# Total Synthesis of Substituted (±)-6,6-Dimethyl-B-norestra-1,3,5(10)-trien-17β-ols and their 9β-Isomers

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Total syntheses of (±)-1,4-dimethoxy-6,6-dimethyl-B-norestra-1,3,5(10)-trien-17β-ol (11a), (±)-2,3-dimethoxy-6,6-dimethyl-B-norestra-1,3,5(10)-trien-17β-ol (11b), and (±)-3-methoxy-6,6-dimethyl-B-norestra-1,3,5(10)-trien-17β-ol (11c), have been carried out starting from 4,7-dimethoxy-3,3-dimethylindan-1-one (1), 5,6-dimethoxy-3,3-dimethylindan-1-one (2), and 4'-methoxy-3-methylbut-2-enophenone (4), respectively. Generally, it is found that the intermediate 6,6-dimethyl-B-norestra-1,3,5(10),8-tetraen-17β-ols (10), on lithium–liquid ammonia reduction, yield a mixture of 8β,9α- and 8β,9β-trienols, (11) and (12) respectively, in the ratio 1 : 1. This is due to the comparable stabilities of these two isomers. However, the reduction carried out in presence of aniline affords a higher percentage of the 8β,9α-trienol (11). The assignment of configurations is made by chemical and ¹H n.m.r. analysis. Catalytic hydrogenation of the tetraenols (10) is shown to proceed *via* initial isomerisation to the corresponding 6,6-dimethyl-B-norestra-1,3,5(10),9(11)-tetraen-17β-ols (26), followed by hydrogenation from the β-side to give, exclusively, the 8β,9β-trienols (12).

THE contraction of the B-ring in the natural steroid hormones to a five-membered ring results in lowering of the classical types of steroid hormone biological activity.[1]


(1) R¹ = OMe, R² = R³ = H
(2) R¹ = H, R² = R³ = OMe
(3) R¹ = R² = H, R³ = OMe

(4)   (5)
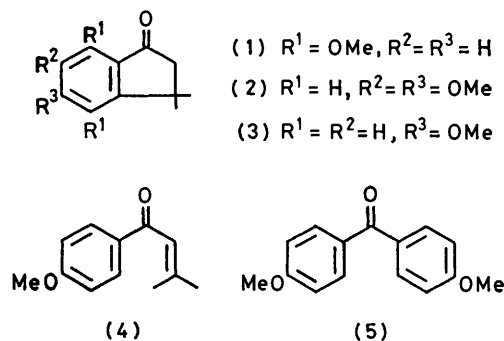
On the other hand incorporation of extra methyl groups into the steroid skeleton leads to enhanced biological activity of the parent steroid.[2] In order to investigate the effect of introduction of extra methyl groups to B-

been extended to the synthesis of B-norestrone,[4] appeared appropriate for the synthesis of the above analogues starting from 4,7-dimethoxy-3,3-dimethyl-(1), 5,6-dimethoxy-3,3-dimethyl-(2), and 5-methoxy-3,3-dimethyl-indan-1-one (3) respectively. The indanones (1) and (2) have been prepared by reported methods.[5,6]

Friedel–Crafts reaction of anisole and ββ-dimethyl-acryloyl chloride, using anhydrous aluminium chloride, resulted in the ketone (4) exclusively, instead of the desired indanone (3).[7] Further attempts to convert this ketone into the indanone (3), as described below, were unsuccessful.
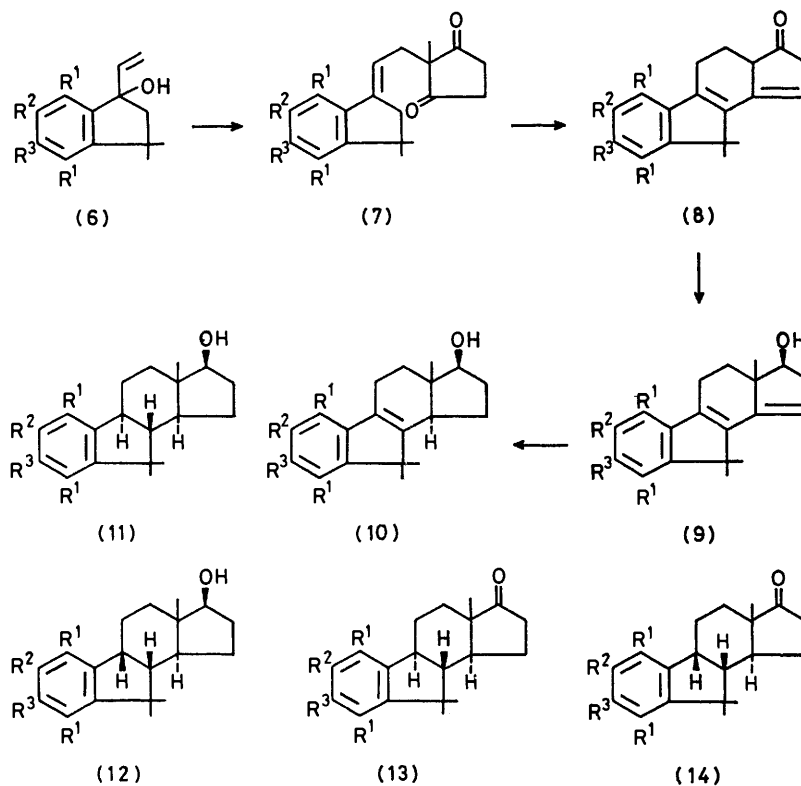
Treatment of the ketone (4) with polyphosphoric acid gave 4,4'-dimethoxybenzophenone [8] (5). The formation of the ketone (5) could take place as indicated in Scheme 1. The ketone (4) was recovered unchanged on treatment with concentrated H₂SO₄.[9] Having failed to obtain the desired indanone (3), the synthesis of the corresponding analogue was attempted using the ketone (4) itself, by the method of Kasturi *et al.*[10] (see later).
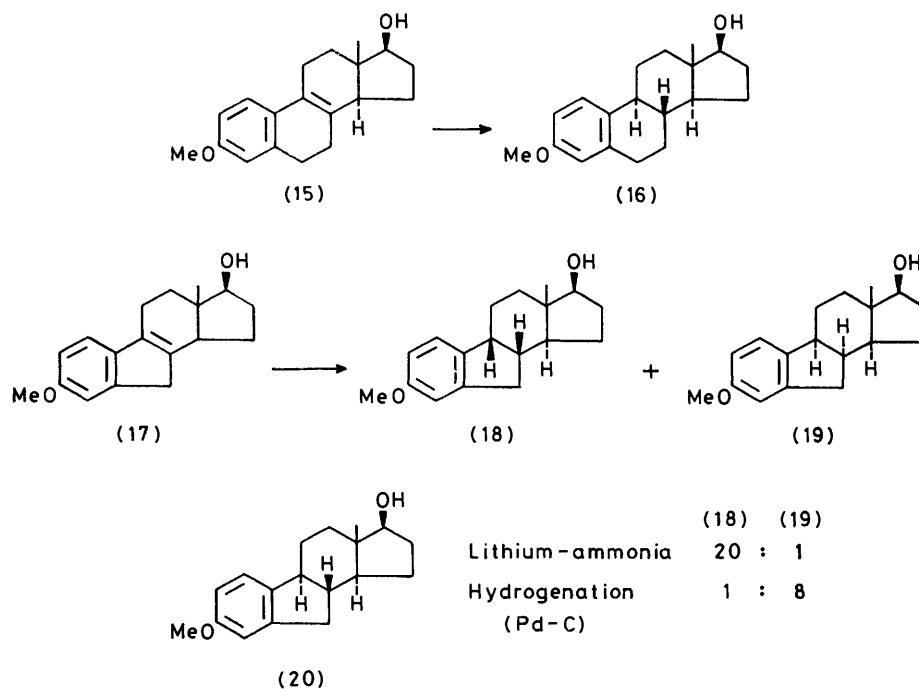

A + B ⟶ (5)
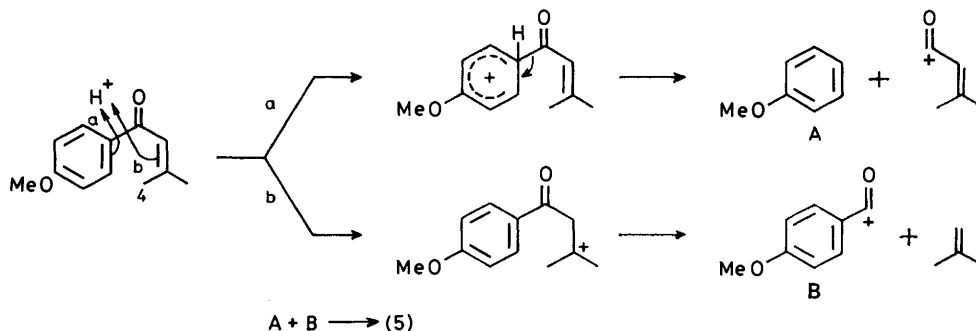
SCHEME 1

norsteroids, and in continuation of our earlier work,[3] we proposed to synthesise the B-norsteroid derivatives, 1,4-dimethoxy-6,6-dimethyl-, 2,3-dimethoxy-6,6-dimethyl-, and 3-methoxy-6,6-dimethyl-B-norestra-1,3,5(10)-trien-17β-ol. The classic approach of Torgov, which has

Synthesis of (±)-1,4-Dimethoxy-6,6-dimethyl-B-norestra-1,3,5(10)-trien-17β-ol and its 9β-isomer.—The indanone (1) was treated with vinylmagnesium bromide to obtain the vinyl alcohol (6a) (Scheme 2) which was treated with 2-methylcyclopentane-1,3-dione in refluxing xylene in

a ; R^1 = OMe, R^2 = R^3 = H

b ; R^1 = H, R^2 = R^3 = OMe

c ; R^1 = R^2 = H, R^3 = OMe

SCHEME 2

	(18)	(19)
Lithium-ammonia	20	:	1
Hydrogenation (Pd-C)	1	:	8

SCHEME 3

the presence of Triton B to obtain the seco-dione (7a).* Cyclisation of (7a) using a mixture of acetic and hydrochloric acids gave the desired pentaenone (8a).

The next step in the synthesis is the stereoselective *reduction* of the Δ^{14}-double bond. Banerjee *et al.*[11] have found that conversion of the keto-group to 17β-OH prior to reduction of the Δ^{14}-double bond results in higher stereoselectivity leading to the desired 14α-tetraenol. The pentaenone (8a) was reduced using $NaBH_4$ to the pentaen-17β-ol † (9a) which on partial catalytic hydrogenation over Pd–$CaCO_3$ (2%) afforded the tetraenol (10a), exhibiting the 18-methyl signal in the n.m.r. spectrum at δ 0.8 characteristic of 14α-estratetraenols.[12]

Lithium–liquid ammonia reduction of the tetraenol

(10a) afforded a single trienol isomer identified ¶ as the 8β,9β-trienol (12a).

Metal–ammonia reduction of styrenoid double-bond in a cyclic system usually affords the most stable isomer.[13] For example, the estratetraenol (15) (Scheme 3) gives 8β,9α-trienol (16),[14] while the B-norestratetraenol (17) gives mainly the 8β,9β-trienol (18).[4] In the present case, however, the two trienols (11a) and (12a) are obtained in equal amounts suggesting their comparable stabilities. This was further substantiated by the following experiments.

When the trienol (11a) was treated with NaOMe–MeOH–DMSO, a mixture of the trienols (11a) and (12a), in the ratio 1 : 1, was obtained (n.m.r.). Similar treat_

$(4) \longrightarrow$ (21) $\longrightarrow$ (22) $\longrightarrow$ (9c)

(23)

(24)
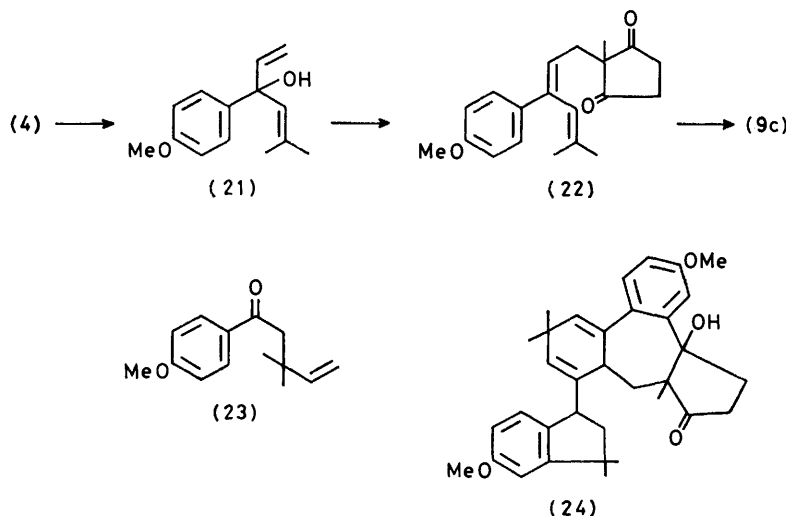
SCHEME 4

(10a) resulted in a mixture of two trienol isomers, designated A and B, in the ratio 1 : 1 [as determined by the relative intensities of the two 18-methyl signals (δ 0.83 and 0.97) in the n.m.r. spectrum]. However, only isomer A could be obtained in a pure form by fractional crystallisation of the mixture from ethanol. When the above reduction was carried out in presence of aniline,‡ the mixture of trienols A and B was obtained in the ratio 2 : 1 (n.m.r.). Here also, only isomer A could be obtained in pure form by fractional crystallisation. Isomers A and B have been tentatively assigned 8β,9α- and 8β,9β-configurations § (11a) and (12a) respectively (see later). Catalytic hydrogenation of the tetraenol

ment of the trienol (12a) also afforded the same mixture of trienols. The trienols (11a) and (12a) differ in their configurations only at C-8 and/or C-9 as they are obtained by the reduction of Δ^8-double bond. The above-mentioned interconversions of these two isomers in the presence of base further indicated that they are isomeric only at C-9.

Comparison of the n.m.r. spectra of the trienols (11a) and (12a) indicated few significant differences: compound (11a) exhibited H_α-17 and H-9 multiplets in the region δ 3.8—4.0 and 2.4—2.6 respectively, while compound (12a) exhibited a multiplet (2 H) at δ 3.2—3.4 for these two protons. The trienones (13a) and (14a), obtained by chromium trioxide–pyridine oxidation of the trienols (11a) and (12a) exhibited H-9 signals in the

* The structural formulae containing one or more asymmetric carbon atoms depict one diastereoisomer but refer to racemic compounds throughout. Each racemate is arbitrarily represented by the diastereoisomer having the 13-methyl group in the β-configuration. Subsequently in the text the (±)-prefix will be omitted and the steroids and intermediates thereto are to be assumed to be racemic.

† The n.m.r. spectrum of this pentaenol exhibited the H_α-17 signal as a triplet-like multiplet in the region δ 3.80—4.00, comparable to that of testosterone.

‡ In the case of the related tetraenol (17) (Scheme 3), it is reported that metal–ammonia reduction in the presence of aniline leads to 8α,9α-trienol (20) as the minor product. In the absence of aniline this isomer is not formed.

§ The other possible pair of configurations, *viz.*, 8α,9α- and 8α,9β-, for the trienols A and B is ruled out because formation of a highly-strained dianion of the type (25) with 8α,9β-configuration during metal–ammonia reduction is highly improbable.[4]

¶ When one part of the catalytic hydrogenation product (12a) was added to a solution of one part of the metal–ammonia reduction product [a mixture of (11a) and (12a) in the ratio 1 : 1] no new peaks appeared in the n.m.r. spectrum of the latter, except that the signals arising from (12a) were intensified. The relative intensities of the 18-methyl signals of (11a) and (12a) in the above spectrum were in the ratio 1 : 3.

regions δ 2.4—2.6 and 3.2—3.4 respectively. Clearly, the H-9 protons of the trienol (11a) and the corresponding trienone (13a) resonate at a higher frequency compared to those of (12a) and the corresponding trienone (14a). It has been well-established [15] that axial protons in a cyclohexane resonate at a higher frequency than equatorial ones. Drieding models of (11a) and (12a) indicated that H-9 is axial in the former compound and equatorial in the latter, thus suggesting 8β,9α-, and 8β,9β-configurations for the trienols (11a) and (12a) respectively. These assignments have been further substantiated by spin-decoupling experiments on related compounds (see later).

Synthesis of (±)-2,3-*Dimethoxy*-6,6-*dimethyl*-B-*norc-stra*-1,3,5(10)-*trien*-17β-*ol and Its* 9β-*isomer.*—The indanone (2) was subjected to the same sequence of reactions as above (Scheme 2) to afford the tetraenol (10b). Lithium–liquid ammonia reduction of the tetraenol (10b) afforded a mixture of two trienols in the ratio 1 : 1, while in the presence of aniline the same mixture of trienols was obtained in the ratio 4 : 3 (n.m.r.). Surprisingly, all attempts to separate the two isomers by usual crystallisation and chromatographic methods proved futile. Even the mixture of the corresponding 17β-acetates and 17-ketones failed to crystallise. However, the mixture of trienols exhibited n.m.r. signals, *viz.*, multiplets at δ 2.4—2.6 (1 H), 3.2—3.4 (2 H), and 3.8—4.0 (1 H) similar to those exhibited by the mixture of 8β,9α- and 8β,9β-trienols discussed earlier.

Catalytic hydrogenation of the tetraenol (10b) afforded a single trienol isomer exhibiting an 18-methyl signal at δ 0.83 and a multiplet (2 H) between δ 3.2—3.4 in the n.m.r. spectrum, which are identical with those exhibited by one of the trienol isomers present in the aforementioned mixture of trienols. This pure trienol was oxidised to the trienone, which also exhibited the H-9 resonance between δ 3.2—3.4 in the n.m.r. spectrum. The trienol and the trienone were assigned structures (12b) and (14b) respectively, in analogy with the previous results. The other trienol isomer present in the mixture was assigned structure (11b).

The 270 MHz FT n.m.r. spectrum * of the ketone (12b) exhibited the benzylic proton signal as a quartet (J_{av} 7.0 Hz). The benzylic proton in (12b), being adjacent to H-8 and the 11-methylene protons, is expected to exhibit a complex multiplet.[16] A simple quartet-like appearance for this multiplet is possible only if $J_{8,9}$, $J_{9,11\alpha}$, and $J_{9,11\beta}$ are nearly equal. In such a situation, the system approximates to an A_3X spin system. The relative intensities of the four component lines of the quartet (1 : 3 : 3 : 1) were as expected for an A_3X system. The following decoupling experiments also substantiated these observations.

Comparison of the region 610—630 Hz † (H-9) of the undecoupled spectrum [Figure 1(a)] with the same region of the decoupled spectrum [Figure 1(c)], in which the

* Recorded on a Bruker WH 270 spectrometer of the Bangalore N.M.R. Facility.
† With reference to 270 MHz spectrometer.

frequency of the proton at δ 2.5 (H-8) is irradiated, shows the collapse of the quartet into a triplet (J_{av} 6.2 Hz). The quartet [Figure 1(a)], triplet [Figure 1(c)], and doublet [Figure 1(d)] nature of the benzylic proton signal when it is coupled to three, two, and one protons clearly
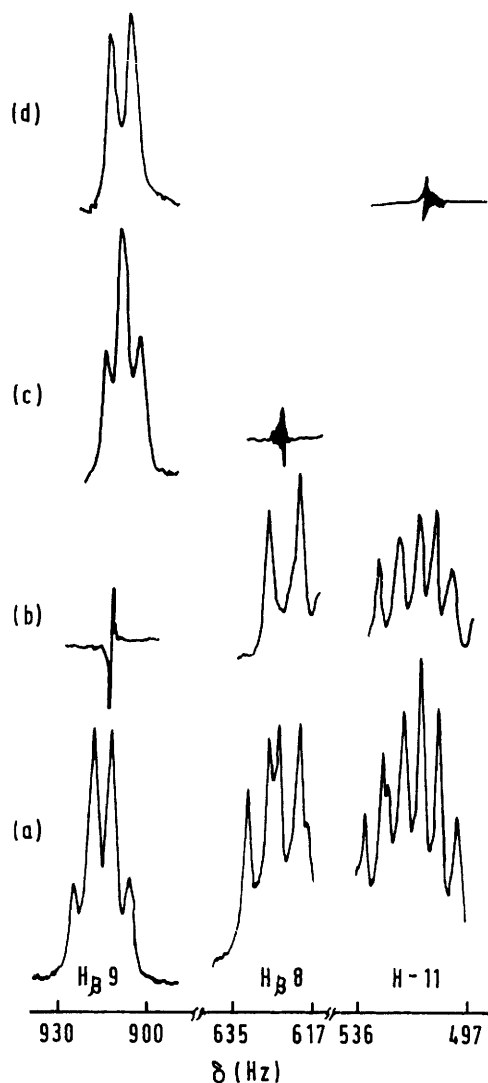

FIGURE 1 H-8, H-9, and H-11 protons in the 270 MHz n.m.r. spectra of the trienone (12b): (a) undecoupled; (b) H-9 decoupled; (c) H-8 decoupled; and (d) H-11 decoupled spectra

indicated that $J_{8,9}$, $J_{9,11\alpha}$, and $J_{9,11\beta}$ are nearly equal. A Drieding model of the 8β,9β-trienol also indicated that the dihedral angles, H_β–C_9–C_8–H_β, H_β–C_9–C_{11}–H_α, H_β–C_9–C_{11}–H_β, between the interacting protons fall in the range 40—60° for which a coupling constant of the order of 5—6 Hz could be derived using a modified Karplus equation. This is in good agreement with the observed value.

Synthesis of (±) 3-*Methoxy*-6,6-*dimethyl*-B-*norestra*-1,3,5(10)-*trien*-17β-*ol and its* 9β-*isomer.*—Kasturi *et al.*[10] have developed a method of obtaining the B-norsteroid intermediate starting from open-chain ketones of the type 2′,4′-dimethoxy-3-methylbut-2-enophenone. A similar

sequence of reactions (Scheme 4) was carried out using the ketone (4) to afford the pentaenone (8c).

Reaction of the ketone (4) with vinylmagnesium bromide afforded a mixture of products showing i.r. absorptions at 3 500—3 600, 1 680, 985, and 911 cm⁻¹. Preparative t.l.c. of this mixture gave mainly a single compound exhibiting i.r. absorptions at 1 680 (conjugated C=O), and 985 and 911 cm⁻¹ (terminal methylene). Based on its n.m.r. and mass spectral data (see Experimental section), structure (23) was assigned to this
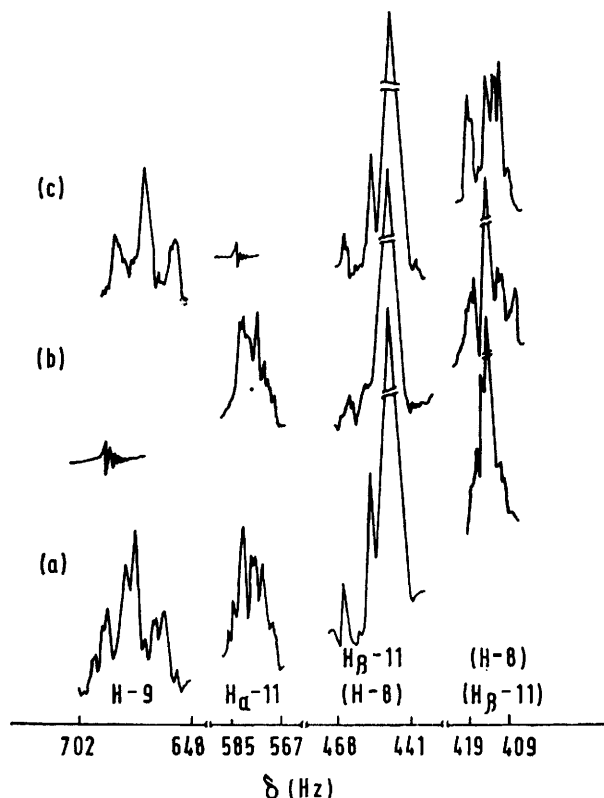

FIGURE 2   H-8, H-9, and H-11 protons in the 270 MHz n.m.r. spectra of the trienol (11c): (a) undecoupled; (b) H-9 decoupled; and (c) Hα-11 decoupled spectra

ketone. This ketone (23) is formed by 1,4-addition of vinylmagnesium bromide to the αβ-unsaturated ketone (4).

As mentioned above, the crude product exhibited also hydroxy stretching absorption (3 500—3 600 cm⁻¹) in the i.r. spectrum, which could correspond to that of the desired vinyl alcohol (21). However, this crude reaction mixture itself was employed for condensation with 2-methylcyclopentane-1,3-dione. The resulting mixture of the ketone (23) and the seco-dione (22) was separated by column chromatography. The seco-dione (22) was cyclised using concentrated H_2SO_4–CH_2Cl_2 to afford three products, 1-(4-methoxyphenyl)-5-methylcyclohexa-1,4-diene [17] (2.5%), the desired pentaenone (8c) (10%), and an unusual product (50%) for which a tentative structure (24) has been proposed.[17] The pentaenone (8c) was reduced to the pentaenol (9c) and partially hydrogenated to the tetraenol (10c).

Lithium–liquid ammonia reduction of (10c) in the presence of aniline gave a mixture of two trienols in the ratio 3 : 1 (n.m.r.), from which the major isomer was obtained in pure form by fractional crystallisation. This pure trienol exhibited multiplets in the region δ 2.4—2.6 (1 H) and 3.8—4.0 (1 H) in the n.m.r. spectrum and was assigned the 8β,9α-trienol structure (11c) in analogy with the earlier results. The minor isomer in the aforementioned mixture of trienols exhibited a multiplet (2 H) in the region δ 3.2—3.4 (in the n.m.r. spectrum of the mixture) and was assigned 8β,9β-configuration (12c).

Spin-decoupling experiments using the trienol (11c) * further supported the above assignments. Figure 2(a) shows the undecoupled spectrum. Irradiation at δ 2.48 (H-9) resulted in small chemical shift differences in the regions 567—585, 441—468, and 405—419 Hz † as shown in Figure 2(b). When the signal in the region 560—580 Hz [Figure 2(c)] was irradiated the doublet of triplets at 668 Hz (H-9) collapsed into a triplet (J 16.8 Hz) by losing the coupling interaction of J 3.6 Hz. The magnitudes of these coupling constants are of the order of $J_{ax,ax}$ and $J_{ax,eq}$ respectively. Therefore, H-9 must be axial and should be coupled to two axial and one equatorial protons. A Drieding model of the 8β,9α-trienol indicated the axial disposition of $H_α$-9, $H_α$-11, and $H_β$-8 and the equatorial disposition for $H_β$-11. These are in good agreement with the above expectations based on n.m.r. data.

Clearly, metal–ammonia reduction of 6,6-dimethyl-B-norestra-1,3,5(10),8-tetraenols of the type (10) gives a mixture of the 8β,9α- and 8β,9β-trienols (11) and (12)

(25)   (26)
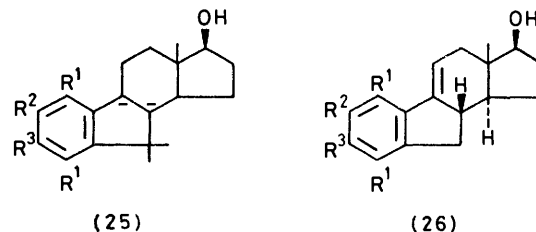
a ; R^1 = OMe, R^2 = R^3 = H

b ; R^1 = H. R^2 = R^3 = OMe

respectively. The non-formation of the 8α,9β-trienol in the present case could probably be due to the severe interaction between the 6β- and 18-methyl groups in the dianion intermediate of the type (25) with 8α,9α-configuration.

Catalytic hydrogenation of the tetraenols of type (10) yields the 8β,9β-trienols (12), in contrast to the catalytic reduction of the tetraenol (17).[4] This could be explained by assuming an initial isomerisation of (10) to the $\Delta^{9(11)}$-tetraenol (26) during catalytic hydrogenation (Pd–C) followed by hydrogenation from the β-face to

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* As the $H_α$-17 and $H_α$-9 signals do not overlap, unlike for the 8β,9β-trienols, the trienol itself could be employed.

† With reference to the 270 MHz spectrum.

give the trienol (12). Similar β-face attack during hydrogenation of 8β-methyl-D-homo-B-norestra-1,3,5(10),9-(11)-tetraenol has been reported.[18]

Refluxing the tetraenol (10a) with MeOH–HCl resulted in a mixture of tetraenols (u.v.) (10a) and (26a), identified by two 18-methyl signals and a C-11 olefinic H signal in the n.m.r. spectrum. Hydrogenation of this mixture gave a single trienol (12a), in conformity with the above assumption. Similar treatment of the tetraenol (10b) also gave a mixture of the tetraenols (10b) and (26b) which on hydrogenation gave only the trienol (12b).

Further work on the resolution and biological evaluation of the B-norsteroids synthesised is in progress.

EXPERIMENTAL

Melting points were recorded on a hot stage apparatus. U.v. spectra were recorded for solutions in 95% ethanol on a Unicam SP 700A spectrometer and i.r. spectra on Perkin-Elmer models 700 and 137B Infracord spectrometers. Unless otherwise stated, n.m.r. spectra were recorded on Varian HA-100D or T-60 spectrometers. Chemical shifts are reported as δ values (CDCl$_3$ as solvent) with Me$_4$Si as internal standard. Mass spectra were recorded on an Atlas CH-4 spectrometer with a built-in direct inlet system. All organic extracts were dried over anhydrous sodium sulphate. General procedures for the experiments are described except where indicated otherwise.

4'-Methoxy-3-methylbut-2-enophenone (4).—Anhydrous AlCl$_3$ (35 g, 0.025 mol) was introduced in portions to a stirred and cooled solution (0—5°) of anisole (81 ml, 0.075 mol) and ββ-dimethylacryloyl chloride (27 g, 0.025 mol) in CS$_2$ (200 ml). The mixture was stirred at room temperature for 4 h (until evolution of HCl had ceased). The CS$_2$ was removed in vacuo and the residue decomposed using cold dilute HCl. The product was extracted with ether and the ether extract washed with water, saturated NaHCO$_3$ solution, and brine, and dried. The solvent was removed and the ketone (4) (37 g) distilled in vacuo, b.p. 160° at 10 mmHg (lit.,[7] 166° at 12 mmHg).

Treatment of the Ketone (4) with Polyphosphoric Acid.—The ketone (4) (1 g) was added to polyphosphoric acid (25 g) maintained at 135—140° (bath temperature). After stirring for an additional 45 min at this temperature, the mixture was cooled and poured into ice–water. The precipitated solid was extracted with ether and the ether extract washed with saturated NaHCO$_3$ solution and brine, and dried. Removal of the solvent, followed by trituration with hexane gave crystals of the benzophenone (5) (0.5 g), m.p. 146° (ethanol) (lit.,[10] 146°).

Reaction of the Ketones (1), (2), and (4) with Vinylmagnesium Bromide.—To a stirred suspension of magnesium turnings (0.04 g mol) in dry tetrahydrofuran (20 ml) containing a crystal of iodine, was added vinyl bromide (6 ml) in dry THF (10 ml) at such a rate that gentle refluxing was maintained. After complete addition, the mixture was stirred for 30 min and then cooled to 0°. The solution of the ketone (1), (2), or (4) (0.02 mol) in dry ether (20 ml) was slowly added. After refluxing for 2 h, the solution was cooled and decomposed by careful addition of saturated NH$_4$Cl solution. The organic layer was separated and the aqueous layer extracted with ether. The combined organic extracts were washed with water and brine, and dried. The solvent was removed in vacuo and the residue containing the vinyl alcohol (6a), (6b), or (21) [ν$_{max.}$ 3 500—3 600 (OH), 980, and 911 cm^{-1} (terminal methylene)] was used for further reaction without purification.

In the case of reaction of the ketone (4) (15.1 g) with vinylmagnesium bromide, a mixture of the vinyl alcohol (21) and 4'-methoxy-3,3-dimethylpent-4-enophenone (23) was obtained in the ratio 2 : 1. A sample of the latter was purified for analysis by preparative t.l.c. followed by short-path distillation, b.p. 110° at 0.2 mmHg; δ 1.16 (6 H, s, gem-dimethyl), 2.80 (2 H, s, ⁻CH$_2$⁻), 3.80 (3 H, s, OMe), 4.60—5.18 (3 H, m, olefinic H), and 5.68 and 6.18 (4 H, 2 d, J 9 Hz, ArH); m/e 218 (M$^+$, 44%), 150 (M$^+$ − C$_5$H$_8$, 60), and 135 (M$^+$ − C$_6$H$_{11}$, 100) (Found: C, 77.0; H, 8.25. C$_{14}$H$_{18}$O$_2$ requires C, 77.05; H, 8.2%).

Condensation of the Vinyl Alcohols (6a), (6b), and (21) with 2-Methylcyclopentane-1,3-dione.—A mixture of the vinyl alcohol (6a), (6b), or (21) (0.02 mol), 2-methylcyclopentane-1,3-dione (25 g), Triton B (2 ml), and dry xylene (60 ml) was refluxed for 18 h using a Dean–Stark apparatus for azeotropic removal of water. The cooled mixture was diluted with benzene and the unchanged 2-methylcyclopentane-1,3-dione filtered off. The filtrate was washed with 5% v/v KOH–water, water, and brine, and dried. The solvent was evaporated off in vacuo and the residue chromatographed over neutral alumina. Elution with benzene afforded the seco-diones.

Thus, reaction of the vinyl alcohol (6a) (4.4 g) gave (±)-1,4-dimethoxy-6,6-dimethyl-8,14-seco-B-norestra-1,3,5(10),9-(11)-tetraene-14,17-dione (7a) (6 g), m.p. 145° (from benzene–hexane); ν$_{max.}$ 1 765 and 1 730 cm^{-1} (2,2-disubstituted cyclopentane-1,3-dione); δ 1.06 (3 H, s, 18-Me), 1.33 (6 H, s, gem-dimethyl), 3.72, 3.75 (6 H, 2s, ArOMe), 5.86—6.26 (1 H, m, olefinic H), and 6.46 (2 H, s, ArH) (Found: C, 73.35; H, 7.5. C$_{21}$H$_6$O$_4$ requires C, 73.7; H, 7.6%).

The vinyl alcohol (6b) (4.6 g) afforded (±)-2,3-dimethoxy-6,6-dimethyl-8,14-seco-B-norestra-1,3,5(10),9(11)-tetraene-14,17-dione (7b) (6.5 g), m.p. 105° (from benzene–hexane); ν$_{max.}$ 1 770 and 1 725 cm^{-1}; δ 1.10 (3 H, s, 18-Me), 1.26 (6 H, s, gem-dimethyl), 3.80 (6 H, s, ArOMe), and 6.70 (2 H, s, ArH) (Found: C, 73.7; H, 8.15. C$_{21}$H$_{26}$O$_4$ requires C, 73.7; H, 7.6%).

The crude vinyl alcohol (21) (18 g) containing the ketone (23), on condensation followed by chromatography gave two fractions. Elution with hexane–benzene (1 : 1) gave the ketone (23) (5.0 g); elution with benzene gave a mixture of E- and Z-isomers of (±)-1,3-(4-methoxyphenyl)-5-methyl-(1-methyl-2,5-dioxocyclopentyl)hexa-2,4-diene (22), b.p. 180° at 0.02 mmHg; ν$_{max.}$ 1 760 and 1 722 cm^{-1}; δ 0.96 and 1.06 (3 H, 2s, 18-Me), 1.33—1.50 (3 H, br s, allylic Me), 1.70—1.90 (3 H, 2s, allylic Me), 3.73 (3 H, s, ArOMe), 5.20—5.60 (ca. 0.5 H, t, olefinic H), 5.60—5.80 (ca. 1.5 H, m, olefinic H), and 6.50—7.20 (4 H, m, ArH) (Found: C, 76.5; H, 7.8. C$_{20}$H$_{24}$O$_3$ requires C, 76.9; H, 7.7%).

Cyclodehydration of the Seco-diones (7a), (7b), and (21).—(a) Using HOAc–HCl. The solution of the seco-dione (7a) or (7b) (0.003 mol) in HOAc–HCl (5 : 1, 20 ml) was stirred for 1 h at 0—5°. After dilution with ice–water the precipitated solid was extracted with ether. The extract was washed with water, saturated NaHCO$_3$ solution, and brine, and dried. The solvent was removed and the residue crystallised to obtain the pentaenone.

The seco-dione (7a) (1.0 g) gave (±)-1,4-dimethoxy-6,6-dimethyl-B-norestra-1,3,5(10),8,14-pentaen-17-one (8a) (0.8 g), m.p. 149° (from ethanol–water); ν$_{max.}$ 1 742 cm^{-1}; δ 1.06 (3 H, s, 18-Me), 1.40 and 1.46 (6 H, 2s, gem-dimethyl),

3.74 and 3.77 (6 H, 2s, ArOMe), 5.60—5.80 (1 H, m, olefinic H), and 6.60 (2 H, s, ArH) (Found: C, 77.4; H, 7.85. $C_{21}H_{24}O_3$ requires C, 77.8; H, 7.4%).

The seco-dione (7b) (2.0 g) gave ($\pm$)-2,3-*dimethoxy*-6,6-*dimethyl*-B-*norestra*-1,3,5(10),8,14-*pentaen*-17-*one* (8b) (1.70 g), m.p. 146° (from ethanol–water); $\nu_{max.}$ 1 750 cm^{-1}; δ 1.12 (3 H, s, 18-Me), 1.26 and 1.32 (6 H, 2 s, *gem*-dimethyl), 4.00, 4.02 (6 H, 2 s, ArOMe), 5.86—5.96 (1 H, m, olefinic H), and 6.92 and 7.02 (2 H, 2 s, ArH) (Found: C, 77.55; H, 7.6. $C_{21}H_{24}O_3$ requires C, 77.8; H, 7.4%).

(b) *Using Concentrated* H_2SO_4–CH_2Cl_2. To a stirred and cooled (0—5°) solution of the seco-dione (22) (3.0 g) in CH_2Cl_2 (20 ml) was added concentrated H_2SO_4 (5.5 ml) during 20 min. The mixture was stirred at the same temperature for an additional 1 h and cold water was then cautiously added. The mixture was extracted with ether and the extract was washed with water, saturated $NaHCO_3$ solution, and brine, and dried. Removal of the solvent followed by chromatography over neutral alumina afforded (i) 1-(4-methoxyphenyl)-5-methylcyclohexa-1,4-diene [17] (0.02 g), eluted with hexane; (ii) ($\pm$)-3-*methoxy*-6,6-dimethyl-B-*norestra*-1,3,5(10),8,14-pentaen-17-one (8c) (0.35 g), m.p. 142°; $\nu_{max.}$ 1 742 cm^{-1}; δ 1.10 (3 H, s, 18-Me), 1.32 and 1.38 (6 H, 2 s, *gem*-dimethyl), 3.84 (3 H, s, ArOMe), 5.72—5.94 (1 H, m, olefinic H), and 6.66—7.14 (3 H, m, ArH); and (iii) compound (24) [17] (1.6 g), eluted with benzene–chloroform (1 : 1).

Sodium Borohydride Reduction of the Pentaenones (8a—c). —To a stirred suspension of the pentaenone (8) (0.005 mol) in ethanol (25 ml) was added sodium borohydride (0.09 g). The mixture was stirred for an additional 4—5 h and decomposed by addition of cold water followed by a few drops of acetic acid. The precipitated solid was extracted with ether and the ether layer washed with water and brine, and dried. The solvent was removed *in vacuo* and the residue crystallised to obtain the pentaenol (9).

The pentaenone (8a) (1.2 g) afforded ($\pm$)-1,4-*dimethoxy*-6,6-*dimethyl*-B-*norestra*-1,3,5(10),8,14-*pentaen*-17β-*ol* (9a) (1.0 g), m.p. 160° (from hexane); $\nu_{max.}$ 3 500—3 600 cm^{-1} (OH); δ 0.90 (3 H, s, 18-Me), 1.40 and 1.46 (6 H, 2 s, *gem*-dimethyl), 3.83 and 3.85 (6 H, 2 s, ArOMe), 3.80—4.20 (1 H, t, *J* 8 Hz, H_α-17), 5.30—5.63 (1 H, m, olefinic H), and 6.60 (2 H, s, ArH) (Found: C, 77.15; H, 8.2. $C_{21}H_{28}O_3$ requires C, 77.3; H, 7.95%).

The pentaenone (8b) (1.5 g) gave ($\pm$)-2,3-*dimethoxy*-6,6-*dimethyl*-B-*norestra*-1,3,5(10),8,14-pentaen-17β-ol (9b) (1.4 g), m.p. 138° (from ethanol–water); $\nu_{max.}$ 3 550 cm^{-1}; δ 0.96 (3 H, s, 18-Me), 1.30 and 1.33 (6 H, 2 s, *gem*-dimethyl), 3.96 (6 H, s, ArOMe), 3.80—4.20 (1 H, t, *J* 8 Hz, H_α-17), 5.40—5.60 (1 H, m, olefinic H), and 6.83 and 6.93 (2 H, 2s, ArH) (Found: C, 77.75; H, 7.7. $C_{21}H_{28}O_3$ requires C, 77.3; H, 7.95%).

The pentaenone (8c) (0.6 g) gave ($\pm$)-3-*methoxy*-6,6-*dimethyl*-B-*norestra*-1,3,5(10),8,14-*pentaen*-17β-ol (9c) (0.4 g), m.p. 152° (from methanol–water); $\nu_{max.}$ 3 560 cm^{-1}; δ 0.86 (3 H, s, 18-Me), 1.30 and 1.33 (6 H, 2 s, *gem*-dimethyl), 3.86 (3 H, s, ArOMe), 3.86—4.33 (1 H, t, *J* 8 Hz, H_α-17), 5.36—5.50 (1 H, m, olefinic H), and 6.30—7.26 (3 H, m, ArH) (Found: C, 80.9; H, 8.45. $C_{20}H_{22}O_2$ requires C, 81.1; H, 8.1%).

Catalytic Hydrogenation of the Pentaenols (9a—c).—The solution of the pentaenol (9) (0.003 mol) in ethanol (20 ml) was introduced into a suspension of freshly reduced 2% Pd–$CaCO_3$ (10%) catalyst in the same solvent. The mixture was stirred in hydrogen atmosphere until 1 molar

equivalent of hydrogen had been absorbed. The catalyst was filtered off and the residue washed with solvent. The combined filtrate was concentrated *in vacuo* and the residue crystallised to obtain the tetraenol (10).

The pentaenol (9a) (1.0 g) gave ($\pm$)-1,4-*dimethoxy*-6,6-*dimethyl*-B-*norestra*-1,3,5(10),8-*tetraen*-17β-*ol* (10a) (0.95 g), m.p. 154° (from ethanol–water); $\lambda_{max.}$ 270 (ε 7 058), 278 (5 169), 313 (4 771), and 325 nm (3 778); δ 0.83 (3 H, 18-Me), 1.33 (6 H, s, *gem*-dimethyl), 3.80—3.96 (7 H, br d, ArMe and H_α-17), and 7.30—7.40 (2 H, 2 s, ArH) (Found: C, 76.5; H, 8.6. $C_{21}H_{28}O_3$ requires C, 76.85; H, 8.55%).

The pentaenol (9b) (0.20 g) afforded ($\pm$)-2,3-*dimethoxy*-6,6-*dimethyl*-B-*norestra*-1,3,5(10),8-*tetraen*-17β-*ol* (10b) (0.16 g), m.p. 132° (from methanol–water); $\lambda_{max.}$ 282 (ε 9 842) and 305 nm (8 851); δ 0.83 (3 H, s, 18-Me), 1.30 (6 H, s, *gem*-dimethyl), 3.86 (7 H, br s, ArOMe and H_α-17), and 6.66 and 6.80 (2 H, 2 s, ArH) (Found: C, 76.45; H, 8.7. $C_{21}H_{28}O_3$ requires C, 76.85; H, 8.5%).

The pentaenol (9c) (0.5 g) gave ($\pm$)-3-*methoxy*-6,6-*dimethyl*-B-*norestra*-1,3,5(10),8-*tetraen*-17β-*ol* (10c) (0.4 g), m.p. 109° (from CH_2Cl_2–hexane); $\lambda_{max.}$ 262 (ε 7 055), 308 (4 580), and 324 nm (3 465); δ 0.76 (3 H, s, 18-Me), 1.20 (6 H, s, *gem*-dimethyl), 3.78—3.84 (4 H, br s, ArOMe and H_α-17), and 6.60—6.95 (3 H, s, ArH).

Lithium–Liquid Ammonia Reduction of the Tetraenols (10a and b).—A solution of the tetraenol (10a or b) (0.002 mol) in anhydrous THF (20 ml) was added to liquid ammonia (100 ml) and the clear colourless solution was treated with lithium (0.07 g) in small pieces, added during 1 min. The deep blue solution was stirred for an additional 20 min and decomposed by rapid addition of NH_4Cl (0.5 g). The solvents were evaporated off and the residue was dissolved in ether–water. The organic layer was separated and washed with water, Claisen's alkali, water, and brine, and dried. The solvent was removed and the gummy residue, a mixture of the trienols (11) and (12), was subjected to fractional crystallisation.

The tetraenol (10a) (0.2 g) afforded a mixture (0.16 g) of ($\pm$)-1,4-*dimethoxy*-6,6-*dimethyl*-B-*norestra*-1,3,5(10)-*trien*-17β-*ol* (11a) and its 9β-isomer (12a) in the ratio 1 : 1. Fractional crystallisation from methanol gave the pure trienol (11a) (0.025 g), m.p. 164° (from CH_2Cl_2–hexane); $\lambda_{max.}$ 287 nm (ε 1 895); δ 0.83 (3 H, s, 18-Me), 1.08 and 1.46 (6 H, 2 s, *gem*-dimethyl), 2.40—2.60 (1 H, m, H_α-9), 3.70—3.78 (7 H, br s, ArOMe and H_α-17), and 6.64 (2 H, s, ArH) (Found: C, 76.45; H, 9.7. $C_{21}H_{30}O_3$ requires C, 76.35; H, 9.1%).

The tetraenol (10b) (0.5 g) gave a mixture of (11b) and its 9β-isomer (12b), in the ratio 1 : 1. This mixture could not be separated by fractional crystallisation using a variety of solvents or by chromatography.

Lithium–Liquid Ammonia Reduction of the Tetraenols (10a—c), *in the Presence of Aniline.*—The reduction was carried out as above except that aniline (0.18 ml) was added to the liquid ammonia before addition of the tetraenol (10).

The tetraenol (10a) (1.0 g) gave a mixture of the trienols (11a) and (12a), in the ratio 2 : 1, from which the trienol (11a) (0.4 g) was obtained in pure form by fractional crystallisation from methanol.

The tetraenol (10b) (0.8 g) gave an inseparable mixture of trienols (11b) and (12b) in the ratio 4 : 3.

The tetraenol (10c) (0.4 g) gave a mixture of ($\pm$)-3-*methoxy*-6,6-*dimethyl*-B-*norestra*-1,3,5(10)-*trien*-17β-*ol* (11c) and its 9β-isomer (12c), in the ratio 2 : 1. The pure trienol (11c) (0.20 g) was obtained by fractional crystallisation from

methanol, m.p. 135° (from ethanol); $\lambda_{max.}$ 286 nm (ε 5 500); δ 0.78 (3 H, s, 18-Me), 1.00 and 1.30 (6 H, 2 s, *gem*-dimethyl), 2.40—2.60 (1 H, m, H_α-9), 3.75 (4 H, br s, ArOMe and H_α-17), and 6.50—7.00 (3 H, m, ArH) (Found: C, 80.25; H, 9.15. $C_{20}H_{28}O_2$ requires C, 80.0; H, 9.35%).

Catalytic Hydrogenation of the Tetraenols (10a and b).— The solution of the tetraenol (10a or b) (0.005 mol) in ethanol (15 ml) containing 10% Pd–C (0.2 g) was stirred under hydrogen until the absorption of hydrogen ceased. The catalyst was filtered off and the residue washed with ethanol. The solvent was removed from the filtrate and the residue crystallised to obtain the trienol (12a or b).

The tetraenol (10a) (0.5 g) gave ($\pm$)-1,4-*dimethoxy*-6,6-*dimethyl*-B-*nor*-9β-*estra*-1,3,5(10)-*trien*-17β-*ol* (12a) (0.47 g), m.p. 184° (from ethanol–water); $\lambda_{max.}$ 284 nm (ε 1 732); δ 0.97 (3 H, s, 18-Me), 1.27 and 1.42 (6 H, 2 s, *gem*-dimethyl), 3.28—3.54 (2 H, m, H_β-9 and H_α-17), 3.78 (6 H, s, ArOMe), and 6.64 (2 H, s, ArH) (Found: C, 76.0; H, 8.85. $C_{21}H_{30}O_3$ requires C, 76.35; H, 9.1%).

The tetraenol (10b) (0.4 g) gave ($\pm$)-2,3-*dimethoxy*-6,6-*dimethyl*-B-*nor*-9β-*estra*-1,3,5(10)-*trien*-17β-*ol* (12b) (0.35 g), m.p. 124° (from ethanol–water); $\lambda_{max.}$ 284 nm (ε 5 438); δ 0.82 (3 H, s, 18-Me), 1.18 and 1.26 (6 H, 2 s, *gem*-dimethyl), 3.30—3.66 (2 H, m, H_β-9 and H_α-17), 3.86 (2 H, 2 s, ArOMe), and 6.68 and 6.70 (2 H, 2 s, ArH) (Found: C, 75.9; H, 9.25. $C_{21}H_{30}O_3$ requires C, 76.35; H, 9.1%).

Oxidation of the Trienols (11a), (12a), *and* (12b) *using Chromium Trioxide–Pyridine Complex*.—Chromium trioxide (0.03 mol) was added to a vigorously stirred mixture of pyridine (0.15 mol) in CH_2Cl_2 (50 ml). The mixture was stirred at room temperature for 15 min. A solution of the trienol (11a), (12a), or (12b) (0.005 mol) in CH_2Cl_2 (20 ml) was added to the complex in one lot and the mixture stirred for 2 h. The solid was filtered off and the residue washed with ether. The combined filtrates were washed with 5% w/v KOH–H_2O, 5% w/v HCl–H_2O, and saturated $NaHCO_3$ solution, and dried. The solvent was removed and the residue crystallised to obtain the trienone.

The trienol (11a) (0.42 g) afforded ($\pm$)-1,4-*dimethoxy*-6,6-*dimethyl*-B-*norestra*-1,3,5(10)-*trien*-17-*one* (13a) (0.35 g), m.p. 197° (from ethanol); $\nu_{max.}$ 1 743 cm^{-1}; δ 0.94 (3 H, s, 18-Me), 1.16 and 1.54 (6 H, 2 s, *gem*-dimethyl), 2.40—2.60 (1 H, m, H_α-9), 3.74 and 3.78 (6 H, 2 s, ArOMe), and 6.66 (2 H, s, ArH) (Found: C, 77.0; H, 9.0. $C_{21}H_{28}O_3$, requires C, 76.85; H, 8.55%).

The trienol (12a) (0.2 g) gave ($\pm$)-1,4-*dimethoxy*-6,6-*dimethyl*-B-*nor*-9β-*estra*-1,3,5(10)-*trien*-17β-*ol* (14a) (0.17 g), m.p. 191° (from ethanol); $\nu_{max.}$ 1 745 cm^{-1}; δ 0.98 (3 H, s, 18-Me), 1.26 and 1.28 (6 H, 2 s, *gem*-dimethyl), 3.30—3.55 (1 H, m, H_β-9), 3.80 and 3.82 (6 H, 2 s, ArOMe), and 6.64 (2 H, s, ArH) (Found: C, 76.6; H, 8.85. $C_{21}H_{28}O_3$ requires C, 76.85; H, 8.55%).

The trienol (12b) (0.20 g) gave ($\pm$)-2,3-*dimethoxy*-6,6-*dimethyl*-B-*nor*-9β-*estra*-1,3,5(10)*trien*-17-*one* (14b) (0.16 g), m.p. 130° (from ethanol); $\nu_{max.}$ 1 745 cm^{-1}; δ 100 (3 H, s, 18-Me), 1.25 and 1.31 (6 H, 2 s, *gem*-dimethyl), 3.33—3.45 (1 H, q,* J 7 Hz, H_β-9), 3.86 and 3.90 (6 H, 2 s, ArOMe), and 6.66—6.70 (2 H, 2 s, ArH) (Found: C, 76.6; H, 8.7. $C_{21}H_{28}O_3$ requires C, 76.85; H, 8.55%).

Treatment of the Trienols (11) *and* (12) *with* NaOMe–MeOH–DMSO.—To a solution of NaOMe (0.01 g) in absolute methanol (1.0 ml) and dry DMSO (4 ml), was added the trienol (11a), (11b), (12b), or (11c) (0.005 mol). After heating under reflux for 18 h, the solution was concentrated

* 270 MHz N.m.r. spectrum.

to half-volume, diluted with water, and acidified with concentrated HCl, and extracted with ether. The extract was washed with water, aqueous $NaHCO_3$, and brine. The solvent was removed and the residue, in all cases, was a mixture of the 8β,9α- and 8β,9β-trienols (11) and (12) in nearly equal amounts.

Isomerisation of the Tetraenols (10a—b) *using* MeOH–HCl. —A solution of the tetraenol (10) (0.003 mol) in methanol (50 ml) and 10N-HCl (10 ml) was refluxed on a steam-bath for 15 min. The cooled mixture was diluted with water and extracted with ether. The organic extract was washed successively with water, saturated $NaHCO_3$ solution, and brine, and dried. The solvent was removed under vacuum to afford a mixture of Δ^8- and $\Delta^{9(11)}$-tetraenols. No attempt was made to separate the mixture and it was employed as such for further reaction.

The tetraenol (10a) (0.1 g) gave a mixture of the tetraenols (10a) and (26a), in the ratio 1 : 1 (0.09 g): $\lambda_{max.}$ 265 nm (ε 8 000); δ 0.83 and 1.03 (3 H, 6 s, Me), 1.36 and 1.50 (6 H, 2 s, *gem*-dimethyl), 3.7—3.90 (7 H, m, ArOMe and H_α-17), 6.33—6.56 (*ca.* 0.5 H, m, olefinic H), and 6.66—6.80 (2 H, m, ArH).

The tetraenol (10b) (0.1 g) afforded a mixture of the tetraenols (10b) and (26b) in the ratio 1 : 1 (0.08 g); δ 0.82 and 0.92 (3 H, 2 s, Me), 1.24 and 1.38 (6 H, 2 s, *gem*-dimethyl), 3.76—3.90 (7 H, br d, ArOMe and H_α-17), 5.70—5.90 (*ca.* 0.5 H, m, olefinic H), and 6.66—6.86 (2 H, m, ArH).

Hydrogenation of the Mixture of Δ^8- and $\Delta^{9(11)}$-Tetraenols.— Hydrogenation of the mixture of (10a) and (26a), or (10b) and (26b) was carried out as described earlier using 10% Pd–C catalyst. The product in either case was the corresponding 8β,9β-trienol (12a) or (12b), respectively, obtained quantitatively.

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