further two times. The material thus obtained was dissolved in water (15 ml) and washed with diethyl ether (3 × 15 ml). The water layer was partly evaporated *in vacuo* (30°C) and thereafter lyophilized. 63 mg (89%) of a slightly yellow coloured fluffy material was obtained. TLC (cellulose F_{254}, DC-Alufolien, Merck; solvent VI): major compound R_f 0.72 (Ninh.$^+$). Several minor compounds were detected. **7** was used without further purification.

H-Ala-Ser(βGal)-Ala-OH (**8**)

Hydrazine hydrate (97 µl, 2.0 mmol) was added to a stirred solution of **7** (58 mg, 0.1 mmol) in CH_3OH (1.0 ml) at room temperature. After 40 min, the solution was cooled to 0°C, 2,4-pentanedion (205 µl, 2.0 mmol) was added and stirring was continued at room temperature for 15 min. The solution was diluted with water (25 ml) and washed with $CHCl_3$ (3 × 10 ml). The water layer was partly vaporated *in vacuo* and thereafter lyophilized. The material thus obtained was purified by chromatography on a 60 × 1.5 cm column of Sephadex G-10 (Pharmacia). Elution was effected using water at a flow rate of 20 ml/h. Fractions of 5 ml were collected. Aliquots of each fraction were spotted on TLC plates. Spots were visualized with ninhydrine reagent and methanolic H_2SO_4. **8** (37.2 mg, 91%) was obtained by lyophilization of fraction 8–12. Using 300 MHz ^{1}H NMR, the purity was estimated to be over 97% (a small quantity of aromatic material together with some uncompletely deacetylated glycopeptide were present). A sample of **8** was purified by chromatography on a 20 × 0.3 cm CP-TM-Spher C_{18} HPLC column (Chrompack). Elution was effected using water at a flow rate of 0.5 ml/min. The eluate containing unretarded material (UV detection at 205 nm) was collected and lyophilized. TLC (Cellulmose F_{254}, DC-Alufolien, Merck): IV, R_f 0.23; V, 0.12; VI, 0.21 (Ninh$^+$).
100 MHz ^{13}C NMR (D_2O, pH 5.48 meter reading): δ 105.4 (d, Gal C^1); 63.7 (t, Gal C^6); 71.0 (t, Ser C^β); 182.2, 173.6, 172.4 (3 × s, C=O); 78.0, 75.3, 73.3, 71.3 (4 × d, Gal carbons, probably C^5, C^3, C^2 and C^4, respectively[43-46]); 56.4, 53.8, 51.7 (3 × d, amino acid C^α); 20.2, 19.2 (2 × q, Ala CH_3).
300 MHz ^{1}H NMR (D_2O, pH 5.48 meter reading): δ 4.55 (dd, Ser H^α, $J_{\alpha,\beta a}$ 6.5 Hz, $J_{\alpha,\beta b}$ 5 Hz); 4.27 (d, H^1, $J_{1,2}$ 8 Hz); 4.07–3.94 (m, 3H, 2 × Ala H^α, Ser $H^{\beta a}$); 3.83 (dd, Ser $H^{\beta b}$, J_{gem} 10.5 Hz); 3.76 (br d, H^4, $J_{4,5}$ < 0.,5 Hz); 3.69–3.52 (m, 3H, H^5, H^{6a}, H^{6b}); 3.49 (dd, H^3, $J_{3,4}$ 3.5 Hz); 3.38 (dd, H^2, $J_{2,3}$ 10 Hz); 1.41 (d, Ala CH_3, *J* 7 Hz); 1.18 (d, Ala CH_3, *J* 7 Hz). Assignments are based on a 2D-COSY-45 experiment (see Fig. 1).

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BIOMIMETIC TOTAL SYNTHESIS OF STEROIDS, IX. Stereospecific synthesis of C-homo-19-norsteroids

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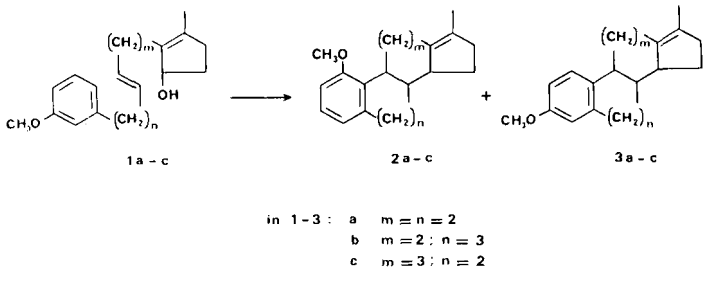
Abstract. Cationic cyclization of 2-[7-(3-methoxyphenyl)-(*E*)-4-heptenyl]-3-methyl-2-cyclopentenol (**1c**) produced 3-methoxy-17-methyl-C-homo-1,3,5(10),13(17)-gonatetraene (**3c**) and its 1-methoxy isomer **2c**. Epoxidation of **3c** with *tert*-butyl hydroperoxide in the presence of molybdenum hexacarbonyl produced the corresponding 13α,17α-epoxide **14** as the major product, which, in three steps, was converted into C-homo-1,3,5(10)-estratriene-3,17β-diol (**18**).

Introduction

Recently, we reported the synthesis of B-homo-19-norsteroids via a biomimetic polyene cyclization reaction[1]. It was shown that treatment of the substrate **1b** with appropriate *Lewis* acids gave the tetracyclic products **2b** and **3b** in good yields. The formation of these products, which possess a seven-membered B ring, was only slightly less efficient than the formation of the lower homologues **2a** and **3a** from the substrate **1a** under similar conditions[2]. This prompted us to examine the cyclization of the substrate **1c** in the hope of obtaining the C-homogonane derivatives **2c** and **3c**, which could serve as precursors to C-homo-19-norsteroids.
The latter compounds have been synthesized only recently via a lengthy route starting from hecogenin[3]. C-Homo-19-norsteroids, having an aromatic A ring, were reported to exhibit surprisingly strong estrogenic activity[3].



Scheme 1

[1] *M. B. Groen* and *F. J. Zeelen*, Recl. Trav. Chim. Pays-Bas **103**, 169 (1984).
[2] *P. A. Bartlett* and *W. S. Johnson*, J. Am. Chem. Soc. **95**, 7501 (1973).
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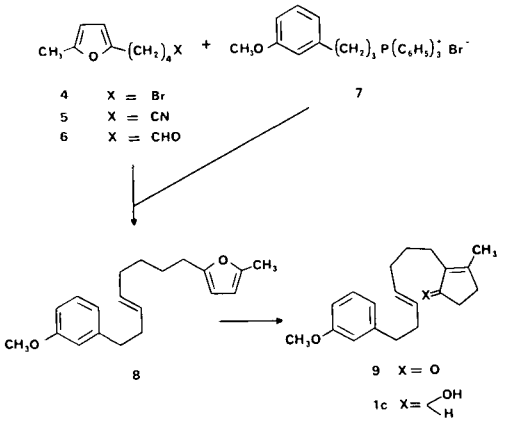
SIn this paper we report the synthesis of **1c**, its cyclization and the further conversion of the major cyclization product into C-homo-19-norsteroids.

Results and discussions

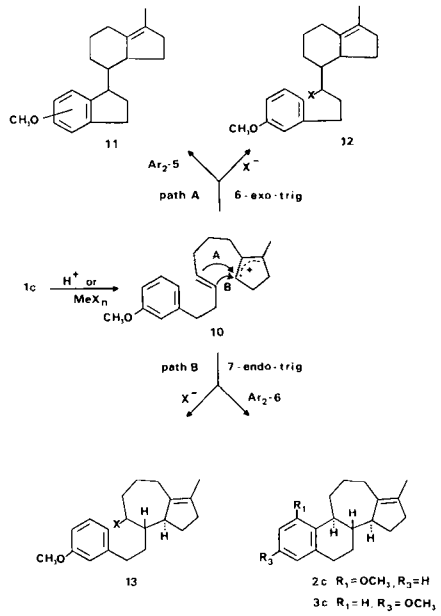
Synthesis of the substrate and cyclization experiments

The synthesis of the substrate **1c**, outlined in Scheme 2, was completely analogous to that described previously for **1b**. Thus, the aldehyde **6**, easily prepared from the known bromide **4**[4] via the nitrile **5**, was condensed with the ylide derived from the phosphonium salt **7**[5] under *Wittig–Schlosser* conditions. The resulting (*E*)-olefin **8**, obtained in 60% yield, was heated with a trace of sulphuric acid in acetic acid to effect ring opening of the furan ring. Subsequent cyclodehydration with KOH in ethanol/water gave the cyclopentenone **9**[6] in 89% yield, which, upon reduction with $LiAlH_4$, gave the desired substrate **1c**. Since the central olefinic linkage in **1c** is electronically unbiased, or nearly so[7], cyclization of **1c** could take place in two fundamentally different ways, indicated as pathways A and B in Scheme 3: the cyclopentenyl group in the initially formed cation **10** may attack either the proximal olefinic carbon atom (path A) or the distal one (path B), generating a six- or a seven-membered ring, respectively. According to *Baldwin*'s classification, pathways A and B represent examples of 6-*exo-trig* and 7-*endo-trig* ring-closure reactions, respectively, and both are listed as favoured processes[8]. Therefore, *Baldwin*'s rules do not predict preference of one pathway over the other. A further complication is that both pathways may produce a variety of products depending upon the way the cyclization of **10** is terminated. Thus, a second ring closure, involving the aromatic ring, gives rise to the desired products **2c** and **3c** (path B) or to products such as **11** (path A). Alternatively, trapping of intermediates by an external nucleophile X^- may give rise to the partially cyclized products **12** (path A) or **13**[9] (path B). Finally, hydride shifts – for which there is ample precedent in cyclialkylation



Scheme 2

reactions[10] – could give rise to additional products. It therefore came as no great surprise to find that treatment of **1c** with formic acid or *Lewis* acids, such as tin(IV) chloride and zinc chloride, resulted in complex mixtures. Fortunately, however, the reaction of **1c** with $BF_3.Et_2O$ (3 equiv.) in CH_2Cl_2 at −78°C proceeded cleanly, giving two major products. These were readily separated by chromatography and purified by recrystallization from methanol. The more polar product, obtained in 38% yield, was assigned the structure **3c** on the basis of its ^1H NMR spectrum. Thus, the aromatic region clearly indicated the presence of a 3,4-disubstituted anisole ring, ruling out structures such as **12** and **13**. The proton at C(9) gave rise to a well-resolved multiplet at δ 2.82 (ddd, *J* 4.5, 8.5 and 11 Hz).



Scheme 3

By means of decoupling experiments the coupling constants of 4.5 and 11 Hz were found to correspond to signals at δ 2.25 and δ 1.5, respectively, which are due to the protons at C(11). The remaining coupling constant of 8.5 Hz, due to the proton at C(8), is somewhat smaller than that found in common steroids (*viz.* 10–12 Hz[11]) but much larger than that found in steroids with *cis* fusion of the B and C rings (3–4 Hz[12]). The structure assignment of **3c** was confirmed by its conversion into known C-homosteroids **16–18** (*vide infra*).

The second cyclization product, isolated in 19% yield, was identified as the 1-methoxy isomer **2c**. The ^1H NMR spectrum of this compound showed the presence of three aromatic protons, which gave rise to the pattern expected for a 2,3-disubstituted anisole ring. The C(9) proton signal showed a similar splitting pattern as found for **3c** (*vide supra*). Its low-field position (δ 3.14) revealed additional deshielding due to the proximity of the methoxy substituent[13].

In addition to the two major products, a number of other products were isolated in small amounts. Since none of these represented more than 3% of the reaction mixture, they were not fully characterized[14]. Therefore, product formation via

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[4] *M. B. Gravestock, W. S. Johnson, B. E. McCarry, R. J. Parry* and *B. E. Ratcliffe*, J. Am. Chem. Soc. **100**, 4274 (1978).

[5] *M. B. Groen* and *F. J. Zeelen*, Recl. Trav. Chim. Pays-Bas **98**, 32 (1978).

[6] The stereochemical purity of this compound was 98% as determined by GLC analysis.

[7] The −*I* effect of the aryl group may bias the double bound slightly in favour of electrophilic attack according to path B.

[8] *J. E. Baldwin*, J. Chem. Soc., Chem. Commun. 734 (1976).

[9] Analogous products (X = Cl) have been observed previously[1]

[10] *Cf. R. A. Barnes*, J. Am. Chem. Soc. **75**, 3004 (1953); *A. A. Khalaf* and *R. M. Roberts*, J. Org. Chem. **37**, 4227 (1972); *T. J. Mason* and *R. O. C. Norman*, J. Chem. Soc. Perkin II 1840 (1973).

[11] *L. D. Hall* and *J. K. M. Sanders*, J. Am. Chem. Soc. **102**, 5703 (1980); J. Org. Chem. **46**, 1132 (1981).

[12] *M. B. Groen, B. Hindriksen* and *F. J. Zeelen*, Recl. Trav. Chim. Pays-Bas **101**, 148 (1982).

[13] The ^1H NMR data for **2c** and **3c** indicate that the seven-membered ring in these compounds probably occurs in a twist-chair conformation with an approximate C_2 axis passing through C(11) and the centre of the C(13)–C(14) bond.

[14] In the mother liquor of **3c** a major by-product was detected, which, in the ^1H NMR spectrum, showed signals for four aromatic protons and a doublet (*J* 47 Hz!) of multiplets centred at δ 4.58. Presumably this compound has the structure **13** (X = F).

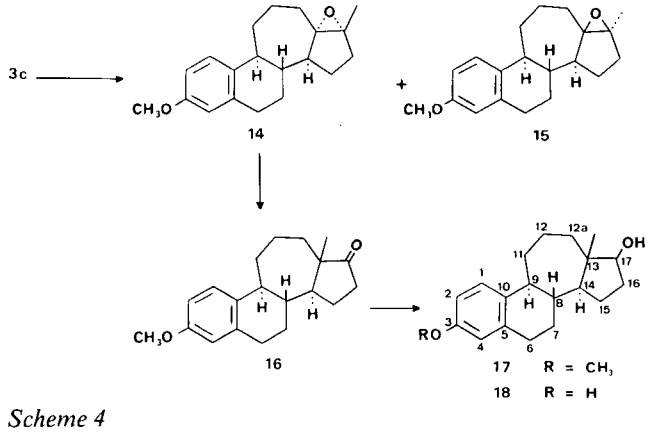
pathway A cannot be ruled out completely, but it is evident that by applying favourable reaction conditions, the substrate **1c** can be made to cyclize predominantly via the 7-*endo-trig* process.

These results contrast with the generally observed greater ease of formation of six-membered carbocyclic rings as compared to that of seven-membered rings[15]. The efficient formation of seven-membered rings in the present case is probably due to anchimeric assistance of the aromatic ring. It can be seen that in path B the anisole ring can assist via the very favourable Ar_2-6 (or Ar_1-5) participation, whereas in path A, participation of the aromatic ring would be of the very unfavourable Ar_2-5 (or Ar_1-4) type[16].

Synthesis of C-homoestrone derivatives

The conversion of **3c** into C-homoestrone methyl ether (**16**) was carried out using essentially the same procedure as that described previously for analogous compounds[17]. Epoxidation of **3c** with *tert*-butyl hydroperoxide (2 equiv.) in refluxing benzene, using molybdenum hexacarbonyl as a catalyst[18], gave predominantly the α-epoxide **14**. However, the stereoselectivity of the reaction, as reflected in the isolated amounts of **14** and **15** (**14/15** = 2.2 to 4.5), varied in a curious manner[19] and was never as high as observed in the epoxidation of **2a**, **3a** and related compounds (α-epoxide/β-epoxide ≈5[17]). Moreover, the reaction was far more sensitive to traces of moisture and other polar impurities than observed in previous cases. Thus, in some runs, the epoxidation of **3c** was complete in 20 min with only 1 mol % of catalyst, whereas in others, starting material was still present after $1\frac{1}{2}$ h despite the use of 5 mol % of catalyst[20]. With rigorous exclusion of moisture, a 55% yield of **14** could be achieved, while the undesired isomer **15** was isolated in 25% yield.

Treatment of **14** with freshly distilled $BF_3 \cdot Et_2O$ in toluene resulted in rearrangement to the 17-ketone **16**, isolated in 47% yield. This compound was identical (^{1}H NMR, IR, chromatographic properties) to authentic material[21], thus



Scheme 4

confirming the structures assigned to **3c** and **14**.

Finally, **16** was reduced to the corresponding alcohol **17**, which, upon demethylation, afforded DL-C-homoestradiol (**18**) in good yield. These products were also identical to authentic samples prepared by partial synthesis[3].

Conclusions

We have shown that C-homosteroids can be prepared via cationic polyene cyclizations, thus leading to the first successful, total synthesis of DL-C-homoestradiol (**18**) and related compounds[22]. The synthesis described above produced **18** in 10 steps from the readily available starting material **4** in 2.2% overall yield. By comparison, the reported partial synthesis of **18** from hecogenin required 19 steps but proceeded in higher overall yield (*viz.* 3.8%).

The latter synthesis, however, has the advantage of producing **18** in the optically active, natural form only.

Thus, **18**, prepared via total synthesis and therefore being racemic, showed half of the estrogenic activity of the natural enantiomer, which had a potency comparable to estradiol in a number of tests (*Allen–Doisy* test and uterotrophic test in rats, subcutaneous administration). The present results raise the question as to at which ring size cationic polyene cyclizations will fail to proceed in useful yields. Obviously medium-sized (e.g. eight- and nine-membered) rings, the formation of which is notoriously difficult, are a challenging target for further study in this field.

Experimental

General remarks

Melting points, determined in capillary tubes, are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ solution with TMS (δ 0) as internal standard on a Bruker HX-90 E or WP 200 instrument by the Analytical R&D Labs, Organon Scientific Development Group. Oss, The Netherlands. Microanalyses were carried out by Dr. *W. McMeekin*, Analytical Department, Organon Laboratories, Newhouse, Scotland. For column chromatography, Woelm silica gel (70–230 mesh, activity grade I) was used and, for preparative HPLC, Merck Lobar® Fertigsäule. All reactions were carried out under a dry nitrogen atmosphere.

5-Methyl-2-furanpentanenitrile (**5**)

A mixture of 21.7 g (0.1 mol) 2-(4-bromobutyl)-5-methyl-furan (**4**), 13.2 g (0.2 mol) of powdered KCN and 100 ml of dry DMSO was heated at 85 °C for 16 h with stirring.

The reaction mixture was cooled, diluted with water and extracted with ether (3 × 100 ml). The extracts were washed with water, dried over anhyd. Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed with hexane/ethyl acetate 9/1 to give 3.5 g of starting material and 11.1 g (81%, based on converted **4**) of **5**. ^{1}H NMR: δ 1.5–2.4 (m, 6), 2.23 (s, 3, CH_3-furan), 2.62 (br.t, *J* 7, CH_2-furan), 5.84 (m, 2, furan H's).

5-Methyl-2-furanpentanal (**6**)

To a solution of 16.3 g (0.1 mol) of the nitrile **5** in 160 ml of dry toluene was added dropwise with stirring 88 ml of 1.2 M diisobutylaluminium hydride solution in toluene (~1.05 equiv.) at −70 °C. The resulting solution was stirred at −70 °C for $\frac{1}{2}$ h, allowed to warm to room temperature and mixed with an excess of 2 N HCl. The organic layer was separated and the aqueous layer extracted with ether. The combined organic layers were washed with dilute aqueous HCl, followed by water, until neutral and dried over anhyd.

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[15] This is strikingly demonstrated by the fact that solvolysis of 5-hexenyl and 6-heptenyl *p*-nitrobenzenesulphonate produces cyclohexanol and cycloheptanol in 50–70% and 1% (!) yield, respectively: *W. S. Johnson, D. M. Bailey, R. Owyang, R. A. Bell, B. Jacques* and *J. K. Crandall*, J. Am. Chem. Soc. **86**, 1959 (1964).

[16] *R. Heck* and *S. Winstein*, J. Am. Chem. Soc. **79**, 3105, 3114 (1957).

[17] *M. B. Groen* and *F. J. Zeelen*, Tetrahedron Lett. **23**, 3611 (1982).

[18] *cf. K. B. Sharpless* and *T. R. Verhoeven*, Aldrichimica Acta **12**, 63 (1979).

[19] As **14** is somewhat unstable under the reaction conditions, the **14/15** ratio is adversely affected by prolonged reaction times. However, this cannot be the sole explanation for our results since the yield of **15** also varied to some degree.

[20] Longer reaction times caused a considerable drop in the yield of **14**.

[21] The synthesis of the natural enantiomer of this compound has been reported[3]. In our laboratory, the natural enantiomers of **16–18** have been prepared via a similar strategy, starting from a more advanced intermediate: *M. B. Groen, J. Leemhuis* and *H. Geurds*, unpublished results.

[22] A total synthesis of C-homo-9β-estrogens has been reported: *G. Neef, U. Eder, G. Haffer, G. Sauer* and *R. Wiechert*, Chem. Ber. **110**, 3377 (1977).

Na_2SO_4. Evaporation of the solvents *in vacuo* gave 12.1 g (73%) of the crude aldehyde **6** (purity >95%), which was used in the next step without further purification. ^{1}H NMR: δ 1.4–1.9 (m, 4), 2.23 (s, 3, CH_3-furan), 2.2–2.8 (m, 4), 5.84 (m, 2, furan H's), 9.78 (t, *J* 1.3 Hz, 1, CHO).

2-[8-(3-Methoxyphenyl)-(E)-5-octen-1-yl]-5-methylfuran (**8**)

To a stirred suspension of 49.2 g (0.1 mol) of **7** in 200 ml of dry THF was added at 0–5 °C a 1.3 M solution of phenyllithium in ether (80 ml, ~1 equiv.). The orange-red solution was stirred without cooling for ½ h and then cooled to −70 °C. A solution of 15.0 g (0.09 mol) of **6** in 40 ml of dry THF was added dropwise, followed by 150 ml of 1.3 M phenyllithium solution in ether (~2 equiv.). The resulting red solution was allowed to warm to −30 °C and maintained at that temperature for 15 min. Methanol (50 ml) was then added slowly, followed by water and ether. The organic layer was separated, washed several times with water and dried over anhyd. Na_2SO_4. The solvents were evaporated *in vacuo* and the residue chromatographed with hexane containing 5–10% ethyl acetate. This gave 17.9 g (60%) of **8** as a colourless oil (purity according to GLC >99%). ^{1}H NMR: δ 1.2–1.8 (m, 4), 1.9–2.4 (m, 4), 2.22 (s, 3, CH_3-furan), 2.4–2.8 (m, 4), 3.77 (s, 3, OCH_3), 5.44 (m, 2, CH = CH), 5.81 (s, 2, furan H's), 6.65–7.3 (m, 4, aromatic H's).

2-[7-(3-Methoxyphenyl)-(E)-4-heptenyl]-3-methyl-2-cyclopentenone (**9**)

A mixture of 8.95 g (0.03 mol) of **8**, 360 ml of glacial acetic acid, 180 ml of distilled water and 0.3 ml of 4 N sulphuric acid was refluxed for 2 h. The reaction mixture was cooled, diluted with water and extracted with CH_2Cl_2 (3 × 100 ml). The combined extracts were washed several times with water, then with 5% aqueous sodium bicarbonate until neutral, and dried briefly over anhyd. K_2CO_3.
The solvent was evaporated and the residue dissolved in 450 ml of ethanol/water 2/1. Solid KOH (1.8 g) was added and the resulting mixture was refluxed for 4 h. The reaction mixture was neutralized with 2 N HCl and most of the ethanol was evaporated *in vacuo*. The resulting mixture was extracted with ether. The ether extracts were dried over anhyd. Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed with hexane/ethyl acetate 8/2 to give 8.0 g (89%) of **9** as a colourless oil. $C_{20}H_{26}O_2$ (298.41) calcd.: C 80.49, H 8.78; found: C 80.62, H 8.78. ^{1}H NMR: δ 2.02 (s, 3, allylic CH_3), 3.79 (s, 3, OCH_3), 5.43 (m, 2, CH = CH), 6.6–7.3 (m, 4, aromatic H's).

Reduction of **9** *and cyclization of* **1c**

To a solution of 6.0 g (20 mmol) of **9** in 100 ml of dry ether was added 0.76 g (20 mmol) of $LiAlH_4$ at −20 °C.
The mixture was allowed to warm to 0 °C over 1 h and then worked up with saturated aqueous Na_2SO_4. Filtration and evaporation of the solvent gave 6.0 g of **1c** as a colourless oil. This product was dissolved in 50 ml of dry CH_2Cl_2 and added dropwise to a stirred solution of 7.4 ml (8.5 g, 60 mmol) of boron trifluoride etherate in 300 ml of dry CH_2Cl_2 at −78 °C. The resulting mixture was stirred at −78 °C for 15 min and then poured into an excess of ice-cold 2N aqueous KOH with vigorous stirring. The organic layer was separated, dried over anhyd. K_2CO_3 and concentrated *in vacuo*. The residue was chromatographed via preparative HPLC using hexane/toluene 95/5, which gave 1.20 g (21%) of **2c** and 2.72 g (48%) of **3c**.
Further purification by recrystallization from methanol gave 1.07 g (19%) of **2c**, m.p. 90–92 °C, and 2.14 g (38%) of **3c**, m.p. 46–47 °C. $C_{20}H_{26}O$ (282.41) calcd.: C 85.05, H 9.28; found for **2c**: C 85.27, H 9.44; for **3c**: C 84.87, H 9.26. ^{1}H NMR for **2c**: δ 1.65 (br.s, 3, 17-CH_3), 2.64 (dd, *J* 3.5 and 6.5 Hz, 2, 6-H's), 3.14 (ddd, *J* 4, 8 and 10 Hz, 1, 9-H), 3.82 (s, 3, OCH_3), 6.70 (d, *J* 8 Hz, 2, 2-H and 4-H), 7.06 (t, *J* 8 Hz, 1, 3-H); for **3c**: δ 1.63 (br.s, 3, 17-CH_3), 2.67 (dd, *J* 3.5 and 8 Hz, 2, 6-H's), 2.82 (ddd, *J* 4.5, 8.5 and 11 Hz, 1, 9-H), 3.77 (s, 3, OCH_3), 6.62 (d, *J* 2.8 Hz, 1, 4-H), 6.74 (dd, *J* 2.5 and 8 Hz, 1, 2-H), 7.18 (d, *J* 8 Hz, 1, 1-H).

DL-*13,17α-Epoxy-3-methoxy-17-methyl-C-homo-13α-gona-1,3,5(10)triene* (**14**) *and its 13β, 17β-isomer* (**15**)

To a solution of 2.82 g (10 mmol) of **3c** in 150 ml of dry benzene was added 310 mg of anhydrous Na_2HPO_4 and 155 mg of molybdenum hexacarbonyl. *Ca.* 30 ml of benzene was distilled off in order to remove traces of water. A dry solution of *tert*-butyl hydroperoxide in benzene (5 ml of 4 M solution was added and the resulting mixture was refluxed with stirring for between ½ and 1 h. The reaction mixture was cooled, washed with 10% aqueous Na_2SO_3 and dried over anhyd. Na_2SO_4. Evaporation of the solvent left a mixture of **14** and **15** which was separated by preparative HPLC using hexane/ethyl acetate 95/5. In a typical experiment, 0.70 g of **14** (25% yield) and 1.55 g (55% yield) of **15** were isolated.
The desired product **14** had m.p. 86–88 °C (from ether). ^{1}H NMR: δ 1.39 (s, 3, 17-CH_3), 3.76 (s, 3, OCH_3), 6.61 (d, *J* 2.5 Hz, 1, 4-H), 6.75 (dd, *J* 9 and 2.5 Hz, 1, 2-H), 7.13 (d, *J* 9 Hz, 1, 1-H).
The less polar isomer **15** had m.p. 116–119 °C (from ether). ^{1}H NMR: δ 1.33 (s, 3, 17-CH_3), 3.74 (s, 3, OCH_3), 6.60 (d, *J* 2.5 Hz, 1, 4-H), 6.75 (dd, *J* 8.5 and 2.5 Hz, 1, 2-H), 7.19 (d, *J* 8.5 Hz, 1, 1-H).

DL-*3-Methoxy-C-homo-1,3,5,(10)-estratrien-17-one* (**16**)

A solution of 0.90 g (3 mmol) of the epoxide **14** in 20 ml of dry toluene was treated with 0.4 ml of freshly distilled boron trifluoride etherate at 0 °C. After 5 minutes at 0 °C, the reaction mixture was shaken with aqueous K_2CO_3 until its purple colour had faded. The organic layer was separated and the aqueous layer extracted with ether.The combined organic phases were washed with water, dried over anhyd. K_2CO_3 and concentrated *in vacuo*. The residue was chromatographed with hexane/ethyl acetate 4/1 and the crude product crystallized from ether/hexane to give 0.42 g (47% yield) of **16**, m.p. 121–124 °C. (D-enantiomer: m.p. 157.1 °C[3]). ^{1}H NMR: identical with data reported for D-enantiomer[3].

DL-*C-Homo-1,3,5(10)-estratriene-3,17-diol 3-methyl ether* (**17**)

A solution of 0.42 g (1.4 mmol) of 17-ketone **16** in 30 ml of dry THF was treated with 0.10 g (2.7 mmol) of $LiAlH_4$ at room temperature for ½ h. Work-up gave 0.39 g (93% yield) of the product **17**, m.p. 132–134 °C (from ether). The D-enantiomer[21] had m.p. 110–112 °C. Both products had identical ^{1}H NMR spectra: δ 0.83 (s, 3, 13-CH_3), 3.62 (br.t, *J* 8 Hz, 1, 17-H), 3.76 (s, 3, OCH_3), 6.56 (d, *J* 2.5 Hz, 1, 4-H), 6.72 (dd, *J* 8.5 and 2.5 Hz, 1, 2-H), 7.16 (d, *J* 8.5 Hz, 1, 1-H).

DL-*C-Homo-1,3,5(10)-estratriene-3,17-diol* (**18**)

To a solution of 0.30 g (1.0 mmol) of **16** in 20 ml of dry CH_2Cl_2 was added 0.3 ml (0.8 g, 3.2 mmol) of BBr_3 at −70 °C. The temperature was raised to 0 °C and the reaction mixture maintained at this temperature for 1 h. Water was added cautiously with stirring. The organic layer was separated, washed with aqueous sodium bicarbonate and dried over anhyd. Na_2SO_4. Evaporation of the solvent and recrystallization of the residue from toluene gave 0.22 g (77% yield) of **18**, m.p. 201–202 °C.
The D-enantiomer had m.p. 142–148 °C (from ethyl acetate)[21]; reported [3] m.p. 157 °C (from methanol).
^{1}H NMR ($CDCl_3/CD_3OD$ 4/1)[23]: δ 0.83 (s, 3, 13-CH_3), 3.60 (t, *J* 8 Hz, 1, 17-H), 6.48 (d, *J* 8.5 Hz, 4-H), 6.61 (dd, *J* 8.5 and 2.5 Hz, 1, 2-H), 7.04 (d, *J* 8.5 Hz, 1, 1-H).

[23] The spectrum in pyridine-d_5 has been reported[3].