Total Synthesis of *D*-Homodinordrin

Yushun Li, Bahman Nassim, and Pierre Crabbé *,†
Department of Chemistry, University of Missouri, Columbia, Missouri 65211, U.S.A.

A short and efficient synthesis of optically active *D*-homodinordrin (2b), by the general scheme outlined for the synthesis of dinordrin (1a), is reported. Unexpected observations were made in the chemical and stereochemical course of some reactions.

In the preceding paper [1] we described the total synthesis of dinordrin (1a). Earlier work has shown that rather simple chemical modifications of the steroid skeleton, such as removal of an angular methyl group or addition of a methyl at position 18, can have a dramatic effect on the biological properties. In the *A*-nor series, for example, dinordrin (1a) was shown to be *ca.* 20 times more active than anordrin (1b) as an anti-implantation agent.[2] Thus, the present report details the synthesis of a closely related analogue, *D*-homodinordrin (2b).

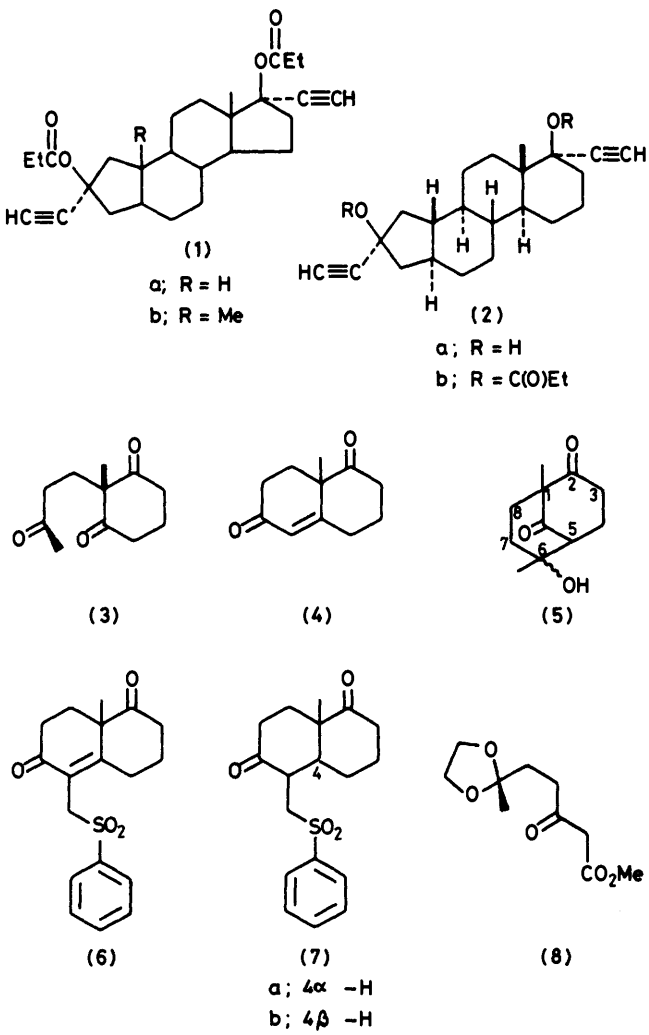
Since few synthetic schemes for the preparation of *D*-homo-*A*-nor-steroids have been reported,[3] we decided to try to extrapolate the route developed for the preparation of *A*-nor-steroids,[1] to the homo-*A*-nor-steroids. When this total synthetic scheme was extended to the *D*-homo analogue (2b), substantial differences were noted in the chemical behaviour of the intermediates, emphasizing that the chemical properties observed in one series cannot necessarily be extrapolated to another.

The Wieland–Miescher ketone (4) [4] was prepared in the optically active form from the prochiral trioxo intermediate (3), by cyclization in the presence of (−)-(*S*)-proline in dimethylformamide (DMF).[4] Although almost quantitative optical yields were obtained in the preparation of dihydroindan-1,5-diones,[1,5] in the present case the ketone (4) was only obtained in an optical yield of *ca.* 85%.[6] The diketone (4) had to be recrystallized several times to improve its optical purity. In order to secure higher optical yields, the reaction conditions were modified [choice of solvent, ratio of (*S*)-proline, temperature], but no major improvement was observed. In some cases one of the reaction products isolated was the bridged 6-hydroxy-1,6-dimethylbicyclo[3.3.1]nonane-2,9-dione (5), in agreement with observations made in the synthesis of the 5-methyl analogue of enone (4).[7]

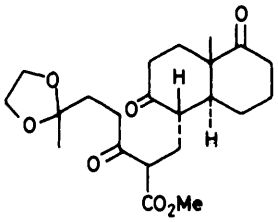
The enedione (4) was converted into the corresponding sulphone (6) by treatment with paraformaldehyde and sodium benzenesulphinate.[1,5,8] Catalytic hydrogenation of the double bond in the enone (6) was achieved in acidic ethanol solution, in the presence of palladium on charcoal. These conditions led to a mixture of the desired *trans*-(7a) and *cis*-(7b) decalones,[9] separated by fractional crystallization.

As in the case of dinordrin (1a),[1] the β-oxoester (8) [10] was treated with the sulphone (7a) to afford the intermediate (9). Although the reaction of sulphone derivatives of the dihydroindan-1,5-dione series [1,5,8] with various β-oxoesters usually led to condensation reactions in high yields, in the case of the decalone (7a) condensation with the 6,6-ethylenedioxy-3-oxoheptanoate (8) [10] gave lower yields. It is conceivable that in the present case the conformational freedom [11] of the decalin (7a) somehow hampers the formation of a new carbon–carbon bond by substitution of the sulphone group.

Catalytic reduction of the double bond in the enone (10) in ethanol with a trace of triethylamine, in the presence of 5% palladium on charcoal, yielded the saturated dione (11) almost quantitatively. Exposure of the acetal group in the intermediate (11) to 1M-aqueous hydrochloric acid in acetone furnished the trione (12) in 90% overall yield from (10). These conditions gave the thermodynamic product (12) with the equatorial configuration for the chain at C-10. Cyclization of the tricyclic ketone (12) into the $\Delta^{3(5)}$-enone (13) was achieved in 80% yield on treatment with potassium t-butoxide in toluene. An *X*-ray determination of compound (13) confirmed the structure and stereochemistry of this *A*-nor-steroid, in particular the *C*: *D trans*-configuration. It is interesting to note that no $\Delta^{1(10)}$-isomer was detected after cyclization, thus indicating that the enone (13), the kinetic product, is fairly stable. Reduction of the enone (13) in tetrahydrofuran (THF) with lithium in ammonia readily provided the expected dioxo-*A*-nor-steroid (14).



† *Present address*: Division of Scientific Research and Higher Education, UNESCO, 7 Place de Fontenoy, Paris 75700, France.



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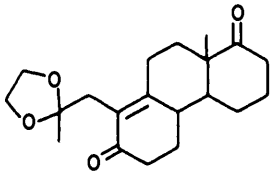

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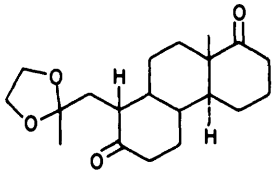

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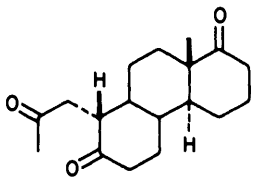

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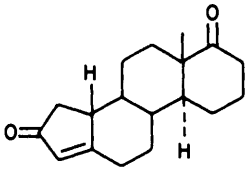

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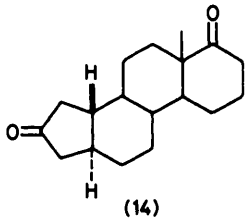

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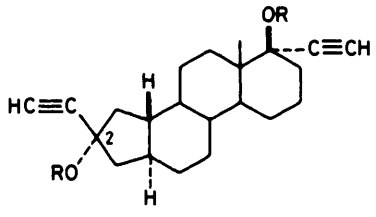

(15)
a; R = H
b; R = C(O)Et

Ethynylation at positions 2 and 17 of the diketone (14) was achieved by addition of potassium acetylide in THF, thus affording a *ca.* 1 : 1 mixture of the isomeric 2-ethynyl derivatives (2a) and (15a), separable by column chromatography. The 2β-hydroxy derivative (2a) was obtained as a crystalline compound, which was esterified to provide the *D*-homo homologue (2b) of dinordrin (1a).*

Experimental

M.p.s were determined with a Fisher-Johns apparatus and were corrected. I.r. spectra were obtained with a Beckman infrared spectrometer model IR-10. U.v. spectra were taken with a Perkin-Elmer 576 ST spectrophotometer. Rotations were taken in chloroform solution (*c* 1.0), between 16 and 22 °C with a 1-dm tube at the sodium D-line with a Carl-Zeiss 42017 polarimeter. Unless otherwise stated, ^{1}H n.m.r. spectra were recorded with a Varian EM-360 60 MHz spectrometer, for 5—8% w/v solutions in deuteriochloroform containing tetramethylsilane as internal reference. Coupling constants are accurate to ±1 Hz. Mass spectra were recorded with a Dupont instrument, model 21-490, ionizing energy 70 eV. *X*-Ray data were collected on an Enraf-Nonius CAD4 Diffractometer using Mo-K_α radiation from a graphite monochromator; the structure was solved using MULTAN.

Column chromatography was carried out using silica gel (Kieselgel 60, Art 9385, 230—400 mesh, Merck Darmstadt). T.l.c. was carried out with Camlab ' Polygram ' pre-coated silica plates, and Merck 2-mm thickness preparative plates were used for preparative t.l.c.

Microanalyses were performed by Galbraith Laboraties, Inc., Knoxville, Tennessee, U.S.A.

Ether refers to diethyl ether.

(+)-(8a*S*)-8a-*Methyl*-3,4,8,8a-*tetrahydronaphthalene*-1,6-(2H,7H)-*dione* (4).—(−)-(*S*)-Proline (1.5 g) was added to a solution of the trione (3) [4,5] (35.3 g, 0.18 mol) in DMF (185 ml). The suspension was stirred at room temperature, under nitrogen, for 24 h. The red coloured solution was filtered and DMF was evaporated on a Rotavapor giving a dark residue (36.5 g). This product was purified by column chromatography (eluted with hexane–ethyl acetate, 7 : 3) to afford the bicyclic enedione (4) (26.5 g, 83%) as an oil containing the desired enantiomer in 80% e.e.

The above oily material (10 g) was dissolved in anhydrous ether (65 ml) and cooled to −15 °C for 20 h. The crystalline material was collected and washed with an ice-cold mixture of hexane–ether (1 : 1), giving the enedione (4) (4.8 g), m.p. 46—48 °C; $[\alpha]_D$ +90° (lit.,[5,12] m.p. 50—51 °C, $[\alpha]_D$ +100°).

A by-product was isolated in some experiments (<10%) and corresponded to 6-hydroxy-1,6-dimethylbicyclo[3.3.1]-nonane-2,9-dione (5), m.p. 112—114 °C; $[\alpha]_D$ 0°; $\nu_{max.}$ ($CHCl_3$) 3 420 and 1 710 cm^{-1}; δ 1.14 (s, 3 H, 1-Me) and 1.43 (s, 3 H, 6-Me); *m/z* 196 (M^+), 178 ($M^+ - H_2O$), 138 ($M^+ - C_2H_6O$), 126, and 69.

(+)-(8a*S*)-8a-*Methyl*-5-(*phenylsulphonylmethyl*)-3,4,8,8a-*tetrahydronaphthalene*-1,6(2H,7H)-*dione* (6).—A mixture of the enedione (4) ($[\alpha]_D$ +90°) (4.5 g, 25.5 mmol), paraformaldehyde (0.9 g 30 mmol), sodium benzenesulphinate (6.2 g, 43.4 mmol), in ethanol (50 ml), DMF (25 ml), and anhydrous acetic acid (2.50 ml) was stirred, under nitrogen, at 60—70 °C for 24 h.[10] Then the reaction mixture was diluted with methylene dichloride and washed with aqueous sodium hydrogen carbonate. The organic solution was dried (Na_2SO_4), filtered, and evaporated to give a brown material. After chromatography over silica gel and elution with hexane–ethyl acetate (6 : 4), starting material (4) (0.702 g) was recovered. The major component obtained by crystallization from ethanol was the desired sulphone (6) (1.7 g), m.p. 109—110 °C; $[\alpha]_D$ +75°; $\nu_{max.}$ (KBr) 1 715, 1 665, and 1 605 cm^{-1}; $\lambda_{max.}$ (EOH) 219 (ε 12 000) and 253 nm (ε 11 300); δ 1.45 (s, 3 H, Me), 4.35 (s, 2 H, CH_2SO_2), and 7.5—8.0 (m, 5 aromatic H) (Found: C, 64.9; H, 6.35; S, 9.8. Calc. for $C_{18}H_{20}O_4S$: C, 65.03; H, 6.06; S, 9.65%).

In addition the racemic sulphone (4) (0.5 g) was obtained.

(+)-(8a*S*)-8a-*Methyl*-5-(*phenylsulphonylmethyl*)*perhydronaphthalene*-1,6-*dione* (7).—A solution containing the sulphone (6) (1 g) dissolved in ethanol (50 ml) was acidified with 1M-hydrochloric acid (1 ml). Then 5% Pd–C (200 mg) was added and the mixture hydrogenated under 30 lb in^{-2} for 3 h, After completion of the hydrogenation (monitored by t.l.c), the mixture was filtered and evaporated to dryness. The residue was dissolved in ethyl acetate and washed with water until the pH reached *ca.* 6.5. After being dried (Na_2SO_4) crude product (0.993 g) was obtained. This material was crystallized in hexane–ethyl acetate, thus giving crystalline

* The biological properties of these new steroids will be published elsewhere.

sulphone (7a) (0.378 g, 38%), m.p. 143—146 °C. Recrystallization from methanol gave the pure material, m.p. 150—151 °C; $[\alpha]_D$ +25°; $\nu_{max.}$ ($CHCl_3$) 1 700, 1 145, and 1 300 cm^{-1}; δ 1.41 (s, 3 H, 18-Me), 4.25, 4.02, and 3.07 (m, 3 H, $CHCH_2SO_2$), and 7.5—8.1 (m, 5 aromatic H) (Found: C, 64.8; H, 6.9; S, 9.85. Calc. for $C_{18}H_{22}O_4S$: C, 64.64; H, 6.63; S, 9.52%).

In addition oily material (0.288 g) containing the isomeric compound (7b) was isolated from the mother-liquors (total yield 66%).

(−)-D-*Homo*-4-*nor*-3,5-*secoestr*-9-*ene*-2,5,17-*trione Ethylene* 2-*Acetal* (10).—A suspension of potassium hydride (396 mg, 9.9 mmol) in toluene (50 ml) was prepared. A solution of β-oxoester (8) [1] (780 mg, 3.6 mmol) in toluene (9 ml) was added slowly to this suspension under nitrogen. After 0.5 h the sulphone (7a) (1 g, 3 mmol) dissolved in toluene (9 ml) was added dropwise and the mixture was stirred at room temperature for 8 h, and then treated with a solution of acetic acid (3.6 ml) in toluene (18 ml). After evaporation of the organic solvent, oily material (9) (2.2 g) was obtained. The latter was treated with 10% aqueous potassium hydroxide (36 ml) in methanol (150 ml), at 0—5 °C. Then the solution was neutralized with acetic acid and evaporated to give a gummy material, which was diluted with toluene (250 ml) and refluxed with a Dean–Stark trap for 2.5 h. Evaporation of the organic solvent afforded an oily product (10) (1.56 g). This product was further purified by column chromatography over silica gel (eluted with hexane–ethyl acetate 1 : 1) to give crude (10) (1.376 g), which was recrystallized in hexane–ethyl acetate. Pure compound (10) had m.p. 130—131 °C; $[\alpha]_D$ −55°; $\nu_{max.}$ (KBr) 1 710, 1 670, and 1 616 cm^{-1}; $\lambda_{max.}$ (EtOH) 249.5 nm (ε 17 000); δ 1.26 (s, 6 H, 2- and 18-Me), 2.8 (s, 2 H, 1-CH_2), and 3.88 (s, 4 H, OCH_2CH_2O); *m/z* 332 (M^+), 317 (M^+ − Me), 288 ($M^+ - C_2H_4O$), 272, 262, 247, and 205 (Found: C, 71.95; H, 8.5. Calc. for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49%).

When the isomeric sulphone (7b) was used the 14β-isomer of compound (10) was formed in *ca.* 40% yield, with a slightly higher R_F value, m.p. 102—105 °C; $[\alpha]_D$ +10°; $\nu_{max.}$ ($CHCl_3$) 1 705, 1 665, and 1 615 cm^{-1}; $\lambda_{max.}$ (EtOH) 249.5 nm (ε 11 200); δ 1.27 and 1.26 (2 s, 3- and 18-Me), 2.77 (s, 2 H, 1-CH_2), and 3.87 (s, 4 H, OCH_2CH_2O); *m/z* 332 (M^+), 317 (M^+ − Me), 288, 277, and 260.

(−)-D-*Homo*-4-*nor*-3,5-*secoestrane*-2,5,17-*trione Ethylene* 2-*Acetal* (11).—The tricyclic compound (10) (50 mg, 0.15 mmol) was dissolved in absolute ethanol (20 ml) and triethylamine (0.015 ml) and 5% Pd–C (25 mg) were added. The suspension was hydrogenated under 30 lb in^{-2} for 3 h. When the hydrogenation was complete (monitored by t.l.c.) the reaction mixture was filtered, evaporated, and chromatographed over silica gel. Elution with hexane–ethyl acetate (7 : 3) gave reduced compound (11) (48 mg, 95%), $[\alpha]_D$ −40°; $\nu_{max.}$ (neat) 1 710 cm^{-1}; δ 1.18 (s, 3 H, 18-Me), 1.27 (s, 3 H, 3-Me), and 3.91 (s, 4 H, OCH_2CH_2O); *m/z* 334 (M^+), 319 (M^+ − Me), 231, 167, 149, and 87 ($CH_3COC_2H_4O^+$).

This compound was used directly for the hydrolysis of the acetal group.

(−)-D-*Homo*-4-*nor*-3,5-*secoestrane*-2,5,17-*trione* (12).—The acetal (11) (62 mg, 0.185 mmol) dissolved in acetone (6.5 ml) was treated with 1M-hydrochloric acid (0.3 ml) and stirred at room temperature for 2 h. After that time sodium hydrogen carbonate powder (45 mg) was added and stirring was continued for 1 h. The solution was filtered and evaporated giving crude trioxo compound (12) (55 mg), m.p. 201—202.5 °C. Recrystallization from ethyl acetate–methylene dichloride afforded a pure sample of the trioxo compound (12), m.p. 202—203 °C; $[\alpha]_D$ −90 °C; $\nu_{max.}$ (KBr) 1 710 cm^{-1}; δ 1.45 (s, 3 H, 18-Me), and 2.25 (s, 3 H, COMe); *m/z* 290 (M^+), 272 ($M^+ - H_2O$), 247 ($M^+ - C_2H_3O$), and 233 ($M^+ - C_2H_5O$) (Found: C, 74.75; H, 8.8. Calc. for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02%).

(−)-D-*Homo*-4-*norestr*-3(5)-*ene*-2,17-*dione* (13).—The triketone (12) (100 mg, 0.034 mmol) was dissolved in toluene (6 ml) with heating, then the solution was cooled to the room temperature. To this solution, potassium t-butoxide (60 mg) was added and the mixture was stirred for 2.5 h. The reaction was quenched by addition of a saturated sodium dihydrogen phosphate solution (6 ml) and the organic layer was separated. The aqueous layer was extracted with ethyl acetate several times and the combined organic extracts were dried (Na_2SO_4) and evaporated to afford an oily product. After column chromatography over silica gel (eluted with hexane–ethyl acetate, 7 : 3), enone (13) (75 mg, 80%) was obtained, m.p. 143—146 °C. Recrystallization from hexane–ethyl acetate gave an analytical sample of the enone (13), m.p. 145—147 °C; $[\alpha]_D$ −90°; $\nu_{max.}$ (KBr) 1 710 and 1 620 cm^{-1}; $\lambda_{max.}$ (EtOH) 232 nm (ε 14 500); δ 1.13 (s, 18-Me) and 5.75 (s, 1 vinylic H); *m/z* 272 (M^+), 257 (M^+ − Me), 254 ($M^+ - H_2O$), and 233 (Found: C, 78.9; H, 9.2. Calc. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88%).

(+)-D-*Homo*-4-*norestrane*-2,17-*dione* (14).—Lithium metal (50 mg) was added to ammonia (20 ml) (twice distilled) with stirring, to give a deep blue solution. The enone (13) (80 mg, 0.28 mmol) dissolved in THF (2 ml) was added and stirred for 8 min. After that time, ammonium chloride crystals were added carefully until the blue colour disappeared. After evaporation of the ammonia, the residue was diluted with water and extracted with methylene dichloride. Then the extracts were washed with water and evaporated to give a crude material (74 mg), which was dissolved in acetone (10 ml) and treated with Jones reagent at 0—5 °C for 15 min.[13] The excess of Jones reagent was destroyed by addition of a sodium hydrogen sulphite solution and neutralized with sodium hydrogen carbonate. After the acetone had been distilled off the residue was extracted with methylene dichloride, washed with water, dried (Na_2SO_4), and filtered, and evaporated to dryness to give the *D*-homo-diketone (14) (76 mg). Purification by column chromatography over silica gel (elution with hexane–ethyl acetate 7 : 3) provided pure material (14) (42 mg); recrystallization from hexane–ethyl acetate gave colourless needles, m.p. 120.5—122 °C; $[\alpha]_D$ +135°; $\nu_{max.}$ (KBr) 1 745 and 1 710 cm^{-1}; δ 1.10 (s, 18-Me); *m/z* 274 (M^+), 259 (M^+ − Me), 256 ($M^+ - H_2O$), 231, 229, 217, 203, and 201 (Found: C, 79.0; H, 9.8. Calc. for $C_{18}H_{26}O_2$: C, 78.78; H, 9.55%).

(−)-2α,17α-*Diethynyl*-2β,14β-*dihydroxy*-4-*nor*-5α-*estrane* (2a) *and* (−)-2β,17α-*Diethynyl*-2α,14β-*dihydroxy*-4-*nor*-5α-*estrane* (15a).—Powdered potassium hydroxide (2.2 g) was suspended in THF (10 ml) (distilled over lithium aluminium hydride), cooled on an ice-bath; then, with stirring under anhydrous conditions, a stream of dry acetylene was passed through the suspension for 15 min. A solution of the diketone (14) (40 mg, 0.145 mmol) in anhydrous THF (2 ml) containing a few drops of pure acetone was then added and stirring was continued for 20 min. The reaction was stopped by addition of enough water to dissolve the solid. The THF solution was separated and the aqueous layer was extracted with methylene dichloride several times. The combined organic extracts were washed with water, then dried ($MgSO_4$) and evaporated to dryness under reduced pressure giving a mixture of the 2α- and 2β-ethynyl steroids (2a) and (15a) (53 mg). The crude diethynyl mixture was separated by column chro-

matography on silica gel (eluting with methylene dichloride–ethyl acetate, 98 : 2), followed by crystallization in wet ethyl acetate, giving the pure 2α-ethynyl isomer (2a) (24 mg), m.p. 61—63 °C; $[\alpha]_D$ −10°; $\nu_{max.}$ (KBr) 3 410, 3 300, and 2 250 cm^{-1}; δ 0.93 (s, 18-Me) and 2.49 (2 s, C≡CH); *m/z* 326 (M^+), 308 ($M^+ - H_2O$), 293, 290, and 243 (Found: C, 78.7; H, 9.65. Calc. for $C_{22}H_{30}O_2 \cdot 0.5H_2O$: C, 78.76; H, 9.31%).

The 2β-ethynyl isomer (15a) (13 mg) was also isolated. After recrystallization from wet ethyl acetate it exhibited m.p. 70—72 °C; $[\alpha]_D$ −45°; $\nu_{max.}$ (KBr) 3 415, 3 300, and 2 350 cm^{-1}; δ 0.98 (s, 18-Me), 2.22 (s, 2 C≡CH), and 2.49 (s, 17-C≡CH); *m/z* 326 (M^+), 308 ($M^+ - H_2O$), 293 ($M^+ - Me - H_2O$), 290 ($M^+ - 2\ H_2O$), and 243 (Found: C, 78.55; H, 9.6. Calc. for $C_{22}H_{30}O_2 \cdot 0.5H_2O$: C, 78.76; H, 9.31%).

(−)-2α,17α-*Diethynyl*-2β,17β-*dipropionyloxy*-D-*homo*-4-*nor*-5α-*estrane* (2b).—A solution containing the 2α-ethynyl compound (2a) (47 mg, 0.157 mmol) in propionic acid (2 ml) and propionic anhydride (1.5 ml) was prepared. A few crystals of toluene-*p*-sulphonic acid were added and the mixture was kept at room temperature, while the reaction was monitored by the t.l.c. When esterification was complete (5 h), water was added to decompose the excess of anhydride and the acid was neutralized with sodium hydrogen carbonate. The solution was extracted with ether, the organic layer was washed with water, dried ($MgSO_4$), filtered, and evaporated to dryness under reduced pressure giving crude dipropionate (2b) (48 mg). Purification by column chromatography over silica gel (elution with hexane–ethyl acetate, 10 : 1) afforded the pure diester (2b) (33 mg) as an oil, $[\alpha]_D$ −10°; $\nu_{max.}$ (neat) 3 290 and 1 735 cm^{-1}; δ 1.0 (s, 18-Me), 1.12 (t, 2 × CH_2CH_3), and 2.64 and 2.53 (2 s, C≡CH); *m/z* 438 (M^+), 382, 364, 308, 307, 290, and 57.

(−)-2β,17α-*Diethynyl*-2α,17β-*dipropionyloxy*-D-*homo*-4-*nor*-5α-*estrane* (15b).—The esterification of the diol (15a) (44 mg, 0.145 mmol) with propionic acid (1.8 ml) and propionic anhydride (1.3 ml) under the same conditions as above afforded crude dipropionate (15b) (53 mg). After chromatography, pure dipropionate (15b) (45 mg) was obtained as a crystalline compound, m.p. 58—60 °C; $[\alpha]_D$ −35°; $\nu_{max.}$ ($CHCl_3$) 3 285 and 1 735 cm^{-1}; δ 0.98 (s, 18-Me), 1.14 (t, 2 Et), and 2.63 and 2.53 (2 s, C≡CH); *m/z* 438 (M^+), 382, 364, 307, 290, and 57.

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