Total Synthesis of (±)-14α-Methyl-19-norsteroids

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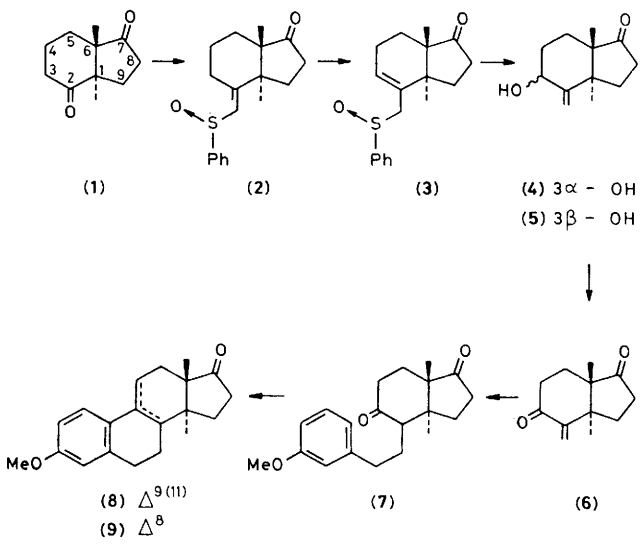
Trans-1,6-Dimethylbicyclo[4.3.0]nonane-2,7-dione was converted, in six steps, into a mixture of (±)-3-methoxy-14-methyl-14α-estra-1,3,5(10),9(11)-tetraen-17-one and the corresponding Δ^8-isomer.

Earlier attempts to prepare 14α-methyl-19-norsteroids, through base-catalysed alkylation of 15-ketones derived from estrone,[1,2] were complicated by the influence of peripheral structural features upon the stereochemical outcome. Furthermore, the modification or transposition of ring D functionality is more difficult after introduction of a 14-methyl group, owing to the increased steric hindrance.[3]

Accordingly, attention was turned to totally synthetic methods. One such approach is suggested by the differing reactivity of the carbonyl groups in *trans*-1,6-dimethylbicyclo-[4.3.0]nonane-2,7-dione (**1**).[4] Although attachment of a 3′-methoxyphenethyl moiety to C(2) of the diketone (**1**) would furnish the elements of the desired carbon skeleton directly, the need to functionalise C(9) (steroid numbering) for subsequent ring closure suggested that prior conversion of (**1**) into the 2-methylene-3,7-diketone (**6**) for attachment to a 3′-methoxybenzyl moiety,[5] would be advantageous.



This objective was realised, using a recently described reaction sequence for converting carbonyl compounds into homologated allylic alcohols.[6] Treatment of (**1**) with α-lithiated diethyl (phenylsulphinyl)methylphosphonate in tetrahydrofuran (THF) (1 h at −78 °C, and 48 h at 25 °C) afforded the 2-(phenylsulphinyl)methylene derivative (**2**) (56%),† m.p. 192—193 °C (from benzene), ν_{max} 1735 cm^{-1} (7-CO). Some unchanged diketone (**1**) (16%) was recovered, but no other products were detected in the reaction mixture. The compound (**2**) was smoothly isomerised to the allylic sulphoxide (**3**) (71%), m.p. 132—135 °C (from benzene–hexane), in the presence of potassium hydride in THF. Treatment of the sulphoxide (**3**) with trimethyl phosphite and dimethylamine in absolute methanol at 60 °C resulted in [2,3] sigmatropic rearrangement,[6,7] to give an inseparable mixture of the 2-methylene-3-alcohols (**4**) and (**5**) (95%), as a gummy crystalline mass, m.p. 45—150 °C (after sublimation); the relative intensities of n.m.r. signals revealed that the ratio of 3-axial and 3-equatorial isomers [(**4**):(**5**)] present in the mixture was *ca.* 1:2 [δ($CDCl_3$) 0.87 and 1.63 (1- and 6-CH_3), 4.45 (1H, br. s, $w_{\frac{1}{2}}$ 10 Hz, 3-H_{eq}), and 4.97 and 5.2 (each 1H, br. s, $w_{\frac{1}{2}}$ 2.5 Hz, C:CH_2) for (**4**); δ 0.96 and 1.07 (1- and 6-CH_3), 4.55 (obsc.) (1H, br. s, $w_{\frac{1}{2}}$ *ca.* 25 Hz, 3-H_{ax}), and 4.81 and 5.31 (each 1H, br. s, $w_{\frac{1}{2}}$ 4 Hz, C:CH_2) for (**5**)].

Oxidation of the mixture [(**4**)+(**5**)] with pyridinium chlorochromate in dichloromethane gave the 2-methylene-3,7-diketone (**6**) (84%), m.p. 130—156 °C (decomp.) (from benzene–hexane), ν_{max} 1740 (7-CO), 1690 and 1625 cm^{-1} (enone), δ($CDCl_3$) 1.06 and 1.09 (1- and 6-CH_3), and 5.22 and 6.05 (each 1H, d, *J* 1 Hz, C:CH_2).

Conjugate addition of the 3-methoxybenzyl moiety to (**6**) was carried out with 3-methoxybenzylmagnesium chloride (8 mol) and copper(II) acetate monohydrate (2 mol) in THF;[5] the compound (**6**) in THF was added slowly (45 min) to the reagent mixture at −20 °C under nitrogen. After a further

† Satisfactory C and H combustion analyses and spectral data were obtained for all new compounds.

20 min at −20 °C and 20 min at −10 °C, the reaction was quenched through rapid addition of the mixture to cold aqueous 0.5 M-sulphuric acid; brief treatment of the resultant product with methanolic 0.1 M-sodium hydroxide furnished the seco-steroid (**7**) (78%), m.p. 78—79 °C (from aqueous methanol).

The compound (**7**) was cyclised in the presence of toluene-*p*-sulphonic acid in refluxing benzene (20 h), to give a mixture of the $\Delta^{9(11)}$- and Δ^{8}-compounds (**8**) and (**9**) (total, 87%); n.m.r. examination showed a *ca.* 1:1 ratio of isomers.

The composition of the mixture remained unchanged upon more prolonged treatment with acid. Although preparative separation of the isomers proved difficult, column chromatography on silica gel afforded some pure (±)-3-methoxy-14-methyl-14α-estra-1,3,5(10),9(11)-tetraen-17-one (**8**), m.p. 178—179 °C (from benzene–hexane), δ($CDCl_3$) 0.79 and 0.98 (13β- and 14α-CH_3), 3.78 (3-OCH_3), 6.22 (1H, br. s, $w_{\frac{1}{2}}$ 8 Hz, 11-H), 6.54—6.82 (2H, m, 2- and 4-H), and 7.62 (1H, d, *J* 9 Hz, 1-H); the remaining fractions were mixed, but those enriched in (**9**) (>90%) were combined and separated by multiple-development p.l.c., to give pure (±)-3-methoxy-14-methyl-14α-estra-1,3,5(10),8-tetraen-17-one (**9**) m.p. 163—164 °C (from benzene–hexane), δ 1.01 and 1.08 (13β- and 14α-CH_3), 3.8 (3-OCH_3), 6.6—6.86 (2H, m, 2- and 4-H), and 7.17 (1H, d, *J* 9 Hz, 1-H).

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