Chiral Construction of the Estrane Ring System by an Intramolecular Double Michael Reaction

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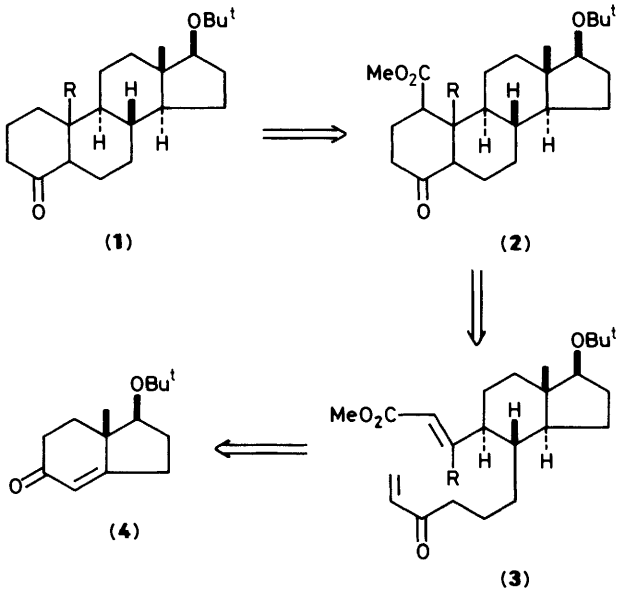
Construction of the estrane ring system was achieved by the intramolecular double Michael reaction as the key step. Heating of the α,β-unsaturated enone ester (**18**), prepared from the optically active indanone (**4**), with chlorotrimethylsilane, triethylamine, and zinc chloride produced three estrane derivatives (**19**), (**22**), and (**25**).

Steroidal compounds are attractive targets for synthetic work due to their medicinal importance as well as their skeletal stereochemical features. Recently we reported a synthesis of androgens *via* A/B ring construction exploiting an intramolecular Diels–Alder reaction.[1] We further studied a synthesis of the steroidal ring system (**1**) through the tetracyclic intermediate (**2**) obtained by an intramolecular double Michael reaction[2–5] of the α,β-unsaturated enone ester (**3**), prepared from the optically active indanone (**4**) (Scheme 1), and we now report a novel route to estranes.[6]

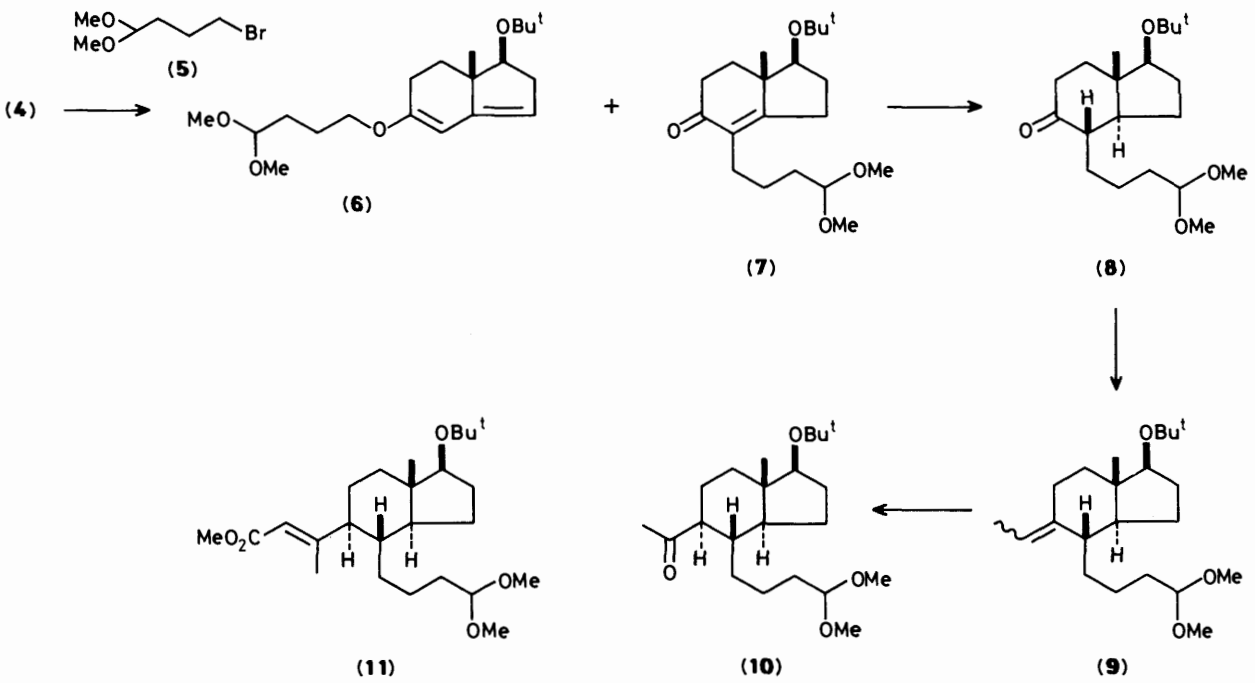


Scheme 1.

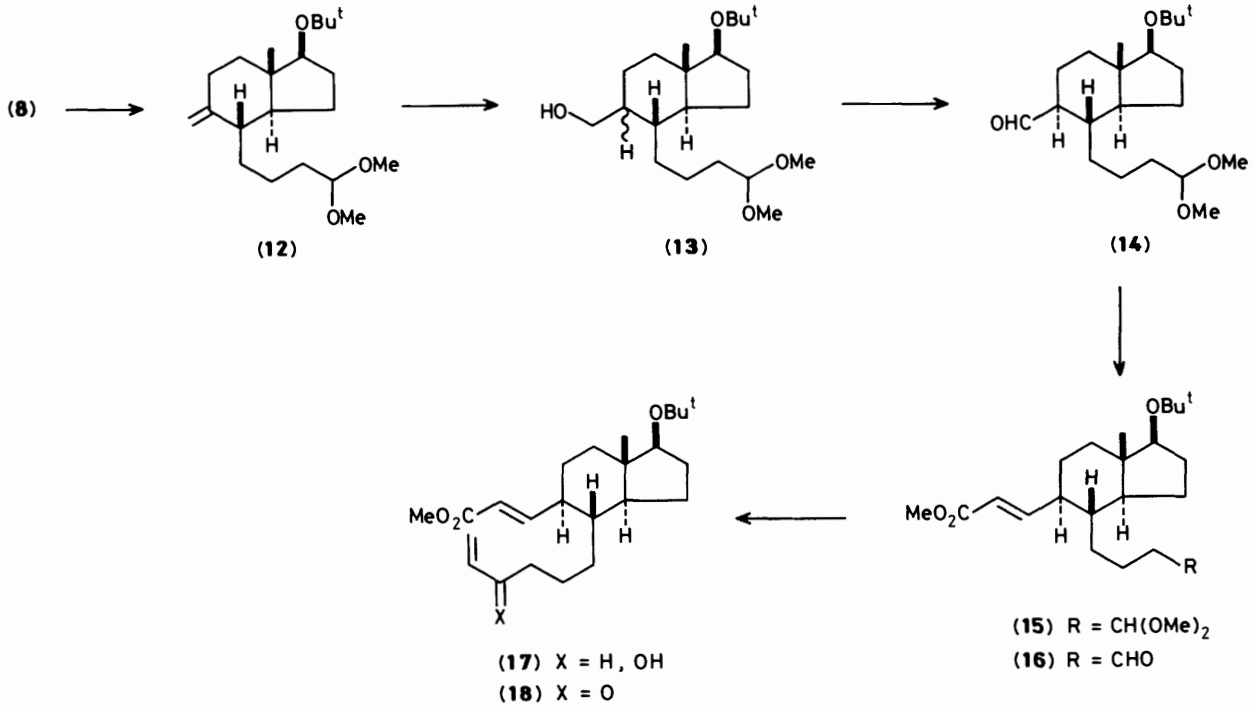
The chiral indanone (**4**)[7] was treated with 4-bromo-1,1-dimethoxybutane (**5**) in the presence of sodium methylsulphinylmethanide in dimethyl sulphoxide (DMSO)[8] to afford a separable mixture of the ether (**6**) in 23% yield and the enone (**7**) in 53% yield. Catalytic hydrogenation of the enone (**7**) in the presence of 10% palladium–charcoal in methanol under 5 atm of hydrogen, followed by oxidation of the resulting saturated alcohols with dipyridine–chromium(VI) oxide[9] and the subsequent equilibration[8] of the crude product with sodium methoxide in methanol, afforded the ketone (**8**) in 64% overall yield together with a small amount of its diastereoisomer, which could be converted into (**8**) by further epimerisation with sodium methoxide. The cyclic ketone (**8**) was transformed into the acetyl compound (**10**) *via* the ethylidene derivative (**9**) in four steps: Wittig reaction using ethyltriphenylphosphonium bromide and potassium t-pentoxide (98% yield), hydroboration–oxidation using borane–dimethyl sulphide complex followed by hydrogen peroxide, oxidation with dipyridine–chromium(VI) oxide,[9] and equilibration with sodium methoxide (71% overall yield for three steps). However, transformation of (**10**) into the α,β-unsaturated ester (**11**) failed (Scheme 2). Therefore our attention focused on the synthesis of 19-norsteroidal compounds.

According to a similar procedure as above, the cyclic ketone (**8**) was converted into the formyl derivative (**14**). Namely, reaction of (**8**) with an ylide, derived from methyltriphenylphosphonium bromide and potassium t-pentoxide, gave in 99% yield the olefin (**12**), which was subjected to hydroboration–oxidation to form two epimeric alcohols (**13**) in 95% yield. Swern oxidation[10] of the epimeric mixture (**13**), followed by epimerisation utilising sodium methoxide, produced the aldehyde (**14**) as a single isomer having the correct stereochemistry at the five chiral centres. Treatment of aldehyde (**14**) with trimethyl phosphonoacetate [methyl (dimethoxyphosphoryl)-acetate] in the presence of sodium hydride in 1,2-dimethoxyethane (DME) produced, in 86% overall yield from (**13**), the α,β-unsaturated ester (**15**) as the *E*-isomer, $[\alpha]_D^{28}$ +38° ($CHCl_3$). The n.m.r. spectrum ($CDCl_3$) of compound (**15**) showed two olefinic hydrogens at δ_H 5.79 (d, *J* 16 Hz) and 6.84 (dd, *J* 9 and 16 Hz). The acetal group of (**15**) was deblocked by treatment with dil. acetic acid at 60 °C to give the aldehyde (**16**) in 98% yield. Condensation of (**16**) with vinylmagnesium bromide in tetrahydrofuran (THF), followed by oxidation of the resulting secondary epimeric alcohols (**17**) with pyridinium dichromate (PDC)[11] in dichloromethane, gave the substrate (**18**), $[\alpha]_D^{24}$ +39° ($CHCl_3$), of the key synthetic step in 81% overall yield (Scheme 3).

Intramolecular double Michael reaction of the α,β-unsaturated enone ester (**18**) was first examined using lithium amides,[3] but the vinyl ketone function was too reactive under the conditions used. Intractable polar products containing an amine moiety were formed. Although tetracyclic products were obtained by the reaction of the ester (**18**) with dimethyl-t-butylsilyl trifluoromethanesulphonate in the presence of triethylamine,[5] the yield was very poor. When the ester (**18**) was heated together with chlorotrimethylsilane, triethylamine, and zinc chloride[4,12] in toluene in a sealed tube at 160 °C for 12 h and the resulting product was then treated with dil. perchloric acid in THF, a mixture of three tetracyclic compounds (**19**), (**22**), and (**25**) was obtained in 63% yield in the proportions ~2:1:1. One stereoisomer, (**22**), m.p. 145—146 °C, $[\alpha]_D^{26}$ +13.6° ($CHCl_3$), was easily purified by silica gel column chromatography, but separation of two isomers (**19**) and (**25**)



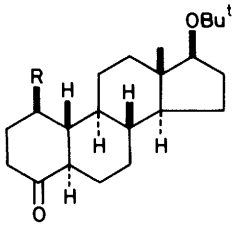
Scheme 2.



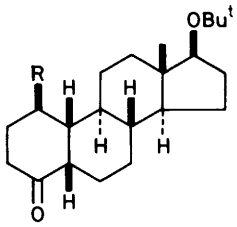
Scheme 3.

was difficult even with h.p.l.c. The course of the above annulation was examined by t.l.c. and n.m.r. analyses and it was found that the substrate (**18**) was directly cyclised to the tetracyclic compounds (**19**), (**22**), and (**25**), which were then converted into a mixture of silyl enol ethers. This fact indicated that the annulation was not the intramolecular Diels–Alder reaction of the siloxydiene (**28**), but the tandem conjugate addition, the intramolecular double Michael reaction.[4]

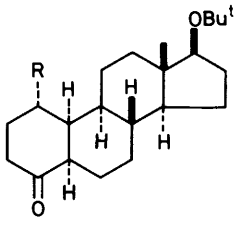
For the purpose of the determination of the stereostructure of the above products (**19**), (**22**), and (**25**), their methoxycarbonyl groups were removed in a three-step sequence; reduction with di-isobutylaluminium hydride (DIBAL) (86—88% yield), Swern oxidation[10] of the resulting diols (97—98% yield), and decarbonylation of the formyl ketones (**20**), (**23**), and (**26**) with tris(triphenylphosphine)rhodium(I) chloride[13] (59—79% yield). Two isomers (**21**) and (**27**), derived from the mixture of



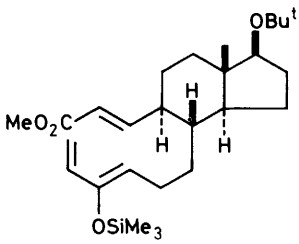
(19) R = CO_2Me
(20) R = CHO
(21) R = H



(22) R = CO_2Me
(23) R = CHO
(24) R = H



(25) R = CO_2Me
(26) R = CHO
(27) R = H

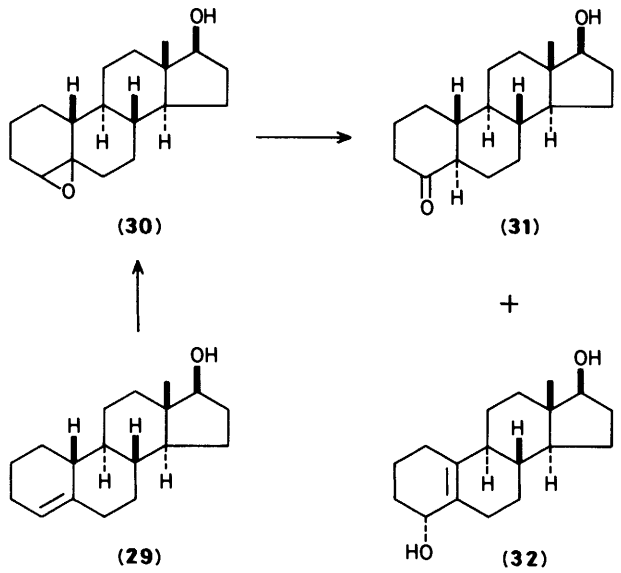


(28)

esters (**19**) and (**25**), were separated by reverse-phase h.p.l.c. Thus three diastereoisomers, (**21**), m.p. 76—79 °C, c.d. [θ] −4 900° (292 nm) (MeOH); (**24**), m.p. 104—107 °C, c.d. [θ] −478° (300 nm) (MeOH); and (**27**), m.p. 60—62 °C, c.d. [θ] −2 092° (292 nm) (MeOH), were obtained pure.

The authentic estran-4-one (**21**) was prepared from (+)-estr-4-en-17β-ol (**29**).[14] Oxidation of the olefin (**29**) with *m*-chloroperbenzoic acid (MCPBA) quantitatively formed a mixture of the epoxides (**30**) in the ratio 2.5:1. Treatment of this mixture of the epoxides (**30**) with boron trifluoride–diethyl ether in benzene gave rise to rearrangement affording the ketone (**31**) in 31% yield along with the allylic alcohol (**32**) in 17% yield (Scheme 4). The stereochemistry of the latter product (**32**) was deduced from the assumption that it was derived from the α-epoxide. Protection of the ketone (**31**) with isobutene in the presence of boron trifluoride–diethyl ether and phosphoric acid[7] gave the t-butyl ether (**21**), m.p. 76—79 °C, c.d. [θ] −4 930° (292 nm) (MeOH), whose spectral data and chromatographic behaviour were identical with those of the above major product (**21**). One of the minor products, (**24**), was readily epimerised with sodium methoxide to give compound (**21**), while the other one, (**27**), was intact under the basic conditions. Therefore the structure of compound (**24**) was determined as a 5β,10β-estran-4-one. The 5α,10α-stereochemistry of compound (**27**) was deduced by the rather large negative Cotton effect.[15]

The configurations at the C-1 position of the products (**19**), (**22**), and (**25**) of the intramolecular double Michael reaction were supposed on the basis of the assumption that the stereochemistry of the *E*-α,β-unsaturated ester was retained during the cyclisation. A new approach to the estran-4-ones, useful intermediates in the synthesis of medicinally important steroidal hormones,[16] was thus developed.



Scheme 4.

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 260-10 spectrophotometer, n.m.r. spectra with JEOL-PMX-60, JEOL-FX-90A, JEOL-PS-100, and JEOL-GX-500 spectrometers (tetramethylsilane as internal reference), and mass spectra with Hitachi M-52G, JMS-01SG-2, and JMS-DX-303 spectrometers. Optical rotations were measured on a JASCO-DIP-340 polarimeter and c.d. spectra were taken with a JASCO-J-400X spectropolarimeter. All new compounds described in the Experimental section were homogeneous on t.l.c. and h.p.l.c. H.p.l.c. analyses were carried out on a Gilson h.p.l.c. system. After extraction, the organic solutions were dried over anhydrous sodium sulphate.

4-*Bromo*-1,1-*dimethoxybutane* (**5**).—To a solution of ethyl 4-bromobutyrate (17.2 g, 0.088 mol) in a mixture of dry DME and dry CH_2Cl_2 (1:1 v/v; 100 ml) was slowly added 1M DIBAL in hexane (93 ml, 0.093 mol) at −78 °C under N_2 during 1 h and the mixture was stirred for 30 min at the same temperature. After MeOH (10 ml) had been slowly added at the same temperature, the resulting mixture was stirred for 30 min at room temperature and then poured into cold 5% hydrochloric acid (100 ml). The mixture was thoroughly extracted with benzene and the combined extracts were washed with brine and dried. Evaporation of the solvent gave the crude aldehyde, to which were added crystalline NH_4Cl (380 mg) and MeOH (120 ml). The mixture had been refluxed for 20 min, before evaporation of the solvent. The residue was partitioned between saturated aqueous $NaHCO_3$ and Et_2O. The ethereal layer was washed with brine, dried, and evaporated to give a residue, which was distilled to give the *bromo acetal* (**5**) (11.9 g, 68%) as an oil, b.p. 98—105 °C (25 mmHg) (Found: C, 36.65; H, 6.55. $C_6H_{13}BrO_2$ requires C, 36.55; H, 6.65%); $\nu_{max.}(CHCl_3)$ 1 120 cm^{-1} (C–O–C); $\delta_H(CCl_4)$ 1.55—2.75 (4 H, m, 2 × CH_2), 3.20 (6 H, s, 2 × OMe), 3.50 (2 H, t, *J* 6 Hz, CH_2Br), and 4.25 [1 H, t, *J* 6 Hz, $CH(OMe)_2$]; *m/z* 166 and 168 (M^+ − OMe).

(+)-(1S,7aS)-4-(4,4-*Dimethoxybutyl*)-7,7a-*dihydro*-7a-*methyl*-1-*t*-*butoxyindan*-5(6H)-*one* (**7**).—A suspension of sodium hydride (60% in mineral oil; 920 mg, 23 mmol) in dry DMSO (40 ml) was stirred and heated for 1.5 h at 50 °C under N_2. After being cooled to room temperature, a solution of the butoxyindanone (**4**)[7] (4.20 g, 19 mmol) in dry DMSO (35 ml) was slowly added and the mixture was stirred for 2 h at room temperature under N_2. When gas evolution had ceased, a solution of the above bromide (**5**) (5.10 g, 26 mmol) in dry DMSO (25 ml) was slowly added and the mixture was stirred for 12 h. After addition of saturated aqueous NH_4Cl (100 ml),

the resulting mixture was thoroughly extracted with Et_2O, and the extract was washed with brine and dried. Evaporation of the solvent gave a residue, which was subjected to silica gel column chromatography. Elution with hexane–AcOEt (50:3 v/v) gave the *ether* (**6**) (1.50 g, 23%) as an oil; $\delta_H(CCl_4)$ 0.87 (3 H, s, Me), 1.12 (9 H, s, Bu^t), 1.55—2.56 (10 H, m, 5 × CH_2), 3.20 (6 H, s, 2 × *OMe*), 3.23 (1 H, m, 1-H), 3.65 (2 H, m, OCH_2), 4.27 [1 H, m, $CH(OMe)_2$], 4.86 (1 H, m, 3-H), and 5.10 (1 H, br s, 4-H); *m/z* 338 (M^+) (Found: M^+, 338.2456. $C_{20}H_{34}O_4$ requires *M*, 338.2456).

Further elution with hexane–AcOEt (9:1 v/v) gave the *enone* (**7**) (3.48 g, 53%) as an oil (Found: C, 70.7; H, 10.25. $C_{20}H_{34}O_4$ requires C, 70.95; H, 10.15%); $\nu_{max.}(CHCl_3)$ 1 655 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 1.07 (3 H, s, Me), 1.17 (9 H, s, Bu^t), 1.20—2.60 (14 H, m, 7 × CH_2), 3.28 (6 H, s, 2 × OMe), 3.30 (1 H, m, 1-H), and 4.33 [1 H, t, *J* 6 Hz, $CH(OMe)_2$]; *m/z* 338 (M^+).

(+)-(1S,3aS,4S,7aS)-4-(4,4-*Dimethoxybutyl*)-3a,6,7,7a-*tetrahydro*-7a-*methyl*-1-*t*-*butoxyindan*-5(4*H*)-*one* (**8**).—A mixture of the above enone (**7**) (700 mg, 2.07 mmol) and 10% palladium–charcoal (100 mg) in MeOH (25 ml) was shaken under H_2 (5 atm) for 14 h at room temperature. The mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to give a residue. To a solution of pyridine (1.49 ml, 18.4 mmol) in dry CH_2Cl_2 (10 ml) at 4 °C was added crystalline chromium(VI) oxide (919 mg, 9.2 mmol) and the mixture was stirred for 1 h at room temperature. After addition of a solution of the above reduction product in dry CH_2Cl_2 (8 ml), the mixture was stirred for 7 h at ambient temperature. After dilution with Et_2O, the mixture was filtered through Celite. The filtrate was washed successively with 10% aqueous $KHSO_4$ and brine, dried, and then evaporated. The residue was dissolved with 1M MeONa–MeOH (3 ml) in MeOH (17 ml) and the mixture was refluxed for 7 h under N_2. The solution was neutralised with saturated aqueous NH_4Cl and extracted with benzene. The extract was washed with brine and dried. Evaporation of the solvent gave a residue, which was chromatographed on silica gel. Elution with hexane–AcOEt (17:3 v/v) afforded the trans-*ketone* (**8**) (454 mg, 64%) as an oil (Found: C, 70.75; H, 10.9. $C_{20}H_{36}O_4$ requires C, 70.55. H, 10.65%); $[\alpha]_D^{26}$ +43° (*c* 0.32 in $CHCl_3$); $\delta_H(CDCl_3)$ 1.02 (3 H, s, Me), 1.12 (9 H, s, Bu^t), 1.20—2.60 (16 H, m, 7 × CH_2 and 2 × CH), 3.27 (6 H, s, 2 × OMe), 3.41 (1 H, *t*, *J* 7 Hz, 1-H), and 4.33 [1 H, t, *J* 6 Hz, $CH(OMe)_2$]; *m/z* 309 (M^+ − OMe).

Further elution gave a mixture of the *trans*-ketone (**8**) and the *cis*-isomer (120 mg), which was further subjected to the epimerisation reaction using NaOMe.

(1S,3aS,4S,5S,7aS)-5-*Acetyl*-4-(4,4-*dimethoxybutyl*)-3a,4,5,6,7,7a-*hexahydro*-7a-*methyl*-1-*t*-*butoxyindane* (**10**).—To a suspension of ethyltriphenylphosphonium bromide (353 mg, 0.95 mmol) in dry benzene (5 ml) was added a mixture of potassium hydride (36 mg, 0.90 mmol) and t-pentyl alcohol (2-methylbutan-2-ol) (88 mg, 1.0 mmol) in dry benzene (5 ml) under N_2 and the mixture was stirred for 30 min at ambient temperature. To the resulting mixture was added a solution of the ketone (**8**) (102 mg, 0.30 mmol) in dry benzene (3 ml) and the mixture was refluxed for 8 h under N_2. After being diluted with benzene, the mixture was washed with brine and dried. Evaporation of the solvents gave a residue, which was purified by silica gel column chromatography. Elution with hexane–AcOEt (97:3 v/v) afforded the olefin (**9**) (103 mg, 98%) as an oil, which was obtained as a mixture of two isomers and was used in the following reaction without further purification; $\nu_{max.}(CHCl_3)$ 1 650 cm^{-1} (>C=CH–); $\delta_H(CCl_4)$ (*inter alia*) 0.82 (3 H, br s, Me), 1.10 (9 H, s, Bu^t), 3.20 (6 H, s, 2 × OMe), 4.25 [1 H, t, *J* 6 Hz, $CH(OMe)_2$], and 5.25 (1 H, br s, CH=C).

To a solution of the above olefin (**9**) (47 mg, 0.134 mmol) in dry hexane (2 ml) at 0 °C was slowly added 10.0M BH_3·Me_2S (0.03 ml) under N_2 and the mixture was stirred for 7 h at room temperature. To the resulting mixture were added dropwise EtOH (2 ml) and 3M NaOH (0.1 ml) at the same temperature before addition of 30% H_2O_2 (0.07 ml) 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 as an oil (46 mg), which was subjected to the following reaction without purification.

To a solution of pyridine (0.14 ml, 1.73 mmol) in dry CH_2Cl_2 (5 ml) at 4 °C was added crystalline chromium(VI) oxide (90 mg, 0.9 mmol) and the mixture was stirred for 1 h at room temperature. After addition of a solution of the above alcohol (46 mg) in dry CH_2Cl_2 (2 ml), the mixture was stirred for 2 h at the same temperature. The mixture was diluted with Et_2O and then filtered through Celite. The filtrate was washed successively with 10% aqueous $KHSO_4$ and brine, dried, and evaporated. A mixture of the resulting oil and 1M NaOMe–MeOH (0.25 ml) in MeOH (2.25 ml) was refluxed for 6 h. Evaporation of the solvent gave a residue, which was partitioned between saturated aqueous NH_4Cl and benzene. The organic layer was washed with brine and dried. Evaporation of the solvent afforded a residue, which was purified by chromatography on silica gel. Elution with hexane–AcOEt (4:1 v/v) yielded the *ketone* (**10**) (38 mg, 71%) as an oil, $\nu_{max.}(CHCl_3)$ 1 700 cm^{-1} (C=O); $\delta_H(CCl_4)$ (*inter alia*) 0.75 (3 H, s, Me), 1.12 (9 H, s, Bu^t), 2.08 (3 H, s, COMe), 3.21 (6 H, s, 2 × OMe), and 4.23 [1 H, t, *J* 6 Hz, $CH(OMe)_2$]; *m/z* 336 (M^+ − OMe − H) [Found: (M^+ − OMe − H)$^+$, 336.2660. $C_{21}H_{36}O_3$ requires *m/z*, 336.2665].

(+)-(1S,3aS,4S,7aS)-4-(4,4-*Dimethoxybutyl*)-3a,4,5,6,7,7a-*hexahydro*-7a-*methyl*-5-*methylene*-1-*t*-*butoxyindane* (**12**).—To a suspension of methyltriphenylphosphonium bromide (1.16 g, 4.51 mmol) in dry benzene (9 ml) was added a mixture of potassium hydride (0.18 g, 4.40 mmol) and t-pentyl alcohol (0.44 g, 4.70 mmol) in dry benzene (17 ml) at room temperature under N_2. After being stirred for 1 h at the same temperature the mixture was treated with a solution of the ketone (**8**) (0.67 g, 1.96 mmol) in dry benzene (8 ml). The mixture was refluxed for 1 h under N_2 and then diluted with benzene. Washing with brine, followed by drying and evaporation of the solvent, gave a residue, which was subjected to silica gel chromatography. Elution with hexane–AcOEt (97:3 v/v) afforded the *olefin* (**12**) (0.66 g, 99%), $[\alpha]_D^{27}$ +11° (*c* 1.32 in $CHCl_3$) (Found: C, 74.65; H, 11.5. $C_{21}H_{38}O_3$ requires C, 74.5; H, 11.3%); $\nu_{max.}(CHCl_3)$ 1 640 cm^{-1} (>C=CH_2); $\delta_H(CDCl_3)$ 0.85 (3 H, s, Me), 1.11 (9 H, s, Bu^t), 1.20—2.15 (16 H, m, 7 × CH_2 and 2 × CH), 3.28 (6 H, s, 2 × OMe), 3.35 (1 H, t, *J* 7 Hz, 1-H), 4.34 [1 H, t, *J* 6 Hz, $CH(OMe)_2$], and 4.53 and 4.69 (each 1 H, each br s, CH_2=C<); *m/z* 307 (M^+ − OMe).

(+)-(1S,3aS,4S,7aS)-[4-(4,4-*Dimethoxybutyl*)-3a,4,5,6,7,7a-*hexahydro*-7a-*methyl*-1-*t*-*butoxyindan*-5-*yl*]*methane* (**13**).—To a solution of the olefin (**12**) (55 mg, 0.163 mmol) in dry hexane (2 ml) at 0 °C was added 10.0M BH_3·Me_2S (0.02 ml) under N_2, and the mixture was stirred for 6 h at ambient temperature. After addition of MeOH (2 ml) and 3M NaOH (0.1 ml) at 0 °C, 30% H_2O_2 (0.02 ml) was slowly added to the resulting mixture at the same temperature. The mixture was stirred for 1 h at 50 °C and then poured into ice–water. Extraction with Et_2O, followed by washing with brine, drying, and evaporation of the solvent, gave a residue, which was chromatographed on silica gel. Elution with hexane–AcOEt (2:1 v/v) afforded the epimeric *alcohols* (**13**) (55 mg, 95%) as an oil (Found: C, 70.7; H, 11.8. $C_{21}H_{40}O_4$ requires C, 70.75; 11.3%); $\nu_{max.}(CHCl_3)$ 3 450 cm^{-1} (OH); $\delta_H(CDCl_3)$ 0.73 and 0.75 [3 H (3:1), each s, Me], 1.12 (9 H, s, Bu^t), 1.25—2.01 (17 H, m, 7 × CH_2 and 3 × CH), 3.29 (6 H, s,

2 × OMe), 3.38 (1 H, t, *J* 7 Hz, 1-H), 3.60 (2 H, m, CH_2OH), and 4.35 [1 H, t, *J* 6 Hz, $CH(OMe)_2$]; *m/z* 324 (M^+ − MeOH).

(+)-*Methyl* (E)-3-[(1S,3aS,4R,5S,7aS)-4-(4,4-*Dimethoxybutyl*)-3a,4,5,6,7,7a-*hexahydro*-7a-*methyl*-1-*t*-*butoxyindan*-5-*yl*]*prop*-2-*enoate* (**15**).—To a solution of oxalyl chloride (0.26 ml, 3.43 mmol) in dry CH_2Cl_2 (5 ml) at −78 °C was added dropwise a mixture of dry DMSO (0.49 ml, 6.86 mmol) and dry CH_2Cl_2 (5 ml) under N_2. After the mixture had been stirred for 5 min, a solution of the alcohol (**13**) (554 mg, 1.56 mmol) in dry CH_2Cl_2 (20 ml) was added. After 10 min, Et_3N (2.17 ml, 15.6 mmol) was added dropwise to the mixture, which was stirred for a further 15 min at −78 °C and then for 1 h at room temperature. After dilution with CH_2Cl_2, the mixture was washed successively with water and brine, dried, and evaporated. A mixture of the crude product and 1M NaOMe–MeOH (3 ml) in MeOH (12 ml) was stirred for 20 min at room temperature under N_2. After acidification by addition of 10% aqueous NH_4Cl, the mixture was extracted with Et_2O. The extract was washed with brine, dried, and evaporated to give the aldehyde (**14**) (552 mg), which was used in the following reaction without purification.

To a suspension of 60% sodium hydride (125 mg, 3.12 mmol) in dry DME (55 ml) was slowly added trimethyl phosphonoacetate [methyl (dimethoxyphosphonyl) acetate] (0.55 ml, 3.43 mmol), and the mixture was stirred for 30 min at room temperature under N_2. To the resulting mixture was added dropwise a solution of the aldehyde (**14**) (552 mg, 1.56 mmol) in dry DME (10 ml). After being stirred for 17 h, the mixture was partitioned between water and Et_2O. The organic layer was washed with brine, dried, and evaporated to give a residue, which was subjected to chromatography on silica gel. Elution with hexane–AcOEt (93:7 v/v) afforded the *ester* (**15**) (548 mg, 86%) as an oil, $[\alpha]_D^{28}$ +38° (*c* 0.8 in $CHCl_3$) (Found: C, 69.95; H, 10.2. $C_{24}H_{42}O_5$ requires C, 70.2; H, 10.3%); $\nu_{max.}$($CHCl_3$) 1 715 (C=O) and 1 645 cm^{-1} (C=C); δ_H($CDCl_3$) 0.73 (3 H, s, Me), 1.12 (9 H, s, Bu^t), 0.90—2.10 (17 H, m, 7 × CH_2 and 3 × CH), 3.28 (6 H, s, 2 × OMe), 3.38 (1 H, t, *J* 7 Hz, 1-H), 3.73 (3 H, s, CO_2Me), 4.32 [1 H, t, *J* 6 Hz, $CH(OMe)_2$], 5.79 (1 H, d, *J* 16 Hz, $=CHCO_2$), and 6.84 (1 H, dd, *J* 9 and 16 Hz, >CH–C*H*=); *m/z* 409 (M^+ − 1).

(+)-*Methyl* (E)-3-[(1S,3aS,4R,5S,7aS)-4-(3-*Formylpropyl*)-3a,4,5,6,7,7a-*hexahydro*-7a-*methyl*-1-*t*-*butoxyindan*-5-*yl*]*prop*-2-*enoate* (**16**).—A stirred mixture of the ester (**15**) (300 mg, 0.732 mmol) and AcOH–water (4:1 v/v, 3 ml) was heated at 60 °C for 30 min. After dilution with benzene, the mixture was washed successively with saturated aqueous $NaHCO_3$ and brine. The benzene solution was dried and evaporated to give a residue, which was purified by silica gel column chromatography. Elution with hexane–AcOEt (23:2 v/v) yielded the *aldehyde* (**16**) (261 mg, 98%) as an oil, $[\alpha]_D^{25}$ +38° (*c* 1.44 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 720 (C=O) and 1 700 cm^{-1} (C=O); δ_H(CCl_4) 0.68 (3 H, s, Me), 1.05 (9 H, s, Bu^t), 0.95—2.05 (15 H, m, 6 × CH_2 and 3 × CH), 2.28 (2 H, t, *J* 7 Hz, CH_2CHO), 3.40 (1 H, t, *J* 7 Hz, 1-H), 3.61 (3 H, s, OMe), 5.62 (1 H, d, *J* 16 Hz, $=CHCO_2$), 6.68 (1 H, dd, *J* 8 and 16 Hz, >C*H*=), and 9.60 (1 H, t, *J* 2 Hz, CHO); *m/z* 364 (M^+) (Found: M^+, 364.2614. $C_{22}H_{36}O_4$ requires *M*, 364.2624).

(+)-*Methyl* (E)-3-[(1S,3aS,4R,5S,7aS)-3a,4,5,6,7,7a-*Hexahydro*-7a-*methyl*-4-(4-*oxohex*-5-*enyl*)-1-*t*-*butoxyindan*-5-*yl*]-*prop*-2-*enoate* (**18**).—To a solution of the aldehyde (**16**) (516 mg, 1.43 mmol) in dry THF (15 ml) was slowly added 1M vinylmagnesium bromide–THF (2.15 ml) at −78 °C under N_2, and the mixture was stirred for 30 min at −78 °C. The mixture was warmed to room temperature and then treated with saturated aqueous NH_4Cl. Extraction with Et_2O, followed by drying and evaporation of the solvents, gave the allylic alcohol (**17**) as a mixture of two stereoisomers, which was used in the next reaction without purification.

To a stirred solution of the alcohol (**17**) in CH_2Cl_2 (66 ml) was added PDC (2.14 g, 5.7 mmol) at room temperature, and the mixture was stirred for 6 h at the same temperature. After dilution with Et_2O, the resulting mixture was filtered through Celite. The filtrate was washed with brine, dried, and evaporated. Purification of the residue by column chromatography on silica gel with hexane–AcOEt (47:3 v/v) as eluant gave the *enone* (**18**) (451 mg, 81%) as an oil, $[\alpha]_D^{24}$ +39° (*c* 0.66 in $CHCl_3$) (Found: C, 73.9; H, 9.65; M^+, 390.2801. $C_{24}H_{38}O_4$ requires C, 73.8; H, 9.8%; *M*, 390.2770); $\nu_{max.}$($CHCl_3$) 1 715 (C=O) and 1 680 cm^{-1} (C=O); δ_H($CDCl_3$) 0.74 (3 H, s, Me), 1.12 (9 H, s, Bu^t), 1.95—2.05 (15 H, m, 6 × CH_2 and 3 × CH), 2.49 (2 H, t, *J* 7 Hz, CH_2CO), 3.38 (1 H, *t*, *J* 7 Hz, 1-H), 3.72 (3 H, s, OMe), 5.78 (1 H, d, *J* 19 Hz, $=CHCO_2$), 6.82 (1 H, dd, *J* 8 and 19 Hz, C*H*=$CHCO_2$), 5.81 (1 H, dd, *J* 3 and 9 Hz, CH_2=C*H*CO), 6.15 (1 H, dd, *J* 3 and 17 Hz, *H*CH=CHCO), and 6.36 (1 H, dd, *J* 9 and 17 Hz, HC*H*=CHCO).

Methyl 4-*Oxo*-17-*t*-*butoxyestrane*-1-*carboxylates* (**19**), (**22**), *and* (**25**).—To a solution of the enone (**18**) (38.6 mg, 0.099 mmol), zinc chloride (150 mg), and triethylamine (0.2 ml) in dry toluene (4 ml) was added chlorotrimethylsilane (0.2 ml) and the mixture was heated for 12 h at 160 °C in a sealed tube. After having been cooled, the mixture was partitioned between benzene and 5% hydrochloric acid. The organic solution was washed successively with saturated aqueous $NaHCO_3$ and brine, dried, and evaporated to give a residue, which was dissolved in a mixture of THF (2 ml) and 10% perchloric acid (2 ml). After having been stirred for 10 min at room temperature, the reaction mixture was diluted with benzene. The benzene solution was washed successively with saturated aqueous $NaHCO_3$ and brine, dried, and evaporated to give a residue, which was subjected to silica gel column chromatography. Elution with hexane–AcOEt (93:7 v/v) afforded the *ketone* (**22**) (6.2 mg, 16%) as needles, m.p. 145—146 °C; $[\alpha]_D^{26}$ +13.6° (*c* 1.0 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 725 (C=O) and 1 710 cm^{-1} (C=O); δ_H($CDCl_3$) (*inter alia*) 0.70 (3 H, s, 13-Me), 1.10 (9 H, s, Bu^t), and 3.67 (3 H, s, OMe); *m/z* 390 (M^+) (Found: M^+, 390.2776. $C_{24}H_{38}O_4$ requires *M*, 390.2770); c.d. [θ] − 657° (297 nm) (*c* 0.0974 in MeOH).

Further elution gave an inseparable mixture of two diastereoisomeric *ketones* (**19**) and (**25**) (18.1 mg, 47%) as a solid in the ratio ~2:1, $[\alpha]_D^{26}$ −15.2° (*c* 2.7 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 725 (C=O); δ_H (500 MHz; $CDCl_3$) (*inter alia*) 0.69 and 0.73 [3 H (2:1), each s, 13-Me], 1.10 (9 H, t, Bu^t), and 3.64 (3 H, s, OMe); *m/z* 390 (M^+) (Found: M^+, 390.2802); c.d. [θ] − 6 604° (293 nm) (*c* 0.159 in MeOH).

17β-*Hydroxy*-5α-*estran*-4-*one* (**31**) and *Estr*-5(10)-*ene*-4α,17β-*diol* (**32**).—To a solution of (+)-estr-4-en-17β-ol (**29**)[14] (197 mg, 0.76 mmol) in CH_2Cl_2 (4 ml) at 0 °C was added a solution of MCPBA (243 mg, 0.98 mmol) in CH_2Cl_2 (2 ml) and the mixture was stirred for 40 min at the same temperature. After dilution with benzene, the mixture was washed successively with 5% aqueous NaOH and brine, and dried. Evaporation of the solvents gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–AcOEt (4:1 v/v) yielded the *epoxides* (**30**) (219 mg, 100%) as a mixture of two diastereoisomers in the ratio 2.5:1, $[\alpha]_D^{26}$ +20.6° (*c* 1.75 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 450 (OH), and 900 and 850 cm^{-1} (epoxide); δ_H(500 MHz; $CDCl_3$) (*inter alia*) 0.75 (3 H, s, 13-Me), 2.90 and 2.95 [1 H (1:2.5), each m, 4-H], and 3.65 (1 H, t, *J* 7 Hz, 17-H); *m/z* 276 (M^+) (Found: M^+, 276.2068. $C_{18}H_{28}O_2$ requires *M*, 276.2089).

To a solution of the diastereoisomeric mixture of the epoxides (**30**) (178 mg, 0.64 mmol) in dry benzene (9 ml) at room

temperature was added boron trifluoride–diethyl ether (0.29 ml, 2.4 mmol). After having been stirred for 6 min at the same temperature, the mixture was basified by saturated aqueous $NaHCO_3$. The organic solution was washed with brine, dried, and evaporated to give a residue, which was purified by silica gel column chromatography. Elution with benzene–acetone (99:1 v/v) yielded the *hydroxy ketone* (**31**) (57 mg, 31%) as an oil, $[\alpha]_D^{21}$ +22.9° (*c* 1.24 in $CHCl_3$); $\nu_{max.}(CCl_4)$ 3 450 (OH) and 1 710 cm^{-1} (C=O); $\delta_H(CDCl_3)$ (*inter alia*) 0.72 (3 H, s, 13-Me) and 3.60 (1 H, t, *J* 7 Hz, 17-H); *m/z* 276 (M^+) (Found: M^+, 276.2085. $C_{18}H_{28}O_2$ requires *M*, 276.2089).

Further elution with benzene–acetone (98:2 v/v) afforded the *allylic alcohol* [**32**) (31 mg, 17%) as needles, m.p. 156—159 °C; $\nu_{max.}(CHCl_3)$ 3 450 cm^{-1} (C=O); $\delta_H(CDCl_3)$ (*inter alia*) 0.85 (3 H, s, 13-Me), 3.63 (1 H, t, *J* Hz, 17-H), and 3.85 (1 H, br s, 4-H); *m/z* 276 (M^+) (Found: M^+, 276.2084. $C_{18}H_{28}O_2$ requires *M*, 276.2089).

17β-*t-Butoxy*-5α-*estran*-4-*one* (**21**).—To a mixture of the ketone (**31**) (43 mg, 0.2 mmol), boron trifluoride–diethyl ether (1.8 μl, 0.018 mmol), and phosphoric acid (0.8 μl) in dry CH_2Cl_2 (4 ml) at −78 °C was added an excess of isobutene and the mixture was stirred for 18 h at room temperature. After being poured into 7% NH_4OH, the mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried, and evaporated to give a residue, which was purified by h.p.l.c. (Microsorb C_{18} 5 μm; 4.6 × 250 mm) with MeOH (1 ml min^{-1}) as eluant to give the *ether* (**21**) (7.6 mg, 11%) as needles, m.p. 76—79 °C; $[\alpha]_D^{21}$ +22.6° (*c* 0.80 in $CHCl_3$); $\nu_{max.}(CHCl_3)$ 1 715 cm^{-1} (C=O); $\delta_H(CDCl_3)$ (*inter alia*) 0.70 (3 H, s, Me), 1.10 (9 H, s, Bu^t), and 3.36 (1 H, t, *J* 7 Hz, 17-H); *m/z* 332 (M^+) (Found: M^+, 332.2722. $C_{22}H_{36}O_2$ requires *M*, 332.2715); c.d. [θ] −4 930° (292 nm) (*c* 0.19 in MeOH).

17β-*t-Butoxy*-5β-*estran*-4-*one* (**24**).—To a stirred solution of the tetracyclic ketone (**22**) (16.2 mg, 0.042 mmol) in dry DME (4.5 ml) at −78 °C was added dropwise 1M DIBAL in hexane (0.20 ml) and the mixture was stirred for 1 h at room temperature under N_2. After addition of water (0.27 ml) and Et_2O (4.5 ml), the mixture was stirred for 1 h. After filtration through Celite, the filtrate was dried and evaporated to give a residue, which was subjected to silica gel column chromatography. Elution with hexane–AcOEt (1:1 v/v) gave the corresponding diols (13.6 mg, 88%), $\nu_{max.}(CHCl_3)$ 3 450 cm^{-1} (OH); $\delta_H(CDCl_3)$ (*inter alia*) 0.72 (3 H, s, Me), 1.10 (9 H, s, Bu^t), 3.50 (1 H, m, 17-H), and 3.50—3.90 (3 H, m, CH_2OH and 4-H); *m/z* 364 (M^+), as a mixture of two diastereoisomers.

To a solution of oxalyl chloride (0.01 ml, 0.138 mmol) in dry CH_2Cl_2 (1 ml) was slowly added dry DMSO (0.02 ml, 0.275 mmol) at −78 °C. After being stirred for 5 min at −78 °C, a solution of the above diols (13.6 mg, 0.037 mmol) in dry CH_2Cl_2 (2 ml) was added dropwise and the mixture was stirred for 10 min at −78 °C. After addition of Et_3N (0.09 ml, 0.625 mmol), the mixture was stirred for 20 min at −78 °C and then for 30 min at room temperature. The reaction mixture was diluted with CH_2Cl_2, washed with water, dried, and evaporated. Purification of the residue by silica gel column chromatography with hexane–AcOEt (19:6 v/v) as eluant gave the keto aldehyde (**23**) (13.0 mg, 97%), $\nu_{max.}(CHCl_3)$ 1 710 cm^{-1} (C=O); $\delta_H(CDCl_3)$ (*inter alia*) 0.73 (3 H, s, Me), 1.10 (9 H, s, Bu^t), 3.40 (1 H, m, 17-H), and 9.88 (1 H, s, CHO); *m/z* 360 (M^+).

A mixture of the above product (**23**) (10 mg, 0.028 mmol) and $(Ph_3P)_3RhCl$ (40 mg, 0.039 mmol) in dry xylene (7 ml) was refluxed for 1.2 h under N_2. Evaporation of the solvent gave a residue, which was taken up in EtOH and the solution was filtered through Celite. Evaporation of the solvent, followed by purification of the residue by silica gel chromatography with hexane–AcOEt (19:1 v/v) as eluant afforded the *ketone* (**24**) (5.4 mg, 59%) as needles, m.p. 104—107 °C; $\nu_{max.}(CHCl_3)$ 1 712 cm^{-1} (C=O); $\delta_H(CDCl_3)$ (*inter alia*) 0.71 (3 H, s, Me), 1.10 (9 H, s, Bu^t), and 3.32 (1 H, t, *J* 7.5 Hz, 17-H); *m/z* 332 (M^+) (Found: M^+, 332.2697. $C_{22}H_{36}O_2$ requires *M*, 332.2715); c.d. [θ] −478° (300 nm) (*c* 0.025 in MeOH).

17β-*t-Butoxy*-5α- *and* -5α,10α-*estran*-4-*one* (**21**) *and* (**27**).—According to the same procedure as above, the mixture of the tetracyclic ketones (**19**) and (**25**) (23.1 mg, 0.059 mmol) was reduced to a mixture of the corresponding diols (18.7 mg, 86%); $\nu_{max.}(CHCl_3)$ 3 400 cm^{-1} (OH); $\delta_H(CDCl_3)$ (*inter alia*) 0.73 (3 H, s, Me), 1.11 (9 H, s, Bu^t), 3.60 (1 H, t, *J* 7 Hz, 17-H), and 3.60—3.90 (3 H, m, CH_2OH and 4-H); *m/z* 364 (M^+).

Swern oxidation of the diols (9.3 mg, 0.025 mmol) gave a mixture of two formyl compounds (**20**) and (**26**) (8.8 mg, 98%), $[\alpha]_D^{26}$ −17.08° (*c* 0.88 in $CHCl_3$); $\nu_{max.}(CHCl_3)$ 1 710 cm^{-1} (C=O); $\delta_H(CDCl_3)$ (*inter alia*) 0.72 (3 H, s, Me), 1.12 (9 H, s, Bu^t), 3.40 (1 H, t, *J* 7.5 Hz, 17-H), and 9.73 (1 H, br s, CHO); *m/z* 360 (M^+) (Found: M^+, 360.2669. $C_{23}H_{36}O_3$ requires *M*, 360.2664).

Decarbonylation of the mixture of aldehydes (**20**) and (**26**) (8.8 mg, 0.024 mmol), followed by purification of the product using h.p.l.c. (Microsorb C_{18} 5 μm; 4.6 × 250 mm) with MeOH (1 ml min^{-1}) as eluant afforded the ketone (**21**) (4.2 mg, 52%) as needles, m.p. 76—79 °C; c.d. [θ] −4 900° (292 nm) (*c* 0.147 in MeOH), and the isomer (**27**) (2.2 mg, 27%) as needles, m.p. 60—62 °C; $\nu_{max.}(CHCl_3)$ 1 710 cm^{-1} (C=O); $\delta_H(CDCl_3)$ (*inter alia*) 0.76 (3 H, s, Me), 1.13 (9 H, s, Bu^t), and 3.39 (1 H, t, *J* 7.5 Hz, 17-H); *m/z* 332 (M^+) (Found: M^+, 332.2677. $C_{22}H_{36}O_2$ requires *M*, 332.2715); c.d. [θ] −2 092° (292 nm) (*c* 0.045 in MeOH). Spectral data and the chromatographic behaviour of the major product (**21**) were identical with those of the above authentic sample.

Epimerisation of 17β-*t-Butoxy*-5β-*estran*-4-*one* (**24**).—A mixture of the ketone (**24**) (1.0 mg, 3 μmol) and 1M MeONa–MeOH (0.01 ml) in MeOH (1 ml) was refluxed for 4 h under N_2. After evaporation of the solvent, the residue was partitioned between Et_2O and water. The organic layer was dried and evaporated to give a residue, which was purified by h.p.l.c. (Microsorb C_{18} 5 μm; 4.6 × 250 mm) with MeOH (1 ml min^{-1}) as eluant to give the 5α-isomer (**21**) (0.9 mg, 90%), m.p. 76—79 °C, whose spectral data and chromatographic behaviour were identical with those of the authentic specimen.

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