The synthesis of 2-cyclohexylideneperhydro-4,7-methanoindenes. Non-steroidal analogues of steroidal $GABA_A$ receptor modulators

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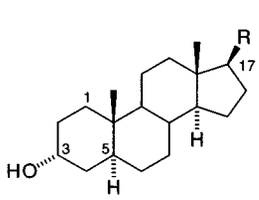
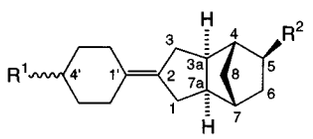
Racemic (3aα,4β,7β,7aα)-2-cyclohexylideneperhydro-4,7-methanoindene derivatives (±)-**3** and (±)-**4** were synthesised as analogues of steroidal $GABA_A$ receptor modulators **1** and **2** respectively. The lithium dianion generated from epimeric 2,3,3a,4,7,7a-hexahydro-4,7-methano-1*H*-indene-2-carboxylic acids, **8** and **9**, reacted with a commercially available cyclohexanone to generate β-hydroxy carboxylic acids. Cyclodehydration to β-lactones followed by the thermal elimination of carbon dioxide gave a suitably functionalised 2-cyclohexylidenehexahydro-4,7-methano-1*H*-indene derivative **18**. Regio- and stereospecific hydrocyanation of the bicyclo[2.2.1]hept-2-ene moiety of **18** was achieved *via* hydroboration affording a racemic nitrile, **19**. This underwent further transformations to give (±)-**3** and (±)-**4** and their hydroxy group epimers (±)-**5** and (±)-**6** respectively. X-Ray structure data was obtained for (±)-**3**. The effects of compounds (±)-**3**–(±)-**6** on the binding of the $GABA_A$ receptor agonist [^{3}H]muscimol to rat synaptic membranes were measured. Compound (±)-**4** was a weak positive modulator while the others were inactive.

Introduction

γ-Aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the mammalian central nervous system (CNS). Over the past ten years it has become established that some endogenous steroids are able to influence the excitability of the CNS by enhancing the activity of $GABA_A$ receptor-chloride ion channel complexes.[1] More recently, interest has focussed on the development of both steroidal and non-steroidal analogues of these steroidal $GABA_A$ receptor enhancers since such compounds may be useful as anxiolytic, sedative/hypnotic or anticonvulsant drugs.[2] Previous *in vitro* structure–activity studies[3] revealed that maximum $GABA_A$ receptor enhancement is shown by 5α-androstanes possessing 3α-hydroxy and 17β-acetyl or cyano substituents, *i.e.* **1** and **2**. Additional substituents in other positions may be tolerated or reduce activity.



1 R = Ac
2 R = CN



(3a*R*)-**3** R^1 = HO⋯, R^2 = Ac
(3a*R*)-**4** R^1 = HO⋯, R^2 = CN
(3a*R*)-**5** R^1 = HO—, R^2 = Ac
(3a*R*)-**6** R^1 = HO—, R^2 = CN

Our earlier work on the development of non-steroidal $GABA_A$ receptor modulators centred on derivatives of the dibenzo[*b*,*f*]oxepine system.[4] Now, with the aim of designing *alicyclic* analogues of steroidal $GABA_A$ receptor modulators, and using the steroid **1** as a model, we have found that the (3aα,4β,7β,7aα)-perhydro-4,7-methanoindene derivative (3a*R*)-**3** in a low energy conformation, is capable of delivering the same spacial arrangement of functional groups as **1** and possesses similar overall planarity (Fig. 1). Similarly, the nitrile (3a*R*)-**4** matches the steroidal nitrile derivative **2**. In this paper we report the synthesis of (±)-**3** and (±)-**4** and their hydroxy epimers, (±)-**5** and (±)-**6**.

Results and discussion

The synthesis of the (3aα,4β,7β,7aα)-2-cyclohexylideneperhydro-4,7-methanoindene ring system has not previously been described. Retrosynthetic analysis of the problem (Scheme 1) indicated that a convergent synthesis between the cyclohexane and (3aα,4β,7β,7aα)-hexahydro-4,7-methano-1*H*-indene moieties would be possible if a method of generating the double bond linkage could be found.

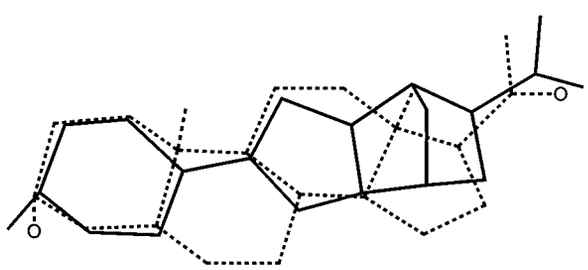
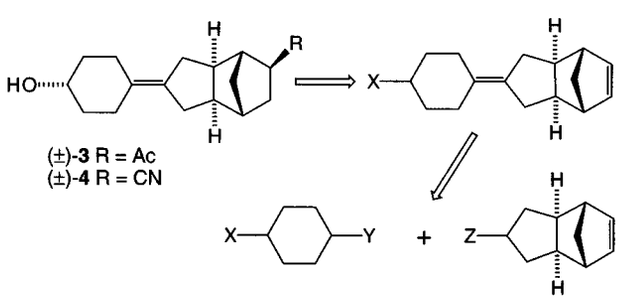


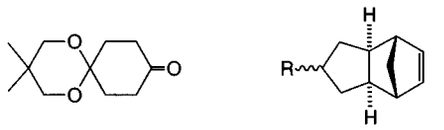
Fig. 1 Computer generated minimum energy conformations of compounds (3a*R*)-**3** and **1** superimposed so that the steroid oxygen atoms shown are matched.



Scheme 1 Retrosynthesis of racemic (3aα,4β,7β,7aα)-2-(4′-hydroxycyclohexylidene)perhydro-4,7-methanoindenes **3** and **4**.

A Wittig reaction between the two fragments would not work since it is known that Wittig couplings between cyclopentane and cyclohexane rings are prevented by enolisation of such hindered ketones.[5] Only two general methods of olefin synthesis have been shown to be useful in the synthesis of unsymmetrical cycloalkylidene-cycloalkanes. The first involves a double extrusion process from 2,5-dihydro-1,3,4-thiadiazole[6] or 2,5-dihydro-1,3,4-selenadiazole intermediates;[7] in the second, a

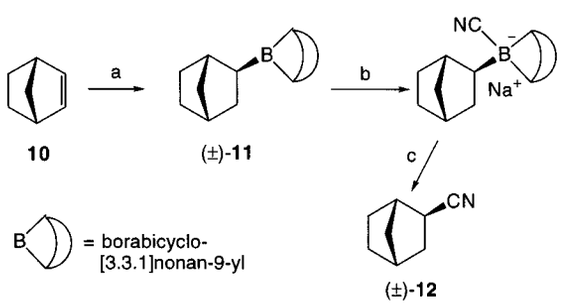
lithium dianion of a carboxylic acid is coupled with a cyclic ketone followed by cyclodehydration and elimination of carbon dioxide.[8] Synthesis *via* the second method appeared simpler and had the advantage of commercial availability of the starting ketone **7** and an existing partial synthesis for the isomeric carboxylic acids **8** and **9**.[9]



7

8 R = HO_2C⋯⋯
9 R = HO_2C▬

In order to obtain (±)-**3** and (±)-**4**, the retrosynthetic analysis shown in Scheme 1 also required the stereospecific *exo*-addition of some functionality to the bicyclo[2.2.1]hept-2-ene double bond from which the nitrile and then the acetyl groups could be derived. The most direct approach would require a suitably mild, regioselective, and specifically *exo*-hydrocyanation of a bicyclo[2.2.1]hept-2-ene double bond. Transition metal catalysed addition of hydrogen cyanide to such a double bond is known to occur with *exo*-specificity but requires forcing, acidic conditions[10] under which an inter-ring double bond would certainly migrate. Brown *et al.*[11] have shown that 9-borabicyclo[3.3.1]nonane (9-BBN) hydroborates bicyclo-[2.2.1]hept-2-ene (**10** in Scheme 2) much more rapidly than fully



10 (±)-**11** (±)-**12**

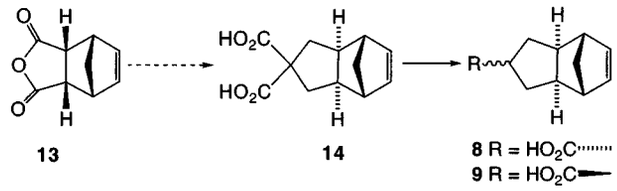
B = borabicyclo-[3.3.1]nonan-9-yl

Scheme 2 *Reagents and conditions*: a, 9-BBN in THF, room temp.; b, NaCN, room temp.; c, $Pb(OAc)_4$–NaCN, −15 °C.

substituted olefins and gives only the expected *exo*-addition product (±)-**11**, thus providing both the regioselectivity and stereospecificity we required. Furthermore, Masuda *et al.*[12] reported that (±)-**11** reacted with excess sodium cyanide to form a sodium trialkylcyanoborate which could be oxidised with lead tetraacetate to give bicyclo[2.2.1]heptane-2-carbonitrile in a 70% yield (Scheme 2). The authors gave no information about the stereochemistry of the product though retention of the *exo*-stereochemistry could be expected, yielding (±)-**12**. In order to confirm this expectation, we repeated the reaction under their conditions and obtained a single product (in 45% yield) which gave a ^{13}C NMR spectrum identical to that reported by Elmes and Jackson for authentic *exo*-bicyclo[2.2.1]-heptane-2-carbonitrile (±)-**12**.[10]

Having established a method by which the bicyclo[2.2.1]hept-2-ene double bond could be functionalised both regioselectively and stereospecifically to an *exo*-nitrile, the remaining requirement (see Scheme 1) was an efficient synthesis of the carboxylic acids **8** and **9**.

From the commercially available anhydride **13**, the diacid **14** was synthesised in five steps (Scheme 3) in an overall yield of 38% using a modification of the route described by Culberson *et al.*[9,13] Culberson and Wilder[9] described the thermal mono-decarboxylation of the diacid in the corresponding *endo*,*endo*-series using diphenyl ether as solvent but apparently did not attempt the monodecarboxylation of the *exo*,*exo*-isomer **14**. Indeed, when the thermolysis of **14** in diphenyl ether was attempted, it proved to be unsatisfactory since the resulting

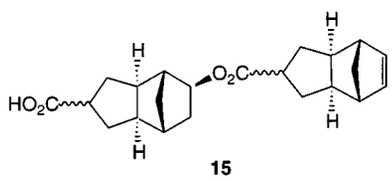


13 **14**

8 R = HO_2C⋯⋯
9 R = HO_2C▬

Scheme 3

monoacid was found to undergo *exo*-addition to the bicyclo-[2.2.1]hept-2-ene double bond (a known type of reaction[14]) generating a mixture of the desired monoacids, **8** and **9**, and the ester addition product **15** in a 1 : 1 ratio. Base hydrolysis of this mixture gave the required monoacids **8** and **9** (in a 1 : 1 ratio) in a yield of 53% from the starting diacid **13**. Clearly, an improvement was required.



15

Decarboxylation of the diacid **14** in 2,4,6-collidine had the desired effect of preventing the formation of the by-product **15** but afforded only a 51% yield of **8** and **9**. Fortunately, the copper(I) catalysed decarboxylation of **14** in acetonitrile according to the method of Toussaint *et al.*[15] gave a 1 : 1 mixture of **8** and **9** in high yield. The two isomers could be readily separated by chromatography and identified by virtue of the greater deshielding effects of the carboxylate function of **9** on the bridging methylene protons. Both isomers were suitable for the next step in the synthesis.

Having established the feasibility of the route indicated by the retrosynthetic analysis in Scheme 1, a synthesis was developed which proceeded according to the route detailed in Scheme 4. A 1 : 1 mixture of isomeric acids **8** and **9** was treated with lithium diisopropylamide to generate a lithium dianion. This was reacted with the ketone **7** to afford the β-hydroxy acid **16** which was cyclodehydrated in benzenesulfonyl choride–pyridine to give the unstable β-lactone **17**. Thermolytic elimination of carbon dioxide from **17**, performed without solvent under the conditions of Krapcho and Jahngen[8] produced some cleavage of the cyclic ketal along with much discolouration of the olefin product **18**. However, thermolysis using 2,4,6-collidine as solvent resulted in a much cleaner reaction, free from deprotected product, to afford the diene **18** in an overall yield of 68% from the starting acids **8** and **9**.

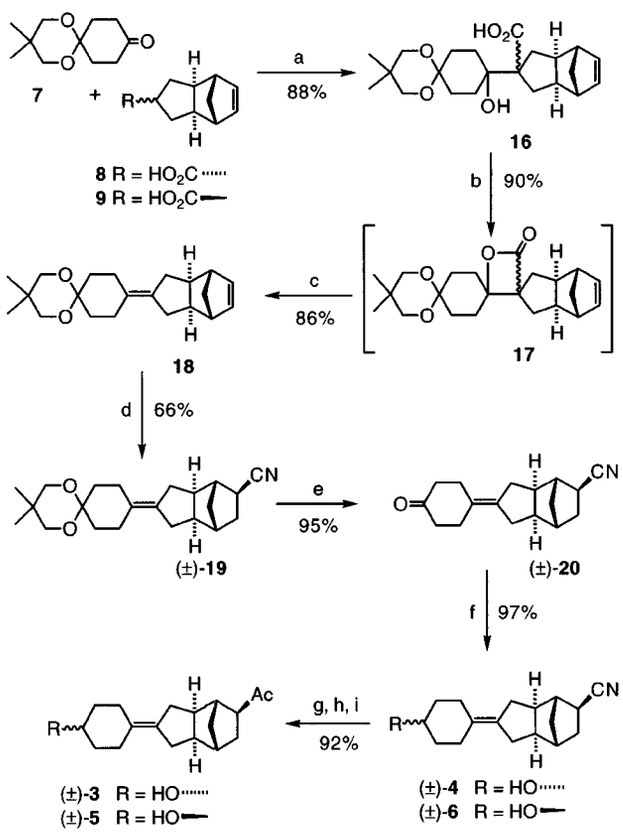
In a one pot reaction, the diene **18** was hydroborated with 9-BBN in tetrahydrofuran then treated with one equivalent of sodium cyanide to give the intermediate sodium trialkyl-cyanoborate (*cf.* Scheme 2). Excess sodium cyanide was added and sonicated to achieve saturation with sodium cyanide before oxidation with lead(IV) tetraacetate. Chromatography of the crude product gave the nitrile (±)-**19** in 66% yield. This single nitrile product indicated that the hydroboration step was both regio- and stereospecific. The cyclic ketal function of (±)-**19** was cleaved with tetrahydrofuran–hydrochloric acid (6 mol dm^{-3}) (10 : 1) to give the ketone (±)-**20** which was reduced with sodium borohydride to give a 1 : 1 mixture of the isomeric alcohols (±)-**4** and (±)-**6** in an overall yield of 61% from the diene **18**. The alcohols were separated by chromatography, to give firstly the 4′α-hydroxy epimer (±)-**4** and then the more polar 4′β-hydroxy epimer (±)-**6**, these identifications being made on the basis of their ^1H NMR spectra and the X-ray structure of the derivative (±)-**3**.

The Grignard reaction of the 1 : 1 mixture of hydroxy nitriles (±)-**4** and (±)-**6** with excess methylmagnesium iodide in reflux-

Table 1 ^{1}H NMR data (360 MHz; $CDCl_3$) for (3aα,4β,7β,7aα)-2-cyclohexylideneperhydro-4,7-methanoindenes (±)-**3**, (±)-**4**, (±)-**5** and (±)-**6**

	Chemical shift (δ), multiplicity and coupling constant (J/Hz)			
Proton	5β-COMe; 4′α-OH (±)-**3**	5β-CN; 4′α-OH (±)-**4**	5β-COMe; 4′β-OH (±)-**5**	5β-CN; 4′β-OH (±)-**6**
1α-H, 3α-H	2.59 (m, 15 and 8.5)	2.59 (m, 13 and 9.5)	2.53 (m, 16)	2.53 (m, 13.5)
1β-H, 3β-H	1.85–1.91 (m)[a]	1.85–1.93 (m)[a]	1.97 (br d, 16)	1.99 (br d, 16)
3a-H, 7a-H	2.10 (m, 8.5 and 4.5)	2.04 (m, 9.5)	2.09 (m, 9)	2.05 (m, 7.5)
4-H	2.22 (s)	2.35 (s)[a]	2.23 (s)	2.36 (s)[a]
5-H	2.35–2.40 (m)[a]	2.31 (dd, 9.5 and 4.5)[a]	2.36–2.43 (m)[a]	2.31 (ddd, 9, 5 and 1.5)
6α-H	1.26–1.38 (m)[a]	1.66 (ddd, 12.5, 9 and 2)	1.26–1.37 (m)[a]	1.66 (ddd, 12.5, 9 and 2.5)
6β-H	1.81 (ddd, 12, 4.5 and 4.5)	1.77 (ddd, 12.5, 4.5 and 4.5)	1.82 (ddd, 12.5, 4.5 and 4.5)	1.77 (ddd, 12.5, 4.5 and 4.5)
7-H	2.02 (d, 4)	2.14 (d, 4)	2.03 (d, 4)	2.15 (d, 4)
8_{anti}-H	1.01 (dt, 10.5 and 1.5)	1.39 (d, 10.5)	1.02 (dt, 10.5 and 1.5)	1.4 (dt, 10.5 and 1.5)
8_{syn}-H	1.26–1.38 (m)[a]	1.55 (d, 10.5)	1.26–1.37 (m)[a]	1.59 (d, 10.5)
2′α-H, 6′α-H	2.35–2.4 (m)[a,b]	2.31–2.39 (m)[a,b]	1.85–1.92 (m)[a,c]	1.82–1.97 (m)[a,c]
2′β-H, 6′β-H	1.85–1.91 (m)[a,c]	1.85–1.95 (m)[a,c]	2.36–2.43 (m)[a,b]	2.35–2.41 (m)[a,b]
3′α-H, 5′α-H	1.26–1.38 (m)[a,c]	1.34 (m, 9 and 4)[c]	1.85–1.92 (m)[a,b]	1.82–1.97 (m)[a,b]
3′β-H, 5′β-H	1.85–1.91 (m)[a,b]	1.85–1.95 (m)[a,b]	1.26–1.37 (m)[a,c]	1.34 (m, 9 and 3.5)[c]
4′-H	3.78 (br m, 8)[c]	3.78 (septet, 9 and 4)[c]	2.77 (br m, 9)[c]	3.79 (septet, 9 and 4.5)[c]
Other	2.16 (s, COMe)		2.16 (s, COMe)	

[a] Overlapping signal. [b] Equatorial. [c] Axial.



Scheme 4 *Reagents and conditions*: a, $LiNPr^i_2$ in THF, −40 °C; b, $PhSO_2Cl$ in pyridine, 4 °C; c, 2,4,6-collidine, 170 °C; d, 9-BBN in THF, room temp. then NaCN–$Pb(OAc)_4$, −15 °C; e, 6 M aq. HCl in dioxane; f, $NaBH_4$ in MeOH–THF, 0 °C; g, Me_3SiCl–NEt_3 in CH_2Cl_2, room temp.; h, MeMgI in C_6H_6, 50 °C; i, H_3BO_3 in THF–MeOH–water, room temp.

ing benzene was slow and required 16 h for completion. This time was reduced to 3 h by protection of the alcohol functions of (±)-**4** and (±)-**6** as their trimethylsilyl ethers by preliminary *in situ* treatment with chlorotrimethylsilane–triethylamine. Instantaneous hydrolysis of the Grignard complex to the ketone was achieved under neutral conditions using aq. ammonium chloride. It was found that the resulting epimeric silyl ethers could be cleaved under mild acidic conditions by using a 7 : 7 : 1 tetrahydrofuran–methanol–aq. boric acid system taking 2 h at 25 °C, pH 6. This system, previously used by Curran *et al.* as a mild hydrolysis of imines,[16] represents a low cost alternative to

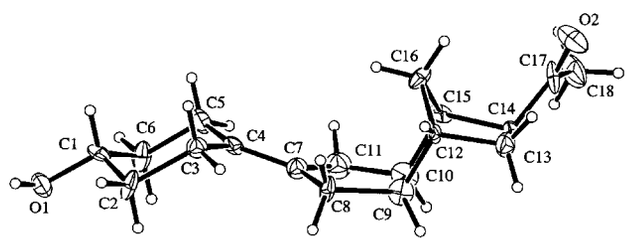


Fig. 2 ORTEP diagram of the crystal structure of (±)-**3** with crystallographic numbering scheme.

the tetra(*n*-butyl)ammonium fluoride–tetrahydrofuran system[17] for the deprotection of trimethylsilyl ethers. This boric acid hydrolysis gave a 1 : 1 mixture of the epimeric alcohols (±)-**3** and (±)-**5** in a 92% yield from the nitriles (±)-**4** and (±)-**6**. The epimeric alcohols (±)-**3** and (±)-**5** were separated by chromatography to give firstly the 4′α-hydroxy epimer (±)-**3** and then the more polar 4′β-hydroxy epimer (±)-**5**.

Identification of the 4′α- and 4′β-hydroxy epimers could be tentatively made by virtue of the different deshielding effects of their hydroxy functions on the 1- and 3-position protons. Hence, on going from the 4′α epimer (±)-**4** to the 4′β epimer (±)-**6**, the resonances of the 1α and 3α protons moved upfield while the 1β and 3β protons moved downfield (see Table 1). The same effect was observed with compounds (±)-**3** and (±)-**5**. This identification was confirmed by the X-ray structure determination of (±)-**3** (Fig. 2). While consistently poor crystal quality lead to deficiencies in the quality of the final refinement of the structure, the α configuration for the 4′-hydroxy group was established. For both the nitrile and the acetyl derivatives the 4′α-hydroxy epimer was found to be less polar than the 4′β-hydroxy epimer.

The synthesis of the required racemic compounds (±)-**3** and (±)-**4** was therefore successfully completed in seven steps from the epimeric acids **8** and **9** in good overall yield.

Pharmacology

The effects of compounds (±)-**3**–(±)-**6** on the binding of the $GABA_A$ receptor agonist [^{3}H]muscimol to rat synaptic membranes were measured.[18] The acetyl derivatives (±)-**3** and (±)-**5** showed no significant effects at 10 μmol dm^{-3} concentrations. However, the nitrile (±)-**4** showed significant dose dependent enhancements of [^{3}H]muscimol binding at 10 μmol dm^{-3} and above, while its hydroxy epimer (±)-**5** was inactive at 10 μmol dm^{-3}. A corresponding dependence of activity on hydroxy group stereochemistry has been observed in the parent steroids

for which 3α-hydroxy compounds such as **1** and **2** are active while their 3β-epimers are much less active.[18]

In conclusion, this work establishes a synthesis of a new alicyclic structure which may mimic the steroid skeleton and has the synthetic versatility to enable the stereospecific synthesis of steroid analogues of biological interest. We are currently investigating the asymmetric functionalisation of the intermediate **18** in order to produce single enantiomer analogues of steroids.

Experimental

^{1}H NMR Data for compounds described herein were measured in $CDCl_3$ using a Brüker wide-bore AM 360 MHz spectrometer equipped with an Aspect 3000 computer and a 5 mm probe. Chemical shifts are given in ppm downfield from the tetramethylsilane internal standard. ^{13}C NMR Data were measured using a JEOL FX-90Q (90 MHz) spectrometer. Melting points were determined on a Reichert hot stage apparatus and are uncorrected. Mass spectral data refer to chemical ionization using methane as reagent gas on a TSQ46 Finnigan/MAT spectrometer except for the high resolution electron impact data which were measured on a Kratos MS902 with a VG console update using a Kratos DS90 data system. In the work-up procedures, washing and drying refer to the use of water and anhydrous sodium sulfate respectively. Chromatographic separations were performed using short column vacuum chromatography on Merck silica gel H (TLC grade). Light petroleum refers to the fraction of bp 65–70 °C.

(3aα,4β,7β,7aα)-2,3,3a,4,7,7a-Hexahydro-4,7-methano-1*H*-indene-2,2-dicarboxylic acid 14

The diacid **14** was prepared according to the method of Culberson *et al.*[9,13] with some modifications. Mp 216–217.5 °C (decomp.) (lit.,[9] 215–216 °C decomp.); δ_H(D_2O–NaOD; dioxane) 1.28–1.34 (3 H, m, 8_{anti}-H, 1β-H and 3β-H), 1.63 (1 H, d, *J* 9, 8_{syn}-H), 1.95 (2 H, m, 3a-H and 7a-H), 2.25 (2 H, dd, *J* 13 and *J* 6, 1α-H and 3α-H), 2.48 (2 H, s, 2 × =CCH) and 6.19 (2 H, t, *J* 1.5,† 2 × =CH).

Thermal decarboxylation of 14. (2α,3aα,4β,7β,7aα)- and (2α,3aβ,4α,7α,7aβ)-2,3,3a,4,7,7a-Hexahydro-4,7-methano-1*H*-indene-2-carboxylic acids 8 and 9

A stirred mixture of the diacid **14** (3 g, 14 mmol) and diphenyl ether (50 cm^3) was heated in an oil bath at 135 °C for 10 min and the bath temperature raised to 185 °C over 30 min. Carbon dioxide was evolved steadily over the range 155–185 °C and continued to be evolved for 20 min at 185 °C. After a total of 30 min at 185 °C the mixture was cooled, diluted with diethyl ether (100 cm^3) and extracted with 5% aq. sodium hydroxide (2 × 20 cm^3). The basic solution was washed with diethyl ether (10 cm^3), acidified with 6 mol dm^{-3} hydrochloric acid, and then extracted with ether (50 cm^3). The ether extract was washed with brine (2 × 10 cm^3), dried and evaporated to give the product (2.21 g) as a colourless oil. This was hydrolysed by refluxing in aq. potassium hydroxide (1.5 mol dm^{-3}, 10 cm^3) for 6 h and worked up as for 'the basic solution' above, to give the product as an oil (1.96 g). Column chromatography, eluting with dichloromethane–ethyl acetate (0–100%), gave the partly separated *isomeric acids* **8** and **9** (1.27 g, 53%, in 1:1 ratio) and then an unresolved mixture of exo-*5-hydroxy isomeric acids* (442 mg, 17%). Pure fractions of acid **8** were combined, evaporated and the residue crystallised from light petroleum as *needles*, mp 92–93 °C. Similarly, the acid **9** crystallised from light petroleum but as *prisms*, mp 93–94 °C (Found for **8**: C, 73.9; H, 7.8. Found for **9**: C, 74.3; H, 7.8. $C_{11}H_{14}O_2$ requires C, 74.1; H, 7.9%); both **8** and **9** showed *m*/*z* 179 (100%, MH^+), 161 (20, $MH^+ - H_2O$), 133 (20, $MH^+ - H_2O - CO$); for **8**: δ_H 1.33–1.39 (3 H, m, 8_{anti}-H, 1β-H and 3β-H), 1.47 (1 H, d, *J* 9, 8_{syn}-H), 2.10–2.20 (4 H, m, 1α-H, 3α-H, 3a-H and 7a-H), 2.51 (2 H, t, *J* 1.5,† 2 × =CCH), 3.15 (1 H, tt, *J* 10 and 3.5, 2-H), 6.09 (2 H, t, *J* 1.5,† 2 × =CH) and 10.95 (1 H, v br s, CO_2H). For **9**: δ_H 1.25–1.34 (2H, m, 1β-H and 3β-H), 1.42 (1 H, d, *J* 9, 8_{anti}-H), 1.60 (1 H, d, *J* 9, 8_{syn}-H), 2.00–2.12 (4 H, m, 1β-H, 3β-H, 3a-H and 7a-H), 2.53 (2 H, t, *J* 1.5,† 2 × =CCH), 2.87 (1 H, septet, *J* 12 and 6, 2-H), 6.09 (2 H, t, *J* 1.5,† 2 × =CH) and 10.14 (1 H, v br s, CO_2H).

† Allylic coupling.

Base catalysed thermal decarboxylation of 14

The diacid **14** (100 mg) was heated in 2,4,6-collidine (1.5 cm^3) from 135 °C to reflux (170 °C) over 20 min and reflux continued for 20 min. The 2,4,6-collidine was mostly removed by distillation at 2.0 mmHg and then as an azeotrope by repeated distillation with xylene. The resulting oil (80 mg) was dissolved in diethyl ether (5 cm^3), extracted with hydrochloric acid (3 mol dm^{-3}, 2 × 2 cm^3), washed, dried and solvent evaporated to give the *isomeric acids* **8** and **9** (41 mg, 51%, as a 1:1 mixture).

Copper(I) oxide catalysed decarboxylation of 14. (2α,3aα,4β,7β,7aα)- and (2α,3aβ,4α,7α,7aβ)-2,3,3a,4,7,7a-Hexahydro-4,7-methano-1*H*-indene-2-carboxylic acids 8 and 9

A stirred suspension of the diacid **14** (6 g, 27 mmol) in dry acetonitrile (300 cm^3) was purged of oxygen by degassing twice at 25 mmHg under a nitrogen atmosphere. Copper(I) oxide (0.24 g, 1.7 mmol) was added, the mixture degassed once more, then refluxed for 12 h under nitrogen. The colourless solution was cooled and acetonitrile removed by distillation under reduced pressure to give a slightly blue oil which was partitioned between diethyl ether (150 cm^3) and hydrochloric acid (0.072 mol dm^{-3}, 100 cm^3). The separated aqueous phase was extracted with diethyl ether (2 × 50 cm^3), the combined ether fractions washed, dried and the solvent evaporated to give the *isomeric acids* **8** and **9** (4.72 g, 98%, as a 1:1 mixture) as a colourless oil which crystallised on standing. This was recrystallised from light petroleum at −15 °C to give a 1:1 mixture which was suitable for use in the next step.

(3aα,4β,7β,7aα)-2-(3,3-Dimethyl-9-hydroxy-1,5-dioxaspiro-[5.5]undecan-9-yl)-2,3,3a,4,7,7a-hexahydro-4,7-methano-1*H*-indene-2-carboxylic acid 16

n-Butyllithium (4.4 cm^3 of a 9 mol dm^{-3} solution in *n*-hexane, 40 mmol) was added over 10 min to a stirred solution of diisopropylamine (4.05 g, 5.67 cm^3, 40 mmol) in dry tetrahydrofuran (80 cm^3) at −40 °C under nitrogen, allowed to warm to −15 °C then recooled to −40 °C for the addition of a solution of the isomeric acids **8** and **9** (3.56 g of a 1:1 mixture, 20 mmol) in tetrahydrofuran (10 cm^3) over 10 min. The resulting solution was stirred at 50 °C for 2 h, cooled to −40 °C and a solution of the ketone **7** (3.96 g, 20 mmol) in tetrahydrofuran (10 cm^3) added over 10 min. After stirring at −40 °C for 2 h then at 20 °C for 16 h, the solution was poured onto ice (300 g), allowed to warm to 20 °C then extracted with diethyl ether (3 × 80 cm^3). The combined ether layers were extracted once with water (20 cm^3), the aqueous phases combined and carefully acidified with 1 mol dm^{-3} hydrochloric acid then extracted with dichloromethane (2 × 250 cm^3). The combined dichloromethane extracts were washed, dried and evaporated to give the *β-hydroxy acid* **16** (6.60 g, 88%, as an approximately 1:1 mixture of C-2 epimers as indicated by NMR spectroscopy), an analytical sample of which crystallised from chloroform–light petroleum as *needles*, mp 231–233 °C (Found: C, 70.3; H, 8.8. $C_{22}H_{32}O_5$ requires C, 70.3; H, 8.6%); *m*/*z* 377 (20%, MH^+), 359 (100, $MH^+ - H_2O$), 313 (10, $MH^+ - H_2O - HCO_2H$), 273 (15, $MH^+ - H_2O - C_5H_{10}O$); δ_H($CDCl_3$ + 1 drop CD_3OD) 0.96 (6 H, s, 2 × Me), 1.36–1.46 (3 H, m, 8_{anti}-H, 2′-H_{eq} and 6′-H_{eq}), 1.55–1.79 (7 H, m, 1-H and 3-H (*trans* to -CO_2H),

3a-H, 7a-H, 2′-H_{ax} and 6′-H_{ax}), 2.00–2.25 (6 H, m, 1-H and 3-H (*cis* to -CO_2H), 2 × 3′-H and 2 × 5′-H), 2.50 (2 H, s, 2 × =CCH), 3.46 (2 H, s, OCH_2), 3.54 (2 H, s, OCH_2) and 6.07 (2 H, s, 2 × =CH).

(3aα,4β,7β,7aα)-9-(2,3,3a,4,7,7a-Hexahydro-4,7-methano-1*H*-inden-2-ylidene)-3,3-dimethyl-1,5-dioxaspiro[5.5]undecane 18

Benzenesulfonyl chloride (7.05 g, 39.9 mmol) was added over 5 min to a stirred solution of the β-hydroxy acid **16** (5 g, 13.3 mmol, as an approximately 1:1 mixture of C-2 epimers) in dry pyridine (125 cm^3) at −5 °C then kept at 4 °C for 20 h. The resulting red solution was poured into ice–water (850 cm^3) and stirred while warming to 20 °C. The solid was filtered off, dried firstly in a stream of nitrogen then *in vacuo* to give the intermediate *oxetanone* **17** as a slightly pink solid (4.29 g, 90%). This was dissolved in a mixture of 2,4,6-collidine (4.3 cm^3) and tetrahydrofuran (4.3 cm^3) then heated to 145 °C (the tetrahydrofuran was driven off in the process). Evolution of carbon dioxide was vigorous for the first ten min and after 90 min the solution was cooled. Hot water (50 cm^3) was added, stirred, then decanted from the solid and this process was repeated two more times. The resulting solid was dried *in vacuo* to give the crude *olefin* **18** (3.71 g) which was then passed through a bed of silica, eluting with 50% dichloromethane–light petroleum, to give pure **18** (3.22 g, 86%) which crystallised from methanol as *needles*, mp 117–119 °C (Found: C, 80.3; H, 9.7. $C_{21}H_{30}O_2$ requires C, 80.2; H, 9.6%); *m*/*z* 315 (100%, MH^+), 229 (60, $MH^+ - C_5H_{10}O$); δ_H 0.98 (6 H, s, 2 × Me), 1.23 (1 H, dt, *J* 9 and 1.5,‡ 8_{anti}-H), 1.49 (1 H, d, *J* 9, 8_{syn}-H), 1.79 (4 H, m, 2 × 2′-H and 2 × 6′-H), 1.98 (2 H, d, *J* 16.5, 1β-H and 3β-H), 2.06 (2 H, m, 3a-H and 7a-H), 2.14 (4 H, br s, 2 × 3′-H and 2 × 5′-H), 2.50 (2 H, dd, *J* 16.5 and 8, 1α-H and 3α-H), 2.52 (2 H, t, *J* 1.5,† 2 × =CCH), 3.51 (4 H, s, 2 × OCH_2) and 6.08 (2 H, t, *J* 1.5,† 2 × =CH).

Hydrocyanation of bicyclo[2.2.1]hept-2-ene. *exo*-(±)-Bicyclo-[2.2.1]heptane-2-carbonitrile 12

A solution of bicyclo[2.2.1]hept-2-ene **10** in tetrahydrofuran (0.72 cm^3 of a 1.37 mol dm^{-3} solution, 1 mmol) was added over a few minutes to a stirred solution of 9-borabicyclo[3.3.1]-nonane in tetrahydrofuran (2.27 cm^3 of a 0.44 mol dm^{-3} solution, 1 mmol) at 20 °C under nitrogen, and stirred for 2.5 h. Finely divided sodium cyanide (49 mg, 1 mmol) was then added in one lot and stirring continued for 16 h. Further quantities of sodium cyanide (245 mg, 5 mmol) and tetrahydrofuran (1.5 cm^3) were added and the mixture sonicated for 5 min. It was then cooled to −10 °C, freshly prepared lead(IV) acetate (1.33 g, 3 mmol) added in one lot and stirred for 15 h at −15 °C under nitrogen. A water–tetrahydrofuran mixture (3:5, 0.7 cm^3) was then added dropwise (causing coagulation of the solid), the mixture allowed to warm to 20 °C, and diluted with light petroleum (5 cm^3). The supernatant was decanted off and the solid further extracted by trituration with light petroleum (3 × 10 cm^3). The combined organic extracts were dried and the solvent evaporated to give an oil (180 mg). This was purified by column chromatography, eluting with dichloromethane–light petroleum (0–60%) to give the racemic *nitrile* **12** (58 mg, 48%) as a colourless oil which slowly crystallised to a waxy solid, *m*/*z* 122 (100%, MH^+); δ_H 1.16–1.25 (2 H, m, 5_{exo}-H and 6_{exo}-H), 1.38 (1 H, m, *J* 10.5, 7_{anti}-H), 1.51–1.64 (3 H, m, 5_{exo}-H, 6_{exo}-H and 7_{syn}-H), 1.69 (1 H, ddd, *J* 12.5, 9 and 2.5, 3_{endo}-H), 1.82 [1 H, m, *J* 12.5, 4.5(2-H), and 4.5(4-H), 3_{exo}-H], 2.36 (1 H, ddd, *J* 9, 4.5 and 1.5,‡ 2-H), 2.40 (1 H, br s, 4-H) and 2.60 (1 H, br s, 1-H); δ_C (90 MHz; $CDCl_3$) 123.3, 41.7, 37.0, 35.9, 30.9, 28.3 and 28.2 [lit.,[10] δ_C (90 MHz; $CDCl_3$) 123.5 (CN), 41.8 (C-1), 37.1 (C-7), 36.0 (C-3 and C-4), 30.9 (C-2) and 28.3 (C-5 and C-6)]; ν_{max} ($CHCl_3$)/cm^{-1} 2220 (C≡N).

‡ W-coupling.

(3aα,4β,5β,7β,7aα)-(±)-2-(3,3-Dimethyl-1,5-dioxaspiro[5.5]-undecan-9-ylidene)perhydro-4,7-methanoindene-5-carbonitrile 19

A solution of the diene **18** (3.14 g, 10 mmol) in tetrahydrofuran (15 cm^3) was added over a few minutes to a stirred solution of 9-borabicyclo[3.3.1]nonane in tetrahydrofuran (26.0 cm^3 of a 0.46 mol dm^{-3} solution, 12 mmol) at 20 °C under nitrogen and stirred for 6 h. Finely divided sodium cyanide (559 mg, 12 mmol) was then added in one lot and stirring continued for 16 h. A further quantity of sodium cyanide (2.94 g, 60 mmol) was added and the mixture sonicated for 10 min. It was then cooled to −15 °C, lead(IV) acetate (16 g, 36 mmol) added in three lots over 4 h and stirring continued for 8 h. A water–tetrahydrofuran mixture (3:5, 8 cm^3) was then added dropwise over a few minutes (causing coagulation of the solid), the mixture allowed to warm to 20 °C, and diluted with light petroleum (50 cm^3). The supernatant was decanted off and the solid further extracted by trituration with light petroleum–dichloromethane (1:1, 3 × 100 cm^3). The combined organic extracts were neutralised with triethylamine, dried and the solvent evaporated to give a light brown tar. This was passed through a bed of silica, eluting with dichloromethane, to give a colourless solid (3.09 g). Column chromatography, eluting with dichloromethane–light petroleum (25–65%) gave firstly the starting *diene* **18** (336 mg) then the *nitrile* (±)-**19** (1.96 g, 66% based on **18** consumed) which crystallised from light petroleum as *needles*, mp 145–147 °C (Found: C, 77.5; H, 9.4; N, 4.2. $C_{22}H_{31}NO_2$ requires C, 77.4; H, 9.1; N, 4.1%); *m*/*z* 342 (100%, MH^+), 256 (5, $MH^+ - C_5H_{10}O$); δ_H 0.97 (6 H, s, 2 × Me), 1.39 (1 H, dt, *J* 11 and 1.5,‡ 8_{anti}-H), 1.56 (1 H, d, *J* 11, 8_{syn}-H), 1.65 (1 H, ddd, *J* 13, 9 and 1.5,‡ 6α-H), 1.74–1.80 (5 H, m, 6β-H, 2 × 2′-H and 2 × 6′-H), 1.95 (2 H, br d, *J* 16.5, 1β-H and 3β-H), 2.03 (2 H, m, *J* 9, 3a-H and 7a-H), 2.10–2.15 (5 H, m, 7-H and 2 × 3′-H and 2 × 5′-H), 2.31 (1 H, ddd, *J* 9, 5 and 1.5,‡ 5α-H), 2.35 (1 H, s, 4-H), 2.50–2.61 (2 H, m, *J* 16 and 8, 1α-H and 3α-H) and 3.51 (4 H, s, 2 × OCH_2); ν_{max} ($CHCl_3$)/cm^{-1} 2250 (C≡N).

(3aα,4β,5β,7β,7aα)-(±)-2-(4′-Oxocyclohexylidene)perhydro-4,7-methanoindene-5-carbonitrile (±)-20

A solution of the ketal (±)-**19** (1.1 g, 3.2 mmol) in 6 mol dm^{-3} hydrochloric acid–tetrahydrofuran (1:10, 110 cm^3) was kept at 20 °C for 1 h, cooled in an ice bath and neutralised with 3 mol dm^{-3} aq. sodium hydroxide. The solvent was mostly removed by distillation under reduced pressure, water (50 cm^3) added, and the product extracted with dichloromethane (3 × 50 cm^3). The combined extracts were washed, evaporated and dried *in vacuo* to give a colourless oil which crystallised on standing. This was chromatographed eluting with dichloromethane–light petroleum (20–100%) to give the *ketone* (±)-**20** (0.648 g, 79%). Recrystallisation from dichloromethane–light petroleum gave an analytical sample of (±)-**20** as *granules*, mp 117–119 °C (Found: C, 80.1; H, 8.1; N, 5.9. $C_{17}H_{21}NO$ requires C, 79.9; H, 8.3; N, 5.5%); *m*/*z* 256 (100%, MH^+); δ_H 1.43 (1 H, dt, *J* 11 and 1.5,‡ 8_{anti}-H), 1.55 (1 H, d, *J* 11, 8_{syn}-H), 1.68 (1H, ddd, *J* 12.5, 9 and 1.5,‡ 6α-H), 1.79 (1 H, ddd, *J* 12.5, 4.5 and 4.5, 6β-H), 1.99 (2 H, br d, *J* 15.5, 1β-H and 3β-H), 2.10 (2 H, m, *J* 8.5, 3a-H and 7a-H), 2.18 (1 H, d, *J* 4, 7-H), 2.33 (1 H, ddd, *J* 9, 5 and 1.5,‡ 5-H), 2.37–2.45 (9 H, m, 4-H, 2′-H, 3′-H, 5′-H and 6′-H) and 2.57–2.66 (2 H, m, *J* 15 and 8.5, 1α-H and 3α-H); ν_{max} ($CHCl_3$)/cm^{-1} 2220 (C≡N) and 1700 (C=O).

(3aα,4β,4′α,5β,7β,7aα)- and (3aα,4β,4′β,5β,7β,7aα)-(±)-2-(4′-Hydroxycyclohexylidene)perhydro-4,7-methanoindene-5-carbonitrile (±)-4 and (±)-6

Sodium borohydride (100 mg) was added over 20 min to a stirred solution of the ketone (±)-**20** (1 g, 3.92 mmol), in tetrahydrofuran–methanol (1:1, 50 cm^3) at 0 °C and stirring

continued for 30 min. The mixture was acidified with glacial acetic acid and the solvent mostly removed by distillation under reduced pressure. Water (60 cm^3) was added, the product extracted with dichloromethane (3 × 50 cm^3) and the combined extracts washed with 5% aq. sodium hydrogen carbonate (25 cm^3) then water (2 × 20 cm^3). The solvent was evaporated, the resulting oil dried by azeotropic removal of water with benzene, and then dried *in vacuo* to give the product as a clear oil (1.23 g). Column chromatography, eluting with dichloromethane–light petroleum (50–100%) then ethyl acetate–dichloromethane (0–8%) gave the partly separated *isomeric alcohols* (±)-**4** and (±)-**6** (1.028 g, 97%, in a 1:1 ratio). The isomeric alcohols were completely separated through further chromatography giving firstly (±)-**4**, which crystallised from benzene–light petroleum as *needles*, mp 100–102 °C, and then (±)-**6**, which crystallised from benzene–light petroleum as *needles*, mp 109–111 °C [Found for (±)-**4**: C, 79.3; H, 8.9; N, 5.3. Found for (±)-**6**: C, 79.2; H, 9.0; N, 5.5. $C_{17}H_{23}NO$ requires C, 79.3; H, 9.0; N, 5.4%]; Both (±)-**4** and (±)-**6** gave *m/z* 258 (100%, MH^+), 240 (20, $MH^+ - H_2O$); Both (±)-**4** and (±)-**6** gave ν_{max} ($CHCl_3$)/cm^{-1} 2230 (C≡N).

(3aα,4β,4′α,5β,7β,7aα)- and (3aα,4β,4′β,5β,7β,7aα)-(±)-1-[2-(4′-Hydroxycyclohexylidene)perhydro-4,7-methanoinden-5-yl]-ethanone (±)-3 and (±)-5

A solution of triethylamine in dichloromethane (0.4 cm^3 of a 2.2 mol dm^{-3} solution, 0.88 mmol) was added to a stirred solution of the nitriles (±)-**4** and (±)-**6** (200 mg of a 1:1 mixture, 0.78 mmol) in dichloromethane (4 cm^3) at 20 °C under nitrogen. After cooling to 0 °C, a solution of chlorotrimethylsilane in dichloromethane (0.4 cm^3 of a 2 mol dm^{-3} solution, 8 mmol) was added dropwise, the mixture allowed to warm to 20 °C, and stirred for 1 h. The solvent was evaporated under reduced pressure, the residue mixed with benzene (1.2 cm^3) then the solid (triethylamine hydrochloride) filtered off and washed with benzene (2 × 0.8 cm^3) under nitrogen. The combined benzene filtrates were added dropwise to a stirred ethereal solution of methylmagnesium iodide (1.96 cm^3 of a 1.64 mol dm^{-3} solution, 3.2 mmol) at 0 °C and stirred at 50 °C for 2 h under nitrogen. The mixture was cooled to 0 °C and saturated aq. ammonium chloride (2 cm^3) added dropwise. Hydrochloric acid (1 mol dm^{-3}, 3.2 cm^3) and benzene (1 cm^3) were added and the mixture stirred vigorously for 30 min. The aqueous layer was run off and extracted with benzene (2 cm^3). The combined benzene solutions were washed and evaporated to give *silylated product* as a colourless solid (242 mg). This was mixed with a solution of boric acid (287 mg, 46 mmol) in tetrahydrofuran–methanol–water (7:7:1, 3.2 cm^3) and the resulting suspension was stirred at 20 °C for 2 h. Water (15 cm^3) was added, the mixture extracted with benzene (15 cm^3) then the benzene extract washed, dried, and evaporated to give the *isomeric alcohols* (±)-**3** and (±)-**5** (197 mg, 92%, in a 1:1 ratio) as a colourless oil which slowly crystallised. Column chromatography, eluting with ethyl acetate–dichloromethane (0–8%), gave firstly (±)-**3** which crystallised from ethyl acetate as *platelets*, mp 132–133.5 °C, and then (±)-**5** which crystallised from ethyl acetate–light petroleum as *needles*, mp 116–117.5 °C [Found for (±)-**3**: C, 78.7; H, 9.3. Found for (±)-**5**: C, 78.6; H, 9.6. $C_{18}H_{26}O_2$ requires C, 78.8; H, 9.6%]; For (±)-**3**, *m/z* 275 (45%, MH^+), 257 (100, $MH^+ - H_2O$); For (±)-**5**, *m/z* 275 (20%, MH^+), 257 (100, $MH^+ - H_2O$).

Crystal structure analysis of compound (±)-3

Crystals of compound (±)-**3** grew from ethyl acetate as fragile platelets which were very susceptible to cleavage perpendicular to the long axis. Consequently, no improvement could be obtained on the data presented. The unit cell contained equal numbers of each enantiomer.

Crystal data. $C_{18}H_{26}O_2$, $M = 274.41$, monoclinic, space group $P2_1/a$, $a = 8.842(8)$, $b = 9.170(5)$, $c = 37.81(4)$ Å; $\beta = 90.59(7)°$, $V = 3064(6)$ $Å^3$, D_c ($Z = 8$) = 1.191 g cm^{-3}. $F(000) = 1200$, $\mu = 0.75$ cm^{-1}, λ(Mo-Kα) = 0.71069 Å. Specimen: colourless prisms, 0.363 × 0.220 × 0.0975, $N = 4109$, $N_o = 1107$, $I > 2.5\sigma(I)$, h,k,l-9→9, 0→9, 0→39, $R^* = 0.12$, $R_w = 0.1281$, $w = 5.974/[\sigma^2(F_o) + 0.0013\ F_o^2]$. Residual extrema, 0.365 and −0.441 e $Å^{-3}$.

$$R^* = \Sigma(\|F_o| - |F_c\|)/\Sigma|F_o|,\ R_w = \Sigma(\omega^{\frac{1}{2}}\|F_o| - |F_c\|)/\Sigma\omega^{\frac{1}{2}}|F_o|$$

Data collection and processing. Lattice parameters at 20 °C were determined by a least-squares fit to the setting parameters of 25 independent reflections. Data were measured on an Enraf-Nonius CAD4F four-circle diffractometer within the limits $1 < \theta < 22°$, with graphite monochromated Mo-Kα radiation. Data reduction and application of Lorentz and polarisation corrections were carried out using the Enraf-Nonius Structure Determination Package.[19]

Structure analysis and refinement. The structure was solved by direct methods using SHELXS-86[20] and the solution was extended by difference Fourier methods. Hydrogen atoms were included at calculated sites (C–H 0.97 Å) with group isotropic thermal parameters and all other atoms refined anisotropically. Refinement was by full-matrix least-squares methods using SHELX-76.[21] Scattering factors and anomalous dispersion terms were those supplied in SHELX-76.[21] All calculations were carried out using SHELX-76[21] and plots were drawn using ORTEP.[22] The atom numbering scheme is given in Fig. 2. Final atomic coordinates, bond lengths, bond angles and thermal parameters (Tables S1-S3) are available from the Cambridge Crystallographic Data Centre. For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 1*, available *via* the RSC Web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/253.

In view of the poor refinement of the structure, the data collection was repeated with a second crystal but this gave identical results. The data was analysed for the presence of twinning but no evidence was found. The presence of an approximate mirror plane was detected and this may have contributed to difficulties in the refinement. However, it is concluded that poor crystal quality was the fundamental problem leading to deficiencies in the quality of the final refinement.

Molecular modelling

Molecules (3a*R*)-**3** and **2** were built and molecular mechanics optimised using Chem-X.[23] After optimisation, the acetyl side-chain of **2** was set to the conformation adopted in crystal structures, where C16–C17–C20–O20 = −21° on average.[24] The effect of rotation of the side-chain acetyl group on the molecular mechanics energy of (3a*R*)-**3** was analysed using a 72 point (5° increments) study to obtain the global minimum. The steroid 3α-hydroxy and 20-ketone oxygen atoms were used as guides for the corresponding oxygen atoms in (3a*R*)-**3** using a rigid fit routine with equal weighting. Since two atoms are insufficient to define a plane, a preliminary fit using additional steroid guide atoms was used to orientate the molecules correctly.

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