Total Synthesis of Dinordrin and 18-Homodinordrin

By PIERRE CRABBÉ,* LOTHAR BIEBER, and BAHMAN NASSIM

(*Department of Chemistry, University of Missouri, Columbia, Missouri 65211 and Laboratoire de Chimie Organique, CERMO, Université Scientifique et Médicale, Grenoble, France)

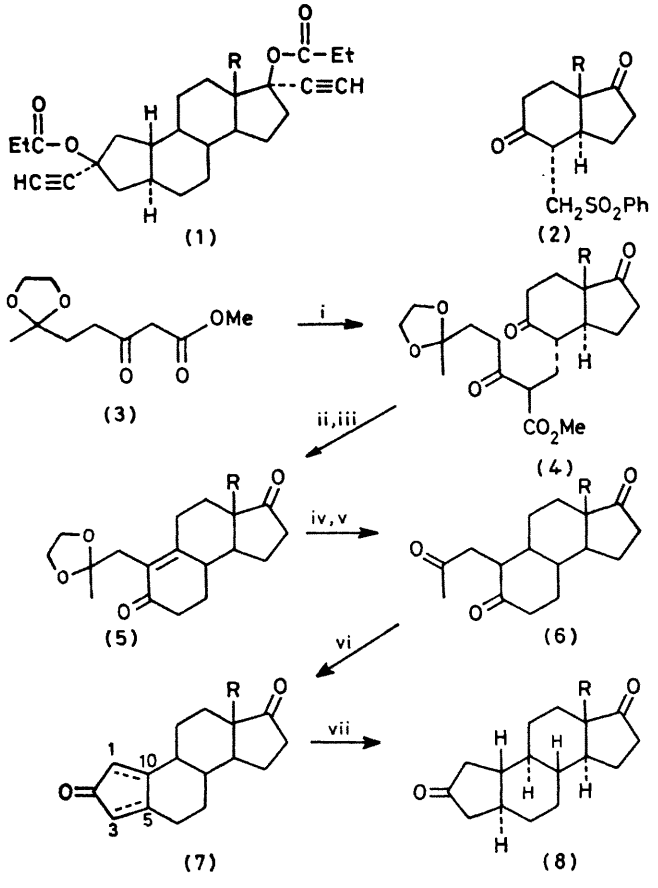
Summary A short and flexible synthetic route to A : B-*trans* A-norsteroids is described.

THE unusual fertility inhibitor properties[1] reported recently for dinordrin (**1a**), about ten times more potent than anordrin, as well as those of 18-homodinordrin (**1b**),[2] confirm that these A-nor-compounds form an interesting class of non-natural steroids. As their preparation from sapogenins and sterols is rather lengthy and low yielding, a versatile total synthetic scheme was desirable. We now report a

* Address for correspondence.

stereocontrolled preparation of both dinordrin (**1a**) and 18-homodinordrin (**1b**) by a short synthetic route based on a remarkable stereospecific condensation reaction.[3,4]

The sulphone (**2a**), prepared by treatment of optically active (+)-7a-β-methyl-6*H*-7,7a-dihydroindane-1,5-dione with paraformaldehyde and benzenesulphinic acid in triethanolamine, followed by catalytic hydrogenation in the presence of palladium on charcoal,[5] was obtained in crystalline form (m.p. 92—94 °C; $[\alpha]_D$ +179°).† Reaction of (**2a**) with 6,6-ethylenedioxy-3-oxoheptanoate (**3**)[3] in anhydrous toluene in the presence of sodium hydride provided the triketoester (**4a**). Treatment of this bicyclic intermediate



a; R = Me, **b**; R = Et. Reagents and conditions, i, NaH, PhMe, ii, NaOH, MeOH, iii, AcOH, iv, H_2/Pd, EtOH–NEt_3, v, HCl, MeCOMe, vi, KOH–MeOH, heat, vii, Li–NH_3.

with an aqueous solution of sodium hydroxide led to hydrolysis, followed by cyclization and decarboxylation, thus affording the ene-dione (**5a**) in >80% yield. Catalytic hydrogenation of (**5a**) in ethanol and a trace of triethylamine, in the presence of 5% palladium on charcoal, yielded the saturated dione, which after brief exposure to 1N aqueous hydrochloric acid in acetone furnished the trione (**6a**) (m.p. 133—134 °C; $[\alpha]_D$ + 129°) in 74% overall yield from (**5a**). Cyclization of the tricyclic keto-derivative (**6a**) into a mixture of $\Delta^{1(10)}$- and $\Delta^{3(5)}$-enones (**7a**) [m.p. 135—138 °C; ν_{max} 1740, 1695, and 1620 cm^{-1}; δ 0·88 (Me) and 0·92 (Me)], was achieved in 75% yield on treatment with methanolic potassium hydroxide.[6] The pure $\Delta^{3(5)}$-isomer of (**7a**) {m.p. 182—184 °C; $[\alpha]_D$ + 51°; λ_{max} 229 nm (ε 13,000); δ 5·67 (vinyl H)}, was obtained by crystallization from hexane. Lithium–ammonia reduction of the mixture (**7a**) in ether solution provided the known A-noroestrane-2,17-dione (**8a**)[2] (m.p. 158—160 °C; $[\alpha]_D$ + 262°), shown to be identical with an authentic sample by the usual methods.

Ethynylation at positions 2 and 17 of the diketone (**8a**) was achieved by addition of lithium acetylide–ethylenediamine complex,[2] affording a *ca.* 3:2 mixture of isomeric 2-ethynyl derivatives which were separable by preparative t.l.c. using cyclohexane–ethyl acetate (7:3) as solvent system. Esterification with propionic anhydride of the 2β-hydroxy-isomer (m.p. 145 °C; $[\alpha]_D$ −6°) then afforded optically active dinordrin (**1a**).

The known methylenesulphone 7a-β-ethyl-6*H*-7,7a-dihydroindane-1,5-dione (**2b**)[5] was submitted to the same reaction sequence, providing the synthetic intermediate (**5b**) {m.p. 94–95 °C; $[\alpha]_D$ + 30°; λ_{max} 248 nm (ε 13,000); ν_{max} 1731, 1659, and 1605 cm^{-1}; δ 3·77 (OCH_2CH_2O), 1·20 (Me), and 0·83 (CH_2CH_3)}. Hydrogenation of (**5b**) was achieved as above (5% Pd/C) to generate the saturated dione, which on treatment with dilute hydrochloric acid in acetone gave the trione (**6b**) {m.p. 140—142 °C; $[\alpha]_D$ + 16°, ν_{max} 1733, 1715, and 1702 cm^{-1}; δ 2·19 (Me) and 0·77 (CH_2CH_3)}. Cyclization of the A-ring was accomplished in methanolic sodium hydroxide and the product (**7b**) was reduced with lithium in liquid ammonia to afford the A-nordiketo-steroid (**8b**) (m.p. 102—104 °C; $[\alpha]_D$ + 211°). The known diketone (**8b**) was then converted into 18-homodinordrin (**1b**) by conventional techniques.[2]

This procedure is short, flexible, and easy to perform, thus constituting a useful synthetic approach to this class of biologically important A-norsteroids. It is noteworthy that the cyclization reaction of the intermediates (**4**), followed by the catalytic reduction of the enones (**5**), condensation, and Birch reduction of the cyclopentenones (**7**) afforded the diones (**8**) with the correct stereochemistry at all asymmetric centres, thus showing the total synthetic scheme of Wiechert *et al.*[5] to be extendable to A-norsteroids with the A:B-*trans* configuration.

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† Spectroscopic properties and satisfactory elemental analyses were obtained for all new compounds.

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