Stereoselective Total Synthesis of Testosterone and Androsterone *via* A/B-Ring Construction of the Steroidal Ring System by Intramolecular Diels–Alder Reaction

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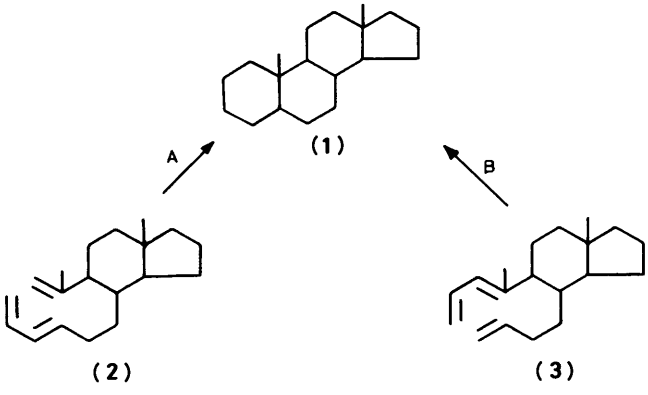
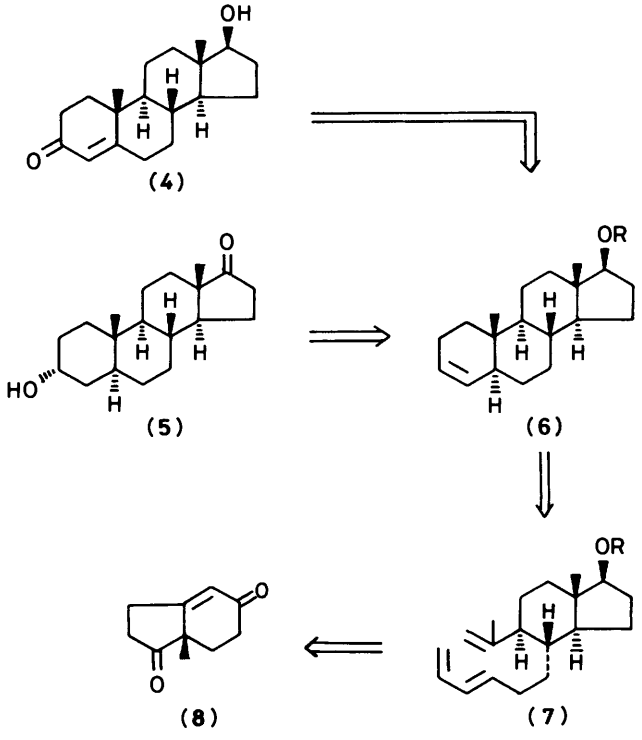
The optically active indandione (**8**) was stereoselectively converted into the (*E*)-triene (**23**), which was subjected to an intramolecular Diels–Alder reaction to give quantitatively A/B-*trans* and A/B-*cis* isomers (**24**) and (**26**) in ratios of 4:1 and 3.8:1. The cycloadduct (**24**) was transformed into testosterone (**4**) and androsterone (**5**).

Numerous methods have been exploited for the total synthesis of steroids which are widely distributed in Nature and which possess practical medical importance. Recently, intramolecular Diels–Alder reaction was shown to offer a versatile method for the stereoselective synthesis of steroids. Particularly, cycloaddition of *o*-quinodimethanes provided an extremely effective assembly of the B/C-ring system.[1] C/D-Ring formation by this strategy was also fruitful.[2] Furthermore, Stork developed an efficient approach through the intramolecular cycloaddition of a *trans*-hydrindan derivative.[3] Moreover, two routes, A and B, are possible for the construction of the steroidal A/B-ring system [(**1**); Scheme 1] but no such approach has been recorded,



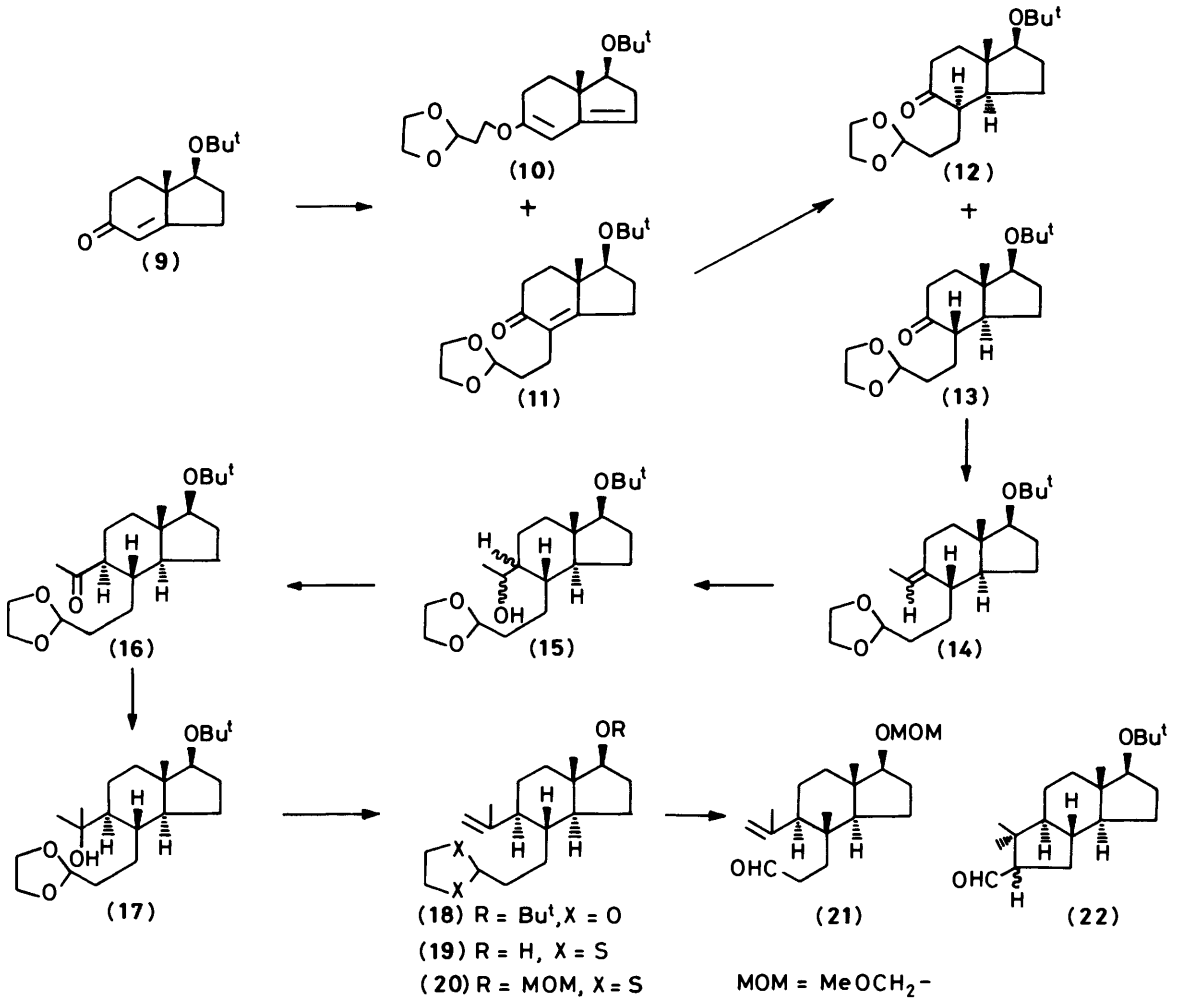
Scheme 1.



Scheme 2.

although these are expected to lead to a straightforward synthesis of saturated steroids.[4] Since it was considered that the stereoselective preparation of the triene (**2**) was easier than that of (**3**), a total synthesis of the androgens testosterone (**4**)[5] and androsterone (**5**)[6] was planned as shown in Scheme 2, in which the stereoselective formation of the *trans*-fused adduct (**6**) is considered to be crucial for the synthesis of the male hormones. It is known that the stereochemical course of the cycloaddition of deca-1,3,9-trienes to bicyclo[4.4.0]decenes is varied by the substituents and depends upon the conformational stability of the intermediates.[7] From a preliminary inspection of Dreiding and CPK molecular models, cycloaddition of an (*E*)-triene (**7**) would appear to favour formation of the *trans*-fused compound (**6**). Therefore the stereoselective synthesis of the (*E*)-triene (**7**) was devised starting from the easily available optically active indandione (**8**).[8]

Condensation of the indanone (**9**)[9] derived from dione (**8**)[8] with 2-(2-bromoethyl)-1,3-dioxolane[10] in the presence of sodium hydride in dimethyl sulphoxide (DMSO)[11] gave the acetal (**11**) in 68% yield along with the ether (**10**) in 17% yield, separable by silica gel column chromatography. Catalytic hydrogenation of enone (**11**) with 2.5 atm of hydrogen in the presence of 10% palladium–charcoal in ethanol followed by equilibration[12] of the crude product with sodium methoxide in hot methanol afforded the desired ketone (**13**) in 73% yield and its epimer (**12**) in 6% yield. Wittig reaction of ketone (**13**) with ethyltriphenylphosphonium bromide and n-butyl-lithium in tetrahydrofuran (THF) produced the olefin (**14**) in 95% yield as an inseparable mixture of two isomers. The n.m.r. spectrum ($CDCl_3$) of alkene (**14**) showed the angular methyl groups at δ_H 0.73 and 0.85 in the ratio *ca.* 3:1. The mixture was subjected to hydroboration–oxidation using borane–dimethyl sulphide complex followed by alkaline hydrogen peroxide to give the secondary alcohol (**15**) as a mixture of four dia-

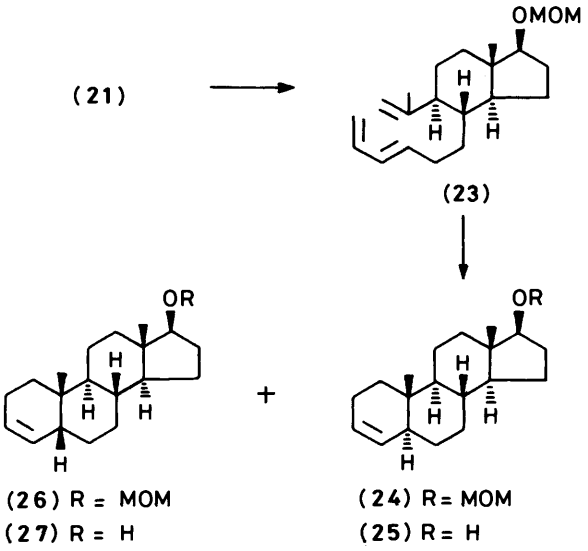


Scheme 3.

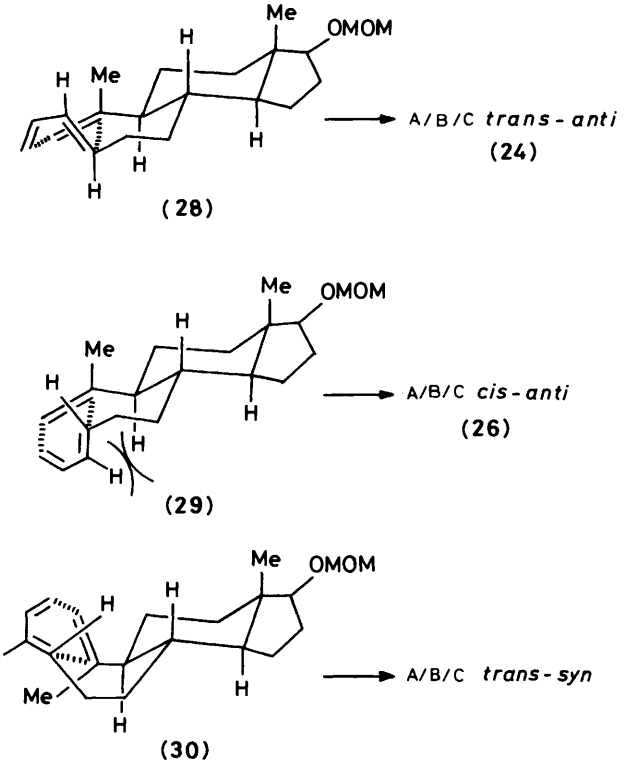
stereoisomers, which was oxidised with chromium trioxide in pyridine without separation. Reaction of the mixture of the resulting two ketones with sodium methoxide in methanol gave rise to an epimerisation to afford the ketone (**16**) as the sole product in 86% overall yield from (**14**). Thus the stereochemistry at the five chiral centres on the C/D-ring system was correctly arranged. Formation of the exoceplic olefin (**18**) was selectively performed in two steps, methylation with methyl-lithium (92% yield) followed by dehydration using phosphoryl trichloride and pyridine (82% yield). Direct deprotection of the acetal group was troublesome; ring formation giving the tricycle (**22**) easily occurred even under the mild acidic conditions used. Deblocking was therefore carried out *via* exchange with a dithioacetal function. Thus, treatment of acetal (**18**) with ethanedithiol in the presence of boron trifluoride–diethyl ether gave in 92% yield the thioacetal (**19**), whose hydroxy group was then protected as the methoxymethyl ether (**20**) in 81% yield. Heating compound (**20**) with methyl iodide and sodium carbonate in aqueous acetonitrile[13] afforded the aldehyde (**21**) in 59% yield (Scheme 3).

Diene formation was attempted by two different procedures which were reported as methods for the selective synthesis of (*E*)-dienes; (A) reaction with allyldiphenylphosphine oxide and n-butyl-lithium in the presence of hexamethylphosphoric triamide (HMPA)[14] and (B) the reaction with allylmagnesium bromide followed by mesylation* and elmination.[15] The exact *E*/*Z* ratios of the triene (**23**), obtained in 37 and 74% yield respectively, were not made clear by spectroscopic or h.p.l.c. analyses. Diels–Alder reaction of the triene (**23**), prepared by both methods, was conducted by heating a toluene solution in the presence of a catalytic amount of Methylene Blue[7e,f] at 220 °C in a sealed tube. After reaction for 100 h, the starting material had completely disappeared and the tetracyclic products were quantitatively formed. It was observed that the reaction proceeded quite slowly in the absence of Methylene Blue. Although the stereoisomers of the products were not separable at this stage, n.m.r. spectra of the crude products indicated that A/B-*trans* (**24**) and A/B-*cis* isomers (**26**) were obtained (Scheme 4) in the ratios 4.0:1 and 3.8:1 from the triene (**23**) prepared by methods A and B, respectively, on the basis of the integrations of the C-19 methyl hydrogens. Separation of two isomers was achieved by h.p.l.c. after conversion into the hydroxy compounds (**25**) and (**27**) by the reaction with ethanethiol and boron trifluoride–diethyl ether,[16] and the above ratios were further confirmed by h.p.l.c. The major product (**25**), m.p. 151—152 °C $[\alpha]_D^{20}$ +49° (chloroform) and the minor one (**27**), m.p. 135.5—136 °C, were identified as the A/B-*trans* and the A/B-*cis* isomers on the basis of direct comparison with authentic sample[18] prepared from testosterone (**4**).

* Mesyl (Ms) = methanesulphonyl

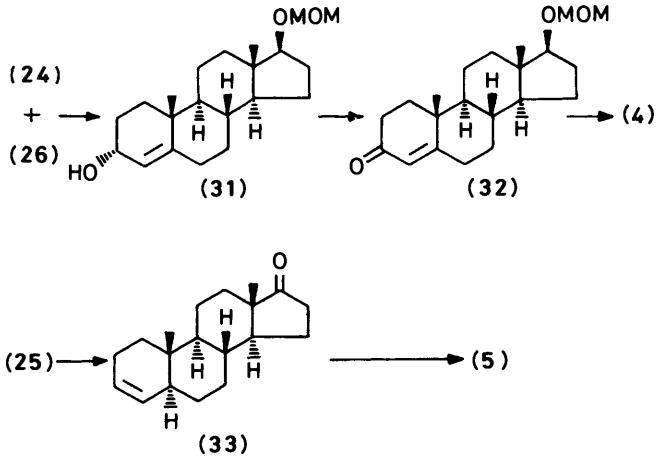


Scheme 4.



The preferred formation of the *trans*-fused isomer, as was expected, can be explained by the consideration of the transition states. The intermediate (**29**) leading to the *cis*-fusion intermediate (**26**) suffers from a severe non-bonded interaction between the vinylic hydrogen and the axial 9-H. Furthermore the transient (**30**) leading to the unnatural isomer has the thermodynamically unstable boat form. On the other hand, the intermediate to the desired compound (**24**) can take a more favourable conformation (**28**). The conformation required for the formation of compound (**24**) from the (*Z*)-triene would not be possible from consideration of molecular models.

Transformation of the cycloadduct into testosterone (**4**),[5] the most biologically active male hormone, was accomplished through oxidation with singlet oxygen. Thus, irradiation of the mixture of cycloadducts (**24**) and (**26**) in the presence of hematoporphyrin in pyridine under oxygen atmosphere with a halogen lamp, followed by treatment of the crude product with sodium iodide,[19] produced the 3α-hydroxy compound (**31**) together with a small amount of the methoxymethyl ether of testosterone, enone (**32**). The crude product was oxidised with manganese dioxide to give the enone (**32**) in 46% overall yield from the cycloadducts (70% overall yield based on the consumed cycloadducts). Some starting material was recovered after column chromatography on silica gel. Oxidation of the allylic alcohol (**31**) with pyridinium chlorochromate (PCC) afforded the enone (**32**) in 44% overall yield (68% overall yield based on the consumed cycloadducts). Deprotection of enone ether (**32**) with ethanethiol and boron trifluoride–diethyl ether[16] furnished, in 96% yield, testosterone (**4**), m.p. 157—158 °C $[\alpha]_D^{15}$ +105° (ethanol), which was identical with an authentic sample in all respects. Furthermore the alcohol (**25**) was oxidised with chromium trioxide in pyridine in 52% yield to the ketone (**33**), which has previously been transformed into androsterone (**5**) in three steps.[20] Thus stereoselective total synthesis of testosterone and androsterone (Scheme 5) was accomplished *via* construction of the A/B-ring system by intramolecular Diels–Alder reaction.



Scheme 5.

Experimental

General Methods.—M.p.s were determined on a Yanaco micro melting point apparatus and are uncorrected. I.r. spectra were taken with a Hitachi 215 spectrophotometer, n.m.r. spectra with JEOL-PMX-60 and JEOL-PS-100 spectrometers ($SiMe_4$ as internal references), and mass spectra with Hitachi M-52G and JMS-01SG-2 spectrometers. Optical rotations were measured on a JASCO DIP-4 apparatus, while h.p.l.c. was carried out on a Hitachi 635 instrument. After extraction, the organic solutions were dried over anhydrous sodium sulphate.

(+)-(1S,7aS)-4-[2-(1,3-*Dioxolan*-2-*yl*)*ethyl*]-7,7a-*dihydro*-7a-*methyl*-1-*t*-*butoxyindan*-5(6H)-*one* (**11**) *and* (1S,7aS)-5-[2-(1,3-*Dioxolan*-2-*yl*)*ethoxy*]-2,6,7,7a-*tetrahydro*-7a-*methyl*-1-*t*-*butoxy*-1H-*indene* (**10**).—To a suspension of NaH (60% in mineral oil; 900 mg, 22.5 mmol), washed with n-hexane and dried, in dry DMSO (25 ml) was added dropwise a solution of the butoxyindanone (**9**) (4.755 g, 21.4 mmol) in dry DMSO (45 ml) at room temperature and the mixture was stirred for 3.5 h at the same temperature under N_2. When gas evolution had

ceased, a solution of 2-(2-bromoethyl)-1,3-dioxolane (4.406 g, 23.6 mmol) in dry DMSO (25 ml) was added dropwise and the mixture was stirred overnight. After addition of saturated aqueous NH_4Cl, the resulting mixture was extracted with ether and the extract was washed with saturated aqueous NaCl and dried. Evaporation of the solvent afforded a residue, which was subjected to chromatography on silica gel. Elution with n-hexane–AcOEt (9:1 v/v) gave the ether (**10**) (1.172 g, 17%) as an oil; $\delta_H(CCl_4)$ 0.87 (3 H, s, Me), 1.15 (9 H, s, Bu^t), 3.30 (2 H, t, *J* 7.5 Hz, OCH_2CH_2), and 4.87 [1 H, t, *J* 5 Hz, $CH(OCH_2)_2$]; *m/z* 322 (M^+).

Further elution with n-hexane–AcOEt (7:3 v/v) gave the *enone* (**11**) (4.692 g, 68%), which was recrystallised from EtOH to afford needles, m.p. 116 °C (Found: C, 70.5; H, 9.15. $C_{19}H_{30}O_4$ requires C, 70.75; H, 9.4%); $[\alpha]_D^{20}$ +31° (*c* 0.21 in $CHCl_3$); $\nu_{max.}(CHCl_3)$ 1 640 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 1.07 (3 H, s, Me), 1.17 (9 H, s, Bu^t), and 4.81 [1 H, t, *J* 4 Hz, $CH(OCH_2)_2$]; *m/z* 322 (M^+).

(+)-(1S,3aS,4S,7aS)- *and* (1S,3aS,4R,7aS)-4-[2-(1,3-*Dioxolan*-2-*yl*)*ethyl*]-3a,6,7,7a-*tetrahydro*-7a-*methyl*-*t*-*butoxyindan*-5(4H)-*one* (**13**) *and* (**12**).—A mixture of the above enone (**11**) (1.83 g, 5.68 mmol) and 10% palladium–charcoal (200 mg) in EtOH (40 ml) was shaken under 2.5 atm of H_2 for 7.5 h at room temperature. After filtration followed by evaporation of the filtrate, the residue was dissolved in 1M-NaOMe–MeOH (1:9 v/v; 80 ml) and the mixture was refluxed for 3 h under N_2. The solution was neutralised with saturated aqueous NH_4Cl and extracted with ether. The extract was washed with saturated aqueous NaCl, dried, and evaporated. The residue was chromatographed on silica gel with n-hexane–AcOEt (9:1 v/v) as eluant to give the *ketone* (**13**) (1.39 g, 73%) as a solid. Recrystallisation from Et_2O–n-hexane afforded needles, m.p. 116—116.5 °C (Found: C, 70.1; H, 9.65. $C_{19}H_{32}O_4$ requires C, 70.35; H, 9.95%); $[\alpha]_D^{20}$ +77° (*c* 0.18 in $CHCl_3$); $\nu_{max.}(CHCl_3)$ 1 690 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 1.04 (3 H, s, Me), 1.12 (9 H, s, Bu^t), 3.43 (1 H, t, *J* 7 Hz, C*H*OBu^t), and 4.82 [1 H, t, *J* 4 Hz, $CH(OCH_2)_2$]; *m/z* 324 (M^+).

Further elution with the same solvent system afforded the isomer (**12**) (0.11 g, 6%), which was recrystallised from Et_2O as needles, m.p. 114—115 °C; $\nu_{max.}(CHCl_3)$ 1 700 cm^{-1} (C=O); $\delta_H(CCl_4)$ 1.00 (3 H, s, Me), 1.10 (9 H, s, Bu^t), 3.31 (1 H, t, *J* 7 Hz, C*H*OBu^t), and 4.69 [1 H, t, *J* 4 Hz, $CH(OCH_2)_2$]; *m/z* 324 (M^+).

(1S,3aS,4S,7aS)-4-[2-(1,3-*Dioxolan*-2-*yl*)*ethyl*]-5-*ethylidene*-3a,4,5,6,7,7a-*hexahydro*-7a-*methyl*-1-*t*-*butoxyindan* (**14**).—To a suspension of ethyltriphenylphosphonium bromide (3.773 g) in dry THF (38 ml) was slowly added 15% w/w Bu^{n}Li in n-hexane (6.3 ml) at room temperature under N_2. After the mixture had been stirred for 2.5 h at room temperature, a solution of the ketone (**13**) (1.063 g) in dry THF (10 ml) was added and the resulting mixture was refluxed for 10 h. Filtration through Celite followed by evaporation of the filtrate gave a residue, which was taken up into Et_2O. The extract was washed with saturated aqueous NaCl, dried, and evaporated. The residue was subjected to silica gel column chromatography. Elution with n-hexane–AcOEt (95:5 v/v) afforded the *olefin* (**14**) (1.046 g, 95%) as a syrup and a mixture of two isomers in the ratio *ca.* 3:1 (Found: C, 74.8; H, 10.8. $C_{21}H_{36}O_3$ requires C, 74.95; H, 10.8%); $\delta_H(CDCl_3)$ 0.73 and 0.85 (3 H, each s, Me), 1.11 (9 H, s, Bu^t), 4.78 [1 H, t, *J* 4 Hz, $CH(OCH_2)_2$], and 5.01—5.31 (1 H, m, CH=); *m/z* 336 (M^+).

(+)-(1S,3aS,4S,5S,7aS)-5-*Acetyl*-4-[2-(1,3-*dioxolan*-2-*yl*)-*ethyl*]-3a,4,5,6,7,7a-*hexahydro*-7a-*methyl*-1-*t*-*butoxyindan* (**16**).—To a solution of the olefin (**14**) (3.015 g) in n-hexane (15 ml) was added dropwise 10.0M-BH_3·Me_2S (1.197 ml) at 0 °C under N_2, and the mixture was stirred for 6 h at room temperature. After addition of EtOH (15 ml) and 3M-NaOH (40 ml) at the same temperature, 30% aqueous H_2O_2 (1.02 ml) was slowly added to the resulting mixture at 0 °C. The mixture was stirred for 1 h at 50 °C and then poured into ice–water. Extraction with Et_2O followed by washing with water, drying, and evaporation of the solvent gave the crude alcohol (**15**) (3.13 g) as a syrup, which was used in the following reaction without purification.

CrO_3 (2.653 g) was slowly added to dry pyridine (30 ml) at room temperature and the mixture was stirred for 30 min at the same temperature. After addition of the solution of the above alcohol (**15**) (3.13 g) in dry pyridine (15 ml), the resulting mixture was stirred for 12 h at the same temperature. After addition of Et_2O (50 ml) followed by filtration through Celite and washing with Et_2O, the organic solution was washed successively with 10% aqueous $KHSO_4$ and saturated aqueous NaCl, dried, and evaporated. The residue was dissolved in 1M-NaOMe–MeOH (1:9 v/v; 120 ml) and the resulting mixture was refluxed for 5 h under N_2. After neutralisation by addition of saturated aqueous NH_4Cl, followed by concentration under reduced pressure, the residue was partitioned between water and Et_2O. The organic layer was washed with saturated aqueous NaCl, dried, and evaporated to give a residue, which was purified by chromatography on silica gel. Elution with n-hexane–AcOEt (4:1 v/v) afforded the *ketone* (**16**) (2.704 g, 86%) as a solid, which was recrystallised from light petroleum (b.p. 30—70 °C) to yield needles, m.p. 58—60 °C (Found: C, 71.3; H, 10.05. $C_{12}H_{36}O_4$ requires C, 71.55; H, 10.3%); $[\alpha]_D^{15}$ +32° (*c* 0.24 in $CHCl_3$); $\nu_{max.}(CHCl_3)$ 1 700 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 0.76 (3 H, s, Me), 1.11 (9 H, s, Bu^t), 2.14 (3 H, s, Ac), 3.34 (1 H, t, *J* 8 Hz, C*H*OBu^t), and 4.72 [1 H, t, *J* 4.5 Hz, $CH(OCH_2)_2$]; *m/z* 352 (M^+).

(1S,3aS,4S,5S,7aS)-4-[2-(1,3-*Dioxolan*-2-*yl*)*ethyl*]-3a,4,5,6,7,7a-*hexahydro*-5-(1-*hydroxy*-1-*methylethyl*)-7a-*methyl*-1-*t*-*butoxyindan* (**17**).—To a solution of the ketone (**16**) (118 mg) in dry Et_2O (4 ml) was dropwise added 1.5M-MeLi in Et_2O (5.74 ml) at 0 °C under N_2 and the mixture was stirred for 5 h at 0 °C. After slow addition of a pH 7 phosphate buffer (10 ml) at 0 °C, the mixture was extracted with Et_2O. The extract was washed with saturated aqueous NaCl, dried, and evaporated to afford a residue, which was chromatographed on silica gel. Elution with n-hexane–AcOEt (4:1 v/v) gave the *t*-*alcohol* (**17**) (114 mg, 92%) as a syrup, $\nu_{max.}(CHCl_3)$ 3 430 cm^{-1} (OH); $\delta_H(CDCl_3)$ 0.72 (3 H, s, Me), 1.15 (9 H, s, Bu^t), 1.20 (6 H, s, 2 × Me), 3.33 (1 H, t, *J* 9 Hz, C*H*OBu^t), and 4.77 [1 H, t, *J* 4 Hz, $CH(OCH_2)_2$]; *m/z* 350 ($M^+ - H_2O$) [Found: $(M - H_2O)^+$, 350.2810. $C_{22}H_{38}O_3$ requires *m/z*, 350.2819].

(+)-(1S,3aS,4R,5S,7aS)-4-[2-(1,3-*Dioxolan*-2-*yl*)*ethyl*]-3a,4,5,6,7,7a-*hexahydro*-5-*isopropenyl*-7a-*methyl*-1-*t*-*butoxyindan* (**18**).—To a solution of the alcohol (**17**) (0.791 g) in dry pyridine (24 ml) was added $POCl_3$ (5.2 ml) at 0 °C and the mixture was stirred for 8 h at room temperature under N_2. After addition of water (20 ml) at 0 °C, the resulting mixture was extracted with Et_2O. The extract was washed successively with 10% aqueous $KHSO_4$ and saturated aqueous NaCl, dried, and evaporated. The residue was subjected to chomatography on silica gel with n-hexane–AcOEt (95:5 v/v) as eluant to give the *olefin* (**18**) (0.619 g, 82%) as a syrup (Found: C, 75.4; H, 10.9. $C_{22}H_{38}O_3$ requires C, 75.4; H, 10.95%); $[\alpha]_D^{15}$ +13° (*c* 0.13 on $CHCl_3$); $\delta_H(CDCl_3)$ 0.75 (3 H, s, Me), 1.11 (9 H, s, Bu^t), 1.65 (3 H, s, =CMe), 3.33 (1 H, t, *J* 8 Hz, C*H*OBu^t), and 4.67 [3 H, br s, $CH(OCH_2)_2$ and C=CH_2]; *m/z* 350 (M^+).

(1S,3aS,4R,5S,7aS)-4-[2-(1,3-*Dithiolan*-2-*yl*)*ethyl*]-3a,4,5,6,7,7a-*hexahydro*-5-*isopropenyl*-7a-*methylindan*-1-*ol* (**19**).—A mixture of the olefin (**18**) (0.313 g), ethane-1,2-dithiol (0.124 ml), and BF_3·Et_2O (0.08 ml) in dry CH_2Cl_2 (5 ml) was stirred for 1 h at room temperature under N_2. After addition of ice–water (5 ml), the mixture was extracted with CH_2Cl_2. The extract was washed with saturated aqueous NaCl, dried, and evaporated. The residue was purified by silica gel column chromatography with n-hexane–AcOEt (9:1 v/v) as eluant to give the *thioacetal* (**19**) (0.266 g, 92%) as a syrup, $\nu_{max.}$($CHCl_3$) 3 430 cm^{-1} (OH); δ_H($CDCl_3$) 0.77 (3 H, s, Me), 1.66 (3 H, s, =CMe), 4.32 [1 H, t, *J* 7 Hz, C*H*(SCH_2)$_2$], and 4.70 (2 H, br s, C=CH_2); *m*/*z* 326 (M^+) (Found: M^+, 326.1737. $C_{18}H_{30}OS_2$ requires *M*, 326.1737).

(1S,3aS,4R,5S,7aS)-4-[2-(1,3-*Dithiolan*-2-*yl*)*ethyl*]-3a,4,5,6,7,7a-*hexahydro*-5-*isopropenyl*-1-*methoxymethoxy*-7a-*methylindan* (**20**).—A mixture of the above alcohol (**19**) (0.6 g), Pr^i_2NEt (0.285 g), and methoxymethyl chloride (0.741 g) in dry CH_2Cl_2 (2 ml) was stirred for 7 h at ambient temperature under N_2. After addition of water (12 ml), the resulting mixture was extracted with CH_2Cl_2. The extract was washed with saturated aqueous NaCl, dried, and evaporated to give a residue, which was purified by chromatography on silica gel. Elution with n-hexane–AcOEt (95:5 v/v) gave the *MOM ether* (**20**) (0.553 g, 81%) as a syrup, δ_H($CDCl_3$) 0.80 (3 H, s, Me), 1.66 (3 H, s, =CMe), 3.32 (3 H, s, OMe), 3.51 (1 H, t, *J* 8 Hz, C*H*OMOM), 4.32 [1 H, t, *J* 8 Hz, C*H*(SCH_2)$_2$], 4.60 (2 H, s, OCH_2O), and 4.70 (2 H, br s, =CH_2); *m*/*z* 370 (M^+) (Found: M^+, 370.1999. $C_{20}H_{34}O_2S_2$ requires *M*, 370.1998).

(1S,3aS,4R,5S,7aS)-4-(2-*Formylethyl*)-3a,4,5,6,7,7a-*hexahydro*-5-*isopropenyl*-1-*methoxymethoxy*-7a-*methylindan* (**21**).—A mixture of the thioacetal (**20**) (114 mg), Na_2CO_3 (62 mg), and MeI (0.18 ml) in MeCN–water (5:1 v/v; 18 ml) was refluxed for 3 h under N_2. After evaporation of the solvent, the residue was taken up in Et_2O. The organic solution was washed successively with 10% aqueous $Na_2S_2O_3$ and saturated aqueous NaCl, dried, and evaporated. The residue was chromatographed on silica gel with n-hexane–AcOEt (95:5 v/v) as eluant to afford the *aldehyde* (**21**) (53 mg, 59%) as a syrup, $[\alpha]_D^{15}$ +15° (*c* 7 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 720 cm^{-1} (C=O); δ_H($CDCl_3$) 0.82 (3 H, s, Me), 1.67 (3 H, s, =CMe), 3.33 (3 H, s, OMe), 3.52 (1 H, t, *J* 8 Hz, C*H*OMOM), 4.60 (2 H, s, OCH_2O), 4.70 (2 H, br s, C=CH_2), and 9.65 (1 H, t, *J* 1.5 Hz, CHO); *m*/*z* 294 (M^+) (Found: M^+, 294.2195. $C_{18}H_{30}O_3$ requires *M*, 294.2193).

(1S,3aS,4R,5S,7aS)-4-(*Hexa*-3,5-*dienyl*)-3a,4,5,6,7,7a-*hexahydro*-5-*isopropenyl*-1-*methoxymethoxy*-7a-*methylindan* (**23**).—(*A*) To a solution of allyldiphenylphosphine oxide (81.5 mg) and HMPA (0.117 ml) in dry THF (2 ml) was added dropwise 15% w/w Bu^nLi in n-hexane (0.216 ml) at −78 °C under N_2 and the mixture was stirred for 15 min at −78 °C. After addition of a solution of the aldehyde (**21**) (66 mg) in dry THF (1 ml), the mixture was stirred for 10 min at −78 °C, 30 min at 0 °C, and 6 h at ambient temperature. Evaporation of the solvent gave a residue which was extracted with n-pentane. The extract was washed with saturated aqueous NaCl and dried. Evaporation of the solvent afforded a residue, which was subjected to silica gel column chromatography with n-hexane–AcOEt (97:3 v/v) as eluant to yield the *triene* (**23**) (26.3 mg, 37%) as a syrup, δ_H($CDCl_3$) 0.82 (3 H, s, Me), 1.67 (3 H, s, =CMe), 3.34 (3 H, s, OMe), 3.52 (1 H, t, *J* 8 Hz, C*H*OMOM), 4.61 (2 H, s, OCH_2O), 4.70 (2 H, br s, =CH_2), and 4.90—6.35 (5 H, m, olefinic H); *m*/*z* 318 (M^+) (Found: M^+, 318.2557. $C_{21}H_{34}O_2$ requires *M*, 318.2557).

(*B*) The Grignard reagent prepared from Mg (60.7 mg) and allyl bromide (76.7 mg) in dry Et_2O (2 ml) was slowly added to a solution of the aldehyde (**21**) (93 mg) in dry ether (2 ml) at 0 °C and the resulting mixture was stirred for 1.5 h at room temperature under N_2. After addition of water (5 ml), the mixture was extracted with Et_2O. The extract was washed with saturated aqueous NaCl, dried, and evaporated. The residue was purified by silica gel column chromatography with n-hexane–AcOEt (9:1 v/v) as eluant to give the allylic alcohol (106 mg, 100%) as a syrup, $\nu_{max.}$($CHCl_3$) 3 470 cm^{-1} (OH); δ_H($CDCl_3$) 0.81 (3 H, s, Me), 1.67 (3 H, s, =CMe), 3.33 (3 H, s, OMe), 3.51 (1 H, t, *J* 8 Hz, C*H*OMOM), and 4.61 (2 H, s, OCH_2O); *m*/*z* 336 (M^+).

To a solution of the above product (48.5 mg), Et_3N (43.8 mg), and a catalytic amount of 4-dimethylaminopyridine (DMAP) in dry CH_2Cl_2 was added MsCl (0.028 ml) at 0 °C and the mixture was stirred for 1 h at 0 °C and for 15 h at ambient temperature under N_2. After addition of CH_2Cl_2, the mixture was washed successively with water and saturated aqueous NaCl, dried, and evaporated. The residue was subjected to chromatography on silica gel with n-hexane–AcOEt (9:1 v/v) as eluant to give the mesylate as a syrup, δ_H(CCl_4) 0.77 (3 H, s, Me), 1.67 (3 H, s, =CMe), 2.85 (3 H, s, Ms), 3.24 (3 H, s, OMe), and 4.48 (2 H, s, OCH_2O); *m*/*z* 414 (M^+).

A solution of the above mesylate (18.2 mg) and Pr^i_2NEt (8.5 ml) in dry HMPA (3 ml) was stirred for 45 min at 140 °C under N_2. After the mixture had cooled, saturated aqueous NH_4Cl was added and the resulting mixture was extracted with Et_2O. The extract was washed with saturated aqueous NaCl, dried, and evaporated. The crude product was purified by silica gel column chromatography with n-hexane–AcOEt (97:3 v/v) as eluant to afford the triene (**23**) (13.7 mg, 99%) as a syrup, whose spectral data and chromatographic behaviour were identical with those of the sample prepared by method (A).

(+)-5α-*Androst*-3-*en*-17β-*ol* (**25**) *and* 5β-*Androst*-3-*ene*-17β-*ol* (**27**).—(*A*) A mixture of the triene (**23**) (20.8 mg), prepared by method (*A*), and a catalytic amount of Methylene Blue in dry toluene (3 ml) was heated for 100 h at 220 °C under Ar in a sealed tube. After addition of benzene, the mixture was washed successively with saturated aqueous NH_4Cl and saturated aqueous NaCl, dried, and evaporated. The crude product was purified by chromatography on silica gel with n-hexane–AcOEt (98:2 v/v) as eluant to give a mixture of the methoxymethyl ethers (**24**) and (**26**) (20.7 mg, 100%) as a powder, δ_H($CDCl_3$) 0.78 and 0.98 (6 H, in the ratio 9:1, each s, 2 × Me), 3.34 (3 H, s, OMe), 3.51 (1 H, t, *J* 8 Hz, C*H*OMOM), 4.61 (2 H, s, OCH_2O), and 5.19—5.68 (2 H, m, CH=CH); *m*/*z* 318 (M^+).

To a solution of the above products (20.7 mg) in dry CH_2Cl_2 (2 ml) was added ethanethiol (20 mg) and BF_3·Et_2O (0.10 ml) at room temperature and the mixture was stirred for 1 h at the same temperature. The reaction mixture was poured into ice–water and extracted with CH_2Cl_2. The extract was washed with saturated aqueous NaCl, dried, and evaporated. The residue was purified by silica gel chromatography with n-hexane–AcOEt (85:15 v/v) as eluant to afford a mixture of alcohols (**25**) and (**27**) (16.4 mg, 92%), which was subjected to h.p.l.c. [ODS-120T; 4 × 250 mm] with MeCN–water (4:1 v/v; 1.5 ml min^{-1}) as eluant to give the 5β-isomer (**27**) (R_t 11.2 min) and the 5α-isomer (**25**) R_t 14.4 min) in the ratio 1:4.0. Compound (**25**) had m.p. 151—152 °C (lit.,[17] 152—153 °C); $[\alpha]_D^{20}$ +49° (*c* 0.0089 in $CHCl_3$) {lit.,[17] $[\alpha]_D$ +50° ($CHCl_3$)}; $\nu_{max.}$($CHCl_3$) 3 420 cm^{-1} (OH); δ_H($CDCl_3$) 0.74 (3 H, s, 18-H_3), 0.77 (3 H, s, 19-H_3), 3.62 (1 H, t, *J* 8 Hz, C*H*OH), and 5.20—5.60 (2 H, *m*, CH=CH); *m*/*z*

274 (M^+). Compound (**27**) had m.p. 135.5—136 °C; $[\alpha]_D^{15}$ 0° (*c* 0.16 in EtOH); $\nu_{max.}$($CHCl_3$) 3 420 cm^{-1} (OH); δ_H($CDCl_3$) 0.73 (3 H, s, 18-H_3), 0.96 (3 H, s, 19-H_3), 3.60 (1 H, t, *J* 8 Hz, C*H*OH), and 5.24—5.75 (2 H, m, CH=CH); *m/z* 274 (M^+).

(*B*) The triene (**23**) (13.7 mg), prepared by method (*B*), was converted as above into the androstenols (**25**) and (**27**) (11.7 mg, 99%) in the ratio 3.8:1, which were identical with the samples prepared by method (*A*) in all respects.

(+)-*Testosterone Methoxymethyl Ether* (**32**).—(*A*) A solution of the mixture of the Diels–Alder products (**24**) and (**26**) (16.1 mg) and hematoporphyrin (2 mg) in dry pyridine (5 ml) was irradiated for 4 days by 500-W halogen lamp through a Pyrex filter with O_2 bubbling. After addition of further hematoporphyrin (2 mg), the mixture was irradiated for another 3 days under the same conditions. After addition of Et_2O (5 ml) and active charcoal (10 mg), the mixture was stirred for 5 min and then filtered through Celite. Evaporation of the solvents gave a residue (17.3 mg), which was dissolved in a mixture of Et_2O (7.5 ml) and EtOH (1.5 ml). After addition of AcOH (1 drop) and NaI (107 mg), the mixture was stirred for 13 h at room temperature. Evaporation of the solvents gave a residue which was taken up in Et_2O and the solution was washed successively with 10% aqueous $Na_2S_2O_3$ and saturated aqueous NaCl. After the solution had been dried and evaporated a crude product (15.6 mg) was obtained which was used in the next reaction without purification.

A mixture of the above product (15.6 mg) and MnO_2 (300 mg) in dry CH_2Cl_2 (5 ml) was stirred for 7 days at room temperature. After filtration through Celite, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on silica gel with n-hexane–AcOEt (98:2 v/v) as eluant to give a mixture of the starting cycloadducts (5.6 mg), composed of compounds (**24**) and (**26**) in the ratio 1.5:1 on the basis of n.m.r. analysis. Further elution with n-hexane–AcOEt (3:1 v/v) then afforded the *enone* (**32**) (7.8 mg, 46%, 70% based on consumed starting material) as a powder. Recrystallisation from MeOH yielded needles, m.p. 125—126 °C (Found: C, 76.05; H, 9.9. $C_{21}H_{32}O_3$ requires C, 75.85; H, 9.7%); $[\alpha]_D^{15}$ +109° (*c* 0.22 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 645 cm^{-1} (C=O); δ_H(CCl_4) 0.77 (3 H, s, 18-H_3), 1.38 (3 H, s, 19-H_3), 3.27 (3 H, s, OMe), 4.50 (2 H, s, OCH_2O), and 5.55 (1 H, br s, 4-H); *m/z* 332 (M^+).

(*B*) A mixture of cycloadducts (**24**) and (**26**) (21.9 mg) was converted, as above, into the crude allylic alcohol (**31**) (21.9 mg), which was oxidised with PCC (17.6 mg) in dry CH_2Cl_2 (2 ml). After the mixture had been stirred for 3.5 h at room temperature, Florisil (20 mg) was added and the mixture was stirred for 20 min and then filtered through Celite. The filtrate was washed successively with saturated aqueous $NaHCO_3$ solution, 10% HCl, and saturated aqueous NaCl, then dried and evaporated. The same work-up as above gave the starting cycloadducts (7.7 mg) and the enone (**32**) (10.2 mg, 44%, 68% yield based on consumed starting material), which was identical with the sample prepared by the above method.

(+)-*Testosterone* (**4**).—To a solution of the above ether (**32**) (50 mg) in CH_2Cl_2 (2 ml) was added ethanethiol (47 mg) and BF_3·Et_2O (0.23 ml) and the mixture was stirred for 30 min at room temperature. After being poured into ice–water, the mixture was extracted with CH_2Cl_2. The extract was washed with saturated aqueous NaCl, dried, and evaporated to give a residue, which was chromatographed on silica gel. Elution with n-hexane–AcOEt (1:1 v/v) gave (+)-testosterone (**4**) (41.8 mg, 96%) as a solid, whose recrystallisation from aqueous acetone afforded needles, m.p. 157—158 °C (lit.,[5] 154—154.5 °C); $[\alpha]_D^{15}$ +105° (*c* 0.24 in EtOH) {lit.,[5] $[\alpha]_D$ +109° (EtOH)}. The spectral data and chromatographic behaviour were identical with those of an authentic sample.

(+)-5α-*Androst*-3-*en*-17-*one* (**33**).—To dry pyridine (1 ml) was added CrO_3 (7.2 mg) and the mixture was stirred for 30 min. After addition of a solution of the alcohol (**25**) (6.6 mg) in dry pyridine (1 ml), the mixture was stirred for a further 10 h at ambient temperature under N_2. The reaction mixture was diluted by the addition of ether and then filtered through Celite. The filtrate was washed successively with 10% aqueous $KHSO_4$ and saturated aqueous NaCl, dried, and evaporated. The residue was subjected to silica gel column chromatography with n-hexane–AcOEt (95:5 v/v) as eluant to afford the ketone (**33**) (3.4 mg, 52%) as crystals, m.p. 121—123 °C (lit.,[17] 125—126 °C); $[\alpha]_D^{20}$ +132° (*c* 0.042 in $CHCl_3$) {lit.,[17] $[\alpha]_D$ +136° ($CHCl_3$)}; $\nu_{max.}$($CHCl_3$) 1 725 cm^{-1} (C=O); δ_H($CDCl_3$) 0.80 (3 H, s, 18-H_3), 0.88 (3 H, s, 19-H_3), and 5.21—5.63 (2 H, CH=CH); *m/z* 272 (M^+).

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