Neurosteroid analogues. Part 5.[1] Enantiomers of neuroactive steroids and benz[*e*]indenes: total synthesis, electrophysiological effects on $GABA_A$ receptor function and anesthetic actions in tadpoles

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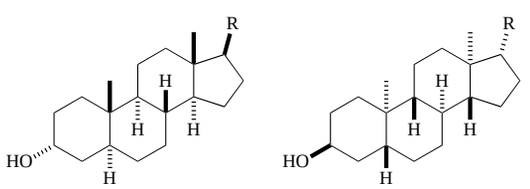
The synthesis of (3β,5β,8α,9β,10α,13α,14β,17α)-3-hydroxypregnan-20-one 2, (3β,5β,8α,9β,10α,13α,14β,17α)-3-hydroxyandrostane-17-carbonitrile 4,† [3*R*-(3α,3aα,5aβ,7α,9aα,9bβ)]-1-[dodecahydro-7-(2-hydroxyethyl)-3a-methyl-1*H*-benz[*e*]inden-3-yl]ethanone 6 and [3*R*-(3α,3aα,5aβ,7α,9aα,9bβ)]-dodecahydro-7-(2-hydroxyethyl)-3a-methyl-1*H*-benz[*e*]indene-3-carbonitrile 8 is reported.‡ Steroids 2 and 4 have been used previously to investigate the enantioselectivity of steroid action on $GABA_A$ receptor function and to correlate steroid action at this receptor with the anesthetic actions of the compounds. The enantioselective actions of benz[*e*]indenes 6 and 8 have been evaluated for the same reasons in this study. Similar correlations between the enantioselective effects of both classes of compounds on $GABA_A$ receptor function and anesthetic potency in tadpoles have been observed.

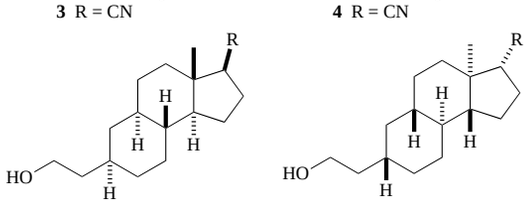
Introduction

The demonstration that the anesthetic actions of barbiturates, ketamine and isoflurane are enantioselective has provided strong evidence for the hypothesis that their mechanisms of anesthetic action involve specific binding sites on ion-channels located in the plasma membranes of neurons (for a review see ref. 2). In a recent study, we reported that the anesthetic actions of anesthetic steroids **1**, **2** and **3**, **4** are also enantioselective.



1 R = $COCH_3$
3 R = CN

2 R = $COCH_3$
4 R = CN



5 R = $COCH_3$
7 R = CN

6 R = $COCH_3$
8 R = CN

Moreover, using these steroid enantiomers as pharmacological tools we concluded, based on correlations between electrophysiological effects on $GABA_A$ receptor/ion channel function and anesthetic potency in tadpoles and mice, that steroid-induced anesthesia probably results from low-level potentiation of GABA-mediated currents.[3] In a separate study, we have reported that the actions of benz[*e*]indenes **5** and **6**, which are tricyclic analogues of steroids **1** and **3**, also alter $GABA_A$ receptor/ion channel function in an enantioselective manner.[4] Herein, we report the synthesis of steroid enantiomers **2** and **4** and benz[*e*]indene enantiomers **6** and **8**. In addition, new information on the enantioselective actions of the benz[*e*]-indenes on $GABA_A$ receptor/ion channel function and their potencies as anesthetics in tadpoles is reported.

Results

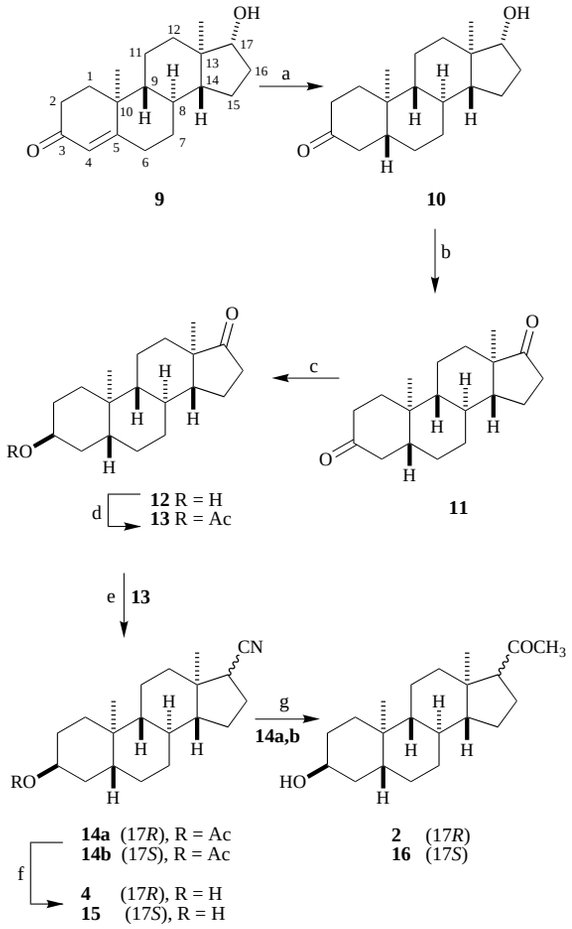
Chemistry

The synthesis of steroids **2** and **4** is summarized in Scheme 1. Steroid **9** was prepared according to a literature procedure,[5] and the subsequent reactions which convert steroid **9** into steroid **13** are either routine transformations or, in the cases where new stereocenters are formed, have been utilized previously for the synthesis of the enantiomers of the steroids shown in the scheme.[6,7] Hence, reduction of the enone system in steroid **9** using Li–NH_3(l) gave compound **10** (82%), and Jones oxidation of compound **10** gave dione **11** (91%). Selective reduction of the C-3 carbonyl group of dione **11** using K-Selectride® in THF at −78 °C gave steroid **12** (86%), and this compound was then acetylated using pyridine–$(Ac)_2O$ to obtain the acetoxy compound **13** (94%).

Compound **13** was converted into a diastereomeric mixture of compounds **14a** and **14b** (82%) by a two step procedure which involves the use of LiCN and diethyl cyanophosphonate to produce intermediate cyanophosphonate diastereomers, and the subsequent reduction of the cyanophosphonates using SmI_2–THF.[8] The uncharacterized steroids **14a** and **14b** were converted into steroids **4** and **15**, respectively, by removal of the acetyl group using CH_3MgBr in THF at 0 °C. After HPLC separation, compounds **4** and **15** were obtained in yields of 44 and 20%, respectively. Alternatively, steroids **14a** and **14b** were converted into steroids **2** and **16** using CH_3MgBr in THF at reflux. After HPLC separation, products **2** and **16** were obtained in yields of 45 and 17%, respectively.

† The steroid nomenclature system has been used to name these and related compounds. See compound **9** (Scheme 1) for the numbering system used.

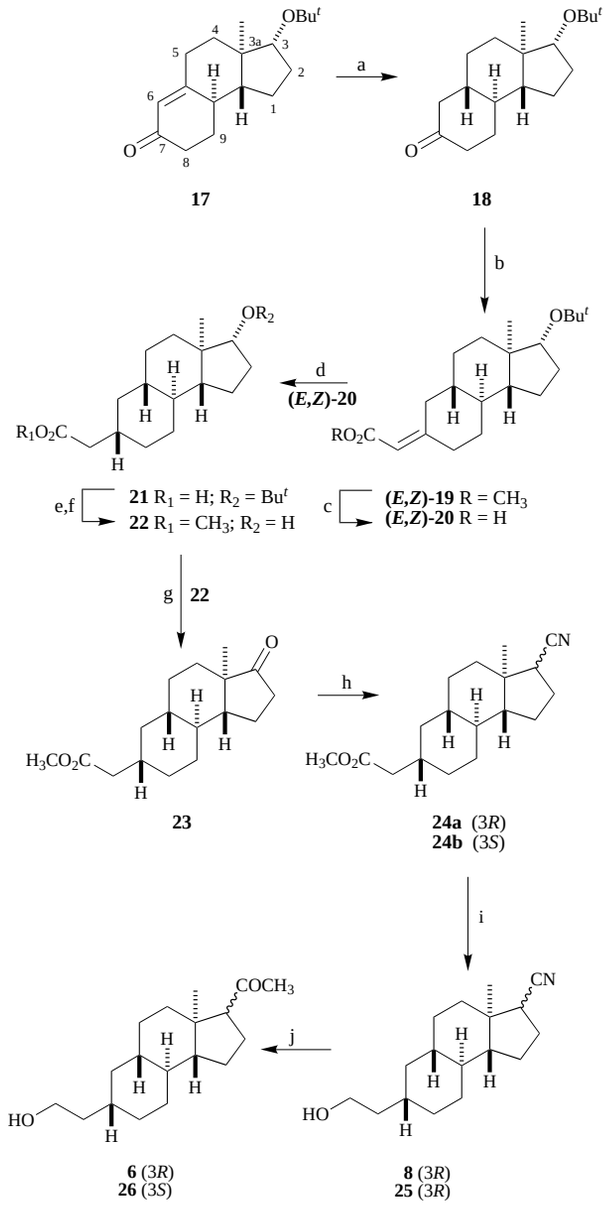
‡ The IUPAC nomenclature system has been used to name these and related compounds. See compound **17** (Scheme 2) for the numbering system used. The (*R*,*S*) stereochemical descriptor is used to identify a specific stereochemistry. The α-side of the reference plane is that side on which the preferred substituent lies at the lowest-numbered stereogenic position.



Scheme 1 *Reagents and conditions*: a, Li–NH_3–Bu′OH, −78 °C; b, Jones reagent, 0 to 5 °C; c, K-Selectride®–THF, −78 °C; d, C_5H_5N–$(CH_3CO)_2O$, 90 °C; e, (i) LiCN–NCP(O)$(OEt)_2$, THF, room temp.; (ii) SmI_2–Bu′OH, THF; f, CH_3MgCl–THF, room temp.; g, CH_3MgCl–THF, reflux

The enantioselectivity achieved for the synthesis of steroids **2** and **4** was determined by optical rotation measurements. Steroid **2** had $[a]_D^{24}$ −98.4 and steroid **4** had $[a]_D^{25}$ −56.8. The corresponding enantiomers **1** and **3** had $[a]_D^{24}$ +101.5 and $[a]_D^{25}$ +57.4, respectively. Accordingly, steroids **2** and **4** were prepared in 97 and 99% ee, respectively.

The synthesis of benz[*e*]indenes **6** and **8** is shown in Scheme 2. The same methods that were described previously for the preparation of the enantiomer of compound **17** were used for the preparation of this compound.[9] The Li–NH_3 (l) reduction of enone **17** gave the saturated ketone **18** as the product (85%). The IR and NMR spectra of compound **18** are identical to those of its previously synthesized enantiomer.[9] Methoxycarbonyl olefination of ketone **18** using (methoxycarbonylmethylene)triphenylphosphorane (without solvent at 165 °C for 15 h) provided a ~1 : 1 isomeric mixture of (*E*)-**19** and (*Z*)-**19** in high yield (90%). For characterization purposes, a portion of this isomeric mixture was separated by HPLC to obtain pure (*E*)-**19** and (*Z*)-**19**. The *E*,*Z* configurations were assigned based on a comparison of the ^{13}C NMR data of the compounds and those previously recorded for the ethyl esters of their enantiomers.[10] Hydrolysis of the (*E*,*Z*)-**19** mixture with 10% aqueous LiOH gave the corresponding acids (*E*,*Z*)-**20**, and without purification or characterization, this isomeric acid mixture was reduced using Li–NH_3 (l) to benz[*e*]indene **21** (84%). Removal of the *tert*-butyl group from compound **21** using 6 M HCl in refluxing EtOH also resulted in partial esterification of the carboxy group and yielded a mixture of acid and ethyl ester products (structures not shown in Scheme 2) which was conveniently converted into methyl ester **22** (72% overall from acid **20**) upon



Scheme 2 *Reagents and conditions*: a, Li–NH_3–Bu′OH, −78 °C; b, $Ph_3P{=}CHCO_2Et$, 165 °C; c, 10% aqueous LiOH, THF–MeOH, reflux; d, Li–NH_3–Bu′OH, −78 °C; e, 6 M aqueous HCl–EtOH, reflux; f, dry HCl–MeOH, 50 to 55 °C; g, Jones reagent, 0 to 5 °C; h, (i) LiCN–NCP(O)$(OEt)_2$, THF, room temp.; (ii) SmI_2–Bu′OH, THF; i, Red-Al®–CH_2Cl_2, −78 to 0 °C; j, CH_3MgCl–THF, reflux

treatment with dry HCl (generated *in situ* by the addition of CH_3COCl to MeOH) in MeOH at 50–55 °C for 6 h.

Jones oxidation of benz[*e*]indene **22** gave compound **23** (87%), which then was converted into diastereomeric carbonitriles **24a** and **24b** (82%) using the same two step procedure described above for the preparation of the steroid carbonitriles. A portion of diastereomeric carbonitriles **24a** and **24b** was separated by HPLC for product characterization and the remaining diastereomeric mixture was converted into diastereomeric benz[*e*]indenes **8** and **25** (89%) by selective reduction of the methoxycarbonyl group with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al®).[11] A portion of diastereomeric carbonitriles **8** and **25** was separated by HPLC for product characterization and biological evaluation, and the remainder of the diastereomeric mixture was converted into diastereomeric benz[*e*]indenes **6** and **26** upon treatment with CH_3MgCl in THF. After separation by HPLC, compounds **6** and **26** were obtained in yields of 42 and 26%, respectively.

As was the case for the steroids, the enantioselectivity achieved for the synthesis of benz[*e*]indenes **6** and **8** was deter-

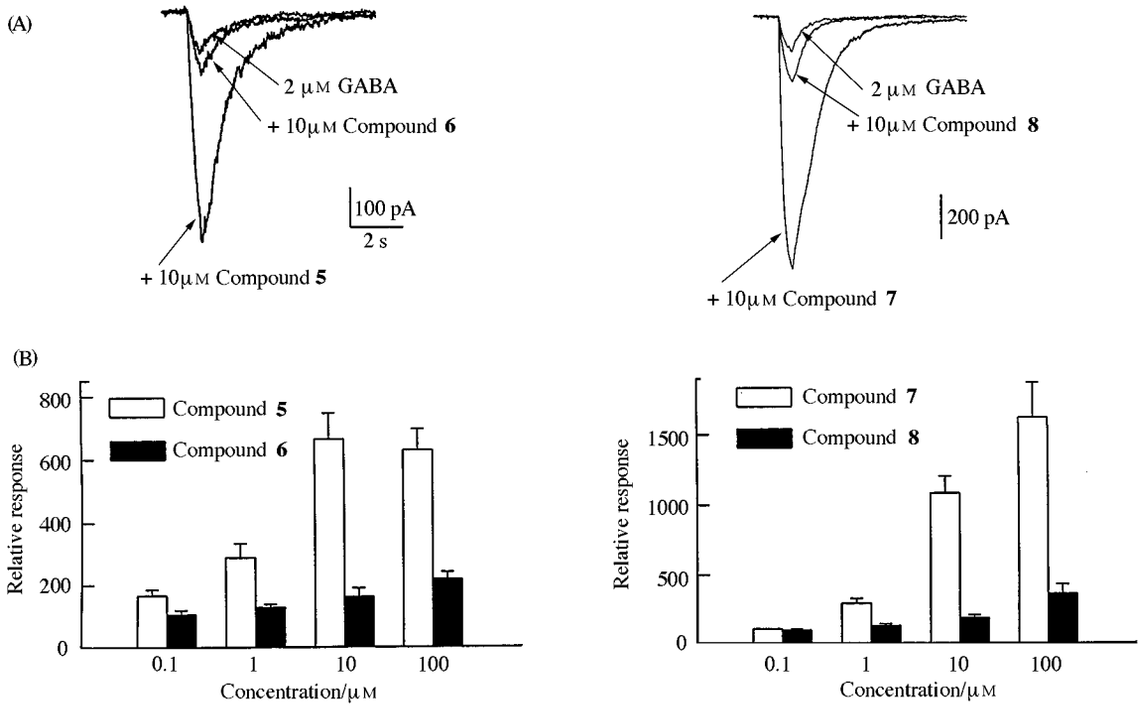


Fig. 1 (A) The traces show recordings from a single hippocampal neuron voltage clamped at −60 mV and exposed to 2 μM GABA in the presence of 10 μM compounds **5** and **6** (left panel) and 10 μM compounds **7** and **8** (right panel). All agents were applied by pressure ejection for 500 ms. (B) The graphs show concentration–response relationships for the effects of compounds **5** and **6** (left panel) and compounds **7** and **8** (right panel). Results are presented as the response in the presence of the compound normalized with respect to the response to 2 μM GABA (100%).

mined by optical rotation measurements. Benz[*e*]indene **6** had $[\alpha]_D^{22}$ −92.4 and benz[*e*]indene **8** had $[\alpha]_D^{22}$ −43.2. The corresponding enantiomers **5** and **7**, which have been prepared previously from naturally occurring steroid precursors,[12–14] had $[\alpha]_D^{24}$ +96.2 and $[\alpha]_D^{25}$ +44.4, respectively. Accordingly, benz[*e*]indenes **6** and **8** were prepared in 96 and 97% ee, respectively.

Pharmacology

Benz[*e*]indene enantiomers **5**–**8** were evaluated using electrophysiological methods for their ability to modulate $GABA_A$ receptor function. Voltage clamp recordings were obtained from cultured rat hippocampal neurons using whole-cell patch clamp methods. Compounds were evaluated for their ability to potentiate GABA-mediated Cl^- current and for their ability to initiate (gate) a Cl^- current in the absence of GABA. Similar evaluations have been reported previously for steroid enantiomers **1**–**4**.[3]

Typical recordings obtained using 10 μM benz[*e*]indenes **5**,**6** and **7**,**8** are shown in Fig. 1A. A comparison of the concentration-response data for potentiation of 2 μM GABA-mediated Cl^- current by the enantiomeric benz[*e*]indene pairs **5**,**6** and **7**,**8** is shown in Fig. 1B. At low concentrations (0.1 μM, 1.0 μM), there are only small differences in the degree of potentiation produced by the enantiomers. Since it was previously shown that benz[*e*]indene **5** at a concentration of 0.01 μM had no effect on the chloride currents mediated by 1 μM GABA, the presence of 2% of benz[*e*]indene **5** in benz[*e*]indene **6** is insufficient to explain the degree of potentiation caused by benz[*e*]-indene **6** at concentrations ≤1 μM.[10] Similarly, the equal extent of potentiation caused by benz[*e*]indenes **7** and **8** at a concentration of 0.01 μM cannot be explained by the presence of 1.5% of enantiomer **7** in enantiomer **8**.

At higher concentrations (10 μM, 100 μM), benz[*e*]indene enantiomers **5** and **7** [*i.e.* the (+)-enantiomers], which have the same absolute configuration as naturally occurring steroids, are clearly more effective than benz[*e*]indene enantiomers **6** and **8** [*i.e.* the (−)-enantiomers], which have an absolute configuration opposite to that of naturally occurring steroids. Additionally,

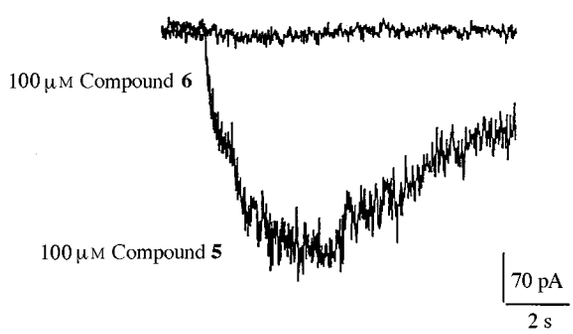


Fig. 2 The traces show responses from a single hippocampal neuron voltage clamped at −60 mV and exposed to 100 μM compounds **5** and **6** for 500 ms. Compound **5** activated a current whereas compound **6** had little effect.

benz[*e*]indenes **7** and **8** are more effective enhancers of GABA-mediated current than benz[*e*]indenes **5** and **6**, respectively.

Representative recordings for the difference in the direct gating actions of benz[*e*]indenes **5** and **6** in the absence of GABA are shown in Fig. 2. At a concentration of 100 μM, benz[*e*]indene **5** directly activated a Cl^- current, whereas benz[*e*]indene **6** was essentially inactive. Similar results (not shown) were obtained for benz[*e*]indene enantiomers **7** and **8**. In some cells small currents were activated by benz[*e*]indenes **6** and **8**. However, in every case the magnitude of the currents (~10 pA) induced by benz[*e*]indenes **6** and **8** were <10% of the magnitude of the currents induced by the corresponding enantiomers **5** and **7**, respectively.

Finally, the benz[*e*]indene enantiomers were evaluated for anesthetic activity in tadpoles using the loss of the tadpole righting reflex (LRR) as a behavioral endpoint (Fig. 3). In each case, the benz[*e*]indenes having the absolute configuration of naturally occurring steroids were more potent in causing LRR than the corresponding enantiomers of opposite absolute configuration. A logistic equation used for curve fitting of the data points shown in Fig. 3 results in EC_{50} (concentration at which half the tadpoles have LRR) values of 1.3 ± 0.1 μM and

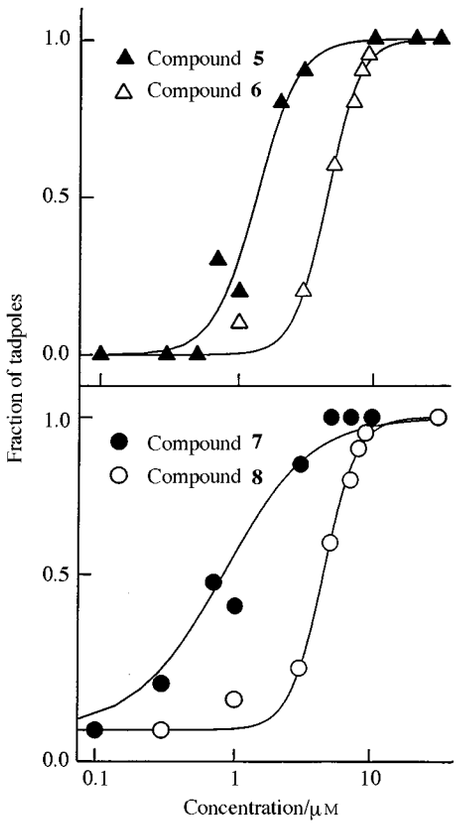


Fig. 3 The graphs show the fraction of tadpoles exhibiting loss of righting reflex as a function of compound concentration. The upper graph shows the effects of compounds **5** and **6** while the lower graph shows the effects of compounds **7** and **8**. Compounds were administered in the solution bathing the tadpoles at the concentrations shown and results were scored quantitatively (loss of righting reflex or no effect). Solid lines represent the fit of a concentration–response equation to the data.

4.5 ± 0.1 μM for benz[*e*]indenes **5** and **6**, respectively, and 0.8 ± 0.3 μM and 5.7 ± 0.6 μM for benz[*e*]indenes **7** and **8**, respectively.

Discussion

The pharmacological results reported for the enantioselectivity of benz[*e*]indene **5**–**8** modulation of $GABA_A$ receptor function and loss of righting reflex in tadpoles are strikingly similar to those reported earlier for the enantioselective effects of the analogous steroids **1**–**4** in these same assays.[3] Accordingly, those enantiomers having the absolute configuration of naturally occurring steroids are the more potent enantiomers in both classes of compounds. The fact that the benz[*e*]indenes and steroids display the same enantioselective preference in their actions provides additional evidence that these two classes of compounds utilize the same binding site(s) on $GABA_A$ receptors. Moreover, the finding that the effects of both benz[*e*]indene and steroid enantiomers on $GABA_A$ receptor function are correlated with their effects as anesthetics in tadpoles further supports the hypothesis that the modulation of these receptors plays a predominant role in steroid-induced anesthesia.

Experimental

All melting points were determined with a capillary melting point apparatus and were uncorrected. NMR spectra were recorded at ambient temperature in $CDCl_3$ (unless noted otherwise) with a 5 mm probe on a Varian Gemini-300 instrument operating at either 300 MHz (^{1}H) or 75 MHz (^{13}C). For ^{1}H NMR and ^{13}C NMR spectra the internal references were $SiMe_4$ (δ 0.00) and $CDCl_3$ (δ 77.00), respectively. *J* Values are given in Hz. IR spectra were recorded as films on a NaCl plate with a Perkin-Elmer 1710 FT-IR spectrophotometer. Optical rotations were recorded on a Perkin-Elmer Model 241 polarimeter. Elemental analyses were carried out by M-H-W Laboratories (Phoenix, AZ, USA). Solvents were used either as purchased or dried and purified by standard methodology. K-Selectride® and Red-Al® were purchased from Aldrich Chem. Co. Inc. (Milwaukee, WI, USA). Flash chromatography was performed using silica gel (32–63 μm) purchased from Scientific Adsorbants (Atlanta, GA, USA). The Econosil HPLC column (250 × 10 mm) was purchased from Alltech Associates, Inc. (Deerfield, IL, USA) and the Ultrasphere Si HPLC column (250 × 10 mm) was purchased from Beckman Instruments, Inc. (Fullerton, CA, USA).

(5β,8α,9β,10α,13α,14β,17α)-17-Hydroxyandrostan-3-one 10
A solution of compound **9**[5] {$[\alpha]_D^{25}$ −114.1 ($CHCl_3$), lit.,[15] $[\alpha]_D^{20}$ −115, 9.0 g, 31 mmol)} in THF (50 cm^3) was added to a blue solution of liquid ammonia (500 cm^3) and dissolved lithium metal (0.7 g, 10 mmol) in THF (25 cm^3) and toluene (250 cm^3) at −78 °C. After 30 min, NH_4Cl (5.0 g) was added carefully to discharge the blue color and the ammonia was allowed to evaporate. The reaction mixture was diluted with 10% aqueous HCl (200 cm^3) and extracted with EtOAc (3 × 100 cm^3). The combined organic layers were washed with water (100 cm^3) and brine (100 cm^3), and dried over Na_2SO_4. The solvent was removed to give a yellow oil which was purified by column chromatography (silica gel, 10% EtOAc in CH_2Cl_2) to give compound **10** (7.4 g, 82%) as white crystals, mp 182–183 °C (from EtOAc) (Found: C, 78.6; H, 10.4. $C_{19}H_{30}O_2$ requires C, 78.6; H, 10.4%); $[\alpha]_D^{27}$ −28.9 ($CHCl_3$); ν_{max}/cm^{-1} 3234, 2924, 2850, 1709, 1471, 1330, 1077, 1050, 1028; δ_H 3.63 (1H, t, *J* 8.3, C*H*OH), 1.01 (3H, s, CH_3), 0.75 (3H, s, CH_3); δ_C 212.04 (C-3), 81.75 (C-17), 11.45 (CH_3), 11.11 (CH_3), 53.86, 50.77, 46.69, 44.63, 42.94, 38.52, 38.10, 36.59, 35.69, 35.38, 31.20, 30.43, 28.75, 23.34, 20.99.

(5β,8α,9β,10α,13α,14β)-Androstane-3,17-dione 11
Jones reagent (8 M) was added dropwise to a stirred solution of compound **10** (3.1 g, 10.5 mmol) in acetone (150 cm^3) at 0 °C until an orange color persisted. After an additional 5 min, propan-2-ol (2.0 cm^3) was added to destroy any excess reagent, and water (150 cm^3) was added. The mixture was extracted with EtOAc (3 × 100 cm^3) and the combined organic layers were washed with brine (100 cm^3), and dried over Na_2SO_4. The solvent was removed to give a solid which was recrystallized from hexanes to give product **11** (2.78 g, 91%) as white crystals, mp 130–130.5 °C (Found: C, 79.35; H, 10.1. $C_{19}H_{28}O_2$ requires C, 79.1; H, 9.8%); $[\alpha]_D^{25}$ −105.1 ($CHCl_3$); ν_{max}/cm^{-1} 2939, 2861, 1733, 1437, 1366, 1273, 1248, 1057; δ_H 1.05 (3H, s, CH_3), 0.89 (3H, s, CH_3); δ_C 220.97 (C-17), 211.64 (C-3), 13.75 (CH_3), 11.41 (CH_3), 53.78, 51.14, 47.68, 46.53, 44.53, 38.36, 38.02, 35.77, 35.74, 34.87, 31.40, 30.46, 28.54, 21.72, 20.64.

(3β,5β,8α,9β,10α,13α,14β)-3-Hydroxyandrostan-17-one 12
K-Selectride® (1.0 M solution in THF, 20 cm^3, 20 mmol) was added to a stirred solution of compound **11** (2.88 g, 10 mmol) in dry THF (100 cm^3) at −78 °C. After 1.5 h, 10% aqueous NaOH (50 cm^3) and then 30% aqueous H_2O_2 (20 cm^3) were added. The mixture was allowed to warm to room temperature, stirred for another 30 min, and extracted with CH_2Cl_2 (3 × 50 cm^3). The combined organic layers were washed with brine (2 × 50 cm^3) and dried over Na_2SO_4. Solvent removal gave a solid which was recrystallized from EtOAc to give compound **12** (2.49 g, 86%) as colorless crystals, mp 183–185 °C (Found: C, 78.4; H, 10.2. $C_{19}H_{30}O_2$ requires C, 78.6; H, 10.4%); $[\alpha]_D^{25}$ −88.7 ($CHCl_3$); ν_{max}/cm^{-1} 3515, 2926, 2854, 1728, 1449, 1245, 1030; δ_H 4.05 (1H, m, C*H*OH), 0.86 (3H, s, CH_3), 0.81 (3H, s,

CH_3); δ_C 221.47 (C-17), 66.29 (C-3), 13.76 (CH_3), 11.12 (CH_3), 54.35, 51.42, 47.75, 39.03, 36.17, 35.79, 35.71, 34.96, 32.07, 31.49, 30.78, 28.93, 28.18, 21.68, 19.97.

(3β,5β,8α,9β,10α,13α,14β)-3-Acetyloxyandrostan-17-one 13

A mixture of steroid **12** (1.2 g, 4.1 mmol) and acetic anhydride (1.0 cm^3) in pyridine (10 cm^3) was heated at 90 °C for 2 h. The excess reagents were removed on a rotary evaporator and the semi-solid residue was diluted with CH_2Cl_2 (100 cm^3). The organic layer was washed with saturated aqueous $NaHCO_3$ (50 cm^3), water (50 cm^3) and brine (50 cm^3), and dried over Na_2SO_4. Solvent removal gave an oil which was purified by column chromatography (silica gel, 10% EtOAc in hexanes) to give product **13** (1.2 g, 94%), mp 164.5–166.5 °C (from EtOEt) (Found: C, 76.1; H, 9.5. $C_{21}H_{32}O_3$ requires C, 75.9; H, 9.7%); $[\alpha]_D^{22}$ −89.5 ($CHCl_3$); ν_{max}/cm^{-1} 2939, 2856, 1737, 1455, 1243, 1015; δ_H 4.97 (1H, s, C*H*OAc), 2.01, (3H, s, CH_3CO), 0.82 (3H, s, CH_3), 0.78 (3H, s, CH_3); δ_C 221.16 (C-17), 170.49 (CH_3CO), 69.77 (*C*HOAc), 13.68 (CH_3), 11.21 (CH_3), 54.14, 51.35, 47.65, 39.88, 35.80, 35.69, 34.86, 32.67, 31.49, 31.41, 30.62, 27.91, 25.91, 21.60, 21.41, 19.92.

(3β,5β,8α,9β,10α,13α,14β,17α)-3-Hydroxyandrostane-17-carbonitrile 4 and (3β,5β,8α,9β,10α,13α,14β,17β)-3-hydroxyandrostane-17-carbonitrile 15

A mixture of compound **13** (1.2 g, 3.6 mmol), diethyl cyanophosphonate (1.76 g, 10.8 mmol) and LiCN (356 mg, 10.8 mmol) in THF (120 cm^3) was stirred at room temperature for 30 min. Then the reaction was quenched by addition of EtOAc (50 cm^3) and water (50 cm^3). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 50 cm^3). The combined organic layers were washed with brine (2 × 50 cm^3) and dried over Na_2SO_4. The solvent was removed to give the intermediate product as a yellow solid which was purified by column chromatography (silica gel, 50% EtOAc in hexanes).

A solution of the product from the above reaction, SmI_2 (0.1 M solution in THF, 108 cm^3, 10.8 mmol) and 2-methylpropan-2-ol (266 mg, 3.6 mmol) was stirred overnight at room temperature under nitrogen. The reaction was quenched by addition of 10% aqueous HCl (50 cm^3) and extracted with EtOEt (3 × 50 cm^3). The combined organic layers were washed with 1% aqueous $Na_2S_2O_3$ (50 cm^3) and dried over Na_2SO_4. Solvent removal gave a yellow oil which, after column chromatography (silica gel, 50% EtOAc in hexanes), gave a mixture of compounds **14a** and **14b** (1.0 g, 82%) as a colorless oil.

Methylmagnesium chloride (3.0 M solution in THF, 1.0 cm^3, 3.0 mmol) was added to a stirred solution of a mixture of compounds **14a** and **14b** (0.5 g, 1.5 mmol) in dry THF (50 cm^3) at 0 °C. After 2 h, the reaction was quenched by addition of saturated aqueous NH_4Cl (50 cm^3) and 10% aqueous HCl (20 cm^3). The mixture was extracted with EtOAc (3 × 50 cm^3) and the combined organic layers were dried over Na_2SO_4. Solvent removal gave a mixture of compounds **4** and **15** as a yellow oil. The compounds were partially separated by column chromatography (silica gel, 4% EtOAc in CH_2Cl_2). Each compound was further purified by HPLC (Econosil, 30% EtOAc in hexanes, 2.5 cm^3 min^{-1}).

Compound **4** (193 mg, 44%) was obtained as white crystals, mp 162–163 °C (from EtOEt) (Found: C, 79.55; H, 10.5; N, 4.6. $C_{20}H_{31}NO$ requires C, 79.7; H, 10.4; N, 4.65%); $[\alpha]_D^{25}$ −56.8 ($CHCl_3$; 99% ee); ν_{max}/cm^{-1} 3464, 2932, 2853, 2237, 1448, 1002; δ_H 4.01 (1H, t, *J* 2.4, C*H*OH), 2.25 (1H, t, *J* 9.6, CHCN), 0.88 (3H, s, CH_3), 0.76 (3H, s, CH_3); δ_C 121.32 (CN), 66.19 (CHOH), 14.25 (CH_3), 11.07 (CH_3), 54.34, 53.90, 44.31, 40.11, 38.88, 37.03, 36.00, 35.77, 35.63, 32.05, 31.82, 28.85, 28.20, 26.43, 24.42, 20.32.

Compound **15** (87 mg, 20%) was obtained as white crystals, mp 185–187 °C (from EtOAc–EtOEt) (Found: C, 79.7, H, 10.3; N, 4.7. $C_{20}H_{31}NO$ requires C, 79.7; H, 10.4; N, 4.65%); ν_{max}/cm^{-1} 3479, 2927, 2855, 2233, 1449, 1006; δ_H 4.01 (1H, s, C*H*OH), 2.53 (1H, dd, *J* 2.0, 8.1, CHCN), 0.78 (3H, s, CH_3), 0.76 (3H, s, CH_3); δ_C 122.21 (CN), 66.16 (CHOH), 17.97 (CH_3), 11.04 (CH_3), 53.39, 52.02, 44.13, 39.86, 38.74, 35.95, 35.71, 35.63, 35.01, 32.02, 31.94, 28.83, 28.24, 27.14, 24.79, 20.33.

(3β,5β,8α,9β,10α,13α,14β,17α)-3-Hydroxypregnan-20-one 2 and (3β,5β,8α,9β,10α,13α,14β,17β)-3-hydroxypregnan-20-one 16

Using the same procedure described in the synthesis of compounds **6** and **26** (*vide infra*), a mixture of steroids **2** and **16** was obtained as an oil from a mixture of steroids **14a** and **14b**. The product mixture was partially separated by column chromatography (silica gel, 4% EtOAc in CH_2Cl_2). Each compound was further purified by HPLC (Econosil, 30% EtOAc in hexanes, 2.5 cm^3 min^{-1}).

Compound **2** (84 mg, 45%) was obtained as white crystals, mp 170–172 °C (from EtOEt–EtOAc) (Found: C, 79.3; H, 10.6. $C_{21}H_{34}O_2$ requires C, 79.2; H, 10.8%); $[\alpha]_D^{24}$ −98.4 ($CHCl_3$; 97% ee); ν_{max}/cm^{-1} 3382, 2930, 2871, 1707, 1447, 1356, 1154, 1004; δ_H 4.04 (1H, s, C*H*OH), 2.53 (1H, t, *J* 9.5, C*H*$COCH_3$), 2.11 (3H, s, $COCH_3$), 0.77 (3H, s, CH_3), 0.60 (3H, s, CH_3); δ_C 209.80 (CO), 66.46 (CHOH), 13.45 (CH_3), 11.15 (CH_3), 63.80, 56.74, 54.15, 44.25, 39.05, 36.07, 35.80, 35.44, 32.15, 31.91, 31.54, 28.95, 28.40, 24.34, 22.72, 20.76.

Compound **16** (31 mg, 17%) was obtained as white crystals, mp 158–159 °C (from EtOEt–hexanes) (Found: C, 79.1; H, 10.6. $C_{21}H_{34}O_2$ requires C, 79.2; H, 10.8%); ν_{max}/cm^{-1} 3461, 2922, 1702, 1445, 1357, 1170, 1071; δ_H 4.01 (1H, s, C*H*OH), 2.77 (1H, dd, *J* 2.4, 8.3, C*H*$COCH_3$), 2.10 (3H, s, $COCH_3$), 0.89 (3H, s, CH_3), 0.75 (3H, s, CH_3); δ_C 212.80 (CO), 66.37 (CHOH), 20.65 (CH_3), 11.07 (CH_3), 61.32, 53.49, 50.28, 45.75, 38.88, 36.01, 35.81, 35.63, 35.31, 32.75, 32.15, 32.09, 28.89, 28.45, 25.80, 24.20, 20.89.

[3*R*-(3α,3aα,9aα,9bβ)]-3-(1,1-Dimethylethoxy)-1,2,3,3a,4,5,8,9,9a,9b-decahydro-3a-methyl-7*H*-benz[*e*]inden-7-one 17

Compound **17** was obtained in 68% yield from the condensation of ethyl acetoacetate and [1*R*-(1α,3aβ,7aα)]-1-(1,1-dimethylethoxy)octahydro-7a-methyl-4-methylene-5*H*-inden-5-one[5] using the synthetic procedure reported for the enantiomer of this compound.[9] Compound **17** was obtained as white crystals, mp 125–127 °C (Found: C, 78.35; H, 10.3. $C_{18}H_{28}O_2$ requires C, 78.2; H, 10.2%); $[\alpha]_D^{27}$ +11.0 ($CHCl_3$) {$[\alpha]_D^{25}$ −11.3 ($CHCl_3$) for its enantiomer}.[16] IR, ^1H NMR and ^{13}C NMR spectra were identical to those of its enantiomer.[9]

[3*R*-(3α,3a,5aβ,9aα,9bβ)]-3α-(1,1-Dimethylethoxy)dodecahydro-3a-methyl-7*H*-benz[*e*]inden-7-one 18

A solution of compound **17** (4.14 g, 15 mmol) and 2-methylpropan-2-ol (1.1 g, 15 mmol) in THF (25 cm^3) was added to a blue solution of liquid ammonia (200 cm^3) and dissolved lithium metal (310 mg, 45 mmol) in toluene (25 cm^3) and THF (25 cm^3) at −78 °C. After 1 h, NH_4Cl (5.0 g) was added carefully to discharge the blue color and the ammonia was allowed to evaporate. Then, 10% aqueous HCl (100 cm^3) was added and the reaction mixture was extracted with EtOAc (2 × 100 cm^3). The combined organic layers were washed with water (100 cm^3) and brine (100 cm^3) and dried over Na_2SO_4. Solvent removal gave an oil which was purified by column chromatography (silica gel, 30% EtOAc in hexanes) to give compound **18** (4.2 g, 86%) as a solid, mp 89–91 °C (from EtOEt) (Found: C, 77.8; H, 10.6. $C_{18}H_{30}O_2$ requires C, 77.65; H, 10.9%); ν_{max}/cm^{-1} 2966, 2918, 2869, 1713, 1452, 1387, 1195, 1072; δ_H 3.41 (1H, t, *J* 8.1, C*H*OBu^t), 1.13 [9H, s, $C(CH_3)_3$], 0.80 (3H, s, CH_3); δ_C 211.70 (C=O), 80.44 (C-3), 72.19 [$OC(CH_3)_3$], 28.67 [$C(CH_3)_3$], 11.65 (CH_3), 49.26, 48.06, 44.46, 43.12, 41.40, 40.08, 36.58, 30.91, 30.65, 29.74, 23.51.

[3*R*-(3α,3aα,5aβ,7*E*,9aα,9bβ)]-[3-(1,1-Dimethylethoxy)-dodecahydro-3a-methyl-7*H*-benz[*e*]inden-7-ylidene]acetic acid methyl ester (*E*)-19 and [3*R*-(3α,3aα,5aβ,7*Z*,9aα,9bβ)]-[3-(1,1-dimethylethoxy)dodecahydro-3a-methyl-7*H*-benz[*e*]inden-7-ylidene]acetic acid methyl ester (*Z*)-19

A mixture of compound **18** (3.5 g, 12.6 mmol) and $Ph_3P{=}CH\text{-}CO_2CH_3$ (12 g, 36 mmol) was heated at 165 °C for 15 h under nitrogen. The reaction was cooled to room temperature and EtOAc (100 cm^3) and water (100 cm^3) were added. The organic layer was separated and washed with water (100 cm^3) and brine (100 cm^3), and dried over Na_2SO_4. Solvent removal gave a brown oil which was purified by column chromatography (silica gel, 30% EtOAc in hexanes) to give compounds (*E*)-**19** and (*Z*)-**19** as a mixture (3.8 g, 91%). A portion (100 mg) of the *E*:*Z* isomer mixture was separated by HPLC (Econosil, 2% EtOAc in hexanes, 2.9 $cm^3\ min^{-1}$) to permit product characterization. The *E*,*Z* configurations were assigned based on a comparison of the ^{13}C NMR data of the compounds and those previously recorded for the ethyl esters of their enantiomers.[10]

Compound (*E*)-**19** (49 mg) was obtained as white crystals, mp 80–81 °C (from hexanes) (Found: C, 75.9; H, 10.45. $C_{21}H_{34}O_3$ requires C, 75.4; H, 10.25%); ν_{max}/cm^{-1} 2973, 2919, 2868, 1721, 1652, 1435, 1383, 1199, 1148; δ_H 5.59 (1H, s, =CH), 3.66 (s, 3H, OCH_3), 3.36 (1H, t, *J* 8.1, C*H*-OBu^t), 1.11 [9H, s, $C(CH_3)_3$], 0.75 (3H, s, CH_3); δ_C 167.25 (C=O), 163.25 (=C), 112.67 (=C), 80.61 (C-3), 72.11 [O*C*$(CH_3)_3$], 28.69 [C(*C*$H_3)_3$], 11.71 (CH_3), 50.76, 49.50, 45.99, 44.24, 43.11, 41.20, 36.87, 31.50, 31.06, 29.47, 29.23, 23.39.

Compound (*Z*)-**19** (43 mg) was obtained as white crystals, mp 89–91 °C (from hexanes) (Found: C, 75.7; H, 10.2. $C_{21}H_{34}O_3$ requires C, 75.4; H, 10.25%); ν_{max}/cm^{-1} 2973, 2918, 2869, 1719, 1650, 1434, 1379, 1199, 1158; δ_H 5.59 (1H, s, =CH), 3.66 (3H, s, OCH_3), 3.36 (1H, t, *J* 8.2, C*H*-OBu^t), 1.11 [9H, s, $C(CH_3)_3$], 0.75 (3H, s, CH_3); δ_C 167.19 (C=O), 163.26 (=C), 112.44 (=C), 80.59 (C-3), 72.10 [O*C*$(CH_3)_3$], 28.68 [C(*C*$H_3)_3$], 11.70 (CH_3), 50.73, 49.60, 45.23, 43.14, 41.76, 37.52, 36.92, 35.85, 32.18, 31.53, 29.64, 23.32.

[3*R*-(3α,3aα,5aβ,7α,9aα,9bβ)]-[3-(1,1-Dimethylethoxy)-dodecahydro-3a-methyl-1*H*-benz[*e*]inden-7-yl]acetic acid 21

A mixture of compound (*E*)-**19** and (*Z*)-**19** (3.7 g, 11.1 mmol) in MeOH (100 cm^3), THF (150 cm^3) and 10% aqueous LiOH (100 cm^3) was refluxed for 2 h under nitrogen. After most of the solvent was removed, the residue was acidified with 10% aqueous HCl at 0 °C and extracted with CH_2Cl_2 (2 × 100 cm^3). The combined organic layers were washed with water (100 cm^3) and brine (100 cm^3), and dried over Na_2SO_4. Solvent removal gave crude acid **20** (3.2 g, 89%) as a solid which was used in the next step without further purification and characterization.

A solution of uncharacterized acid **20** (3.2 g, 9.9 mmol) in THF (50 cm^3) was added to a −78 °C stirred blue solution of liquid ammonia (300 cm^3), lithium (690 mg, 10 mmol) and 2-methylpropan-2-ol (740 mg, 10 mmol) in THF (40 cm^3). After 1 h, NH_4Cl (10 g) was added carefully to quench the reaction and the ammonia was allowed to evaporate. The residue was acidified with 10% aqueous HCl and extracted with EtOAc (2 × 100 cm^3). The combined organic layers were washed with brine (100 cm^3) and dried over Na_2SO_4. Solvent removal gave a solid which was purified by recrystallization from EtOAc–hexanes to give compound **21** (2.7 g, 85%) as white crystals, mp 137–139 °C (Found: C, 74.65; H, 10.4. $C_{20}H_{34}O_3$ requires C, 74.5; H, 10.6%); ν_{max}/cm^{-1} 3398, 2920, 1711, 1447, 1390, 1198, 1075; δ_H 3.37 (1H, t, *J* 8.2, CH-OBu^t), 1.12 [9H, s, $C(CH_3)_3$], 0.72 (3H, s, CH_3); δ_C 179.63 (C=O), 80.85 (C-3), 72.16 [O*C*$(CH_3)_3$], 28.68 [C(*C*$H_3)_3$], 11.70 (CH_3), 49.79, 43.77, 43.14, 41.97, 40.90, 39.44, 37.08, 34.78, 32.70, 31.04, 30.23, 29.38, 23.34.

[3*R*-(3α,3aα,5aβ,7α,9aα,9bβ)]-(Dodecahydro-3-hydroxy-3a-methyl-1*H*-benz[*e*]inden-7-yl)acetic acid methyl ester 22

A mixture of acid **21** (2.7 g, 8.4 mmol), EtOH (50 cm^3) and 6 M aqueous HCl (15 cm^3) was refluxed for 3 h under nitrogen. Most of the solvent was removed and the residue was extracted with EtOAc (2 × 50 cm^3). The combined organic layers were washed with water (2 × 50 cm^3) and brine (50 cm^3), and dried over Na_2SO_4. The solvent was removed to give an oil which was a mixture of the (3-hydroxy-1*H*-benz[*e*]inden-7-yl)acetic acid and the corresponding acid ethyl ester. The crude product was used in the next step without purification and characterization.

Acetyl chloride (1.0 cm^3) was added to a solution of crude product from the above reaction in MeOH (50 cm^3) under nitrogen, and the mixture was warmed to 50–55 °C for 6 h. The solvent was removed and EtOAc (50 cm^3) and water (50 cm^3) were added. The organic layer was separated and washed with saturated aqueous Na_2CO_3 (50 cm^3) and brine (50 cm^3), and dried over Na_2SO_4. Solvent removal gave the product as an oil which was purified by column chromatography (silica gel, 30% EtOAc in hexanes) to give product **22** (1.7 g, 72%) as a colorless oil; ν_{max}/cm^{-1} 3398, 2923, 1739, 1444, 1340, 1196, 1062; δ_H 3.62 (3H, s, OCH_3), 3.62–3.57 (1H, m, C*H*OH), 0.70 (3H, s, CH_3); δ_C 173.53 (C=O), 81.68 (C-3), 11.93 (CH_3), 51.31, 49.75, 43.55, 41.81, 40.97, 39.35, 36.51, 34.89, 32.64, 30.22, 30.14, 29.25, 22.90.

[3a*R*-(3aα,5aβ,7α,9aα,9bβ)]-(Dodecahydro-3a-methyl-3-oxo-1*H*-benz[*e*]inden-7-yl)acetic acid methyl ester 23

Jones reagent (8 M, ~1.0 cm^3) was added to a cold stirred (0–5 °C) solution of compound **22** (1.7 g, 6.1 mmol) in acetone (50 cm^3). After 5 min, the reaction was quenched by addition of propan-2-ol (2.0 cm^3), and EtOAc (100 cm^3) and brine (100 cm^3) were added. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 50 cm^3). The combined organic layers were dried over Na_2SO_4, and the solvent was removed to give a solid which was purified by recrystallization from hexanes to give product **23** (1.47 g, 87%) as white crystals, mp 76–78 °C (from hexanes) (Found: C, 73.6; H, 9.35. $C_{17}H_{26}O_3$ requires C, 73.35; H, 9.4%); ν_{max}/cm^{-1} 2924, 2859, 1741, 1445, 1375; δ_H 3.67 (3H, s, OCH_3), 0.88 (3H, s, CH_3); δ_C 221.17 (C=O), 173.35 (*C*O_2CH_3), 13.84 (CH_3), 51.37, 50.29, 48.37, 43.63, 41.74, 40.38, 39.21, 35.74, 34.81, 32.44, 31.42, 29.47, 28.82, 21.42.

[3*R*-(3α,3aα,5aβ,7α,9aα,9bβ)]-(3-Cyanododecahydro-3-methyl-1*H*-benz[*e*]inden-7-yl)acetic acid methyl ester 24a and [3*S*-(3α,3aβ,5aα,7β,9aβ,9bα)]-(3-cyanododecahydro-3a-methyl-1*H*-benz[*e*]inden-7-yl)acetic acid methyl ester 24b

A mixture of compound **23** (1.5 g, 5.3 mmol), diethyl cyanophosphonate (2.6 g, 15.8 mmol) and LiCN (0.5 g, 15.8 mmol) in dry THF (100 cm^3) was stirred for 30 min at room temperature. EtOAc (100 cm^3) was added to quench the reaction, and the solution was washed with brine (2 × 100 cm^3) and dried over Na_2SO_4. The solvent was removed to give a yellowish solid which was purified by column chromatography (silica gel, 50% EtOAc in hexanes). The product (2.24 g, 96%) was used for the next reaction without characterization.

The mixture of epimeric products (2.24 g, 5.07 mmol) from the above reaction, 2-methylpropan-2-ol (375 mg, 5.1 mmol) and SmI_2 (0.1 M solution in THF, 202 cm^3, 20.2 mmol) were stirred overnight at room temperature under nitrogen. Then 10% aqueous HCl (100 cm^3) was added and the mixture was extracted with EtOEt (2 × 100 cm^3). The combined organic layers were washed with brine (100 cm^3), 5% aqueous $Na_2S_2O_3$ (20 cm^3) and brine (100 cm^3), and dried over Na_2SO_4. The solvent was removed to give an oil which was purified by column chromatography (silica gel, 15% EtOAC in hexane) to give compounds **24a** and **24b** as an epimeric mixture (1.3 g, 82%). A portion (100 mg) of the epimeric compounds was separated by HPLC (Econosil, 25% EtOAc in hexanes) for product characterization.

Compound **24a** (48 mg) was obtained as white crystals, mp 50–52 °C (Found: C, 74.85; H, 9.35; N, 5.0. $C_{18}H_{27}NO_2$ requires

C, 74.7; H, 9.4; N, 4.8%); ν_{max}/cm^{-1} 2920, 2235, 1738, 1448, 1357, 1195, 1157; δ_H 3.65 (3H, s, OCH_3), 2.28 (1H, t, *J* 9.6, CHCN), 0.91 (3H, s, CH_3); δ_C 173.40 (CO_2CH_3), 121.32 (CN), 51.38 (OCH_3), 14.37 (CH_3), 53.19, 44.99, 43.23, 41.71, 41.22, 40.19, 39.09, 36.94, 34.75, 32.53, 30.56, 29.13, 26.45, 24.06.

Compound **24b** (39 mg) was obtained as white crystals, mp 83–85 °C (Found: C, 74.6; H, 9.3; N, 5.0. $C_{18}H_{27}NO_2$ requires C, 74.7; H, 9.4; N, 4.8%); ν_{max}/cm^{-1} 2923, 2233, 1738, 1447, 1383, 1192, 1153; δ_H 3.66 (3H, s, OCH_3), 2.56 (1H, dd, *J* 1.6, 7.4, CHCN), 0.91 (3H, s, CH_3); δ_C 173.40 (CO_2CH_3), 122.31 (CN), 51.41 (OCH_3), 18.12 (CH_3), 50.84, 44.86, 42.78, 41.83, 41.27, 40.00, 39.20, 34.98, 34.72, 32.61, 30.73, 29.23, 27.19, 24.24.

[3*R*-(3α,3aα,5aβ,7α,9aα,9bβ)]-Dodecahydro-7-(2-hydroxyethyl)-3a-methyl-1*H*-benz[*e*]indene-3-carbonitrile 8 and [3*S*-(3α,3aβ,5aα,7β,9aβ,9bα)]-dodecahydro-7-(2-hydroxyethyl)-3a-methyl-1*H*-benz[*e*]indene-3-carbonitrile 25

Red-Al® (3.4 M solution in toluene, 3.0 cm^3, 10.2 mmol) was added to a stirred solution of compounds **24a** and **24b** (1.0 g, 3.5 mmol) in dry CH_2Cl_2 (30 cm^3) at −78 °C. After 10 min, the reaction was allowed to warm to room temperature and stirring was continued for 1 h. The reaction mixture was cooled to 0 °C and propan-2-ol (1.0 cm^3) and aqueous 10% HCl were added. After extraction with CH_2Cl_2 (2 × 50 cm^3), the combined organic layers were washed with water (50 cm^3) and brine (50 cm^3), and dried over Na_2SO_4. The solvent was removed to give an oil which was purified by column chromatography (silica gel, 25% EtOAc in hexanes) to give compounds **8** and **25** as an epimeric mixture (0.8 g, 89%). The epimeric compounds were separated by HPLC (Ultrasphere-Si, 5 μm, 30% EtOAc in hexane, 3.0 cm^3 min^{-1}).

Compound **8** (0.47 g, 52%) was obtained as white crystals, mp 79–81 °C (from EtOEt–hexanes) (Found: C, 78.3; H, 10.3; N, 5.5. $C_{17}H_{27}NO$ requires C, 78.1; H, 10.4; N, 5.4%); $[a]_D^{22}$ −43.2 ($CHCl_3$, 97% ee); ν_{max}/cm^{-1} 3408, 2918, 2235, 1449, 1385, 1051; δ_H 3.64–3.61 (2H, m, C*H*$_2$OH), 2.25 (1H, t, *J* 9.5, CHCN), 0.88 (3H, s, CH_3); δ_C 121.43 (CN), 60.30 (CH_2OH), 14.05 (CH_3), 53.12, 44.71, 43.22, 41.34, 39.95, 39.87, 39.29, 36.76, 33.88, 32.62, 30.54, 29.03, 26.17, 23.79.

Compound **25** (0.21 g, 23%) was obtained as white crystals, mp 44–46 °C (from EtOEt–hexanes) (Found: C, 78.3; H, 10.6; N, 5.4. $C_{17}H_{27}NO$ requires C, 78.1; H, 10.4; N, 5.4%); ν_{max}/cm^{-1} 3365, 2920, 2233, 1474, 1385, 1095; δ_H 3.66 (2H, t, *J* 6.7, C*H*$_2$OH), 2.55 (1H, dd, *J* 6.8, 2.0, CHCN), 0.81 (3H, s, CH_3); δ_C 122.48 (CN), 60.55 (CH_2OH), 17.87 (CH_3), 50.84, 44.71, 42.83, 41.43, 40.04, 39.82, 39.49, 34.85, 33.95, 32.76, 30.76, 29.17, 26.98, 24.20.

[3*R*-(3α,3aα,5aβ,7α,9aα,9bβ)]-1-[Dodecahydro-7-(2-hydroxyethyl)-3a-methyl-1*H*-benz[*e*]inden-3-yl]ethanone 6 and [3*S*-(3α,3aβ,5aα,7β,9aβ,9bα)]-1-[dodecahydro-7-(2-hydroxyethyl)-3a-methyl-1*H*-benz[*e*]inden-3-yl]ethanone 26

Methylmagnesium chloride (3.0 M solution in THF, 5 cm^3, 15 mmol) was added to a mixture of compounds **8** and **25** (130 mg, 5 mmol) in dry THF under nitrogen. The reaction mixture was refluxed for 14 h, cooled to room temperature, and saturated aqueous NH_4Cl (50 cm^3) and then 10% aqueous HCl (50 cm^3) were added. The mixture was extracted with EtOEt (2 × 50 cm^3) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 cm^3) and brine (50 cm^3), and dried over Na_2SO_4. The solvent was removed to give a mixture of products **6** and **26** as an oil. The products were separated by column chromatography (silica gel, 1% CH_3CN in CH_2Cl_2).

Compound **6** (59 mg, 42%) was obtained as white crystals, mp 61–62.5 °C (Found: C, 77.7; H, 10.7. $C_{18}H_{30}O_2$ requires C, 77.65; H, 10.9%); $[a]_D^{22}$ −92.4 ($CHCl_3$, 96% ee); ν_{max}/cm^{-1} 3431, 2918, 1704, 1447, 1357, 1157, 1056; δ_H 3.70 (2H, m, C*H*$_2$OH), 2.55 (1H, t, *J* 9.0, CHCO), 2.11 (3H, s, $COCH_3$), 0.62 (3H, s, CH_3); δ_C 209.89 (CO), 60.83 (CH_2OH), 13.56 (CH_3), 63.88, 55.68, 44.95, 43.62, 41.33, 40.34, 39.75, 39.03, 34.29, 33.10, 31.60, 30.89, 29.83, 24.02, 22.78.

Compound **26** (36 mg, 26%) was obtained as white crystals, mp 47–49 °C (Found: C, 77.6; H, 11.0. $C_{18}H_{30}O_2$ requires C, 77.65; H, 10.9%); ν_{max}/cm^{-1} 3431, 2918, 1704, 1444, 1358, 1161, 1056; δ_H 3.59 (2H, t, *J* 6.6, C*H*$_2$OH), 2.75 (1H, dd, *J* 2.5, 8.2, CHCO), 2.07 (3H, s, $COCH_3$), 0.87 (3H, s, CH_3); δ_C 213.16 (CO), 60.48 (CH_2OH), 20.88 (CH_3), 61.17, 49.09, 46.37, 42.91, 41.41, 40.18, 39.70, 35.14, 34.12, 33.00, 32.74, 31.03, 29.60, 25.28, 24.14.

Biological evaluations

The methods used for the biological evaluations of benz[*e*]-indenes **5**–**8** are identical to those reported previously for the biological evaluations of steroids **1**–**4**.[3]

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