Chiral Derivatives of 2-Cyclohexylideneperhydro-4,7-methanoindenes, a Novel Class of Nonsteroidal Androgen Receptor Ligand: Synthesis, X-ray Analysis, and Biological Activity

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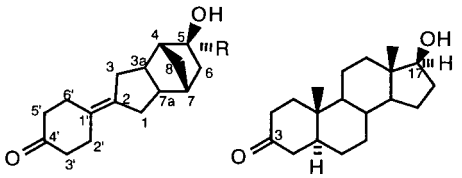
A series of 2-cyclohexylideneperhydro-4,7-methanoindene derivatives was synthesized as novel androgen receptor ligands. Asymmetric hydroboration of key intermediate **2** afforded single enantiomer alcohol derivatives (3a*R*)-**3** and (3a*S*)-**3** which could be further transformed to give 12 variously substituted keto alcohol target compounds. X-ray crystallography of the 4-bromobenzenesulfonyl ester (3a*S*)-**13** was used to establish their absolute configuration. The binding of these compounds to the rat ventral prostate androgen receptor showed moderate affinity with IC_{50} values of 1.2 μM and above but with substantial enantiomeric dependencies which varied in accordance to Pfieffer's rule. Surprisingly, the (3a*S*)-5α-alcohols displayed similar affinity to the (3a*R*)-5β-alcohols, and molecular modeling suggested an alternative mode of binding for the (3a*S*) series. The three compounds with the best androgen receptor affinity were assayed in vivo for antiandrogenic and androgenic effects on sex accessory organ growth in castrated immature rats and were found to be ineffective.

Introduction

Prostate cancer is an androgen-dependent disease which is known to respond to treatment with androgen receptor antagonists.[1] There are at present two broad classes of androgen receptor antagonists used clinically. The steroidal antagonists are typified by cyproterone acetate (Androcur)[2] which is, however, known to also interact with progestin and glucocorticoid receptors. In contrast, the second class comprises specific androgen receptor antagonists typified by the anilides flutamide,[3] bicalutamide (Casodex),[4] and the cyclic variant nilutamide (Anandron).[5]

We have recently reported the synthesis of racemic 2-cyclohexylideneperhydro-4,7-methanoindene derivatives which may be capable of mimicking the steroid nucleus.[6] We postulated that 2-cyclohexylideneperhydro-4,7-methanoindene derivatives of formula **I** would



I **1** (DHT)

be able to bind to the androgen receptor by virtue of their structural similarity to 5α-dihydrotestosterone (**1**, DHT) and may show useful antiandrogen activity. In this paper we give details of molecular modeling, synthesis, and androgen receptor affinity of a series of keto alcohols related to formula **I** and on the antiandrogen/androgen activity of those showing the highest affinity.

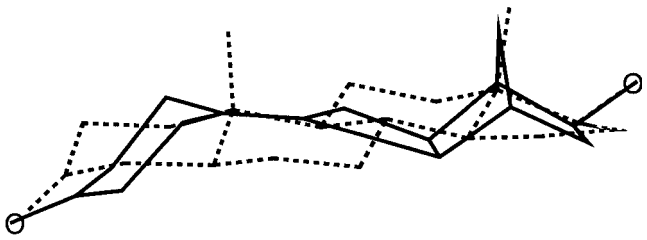


Figure 1. Computer-generated low-energy conformation of (3a*R*)-**4** superimposed onto the crystal structure of DHT (broken lines) so that the steroid oxygen atoms shown are matched. All hydrogen atoms are omitted.

Design Rationale

In molecular modeling studies it was found the global minimum MM energy conformation of (3a*R*)-**4** (i.e. formula **I**, R = H) was able to match position and directionality of the 3-keto and 17-hydroxy functions of a DHT crystal structure template[7] (Figure 1). The overall planarity of the ring systems showed good similarity, and both systems are rigid but with some conformational flexibility in the 'A-rings'. Figure 1 shows best fit is achieved with the analogue's A-ring in the pseudo-chair conformation flexed toward the α-side of the molecule. However, molecular mechanics calculations indicated that the pseudo-chair conformation flexed toward the β-side of the molecule is of similar energy so that we may expect roughly equal populations of the two conformations. For compound (3a*R*)-**4** the methylene bridge of the norbornene moiety occupied the same space as the steroid C-18 methyl, while the lack of a steroid C-19 methyl and the presence of a double

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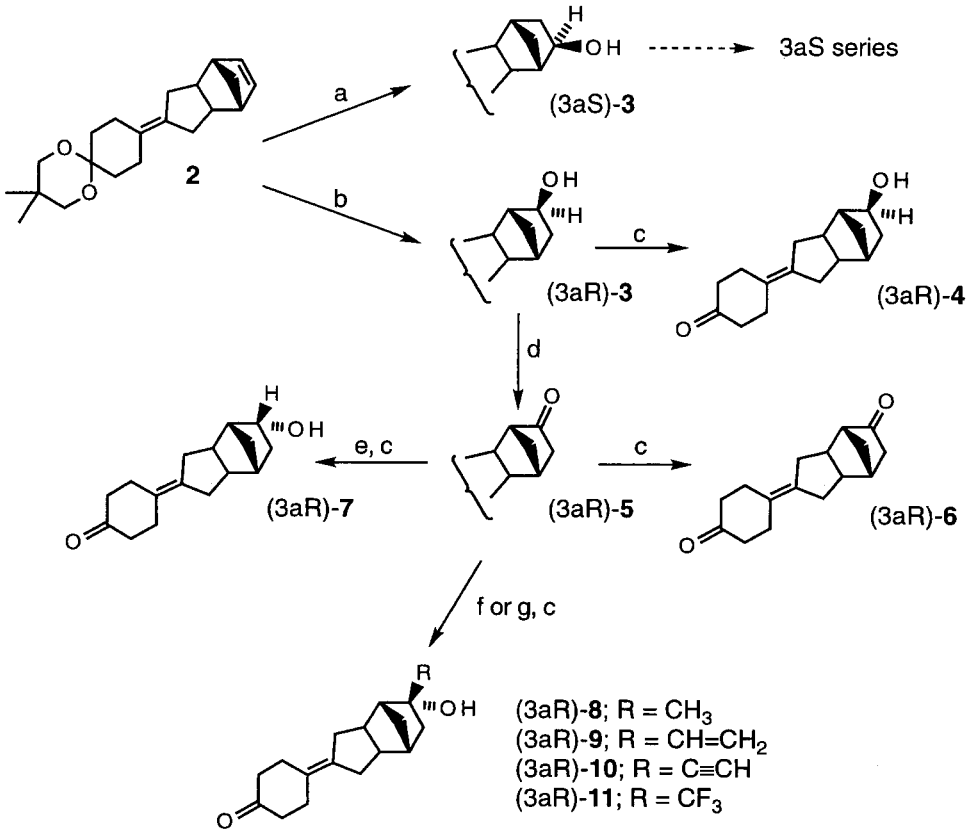
Scheme 1[a]

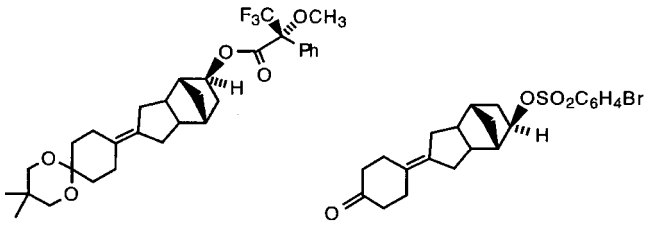


[a] Reagents: (a) (*R*)-diisopinocampheylborane, THF then H_2O_2, NaOH in MeOH; (b) (*S*)-diisopinocampheylborane, THF then H_2O_2, NaOH in MeOH; (c) *p*-TsOH·H_2O, acetone; (d) $PyHClCrO_3$, CH_2Cl_2; (e) $NaBH_4$, MeOH; (f) RMgX, THF or dimethyl ether; (g) CF_3SiMe_3, THF.

bond in this region was known to enhance steroidal androgen receptor affinity.[8] It was postulated that the similarity of the two structures would ensure good binding affinity of (3a*R*)-**4** to androgen receptors, while the differences, in particular the conformational freedom of the A-rings, may result in the desired antagonistic action.

Chemistry

The synthesis of the starting diene **2** has been described elsewhere.[6] We have investigated the asymmetric functionalization of the norbornene moiety in **2** by way of two methods that have been reported as successful using norbornene as a substrate. Asymmetric hydrosilylation of norbornene using trichlorosilane and the chiral catalyst resulting from the coordination of palladium(I) with (*R*)-MOP, followed by oxidation of the intermediate silane, has been reported to give norborneol in over 90% yield (e.e. 96%).[9] Application of this reaction to compound **2** gave only traces of alcohol product, the optical purity of which was not measured. However, asymmetric hydroboration of compound **2** using (*S*)-diisopinocampheylborane and oxidation of the intermediate borane afforded the alcohol (3a*R*)-**3** in good yield (Scheme 1), the configuration predicted by analogy with previous work by Brown.[10] Measurement of the enantiomeric composition of this product by ^{1}H NMR analysis in the presence of chiral shift reagents was unsuccessful as was also chromatographic or ^{1}H NMR analysis of diastereomeric esters derived from chiral acids. However, the 400-MHz ^{19}F NMR spectrum of the ester (3a*R*)-**12**, derived from (*R*)-MTPA, gave two well-separated resonances, one for each enantiomer, analysis of which indicated a 96% e.e of the (3a*R*) enantiomer.[11] Similarly, alcohol (3a*S*)-**3** was obtained using (*R*)-diisopinocampheylborane in e.e. of 96%. The optical rotations measured for (3a*R*)-(−)-**3** and (3a*S*)-(+)-**3** were as predicted by analogy with previous work by Brown[9] but too small to be of use as a measure of optical purity. Optical rotations were not measured routinely for subsequent derivatives since it was reasonable to assume that e.e. values would be conserved at 96% or more through subsequent transformations.



The alcohol (3a*R*)-**3** was transformed to give compounds (3a*R*)-**4**−**11** according to Scheme 1. Deprotection of the ketal function of (3a*R*)-**3** by acid-catalyzed transketalization gave the hydroxy ketone (3a*R*)-**4**. Oxidation of the alcohol (3a*R*)-**3** using Corey's reagent gave the intermediate ketone (3a*R*)-**5**, deketalization of which produced the dione (3a*R*)-**6**. The ketone (3a*R*)-**5** also underwent the following reactions: (i) reduction with

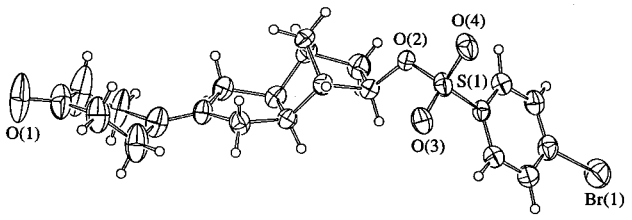
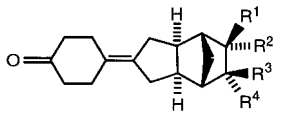


Figure 2. ORTEP diagram of (3a*S*)-**13**.

Table 1. IC_{50} Values for the Inhibition by Test Compounds of Specific [^{3}H]R1881 Binding to Rat Ventral Prostate Cytosolic Androgen Receptors



compd	R^1	R^2	R^3	R^4	$IC_{50} \pm SE$ (μM)	eudismic ratio
(3a*R*)-**4**	OH	H	H	H	3.9 ± 0.8	2.7
(3a*S*)-**4**	H	H	OH	H	10.4 ±1.0	
(3a*R*)-**7**	H	OH	H	H	35.9 ±2.6	15.5
(3a*S*)-**7**	H	H	H	OH	2.32 ± 0.71	
(3a*R*)-**8**	Me	OH	H	H	27.4 ± 6.9	22.8
(3a*S*)-**8**	H	H	Me	OH	1.20 ± 0.11	
(3a*R*)-**9**	CH=CH_2	OH	H	H	62.5 ± 14	6.4
(3a*S*)-**9**	H	H	CH=CH_2	OH	9.73 ± 0.47	
(3a*R*)-**10**	C≡CH	OH	H	H	57.0 ± 6.7	4.2
(3a*S*)-**10**	H	H	C≡CH	OH	13.5 ± 0.8	
(3a*R*)-**11**	CF_3	OH	H	H	41.2 ± 7.6	2.6
(3a*S*)-**11**	H	H	CF_3	OH	15.6 ± 6.1	
(3a*R*)-**6**	C=O		H	H	33.0 ± 2.8	2.3
(3a*S*)-**6**	H	H	C=O		14.2 ± 3.5	
DHT					3.2 ± 0.6 nM	
cyproterone acetate					18 ± 1.1 nM	

$NaBH_4$ and deketalization affording the α-alcohol (3a*R*)-**7**, (ii) addition with a variety of Grignard reagents to give, after deketalization, compounds (3a*R*)-**8**−**10**, and (iii) addition with trimethyl trifluoromethylsilane to give, after deketalization, (3a*R*)-**11.**

Likewise, the alcohol (3a*S*)-**3** was transformed to give compounds (3a*S*)-**4**−**11** using the synthetic methods shown in Scheme 1. The assigned absolute configurations of the two series were confirmed by X-ray crystallographic analysis of (3a*S*)-**13**, the 4-bromophenylsulfonyl ester of (3a*S*)-**4** (see Figure 2). In the crystal structure the pseudo-chair conformation of the A-ring is flexed toward the β-side of the molecule. This is apparently the preferred conformation with respect to maximization of crystal lattice energies.

Pharmacological Results and Discussion

To determine the affinity of 2-cyclohexylideneperhydro-4,7-methanoindene derivatives for androgen receptors, an in vitro binding assay was used and the compounds with the highest affinity were subsequently tested for antiandrogen activity in intact rats.

Binding affinities of test compounds for cytosolic rat ventral prostate androgen receptors were measured in competition experiments using [^{3}H]R1881 as previously described by Christiansen et al.[12] with the results presented in Table 1. Compounds (3a*R*)-**4**, (3a*S*)-**7**, and (3a*S*)-**8** were the most potent displaying moderate affinities (IC_{50} = 1.2−3.8 μM) approximately 500- and 100-fold less than that of DHT and cyproterone acetate, respectively.

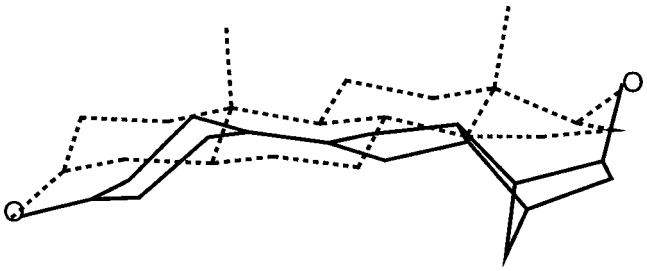


Figure 3. Computer-generated low-energy conformation of (3a*S*)-**7** superimposed onto the crystal structure of DHT (broken lines) so that the steroid oxygen atoms shown are matched. All hydrogen atoms are omitted.

Interestingly, the 5β-alcohol (3a*R*)-**4** and the 5α-alcohol (3a*S*)-**7** showed similar affinities. Molecular modeling indicated that both these molecules could match equally well the spatial arrangement and directionality of the hydroxyl and ketone pharmacophores of DHT but through different modes of binding, the (3a*S*)-5α-alcohols adopting an inverted orientation (cf. Figure 1 with Figure 3). While the methylene bridge of 5β-alcohol (3a*R*)-**4** neatly occupied a similar space to the 18-methyl group of DHT (Figure 1), the methylene bridge of the 5α-alcohol (3a*S*)-**7** protruded into a space below the α-face of DHT where a degree of nonpolar bulk is evidently tolerated (Figure 3). The A-ring for (3a*S*)-**7** gives the best match with a pseudo-chair conformation flexed toward the β-side of the molecule, as found in the crystal structure of (3a*S*)-**13** (Figure 2). The overall inferior match of the ring system in this inverted orientation with the steroid ring system is not accompanied by a reduction in affinity so that a minimal contribution from the novel ring system to the overall binding energy is implied, in either binding mode.

Increasing the electron-withdrawing capacity of the group at the 5β-position in compounds (3a*S*)-**9**−**11** produced only reductions in affinity, the trifluoromethyl derivative (3a*S*)-**11** being 1 magnitude less active than the methyl compound (3a*S*)-**8**. It is therefore probable that the known reduction of affinity accompanying the addition of a 17α-acetylenic group to 17β-hydroxy steroid androgen receptor ligands is also an electronic rather than steric effect.[13]

The presence of a hydrogen bond acceptor group at the 5-position in diones (3a*S*)-**6** and (3a*R*)-**6** led to reduced affinities relative to both 5α- and 5β-alcohols, indicating a receptor preference for a hydrogen bond-donating group at this position as has also been observed for the corresponding 17β-position in steroid androgen receptor ligands.[13]

Of the 5β-alcohols (3a*R*)-**4** and (3a*S*)-**4**, the (3a*R*) enantiomer was the more potent (the eutomer), showing 2.7 times higher affinity than the (3a*S*) enantiomer (the distomer). The 5α-alcohols showed greater stereoselectivity between enantiomers as indicated by their larger eudismic ratios (potency of eutomer/distomer) than the 5β-alcohols but with their (3a*S*) enantiomers being the eutomers suggesting a different binding mode (Figure 3) as was discussed above. The eudismic ratios observed for the 5α-alcohols (Table 1) vary in accordance with Pfeiffer's rule, that is, increasing with eutomer potency.[14]

Compounds (3a*R*)-**4**, (3a*S*)-**7**, and (3a*S*)-**8** were assayed for antiandrogenic activity by measuring their

effects on testosterone propionate-induced growth of the ventral prostate and seminal vesical in Weanling rats, using cyproterone acetate as a reference.[15] Compounds (3a*S*)-**7**, (3a*S*)-**8**, and (3a*R*)-**4** at 10, 30, and 60 mg/kg produced no dose-dependent reductions in prostate and seminal vesicle weight relative to controls, while cyproterone acetate at 15 mg/kg completely blocked testosterone propionate-induced growth in both organs (EC_{50} = 5 mg/kg) in a dose-dependent manner.

Compounds (3a*R*)-**4**, (3a*S*)-**7**, and (3a*S*)-**8** were assayed for androgenic activity by measuring their effects on growth of the ventral prostate and seminal vesicles in castrated immature rats, using testosterone propionate as a reference.[16] Compounds (3a*S*)-**7**, (3a*S*)-**8**, and (3a*R*)-**4** at 10, 30, and 60 mg/kg produced no significant increases in prostate and seminal vesicle weight relative to controls, while testosterone propionate at 3 mg/kg induced substantial growth in both organs. Tabulated results of these in vivo assays for antiandrogenicity and androgenicity are available as Supporting Information.

The effectiveness of parenterally administered androgens and androgen antagonists is dependent on the level of hepatic and renal metabolism, the extent of penetration into the target cell, the extent of metabolic conversion within the cell, and the affinity for the cytosolic androgen receptor protein. For androgens, the effectiveness of this drug−receptor complex in eliciting the required genomic changes is a further factor. The lack of antagonistic or agonistic activity of the test compounds at the doses used may be due to rapid first-pass hepatic metabolism, though metabolism of the 5β-alcohol does not appear to be implicated since compound (3a*R*)-**7**, with a tertiary 5β-alcohol which we would expect to be resistant to metabolism, is also inactive when injected ip. If metabolic deactivation is occurring, then rapid hepatic conversion of the A-ring ketone to the alcohol followed by conjugation is implied.

It could be argued that the inactivity of the new compounds in vivo was due to their moderate affinity for the cytosolic androgen receptors (for (3a*R*)-**7** K_i = 450 nM). However, this is unlikely since the steroidal androgen antagonist WIN 49596, which has K_i of 2.2 μM, is measurably antiandrogenic at 50 mg/kg sc in rats using a protocol similar to that employed by us, significantly inhibiting both ventral prostate and seminal vesicle growth.[17]

Conclusion

We have shown that chirally functionalized 2-cyclohexylideneperhydro-4,7-methanoindenes can be readily synthesized with excellent stereochemical control and are capable of acting as ligands of moderate affinity at androgen receptors. In vivo studies on sex accessory organ growth in castrated rats showed the compounds of best affinity to be incapable of eliciting late antiandrogenic or androgenic effects at the target sex accessory organs. It is probable that rapid metabolism caused insufficient drug bioavailability at the target sex accessory organs for these effects to be observed.

Experimental Section

General Instrumentation and Methods. ^{1}H and ^{13}C NMR data for compounds described herein were measured in $CDCl_3$ using a Varian Gemini-300 spectrometer. Chemical shifts are given in ppm downfield from the tetramethylsilane internal standard. ^{19}F NMR spectra were run on a 400-MHz Brüker spectrometer and chemical shifts were measured relative to C_6F_6 (−163 ppm). Melting points were determined on a Reichert hot stage apparatus and are uncorrected. Mass spectral data refer to chemical ionization using methane (unless indicated otherwise) 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. Elemental analysis was performed on a Perkin-Elmer 2400 elemental analyzer and all results were within 0.4% of theoretical values. All reactions were performed under a N_2 atmosphere. In the workup procedures, washing and drying refer to the use of water and anhydrous Na_2SO_4, respectively. Chromatographic separations were performed using short column vacuum chromatography on Merck silica gel H (TLC grade). X-ray crystallographic measurements were made and refined on an AFC7-R four-circle diffractometer employing graphite monochromated Cu Kα radiation. The structure was solved by direct methods using SHELXS-86.[18] The absolute configuration was established by refining the structure with all coordinates inverted. All calculations were performed using the teXsan[19] crystallographic software package of Molecular Structure Corp., and plots were drawn using ORTEP.[20]

[3a*R*(3aα,4β,5β,7β,7aα)]-(−)-2-(3,3-Dimethyl-1,5-dioxaspiro[5.5]undecan-9-ylidene)perhydro-4,7-methanoinden-5-ol [(3a*R*)-3]. A solution of (3aα,4β,7β,7aα)-2-(2,3,3a,4,7,7a-hexahydro-4,7-methano-1*H*-inden-2-ylidene)-3,3-dimethyl-1,5-dioxaspiro[5.5]undecane[6] (**2**) (4 g, 12.7 mmol) in THF (16 mL) was added dropwise to a stirred mixture of *(R)*-(−)-diisopinocampheylborane (6.6 g, 23 mmol) in THF (10 mL). The mixture was stirred at −30 °C for 24 h then allowed to warm to 0 °C. MeOH (5 mL) was added dropwise followed by 3 M NaOH (6 mL) then 27.5% H_2O_2 (8.3 mL) and the mixture was heated at 55 °C for 1 h. Most of the solvent was removed under reduced pressure then water (30 mL) added. The product was extracted with CH_2Cl_2 and the organic extracts washed then dried. Column chromatography of the isolated crude product gave first the starting diene **2** (0.67 g) then (−)-isocampheol and finally (3a*R*)-**3** as a colorless crystalline solid (2.62 g, 62%) which crystallized from CH_2Cl_2−hexane: mp 153−154 °C; $[\alpha]_D$ = −6.0° (c = 10, $CHCl_3$); MS (CI) m/z = 333 (67%, MH^+), 315 (100%, $MH^+ - H_2O$); ^{1}H NMR ($CDCl_3$) δ 3.76 (d, J = 6.7 Hz, 1 H, C*H*OH), 3.52 (s, 4 H, 2 × CH_2O), 2.54 (m, 2 H), 2.13 (m, 4 H), 2.02 (d, J = 4.5 Hz, 1 H), 1.99−1.84 (m, 5H), 1.78 (m, 4H), 1.64 (dd, J = 13.2, 7.4 Hz, 1 H), 1.36 (s, 2H), 1.23 (ddd, J = 13.1, 4.5, 1.9 Hz, 1 H), 0.98 (s, 6 H, 2 × CH_3); ^{13}C NMR δ 135.4 and 125.7 (C=C), 97.8 (CO_2), 74.1 (CHOH), 70.1 (CH_2O), 51.6, 46.1, 42.3, 42.2, 41.8, 35.8, 35.7, 32.8, 30.2, 28.8, 26.8, 22.8. Anal. ($C_{21}H_{32}O_3$) C, H. The e.e. was 95% as measured by ^{19}F NMR spectroscopy at 400 MHz of its Mosher's ester derivative compound (3a*R*)-**12** (see below).

[3a*S*(3aα,4β,5β,7β,7aα)]-(+)-2-(3,3-Dimethyl-1,5-dioxaspiro[5.5]undecan-9-ylidene)perhydro-4,7-methanoinden-5-ol [(3a*S*)-3]. Diene **2** (1.5 g, 4.8 mmol) was reacted with (*S*)-(+)-diisopinocampheylborane (2.47 g, 8.6 mmol) using the method described above for the preparation of (3a*R*)-**3** to provide compound (3a*S*)-**3** (1.02 g, 64%) which crystallized from CH_2Cl_2−hexane: mp 153−154 °C; $[\alpha]_D$ = +6.5° (c = 10, $CHCl_3$); MS (CI) m/z = 333 (100%, MH^+), 315 (10%, $MH^+ - H_2O$); NMR data of (3a*S*)-**3** were identical to that of (3a*R*)-**3**. Anal. ($C_{21}H_{32}O_3$) C, H. The e.e. was 96% as measured by ^{19}F NMR spectroscopy at 400 MHz of its Mosher's ester derivative (3a*S*)-**12** (see below).

Measurement of Enantiomeric Purity of Alcohols (3a*R*)-3 and (3a*S*)-3. Preparation of Mosher's Acid Esters (3a*R*)-12 and (3a*S*)-12. A solution of the alcohol (3a*R*)-**3** (10 mg, 0.03 mmol), 4-(dimethylamino)pyridine (20 mg, 0.163 mmol) and THF (1 mL) was treated with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride (38 mg, 0.15 mmol, prepared by treatment of the corresponding acid, e.e. 99%, with thionyl chloride) at 0 °C for 2 h. The reaction mixture was poured onto ice (5 g) and the product was extracted into CH_2Cl_2 (2 × 5 mL). The combined extracts were

washed sequentially with water (5 mL), 1 M HCl (2 × 5 mL), water (2 × 5 mL), dried, and evaporated under reduced pressure. The residue was chromatographed over silica gel to provide the Mosher's ester (3a*R*)-**12** as a colorless oil (12 mg, 72%) which was used for spectral measurements. Similarly, Mosher's ester (3a*S*)-**12** was prepared from the alcohol (3a*S*)-**3**. ^{19}F NMR ($CDCl_3$): for (3a*R*)-**12**, δ −68.3 (s, CF_3); for (3a*S*)-**12**, δ −68.2 (s, CF_3). ^{1}H NMR ($CDCl_3$): for (3a*R*)-**12** and (3a*S*)-**12**, δ 7.56−7.36 (m, 5 H, aryl), 4.85 (d, J = 7.0 Hz, 1 H, C*H*OC=O), 3.55 (s, 3 H, OMe), 3.52 (s, 4 H, 2 × CH_2O), 2.58 (m, 2 H), 2.20 (s, 1 H) 2.15 (m, 4 H), 2.1−1.87 (m, 5 H), 1.80 (m, 4 H), 1.55−1.33 (m, 3 H), 1.28 (d, J = 10.5 Hz, 1 H), 0.98 (s, 6 H, 2 × CH_3).

[3a*R*(3aα,4*β*,5*β*,7*β*,7aα)]-2-(4′-Oxocyclohexylidene)perhydro-4,7-methanoinden-5-ol [(3a*R*)-4]. A solution containing (3a*R*)-**3** (200 mg, 0.6 mmol) and *p*-toluenesulfonic acid (20 mg, 0.1 mmol) in Me_2CO (20 mL) was kept at 25 °C for 3 h. The mixture was neutralized with 1 M NaOH and most of the solvent was removed by evaporation under reduced pressure at 40 °C. The remaining solution was poured into water (20 mL), extracted with CH_2Cl_2 (2 × 20 mL), and the combined extracts washed then dried. Evaporation of the solvent under reduced pressure gave (3a*R*)-**4** (140 mg, 94%), which crystallized from MeOH as prisms: mp 108−109 °C; MS (CI) m/z = 247 (100%, MH^+), 229 (37%, $MH^+ - H_2O$); ^{1}H NMR ($CDCl_3$) δ 3.79 (d, J = 6.7 Hz,1 H, C*H*OH), 2.58 (m, 2H), 2.49−2.35 (m, 8H), 2.06−1.89 (m, 6H), 1.67 (ddd, J = 13.3, 6.9, 2.3 Hz, 1 H), 1.41 (d, J = 10.5 Hz, 1 H), 1.33 (d, J = 10.6 Hz, 1 H), 1.26 (ddd, J = 13.1, 4.5, 2.5 Hz, 1 H); ^{13}C NMR δ 212.8 (C=O), 139.1 and 122.8 (C=C), 74.5 (CHOH), 52.2, 46.8, 43.0, 42.3, 40.9, 36.7, 36.6, 29.0, 29.4. Anal. ($C_{16}H_{22}O_2$) C, H.

[3a*S*(3aα,4*β*,5*β*,7*β*,7aα)]-2-(4′-Oxocyclohexylidene)perhydro-4,7-methanoinden-5-ol [(3a*S*)-4]. Ketal (3a*S*)-**3** (200 mg, 0.6 mmol) was deprotected using the method described in the preparation of (3a*R*)-**4** from (3a*R*)-**3**, to give (3a*S*)-**4** which recrystallized from methanol as prisms (120 mg, 81%): mp 110−111 °C; MS (CI) m/z = 247 (100%, MH^+), 229 (28%, $MH^+ - H_2O$); NMR data of (3a*S*)-**4** were identical to that of (3a*R*)-**4**. Anal. ($C_{16}H_{22}O_2$) C, H.

[3a*R*(3aα,4*β*,7*β*,7aα)]-2-(3,3-Dimethyl-1,5-dioxaspiro-[5.5]undecan-9-ylidene)perhydro-4,7-methanoinden-5-one [(3a*R*)-5]. A solution of alcohol (3a*R*)-**3** (1.1 g, 3.3 mmol) in CH_2Cl_2 (10 mL) was added to a stirred mixture of pyridinium chlorochromate (1.75 g, 8.1 mmol) in CH_2Cl_2 (4 mL). After stirring at 25 °C for 1 h, Et_2O (50 mL) was added with stirring and the mixture was filtered through a bed of silica gel. The residue was washed thoroughly with Et_2O (3 × 10 mL). The combined filtrates were evaporated under reduced pressure to provide (3a*R*)-**5** (0.61 g, 56%) which crystallized from MeOH as colorless prisms: mp 143−144 °C; MS (CI) m/z = 331 (100%, MH^+); ^{1}H NMR ($CDCl_3$) δ 3.52 (s, 4 H, 2 × CH_2O), 2.66 (m, 2 H), 2.44−2.31 (m, 4 H), 2.18−1.97 (m, 7 H), 1.88−1.76 (m, 6H), 1.52 (d, J = 10.7 Hz, 1 H), 0.98 (3 H, s, CH_3), 0.97 (3 H, s, CH_3); ^{13}C NMR δ 217.65 (C=O), 134.25 and 126.70 (C=C), 97.6 (CO_2), 70.0 (CH_2O), 56.6, 45.7, 44.8, 42.1, 41.1, 36.0, 35.3, 32.8, 32.5, 31.8, 26.8, 22.7. Anal. ($C_{21}H_{30}O_3$) C, H.

[3a*S*(3aα,4*β*,7*β*,7aα)]-2-(3,3-Dimethyl-1,5-dioxaspiro-[5.5]undecan-9-ylidene)perhydro-4,7-methanoinden-5-one [(3a*S*)-5]. Alcohol (3a*S*)-**3** (0.55 g, 1.7 mmol) was oxidized using the method described in the preparation of (3a*R*)-**5** from (3a*R*)-**3**, to give (3a*S*)-**5** (0.43 g, 78%) which crystallized from MeOH as colorless prisms: mp 143−144 °C; MS (CI) m/z = 331 (100%, MH^+); NMR data of (3a*S*)-**5** were identical to that of (3a*R*)-**5**. Anal. ($C_{21}H_{30}O_3$) C, H.

[3a*R*(3aα,4*β*,7*β*,7aα)]-2-(4′-Oxocyclohexylidene)perhydro-4,7-methanoinden-5-one [(3a*R*)]-6. Ketal (3a*R*)-**5** (96 mg, 0.29 mmol) was deprotected using the method described in the preparation of (3a*R*)-**4** from (3a*R*)-**3**, to afford (3a*R*)-**6** which crystallized from hexane as a colorless powder (60 mg, 85%): mp 90−91 °C; MS (CI) m/z = 245 (100%, MH^+); ^{1}H NMR ($CDCl_3$) δ 2.68 (m, 2H), 2.44−2.28 (m, 12 H), 2.08−1.93 (m, 3 H), 1.83−1.69 (m, 2 H), 1.50 (d, J = 9.4 Hz, 1 H); ^{13}C NMR δ 217.6 and 212.8 (C=O), 137.9 and 123.8 (C=C), 57.1, 46.4, 45.2, 42.7, 41.9, 36.7, 40.7, 36.9, 36.2, 32.4, 28.9. Anal. ($C_{16}H_{20}O_2$) C, H.

[3a*S*(3aα,4*β*,7*β*,7aα)]-2-(4′-Oxocyclohexylidene)perhydro-4,7-methanoinden-5-one [(3a*S*)-6]. Ketal (3a*S*)-**5** (127 mg, 0.38 mmol) was deprotected using the method described for the preparation of (3a*R*)-**4** from (3a*R*)-**3**, to give (3a*S*)-**6** which crystallized from CH_2Cl_2−hexane as colorless prisms (84 mg, 89%): mp 88−89 °C; MS (CI) m/z = 245 (100%, MH^+); NMR data of (3a*S*)-**6** were identical to that of (3a*R*)-**6**. Anal. ($C_{16}H_{20}O_2$) C, H.

[3a*R*(3aα,4*β*,5α,7*β*,7aα)]-2-(4′-Oxocyclohexylidene)perhydro-4,7-methanoinden-5-ol [(3a*R*)-7]. Sodium borohydride (25 mg, 0.66 mmol) was added portionwise to a stirred solution of (3a*R*)-**5** (125 mg, 0.38 mmol) in MeOH (5 mL) at 0 °C over 1 h. The mixture was stirred at 0 °C for a further 30 min. Me_2CO (1 mL) was added and most of the solvent was removed by evaporation under reduced pressure. Water (10 mL) was added and the product was extracted into CH_2Cl_2 (3 × 10 mL). The combined extracts were washed, dried, and evaporated under reduced pressure to give the intermediate ketal which crystallized from MeOH as colorless prisms (80 mg, 64%): mp 144−146 °C; MS (CI) m/z = 333 (90.4%, MH^+), 315 (100%, $MH^+ - H_2O$); ^{1}H NMR ($CDCl_3$) δ 0.98 (6 H, 2 × CH_3), 3.52 (4 H, s, 2 × CH_2O), 4.16 (1 H, m, C*H*OH). Deprotection of the ketal (50 mg, 0.15 mmol) using the method described in the preparation of (3a*R*)-**4** gave (3a*R*)-**7** which recrystallized from Et_2O−hexane as colorless prisms: mp 112−114 °C (28 mg, 76%): MS (CI) m/z = 247 (34%, MH^+), 229 (100%, $MH^+ - H_2O$); ^{1}H NMR ($CDCl_3$) δ 4.20 (1 H, m, C*H*OH), 2.78 (m, 1 H), 2.64 (m, 2 H), 2.30−2.50 (m, 8 H), 2.28 (m, 1 H),2.06 (d, J = 4.0 Hz, 1 H), 1.80−2.03 (m, 5 H), 1.41 (d, J = 10.6 Hz, 1 H), 1.11 (d, J = 10.6 Hz, 1 H), 0.83 (d, J = 12.4 Hz, 1 H); ^{13}C NMR δ 212.8 (C=O), 138.6 and 122.2 (C=C), 72.4 (COH), 49.5, 47.4, 44.0, 40.4, 39.2, 37.0, 36.1, 31.9, 28.5. Anal. ($C_{16}H_{22}O_2$) C, H.

[3a*S*(3aα,4*β*,5α,7*β*,7aα)]-2-(4′-Oxocyclohexylidene)perhydro-4,7-methanoinden-5-ol [(3a*S*)-7]. The ketone (3a*S*)-**5** (150 mg, 0.45 mmol) was reduced with sodium borohydride and then deketalized using the method described for the preparation of (3a*R*)-**7** from (3a*R*)-**5** to give (3a*S*)-**7** which recrystallized from Et_2O−hexane as colorless prisms: mp 108−110 °C (87 mg, 78%); MS (CI) m/z = 247 (22%, MH^+), 229 (100%, $MH^+ - H_2O$); NMR data of (3a*S*)-**7** were identical to that of (3a*R*)-**7**. Anal. ($C_{16}H_{22}O_2$) C, H.

[3a*R*(3aα,4*β*,5α,7*β*,7aα)]-2-(4′-Oxocyclohexylidene)-5-methylperhydro-4,7-methanoinden-5-ol [(3a*R*)-8]. A solution of (3a*R*)-**5** (200 mg, 0.6 mmol) in dry Et_2O (10 mL) was added dropwise over 5 min to stirred ethereal methylmagnesium iodide (2.7 mL of a 1.5 M solution, 4 mmol)) at 0 °C and the mixture was stirred for 30 min at room temperature. Et_2O (20 mL) was then added followed by the dropwise addition of 10% NH_4Cl (20 mL). After stirring for 5 min, the aqueous layer was run off and the Et_2O layer was washed, dried, and evaporated under reduced pressure. The residue crystallized from Et_2O−hexane to give the intermediate ketal (177 mg, 84%) as colorless plates: mp 162−163 °C; MS (CI) m/z = 347 (59%, MH^+), 329 (100%, MH^+); ^{1}H NMR ($CDCl_3$) δ 0.97 (6 H, 2 × CH_3), 1.30 (3 H, s, CH_3), 3.52 (4 H, s, 2 × CH_2O); ^{13}C NMR δ 135.52 and 125.52 (C=C), 97.79 (COH). The intermediate ketal (80 mg, 0.23 mmol) was deprotected using the method described for the preparation of (3a*R*)-**4** affording (3a*R*)-**8** which crystallized from Et_2O−hexane as colorless prisms (55 mg, 92%): mp 111−113 °C; MS (CI) m/z = 243 (100%, $MH^+ - H_2O$); ^{1}H NMR ($CDCl_3$) δ 1.32 (3 H, s, CH_3); ^{13}C NMR δ 212.74 (C=O), 138.76 and 122.12 (C=C), 76.83 (COH). Anal. ($C_{17}H_{24}O_2$) C, H.

[3a*S*(3aα,4*β*,5α,7*β*,7aα)]-2-(4′-Oxocyclohexylidene)-5-methylperhydro-4,7-methanoinden-5-ol [(3a*S*)-8]. The ketone (3a*S*)-**5** (150 mg, 0.45 mmol) was reacted with methylmagnesium iodide and then deketalized according to the method described for the preparation of (3a*R*)-**8** from (3a*R*)-**5** to afford (3a*S*)-**8** which crystallized from Et_2O−hexane as colorless prisms (100 mg, 85%): mp 113−114 °C; MS (CI) m/z

= 243 (100%, $MH^+ - H_2O$); NMR data of (3a*S*)-**8** were identical to that of (3a*R*)-**8**. Anal. ($C_{17}H_{24}O_2$) C, H.

[3a*R*(3aα,4*β*,5α,7*β*,7aα)]-2-(4′-Oxocyclohexylidene)-5-ethenylperhydro-4,7-methanoinden-5-ol [(3a*R*)-9]. Vinylmagnesium bromide (1.7 mL of a 1 M solution in THF, 1.7 mmol) was added to a stirred solution of (3a*S*)-**5** (300 mg, 0.91 mmol) in dry Et_2O (10 mL) at 0 °C. The mixture was allowed to warm to 25 °C and stirring was continued for another 1 h. A solution of 10% NH_4Cl (20 mL) was added slowly and the product was extracted into Et_2O (3 × 20 mL). The combined extracts were washed, dried, and evaporated leaving a residue which crystallized from Et_2O−hexane to give the intermediate ketal as colorless plates (165 mg, 51%): mp 137−139 °C; MS (ammonia CI) 359 (100%, MH^+); ^{1}H NMR ($CDCl_3$) δ 0.98 (s, 6 H, 2 × CH_3), 3.53 (s, 4 H, 2 × CH_2 O), 5.01 (dd, J_{cis} = 10.5 and J_{gem} = 1.2 Hz, 1 H, terminal C=CH), 5.19 (dd, J_{trans} = 17 Hz and J_{gem} = 1.2 Hz, 1 H, terminal C=CH), 6.05 (dd, J = 17 and 10.5 Hz, 1 H, C*H*=CH_2); ^{13}C NMR δ 145.50 (*C*H=CH_2), 135.36 and 125.63 (inter ring C=C), 110.53 (CH=CH_2), 78.72 (COH). This intermediate ketal (120 mg, 0.33 mmol) was deprotected using the method described in the preparation of (3a*R*)-**4** to give (3a*R*)-**9** which crystallized from Et_2O−hexane as colorless prisms (85 mg, 93%): mp 101−102 °C; MS (CI) m/z = 273 (18%, MH^+), 255 (100%, $MH^+ - H_2O$); ^{1}H NMR ($CDCl_3$) δ 5.01 (dd, J_{cis} = 10.5 and J_{gem} = 1.2 Hz, 1 H, terminal C=CH), 5.19 (dd, J_{trans} = 17 Hz and J_{gem} = 1.2 Hz, 1 H, terminal C=CH), 6.05 (dd, J = 17 and 10.5 Hz, 1 H, C*H*=CH_2); ^{13}C NMR δ 212.69 (C=O), 145.4 (*C*H=CH_2), 138.59 and 122.18 (inter ring C=C), 110.73 (CH=*C*H_2), 78.68 (COH). Anal. ($C_{18}H_{24}O_2$) C, H.

[3a*S*(3aα,4*β*,5α,7*β*,7aα)]-2-(4′-Oxocyclohexylidene)-5-ethenylperhydro-4,7-methanoinden-5-ol [(3a*S*)-9)]. The ketone (3a*S*)-**5** (210 mg, 0.64 mmol) was reacted with vinylmagnesium bromide followed by deketalization according to the method described in the preparation of (3a*R*)-**9** from (3a*R*)-**5** to afford (3a*S*)-**9** which crystallized from Et_2O−hexane as colorless prisms (90 mg, 52%): mp 104−106 °C; MS (CI) m/z = 273 (18%, MH^+), 255 (100%, $MH^+ - H_2O$); NMR data of (3a*S*)-**9** were identical to that of (3a*R*)-**9**. Anal. ($C_{18}H_{24}O_2$) C, H.

[3a*R*(3aα,4*β*,5α,7*β*,7aα)]-2-(4′-Oxocyclohexylidene)-5-ethynylperhydro-4,7-methanoinden-5-ol [(3a*R*)-10]. Ethynylmagnesium bromide (3.6 mL of a 0.5 M solution in THF) was added to a stirred solution of (3a*R*)-**5** (250 mg, 0.76 mmol) in dry Et_2O (15 mL) at 0 °C. The solution was allowed to warm to 25 °C and stirring was continued for another 1 h. A solution of 10% NH_4Cl (20 mL) was added dropwise, the mixture stirred for 5 min then the Et_2O layer was run off. The aqueous layer was further extracted with Et_2O (2 × 15 mL) and the combined extracts were washed, dried, and evaporated under reduced pressure to give the intermediate ketal which crystallized from MeOH as colorless plates (248 mg, 92%): mp 180−181 °C; MS (CI) m/z = 357 (100%, MH^+), 339 (60%, $MH^+ - H_2O$); ^{1}H NMR ($CDCl_3$) δ 1.00 (s, 6 H, 2 × CH_3), 2.51 (s, 1 H, C≡CH), 3.54 (s, 4 H, 2 × CH_2O); ^{13}C NMR δ 134.93 and 125.94 (C=C), 89.78 (*C*≡CH), 72.8 (*C*≡CH), 70.79 (COH). This ketal (161 mg, 0.45 mmol) was deprotected using the method described in the preparation of (3a*R*)-**4** to give (3a*R*)-**10** which crystallized from Et_2O−hexane as colorless prisms (111 mg, 91%): mp 148−149 °C, MS (CI) m/z = 271 (13%, MH^+), 255 (100%, MH^+- H_2O); ^{1}H NMR ($CDCl_3$) δ 2.52 (s, 1 H, C≡CH); ^{13}C NMR δ 138.1 and 122.5 (C=C), 89.6 (*C*≡CH), 72.7 (C≡*C*H), 71.0 (COH). Anal. ($C_{18}H_{22}O_2$) C, H.

[3a*S*(3aα,4*β*,5α,7*β*,7aα)]-2-(4′-Oxocyclohexylidene)-5-ethynylperhydro-4,7-methanoinden-5-ol [(3a*S*)-10]. The ketone (3a*S*)-**5** (185 mg, 0.56 mmol) was reacted with ethynylmagnesium bromide and then deketalized according to the method described in the preparation of (3a*R*)-**10** from (3a*R*)-**5** to give (3a*S*)-**10** which crystallized from Et_2O−hexane as colorless needles (124 mg, 82%): mp 142−143 °C; MS (CI) m/z = 271 (13%, MH^+), 255 (100%, $MH^+ - H_2O$); NMR data of (3a*S*)-**10** were identical to that of (3a*R*)-**10**. Anal. ($C_{18}H_{22}O_2$) C, H.

[3a*R*(3aα,4*β*,5α,7*β*,7aα)]-2-(4′-Oxocyclohexylidene)-5-trifluoromethylperhydro-4,7-methanoinden-5-ol [(3a*R*)-11]. To an ice-cold solution of the ketone (3a*R*)-**5** (200 mg, 0.61 mmol) in dry THF (2 mL) were added CF_3SiMe_3 (2.4 mL of 0.5M in THF, 0.6 mmol) and Me_4NF (10 mg). The mixture was stirred at 0 °C for 30 min and then at 25 °C for 1 h. After evaporation of the THF under reduced pressure, the residue was redissolved in MeCN (5 mL) and 45% aqueous HF (1 mL) added. TLC showed that complete desilylation and deketalization occurred after 30 min. The mixture was shaken with 20% aqueous K_2CO_3 (10 mL) and extracted into Et_2O (2 × 20 mL) washed and dried then evaporated under reduced pressure to give (3a*R*)-**11** which recrystallized from CH_2Cl_2−hexane as colorless needles (114 mg, 60%): mp 163−164 °C; MS (CI) m/z = 315 (100%, MH^+), 297 (12, $MH^+ - H_2O$); ^{19}F NMR ($CDCl_3$) δ 81.66 (s, CF_3). Anal. ($C_{17}H_{21}O_2F$) C, H.

[3a*S*(3aα,4*β*,5α,7*β*,7aα)]-2-(4′-Oxocyclohexylidene)-5-trifluoromethylperhydro-4,7-methanoinden-5-ol [(3a*S*)-11]. The ketone (3a*S*)-**5** (150 mg, 0.45 mmol) was treated with CF_3SiMe_3 and then deprotected according to the method described in the preparation of (3a*R*)-**11** from (3a*R*)-**5** to give (3a*S*)-**11** which crystallized from CH_2Cl_2−hexane as colorless needles (88 mg, 62%): mp 162−163 °C; MS (CI) m/z = 315 (100%, MH^+), 297 (9, $MH^+ - H_2O$); NMR data of (3a*S*)-**11** were identical to that of (3a*R*)-**11**. Anal. ($C_{17}H_{21}O_2F_3$) C, H.

[3a*S*(3aα,4*β*,5*β*,7*β*,7aα)]-2-(4′-Oxocyclohexylidene)perhydro-4,7-methanoinden-5-ol 4-Bromobenzenesulfonate [(3a*S*)-13]. A solution of (3a*S*)-**3** (260 mg, 0.78 mmol) in pyridine (10 mL) was treated with 4-bromobenzenesulfonyl chloride (0.5 g, 1.95 mmol) at 25 °C for 16 h. The reaction mixture was poured into cold water (100 mL) and the solids were filtered off, dried, and recrystallized from Et_2O−hexane as colorless plates (300 mg, 54%). This ketal (250 mg, 45 mmol) was deprotected using the method described in the preparation of (3a*R*)-**4** to afford (3a*S*)-**13** which crystallized from CH_2Cl_2−hexane as colorless prisms (190 mg, 90%): mp 112−113 °C; ^{1}H NMR δ 7.77 (d, J = 8.8 Hz, 2 H), 7.69 (d, J = 8.8 Hz, 2 H), 4.46 (dd, J = 6.6, 2.5 Hz, 1 H), 2.57 (m, 2 H), 2.46−2.33 (m, 8 H), 2.22 (s, 1 H), 2.07 (d, J = 4.8 Hz, 1 H), 1.95 (m, 4 H), 1.68−1.49 (m, 2H), 1.40 (s, 2 H); ^{13}C NMR δ 212.3 (C=O), 137.6, 136.7, 132.5, 129.1, 128.6, 122.9, 84.9, 49.1, 46.1, 41.9, 41,8, 39.0, 35.9, 35.8, 29.4, 28.3. Anal. ($C_{22}H_{25}BrO_4S$) C, H

Crystallographic Data and Data Collection Parameters for (3a*S*)-13. [3a*S*(3aα,4*β*,5*β*,7*β*,7aα)]-2-(4′-Oxocyclohexylidene)perhydro-4,7-methanoinden-5-ol 4-bromosulfonate [(3a*S*)-**13**] crystallized from CH_2Cl_2−hexane as colorless prisms: mp 112−113 °C, $C_{22}H_{25}BrO_4S$, M = 465.41, orthorhombic, space group $P2_12_12_1$ (No. 19); cell constants a = 11.372(4) Å, b = 18.373(3) Å, c = 10.164(3) Å; V = 2123.9(8) Å^3, D_c (Z = 4) = 1.523 g cm^{-3}, crystal dimensions 0.35 × 0.25 × 0.20; reflections measured 1834, reflections used 1345, R = 0.046, R_w = 0.054.

Biological Assays. A. [^{3}H]R1881 Radioligand Binding Assay. Binding affinities of test compounds for cytosolic rat ventral prostate androgen receptors were measured in competition experiments using [^{3}H]R1881 as previously described[12] but with minor modifications. Briefly, adult male rats were castrated and 24 h later sacrificed and their ventral prostates removed. All subsequent operations were performed at 4 °C. This tissue was homogenized in 10 vol of TEMDG buffer (10 mM Tris, 1.5 mM EDTA, 10 mM Na_2MoO_4, 1 mM dithiothreitol, 10% glycerol, pH = 7.4) and centrifuged at 100000*g* for 1 h. Aliquots of the supernatant cytosol were incubated in the dark at 4 °C with [^{3}H]R1881 (2 nM final concentration), triamcinolone acetonide (1 μM final concentration), and reference or test compounds dissolved in TEMDG buffer/EtOH (final solvent composition TEMDG buffer/1% EtOH). After 2 h, a dextran T-70/γ-globulin-coated charcoal suspension (10% charcoal, 0.5% dextran T-70, 0.5% γ-globulin in TEMDG buffer) was added to the ligand/cytosol mixture and incubated at 4 °C for 10 min. Nonspecific binding was assessed by addition of an 100-fold excess of [^{3}H]R1881. Centrifugation for 5 min at 1300*g* removed the charcoal from solution and the supernatant was counted. Displacement binding data were analyzed according to a single-site model using a computerized nonlinear fitting program (PRISM)[20] to calculate IC_{50} values.

B. Antiandrogenic Activity in Castrated Immature Rats. The effects of compounds (3a*R*)-**4**, (3a*S*)-**7** and (3a*S*)-**8** (10, 30 and 60 mg/kg) and cyproterone acetate (5 and 15 mg/kg) on testosterone propionate-induced weight increases of ventral prostate and seminal vesicles in immature castrated rats were measured as previously reported.[15] Weanling Sprague−Dawley rats (75−80 g) were castrated and, 24 h after castration, put into weight-matched groups of 5 animals each and injected sc with test drugs (or vehicle) and testosterone propionate (0.5 mg/kg) dissolved in 5% benzyl alcohol/sesame oil for 8 days in a 10-day program with a 2-day break after day 4. On day 11 the rats were sacrificed, ventral prostates and seminal vesicles removed and fixed for 24 h in 10% formaldehyde before dissection and weighing. One-way ANOVA was used to determine statistical significance followed by post hoc Scheffe *F*-test when appropriate.

C. Androgenic Activity in Castrated Immature Rats. The effects of compounds (3a*R*)-**4**, (3a*S*)-**7** and (3a*S*)-**8** (10, 30 and 60 mg/kg) and testosterone propionate (0.5 mg/kg) in inducing growth of the ventral prostate and seminal vesicles in immature castrated rats were measured as previously reported.[16] Sprague−Dawley rats (170−180 g) were castrated and, 7 days after castration, put into weight-matched groups of 5 animals each and injected sc with test drugs dissolved in 5% benzyl alcohol/sesame oil for 9 days in a 9-day program with a 2-day break after day 4. On day 10 the rats were sacrificed, ventral prostates and seminal vesicles removed and fixed for 24 h in 10% formaldehyde before dissection and weighing. One-way ANOVA was used to determine statistical significance followed by post hoc Scheffe *F*-test when appropriate.

Molecular Modeling. Molecules (3a*R*)-**4** and (3a*S*)-**7** were built and molecular mechanics optimized using CHEM-X.[22] These were fitted to the crystal structure of DHT[7] using the steroid 3-keto and 17β-hydroxyl oxygen atoms as guides for the corresponding oxygen atoms in (3a*R*)-**4** and (3a*S*)-**7**, using a rigid fit routine with equal weighting (rms values of 0.09 and 0.18 Å were achieved, respectively). 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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Supporting Information Available: Crystallographic data for (3a*S*)-**13** as a CIF file; table listing elemental analyses; tables showing the effects of compounds (3a*R*)-**4**, (3a*S*)-**7**, and (3a*S*)-**8** and cyproterone acetate on testosterone propionate-induced weight increases of ventral prostate and seminal vesicles in immature castrated rats; tables showing the effects of compounds (3a*R*)-**4**, (3a*S*)-**7**, and (3a*S*)-**8** and testosterone propionate in inducing growth of the ventral prostate and seminal vesicles in immature castrated rats. This material is available free of charge via the Internet at http://pubs.acs.org.

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