The Synthesis of Novel Benzomorphan Analogues: A New Intramolecular Acid-catalysed Aldol Route to Benzannelated Bicyclo[3.3.1]nonane Derivatives. X-Ray Molecular Structure of 8-Hydroxy-1-methoxytricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-trien-10-one

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Novel benzomorphan analogues are described in which the piperidine ring is replaced by an aminocyclohexane ring. The key synthetic intermediate, benzannelated bicyclo[3.3.1]nonane derivative (**12**), is prepared by an efficient three-step synthetic route based on the addition of 2-lithiobenzaldehyde ethylene acetal to cyclohexane-1,4-dione monoethylene acetal followed by methylation, acid-catalysed deprotection, and *in situ* intramolecular aldol condensation. The stereospecificity of the aldol cyclisation to give intermediate (**12**) is noteworthy. Preliminary studies of the synthetic potential of the methodology for the preparation of derivatives with varying oxidation and substitution patterns are also described.

An enormous number of structural analogues of morphine (**1**) have been prepared in the search for clinically useful analgesics devoid of undesirable side-effects.[1] As part of a programme to design and synthesize selective opioid κ-agonists,[2,3] we became interested in the idea of replacing the piperidine ring of morphine-like analgesics with an aminocyclohexane ring; *e.g.*, preparing amino-substituted carbocycles (**3**) to model benzomorphans (**2**). To our knowledge,[1] such an approach has not been explored previously although compounds (**3**) are consistent with the pharmacophore model for opioid activity[4] and it has been demonstrated in non-morphinoid systems that exocyclic amino groups are compatible with analgesic activity.[5]

Retrosynthetic analysis (Scheme 1) indicated that benzannelated bicyclo[3.3.1]nonanone (**4**) would be an ideal precursor to the target system (**3**) *via* a reductive amination process. A literature review for synthetic approaches to systems of this type revealed that (i) the parent hydrocarbon, tricyclo[7.3.1.$0^{2,7}$]-trideca-2,4,6-triene, is known, but the synthetic route is not adaptable to the preparation of functionalised derivatives such as (**3**),[6] and (ii) most synthetic approaches to bicyclo[3.3.1]-nonanones utilise annelation between C-2 and C-6 of cyclohexanones and therefore result in the formation of 9-keto derivatives, *i.e.* the carbonyl group is on the one-carbon bridge.[7] In addition, the published approaches to bicyclo[3.3.1]nonanes have been described as involving 'monumental labor'[8] and so provide little inspiration for the task in hand. A novel approach to compounds of type (**4**) was therefore required.[9]

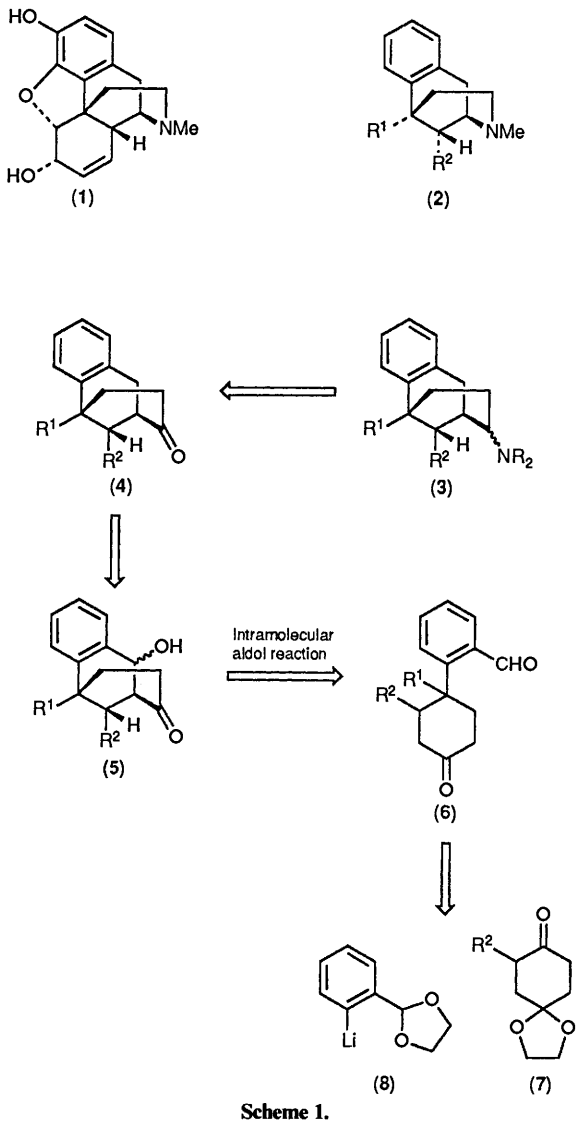
Retrosynthetic analysis indicated that a short, novel route to compounds (**4**) was possible using an intramolecular aldol approach proceeding *via* hydroxy ketones (**5**) as shown in Scheme 1. Given that the key cyclisation precursors (**6**; R^1 = OH) appeared to be readily accessible from monoprotected diones (**7**) and a 2-metallated benzaldehyde derivative (**8**), this approach was explored, initially using the commercially available cyclohexane-1,4-dione monoethylene acetal (**9**) (Scheme 2).†

Treatment of cyclohexane-1,4-dione monoethylene acetal (**9**) with 2-lithiobenzaldehyde ethylene acetal (**8**)[10] gave tertiary alcohol (**10**) (76%), which was methylated to give the ether (**11**) (90%). Attempted deprotection of bis-dioxolane (**11**) by means of toluene-4-sulphonic acid (PTSA) in hot acetone resulted in efficient cyclisation to give the required benzannelated bicyclo-[3.3.1]nonanone (**12**) in 75% recrystallised yield. When the deprotection–cyclisation sequence was effected using pyridinium toluene-4-sulphonate (PPTS)[11] in aq. acetone a small amount of the intermediate dicarbonyl compound (**13**) (7%) was obtained along with the aldol product (**12**) (64%). Confirmation of the gross structure of hydroxy ketone (**12**) was obtained by oxidation to the expected dione (**14**).

Compound (**12**) was shown to be a single diastereoisomer (Figure 1) by 400 MHz ^{1}H NMR spectroscopy. The couplings (see Experimental section) were assigned with the aid of a COSY-45 spectrum.[12] The stereochemical assignments were made by reference to the coupling data, particularly the two ^4J W-couplings between 12e-H and 13e-H, and 9-H and 11e-H, and significant (>2%) nuclear Overhauser effect (NOE) enhancements[11] between 9-H and 8-H, 13e-H, and 13a-H; 8-H and 9-H and 13e-H; OMe and 13e-H (Figure 1). After several hours in solution in the presence of [$^2H_1$]methanol compound (**12**) isomerised to an extent of *ca.* 20%. The changes in chemical shift and the loss of the NOE from 8-H to 13e-H are consistent with epimerisation at C-8. The structure of compound (**12**) was confirmed by X-ray crystallographic analysis (Figure 2).

The stereoselectivity of the aldol cyclisation is noteworthy and has precedent in the recent stereoselective preparation of a hydroxylated bicyclo[4.3.1]decanone *via* an intramolecular aldol process.[13] Intramolecular hydrogen bonding could be responsible for the stereoselective formation of compound (**12**): the intramolecular carbonyl–hydroxy O–O bond distance in

† All synthetic compounds are racemic.



Scheme 1.

compound (**12**) is 3.24 Å, and hydrogen bonding is therefore possible, in contrast to the situation with the C-8 epimer.

It was also demonstrated that the aldol cyclisation methodology could be used to prepare alkyl-substituted benzannelated bicyclo[3.3.1]nonanones (**4**) ($R^2 \neq H$) as shown in Scheme 3.

Bis-dioxolane (**20**) was readily prepared *via* alcohol (**19**) obtained from 3-methylcyclohexane-1,4-dione 1-monoethylene acetal (**18**)[14] and 2-lithiobenzaldehyde ethylene acetal (**8**). The stereochemistry of compound (**20**) was determined by low-temperature 400 MHz ^1H NMR studies including NOE difference spectroscopy. At room temperature many resonances were broad, but two rotamers were completely identifiable at −50 °C in $CDCl_3$, and were largely assignable with the aid of decoupling at the ring methyl doublets (δ 0.80, 72% and δ 0.59, 28%). The stereochemistry was defined by the qualitative observation of axial–axial couplings, which were the same in each rotamer, and by NOE difference spectroscopy at −50 °C. In particular, enhancements were observed from the ring methyl and the axial *O*-methyl to the unique dioxolane proton [δ 6.69, major rotamer (**20a**) only] and from the same methyl groups in the minor rotamer (**20b**) to an aromatic doublet at δ 7.42. Thus, in the minor rotamer (**20b**) the aromatic dioxolane substituent is approximately *trans* to methoxy group. In addition the methine proton on the cyclohexane ring is axial in both rotamers (*J* 13 Hz).

Acid-catalysed cyclisation as before gave a *ca.* 1:1 mixture of the isomeric tricyclic hydroxy ketones (**21**) and (**22**) in 68% yield. The structural assignments shown are tentative and were made by analogy with structure (**12**).

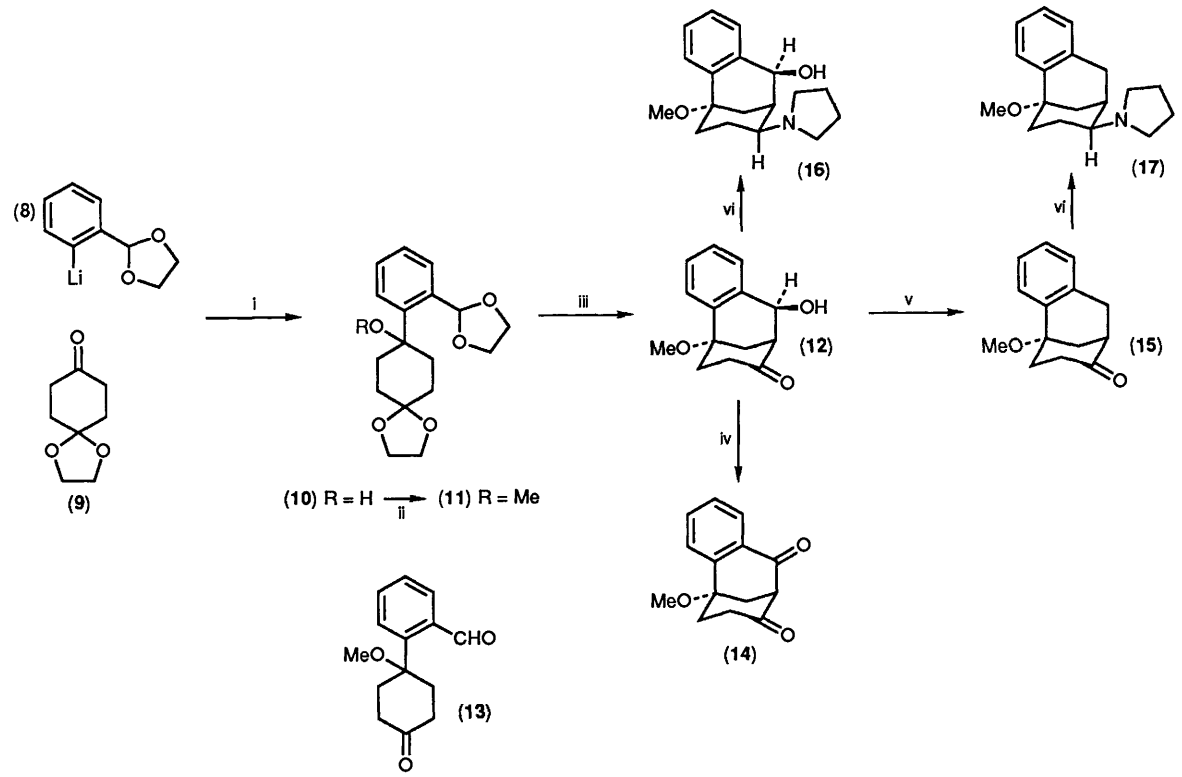
The requisite dehydroxylated analogue (**15**) was obtained in good yield by reduction of compound (**12**) with triethylsilane,[15] followed by reoxidation of the reduced 10-keto group as shown in Scheme 2. Ketones (**12**) and (**15**) were converted into amines (**16**) and (**17**) with pyrrolidine and $NaBH_3CN$ under standard[16] reductive amination conditions. Pyrrolidine was chosen as the amine in view of the success of PD117302 (**23**) as a selective κ agonist.[3] Amines (**16**) and (**17**) were rather unstable and so were characterised and stored as their picrate salts. The ^1H NMR spectra of these compounds showed extensive overlapping of resonances, even at 400 MHz, but an almost complete assignment was nevertheless possible for amine (**16**) on using a COSY-45 2D spectrum.[12] The shifts, couplings, and NOEs of the fused-ring resonances were similar to those of compound (**12**) when resolvable, after due allowance had been made for the replacement of the carbonyl group. The stereochemistry was confirmed by NOE enhancements from 13e-H to 9-H, 8-H, and OMe; from 13a-H to 10-H; and from 10-H to 12a-H. These latter showed the nitrogen to be *cis* to the neighbouring ring junction, and the 8-H enhancement showed the same to be true for the OH group. Also the high shift of the OH proton [δ 6.93; *cf.* δ 3.21 for (**12**)] implied internal H-bonding to NH^+. The stereoselective formation of amine (**16**) was expected on steric grounds. The assignment of stereochemistry to amine (**17**) was not possible by NMR spectroscopy and therefore must be considered tentative.

Amines (**16**) and (**17**) (as their tosyl salts) were tested for binding to μ and κ opioid receptors[17] but proved to be essentially inactive in both binding assays at 10^{-5}M.

Experimental

M.p.s were recorded on a Kofler hot-stage melting point apparatus, and are uncorrected. IR spectra (ν_{max}) were recorded using a Perkin-Elmer 1720X FT-IR spectrometer. ^1H NMR spectra were recorded using a JEOL JNM-PMX60, JEOL FX400, or Bruker WH400 instrument, and ^{13}C NMR spectra were recorded using a JEOL FX400 or Bruker WH400 instrument. The spectra were recorded at 60 MHz (^1H) and 100.6 MHz (^{13}C) unless stated otherwise. Samples for NMR spectrometry were prepared as solutions in deuteriochloroform, containing tetramethylsilane as internal standard. Mass spectra (*m/z*) were recorded on Kratos MS25, MS30, and VG Zab-E instruments.

All reactions involving organometallic reagents were carried out under nitrogen, in flame-dried apparatus. Butyl-lithium (in hexane) was purchased from the Aldrich Chemical Company and was titrated[18] before use. All other starting materials were obtained commercially and used as received. Ether refers to diethyl ether, and light petroleum refers to that fraction of boiling range 40–60 °C, which was redistilled before use. Tetrahydrofuran (THF) was dried over sodium and distilled immediately before use, and dichloromethane was distilled from calcium hydride. A standard work-up procedure consisted of two extractions with the specified solvent, washing of the combined extracts twice with water, drying ($MgSO_4$), and removal of the solvent on a rotary evaporator under reduced pressure. Chromatography refers to column chromatography carried out at medium pressure on a column of silica gel (Fisons Matrex flash 60 grade).



Scheme 2. *Reagents and conditions:* i, THF, −70 °C (76%); ii, NaH, MeI, THF (85–90%); iii, PTSA·H_2O, acetone, heat (75%); iv, PDC, CH_2Cl_2, 4 Å mol. sieves (75%); v, Et_3SiH, TFA then KOH, MeOH (75%); then PDC, CH_2Cl_2, 4 Å mol. sieves (77%); vi, C_4H_9N, $NaBH_3CN$, MeOH [(**16**) 85–95%; (**17**) 80–96%].

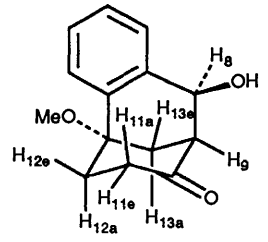


Figure 1. Structure of aldol (**12**) with numbering system used in the Experimental section.

X-Ray Crystallographic Analysis of Compound (**12**).—A cube-like crystal of approximate dimensions 0.3 × 0.3 × 0.35 mm was cut from a large block and used for data collection.

Crystal data: $C_{14}H_{16}O_3$, M = 232.3, monoclinic, a = 26.529(9), b = 8.661(4), c = 10.314(4) Å, β = 101.71(2), V = 2 320.6 Å^3, space group $C2/c$, Z = 8, D_c = 1.61 g cm^{-3}, μ(Mo-K_α) = 0.27 cm^{-1}, F(000) = 992. Data were measured at room temperature on a Hilger and Watts Y290 four-circle diffractometer in the range $2 < \theta < 24°$. 3 811 Reflections were collected, of which 1 451 were unique with $I \geqslant 3\sigma(I)$. Data were corrected for Lorentz and polarisation effects but not for absorption. The structure was solved by conventional direct methods and refined using the SHELX[19,20] suite of programs. In the final least-squares cycles the phenyl carbons were allowed to vibrate isotropically while all other atoms were treated anisotropically. Hydrogen atoms were included at calculated positions.

Analysis of the overall structure revealed that hydrogen bonds exist between neighbouring pairs of molecules at the hydroxy groups [O(3)]. The intermolecular O(3)–O(3) distance is 2.79 Å. Final residuals after 14 cycles of full-matrix least-squares refinement were $R = R_w = 0.0704$ for unit weights. The total number of parameters varied was 124. Maximum final shift/esd was 0.01, the average being 0.002. The maximum and minimum residual densities were 0.17 and −0.12 eÅ^{-3},

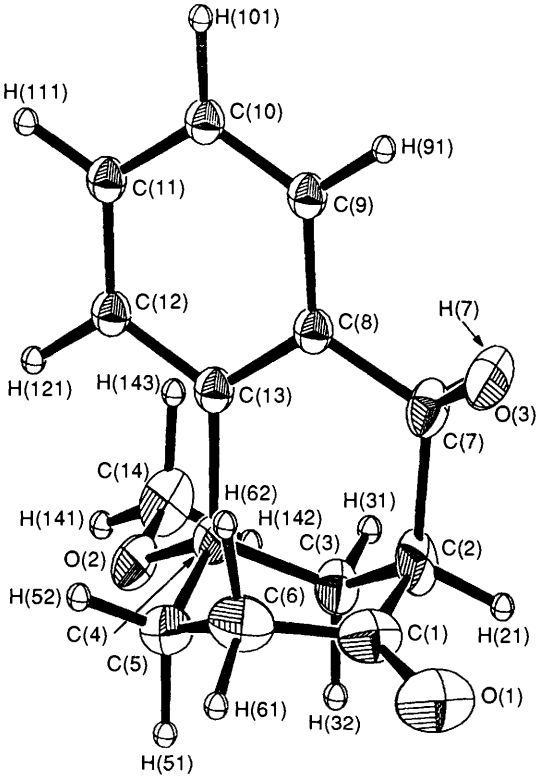
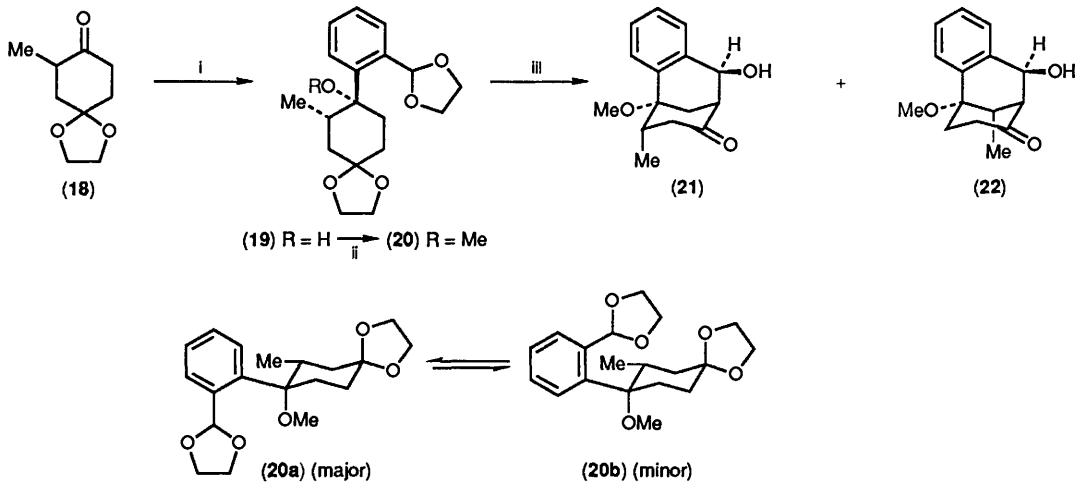
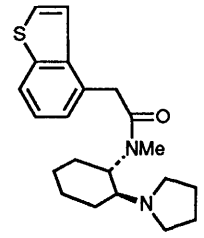


Figure 2. ORTEP view of aldol (**12**) with numbering system used in the Tables.



Scheme 3. *Reagents and conditions:* i, (**8**), THF, −70 °C (81%); ii, NaH, MeI, THF (86%); iii, PTSA·H_2O, acetone, neat [68%; (**21**):(**22**) *ca.* 1:1].



(**23**) (PD117302)

Table 1. Fractional atomic co-ordinates with standard deviations in parentheses, for compound (**12**).

Atom	*x*	*y*	*z*
O(1)	−0.017 78(1)	0.165 38(4)	0.502 90(5)
O(2)	0.187 75(1)	0.099 99(3)	0.589 21(2)
O(3)	0.024 94(1)	0.487 86(3)	0.643 26(3)
C(1)	0.027 98(2)	0.192 95(5)	0.519 87(6)
C(2)	0.059 53(1)	0.224 54(5)	0.657 64(4)
C(3)	0.110 55(1)	0.136 62(4)	0.680 51(4)
C(4)	0.139 66(1)	0.181 29(4)	0.573 85(3)
C(5)	0.109 49(1)	0.126 91(5)	0.441 31(4)
C(6)	0.056 07(2)	0.197 59(5)	0.407 76(5)
C(7)	0.070 91(1)	0.395 53(5)	0.680 62(4)
C(8)	0.113 1(1)	0.456 0(4)	0.615 0(3)
C(9)	0.119 4(1)	0.615 1(5)	0.602 7(4)
C(10)	0.158 7(1)	0.673 3(5)	0.547 7(4)
C(11)	0.192 1(2)	0.574 8(5)	0.503 6(4)
C(12)	0.186 2(1)	0.416 7(4)	0.514 6(4)
C(13)	0.147 2(1)	0.355 4(4)	0.571 2(3)
C(14)	0.221 39(1)	0.115 80(5)	0.713 47(4)

respectively. Final fractional atomic co-ordinates, bond distances, and bond angles are given in Tables 1–3. The asymmetric unit is shown in Figure 2 along with the labelling scheme used.*

* *Supplementary data* (see section 5.6.3 of Instructions for Authors, in the January issue). Full details of compound (**12**) have been deposited at the Cambridge Crystallographic Data Centre.

Table 2. Bond lengths (Å).

O(1)–C(1)	1.214(5)	O(2)–C(4)	1.438(4)
O(2)–C(14)	1.412(4)	O(3)–C(7)	1.444(4)
C(1)–C(2)	1.520(6)	C(1)–C(6)	1.498(7)
C(2)–C(3)	1.529(5)	C(2)–C(7)	1.520(6)
C(3)–C(4)	1.517(5)	C(4)–C(5)	1.512(5)
C(4)–C(13)	1.522(5)	C(5)–C(6)	1.518(5)
C(7)–C(8)	1.514(5)	C(8)–C(9)	1.397(5)
C(8)–C(13)	1.395(5)	C(9)–C(10)	1.380(5)
C(10)–C(11)	1.371(6)	C(11)–C(12)	1.385(5)
C(12)–C(13)	1.393(5)		

Table 3. Bond angles (°).

C(14)–O(2)–C(4)	115.8(3)	C(2)–C(1)–O(1)	121.0(5)
C(6)–C(1)–O(1)	122.2(5)	C(6)–C(1)–C(2)	116.8(3)
C(3)–C(2)–C(1)	110.9(4)	C(7)–C(2)–C(1)	112.0(3)
C(7)–C(2)–C(3)	108.6(3)	C(4)–C(3)–C(2)	109.0(3)
C(3)–C(4)–O(2)	111.5(3)	C(5)–C(4)–O(2)	104.0(3)
C(5)–C(4)–C(3)	108.8(3)	C(13)–C(4)–O(2)	111.8(3)
C(13)–C(4)–C(3)	110.7(3)	C(13)–C(4)–C(5)	109.8(3)
C(6)–C(5)–C(4)	112.3(3)	C(5)–C(6)–C(1)	113.6(4)
C(2)–C(7)–O(3)	111.6(3)	C(8)–C(7)–O(3)	110.5(3)
C(8)–C(7)–C(2)	114.1(3)	C(9)–C(8)–C(7)	119.7(3)
C(13)–C(8)–C(7)	121.0(3)	C(13)–C(8)–C(9)	119.3(3)
C(10)–C(9)–C(8)	120.8(4)	C(11)–C(10)–C(9)	120.1(4)
C(12)–C(11)–C(10)	119.8(4)	C(13)–C(12)–C(11)	121.1(4)
C(8)–C(13)–C(4)	121.2(3)	C(12)–C(13)–C(4)	119.8(3)
C(12)–C(13)–C(8)	118.9(3)		

8-[2-(1,3-*Dioxolan*-2-*yl*)*phenyl*]-1,4-*dioxaspiro*[4.5]*decan*-8-*ol* (**10**).—To a solution of 2-(2-bromophenyl)-1,3-dioxolane[10] (48.0 g, 0.21 mol) in dry THF (200 ml) under nitrogen at −72 °C was added a solution of butyl-lithium in hexane (2.4M; 84.6 ml, 0.2 mol) dropwise during 15 min; the resulting mixture was stirred for 2 h, and then added dropwise *via* a cannula during 20 min to a solution cyclohexane-1,4-dione monoethylene acetal (**9**) (21.7 g, 0.139 mol) in THF (100 ml) at −70 °C under nitrogen. The resulting solution was allowed slowly to warm to room temperature and was stirred for 18 h before being quenched by being poured into saturated aq. NH_4Cl (200 ml). Standard extractive work-up (ethyl acetate) gave a yellow solid, which was recrystallised from ethanol to give the *title compound* (**10**) (32.0 g, 76%) as white crystals, m.p. 130–131 °C; R_f 0.3 (hexane–ethyl acetate, 2:1); ν_{max} 3 250 cm^{-1}; δ_H 7.63–7.05 (4 H,

m), 6.62 (1 H, s), 4.00 (4 H, s), 3.86 (4 H, s), 3.18 (1 H, s, OH), and 2.35–1.54 (8 H, m); *m/z* 306 (M^+, 1.9%) (Found: C, 66.9; H, 7.2. $C_{17}H_{22}O_5$ requires C, 66.65; H, 7.23%).

8-[2-(1,3-*Dioxolan*-2-*yl*)-*phenyl*]-8-*methoxy*-1,4-*dioxaspiro*-[4.5]*decane* (**11**).—To a stirred suspension of sodium hydride (60% dispersion in mineral oil; 5.9 g, 148 mmol) in THF (300 ml) at 45 °C under nitrogen was added iodomethane (19 ml, 43.32 g, 305 mmol) followed by a solution of the alcohol (**10**) (30.0 g, 98 mmol) in THF (200 ml) dropwise during 1 h. The mixture was stirred at 45 °C for 1 h and quenched by cautious addition of water (200 ml). Standard extractive work-up (ether) gave a yellow solid, which was recrystallised from ethanol to give the *title compound* (**11**) (26.5 g, 85%) as white crystals, m.p. 111–112 °C; R_f 0.5 (hexane–ethyl acetate, 3:1); ν_{max}(Nujol) 2 965 cm^{-1}; δ_H 7.68–7.25 (4 H, m), 6.73 (1 H, s), 4.05 (4 H, m), 3.97 (4 H, m), 3.02 (3 H, s), and 2.26–1.65 (8 H, m); *m/z* 320 (M^+, 1%) (Found: C, 67.4; H, 7.5. $C_{18}H_{24}O_5$ requires C, 67.48; H, 7.55%).

When carried out on a smaller scale with the alcohol (**10**) (15 mmol) a 90% yield of compound (**11**) was obtained.

(1RS,8RS,9RS)-8-*Hydroxy*-1-*methoxytricyclo*[7.3.1.$0^{2,7}$]*trideca*-2,4,6-*trien*-10-*one* (**12**).—(*a*) A solution of bis-dioxolane (**11**) (25.0 g, 78.12 mmol) and PTSA monohydrate (5 g) in acetone-water (10:1; 600 ml) was boiled under reflux until TLC analysis indicated that the reaction was complete (0.5 h). The reaction mixture was cooled and most of the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate, the solution was washed successively twice with saturated aq. $NaHCO_3$ and once with brine, dried ($MgSO_4$), and the solvent was removed under reduced pressure to give a pale yellow solid (17 g). Recrystallisation from ethanol gave the *title compound* (**12**) (13.5 g, 75%) as white crystals, m.p. 148–150 °C; R_f 0.3 (hexane–EtOAc, 3:1); ν_{max}(CH_2Cl_2) 3 390br and 1 715 cm^{-1}; δ_H(400 MHz) 7.64–7.58 (1 H, m, 6-H), 7.50–7.45 (1 H, m, 3-H), 7.39–7.33 (2 H, m, 4- and 5-H), 5.14 (1 H, d, *J* 6.8 Hz, 8-H), 3.21 (3 H, s, OMe and 1 H, br s, OH), 3.15 (1 H, ddt, *J* 6.8, 4.4, 2.3 Hz, 9-H), 2.52 (1 H, ddd, *J* 12.7, 2.9, 2.3 Hz, 13e-H), 2.39 (1 H, ddd, *J* 14.5, 5.4, 2.3 Hz, 11e-H), 2.21–2.11 (1 H, m, 12a-H), 2.05 (1 H, dd, *J* 12.7, 4.4 Hz, 13a-H), 1.96–1.86 (2 H, m, 11b- and 12b-H); δ_C(100.6 MHz; multiplicities determined by DEPT experiment) 211.8, 138.7, 137.3 (C), 127.8, 127.7, 126.8, 124.0 (CH), 75.2 (C), 69.4, 53.2 (CH), 50.3 (CH_3), 39.5, 37.7, and 32.9 (CH_2); *m/z* (EI) 232 (M^+, 2.3%) and 175 (100) [Found: (NH_3 CI): $(M + NH_4)^+$, 250.146 50. $C_{14}H_{20}NO_3$ requires *m/z*, 250.144 32. Found: C, 72.4; H, 7.0. $C_{14}H_{16}O_3$ requires C, 72.39; H, 6.94%).

(*b*) When the reaction was repeated using PPTS (2.6 g, 10.3 mmol) in acetone–water (10:1; 100 ml) for 3 h (reflux), and the product mixture purified by chromatography on silica (hexane–ethyl acetate, 3:1), bis-dioxolane (**11**) (4.1 g, 12.8 mmol) gave the title compound (**12**) (1.9 g, 64%) together with *keto aldehyde* (**13**) (200 mg, 7%) as a white solid, m.p. 94–96 °C; R_f 0.6 (hexane–ethyl acetate, 3:1); ν_{max}(Nujol) 1 715 and 1 685 cm^{-1}; *m/z* 232 (M^+, 8.2%) (Found: C, 72.15; H, 6.8. $C_{14}H_{16}O_3$ requires C, 72.39; H, 6.94%).

(1RS,9SR)-1-*Methoxytricyclo*[7.3.1.$0^{2,7}$]*trideca*-2,4,6-*triene*-8,10-*dione* (**14**).—To a stirred suspension of pyridinium dichromate (PDC) (170 mg, 0.45 mmol) and powdered 4 Å molecular sieves (100 mg) in CH_2Cl_2 (1.5 ml) at room temperature was added aldol (**12**) in one portion. The resulting black suspension was stirred for 1 h at room temperature before being filtered through a short bed of silica. The residual solids were washed thoroughly with ether and the solvent was removed to give a green oil, which was chromatographed on silica (hexane–ethyl acetate, 5:1) to give the title compound (**14**) (37.5 mg, 70%) as a green oily solid, m.p. 64–75 °C; R_f 0.3 (hexane–ethyl acetate, 5:1); ν_{max}(CH_2Cl_2) 1 714 and 1 685 cm^{-1}; δ_H 8.00–7.30 (4 H, m), 3.70 (1 H, m), 3.20 (3 H, s), and 2.50–2.00 (6 H, m); *m/z* 230 (M^+, 3.4%).

(1RS,9SR)-1-*Methoxytricyclo*[7.3.1.$0^{2,7}$]*trideca*-2,4,6-*trien*-10-*one* (**15**).—(*a*) A mixture of aldol (**12**) (4.0 g, 17.24 mmol), triethylsilane (8.2 ml, 5.97 g, 51.3 mmol), and trifluoroacetic acid (TFA) (40 ml) was stirred at room temperature for 5 h. The mixture was diluted with water (150 ml), and standard extractive work-up (CH_2Cl_2) gave 1-methoxy-10-trifluoroacetoxytricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene as a white solid, to which was added a solution of KOH (1 g) in MeOH (20 ml) and the mixture was stirred at room temperature for 2 h, then acidified with conc. hydrochloric acid; standard extractive work-up (ethyl acetate) gave a yellow oil, which was chromatographed on silica (hexane–ethyl acetate, 3:1) to give 1-methoxytricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-trien-10-ol (2.8 g, 75%) as a white solid, m.p. 89–92 °C; R_f 0.15 (hexane–ethyl acetate, 3:1), which was fully characterised.

(*b*) To a stirred suspension of PDC (2.5 g, 6.65 mmol) and powdered 4 Å molecular sieves (1.5 g) in dry dichloromethane (10 ml) at room temperature was added in one portion the alcohol from method (*a*) (720 mg, 3.30 mmol). The resulting black suspension was stirred at room temperature for 15 h and then filtered through a short bed of silica. The brown solid residues were washed thoroughly with ether, the filtrates, and washings were combined, and the solvent was removed to give a pale yellow solid, which was recrystallised from hexane to give the *title compound* (**15**) (550 mg, 77%) as white needles, m.p. 86–88 °C; R_f 0.7 (hexane–ethyl acetate, 3:1); ν_{max} 1 716 cm^{-1}; δ_H 7.11–7.53 (4 H, m), 3.22 (3 H, s), 3.18 (2 H, d, *J* 3 Hz), 3.00 (1 H, s), 2.80 (1 H, m), and 2.48–1.90 (5 H, m); *m/z* 216 (M^+, 4.4%) (Found: C, 77.7; H, 7.4. $C_{14}H_{16}O_2$ requires C, 77.74; H, 7.45%).

8-[2-(1,3-*Dioxolan*-2-*yl*)*phenyl*]-7-*methyl*-1,4-*dioxaspiro*-[4.5]*decan*-8-*ol* (**19**).—To a solution of 2-(2-bromophenyl)-1,3-dioxolane (9.5 g, 41.6 mmol) in dry THF (15 ml) at −70 °C under nitrogen was added a solution of butyl-lithium in hexane (2.4M; 17.5 ml, 42.0 mmol) dropwise during 10 min and the resulting mixture was stirred for 2 h at −70 °C. The brown aryllithium suspension was added *via* a cannula during 15 min to a solution of 3-methylcyclohexane-1,4-dione 1-monoethylene acetal (**18**)[14] (4.7 g, 27.7 mmol) at −70 °C under nitrogen. The resulting solution was allowed to warm slowly to room temperature and was then stirred for 24 h before being quenched by being poured into saturated aq. NH_4Cl (150 ml). Standard extractive work-up (ethyl acetate) gave an orange oil, which was chromatographed on silica (hexane–ethyl acetate, 2:1) to give a yellow solid. Recrystallisation from ethanol gave the *title compound* (**19**) (7.2 g, 81%) as white needles, m.p. 111–113 °C; R_f 0.25 (hexane–ethyl acetate, 2:1); ν_{max}(CH_2Cl_2) 3 250 and 2 987 cm^{-1}; δ_H 7.60–7.20 (4 H, m), 6.58 (1 H, s), 3.90 (4 H, s), 3.80 (4 H, s), 2.15–1.35 (7 H, m), and 0.70 (3 H, d, *J* 7 Hz); *m/z* 320 (M^+, 2.1%) (Found: C, 67.3; H, 7.7. $C_{18}H_{24}O_5$ requires C, 67.48; H, 7.55%).

8-[2-(1,3-*Dioxolan*-2-*yl*)*phenyl*]-8-*methoxy*-7-*methyl*-1,4-*dioxaspiro*[4.5]*decane* (**20**).—To a stirred suspension of sodium hydride (60% dispersion in mineral oil; 1.2 g, 30 mmol) in dry THF (30 ml) at 45 °C under nitrogen was added iodomethane (4.2 ml, 9.58 g, 67.5 mmol) followed by a solution of the alcohol (**19**) (3.5 g, 10.9 mmol) in dry THF (20 ml) dropwise during 15 min. The mixture was stirred at 45 °C for 3 h and quenched by cautious addition of water (50 ml). Standard extractive work-up (ether) gave a yellow solid, which was recrystallised from ethanol to give the *title compound* (**20**) (3.0 g, 86%), m.p. 118–120 °C; R_f 0.3 (hexane–ethyl acetate, 4:1); ν_{max}(Nujol) 2 965 cm^{-1}; δ_H 7.90–7.20 (4 H, m), 6.59 (1 H, s), 4.40–3.90 (4 H, m), 4.00

(4 H, s), 3.20 (3 H, s), 2.60–1.40 (7 H, m), and 0.79 (3 H, br d); δ_C 141.4, 128.6, 127.4, 126.9, 108.7, 100.4, 81.9, 65.3, 64.2, 50.8, 40.5, 39.2, 30.4, and 16.1; *m/z* 302 (M^+ − MeOH, 2.6%) (Found: C, 68.0; H, 7.8. $C_{19}H_{26}O_5$ requires C, 68.24; H, 7.83%).

(1RS,8SR,9SR,12SR)-8-*Hydroxy*-1-*methoxy*-12-*methyltricyclo*[7.3.1.$0^{2,7}$]*trideca*-2,4,6-*trien*-10-*one* (**21**) *and its* (1RS,8RS,9RS,13SR)-13-*Methyl Isomer* (**22**).—A mixture of compound (**20**) (500 mg, 1.51 mmol) and PTSA monohydrate (285 mg) was boiled under reflux in acetone–water (10:1, 10 ml) for 1 h. The reaction mixture was cooled and most of the solvent was removed under reduced pressure. Standard extractive work-up (ethyl acetate) gave a white solid, which was recrystallised from ethyl acetate–hexane to give a mixture (*ca.* 55:45 by ^{1}H NMR) of the *title compounds* (**21**) and (**22**) (250 mg, 68%) as white needles, m.p. 149–151 °C; R_f 0.25 (hexane–ethyl acetate, 4:1); ν_{max}(CH_2Cl_2) 3 390 and 1 716, cm^{-1}; δ_H(400 MHz) 7.64–7.35 (8 H, m), 5.21–5.17 (2 H, m), 3.80 (2 H, br s, OH), 3.14 {6 H, s + 1 H, m [from (**21**)]}, 3.00 {1 H, d, *J* 3 Hz [from (**22**)]}, 2.60 (1 H, m), 2.35–2.27 (1 H, m), 2.20–2.12 (4 H, m), 1.96–1.86 (1 H, m), 1.75–1.70 (3 H, m), 1.13 {3 H, d, *J* 3 Hz [from (**21**)]}, and 1.09 {3 H, d, *J* 3 Hz [from (**22**)]}; *m/z* 246 (M^+, 7.3%) (Found: C, 73.0; H, 7.5. $C_{15}H_{18}O_3$ requires C, 73.14; H, 7.36%).

(1RS,8RS,9SR,10RS)-1-*Methoxy*-10-*pyrrolidinotricyclo*-[7.3.1.$0^{2,7}$]*trideca*-2,4,6-*triene* (**16**).—To a solution of pyrrolidine (0.66 ml, 562 mg, 7.9 mmol) in methanol (2.5 ml) at room temperature were added methanolic hydrogen chloride (5M; 0.264 ml, 1.32 mmol) and sodium cyanoborohydride (81 mg, 1.29 mmol), followed by aldol (**12**) (300 mg, 1.29 mmol). The resulting mixture was stirred at room temperature for 72 h. The solvent was removed and water (10 ml) was added to the mixture. The pH was adjusted to <2 using conc. hydrochloric acid and the mixture was extracted with ether (3 × 20 ml). The pH of the aqueous layer was adjusted to >10 using solid KOH. Standard extractive work-up (ether) gave the title compound (**16**) (350 mg, 95%) as an unstable oil which was characterised and stored as its picrate salt,[21] m.p. 195–197 °C (from acetone); ν_{max}(free amine: liquid film) 3 400 and 2 940 cm^{-1}; δ_H—for details see text; δ_C(100.6 MHz) 160.8, 141.8, 141.3, 139.7, 138.7, 138.3, 127.2, 127.0, 126.3, 125.1, 74.7, 69.4, 67.5, 54.0, 53.0, 49.8, 38.8, 36.7, 32.8, 23.5, 22.4, and 22.3; *m/z* 287 (M^+ − picric acid, 1.2%) (Found: C, 55.6; H, 5.4; N, 10.9. Calc. for $C_{24}H_{28}N_4O_9$: C, 55.81; H, 5.46; N, 10.84%).

On a smaller scale [1.3 mmol of aldol (**12**)] the yield of amine (**16**) was 85%.

(1RS,9SR,10RS)-1-*Methoxy*-10-*pyrrolidinotricyclo*-[7.3.1.$0^{2,7}$]*trideca*-2,4,6-*triene* (**17**).—To a solution of pyrrolidine (0.7 ml, 596 mg, 8.39 mmol) in methanol (2.5 ml) at room temperature were added methanolic hydrogen chloride (5M; 0.28 ml, 1.4 mmol) and sodium cyanoborohydride (87 mg, 1.38 mmol), followed by ketone (**15**) (300 mg, 1.39 mmol). The resulting mixture was stirred at room temperature for 72 h. The solvent was removed and water (10 ml) was added to the mixture. The pH was adjusted to <2 using conc. hydrochloric acid and the mixture was extracted with ether (3 × 20 ml). The pH of the aqueous layer was adjusted to >10 using solid KOH. Standard extractive work-up (ether) gave the title compound (**17**) (360 mg, 96%) as an oil which was characterised as its picrate salt,[21] m.p. 97–99 °C (from acetone); ν_{max}(free amine: liquid film) 2 994 and 2 775 cm^{-1}; δ_H(free amine) 7.60–7.20 (4 H, m), 3.20 (3 H, s), 3.10–2.90 (3 H, m), 2.70–2.40 (6 H, m), 2.30–2.10 (3 H, m), and 2.00–1.60 (6 H, m); *m/z* 271 (M^+ − picric acid, 1.1%) (Found: C, 57.9; H, 5.6; N, 11.0. Calc. for $C_{24}H_{28}N_4O_8$: C, 57.59; H, 5.63; N, 11.19%).

On a smaller scale [1.40 mmol of (**15**)] the yield of amine (**17**) was 80%.

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