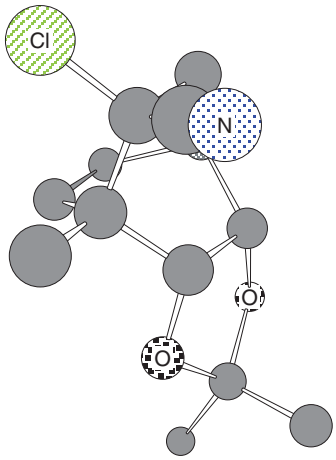



**Fig. 2.** CS Chem3D Pro drawing of Diels–Alder adduct **8** generated using data derived from an X-ray crystallographic study (H atoms omitted for clarity).

this exchange of diol protecting groups has been overcome by using the *p*-methoxybenzylidene acetal moiety from the beginning of the synthesis, as demonstrated in the following paper.

Methylenation of compound **12** with the Wittig reagent gave alkene **13** (89%), thus installing one of the two double bonds required for the anionic oxy-Cope rearrangement reaction. In anticipation of installing the second such moiety, compound **13** was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) thus providing a 1:1 and rapidly interconverting mixture of diol mono-ester **14** and its regioisomer **15** (99% combined yield). These were completely characterized as their individual and stable acetate derivatives. Swern oxidation of the mixture of free alcohols **14** and **15** gave ketone **16** (30%) and its regioisomer **17** (53%) which could be separated from one another by flash chromatography. The assignment of structure to each of these ketones follows from an X-ray analysis of a vinylated derivative of the later product. Thus, reaction of compound **17** with vinylmagnesium bromide then KOH to give diol **18** (92% from **17**). The stereochemical relationship between the two double bonds within this last compound was established by single-crystal X-ray analysis (see Fig. 3 and Experimental section) and is as required for anionic oxy-Cope rearrangement. However, prior to effecting this key reaction, the less hindered 2°-hydroxy group was protected as its benzyl ether **19** (74%) so as to avoid having to effect a double deprotonation in order to initiate the anionic oxy-Cope process.

With the relevant substrate, **19**, to hand this pivotal rearrangement reaction could be investigated. In the event, treatment of compound **19** with potassium hexamethyldisilazide (KHMDS) between −78 and 18°C resulted in a smooth conversion into the enolate **20** which was quenched with ammonium chloride to provide the bicyclo[5.3.1]undecenone **21** in 73%. No attempt has been made to intercept intermediate **20** with anything other than a proton source. However, Martin et al. have shown[4] that closely related enolates can be trapped, in a highly stereoselective

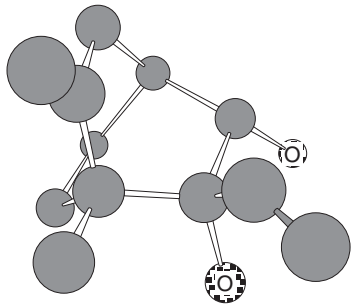
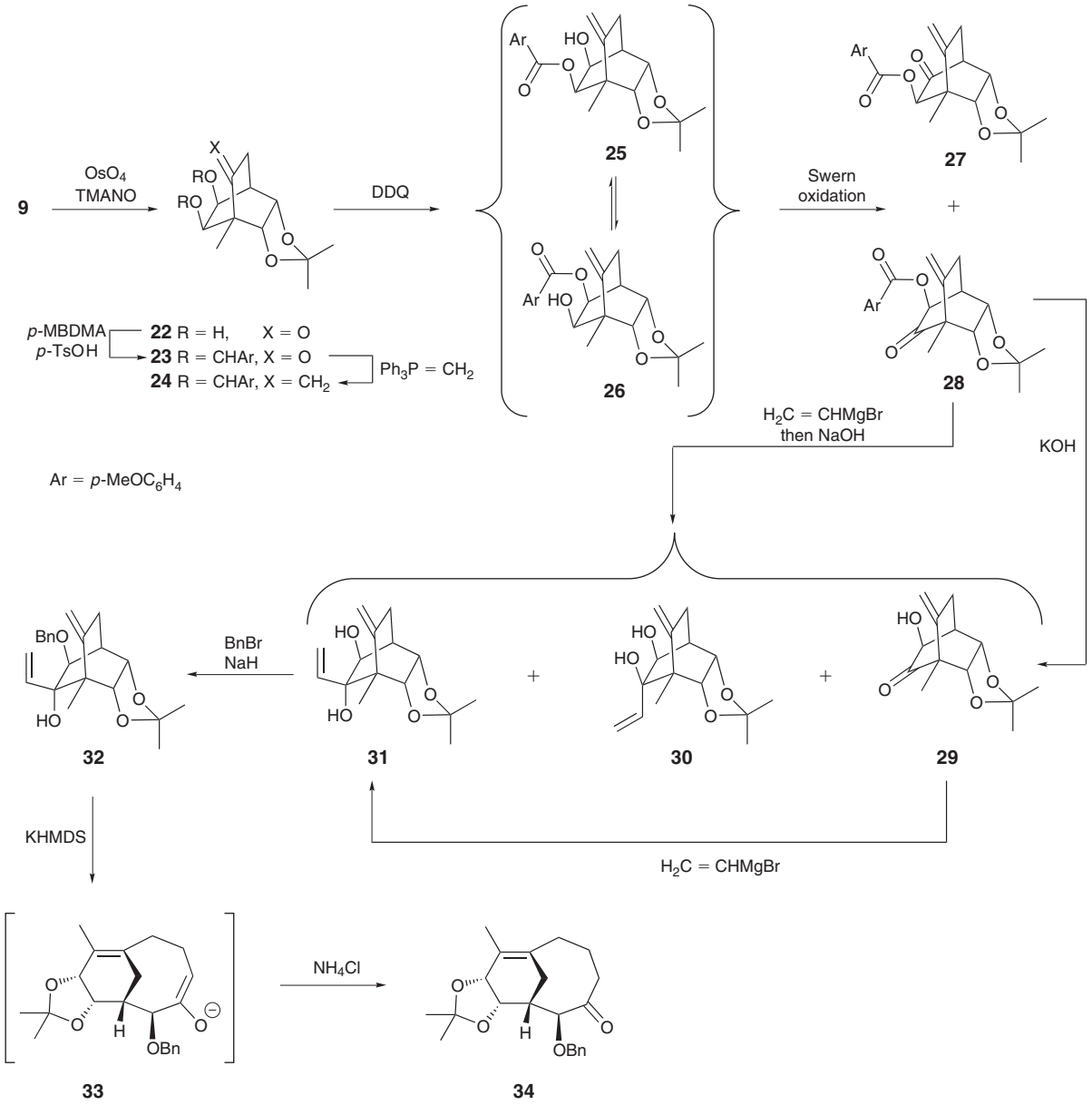



**Fig. 3.** CS Chem3D Pro drawing of 1,5-diene-diol **18** generated using data derived from an X-ray crystallographic study (H atoms omitted for clarity).

manner, with carbon-centred electrophiles. Furthermore, subsequent work in these laboratories (see following paper) has revealed similar possibilities. The structure of the non-crystalline bicyclo[5.3.1]undecenone **21** follows from spectral data. In particular, a comparison of the $^{1}$H NMR spectrum of this compound with that of precursor **19** reveals that the former lacks any resonances due to alkenic protons whilst the latter exhibits five such signals. In the $^{13}$C NMR spectrum of compound **21** a signal due to a ketone carbonyl is observed at $\delta$ 211.2 and a carbonyl stretching band appears at 1713 cm$^{-1}$ in the infra-red spectrum. Signals due to three quaternary and sp$^2$-hybridized carbons are observed in the former spectrum and two of these are assigned to C7 and C8 in **21** whilst the third arises from C1′ of the aromatic ring associated with the benzyl ether moiety. Similarly, only two resonances due to oxygenated sp$^3$-hybridized carbons are observed in the $^{13}$C NMR spectrum of compound **21** whilst three such signals appear in the equivalent spectrum of precursor **19**. Such data when taken together with our recent acquisition[10] of an X-ray crystal structure on a closely related bicyclo[5.3.1]undecenone obtained by anionic oxy-Cope rearrangement of a more extensively C-methylated analogue of compound **19** allows for confident assignment of structure **21**.

The reaction sequence shown in Scheme 1 provides a means for converting *cis*-1,2-dihydrocatechol **2** into a product, **21**, which embodies the AB-ring system associated with *ent*-taxoids. Since the enantiomer of compound **2**, namely *ent*-**2**, is also available (in about 98% *e.e.*), via a two-step sequence involving microbial oxidation of *p*-iodotoluene and reductive de-iodination of the resulting *cis*-1,2-dihydrocatechol,[11] then the enantiomer of compound **21** must also be accessible by this same pathway. However, as noted earlier (Fig. 1), by proper positioning of the vinyl group within a bicyclo[2.2.2]octanyl framework, for example **5**, derived from compound **2** it is possible to imagine producing compounds, for example **4**, that, upon anionic oxy-Cope rearrangement, deliver bicyclo[5.3.1]undecenones corresponding to the natural series of taxoids. Such potential for the enantiodivergent synthesis of the AB-ring substructures of taxoids from a common and enantiomerically pure precursor, namely **2**, has now been realized through successful prosecution of the reaction sequence shown in Scheme 2.




**Scheme 2.**

*cis*-Dihydroxylation (Scheme 2) of alkene **9** was effected using Matteson's procedure[12] and this reaction proceeded with high diastereofacial selectivity to give diol **22** (89%) which was then converted into the corresponding *p*-methoxybenzylidene acetal **23** (79%). As observed in the earlier conversion **11** → **12** (Scheme 1), compound **23** was produced as a single epimer and this is attributed to the acetalization reaction proceeding under conditions of kinetic control and thus affording (as confirmed by nOe studies) an *endo*-configured *p*-methoxyphenyl group. Methylenation of ketone **23** was readily achieved using the Wittig reagent and the product of this reaction, alkene **24** (90%), was then subjected to DDQ-promoted oxidative cleavage of the acetal moiety. As a result, and as observed before for compounds **14** and **15**, an inseparable 1 : 1 mixture of diol mono-benzoate **25** and regio-isomer **26** was produced. These materials, which were comprehensively characterized as their corresponding (and stable) acetate derivatives, were immediately subjected to Swern oxidation and the resulting ketones **27** (46% from **24**) and **28** (46% from **24**) separated by column chromatography. This oxidation reaction could also be carried out using the operationally more straightforward Ley–Griffith protocol[13] but yields were lower (38% of each ketone). Reaction of compound **28** with vinylmagnesium bromide followed by treatment with sodium hydroxide led to acyloin **29** (11%) together with a ca. 1 : 3 mixture of vinylated products **30** (34%) and **31** (11%). These products were readily separated by column chromatography and the structure of the predominant but undesired vinylated material **30** was confirmed by single crystal X-ray analysis (see Fig. 4 and Experimental section). A more selective route to compound **31** involved KOH-promoted hydrolysis of ester **28** to the corresponding α-hydroxyketone **29** (95%) which was then reacted with vinylmagnesium bromide in a ligand assisted

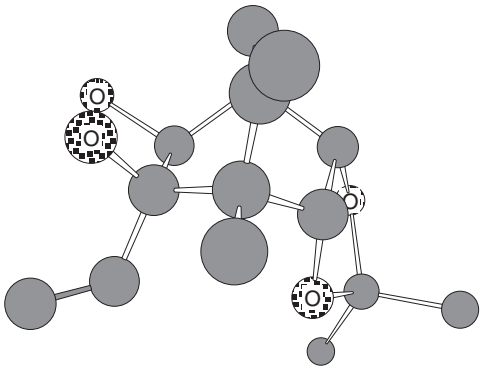


**Fig. 4.** CS Chem3D Pro drawing of diol **30** generated using data derived from an X-ray crystallographic study (H atoms omitted for clarity).

nucleophilic addition (LANA) reaction.[14] In this manner a ca. 1 : 10 mixture **30** and **31** was obtained (55% combined yield). The mono-benzyl ether **32** (53%) derived from **31** underwent smooth anionic oxy-Cope rearrangement upon treatment with KH/[18]crown-6 at 0–18°C and after quenching the intermediate enolate anion **33** with saturated aqueous ammonium chloride the bicyclo[5.3.1]undecenone **34** (47%), which embodies the AB-ring system associated with taxoids, was obtained as a clear, colourless oil. As with congener **21**, the spectral data derived from compound **34** are fully consistent with the assigned structure. Interestingly, the specific rotations of compounds **21** and **34** are of almost equal value but opposite sign, namely +37 and −33 respectively.

## Conclusions

On the basis of the foregoing it is clear that by appropriate choice of reaction pathways usefully functionalized AB-ring sub-structures (such as **21** and **34**) associated with both taxoids and *ent*-taxoids are accessible from the SAME readily available chiron, namely the toluene-derived *cis*-1,2-dihydrocatechol **2**. While compounds **21** and **34** lack the two quaternary carbon centres, at C8 and C15 (for taxane numbering see structure **1**), associated with taxoids the strategy described above does allow for the introduction of these structurally demanding features. Thus, the following paper[15] details a highly efficient synthesis of compounds which incorporate these centres and the novel chemistry that follows from their presence.

## Experimental

### *General Procedures and Protocols*

$^1$H and $^{13}$C NMR spectra were recorded on a Varian Gemini-300 spectrometer. All $^1$H NMR spectra were recorded in $CDCl_3$ and referenced to the signal arising from residual $CHCl_3$ (7.26 ppm). $^{13}$C NMR spectra were also recorded in $CDCl_3$ and referenced to the central line of the $CDCl_3$ triplet (77.0 ppm). Infrared spectra were recorded on a Perkin–Elmer 683 Infrared Spectrometer or a Perkin–Elmer 1800 Fourier transform infrared spectrometer. Samples were analyzed either as thin films on NaCl or KBr plates (for liquids) or as KBr discs (for solids). Low and high resolution electron impact (EI, 70 eV electron beam) mass spectra were recorded on an AUTOSPEC spectrometer. Optical rotations were measured at the wavelength of the sodium D-line, on a Perkin–Elmer 241 polarimeter, in spectroscopic grade chloroform at 20–25°C. Melting points were recorded on a Reichert hot-stage apparatus and are uncorrected. Elemental analyses were carried out by the Australian National University Microanalytical Service on a Carbo–Erba EA 1106 CHN-O elemental analyzer. A titrometric method using mercury nitrate was employed for halogen analyses. Analytical thin layer chromatography (TLC) was conducted on aluminium-backed 0.2 mm thick silica gel 60 $GF_{254}$ plates (supplied by Merck) and the chromatograms were visualized under a 254 nm UV lamp and/or by treatment with anisaldehyde/sulfuric acid/ethanol (2 : 5 : 93 v/v/v mixture) reagent dip or phosphomolybdic acid/cesium(IV) sulfate/sulfuric acid/water (37.5 g : 7.5 g : 37.5 mL : 720 mL) reagent dip, followed by heating. Flash chromatography was conducted according to the method of Still and coworkers[16] using Merck silica gel 60 (230–400 mesh) and AR grade solvents.

Many reagents were available from the Aldrich Chemical Company and were used as supplied. Certain solvents and reagents were purified according to well-established procedures.[17] Thus, tetrahydrofuran (THF) and benzene were purified by distillation from sodium benzophenone ketyl. Ethanol was distilled from magnesium ethoxide. Dimethylformamide (DMF) and dichloromethane were distilled from $CaH_2$. Pyridine and triethylamine were distilled from potassium hydroxide pellets. Dimethyl sulfoxide (DMSO) was distilled from $CaH_2$ at reduced pressure (ca. 15 mmHg) and the initial 20% of the distillate was discarded before collection began. Sodium and potassium hydrides were washed with hexane, then dried under high vacuum and stored in a desiccator. 4 Å Molecular sieves were dried by heating under high vacuum above 150°C for at least 24 h in a drying pistol charged with $P_2O_5$ or by heating in a 1000 W microwave oven (running at full power for 5 min) and transferring the sieves to a new and open container and repeating this process for 0.5 h.

Unless otherwise specified, reactions were carried out under an atmosphere of dry, oxygen-free nitrogen. Those reactions employing air- and/or moisture-sensitive reagents were performed in oven- or flame-dried apparatus. In those instances requiring the use of oil or graphite heating baths, the bath temperatures were monitored with an IKATRON ETS D3 temperature regulator. When low temperature (<0°C) reactions were involved the internal reaction temperature was monitored using an alcohol thermometer. After normal work-up procedures, solutions were concentrated under reduced pressure on a rotary evaporator with the bath temperature generally not exceeding 30°C. Residual solvent was then removed using a JAVAC Double Stage high vacuum pump.

### *Synthetic Studies*

*(3a*S*,4*R*,7*S*,7a*R*,8*S*)-8-Chloro-3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxole-8-carbonitrile **7** and (3a*S*,4*R*,7*S*,7a*R*,8*R*)-8-Chloro-3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxole-8-carbonitrile **8***

A magnetically stirred solution of diene **6** (8.66 g, 52.1 mmol) and α-chloroacrylonitrile (12.5 mL, 156 mmol) in benzene (100 mL) was heated at reflux for 21 h while being maintained under a nitrogen atmosphere. The cooled reaction mixture was then concentrated under reduced pressure to give a 4 : 1 mixture (as judged by $^1$H NMR and HPLC analysis) of the expected Diels–Alder adducts as a pale-yellow oil (11.6 g) which crystallized upon standing. Subjection of this mixture to flash chromatography (silica, 1 : 4 v/v ethyl acetate/hexane elution) gave two fractions, A and B.

Concentration of fraction A [$R_f$ 0.5(4)] afforded a colourless, crystalline solid. Recrystallization (ethanol) of this material afforded *Diels–Alder adduct* **7** (9.28 g, 70%) as colourless cubes, mp 144–146°C, $[\alpha]_D$ +47° (*c* 0.6) (Found: $M^{+\bullet}$ 253.0874, C 61.4, H 6.4, N 5.4, Cl 14.0. $C_{13}H_{16}N^{35}ClO_2$ requires $M^{+\bullet}$ 253.0870, C 61.5, H 6.4, N 5.5, Cl 14.0%). $\nu_{max}$/cm$^{-1}$ 3383, 2974, 2933, 2883, 2234, 1496, 1213, 1087, 1032, 745. $\delta_H$ (300 MHz) 6.24 (1 H, t, *J* 7), 5.75 (1 H, dd, *J* 7 and 1), 4.31 (2 H, m), 2.96 (1 H, m), 2.51 (1 H, dd, *J* 16 and 3), 2.24 (1 H, dd, *J* 16 and 5), 1.59 (3 H, s), 1.34 (3 H, s), 1.29 (3 H, s). $\delta_C$ (75 MHz) 131.9 (CH), 131.1 (CH), 118.9 (C), 110.0 (C), 79.1 (CH), 77.7 (CH), 59.0 (C), 46.9 (C), 42.1 ($CH_2$), 34.1 (CH), 25.4 ($CH_3$), 25.0 ($CH_3$), 17.5 ($CH_3$).

*m/z* 255 and 253 ($M^{+\bullet}$, 1 and 3%), 240 and 238 ($[M - CH_3^\bullet]^+$, 29 and 77), 197 and 195 (15 and 43), 160 (87), 127 (77), 121 (100), 100 (33).

Concentration of fraction B ($R_f$ 0.5) provided a colourless, crystalline solid. Recrystallization (ethanol) of this material afforded *Diels–Alder adduct* ***8*** (2.32 g, 18%) as colourless needles, mp 178–180°C, $[\alpha]_D$ +83° (*c* 0.2) (Found: $[M - CH_3^\bullet]^+$ 238.0637, C 61.1, H 6.4, N 5.4, Cl 13.8. $C_{13}H_{16}N^{35}ClO_2$ requires $[M - CH_3^\bullet]^+$ 238.0635, C 61.5, H 6.4, N 5.5, Cl 14.0%). $\nu_{max}/cm^{-1}$ 3001, 2973, 2922, 2243, 1460, 1258, 1211, 1083, 1047, 879. $\delta_H$ (300 MHz) 6.34 (1 H, t, *J* 7), 5.89 (1 H, dd, *J* 7 and 1), 4.39 (2 H, m), 2.97 (1 H, m), 2.62 (1 H, dd, *J* 15 and 4), 2.12 (1 H, dd, *J* 15 and 2), 1.61 (3 H, s), 1.33 (3 H, s), 1.30 (3 H, s). $\delta_C$ (75 MHz) 134.1 (CH), 133.3 (CH), 119.3 (C), 109.1 (C), 77.9 (CH), 77.5 (CH), 60.2 (C), 46.2 (C), 42.1 ($CH_2$), 34.8 (CH), 25.4 ($CH_3$), 24.9 ($CH_3$), 17.2 ($CH_3$). *m/z* 255 and 253 ($M^{+\bullet}$, <1 and <1%), 240 and 238 ($[M - CH_3^\bullet]^+$, 33 and 64), 195 ($[M - CH_3CO^\bullet]^+$, 21), 160 (78), 121 (100).

*(3a*S*,4*R*,7*S*,7a*R*)-3a,4,7,7a-Tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-8-one* ***9***

A magnetically stirred and ice-cold solution of potassium hydroxide (120 g in 150 mL of water, 14.3 M) was added to a 250 mL round-bottom flask containing compounds **7** and **8** (5.41 g, 21.3 mmol) and the resulting mixture was heated at reflux for 16 h. The cooled reaction mixture was then poured into ether (100 mL) and the separated aqueous layer was treated with potassium carbonate (ca. 2 g) then extracted with ether (3 × 100 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a colourless solid. Subjection of this material to flash chromatography (silica, 1 : 4 v/v ethyl acetate/hexane elution) afforded, after concentration of the appropriate fractions ($R_f$ 0.3), the ketone **9** (3.61 g, 81%) as colourless, crystalline plates, mp 81–82°C, $[\alpha]_D$ +334° (*c* 0.7), (Found: $M^{+\bullet}$ 208.1101, C 69.4, H 7.7. $C_{12}H_{16}O_3$ requires $M^{+\bullet}$ 208.1099, C 69.2, H 7.7%). $\nu_{max}/cm^{-1}$ 2970, 2880, 1729, 1382, 1273, 1253, 1201, 1094, 1049, 877. $\delta_H$ (300 MHz) 6.36 (1 H, t, *J* 7), 5.74 (1 H, d, *J* 7), 4.51 (1 H, dd, *J* 6 and 4), 4.06 (1 H, dd, *J* 6 and 2), 3.18 (1 H, m), 2.14 (1 H, dd, *J* 19 and 4), 1.89 (1 H, dd, *J* 19 and 2), 1.38 (3 H, s), 1.32 (6 H, s). $\delta_C$ (75 MHz) 210.2 (C), 133.4 (CH), 131.3 (CH), 110.6 (C), 79.6 (CH), 79.1 (CH), 54.5 (C), 35.3 (CH), 35.0 ($CH_2$), 25.3 ($CH_3$), 24.9 ($CH_3$), 14.3 ($CH_3$). *m/z* 208 ($M^{+\bullet}$, 18%), 193 ($[M - CH_3^\bullet]^+$, 21), 161 (27), 150 ($[M - (CH_3)_2CO]^{+\bullet}$, 57), 121 (75), 108 (100), 100 (68).

*(3a*S*,4*R*,7*S*,7a*R*)-3a,4,5,6,7,7a-Hexahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-8-one* ***10***

A solution of alkene **9** (6.11 g, 29.4 mmol) in ethanol (100 mL) was treated with 10% palladium on carbon (8.63 g) and the resulting suspension stirred at 18°C under a hydrogen atmosphere (1 atm) for 16 h then filtered through a 0.5 cm deep pad of Celite placed atop a 7 cm deep plug of silica gel. The retained solids were washed with ethanol (100 mL) and the combined filtrates were concentrated under reduced pressure to give *compound* ***10*** (5.91 g, 96%) as a colourless, crystalline solid, mp 50–51°C, $[\alpha]_D$ −35° (*c* 0.55), (Found: $M^{+\bullet}$ 210.1253, C 68.3, H 8.9. $C_{12}H_{18}O_3$ requires: $M^{+\bullet}$ 210.1256, C 68.6, H 8.6%). $\nu_{max}/cm^{-1}$ 2972, 2936, 1727, 1384, 1374, 1266, 1208, 1085, 1062, 1020. $\delta_H$ (300 MHz) 4.29 (1 H, dd, *J* 8, 4 and 2), 3.90 (1 H, dd, *J* 8 and 2), 2.39–2.31 (2 H, complex m), 2.18–1.94 (3 H, complex m), 1.57 (3 H, s), 1.44 (1 H, m), 1.37 (3 H, s), 1.23 (1 H, m), 1.02 (3 H, s). $\delta_C$ (75 MHz) 214.4 (C), 110.2 (C), 76.1 (CH), 75.1 (CH), 47.5 (C/$CH_2$), 40.1 (C/$CH_2$), 31.2 (CH), 25.7 ($CH_3$), 24.2 ($CH_3$), 23.0 ($CH_2$), 18.1 ($CH_2$), 16.7 ($CH_3$). *m/z* 210 ($M^{+\bullet}$, 5%), 195 ($[M - CH_3^\bullet]^+$, 100), 153 ($[M - CH_3^\bullet - CH_2CO]^+$, 99), 109 (48), 93 (80), 81 (59), 69 (61).

*(1*S*,4*S*,5*S*,6*R*)-5,6-Dihydroxy-1-methylbicyclo-[2.2.2]octan-2-one* ***11***

A magnetically stirred solution of acetonide **10** (490 mg, 2.33 mmol) in acetic acid/water (250 mL of a 4 : 1 v/v solution) was heated at 80°C for 18 h. The cooled reaction mixture was concentrated under reduced pressure and the resulting oil partitioned between water (50 mL) and ethyl acetate (50 mL). The separated aqueous layer was extracted with ethyl acetate (2 × 50 mL) and the combined organic phases were then washed with water (1 × 50 mL) and $NaHCO_3$ (1 × 50 mL of a 10% w/v aqueous solution) 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, 1 : 1 ethyl acetate/petrol elution) afforded two fractions, A and B.

Concentration of fraction A ($R_f$ 0.6) afforded the starting acetonide **10** (69 mg, 14% recovery) which was identical, in all respects, with an authentic sample.

Concentration of fraction B ($R_f$ 0.2) afforded *compound* ***11*** (229 mg, 67% at 86% conversion) as a colourless solid, mp 156–157°C, $[\alpha]_D$ +4° (*c* 0.55), (Found: $M^{+\bullet}$ 170.0942, C 63.2, H 8.0. $C_9H_{14}O_3$ requires $M^{+\bullet}$ 170.0943, C 63.5, H 8.3%). $\nu_{max}/cm^{-1}$ 3355, 2933, 2907, 1714, 1401, 1076, 1002, 982, 951, 433. $\delta_H$ (300 MHz) 3.97 (1 H, ddd, *J* 8, 3 and 2), 3.61 (1 H, dd, *J* 8 and 2), 3.17 (2 H, br s), 2.36 (1 H, dd, *J* 19 and 3), 2.29–1.92 (4 H, complex m), 1.47 (1 H, m), 1.28 (1 H, m), 1.02 (3 H, s). $\delta_C$ (75 MHz) 215.3 (C), 68.3 (CH), 67.6 (CH), 48.9 (C), 41.7 ($CH_2$), 33.8 (CH), 22.9 ($CH_2$), 18.0 ($CH_2$), 16.5 ($CH_3$). *m/z* 170 ($M^{+\bullet}$, 89%), 152 ($[M - H_2O]^{+\bullet}$, 22), 137 ($[M - H_2O - CH_3^\bullet]^+$, 47), 110 (100), 109 (89), 95 (72), 69 (75).

*(2*S*,3a*R*,4*S*,7*S*,7a*S*)-Hexahydro-2-(4-methoxyphenyl)-4-methyl-4,7-ethano-1,3-benzodioxol-5-one* ***12***

A magnetically stirred solution of the diol **11** (200 mg, 1.18 mmol) and *p*-methoxybenzaldehyde dimethyl acetal (303 μL, 321 mg, 1.77 mmol) in THF (5 mL) was cooled to 0°C then treated with *p*-toluenesulfonic acid monohydrate (10 mg, 4 mol %). After stirring at 0°C for 2 h, the reaction mixture was quenched with triethylamine (0.5 mL) and concentrated under reduced pressure to afford a pale-yellow solid which was dissolved in dichloromethane (50 mL). The resulting solution was treated with NaOH (1 × 50 mL of a 1 M aqueous solution) and the separated aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined organic phases were washed with brine (1 × 50 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow solid. Subjection of this material to flash chromatography (silica, dichloromethane elution) and concentration of the appropriate fractions ($R_f$ 0.3) afforded the *title acetal* ***12*** (339 mg, 100%) as a colourless solid, mp 162–163°C, $[\alpha]_D$ −22° (*c* 2.8), (Found: $M^{+\bullet}$ 288.1351, C 70.5, H 6.8. $C_{17}H_{20}O_4$ requires $M^{+\bullet}$ 288.1362, C 70.8, H 7.0%). $\nu_{max}/cm^{-1}$ 2924, 1717, 1615, 1518, 1313, 1254, 1170, 1063, 1021, 843. $\delta_H$ (300 MHz) 7.51 (2 H, d, *J* 8), 6.95 (2 H, d, *J* 8), 5.82 (1 H, s—shows 20%, 9% and 4% nOe to signals at $\delta_H$ 7.51, 4.32, and 3.94, respectively), 4.32 (1 H, ddd, *J* 8, 4 and 1), 3.94 (1 H, dd, *J* 8 and 2), 3.83 (3 H, s), 2.50 (1 H, m), 2.41 (1 H, dd, *J* 19 and 4), 2.32–2.12 (3 H, complex m), 1.53–1.25 (2 H, complex m), 1.09 (3 H, s). $\delta_C$ (75 MHz) 214.0 (C), 160.8 (C), 128.3 (2 × CH), 128.2 (C), 113.9 (2 × CH), 104.3 (CH), 76.6 (CH), 76.0 (CH), 55.3 ($CH_3$), 47.6 (C), 40.2 ($CH_2$), 31.0 (CH), 23.3 ($CH_2$), 18.3 ($CH_2$), 16.7 ($CH_3$). *m/z* 288 ($M^{+\bullet}$, 42%), 287 ($[M - H^\bullet]^+$, 53), 257 ($[M - CH_3O^\bullet]^+$, 8), 135 (100), 121 (31), 108 (39), 94 (73).

*(2*S*,3a*R*,4*R*,7*S*,7a*S*)-Hexahydro-2-(4- methoxyphenyl)-4-methyl-5-methylene-4,7-ethano-1,3-benzodioxole* ***13***

A magnetically stirred suspension of sodium hydride (208 mg, 8.68 mmol) in DMSO (7.5 mL) was heated at 78°C for 1 h while being maintained under a nitrogen atmosphere. The resulting green solution was cooled to 0°C then treated with a warm solution of methyltriphenylphosphonium bromide (3.10 g, 8.68 mmol) in DMSO (10 mL). The caramel-coloured reaction mixture was stirred at 18°C for 0.25 h then treated with ketone **12** (500 mg, 1.74 mmol). After stirring the resulting mixture at 18°C for 1 h it was poured into water/pentane (200 mL of a 1 : 1 v/v mixture). The separated aqueous layer was extracted with pentane (3 × 100 mL) and the combined organic phases were washed with $NaHCO_3$ (1 × 100 mL of a saturated aqueous solution) and brine (1 × 100 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a colourless, waxy solid. Subjection of this material to flash chromatography (silica, 1 : 19 v/v ethyl acetate/hexane elution) and concentration of the appropriate

fractions ($R_f$ 0.3) afforded *compound* ***13*** (445 mg, 89%) as a colourless solid, mp 41–42°C, $[\alpha]_D$ +47° (*c* 1.3), (Found: $M^{+\bullet}$ 286.1557. $C_{18}H_{22}O_3$ requires $M^{+\bullet}$ 286.1569). $\nu_{max}/cm^{-1}$ 2934, 2912, 1616, 1519, 1402, 1249, 1074, 1030, 1009, 831. $\delta_H$ (300 MHz) 7.51 (2 H, d, *J* 9), 6.93 (2 H, d, *J* 9), 5.73 (1 H, s), 4.92 (1 H, br s), 4.89 (1 H, br s), 4.15 (1 H, dd, *J* 8 and 4), 3.82 (3 H, s), 3.73 (1 H, dd, *J* 8 and 2), 2.48 (1 H, ddd, *J* 19, 8 and 3), 2.28 (1 H, dm, *J* 19), 2.17–1.94 (3 H, complex m), 1.40 (1 H, m), 1.20 (1 H, m), 1.10 (3 H, s). $\delta_C$ (75 MHz) 160.6 (C), 150.2 (C), 129.0 (C), 128.4 (CH), 113.8 (CH), 107.7 ($CH_2$), 103.0 (CH), 80.0 (CH), 76.9 (CH), 55.3 ($CH_3$), 38.3 (C), 32.2 ($CH_2$), 30.2 (CH), 25.7 ($CH_2$), 20.3 ($CH_3$), 19.2 ($CH_3$). *m*/*z* 286 ($M^{+\bullet}$, 60%), 285 ($[M - H^{\bullet}]^+$, 55), 257 (21), 137 (66), 135 (100), 121 (98), 107 (48), 91 ($C_7H_7^+$, 47).

*(1*R*,2*R*,3*S*,4*S*)-2-Hydroxy-1-methyl-6- methylenebicyclo-[2.2.2]octan-3-yl 4-Methoxybenzaote* ***14***
*and (1*R*,2*R*,3*S*,4*S*)-3-Hydroxy-1-methyl-6-methylenebicyclo-[2.2.2]octan-2-yl 4-Methoxybenzaote* ***15***

A magnetically stirred solution of compound **13** (445 mg, 1.56 mmol) in dichloromethane/water (20 mL of a 17 : 1 v/v mixture) was treated with DDQ (530 mg, 2.33 mmol, 1.5 mole equiv.). After 4 h at 18°C the reaction mixture was poured into $NaHCO_3$ (50 mL of a 5% w/v aqueous solution) and the separated aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined organic phases were washed with $NaHCO_3$ (1 × 100 mL of a 5% w/v aqueous solution), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a colourless solid. Subjection of this material to flash chromatography (silica, 1 : 4 ethyl acetate/petrol elution) afforded two fractions, A and B.

Concentration of fraction A ($R_f$ 0.4) afforded *compound* ***14*** (236 mg, 50%) as a colourless solid. $^1$H NMR analysis of this material indicated that it was contaminated with ca. 0.5% of its regioisomer **15**.

Concentration of fraction B containing the less mobile component ($R_f$ 0.2) afforded *compound* ***15*** (230 mg, 49%) as a colourless solid. $^1$H NMR analysis of this material indicated that it was contaminated with ca. 2% of compound **14**.

Compounds **14** and **15** interconvert on standing. Consequently, no attempt was made to characterize them in a comprehensive manner. Rather, the crude mixture of these compounds was acetylated (see below) and the derived acetates were then separated and characterized spectroscopically.

*(1*R*,2*R*,3*S*,4*S*)-2-Acetoxy-1-methyl-6-methylenebicyclo-[2.2.2]octan-3-yl 4-Methoxybenzoate*
*and (1*R*,2*R*,3*S*,4*S*)-3-Acetoxy-1-methyl-6-methylenebicyclo-[2.2.2]octan-2-yl 4-Methoxybenzoate*

A solution of a ca. 1 : 1 mixture of compounds **14** and **15** (219 mg, 0.725 mmol) in pyridine (2 mL) was treated with acetic anhydride (630 μL, 6.62 mmol) and the resulting mixture stirred at 18°C for 16 h then concentrated under reduced pressure to give a pale-yellow oil. This material was subjected to flash chromatography (silica, 1 : 4 v/v ethyl acetate/hexane elution) thus affording two fractions, A and B.

Concentration of fraction A ($R_f$ 0.2) gave a colourless solid. Recrystallization (hexane) of this material afforded *(1*R*,2*R*,3*S*,4*S*)-2-acetoxy-1-methyl-6-methylenebicyclo[2.2.2]octan-3-yl 4-methoxybenzoate*, the acetate derivative of compound **14**, (100 mg, 40%) as colourless, crystalline needles, mp 73–74°C (Found: $M^{+\bullet}$ 344.1631, C 69.6, H 7.0. $C_{20}H_{24}O_5$ requires $M^{+\bullet}$ 344.1624, C 69.8, H 7.0%). $\nu_{max}/cm^{-1}$ 1741, 1723, 1607, 1286, 1267, 1237, 1168, 1125, 1100, 1020. $\delta_H$ (300 MHz) 7.99 (2 H, d, *J* 9), 6.92 (2 H, d, *J* 9), 5.21 (1 H, ddd, *J* 8, 3 and 2), 4.94 (1 H, br s), 4.88 (1 H, br s), 4.85 (1 H, dd, *J* 8 and 2), 3.86 (3 H, s), 2.44 (2 H, br s), 2.15–2.03 (2 H, complex m), 1.98–1.88 (1 H, complex m), 1.93 (3 H, s), 1.50 (1 H, m), 1.30 (1 H, m), 0.98 (3 H, s). $\delta_C$ (75 MHz) 170.2 (C), 165.2 (C), 163.4 (C), 149.0 (C), 131.5 (2 × CH), 122.6 (C), 113.6 (2 × CH), 108.2 ($CH_2$), 71.9 (CH), 69.8 (CH), 55.4 ($CH_3$), 38.1 (C/$CH_2$), 32.8 (C/$CH_2$), 30.7 (CH), 26.6 ($CH_2$), 20.6 ($CH_3$), 20.1 ($CH_2$), 19.6 ($CH_3$). *m*/*z* 344 ($M^{+\bullet}$, 17%), 150 (24), 135 (100), 108 (18), 77 (16).

Concentration of the fractions containing the less mobile component [$R_f$ 0.1(6)] afforded *(1*R*,2*R*,3*S*,4*S*)-3-acetoxy-1-methyl-6-methylenebicyclo[2.2.2]octan-2-yl 4-methoxybenzoate*, the acetate derivative of compound **15**, (93 mg, 37%), as a clear, colourless oil (Found: $M^{+\bullet}$ 344.1621. $C_{20}H_{24}O_5$ requires $M^{+\bullet}$ 344.1624). $\nu_{max}/cm^{-1}$ 1746, 1719, 1607, 1512, 1282, 1258, 1238, 1168, 1103, 788. $\delta_H$ (300 MHz) 8.03 (2 H, d, *J* 9), 6.95 (2 H, d, *J* 9), 5.04 (1 H, dd, *J* 8 and 2), 4.98–4.87 (3 H, complex m), 3.87 (3 H, s), 2.43 (2 H, br s), 2.11–1.93 (3 H, complex m), 1.80 (3 H, s), 1.54 (1 H, m), 1.35 (1 H, m), 1.04 (3 H, s). $\delta_C$ (75 MHz) 170.0 (C), 165.6 (C), 163.4 (C), 148.8 (C), 131.6 (2 × CH), 122.6 (C), 113.7 (2 × CH), 108.4 ($CH_2$), 72.3 (CH), 70.0 (CH), 55.4 ($CH_3$), 38.4 (C/$CH_2$), 33.0 (C/$CH_2$), 30.7 ($CH_3$), 26.7 ($CH_2$), 20.7 ($CH_3$), 19.9(9) ($CH_3$), 19.9(5) ($CH_2$). *m*/*z* 344 ($M^{+\bullet}$, 4%), 284 ($[M - CH_3CO_2H]^{+\bullet}$, 25), 243 (16), 242 (16), 135 (100), 107 (19), 92 (27), 77 (24).

*(1*S*,2*R*,4*R*)-4-Methyl-5-methylene-2-oxobicyclo[2.2.2]octan-3-yl 4-Methoxybenzoate* ***16***
*and (1*R*,3*S*,4*S*)-1-Methyl-6-methylene-2-oxobicyclo[2.2.2]octan-3-yl 4-Methoxybenzoate* ***17***

Trifluoroacetic anhydride (234 μL, 1.67 mmol, 1.5 mole equiv.) was added dropwise to a magnetically stirred solution of DMSO (157 μL, 2.19 mmol, 2 mole equiv.) in dichloromethane (6 mL) maintained at −60°C (dry ice/chloroform bath) under a nitrogen atmosphere. The resulting solution was stirred at −60°C for 10 min before a solution of a 1 : 1 mixture of compound **14** and regioisomer **15** (334 mg, 1.11 mmol) in dichloromethane (1 mL) was added dropwise. After stirring for 3 h at −60°C, triethylamine (1 mL) was added and the mixture then warmed to 18°C. The orange solution thus obtained was poured into HCl (1 × 50 mL of a 2 M aqueous solution) and extracted with dichloromethane (3 × 50 mL). The combined organic phases were washed with water (1 × 50 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford an orange oil (332 mg). Subjection of this material to flash chromatography (silica, 1 : 4 ethyl acetate/petrol elution) provided two fractions, A and B.

Concentration of fraction A ($R_f$ 0.4) afforded *compound* ***16*** (100 mg, 30%) as a pale-yellow oil, $[\alpha]_D$ +164° (*c* 2.8), (Found: $M^{+\bullet}$ 300.1358. $C_{18}H_{20}O_4$ requires $M^{+\bullet}$ 300.1362). $\nu_{max}/cm^{-1}$ 1719, 1606, 1512, 1325, 1257, 1168, 1100, 1027, 847, 767. $\delta_H$ (300 MHz) 8.03 (2 H, d, *J* 8), 6.94 (2 H, d, *J* 8), 5.25 (1 H, d, *J* 2), 5.11 (1 H, br s), 5.02 (1 H, br s), 3.86 (3 H, s), 2.70 (2 H, m), 2.60 (1 H, m), 2.09–1.82 (3 H, br m), 1.50 (1 H, m), 1.10 (3 H, s). $\delta_C$ (75 MHz) 211.0 (C), 165.1 (C), 163.4 (C), 147.0 (C), 131.8 (CH), 121.6 (C), 113.5 (CH), 109.0 ($CH_2$), 76.4 (CH), 55.2 ($CH_3$), 43.1 (C), 42.8 (CH), 31.3 ($CH_2$), 27.2 ($CH_2$), 25.5 ($CH_2$), 18.5 ($CH_3$). *m*/*z* 300 ($M^{+\bullet}$, 15%), 135 (100), 107 (12), 92 (7), 77 (10).

Concentration of the fraction B ($R_f$ 0.5) gave a colourless solid. Recrystallization ($CHCl_3$/hexane) of this material afforded *compound* ***17*** (175 mg, 53%) as colourless needles, mp 78–79°C, $[\alpha]_D$ +44° (*c* 2.2), (Found: $M^{+\bullet}$ 300.1360, C 71.8, H 6.6. $C_{18}H_{20}O_4$ requires $M^{+\bullet}$ 300.1362, C 72.0, H 6.7%). $\nu_{max}/cm^{-1}$ 1739, 1711, 1607, 1510, 1304, 1260, 1176, 1118, 1026, 767. $\delta_H$ (300 MHz) 8.02 (2 H, d, *J* 9), 6.92 (2 H, d, *J* 9), 5.30 (1 H, t, *J* 2), 4.97 (2 H, dt, *J* 6 and 2), 3.86 (3 H, s), 2.77–2.68 (2 H, complex m), 2.47 (1 H, m), 2.05 (1 H, m), 1.87 (2 H, m), 1.72 (1 H, m), 1.19 (3 H, s). $\delta_C$ (75 MHz) 208.8 (C), 165.3 (C), 163.5 (C), 143.9 (C), 131.9 (CH), 122.0 (C), 113.6 (CH), 110.0 ($CH_2$), 75.6 (CH), 55.4 ($CH_3$), 50.3 (C), 33.7 ($CH_2$), 33.2(2) (CH), 33.1(9) ($CH_2$), 20.4 ($CH_2$), 15.8 ($CH_3$). *m*/*z* 300 ($M^{+\bullet}$, 17%), 135 (100), 107 (6), 92 (9), 77 (12).

*(1*R*,2*R*,3*S*,4*S*)-2-Ethenyl-1-methyl-6-methylenebicyclo-[2.2.2]octane-2,3-diol* ***18***

A magnetically stirred solution of ketone **17** (61 mg, 0.203 mmol) in THF (3 mL) maintained at 0°C under a nitrogen atmosphere was treated, in one portion, with vinylmagnesium bromide (0.55 mL of a 1.2 M solution in THF, 0.660 mmol, 3.25 mole equiv.). After stirring the resulting mixture at 0°C for 3 h, $NH_4Cl$ (10 mL of a saturated aqueous solution) was added and the resulting suspension partitioned between water (20 mL) and ethyl acetate (50 mL). The separated aqueous layer was

extracted with ethyl acetate (2 × 50 mL), and the combined organic phases dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil. A solution of this material in methanol (2 mL) was treated with potassium hydroxide (ca. 1 g) and after stirring the reaction mixture at 18°C for 0.33 h it was poured into water (10 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide an orange oil. Subjection of this material to flash chromatography (silica, 3 : 17 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f$ 0.2) afforded an oil which solidified upon standing. Recrystallization (hexane) of this solid afforded *compound* ***18*** (36 mg, 92%) as colourless needles, mp 97–98°C, $[\alpha]_D$ –18° (*c* 2.1), (Found: $M^{+\bullet}$ 194.1306, C 74.0, H 9.6. $C_{12}H_{18}O_2$ requires $M^{+\bullet}$ 194.1307, C 74.2, H 9.3%). $\nu_{max}/cm^{-1}$ 3311, 2958, 2946, 2915, 1644, 1082, 1072, 984, 921, 894. $\delta_H$ (300 MHz) 5.83 (1 H, dd, *J* 17 and 11), 5.26 (1 H, dd, *J* 17 and 2), 5.07 (1 H, dd, *J* 11 and 2), 4.83 (2 H, m), 3.50 (1 H, br s), 2.79 (1 H, br s), 2.65 (1 H, br m), 2.44 (1 H, ddd, *J* 17, 5 and 3), 2.32 (1 H, dddd, *J* 17, 7, 3 and 2), 2.01–1.79 (3 H, complex m), 1.40 (1 H, m), 1.22 (1 H, ddd, *J* 18, 12 and 6), 0.89 (3 H, s). $\delta_C$ (75 MHz) 141.7 (C), 111.6 (C/$CH_2$), 110.5 (C/$CH_2$), 107.6 (C/$CH_2$), 74.0 (CH), 44.4 (CH), 44.3 (C), 33.6 ($CH_2$), 33.2 (C), 27.8 ($CH_2$), 18.8 ($CH_2$), 17.8 ($CH_3$). *m*/*z* 194 ($M^{+\bullet}$, 0.2%), 176 ($[M - H_2O]^{+\bullet}$, 4), 161 (13), 118 (27), 108 (100), 93 (45), 91 (28), 79 (24), 55 (30).

*(1*R*,2*R*,3*S*,4*S*)-2-Ethenyl-1-methyl-6-methylene-3-(phenylmethoxy)bicyclo[2.2.2]octan-2-ol* ***19***

Sodium hydride (66 mg, 2.75 mmol, 3 mole equiv.) was added to a magnetically stirred and ice-cold solution of diol **18** (180 mg, 0.927 mmol) in benzyl bromide (10 mL of a 0.1 M solution in DMF, 1.00 mmol) maintained under a nitrogen atmosphere. After stirring the resulting mixture at 0°C for 2 h it was quenched with water (50 mL) (CAUTION) then extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a yellow oil. Subjection of this material to flash chromatography (silica, 1 : 9 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f$ 0.3) then gave the *benzyl ether* ***19*** (194 mg, 74%) as a pale-yellow oil, $[\alpha]_D$ –23° (*c* 3.2), (Found: $M^{+\bullet}$ 284.1772. $C_{19}H_{24}O_2$ requires $M^{+\bullet}$ 284.1776). $\nu_{max}/cm^{-1}$ 3508, 2936, 1642, 1455, 1402, 1348, 1135, 1094, 1074, 697. $\delta_H$ (300 MHz) 7.32 (5 H, m), 5.83 (1 H, dd, *J* 17 and 10), 5.36 (1 H, dd, *J* 17 and 2), 5.03 (1 H, dd, *J* 10 and 2), 4.80 (2 H, br s), 4.59 (2 H, s), 3.55 (1 H, s), 3.30 (1 H, br s), 2.44 (1 H, ddd, *J* 17, 6 and 1), 2.26 (1 H, br d, *J* 17), 1.99 (1 H, m), 1.95 (2 H, m), 1.39 (1 H, ddd, *J* 10, 8 and 3), 1.16 (1 H, m), 0.88 (3 H, s). $\delta_C$ (75 MHz) 150.6 (C), 142.9 (CH), 137.8 (C), 128.4 (CH), 127.8 (2 × CH), 127.7 (2 × CH), 112.2 ($CH_2$), 107.6 ($CH_2$), 81.2 (CH), 73.8 (C), 72.6 ($CH_2$), 42.0 (C), 33.5 ($CH_2$), 30.5 (CH), 28.1 ($CH_2$), 19.3 ($CH_2$), 17.6 ($CH_3$). *m*/*z* 284 ($M^{+\bullet}$, 0.4%), 229 (4), 176 (85), 107 (96), 91 (100), 77 (23).

*(1*S*,2*S*)-8-Methyl-2-(phenylmethoxy)bicyclo[5.3.1]undec-7(8)-en-3-one* ***21***

A solution of compound **19** (22 mg, 0.0775 mmol) in THF (1 mL) maintained at −78°C (dry ice/acetone bath) under a nitrogen atmosphere was treated with potassium hexamethyldisilazane (0.5 mL of a 0.5 M solution in toluene, 0.250 mmol, 3 mole equiv.). After stirring at −78°C for 0.26 h, the reaction mixture was warmed to 18°C then treated with $NH_4Cl$ (10 mL of a saturated aqueous solution). The resulting suspension was treated with water (5 mL) and the separated aqueous layer extracted with dichloromethane (2 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a pale-yellow oil (20 mg). Subjection of this material to flash chromatography (silica, 1 : 9 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f$ 0.4) afforded *compound* ***21*** (16 mg, 73%) as a clear, colourless oil, $[\alpha]_D$ –33° (*c* 1.7), (Found: $M^{+\bullet}$ 284.1769. $C_{19}H_{24}O_2$ requires $M^{+\bullet}$ 284.1776). $\nu_{max}/cm^{-1}$ 2937, 2871, 1713, 1452, 1257, 1113, 1062, 1027, 786, 761. $\delta_H$ (300 MHz) 7.31 (5 H, m), 4.53 (1 H, d, *J* 12), 4.25 (1 H, d, *J* 12), 4.16 (1 H, d, *J* 5), 2.71 (1 H, br m), 2.47 (1 H, m), 2.31 (1 H, m), 2.20–1.76 (9 H, complex m), 1.60 (1 H, m), 1.54 (3 H, s). $\delta_C$ (75 MHz) 211.2 (C), 138.0 (C), 133.9 (C), 129.9 (C), 128.3 (2 × CH), 127.8 (CH), 127.6 (2 × CH), 84.5 (CH), 70.7 ($CH_2$), 43.1 ($CH_2$), 40.0 (CH), 31.9 ($CH_2$), 31.6 ($CH_2$), 28.4 ($CH_2$), 24.8 ($CH_2$), 19.0 ($CH_2$), 18.1 ($CH_3$). *m*/*z* 284 ($M^{+\bullet}$, 3%), 193 (23), 176 (28), 175 (27), 107 (22), 91 (100), 55 (26).

*(3a*R*,4*S*,7*R*,7a*S*,8*S*,9*R*)-Tetrahydro-8,9-dihydroxy-2,2,4-trimethyl-4,7-ethano-1,3-benzodioxol-5(4*H*)-one* ***22***

A magnetically stirred mixture of alkene **9** (7.86 g, 37.8 mmol), *t*-butanol (152 mL), water (47.4 mL), pyridine (6.4 mL), and trimethylamine-*N*-oxide (9.20 g) maintained under a nitrogen atmosphere was treated, in one portion, with osmium tetroxide (3.2 mL of 2.5 wt-% solution in *t*-butanol). The resulting pale-brown solution was heated at reflux for 5 h then cooled and treated with $Na_2S_2O_5$ (200 mL of a 20% w/v aqueous solution). The ensuing mixture was concentrated under reduced pressure and the residue acidified to pH 2 with $H_2SO_4$ (6 wt-% solution in water) then the separated aqueous layer was extracted with ether (4 × 250 mL). The combined organic phases were washed with brine (1 × 250 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a pale-yellow solid. Recrystallization (ethyl acetate/hexane) of this material afforded *diol* ***22*** (8.16 g, 89%) as colourless needles, mp 182–182.5°C, $[\alpha]_D$ –38° (*c* 1.0), (Found: $[M - CH_3^{\bullet}]^+$ 227.0920, C 59.3, H 7.7. $C_{12}H_{18}O_5$ requires $[M - CH_3^{\bullet}]^+$ 227.0920, C 59.5, H 7.5%). $\nu_{max}/cm^{-1}$ 3512, 3456, 1726, 1377, 1210, 1158, 1083, 1053, 1040, 858. $\delta_H$ (300 MHz) 4.51 (1 H, m), 4.33 (1 H, dd, *J* 8 and 4), 4.18 (1 H, dm, *J* 8), 3.93 (1 H, d, *J* 8), 2.80–2.53 (4 H, complex m), 1.98 (1 H, dt, *J* 19 and 2), 1.50 (3 H, s), 1.32 (3 H, s), 1.27 (3 H, s). $\delta_C$ (75 MHz) 210.7 (C), 110.3 (C), 76.8 (CH), 74.8 (CH), 69.2 (CH), 62.6 (CH), 54.5 (C), 38.8 (CH), 34.1 ($CH_2$), 25.5 ($CH_3$), 23.6 ($CH_3$), 14.1 ($CH_3$). *m*/*z* 227 ($[M - CH_3^{\bullet}]^+$, 13%), 209 ($[M - H_2O - CH_3^{\bullet}]^+$, 14), 149 (30), 125 (50), 124 (45), 121 (100), 109 (41), 85 (42).

*(3a*S*,4*R*,4a*S*,6*S*,7a*R*,8*S*,8a*R*)-Hexahydro-6-(4-methoxyphenyl)-2,2,8-trimethyl-4,8-ethanobenzo[1,2-d : 4,5-d′]bis[1,3]-dioxol-9-one* ***23***

A magnetically stirred solution of diol **22** (677 mg, 2.78 mmol) and *p*-methoxybenzaldehyde dimethyl acetal (0.7 mL, 4.17 mmol, 1.5 mole equiv.) in THF (10 mL) maintained under a nitrogen atmosphere was cooled to 0°C and treated with *p*-toluenesulfonic acid monohydrate (25 mg, 5 mol %). The resulting mixture was warmed to 18°C, stirred for 16 h then quenched with triethylamine (1 mL) and concentrated under reduced pressure. The residue was dissolved in dichloromethane (50 mL) and the resulting solution treated with NaOH (1 × 50 mL of a 1 M aqueous solution). The separated aqueous phase was extracted with dichloromethane (3 × 50 mL), and the combined organic phases were washed with brine (1 × 50 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow oil (1.32 g). Subjection of this material to flash chromatography (silica, 3 : 7 ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f$ 0.4) gave *compound* ***23*** (792 mg, 79%) as a colourless, crystalline solid, mp 118.5–119.5°C, $[\alpha]_D$ +18° (*c* 1.3), (Found: $M^{+\bullet}$ 360.1563, C 66.6, H 6.8. $C_{20}H_{24}O_6$ requires $M^{+\bullet}$ 360.1573, C 66.7, H 6.7%). $\nu_{max}/cm^{-1}$ 3425, 2932, 1734, 1615, 1381, 1257, 1210, 1170, 1071, 1033, 998. $\delta_H$ (300 MHz) 7.30 (2 H, d, *J* 9), 6.87 (2 H, d, *J* 9), 5.60 (1 H, s—shows 23%, 3% and 7% nOe to signals at $\delta$ 7.30, 4.72 and 4.44, respectively), 4.72 (1 H, ddd, *J* 8, 3 and 1), 4.50 (1 H, dd, *J* 8 and 4), 4.44 (1 H, d, *J* 8), 3.97 (1 H, d, *J* 8), 3.78 (3 H, s), 2.91 (1 H, m), 2.75 (1 H, dd, *J* 19 and 4), 1.95 (1 H, br d, *J* 19), 1.52 (3 H, s), 1.36 (3 H, s), 1.34 (3 H, s). $\delta_C$ (75 MHz) 209.7 (C), 160.7 (C), 128.3 (2 × CH), 127.5 (CH), 113.9 (2 × CH), 110.4 (C), 102.2 (CH), 77.4 (CH), 76.5 (CH), 75.1 (CH), 71.6 (CH), 55.3 ($CH_3$), 52.9 (C), 35.5 (CH), 34.8 ($CH_2$), 25.4 ($CH_3$), 23.3 ($CH_3$), 13.8 ($CH_3$). *m*/*z* 360 ($M^{+\bullet}$, 54%), 359 ($[M - H^{\bullet}]^+$, 78), 345 ($[M - CH_3^{\bullet}]^+$, 4), 329 ($[M - CH_3O^{\bullet}]^+$, 15), 149 (28), 135 (100), 108 (67).

*(3a*R*,4*S*,4a*R*,6*S*,7a*S*,8*R*,8a*S*)-Hexahydro-6-(4-methoxyphenyl)-2,2,4-trimethyl-10-methylene-4,8-ethanobenzo[1,2-d : 4,5-d′]-bis[1,3]dioxole* ***24***

A magnetically stirred suspension of sodium hydride (1.30 g, 54.3 mmol) in DMSO (30 mL), maintained under a nitrogen atmosphere

was heated at 78°C for 1 h. The resultant green solution was then chilled to 0°C and treated with a warm solution of methyltriphenylphosphonium iodide (21.9 g, 54.3 mmol) in DMSO (85 mL). The ensuing caramel-coloured mixture was stirred at 18°C for 0.25 h then treated with ketone **23** (9.78 g, 27.2 mmol). After stirring the resulting mixture at 65°C for 16 h, TLC analysis (1 : 4 v/v ethyl acetate/hexane elution) indicated that starting material ($R_f$ 0.2) remained. Consequently, another portion of triphenylphosphonium methylide (2 mole equiv.) was prepared (as described above) and added (via cannula) to the hot reaction mixture which was stirred at 78°C for 3 h. The cooled reaction mixture was then poured (CAUTION!) into pentane/water (200 mL of a 1 : 1 v/v mixture) and the separated aqueous layer was extracted with pentane (4 × 100 mL). The combined organic phases were washed with $NaHCO_3$ (1 × 200 mL of a saturated aqueous solution) and brine (1 × 200 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a viscous, golden oil (19.1 g). Subjection of this material to flash chromatography (silica, 1 : 4 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f$ 0.4) provided *compound* ***24*** (8.78 g, 90%) as a clear, colourless oil, $[\alpha]_D$ +84° (*c* 1.4), (Found: $M^{+\bullet}$ 358.1776. $C_{21}H_{26}O_5$ requires $M^{+\bullet}$ 358.1780). $\nu_{max}/cm^{-1}$ 2936, 1616, 1519, 1398, 1383, 1250, 1209, 1171, 1072, 1037. $\delta_H$ (300 MHz) 7.42 (2 H, d, *J* 8), 6.88 (2 H, d, *J* 8), 5.60 (1 H, s), 5.07 (1 H, br s), 5.03 (1 H, br s), 4.51 (1 H, ddd, *J* 8, 4 and 1), 4.36 (1 H, dd, *J* 8 and 4), 4.24 (1 H, d, *J* 8), 3.87 (1 H, d, *J* 8), 3.80 (3 H, s), 2.83 (1 H, ddd, *J* 18, 5 and 2), 2.60 (1 H, m), 2.04 (1 H, br d, *J* 18), 1.49 (3 H, s), 1.35 (3 H, s), 1.33 (3 H, s). $\delta_C$ (75 MHz) 160.6 (C), 144.1 (C), 128.9 (C), 128.8 (2 × CH), 113.7 (2 × CH), 111.6 (C/$CH_2$), 108.5 (C/$CH_2$), 102.2 (CH), 78.6 (CH), 76.8 (CH), 75.7 (CH), 72.1 (CH), 55.2 ($CH_3$), 43.5 (C), 34.4 (CH), 25.8 ($CH_2$), 25.5 ($CH_3$), 23.4 ($CH_3$), 17.1 ($CH_3$). *m*/*z* 358 ($M^{+\bullet}$, 22%), 300 (20), 148 (59), 135 (100), 119 (35), 107 (42), 100 (41).

*(3a*R*,4*R*,5*R*,6*S*,7*R*,7a*S*)-Hexahydro-6-hydroxy-2,2,4-trimethyl-9-methylene-4,7-ethano-1,3-benzodioxol-5-yl 4-Methoxybenzoate* ***25*** *and (3a*S*,4*S*,5*S*,6*R*,7*S*,7a*R*)-Hexahydro-6-hydroxy-2,2,7-trimethyl-8-methylene-4,7-ethano-1,3-benzodioxol-5-yl 4-Methoxybenzoate* ***26***

A magnetically stirred solution of compound **24** (8.23 g, 23.0 mmol) in dichloromethane/water (90 mL of a 17 : 1 v/v mixture) was treated with DDQ (7.83 g, 34.5 mmol, 1.5 mole equiv.). After 5 h at 18°C the reaction mixture was poured into $NaHCO_3$ (100 mL of a 5% w/v aqueous solution) and the separated aqueous layer was extracted with dichloromethane (3 × 300 mL). The combined organic phases were then washed with $NaHCO_3$ (2 × 100 mL of a 5% w/v aqueous solution) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford an orange oil (12.5 g). Subjection of this material to flash chromatography (silica, 3 : 7 ethyl acetate/hexane elution) afforded two fractions, A and B.

Concentration of fraction A ($R_f$ 0.3) afforded *compound* ***25*** (3.43 g, 40%) as a clear, colourless oil. $^1$H NMR analysis of this material indicated that it was contaminated with ca. 1% of the regioisomer **26**.

Concentration of fraction B ($R_f$ 0.5) afforded *compound* ***26*** (3.47 g, 40%) as a clear, colourless oil. $^1$H NMR analysis of this material indicated that it was contaminated with ca. 0.5% of the regioisomer **25**.

Compounds **25** and **26** interconvert on standing. Consequently, no attempt was made to characterize them in a comprehensive manner. Rather, the crude mixture of these compounds was acetylated (see below) and the derived acetates separated and characterized spectroscopically.

*(3a*R*,4*R*,5*R*,6*S*,7*R*,7a*S*)-Hexahydro-6-acetoxy-2,2,4-trimethyl-9-methylene-4,7-ethano-1,3-benzodioxol-5-yl 4-Methoxybenzoate and (3a*S*,4*S*,5*S*,6*R*,7*S*,7a*R*)-Hexahydro-6-acetoxy-2,2,7-trimethyl-8-methylene-4,7-ethano-1,3-benzodioxol-5-yl 4-Methoxybenzoate*

A magnetically stirred and 1 : 1 mixture of compounds **25** and **26** (685 mg, 1.83 mmol) in pyridine (5 mL) was treated with acetic anhydride (1.7 mL, 18.3 mmol) and the resulting solution kept at 18°C for 16 h then concentrated under reduced pressure to an orange oil. Subjection of this material to flash chromatography (silica, 1 : 4 v/v ethyl acetate/hexane elution) afforded two fractions, A and B.

Concentration of the fractions containing the less mobile component [$R_f$ 0.1(8)] gave a colourless solid. Recrystallization (ether) of this material afforded *(3a*R*,4*R*,5*R*,6*S*,7*R*,7a*S*)-hexahydro-6-acetoxy-2,2, 4-trimethyl-9-methylene-4,7-ethano-1,3-benzodioxol-5-yl-4-methoxybenzoate*, the acetate derivative of compound **25**, (280 mg, 37%) as colourless needles, mp 107–108°C, $[\alpha]_D$ +28° (*c* 2.9), (Found: $M^{+\bullet}$ 416.1835, C 66.1, H 6.9. $C_{23}H_{28}O_7$ requires $M^{+\bullet}$ 416.1835, C 66.3, H 6.8%). $\nu_{max}/cm^{-1}$ 2984, 1732, 1709, 1604, 1284, 1257, 1243, 1209, 1169, 1064. $\delta_H$ (300 MHz) 7.94 (2 H, d, *J* 9), 6.90 (2 H, d, *J* 9), 5.49 (1 H, dt, *J* 8 and 2), 5.41 (1 H, d, *J* 8), 5.10 (1 H, br s), 5.03 (1 H, br s), 4.23 (1 H, dd, *J* 8 and 4), 3.86 (1 H, d, *J* 8), 3.84 (3 H, s), 2.81 (1 H, ddd, *J* 17, 5 and 3), 2.31 (1 H, m), 2.19 (1 H, dt, *J* 17 and 2), 1.76 (3 H, s), 1.59 (3 H, s), 1.33 (3 H, s), 1.21 (3 H, s). $\delta_C$ (75 MHz) 169.7 (C), 165.4 (C), 163.3 (C), 144.1 (C), 131.6 (2 × CH), 122.3 (C), 113.6 (2 × CH), 111.2 (C/$CH_2$), 109.2 (C/$CH_2$), 79.4 (CH), 75.1 (CH), 69.4 (CH), 65.1 (CH), 55.4 ($CH_3$), 43.9 (C), 35.8 (CH), 26.1 ($CH_2$), 25.8 ($CH_3$), 23.8 ($CH_3$), 20.6 ($CH_3$), 17.1 ($CH_3$). *m*/*z* 416 ($M^{+\bullet}$, 1%), 401 ([M – $CH_3^{\bullet}$]$^+$, 6), 358 (7), 257 (11), 147 (25), 135 (100), 92 (6), 77 (11).

Concentration of fraction B ($R_f$ 0.2) gave a colourless solid. Recrystallization (ethyl acetate/hexane) of this material afforded *(3a*S*,4*S*,5*S*,6*R*,7*S*,7a*R*)-hexahydro-6-acetoxy-2,2,7- trimethyl-8-methylene-4,7-ethano-1,3-benzodioxol-5-yl 4-methoxybenzoate*, the acetate derivative of compound **26**, (350 mg, 49%) as long, colourless prisms, mp 117–118°C, $[\alpha]_D$ +64° (*c* 2.4), (Found: $M^{+\bullet}$ 416.1839, C 66.2, H 6.6. $C_{23}H_{28}O_7$ requires $M^{+\bullet}$ 416.1835, C 66.3, H 6.8%). $\nu_{max}/cm^{-1}$ 1739, 1709, 1605, 1377, 1278, 1259, 1240, 1126, 1064, 1048. $\delta_H$ (300 MHz) 7.96 (2 H, d, *J* 9), 6.90 (2 H, d, *J* 9), 5.60 (1 H, ddd, *J* 8, 3 and 2), 5.37 (1 H, d, *J* 8), 5.08 (1 H, br s), 5.00 (1 H, br s), 4.26 (1 H, dd, *J* 8 and 4), 3.86 (1 H, d, *J* 8), 3.85 (3 H, s), 2.85 (1 H, ddd, *J* 17, 5 and 3), 2.45 (1 H, m), 2.19 (1 H, br d, *J* 17), 1.84 (3 H, s), 1.60 (3 H, s), 1.34 (3 H, s), 1.16 (3 H, s). $\delta_C$ (75 MHz) 170.2 (C), 164.9 (C), 163.3 (C), 143.8 (C), 131.5 (2 × CH), 122.5 (C), 113.6 (2 × CH), 111.4 (C/$CH_2$), 109.3 (C/$CH_2$), 79.5 (CH), 75.0 (CH), 69.0 (CH), 65.3 (CH), 55.4 ($CH_3$), 43.6 (C), 35.8 (CH), 26.3 ($CH_2$), 25.8 ($CH_3$), 23.9 ($CH_3$), 20.6 ($CH_3$), 16.8 ($CH_3$). *m*/*z* 416 ($M^{+\bullet}$, 3%), 401 ([M – $CH_3^{\bullet}$]$^+$, 5), 264 (6), 135 (100).

*(3a*R*,4*R*,5*R*,7*S*,7a*S*)-Hexahydro-2,2,4- trimethyl-9-methylene-6-oxo-4,7-ethano-1,3-benzodioxol-5-yl 4-Methoxybenzoate* ***27*** *and (3a*S*,4*S*,5*S*,7*R*,7a*R*)-Hexahydro-2,2,7-trimethyl-8-methylene-6-oxo-4,7-ethano-1,3-benzodioxol-5-yl 4-Methoxybenzoate* ***28***

*Method A*

Trifluoroacetic anhydride (3.5 mL, 24.7 mmol) was added dropwise to a magnetically stirred solution of DMSO (2.3 mL, 32.4 mmol) in dichloromethane (50 mL) maintained at −60°C (dry ice/chloroform bath) under a nitrogen atmosphere. The ensuing mixture was stirred for 10 min at −60°C then treated, dropwise, with a solution of a ca. 1 : 1 mixture of alcohols **25** and **26** (3.06 g, 8.18 mmol) in dichloromethane (20 mL). After stirring for 4 h at −60°C, the reaction mixture was quenched with triethylamine (1 mL) then slowly warmed to 18°C. The resulting orange solution was poured into HCl (100 mL of a 2 M aqueous solution), and the separated aqueous layer was extracted with dichloromethane (3 × 100 mL). The combined organic phases were washed with water (1 × 100 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give an orange oil. Subjection of this material to flash chromatography (silica, 1 : 4 v/v ethyl acetate/hexane elution) afforded two fractions, A and B.

Concentration of fraction A ($R_f$ 0.4) gave a colourless solid. Recrystallization (ethyl acetate–hexane) of this material afforded *compound* ***27*** (1.40 g, 46%) as colourless plates, mp 154–156°C, $[\alpha]_D$ –38° (*c* 0.50), (Found: $M^{+\bullet}$ 372.1567, C 67.5, H 6.5. $C_{21}H_{24}O_6$ requires $M^{+\bullet}$ 372.1573, C 67.7, H 6.5%). $\nu_{max}/cm^{-1}$ 1747, 1718, 1606, 1512, 1256, 1210, 1168, 1098, 1045, 767. $\delta_H$ (300 MHz) 7.95 (2 H, d, *J* 9), 6.89 (2 H, d, *J* 9), 5.68 (1 H, s), 5.18 (2 H, m), 4.51 (1 H, dd, *J* 8 and 4), 4.09

(1 H, d, *J* 8), 3.84 (3 H, s), 3.01 (1 H, dd, *J* 7 and 4), 2.73 (1 H, m), 2.60 (1 H, m), 1.55 (3 H, s), 1.37 (3 H, s), 1.21 (3 H, s). $\delta_C$ (75 MHz) 206.8 (C), 165.3 (C), 163.5 (C), 141.2 (C), 131.9 (2 × CH), 121.7 (C), 113.6 (2 × CH), 113.1 (C/$CH_2$), 109.6 (C/$CH_2$), 78.7 (CH), 74.9 (CH), 73.0 (CH), 55.4 ($CH_3$), 47.8 (CH), 47.1 (C), 29.4 ($CH_2$), 25.6 ($CH_3$), 23.8 ($CH_3$), 15.1 ($CH_3$). *m/z* 372 ($M^{+\bullet}$, 7%), 357 ($[M - CH_3^\bullet]^+$, 2), 221 (29), 163 (37), 135 (100), 107 (11), 77 (15).

Concentration of the fraction B ($R_f$ 0.5) gave a colourless oil which solidified on standing. Recrystallization (ethyl acetate–hexane) of this material afforded *compound* ***28*** (1.40 g, 46%) as long, colourless prisms, mp 156–157°C, $[\alpha]_D$ –37° (*c* 2.4), (Found: $M^{+\bullet}$ 372.1570, C 67.5, H 6.7. $C_{21}H_{24}O_6$ requires $M^{+\bullet}$ 372.1573, C 67.7, H 6.5%). $\nu_{max}/cm^{-1}$ 1744, 1725, 1604, 1283, 1255, 1209, 1170, 1115, 1093, 1059. $\delta_H$ (300 MHz) 7.98 (2 H, d, *J* 9), 6.90 (2 H, d, *J* 9), 5.75 (1 H, t, *J* 2), 5.13 (2 H, m), 4.44 (1 H, dd, *J* 8 and 4), 4.09 (1 H, d, *J* 8), 3.85 (3 H, s), 2.82 (1 H, ddd, *J* 18, 5 and 2), 2.72 (1 H, m), 2.38 (1 H, dt, *J* 18 and 2), 1.53 (3 H, s), 1.35 (3 H, s), 1.34 (3 H, s). $\delta_C$ (75 MHz) 205.2 (C), 165.0 (C), 163.5 (C), 141.3 (C), 131.9 (2 × CH), 121.9 (C), 113.6 (2 × CH), 113.1 (C/$CH_2$), 109.6 (C/$CH_2$), 79.9 (CH), 74.9 (CH), 70.5 (CH), 56.5 (C), 55.4 ($CH_3$), 37.0 (CH), 26.5 ($CH_2$), 25.6 ($CH_3$), 23.9 ($CH_3$), 13.1 ($CH_3$). *m/z* 372 ($M^{+\bullet}$, 0.6%), 357 ($[M - CH_3^\bullet]^+$, 3), 314 ($[M - (CH_3)_2CO]^{+\bullet}$, 3), 162 (46), 135 (100).

*Method B*

Solid tetrapropylammonium perruthenate (7.5 mg, 0.0213 mmol) was added in one portion to a magnetically stirred mixture of compounds **27** and **28** (402 mg, 1.07 mmol), *N*-methylmorpholine-*N*-oxide (879 mg, 7.50 mmol, 7 mole equiv.) and powdered 4 Å molecular sieves (537 mg) in acetonitrile (5 mL) maintained under a nitrogen atmosphere. The resulting mixture was stirred at 18°C for 16 h then filtered through a 7 cm deep pad of TLC-grade silica gel. The retained solids were washed with dichloromethane (80 mL) and the combined filtrates concentrated under reduced pressure to give a colourless solid. Subjection of this material to flash chromatography (silica, 1 : 4 ethyl acetate/petrol elution) provided two fractions, A and B.

Concentration of fraction A ($R_f$ 0.4) afforded *compound* ***27*** (152 mg, 38%) as a colourless solid which was identical, in all respects, with the material obtained as described above.

Concentration of fraction B ($R_f$ 0.5) afforded *compound* ***28*** (152 mg, 38%) as a colourless solid which was identical, in all respects, with the material obtained as described above.

*(3a*R*,4*R*,6*S*,7*R*,7a*S*)-Tetrahydro-6-hydroxy-2,2,4-trimethyl-9-methylene-4,7-ethano-1,3-benzodioxol-5(4*H*)-one* ***29****, (3a*R*,4*R*,5*R*,6*S*,7*R*,7a*S*)-5-Ethenylhexahydro-2,2,4-trimethyl-9-methylene-4,7-ethano-1,3-benzodioxole-5,6-diol* ***30****, and (3a*R*,4*R*,5*S*,6*S*,7*S*,7a*S*)-5-Ethenylhexahydro-2,2,4-trimethyl-9-methylene-4,7-ethano-1,3-benzodioxole-5,6-diol* ***31***

A magnetically stirred solution of ketone **28** (703 mg, 1.89 mmol) in THF (7 mL) maintained at 0°C under a nitrogen atmosphere was treated, in one portion, with vinylmagnesium bromide (7.9 mL of a 1.2 M solution in THF, 9.48 mmol, 5 mole equiv.). The resulting mixture was stirred at 0°C for 0.5 h then warmed to 18°C. After 16 h the reaction mixture was re-cooled to 0°C and treated with $NH_4Cl$ (30 mL of a saturated aqueous solution) and water (50 mL) then extracted with ethyl acetate (3 × 100 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to an orange oil (895 mg). This material was dissolved in methanol (15 mL) and the resulting solution treated with potassium hydroxide (1.06 g), allowed to stand at 18°C for 16 h then poured into water (50 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to an orange oil (1.25 g). Subjection of this material to flash chromatography (silica, 3 : 17 v/v ethyl acetate/dichloromethane elution) afforded three fractions, A–C.

Concentration of fraction A ($R_f$ 0.4) afforded *acyloin* ***29*** (56 mg, 11%) as a colourless, crystalline solid, mp 52–53°C, $[\alpha]_D$ –30° (*c* 2.4), (Found: $M^{+\bullet}$ 238.1203, C 65.7, H 7.9. $C_{13}H_{18}O_4$ requires $M^{+\bullet}$ 238.1205, C 65.5, H 7.6%). $\nu_{max}/cm^{-1}$ 3461, 1738, 1379, 1267, 1210, 1164, 1142, 1063, 1032, 890. $\delta_H$ (300 MHz) 5.02 (2 H, dt, *J* 7 and 2), 4.35 (1 H, dd *J* 8 and 4), 4.22 (1 H, dd, *J* 4 and 2), 4.00 (1 H, dd, *J* 8 and 1), 3.01 (1 H, br s), 2.74 (1 H, ddd, *J* 18, 5 and 3), 2.56 (1 H, m), 2.22 (1 H, ddd, *J* 18 and 3 and 2), 1.38 (3 H, s), 1.29 (3 H, s), 1.27 (3 H, s). $\delta_C$ (75 MHz) 211.7 (C), 142.0 (C), 112.5 (C/$CH_2$), 109.2 (C/$CH_2$), 79.2 (CH), 74.9 (CH), 69.8 (CH), 55.8 (C), 37.8 (CH), 25.8 ($CH_2$), 25.4 ($CH_3$), 23.7 ($CH_3$), 12.8 ($CH_3$). *m/z* 238 ($M^{+\bullet}$, 56%), 223 ($[M - CH_3^\bullet]^+$, 85), 181 (50), 180 ($[M - (CH_3)_2CO]^{+\bullet}$, 58), 163 (80), 152 (83), 151 (98), 134 (80), 123 (100), 107 (43).

Concentration of fraction B ($R_f$ 0.3) afforded *diene* ***30*** (170 mg, 34%) as a colourless, crystalline solid, mp 138–139°C, $[\alpha]_D$ –49° (*c* 2.4), (Found: $M^{+\bullet}$ 266.1517, C 67.9, H 8.2. $C_{15}H_{22}O_4$ requires $M^{+\bullet}$ 266.1518, C 67.7, H 8.3%). $\nu_{max}/cm^{-1}$ 3516, 3402, 2945, 1645, 1385, 1280, 1210, 1073, 1051, 1033, 889. $\delta_H$ (300 MHz) 6.27 (1 H, dd, *J* 17 and 11), 5.33 (1 H, dd, *J* 17 and 2), 5.12 (1 H, dd, *J* 11 and 2), 5.04 (2 H, m), 4.15 (1 H, dd, *J* 8 and 3), 4.02 (1 H, br m), 3.80 (1 H, d, *J* 8), 2.88 (1 H, br d, *J* 6), 2.73 (1 H, ddd, *J* 17. 5 and 3), 2.55 (1 H, s), 2.16–2.07 (2 H, complex m), 1.53 (3 H, s), 1.30 (3 H, s), 1.14 (3 H, s). $\delta_C$ (75 MHz) 146.5 (C), 142.8 (CH), 113.1 (C/$CH_2$), 111.4 (C/$CH_2$), 108.9 (C/$CH_2$), 80.0 (CH), 75.7 (CH), 74.3 (C), 67.4 (CH), 47.5 (C), 38.2 (CH), 25.8 ($CH_2$), 25.5 ($CH_3$), 23.4 ($CH_3$), 15.8 ($CH_3$). *m/z* 266 ($M^{+\bullet}$, 6%), 251 ($[M - CH_3^\bullet]^+$, 33), 208 ($[M - (CH_3)_2CO]^{+\bullet}$, 44), 190 (45), 161 (33), 135 (81), 123 (99), 122 (90), 107 (100), 91 (52), 79 (41).

Concentration of fraction C ($R_f$ 0.2) gave a clear, colourless oil which solidified upon refrigeration. Recrystallization (pentane) of this material afforded *diene* ***31*** (56 mg, 11%) as colourless cubes, mp 72–73°C, $[\alpha]_D$ −25° (*c* 0.95), (Found: $[M - CH_3^\bullet]^+$ 251.1287, C 67.5, H 8.6. $C_{15}H_{22}O_4$ requires $[M - CH_3^\bullet]^+$ 251.1283, C 67.7, H 8.3%). $\nu_{max}/cm^{-1}$ 3490, 2987, 1643, 1423, 1377, 1331, 1260, 1210, 1167, 1064, 1021. $\delta_H$ (300 MHz) 5.62 (1 H, dd, *J* 17 and 10), 5.49 (1 H, dd, *J* 17 and 3), 5.27 (1 H, dd, *J* 9 and 3), 4.99 (2 H, br d, *J* 9), 4.48 (1 H, br s), 4.24 (1 H, t, *J* 2), 4.21 (1 H, d, *J* 3), 3.86 (1 H, d, *J* 8), 2.70 (1 H, ddd, *J* 17, 8 and 2), 2.24 (1 H, m), 2.09 (1 H, ddd, *J* 17, 3 and 2), 1.80 (1 H, br s), 1.57 (3 H, s), 1.32 (3 H, s), 1.17 (3 H, s). $\delta_C$ (75 MHz) 145.8 (C), 136.7 (CH), 116.5 ($CH_2$), 111.6 (C/$CH_2$), 109.1 (C/$CH_2$), 80.9 (CH), 79.2 (C), 75.9 (CH), 75.6 (CH), 46.5 (C), 37.3 (CH), 25.6 ($CH_3$), 25.5 ($CH_2$), 23.1 ($CH_3$), 14.4 ($CH_3$). *m/z* 251 ($[M - CH_3^\bullet]^+$, 12%), 208 ($[M - (CH_3)_2CO]^{+\bullet}$, 30), 190 (30), 161 (30), 135 (78), 123 (90), 122 (86), 107 (100), 91 (71).

*(3a*R*,4*R*,6*S*,7*S*,7a*R*)-Tetrahydro-6-hydroxy-2,2,4-trimethyl-9-methylene-4,7-ethano-1,3-benzodioxol-5(4*H*)-one* ***29***

A magnetically stirred solution of compound **28** (320 mg, 0.860 mmol) in methanol (50 mL) maintained at 18°C under a nitrogen atmosphere was treated with powdered potassium hydroxide (150 mg, 2.68 mmol). The reaction mixture was stirred at 18°C for 1 h then poured into water (50 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a pale-yellow oil (336 mg). Subjection of this material to flash chromatography (silica, 1 : 4 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f$ 0.2) afforded the *title acyloin* ***29*** (192 mg, 95%) as a colourless solid which was identical, in all respects, with the material obtained as described above.

*(3a*R*,4*R*,5*R*,6*S*,7*R*,7a*S*)-5-Ethenylhexahydro-2,2,4-trimethyl-9-methylene-4,7-ethano-1,3-benzodioxole-5,6-diol* ***30*** *and (3a*R*,4*R*,5*S*,6*S*,7*S*,7a*S*)-5-Ethenylhexahydro-2,2,4-trimethyl-9-methylene-4,7-ethano-1,3-benzodioxole-5,6-diol* ***31***

A magnetically stirred solution of acyloin **29** (82 mg, 0.344 mmol) in THF (5 mL) maintained at 0°C under a nitrogen atmosphere was treated, in one portion, with vinylmagnesium bromide (2.9 mL of a 1.2 M solution in THF, 3.48 mmol, 10 mole equiv.) and the resulting mixture stirred at 0°C for 0.5 h then warmed to 18°C. After 5 days the reaction mixture was re-cooled to 0°C and $NH_4Cl$ (5 mL of a saturated aqueous solution) then water (20 mL) were carefully added. The resulting mixture was extracted with ethyl acetate (3 × 20 mL) and the combined organic

phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give an orange oil (90 mg). Subjection of this material to flash chromatography (silica, 3 : 17 v/v ethyl acetate/dichloromethane elution) afforded two fractions, A and B.

Concentration of fraction A ($R_f$ 0.3) afforded *diol* ***30*** (5 mg, 5%) which was identical, in all respects, with the material obtained as described above.

Concentration of fraction B ($R_f$ 0.2) afforded *compound* ***31*** (46 mg, 50%) which was identical, in all respects, with the material obtained as described above.

*(3a*R*,4*R*,5*R*,6*S*,7*S*,7a*S*)-5-Ethenylhexahydro-2,2,4-trimethyl-9-methylene-6-(phenylmethoxy)-4,7-ethano-1,3-benzodioxol-5-ol* ***32***

A magnetically stirred and ice-cooled solution of compound **31** (100 mg, 0.376 mmol) in benzyl bromide (0.4 mL of a 1.0 M solution in DMF, 0.400 mmol) maintained under a nitrogen atmosphere was treated with sodium hydride (29 mg, 1.21 mmol, 3.2 mole equiv.). After 5 h at 0°C the reaction mixture was quenched with water (20 mL) (CAUTION) then extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a pale-yellow oil (57 mg). Subjection of this material to flash chromatography (silica, 1 : 19 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f$ 0.1) provided *compound* ***32*** (72 mg, 53%) as a clear, colourless oil, $[\alpha]_D$ –35° (*c* 1.9), (Found: $[M - CH_3^{\bullet}]^+$ 341.1748. $C_{22}H_{28}O_4$ requires $[M - CH_3^{\bullet}]^+$ 341.1753). $\nu_{max}/cm^{-1}$ 3494, 3019, 2989, 1643, 1456, 1375, 1213, 1069, 1026, 756. $\delta_H$ (300 MHz) 7.35–7.20 (5 H, complex m), 6.22 (1 H, dd, *J* 17 and 11), 5.41 (1 H, dd, *J* 17 and 2), 5.09 (1 H, dd, *J* 11 and 2), 4.95 (2 H, m), 4.75 (1 H, d, *J* 16), 4.48 (1 H, d, *J* 16), 4.45 (1 H, s), 4.14 (1 H, dd, *J* 8 and 3), 3.84 (1 H, br s), 3.76 (1 H, d, *J* 8), 2.81 (1 H, ddd, *J* 17, 6 and 1), 2.25 (1 H, br m), 2.06 (1 H, br d, *J* 17), 1.46 (3 H, s), 1.29 (3 H, s), 1.13 (3 H, s). $\delta_C$ (75 MHz) 145.9, 138.7, 137.4, 128.1, 127.7, 127.3, 114.5, 111.3, 109.0, 82.6, 80.9, 79.0, 75.8, 72.2, 46.9, 36.9, 26.1, 25.6, 23.3, 13.9. *m*/*z* 341 ($[M - CH_3^{\bullet}]^+$, 5%), 298 ($[M - (CH_3)_2CO]^{+\bullet}$, 4), 192 (22), 189 (22), 135 (38), 107 (40), 105 (40), 91 ($C_7H_7^+$, 100).

*(3a*S*,4*S*,5*S*,11a*R*)-4,5,7,8,9,11a-Hexahydro-2,2,11-trimethyl-5-(phenylmethoxy)-4,10-methanocyclodeca-1,3-dioxol-6(3a*H*)one* ***34***

A magnetically stirred solution of compound **32** (17 mg, 0.0478 mmol) and [18]crown-6 (39 mg, 0.148 mmol) in THF (1 mL) maintained under nitrogen atmosphere at 0°C was treated, in one portion, with potassium hydride (10 mg, 0.250 mmol). The resulting mixture was stirred at 0°C for 1 h then warmed to 18°C over a period of 0.5 h. After this time $NH_4Cl$ (10 mL of a saturated aqueous solution) was slowly added to the reaction mixture which was then diluted with water (5 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a pale-yellow oil (26 mg). Subjection of this material to flash chromatography (silica, 1 : 19 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f$ 0.2) afforded *compound* ***34*** (8 mg, 47%) as a clear, colourless oil, $[\alpha]_D$ +38° (*c* 0.7), (Found: $M^{+\bullet}$ 356.1988. $C_{22}H_{28}O_4$ requires $M^{+\bullet}$ 356.1987). $\nu_{max}/cm^{-1}$ 2928, 1705, 1455, 1381, 1259, 1210, 1073, 1028, 789, 699. $\delta_H$ (300 MHz) 7.35–7.26 (5 H, m), 4.52 (1 H, t, *J* 8), 4.40 (1 H, d, *J* 15), 4.37 (1 H, d, *J* 15), 4.35 (1 H, m), 4.16 (1 H, d, *J* 2), 2.95 (1 H, m), 2.72 (1 H, m), 2.54–2.43 (2 H, complex m), 2.18–2.11 (2 H, complex m), 2.10–1.85 (3 H, complex m), 1.67 (3 H, br s), 1.59 (3 H, s), 1.38 (3 H, s). $\delta_C$ (75 MHz) 213.5 (C), 137.8 (C), 131.9 (C), 131.8 (C), 128.4 (2 × CH), 127.8 (2 × CH), 127.7(6) (CH), 108.9 (C), 83.7 (CH), 75.1 (CH), 74.5 (CH), 72.3 ($CH_2$), 42.6 (CH), 37.4 ($CH_2$), 31.9 ($CH_2$), 29.5 ($CH_2$), 26.7 ($CH_2$), 25.8 ($CH_3$), 23.9 ($CH_3$), 13.6 ($CH_3$). *m*/*z* 356 ($M^{+\bullet}$, 2%), 341 ($[M - CH_3^{\bullet}]^+$, 6), 161 (16), 149 (16), 105 (18), 91 (100), 65 (15).

### *Crystallographic Studies*

Crystal data for compound **8**: $C_{13}H_{16}ClNO_2$, *M* 253.73, *T* 213(1) K, orthorhombic, space group $P2_12_12_1$, *a* 6.439(1), *b* 11.009(2), *c* 17.847(2) Å, *V* 1265.0(3) $Å^3$, $D_c$ (*Z* 4) 1.332 g $cm^{-3}$, *F*(000) 536, $\mu(Cu_{K\alpha})$ 25.94 $cm^{-1}$, semi-empirical absorption correction; 1141 unique data ($2\theta_{max}$ 120.0°), 1079 with $I > 3\sigma(I)$; *R* 0.023, *wR* 0.023, GoF 2.76.

Crystal data for compound **18**: $C_{12}H_{18}O_2$, *M* 194.27, *T* 296(1) K, orthorhombic, space group $P2_12_12_1$, *a* 6.689(3), *b* 12.000(2), *c* 13.904(2) Å, *V* 1116.1(5) $Å^3$, $D_c$ (*Z* 4) 1.156 g $cm^{-3}$, *F*(000) 424, $\mu(Cu_{K\alpha})$ 5.76 $cm^{-1}$, semi-empirical absorption correction; 1013 unique data ($2\theta_{max}$ 120.1°), 395 with $I > 3\sigma(I)$; *R* 0.039, *wR* 0.046, GoF 1.47.

Crystal data for compound **30**: $C_{15}H_{22}O_4$, *M* 266.34, *T* 296(1) K, tetragonal, space group $P4_32_12$, *a* 11.058(2), *c* 23.818(3) Å, *V* 2912(1) $Å^3$, $D_c$ (*Z* 8) 1.215 g $cm^{-3}$, *F*(000) 1152, $\mu(Mo_{K\alpha})$ 0.87 $cm^{-1}$, semi-empirical absorption correction; 2032 unique data ($2\theta_{max}$ 55.0°), 1268 with $I > 3\sigma(I)$; *R* 0.043, *wR* 0.040, GoF 2.65.

Intensity data were collected on a Rigaku AFC6R diffractometer using the $\omega$–$2\theta$ scan technique to a maximum $2\theta$ value of 120° (for **30**: 55°).

Three representative reflections were measured after every 150 reflections which revealed that no decay correction was required for **8** and **30**, however a correction was required for the crystal of **18** which decayed rapidly. An empirical absorption correction based on azimuthal scans was applied and the data were corrected for Lorentz and polarization effects.

The structures were solved by direct methods[18] and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included at geometrically determined positions which were periodically recalculated but were not refined. The rapid decay of **18** compromised the number of observed reflections. Although the identity of the molecule has been unambiguously determined, the data to parameter ratio is low which results in the bond distances and angles having poor precision. All calculations were performed using the teXsan[19] crystallographic software package.

Atomic coordinates, bond lengths, and angles, together with displacement parameters have been deposited with the Cambridge Crystallographic Data Centre (deposition nos: **8** 210946, **18** 210947, **30** 101611).

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