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STEREOSELECTIVE SYNTHESIS OF (+)-TESTOSTERONE VIA INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITION OF NITRILE OXIDE

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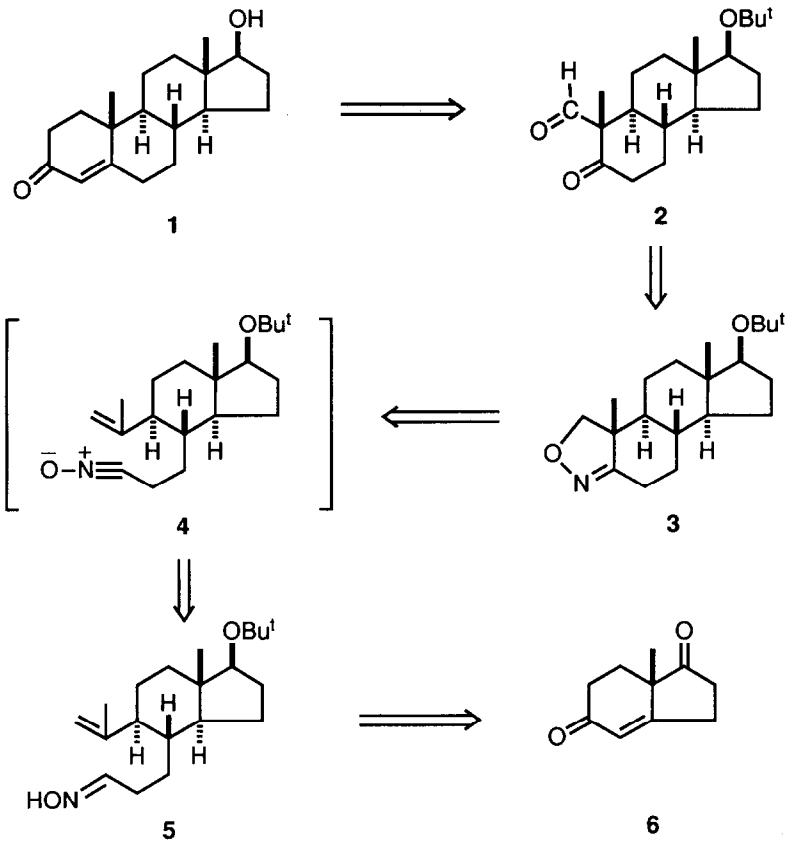
Abstract: *A new approach for construction of the A/B ring system of steroids was developed by way of an intramolecular 1,3-dipolar cycloaddition of a nitrile oxide* **4**, *followed by an incorporation of a* C_3 *unit. A highly stereocontrolled synthesis of (+)-testosterone* **1** *was accomplished by this strategy.*

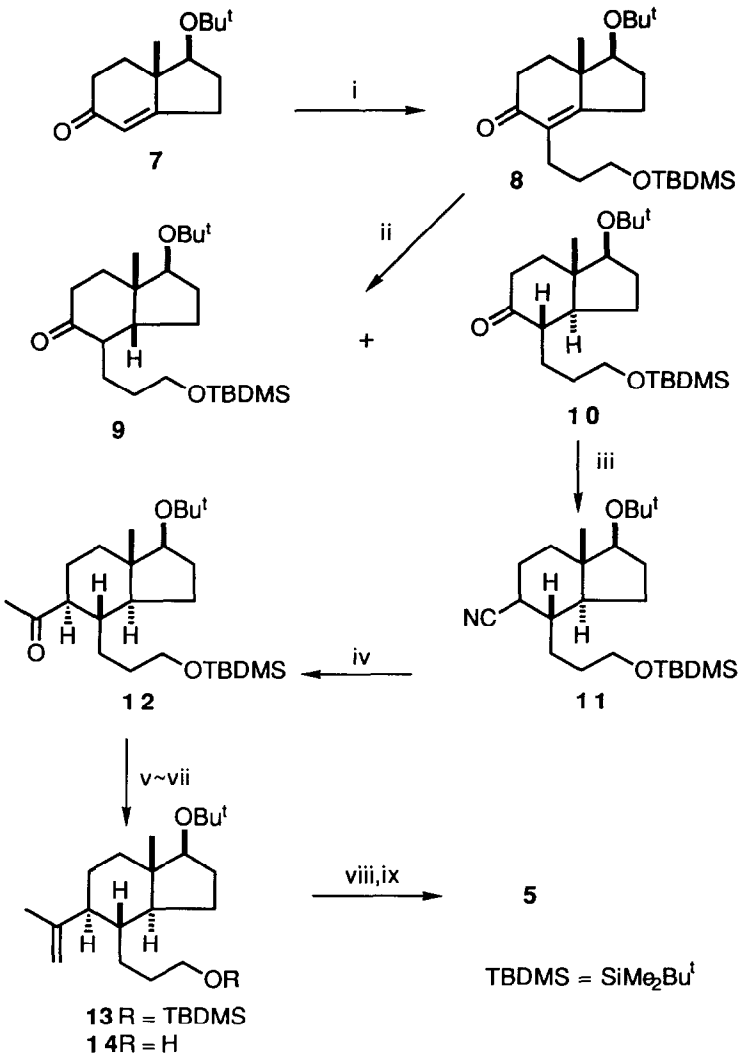
Steroids have been the focus of synthetic attention,[1] because of their biological importance as well as their architectural features. Recently we have studied the construction of steroidal A/B ring system employing an intramolecular Diels-Alder reaction[2] and an intramolecular double Michael reaction.[3] Although two new routes for synthesis of androgens have been developed using both reactions, their stereochemical outcomes were unsatisfactory. A further approach was therefore designed by way of an intramolecular 1,3-dipolar cycloaddition[4] as shown in Scheme 1. Namely natural testosterone **1** would be synthesised by incorporation of a C_3 unit into the keto aldehyde **2**, which would be derived from the isoxazoline **3**, obtainable by an intramolecular 1,3-dipolar cycloaddition of the nitrile oxide **4**. The stereoselective construction of a steroidal B ring was anticipated from the result on the synthesis of drimane-type sesquiterpenes.[5] It was further considered that the olefinic oxime **5**, the precursor of **4**,

would be prepared from the known diketone **6**[6] by the modification of the previous methods.[2,5] We describe the details of the highly stereocontrolled synthesis of (+)-testosterone **1** according to the above synthetic strategy.[7]



Scheme 1

The optically active indanedione **6**[6] was converted into the indanone **7** by the known method.[8] The anion,[8] formed from **7** by the action of sodium hydride in dimethyl sulphoxide (DMSO), was reacted with 3-*t*-butyldimethylsiloxypropyl iodide,[9] derived from 3-chloropropan-1-ol, at the ambient temperature to afford the 4-alkylated indanone **8** in 63% yield. Hydrogenation of **8** in the presence of palladium carbon in a mixture of triethylamine and ethyl acetate[10] produced a mixture of *trans*- and *cis*-tetrahydroindan-5(6*H*)-ones in a ratio of 2.5:1. Hydrogenation of **8** using Adams catalyst, followed by oxidation and the subsequent equilibration with sodium methoxide[3] gave the desired *trans*-isomer **10** in only 30% yield. Danishefsky and Cain also reported a poor selectivity in formation of a



Scheme 2 *Reagents and conditions:* i, $NaCH_2SOMe$, DMSO, $TBDMSOCH_2CH_2CH_2I$; ii, $CoCl_2$, $NaBH_4$, -20 °C or $NiCl_2$, $NaBH_4$, -78 °C; iii, TosMIC, $KOBu^t$; iv, MeLi then silica gel; v, MeLi; vi, $POCl_3$, pyridine; vii, $Bu^n{}_4NF$; viii, DMSO, SO_3 pyridine, Et_3N; ix, H_2NOH

trans-indanone by catalytic hydrogenation.[11] After examinations of various reductive conditions, the desired *trans*-indanone **10** was obtained in a stereoselective manner by reduction using sodium borohydride in the presence of cobalt(II) chloride or nickel(II) chloride.[12] Thus reduction of **8** with sodium borohydride and cobalt(II) chloride gave a mixture of *cis*- and *trans*-isomers **9** and **10** in 73% yield in a ratio of 1:13.4, while the objective

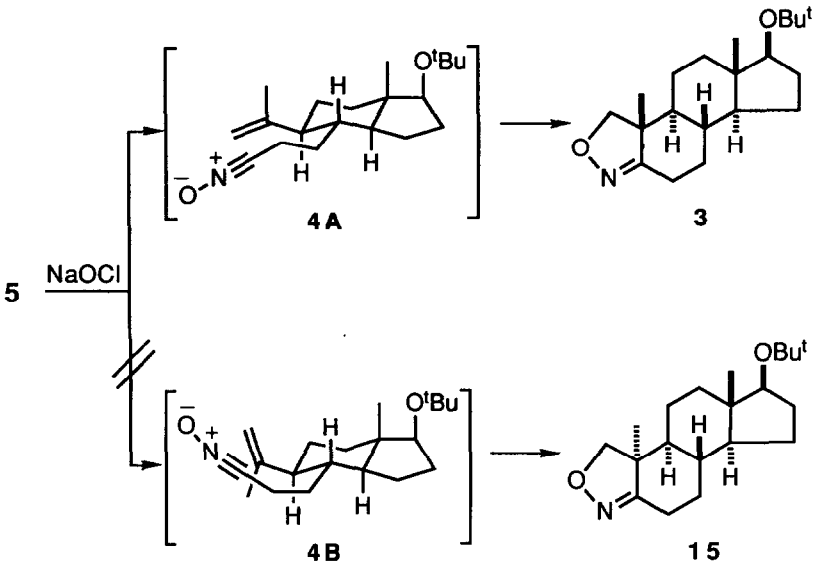
isomer **10** was produced as a single stereoisomer in 62% yield on reduction of **8** with sodium borohydride in the presence of nickel(II) chloride. In ^{1}H NMR spectra, the signals due to the angular methyl group of *cis*- and *trans*-isomers **9** and **10** were observed at 1.15 and 1.02 p.p.m., respectively. The *cis*-isomer **9** was identical with the major product in the reduction of **8** with lithium in the presence of *t*-butanol in liquid ammonia.

Treatment of the *trans*-indanone **10** with tosylmethyl isocyanide (TosMIC)[13] in the presence of potassium *t*-butoxide provided an epimeric mixture (54:46) of nitriles **11** in 97% yield. The epimeric mixture **11** was transformed into a single ketone **12** in 84% yield by reaction of **11** with methyllithium, followed by treatment of the products with silica gel for 15 h at the ambient temperature. During the above treatment with silica gel, a complete epimerization was taken place after hydrolysis of imines.

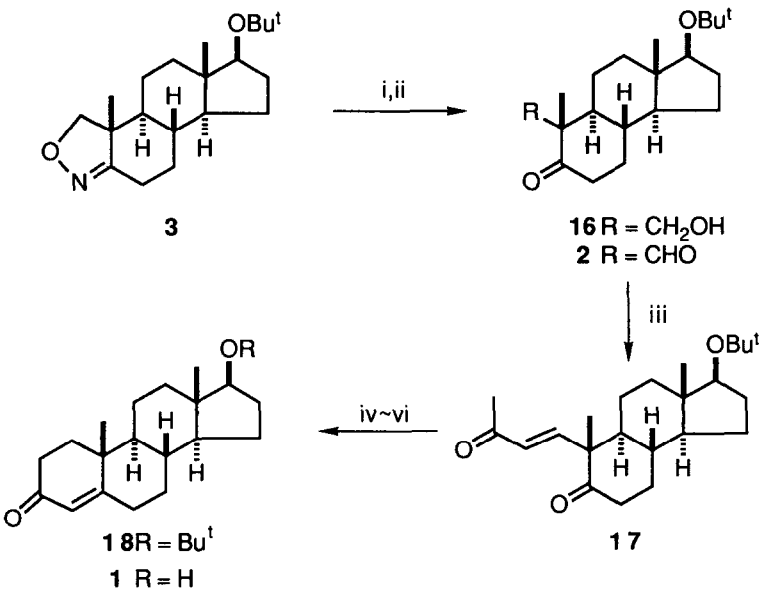
Direct formation of *exo*-olefin utilizing Wittig reaction or Nozaki-Lombardo method[14] failed. Therefore the ketone **12** was reacted with methyllithium, and the resulting tertiary alcohol was subjected to dehydration using phosphorous oxychloride in pyridine. The *exo*-olefin **13** was gained in 63% overall yield from **12** (89% overall yield on the consideration of the recovered **12**) and no tetra-substituted olefin formed. The silyl ether of **13** was deprotected with tetra-*n*-butylammonium fluoride. The resulting alcohol **14**, obtained in 99% yield, was oxidized with dimethyl sulphoxide and sulphur trioxide-pyridine complex in the presence of triethylamine[15] to aldehyde, which was treated with hydroxylamine hydrochloride in the presence of sodium acetate.[16] The oximes **5** were obtained in 95% overall yield from **14** as a *ca.* 1:1 mixture of two geometrical isomers (Scheme 2).

Oxidation of the geometrical mixture of oximes **5** with 6% sodium hypochlorite[17] at the ambient temperature was accompanied by the 1,3-dipolar cycloaddition of the resulting nitrile oxide to give the isoxazoline **3** as a single product in 87% yield. Resonances due to the two hydrogens on the isoxazoline ring of **3** were observed at 3.87 and 4.11 p.p.m. as doublet with *J* 7.6 Hz, respectively, and signals due to the two angular methyl groups resonated at 0.75 and 1.18 p.p.m. as singlet, respectively, in the ^{1}H NMR spectrum. Although the stereochemistry of the product **3** was not readily apparent from the spectroscopic inspection, it was considered that the formation of **3** through a chairlike transition state **4A** would be more favourable than that of isomer **15** through a boatlike transition state **4B** (Scheme 3).[2,5,18]

According to Curran's procedure,[19] the isoxazoline **3** was subjected to reductive hydrolysis. Namely, **3** was treated with Raney nickel(W-2) and trimethyl borate under a hydrogen atmosphere to afford the β-hydroxy ketone



Scheme 3



Scheme 4 *Reagents and conditions:* i, H_2 (1 kg cm^{-2}), Raney Ni, $B(OMe)_3$, H_2O-MeOH; ii, DMSO, SO_3 pyridine, Et_3N; iii, $MeCOCH{=}PPh_3$, heat; iv, H_2 (3 kg cm^{-2}), Pd-C; v, KOH; vi, CF_3CO_2H

16 in 97% yield. The hydroxyl group of **16** was oxidized with dimethyl sulphoxide and sulphur trioxide-pyridine complex in the presence of triethylamine[15] to the aldehyde **2** in 97% yield. Reaction of **2** with diethyl oxopropylphosphate in the presence of sodium hydride gave rise to a deformylation. Therefore the formyl ketone **2** was heated for 90 h with 1-triphenylphosphoranylidene-2-propanone in refluxing xylene. The (*E*)-α,β-unsaturated ketone **17**, obtained in 89% yield, was hydrogenated in the presence of 10% palladium on carbon in ethanol under 3.0 kg cm^{-2} of hydrogen. The crude product was treated with potassium hydroxide to produce the tetracyclic compound **18** in 81% yield. Deblocking **18** using trifluoroacetic acid[20] afforded in 86% yield (+)-testosterone **1**, m.p. 154-155.5 °C; $[\alpha]_D^{25}$ +107.26° (*c* 1.25 in EtOH) [lit.,[21] m.p. 154-154.5 °C; $[\alpha]_D$ +109° (EtOH)], which was identical with the authentic compound in all respects (Scheme 4).

Total synthesis of natural testosterone **1** was thus achieved in a highly stereocontrolled manner. The present approach, the construction of the A/B skeleton, exploiting the 1,3-dipolar cycloaddition of olefinic nitrile oxide, followed by incorporation of a C_3 unit, provides an effective route to the synthesis of other medicinally important steroidal hormones.

Experimental

General.--M.p.s. were determined on a Yanako micromelting-point apparatus and are uncorrected. ^1H NMR spectra were measured on JEOL FX-90A and JEOL-GX-500 spectrometers with $CDCl_3$ as solvent and are recorded in p.p.m. relative internal tetramethylsilane. Values of coupling constants *J* are given in Hz. IR spectra were obtained on a JASCO Report-100 spectrophotometer. Ordinary mass spectra were measured with a JEOL JMS-01SG-2, and high-resolution mass spectroscopy was performed on JEOL-DX-300 and JEOL-JMS-DX-303 instruments. All reactions except hydrogenation were run under an atmosphere of dry N_2 or Ar. Solvents were freshly distilled prior to use; hexane, Et_2O and DME were distilled from Na-benzophenone: CH_2Cl_2 was distilled from P_2O_5 and kept over 4Å molecular sieves (MS): DMSO was distilled from CaH_2 and kept over 4Å MS: *t*-BuOH was distilled from Na and kept over 4Å MS: pyridine and Et_3N were distilled from KOH and kept over 4Å MS and KOH, respectively. Silica gel column chromatography was carried out with Merck Kiesel gel 60 Art 7734[R] or Merck Kiesel gel 60 Art 9387[R]. Oily NaH was washed with dry hexane three times prior to use. The all extracts were dried over $MgSO_4$ before evaporation under reduced pressure.

(+)-(1S,7aS)-1-*t*-Butoxy-4-(3-*t*-butyldimethylsiloxypropyl)-7,7a-dihydro-7a-methylindan-5(6*H*)-one 8.--After the mixture of NaH in

oil (60%; 0.282 g, 7.10 mmol) in anhydrous DMSO (3.5 cm^3) had been stirred at 55 °C until a cease of an evolution of hydrogen gas, to the resulting solution was added a solution of the indanone **7** (0.877 g, 0.395 mmol) in anhydrous DMSO (2.5 cm^3) during 10 min at room temperature. After having been stirred for 2 h at the ambient temperature, a solution of 3-*t*-butyldimethylsiloxypropyl iodide (2.11 g, 7.10 mmol) in anhydrous DMSO (1.0 cm^3) was added to the mixture. The mixture was stirred for 15 h at the same temperature and then treated with saturated aqueous NH_4Cl at 0 °C. The resulting mixture was extracted thoroughly with Et_2O. The extract was washed with brine, dried, and evaporated under reduced pressure to give a residue, which was subjected to silica gel column chromatography. Elution with hexane-AcOEt (95:5) afforded the title compound **8** (0.974 g, 63%) as a solid, recrystallisation of which from EtOH gave prisms, m.p. 38.5-39 °C (Found: C, 70.11; H, 10.90. $C_{23}H_{42}O_3Si$ requires C, 70.00; H, 10.73%); $[\alpha]_D^{23}$ +30.03° (*c* 0.83 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 1655 and 1645 (C=O); δ_H (500 MHz; $CDCl_3$) 0.03 (6 H, s, Me_2Si), 0.87 (9 H, s, Bu^tSi), 1.16 (9 H, s, Bu^tO), 1.05 (3 H, s, 7a-Me), 1.47-2.60 (12 H, m), 3.52 (1 H, dd, *J* 10.9 and 7.4, 1-H) and 3.52 (2 H, t, *J* 6.6, CH_2O); *m/z* 394 (M^+).

(+)-(1*S*,3a*S*,4*S*,7a*S*)-1-*t*-Butoxy-4(3-*t*-butyldimethylsiloxypropyl)-3a,4,7,7a-tetrahydro-7a-methylindan-5(6*H*)-one 10.--(*A*) To a mixture of $CoCl_2 \cdot 6H_2O$ (159 mg, 0.669 mmol) and the enone **8** (52.7 mg, 0.134 mmol) in MeOH (3.2 cm^3) was added portionwise at -20 °C $NaBH_4$ (50.6 mg, 1.34 mmol) and the mixture was stirred for 30 min at -20 °C and then for 1 h at the ambient temperature. After evaporation of the solvent, the residue was purified by column chromatography on silica gel eluating with hexane-AcOEt (40:1) to afford the mixture of two ketones **9** and **10** (38.8 mg, 73%) in a ratio of 1:13.4 as an oil. Further purification of the mixture by chromatography on silica gel with hexane-AcOEt (50:1) as eluant gave the title compound **10** as an oil (Found: C, 69.73; H, 11.23. $C_{23}H_{44}O_3Si$: requires C, 69.64; H, 11.18%); $[\alpha]_D^{26}$ +30.48° (*c* 0.31 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 1710 (C=O); δ_H (500 MHz; $CDCl_3$) 0.02 (6 H, s, Me_2Si), 0.87 (9 H, s, Bu^tSi), 1.02 (3 H, s, 7a-Me), 1.06 (9 H, s, Bu^tO), 2.27 [1 H, ddd, *J* 15.3, 5.2 and 1.8, 6-H(ax)], 2.31 [1 H, ddd, *J* 12.5, 7.8 and 2.8, 6-H(eq)], 2.43 (1 H, dt, *J* 14.6 and 7.2, 4-H), 3.41 (1 H, t, *J* 9.0, 1-H) and 3.56 (2 H, t, *J* 6.5, CH_2O); *m/z* 396 (M^+).

(*B*) To a mixture of $NiCl_2 \cdot 6H_2O$ (37.1 mg, 1.56 mmol) and the enone **8** (118 mg, 3.12 mmol) in MeOH (6.1 cm^3) was added portionwise at -78 °C $NaBH_4$ (118 mg, 3.12 mmol) and the mixture was stirred for 30 min at -78 °C and then for 2 h at the ambient temperature. After addition of silica gel (3 g) at 0 °C, the mixture was stirred for 10 min at 0 °C and then filtered through Celite®.

Evaporation of the filtrate under reduced pressure gave a residue, which was chromatographed on silica gel with hexane-AcOEt (40:1) as eluant to afford **10** (76.2 mg, 62%) as an oil, whose ^{1}H NMR spectrum ($CDCl_3$) and TLC behaviors were identical with those of the compound **10** prepared by the method (A).

(+)-(1S,3aS,4S,5S,7aS)- and (1S,3aS,4S,5R,7aS)-1-t-Butoxy-4-(3-t-butyldimethylsiloxypropyl)-5-cyano-3a,4,5,6,7,7a-hexahydroindanes 11.--To *t*-BuOH (4.3 cm^3) was added K (0.168 g, 4.30 mg-atom) and the mixture was heated until the disappearance of metallic K. After addition of DME (1.5 cm^3) at the ambient temperature, to the resulting mixture was added a solution of the ketone **10** (0.379 g, 0.956 mmol) and TosMIC (0.560 g, 2.87 mmol) in DME (2.4 cm^3), and the mixture was stirred for 3 h at the same temperature. After addition of saturated aqueous $NaHCO_3$ at 0 °C, the mixture was stirred for 10 min at 0 °C and then thoroughly extracted with $CHCl_3$. The extract was washed with brine, dried and evaporated under reduced pressure to give a residue, which was purified by chromatography on silica gel. Elution with hexane-AcOEt (37:3) afforded the epimeric mixture of nitriles **11** (0.377 g, 97%) as an oil in a ratio of 54:46 (Found: M^+, 407.3207. $C_{24}H_{45}NO_2Si$ requires M, 407.3105); $[\alpha]_D^{27}$ +5.56° (*c* 0.62 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 2240 (C=N); δ_H (500 MHz, $CDCl_3$) 0.03 (6 H, s, Me_2Si), 0.70 and 0.74 (3 H, each s, 7a-Me), 0.868 and 0.871 (9 H, each s, Bu^tSi), 1.09 and 1.11 (9 H, each s, Bu^tO), 3.33 (1/2.17 H, t, *J* 14.1, 1-H), 3.44 (1.17/2.17 H, t, *J* 13.4, 1-H) and 3.52-3.65 (2 H, m, CH_2O); *m/z* 407 (M^+).

(+)-(1S,3aS,4S,5S,7aS)-5-Acetyl-1-t-butoxy-4-(3-t-butyldimethylsiloxypropyl)-3a,4,5,6,7,7a-hexahydro-7a-methylindane 12.--To a solution of MeLi in Et_2O (1.5 mol dm^{-3}; 10.1 cm^3, 15.2 mmol) in dry hexane (29 cm^3) was added dropwise at 0 °C a solution of the nitrile **11** (1.24 g, 3.04 mmol) in dry hexane (8 cm^3) and the mixture was stirred for 30 min at the ambient temperature. After addition of saturated aqueous NH_4Cl at 0 °C, the resulting mixture was extracted with Et_2O. The extract was washed with brine, dried and evaporated under reduced pressure to give a residue, which was adsorbed on silica gel. After having been allowed to stand for 15 h at the ambient temperature, elution with hexane-AcOEt (17:3) afforded the title compound **12** (1.08 g, 84%) as an oil (Found: C, 70.63; H, 11.52. $C_{25}H_{48}O_3Si$ requires C, 70.70; H, 11.39%); $[\alpha]_D^{26}$ +21.23° (*c* 1.43, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1710 (C=O); δ_H (500 MHz, $CDCl_3$) 0.01 (6 H, s, Me_2Si), 0.76 (3 H, s, 7a-Me), 0.86 (9 H, s, Bu^tSi), 1.11 (9 H, s, Bu^tO), 2.13 (3 H, s, MeCO), 2.24 (1 H, dt, *J* 11.4 and 4.8, 5-H), 3.35 (1 H, t, *J* 8.5, 1-H) and 3.49 (2 H, t, *J* 6.3, CH_2O); *m/z* 424 (M^+).

(+)-(1S,3aS,4S,5S,7aS)-1-t-Butoxy-4-(3-t-butyldimethylsiloxypropyl)-3a,4,5,6,7,7a-hexahydro-5-isopropenyl-7a-methylindane 13.--To a stirred solution of MeLi in Et_2O (1.5 mol dm^{-3}; 2.91 cm^3, 4.37 mmol) in dry hexane (11 cm^3) was added at 0 °C a solution of the ketone **12** (0.371 g, 0.874 mmol) in dry hexane (4 cm^3) and the mixture was stirred for 40 min at 0 °C. After addition of saturated aqueous NH_4Cl at 0 °C, the resulting mixture was extracted with Et_2O. The extract was washed with brine, dried and evaporated to give a crude alcohol (0.389 g) as an oil, ν_{max} ($CHCl_3$)/cm^{-1} 3620 (OH); δ_H (90 MHz; $CDCl_3$) 0.01 (6 H, s, Me_2Si), 0.68 (3 H, s, 7a-Me), 0.86 (9 H, s, Bu^tSi), 1.09 (9 H, s, Bu^tO), 1.17 (6 H, s, Me_2COH), 3.24 (1 H, t, *J* 8.8, 1-H) and 3.51 (2 H, t, *J* 6.3, CH_2O), which was used for the next reaction without purification.

To a stirred solution of the above product (0.389 g) in dry pyridine (11 cm^3) was added dropwise at 0 °C $POCl_3$ (3.36 g, 2.19 mmol) and the mixture was stirred for 12 h at the ambient temperature. After addition of Et_2O and H_2O, the aqueous layer was thoroughly extracted with Et_2O. The extract was washed with brine, dried and evaporated to give a residue, which was chromatographed on silica gel. Elution with hexane-AcOEt (98:2) afforded the title compound **13** (239 mg, 63%; 89% yield based on the consumed starting material) as an oil (Found: M^+-Bu^t, 365.2863. $C_{22}H_{41}O_2Si$ requires *m/z* 365.2882); $[\alpha]_D^{27}$ +13.25° (*c* 1.59 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 1645 (C=C); δ_H (500 MHz; $CDCl_3$) 0.03 (6 H, s, Me_2Si), 0.76 (3 H, s, 7a-Me), 0.89 (9 H, s, Bu^tSi), 1.13 (9 H, s, Bu^tO), 1.66 (3 H, s, MeC=C), 3.37 (1 H, t, *J* 8.3, 1-H), 3.45-3.55 (2 H, m, CH_2O) and 4.70 (2 H, br s, $=CH_2$); *m/z* 422 (M^+). Further elution with hexane-AcOEt (95:5) gave the starting ketone **12** (100 mg).

(+)-(1S,3aS,4S,5S,7aS)-1-t-Butoxy-3a,4,5,6,7,7a-hexahydro-4-(3-hydroxypropyl)-5-i-propenyl-7a-methylindane 14.--To a stirred solution of the silyl ether **13** (140 mg, 0.332 mmol) in THF (4.2 cm^3) was added tetra-*n*-butylammonium fluoride in THF (1.0 mol dm^{-3}; 0.66 cm^3, 0.66 mmol) and the mixture was stirred for 12 h at the ambient temperature. After evaporation of the solvent, the residue was subjected to silica gel column chromatography. Elution with hexane-AcOEt (85:15) afforded the title compound **14** (102 mg, 99%) as a solid, which was recrystallised from pentane to give a powder, m.p. 74-75 °C (Found: C, 77.68; H, 11.80. $C_{20}H_{36}O_2$ requires C, 77.87; H, 11.87%); $[\alpha]_D^{29}$ +17.05° (*c* 1.02 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3630 (OH) and 1645 (C=C); δ_H (500 MHz, $CDCl_3$) 0.74 (3 H, s, 7a-Me), 1.11 (9 H, s, Bu^tO), 1.19 (1 H, t, *J* 5.1, OH disappeared with D_2O), 1.67 (3 H, s, MeC=C), 3.38 (1 H, t, *J* 8.2, 1-H), 3.56 (2 H, m, CH_2OH) and 4.68-4.72 (2 H, m, $=CH_2$); *m/z* 308 (M^+).

(+)-(1S,3aS,4S,5S,7aS)-1-*t*-Butoxy-3a,4,5,6,7,7a-hexahydro-4-(3-hydroxyiminopropyl)-7a-methyl-5-*i*-propenylindane 5.--To a stirred solution of the above alcohol **14** (30.2 mg, 0.098 mmol) and Et_3N (98.9 mg, 0.98 mmol) in anhydrous DMSO (1.0 cm^3) was added slowly at the ambient temperature a solution of SO_3·pyridine (50.0 mg, 0.314 mmol) in anhydrous DMSO (1.0 cm^3), and the mixture was stirred for 20 min at the same temperature. After addition of saturated aqueous $NaHCO_3$, the resulting mixture was thoroughly extracted with Et_2O. The extract was washed with brine, dried and evaporated to give the corresponding aldehyde (51.8 mg) as a pale yellowish oil, ν_{max} (neat)/cm^{-1} 1725 (C=O); δ_H (90 MHz; $CDCl_3$) 0.73 (3 H, s, 7a-Me), 1.10 (9 H, s, Bu^tO), 1.64 (3 H, br s, MeC=C), 3.37 (1 H, t, *J* 7.8, 1-H), 4.67 (2 H, br s, $=CH_2$) and 9.67 (1 H, t, *J* 1.9, CHO). This was used for the next reaction without further purification.

To a solution of the above aldehyde (51.8 mg) in MeOH (1.5 cm^3) were added NH_2OH·HCl (20.4 mg, 0.294 mmol) and NaOAc (27.3 mg, 0.333 mmol), and the mixture was stirred for 2 h at the ambient temperature. After evaporation of the solvent, the residue was partitioned between $CHCl_3$ and brine. The organic layer was dried and evaporated under reduced pressure to afford a residue, which was chromatographed on silica gel. Elution with hexane-AcOEt (4:1) gave the mixture of oximes **5** (29.8 mg, 95% from **14**) as an oil in a ratio of 1:1 (Found: M^+, 321.2690. $C_{20}H_{35}NO_2$ requires M, 321.2713); $[\alpha]_D^{25}$ +18.50° (*c* 1.27 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3585 (OH) and 1640 (C=N); δ_H (500 MHz, $CDCl_3$) 0.760 and 0.764 (3 H, each s, 7a-Me), 1.13 (9 H, s, Bu^tO), 1.66 and 1.67 (3 H, each s, MeC=C), 3.36 and 3.37 (1 H, each t, each *J* 8.2, 1-H), 4.71-4.75 (2 H, m, $=CH_2$), 6.64 [1/2 H, br t, *J* 10.3, C*H*=NOH (*Z*)] and 7.35 [1/2 H, t, *J* 12.3, C*H*=NOH (*E*)]; *m/z* 321 (M^+).

(+)-(5aS,5bS,8S,8aS,10aS,10bR)-8-*t*-Butoxy-des-A-androstano-[5,10-*c*]isoxazole 3.--To a stirred solution of the oximes **5** (74.4 mg, 0.232 mmol) in CH_2Cl_2 (6.7 cm^3) was added at the ambient temperature 6% aqueous NaOCl (0.38 cm^3, 0.301 mmol), and the mixture was stirred for 1 h at the same temperature. After further addition of 6% aqueous NaOCl (0.11 cm^3, 0.089 mmol), the mixture was stirred for 15 min at the same temperature. After dilution with $CHCl_3$, the resulting mixture was washed with brine, dried and evaporated under reduced pressure. The residue was purified by chromatography on silica gel with hexane-AcOEt (4:1) as eluant to give the title compound **3** (64.1 mg, 87%) as a solid, recrystallisation of which from hexane afforded prisms, m.p. 187.5-188 °C (Found: C, 75.05; H, 10.47; N, 4.33. $C_{20}H_{33}NO_2$ requires C, 75.19; H, 10.41; N, 4.38%); $[\alpha]_D^{26}$ +25.01° (*c* 1.24 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 1630 (C=N); δ_H (500 MHz, $CDCl_3$) 0.75 (3 H, s, 8a-Me), 1.13 (9 H, s, Bu^tO), 1.18 (3 H, s, 10b-Me), 2.19 [1 H, dt, *J* 14.3 and

5.5, 4-H(ax)], 2.65 [1 H, ddd, *J* 14.3, 4.4 and 2.0, 4-H(eq)], 3.38 (1 H, d, *J* 8.2, 8-H), 3.87 (1 H, d, *J* 7.6, 1-H) and 4.11 (1 H, d, *J* 7.6, 1-H); *m/z* 319 (M^+).

(+)-(8S,9S,10S,13S,14S,17S)-17-t-Butoxy-10-hydroxymethyl-5-oxo-des-A-androstane 16.--A mixture of the isoxazoline **3** (70.7 mg, 0.222 mmol), Raney Ni (W-2) (*ca.* 10 mg) and $B(OMe)_3$ (0.23 g, 2.22 mmol) in MeOH-H_2O (15:1; 6.4 cm^3) was stirred for 20 h at the ambient temperature under H_2 (1 kg cm^{-2}). After filtration through Celite^R, the filtrate was concentrated under reduced pressure. After an azeotropical removal of H_2O using benzene, the residue was taken up into $CHCl_3$ and then filtered to remove undissolved materials. Evaporation of the filtrate under reduced pressure, followed by chromatography of the residue on silica gel with hexane-AcOEt (7:3) as eluant, gave the title compound **16** (69.3 mg, 97%) as a solid, which was recrystallised from hexane to afford needles, m.p. 130-131 °C (Found: C, 74.44; H, 10.51. $C_{20}H_{34}O_3$ requires C, 74.49; H, 10.63%); $[\alpha]_D^{26}$ +35.60° (*c* 1.23 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3615 (OH) and 1695 (C=O); δ_H (500 MHz, $CDCl_3$) 0.78 (3 H, s, 13-Me), 1.06 (3 H, s, 10-Me), 1.13 (9 H, s, Bu^tO), 2.26 (1 H, ddd, *J* 14.0, 4.3 and 2.4, 6-H), 2.55 (1 H, dd, *J* 8.6 and 6.1, OH disappeared with D_2O), 2.59 (1 H, dt, *J* 14.0 and 6.1, 6-H), 3.38 (1 H, t, *J* 8.2, 17-H), 3.44 (1 H, dd, *J* 11.6 and 8.6, C*H*HOH) and 3.74 (1 H, dd, *J* 11.6 and 6.1, CH*H*OH); *m/z* 322 (M^+).

(-)-(8S,9S,10S,13S,14S,17S)-17-t-Butoxy-10-formyl-5-oxo-des-A-androstane 2.--To a stirred solution of the hydroxy ketone **16** (29.3 mg, 0.091 mmol) and Et_3N (183 mg, 1.81 mmol) in anhydrous DMSO (1.2 cm^3) was slowly added at the ambient temperature a solution of SO_3·pyridine (92 mg, 0.58 mmol) in anhydrous DMSO (0.8 cm^3), and the mixture was stirred for 1.5 h at the same temperature. After dilution with Et_2O, the resulting mixture was washed with brine. The aqueous layer was thoroughly extracted with Et_2O. The combined extracts were dried and evaporated under reduced pressure to give a residue, which was subjected to chromatography on silica gel. Elution with hexane-AcOEt (4:1) afforded the title compound **2** (28.1 mg, 97%) as a solid, recrystallisation of which from hexane yielded needles, m.p. 149-150.5 °C (Found: C, 74.45; H, 10.05. $C_{20}H_{32}O_3$ requires C, 74.95; H, 10.05%); $[\alpha]_D^{25}$ -22.05° (*c* 0.52 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 1735 (C=O) and 1705 (C=O); δ_H (500 MHz, $CDCl_3$) 0.78 (3 H, s, 13-Me), 1.13 (9 H, s, Bu^tO), 1.27 (3 H, s, 10-Me), 2.36 [1 H, ddd, *J* 14.8, 4.0 and 2.6, 6-H(eq)], 2.53 (1 H, dt, *J* 14.8 and 6.5, 6-H(ax)], 3.40 (1 H, t, *J* 11.8, 17-H) and 9.52 (1 H, s, CHO); *m/z* 320 (M^+).

(+)-(8S,9S,10S,13S,14S,17S)-17-t-Butoxy-10-(3-oxo-1-butenyl)-5-oxo-des-A-androstane 17.--A mixture of the formyl ketone **2** (42.1 mg, 0.132 mmol) and 1-triphenylphosphoranylidene-2-propanone (25.1 mg, 0.789 mmol) in xylene (7 cm^3) was heated for 90 h under reflux. After evaporation under reduced pressure, the residue was chromatographed on silica gel with hexane-AcOEt (9:1) as eluant to give the title compound **17** (42.1 mg, 89%) as an oil (Found: M^+, 360.2657. $C_{23}H_{36}O_3$ requires M, 360.2649); $[\alpha]_D^{25}$ +41.19° (*c* 0.99 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 1705 (C=O), 1680 (C=O) and 1625 (C=C); δ_H (500 MHz, $CDCl_3$) 0.78 (3 H, s, 13-Me), 1.12 (9 H, s, Bu^tO), 1.31 (3 H, s, 10-Me), 2.30 (3 H, s, MeCO), 2.65 (1 H, dt, *J* 14.2 and 6.3, 6-H), 3.38 (1 H, t, *J* 8.4, 17-H), 6.02 (1 H, d, *J* 16.5, COCH=C) and 6.79 (1 H, d, *J* 16.5, COCH=C*H*); *m/z* 360 (M^+).

(+)-(8R,9S,10R,13S,14S,17S)-17-t-Butoxy-4-androsten-3-one 18.--A mixture of the enone **17** (56.9 mg, 0.158 mmol) and 10% Pd-C (12 mg) in EtOH (2 cm^3) was shaken for 6 h at the ambient temperature under H_2 (3.0 kg cm^{-2}). After filtration through Celite^R, evaporation of the filtrate under reduced pressure gave the crude diketone (53.4 mg) as an oil, ν_{max} (neat)/cm^{-1} 1705 (C=O); δ_H (90 MHz; $CDCl_3$) 0.75 (3 H, s, 13-Me), 1.10 (9 H, s, Bu^tO), 2.12 (3 H, s, MeCO) and 3.35 (1 H, t, *J* 7.5, 17-H), which was subjected to the following reaction without purification.

To a stirred solution of the above product (53.4 mg) in MeOH (3 cm^3) was added 10% aqueous KOH (0.3 cm^3), and the mixture was stirred for 4 h at the ambient temperature. After addition of small amount of brine, the mixture was concentrated under reduced pressure and the resulting mixture was taken up into $CHCl_3$. The organic layer was washed with brine, dried and evaporated under reduced pressure to give a residue, which was chromatographed on silica gel. Elution with hexane-AcOEt (4:1) yielded the title compound **18** (43.8 mg, 81% from **17**) as a solid, which was recrystallised from ether to afford needles, m.p. 168.5-169 °C (lit.,[20] m.p. 165-166 °C); $[\alpha]_D^{25}$ +100.52° (*c* 1.60 in $CHCl_3$) [lit.,[20] $[\alpha]_D$ +103° (*c* 2.4 in $CHCl_3$)].

(+)-Testosterone 1.--A solution of the protected testosterone **18** (56.2 mg, 0.163 mmol) in CF_3CO_2H (3.0 cm^3 38.9 mmol) was stirred for 70 min at the ambient temperature. After evaporation under reduced pressure, followed by addition of MeOH (1.0 cm^3), H_2O (0.2 cm^3) and LiOH (34.0 mg, 0.817 mmol), the resulting mixture was stirred for 30 min at the ambient temperature. After addition of H_2O, MeOH was removed by distillation under reduced pressure. The residue was partitioned between H_2O and $CHCl_3$. The combined $CHCl_3$ extracts were washed with brine, dried and evaporated under reduced pressure. The residue was purified by chromatography on silica gel

with hexane-AcOEt (1:1) as eluant to afford (+)-testosterone **1** (40.4 mg, 86%) as a solid, which was recrystallised from acetone-H_2O to give needles, m.p. 154-155.5 °C (lit.,[21] m.p. 154-154.5 °C); $[\alpha]_D^{25}$ +107.26° (*c* 1.25 in EtOH) [lit.,[21] $[\alpha]_D$ +103° (*c* 2.4 in EtOH)], whose spectral data were identical with those of the authentic sample.

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