14-Methyl Steroids. Part 5.[1] Structural Features Influencing Stereoselectivity of 14-Methylation of 15-Oxo-19-norsteroids: Synthesis of 14α-Methyl-19-norprogesterone

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Methylation of 3-methoxy-14β-estra-1,3,5(10),8-tetraen-15-one (**5**) in the presence of base affords a *ca.* 5:1 mixture of the corresponding 14α- and 14β-methyl compounds (**6**) and (**7**) respectively, whereas similar treatment of 20,20-ethylenedioxy-3-methoxy-19-norpregna-1,3,5(10)-trien-15-one (**15**) results in exclusive formation of the 14α-methyl product (**18**). The latter compound (**18**) has been converted into 14α-methyl-19-norprogesterone (**23**). The stereoselectivity of 14-methylation of 15-ketones is correlated with the propensity of ring D to adopt a quasi-*trans* or quasi-*cis* conformation in the derived enolate, leading to preferred 14α-or 14β-methylation respectively.

The sterically directing role of unsaturation in rings B or C, and of 17-functionality, upon the course of base-mediated alkylation of steroidal 15-ketones is implied in earlier reports in the literature.[2–4] We have shown[2] that highly stereoselective 14β-methylation takes place in simple 15-oxo-19-norsteroids, and that this reaction course is retained in 17,17-ethylenedioxy- and 17β-acetoxy-15-ketones, both of which proceed through Δ^{16}-intermediates. However, it has been reported that only 14α-alkylation occurs in cholest-8(14)-en-15-ones[3] and in pregnan-15-ones.[4] The former result was authenticated through eventual correlation of the derived products with the synthetic target, lanosterol,[3] and has, more recently been successfully adapted for a synthesis of methyl 14α-methyl-15-oxo-5β-chol-8-en-24-oate from cholic acid.[5]

It is tempting to conclude that the stereochemical course of the reaction is dictated by the conformation imposed upon ring D by the 14(15)-en-15-olate anion or a derived transition state, since such an influence would be comparable to that which is believed to determine the stereochemistry of addition to steroidal Δ^{14}-bonds.[6] In this rationalisation, α- or β-face addition to the olefinic bond is correlated with adoption of a quasi-*trans* or quasi-*cis* conformation of ring D.

Such conformational preferences may be influenced by substitution and conformational transmission effects, and we undertook to examine the influence of certain structural features in 15-oxo-19-norsteroids upon the stereochemical outcome of 14-alkylation. Those features were considered, which might predispose ring D toward the adoption of a conformation which would promote 14α-alkylation. This would serve, not only to give credence to the proposed analogy, but also to provide alternative synthetic pathways to 14α-methyl-19-norsteroids.[7]

In the first instance, the preparation and alkylation of a $\Delta^{8(14)}$-15-oxo-19-norsteroid was undertaken,[8] in order to ascertain whether unsaturation in the absence of a 17β-alkyl residue would suffice to reverse the preference for 14β-alkylation which obtains in the saturated derivative.[2]

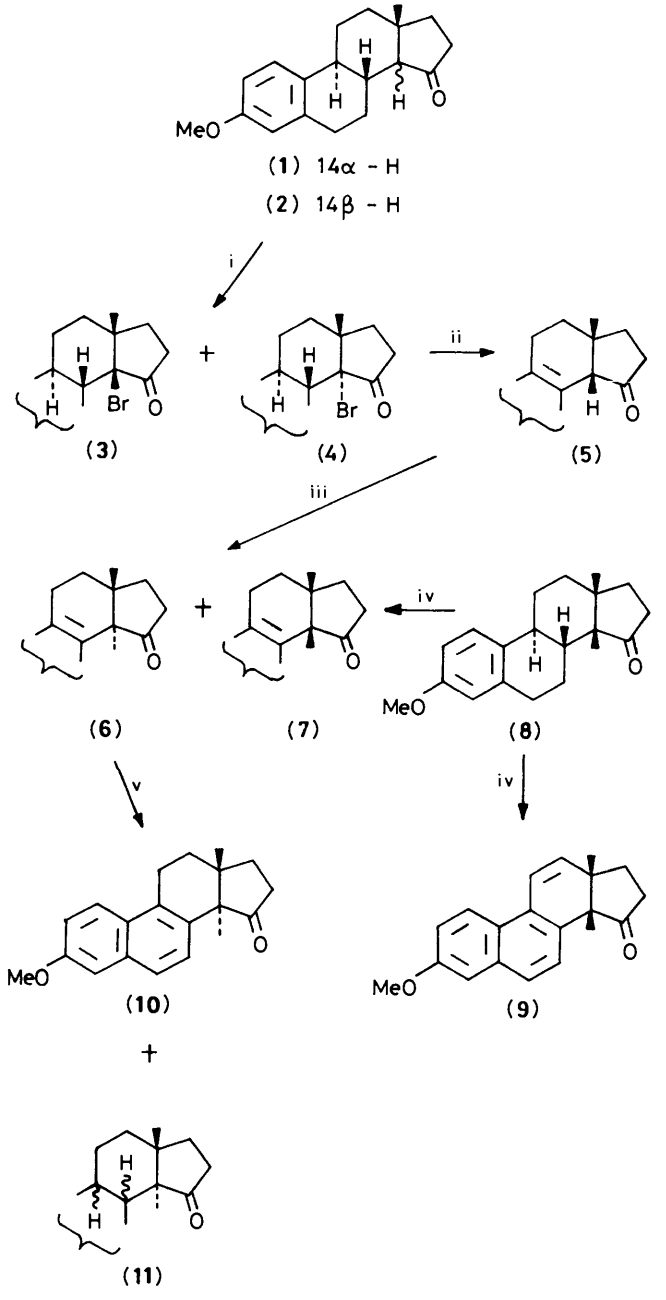
Treatment of 3-methoxyestra-1,3,5(10)-trien-15-one (**1**) [or its 14β-epimer (**2**)] with pyridinium hydrobromide perbromide in acetic acid at 15 °C afforded a chromatographically separable mixture of 14β- and 14α-bromo 15-ketones (**3**) (31%) and (**4**) (28%). The modest overall yield resulted from some competing bromination of ring A, but the ratio of isomers is similar to that found upon bromination of 5α-androstan-15-one.[9]

The isomers were readily differentiated with the aid of c.d. spectroscopy; thus, the positive increment ($\Delta\Delta\varepsilon$ + 5.9) associated with the 14β-bromo group in the Cotton effect of (**3**) [$\Delta\varepsilon_{317}$ + 3.5, compared with $\Delta\varepsilon_{302}$ − 2.4 for the parent ketone (**2**)], and the negative increment ($\Delta\Delta\varepsilon$ − 7.2) associated with the 14α-bromo group in (**4**) [$\Delta\varepsilon_{314}$ − 4.3, compared with $\Delta\varepsilon_{306}$ + 2.9 for the parent ketone (**1**)] are uniquely compatible with the assignments.

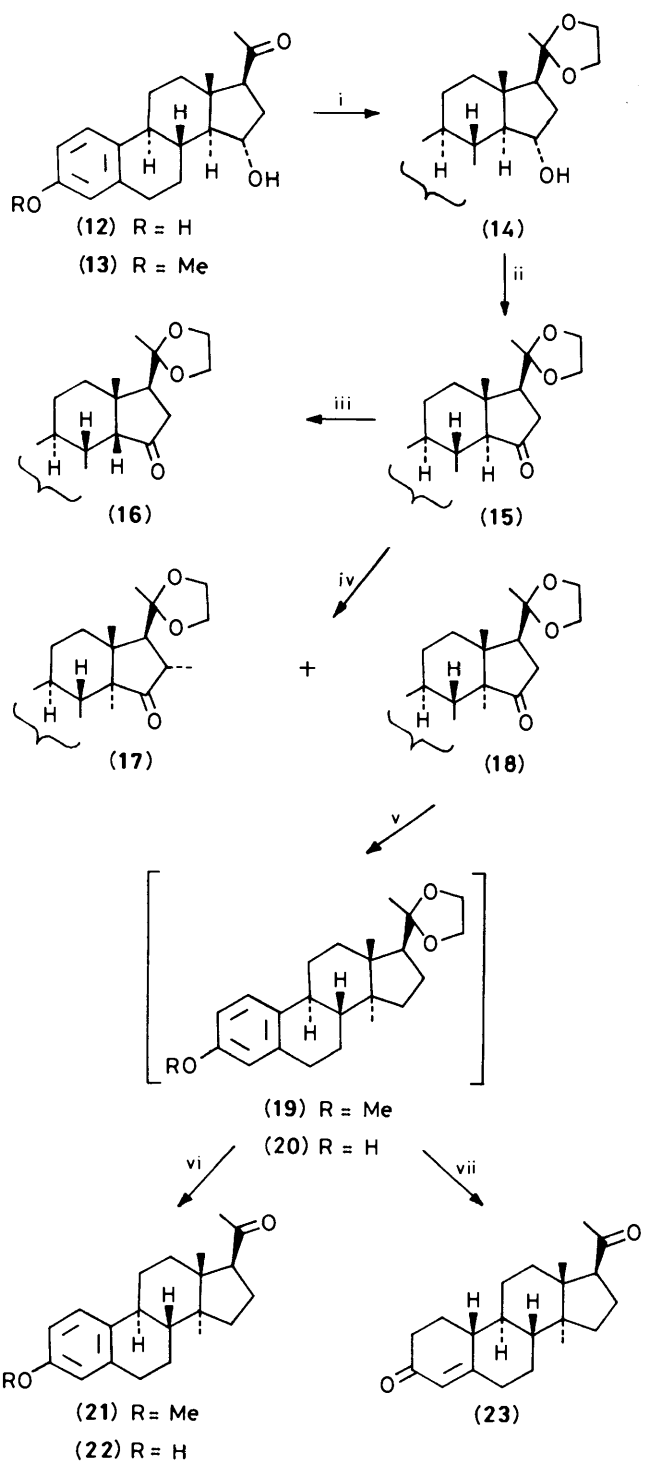
The 14α-bromo 15-ketone (**4**) underwent dehydrobromination in the presence of lithium bromide–lithium carbonate in dimethylformamide at 100 °C to give a product, whose spectroscopic properties revealed that the primary elimination product had undergone subsequent isomerisation to give 3-methoxy-14β-estra-1,3,5(10),8-tetraen-15-one (**5**). The u.v. spectrum of compound (**5**) was typical for a styryl chromophore, and the Cotton effect of the n→π* transition ($\Delta\varepsilon_{312}$ − 2.4) was strongly suggestive of 14β-configuration.

Although the formation of the Δ^8-compound (**5**) was unexpected,[9] it served the intended purpose, since the derived 8,14-dien-15-olate species was expected to be identical with the intermediate which the targeted $\Delta^{8(14)}$-15-ketone would have formed under conditions for 14-alkylation.

Treatment of the Δ^8-15-ketone (**5**) with potassium t-butoxide in t-butyl alcohol at 30 °C, followed by reaction with methyl iodide for 1 h, gave a mixture which was separated by column chromatography and p.l.c., to give the 14α-methyl compound (**6**) (*ca.* 57%) accompanied by some 14β-methyl isomer (**7**) (*ca.* 12%). The assignment of the structure of the 14α-methyl compound (**6**) was not obvious from the c.d. data ($\Delta\varepsilon_{307}$ − 1.1) since a parent Δ^8-15-ketone was not available for comparison. Comparison with the 15-ketone (**1**) ($\Delta\varepsilon$ + 2.9) results in an apparent α-axial methyl increment of $\Delta\Delta\varepsilon$ − 4, which is excessive,[10] and implies that the Δ^8-bond must perturb the Cotton effect of the 15-oxo group in compound (**6**). Furthermore, the sign and magnitude of the Cotton effect in (**6**) were quite similar to those of 3-methoxy-14-methyl-14β-estra-1,3,5(10)-trien-15-one.[2] However, the minor 14β-methyl isomer (**7**) displayed a remarkably large Cotton effect ($\Delta\varepsilon_{313}$ − 21.5), the magnitude of which is diagnostic for an inherently disymmetric chromophore.[11] The geometry to accommodate a major overlap of the interacting chromophores is only possible in the 14β-isomer (**7**), and the absence of a comparable effect in the long wavelength transition of the Δ^8-14β*H* 15-ketone parent (**5**) implies that conformational constraints imposed by the 14β-methyl group are essential for this effect. Accordingly, the structure of the 14α-methyl isomer (**6**) can be assigned by exclusion.



Scheme 1. *Reagents:* i, $C_5H_5N^+HBr_3^-$–AcOH, 15° C; ii, LiBr–Li_2CO_3–DMF, 100 °C; iii, Bu^{t}OK–Bu^{t}OH–MeI, 30 °C; iv, DDQ–dioxane, 95 °C; v, 5% Pd–C, H_2



Scheme 2. *Reagents:* i, $(CH_2OH)_2$–*p*-TsOH–C_6H_6, 75 °C; ii, $C_5H_5N^+HCrO_3Cl^-$–NaOAc–CH_2Cl_2, 0 °C; iii, KOH–MeOH, 25 °C; iv, $NaNH_2$–THF–MeI, −60 °C; v, N_2H_4–DEG–KOH, 150—230 °C; vi, *p*-TsOH–EtOAc, 25 °C; vii, Li–NH_3–Bu^{t}OH–THF, −35 °C, then HCl–MeOH, 25 °C

Further evidence for the assignments was obtained through dehydrogenation of 3-methoxy-14-methyl-14β-estra-1,3,5(10)-trien-15-one (**8**) with 2,3-dichloro-4,5-dicyanobenzoquinone in refluxing dioxane, which proceeded slowly to give two products, one of which was identical with the minor product (**7**) derived from the alkylation of the Δ^8-15-ketone (**5**). The second product was the exhaustively dehydrogenated hexaene (**9**), the structure of which was deduced from characteristic[12] u.v. and n.m.r. data. Interestingly, the course of dehydrogenation of the 14β-methyl 15-ketone (**8**) was neither as ordered nor as efficient as in the related 14α-methyl series.[12] However, it was concluded that the first step in dehydrogenation of compound (**8**) leads to a mixture of the Δ^8- (**7**) and $\Delta^{9(11)}$-isomers, and that the former compound resists further dehydrogenation whereas the latter is converted, *via* a $\Delta^{8,11}$-intermediate, into the hexaene (**9**).

An attempt to ascertain the stereoselectivity of hydrogenation of the 14α-methyl Δ^8-15-ketone (**6**) proved disappointing, since the preferred reaction course in the presence of 5% palladium on

charcoal proved to be dehydrogenation to the pentaene (**10**) (54%), a result similar to that obtained upon attempted hydrogenation of the related 14α-methyl Δ^8-17-ketone;[13] the hydrogenation product (37%) was shown to be a mixture of three 8,9-dihydro isomers (**11**) which could not be further characterised owing to scarcity of material.

Although the foregoing experiments suggested the way in which earlier obstacles[2] to an alkylation pathway to 14α-methyl steroids could be overcome, the development of a practical synthesis of 14α-methyl 19-norsteroids was not pursued, owing to problems envisaged in restoration of functionality at C(17).[1] A parallel series of experiments upon the preparation and alkylation of 17-functionalised analogues of the Δ^8-15-ketone (**5**) was abandoned, after that approach was superseded by the successful completion of a total synthesis of 14α-methyl 19-norsteroids.[12,13]

However, the experiments confirmed that the presence of a Δ^8-bond indeed reverses the stereoselectivity of 14-alkylation, and attention was then turned to the role of a 17β-alkyl group, in order to verify an earlier claim[4] that this feature, alone, also has that effect.

20,20-Ethylenedioxy-3-methoxy-19-norpregna-1,3,5(10)-trien-15-one (**15**) was selected as a model substrate, since the product of a successful experiment could be used for a practical synthesis of 14α-methyl-19-norprogesterone (**23**). 3,15α-Dihydroxy-19-norpregna-1,3,5(10)-trien-20-one (**12**) was converted sequentially into the 3-methyl ether (**13**) and the derived 20,20-ethylenedioxy compound (**14**), which underwent oxidation with pyridinium chlorochromate in buffered medium at 0 °C to give the desired 15-ketone (**15**).

Initial alkylation experiments upon compound (**15**) were carried out with potassium t-butoxide in t-butyl alcohol, at temperatures between 0 and 60 °C, followed by addition of methyl iodide. Although methylation took place under these conditions, the reactions could not be forced to completion, and the residual starting material (**15**) also underwent partial isomerisation to the 14β-isomer (**16**), which proved to be exceptionally difficult to separate from the alkylation products, The ease of isomerisation at C(14) was demonstrated in a separate experiment, in which the 15-ketone (**15**) was treated with methanolic 0.015M-potassium hydroxide at 25 °C for 20 h to give an equilibrium mixture of isomers (**15**) and (**16**) (*ca.* 1:1), which corresponds reasonably well with results reported for 17β-methyl and 17β-ethyl 15-ketones.[14]

More forcing alkylation conditions were attempted, in which the 15-ketone (**15**) was treated with sodium amide in tetrahydrofuran at 0 °C, followed by brief treatment with an excess of methyl iodide. This resulted in complete reaction, but gave an unacceptable yield of an over-alkylation product. However, a similar experiment conducted at −60 °C, with a reaction time of *ca.* 1 min, gave a good yield (70%) of a single 14-methyl product (**18**) accompanied by smaller amounts (23%) of a 14,16-dimethyl compound (**17**).

Spectroscopic evidence confirmed that the major product was the 14α-methyl 15-ketone (**18**). Most of the signals in a 500 MHz n.m.r. spectrum of compound (**18**) could be assigned,[15] and those of the ring D protons were diagnostic for the presence of a C,D-trans ring junction. Although the signal for the 17α-proton (t, *J* 9.0 Hz, at 2.58 p.p.m.) in compound (**18**) could not be compared with that of the starting material (**15**), in which the signals for the 16- and 17-protons are obscured, it differed clearly from that of the 17α-proton (dd, *J* 9.8 and 2.5 Hz, at 2.08 p.p.m.) in the 14β*H* 15-ketone (**16**). Similarly, the chemical shift of the 13β-methyl signal in the product (**18**) (0.94 p.p.m.) correlates more closely with that of the 14α*H* 15-ketone (**15**) (0.87 p.p.m.) than that of the 14β*H* 15-ketone (**16**) (1.33 p.p.m.). Furthermore, the Cotton effect of the 15-oxo group in (**18**) ($\Delta\varepsilon_{300}$ + 0.77), compared with that of starting material (**15**) ($\Delta\varepsilon_{295}$ + 3.14), gives rise to a negative increment ($\Delta\Delta\varepsilon$ − 2.37) for the α-axial methyl group. Although this is somewhat greater than the increment (1.9) normally associated with such functionality,[9] the discrepancy would be considerably greater ($\Delta\Delta\varepsilon$ + 3.17) for a 14β-methyl assignment.

The bridgehead assignment of the 14,16-dimethyl compound (**17**) follows from its derivation from compound (**18**), and the small positive increment ($\Delta\Delta\varepsilon$ + 0.34) to the Cotton effect of the 15-oxo group is consonant with the presence of a 16α-methyl group.

Wolff-Kishner reduction of the 14α-methyl 15-ketone (**18**) was accompanied by partial cleavage of the 3-methoxy group, and the attempted isolation of the products (**19**) and (**20**) was further complicated by the exceptional lability of the 20,20-ethylenedioxy group. Accordingly, the crude product (**19**) + (**20**) was treated with toluene-*p*-sulphonic acid, to give a readily separable mixture of 3-methoxy-14-methyl-19-norpregna-1,3,5(10)-trien-20-one (**21**) and the corresponding 3-hydroxy compound (**22**).

The 3-methyl ether (**21**) was converted into the crude 20-acetal (**19**), which was immediately subjected to Birch reduction, followed by acid treatment, to give 14α-methyl-19-norprogesterone (**23**), the chiroptical and spectroscopic properties of which confirmed its structure.

Discussion

The results demonstrate that a Δ^8-bond or a protected 17β-acetyl group separately reverse the stereoselectivity of 14-alkylation of steroidal 15-ketones and, accordingly, an explanation was sought in the analogous behaviour of Δ^{14}-steroids in addition reactions. It is known[16] that hydrogenation of 17β-alkyl Δ^{14}-steroids favours α-face addition, whereas the reverse stereoselectivity prevails in 17α-alkyl Δ^{14}-steroids. Similar tendencies have been noted[6,17] in electrophilic additions to 17-substituted Δ^{14}-steroids, and the results may be correlated[6] with the adoption of a quasi-*trans* or quasi-*cis* conformation by ring D.

We propose a similar correlation, based upon the preferred

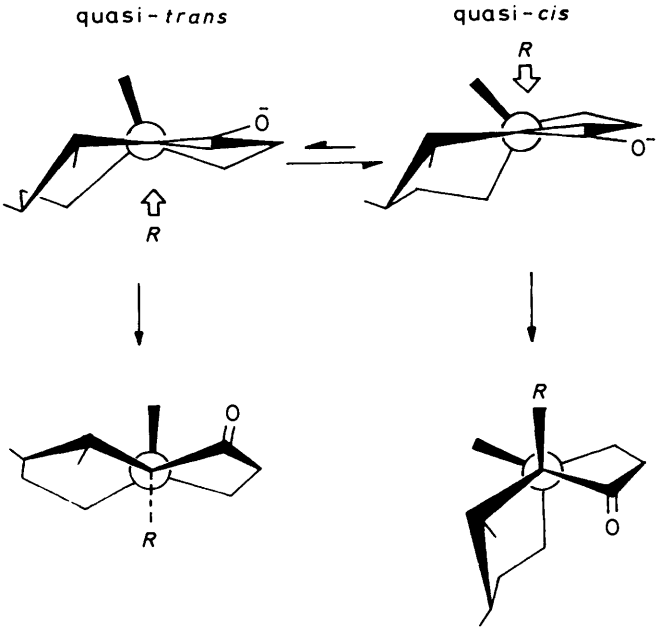


Figure. Proposed ring D conformers [C(14)–C(13) projections] of 14-en-15-olate anion for stereoselective 14α- or 14β- alkylation

ring D conformation in the 14-en-15-olate anion or a derived transition state, in which 14α- or 14β-methylation proceeds through quasi-*trans* or quasi-*cis* conformers respectively (see Figure). This implies that the favoured reactive state of the enolate species derived from 3-methoxyestra-1,3,5(10)-trien-15-one is quasi-*cis*, leading to exclusive 14β-methylation.[2] Furthermore, this preferred conformation and attendant stereoselectivity are unaltered by the additional presence of the Δ^{16}-bond which forms during the corresponding reactions of the related 17β-acetoxy- and 17,17-ethylenedioxy 15-ketones.[2]

However, a 17β-alkyl group acts as a conformational anchor to preserve its pseudo-equatorial orientation and, hence, the quasi-*trans* state of ring D. Consequently, the exclusive reaction course in 17β-alkyl-15-ketones is 14α-methylation.

The effect of the Δ^8-bond upon ring D may be rationalised in terms of conformational transmission which opposes the adoption of the otherwise favoured quasi-*cis* state. Indeed, unsaturation at the 8,9-position has the effect of diminishing the ring-junction torsion angle, $\varphi_{8,14,13,12}$, and thereby stabilising the quasi-*trans* conformer, in which this torsion angle is smaller than in the quasi-*cis* conformer.[18] Although this effect is perhaps not as pronounced as that of the 17β-alkyl group, it is suggested that any structural feature which closes that torsion angle will contribute toward increasing the 14α-stereoselectivity of the reaction. It may thus be argued that the Δ^7-bond, in the dienolate derived from the cholest-8(14)-en-15-one,[3] or the Δ^8-bond in that derived from the cholane series Δ^8-15-ketone,[5] play a complementary role to that of the 17β-side chain in stabilising the quasi-*trans* conformation of ring D and, hence, the experimental outcome of exclusive 14α-methylation. Furthermore, it would be expected that reaction of a Δ^{11}-15-ketone would lead to favoured 14α-alkylation, whereas reaction of a $\Delta^{9(11)}$-15-ketone would follow the course of the saturated 15-ketone.

Experimental

For general instructions, see ref. 1. N.m.r. data for compounds (**15**)—(**18**) were recorded at 500 MHz, and assignments for signals of the protons on C(6)—C(12) generally correspond to those reported elsewhere[15] for similar compounds, and are omitted.

Bromination of the 15-*Ketones* (**1**) *or* (**2**).—(*a*) A stirred mixture of the 15-ketone (**2**) (1.0 g) and pyridinium hydrobromide perbromide (1.4 g) in acetic acid (40 ml) was maintained at 15 °C for 45 min. Aqueous 2M-sodium hydroxide (350 ml) was added, and the product was isolated by extraction with ethyl acetate, and chromatographed on silica gel (150 g). Elution with benzene gave mixed fractions (*m/z* 440, 442, and 444) followed by 14-*bromo*-3-*methoxy*-14β-*estra*-1,3,5(10)-*trien*-15-*one* (**3**) (398 mg), m.p. 116—118 °C (from acetone–methanol); $[\alpha]_D$ +118° (*c* 0.7); $\nu_{max.}$ 1 741 cm^{-1}; $\Delta\varepsilon_{max.}$ + 3.5 (317 nm); δ 1.33 (3 H, s, 13β-Me), 3.77 (3 H, s, OMe), and 6.58—7.2 (3 H, m, 1-, 2-, and 4-H) (Found: C, 62.9; H, 6.2; Br, 23.0%; M^+, 362 and 364. $C_{19}H_{23}BrO_2$ requires C, 62.8; H, 6.4; Br, 22.0%; *M*, 362 and 364), and 14-*bromo*-3-*methoxyestra*-1,3,5(10)-*trien*-15-*one* (**4**) (357 mg), m.p. 109—111 °C (from acetone–methanol); $[\alpha]_D$ −59° (*c* 0.6); $\nu_{max.}$ 1 741 cm^{-1}; $\Delta\varepsilon_{max.}$ −4.3 (314 nm); δ 1.06 (3 H, s, 13β-Me), 3.75 (3 H, s, OMe), and 6.58—7.17 (3 H, m, 1-, 2-, and 4-H) (Found: C, 62.8; H, 6.4; Br, 22.2%; M^+, 326 and 364).

(*b*) Bromination of the 15-ketone (**1**) (100 mg) as described in the foregoing experiment gave compounds (**3**) (35 mg) and (**4**) (32 mg).

3-*Methoxy*-14β-*estra*-1,3,5(10),8-*tetraen*-15-*one* (**5**).—A mixture of the 14α-bromo 15-ketone (**4**) (240 mg), lithium bromide (500 mg), and lithium carbonate (400 mg) in dimethylformamide (15 ml) was stirred at 100 °C under nitrogen for 16 h. The mixture was cooled, diluted with water, and extracted with ethyl acetate, and the product was chromatographed on silica gel (30 g), with ethyl acetate–hexane (3:7) as eluant, to give the Δ^8-15-*ketone* (**5**) (133 mg), m.p. 117—118 °C (from acetone–methanol); $[\alpha]_D$ −49° (*c* 0.7); $\nu_{max.}$ 1 732 cm^{-1}; $\lambda_{max.}$ 275 nm (log ε 4.22); $\Delta\varepsilon_{max.}$ −12.2 (217 nm), +6.8 (273 nm), and −2.4 (312 nm); δ 1.14 (3 H, s, 13β-Me), 3.8 (3 H, s, OMe), and 6.6—7.21 (3 H, m, 1-, 2-, and 4-H) (Found: C, 80.8; H, 7.7%; M^+, 282. $C_{19}H_{22}O_2$ requires C, 80, 8; H, 7.85%, *M*, 282).

Base-mediated Methylation of the Δ^8-15-*Ketone* (**5**).—A M-solution (6 ml) of potassium t-butoxide in t-butyl alcohol was added to a stirred solution of the Δ^8-15-ketone (**5**) (155 mg) in t-butyl alcohol (15 ml) at 30 °C under nitrogen. After 5 min, methyl iodide (1 ml) was added and the mixture was stirred at 30 °C for 1 h. Aqueous sodium sulphite was added and the product was isolated by extraction with ethyl acetate. Column chromatography on silica gel and p.l.c. of enriched fractions, using ethyl acetate–benzene (3:97) as eluant, afforded 3-*methoxy*-14-*methylestra*-1,3,5(10),8-*tetraen*-15-*one* (**6**) (94 mg), m.p. 127—129 °C (from methanol); $[\alpha]_D$ +14° (*c* 1.0); $\nu_{max.}$ 1 732 cm^{-1}; $\lambda_{max.}$ 218 (log ε 4.19), 273sh (4.2), and 278 nm (4.21); $\Delta\varepsilon_{max.}$ −3.2 (221 nm), +4.5 (270 nm) and −1.1 (307 nm); δ 0.93 (3 H, s, 13β-Me), 1.22 (3 H, s, 14α-Me), 3.79 (3 H, s, OMe), and 6.6—7.23 (3 H, m, 1-, 2-, and 4-H) (Found: C, 81.3; H, 8.3%; M^+, 296. $C_{20}H_{24}O_2$ requires C, 81.0; H, 8.2%, *M*, 296), and 3-*methoxy*-14-*methyl*-14β-*estra*-1,3,5(10),8-*tetraen*-15-*one* (**7**) (19 mg), m.p. 149.5—150 °C (from methanol); $[\alpha]_D$ −246° (*c* 0.2); $\nu_{max.}$ 1 727 cm^{-1}; $\lambda_{max.}$ 215 (log ε 4.15), 218sh (4.14), 280 (4.15), and 304sh nm (3.78); $\Delta\varepsilon_{max.}$ +5.8 (228 nm), +15.4 (277 nm), and −21.5 (313 nm); δ 0.97 and 1.1 (each 3 H, s, 13β- and 14β-Me), 3.82 (3 H, s, OMe), and 6.62—7.2 (3 H, m, 1-, 2-, and 4-H) (Found: C, 81.4; H, 8.3%; M^+, 296).

Dehydrogenation of 3-*Methoxy*-14-*methyl*-14β-*estra*-1,3,5-(10)-*trien*-15-*one* (**8**).—2,3-Dichloro-5,6-dicyanobenzoquinone (300 mg) was added to a solution of compound (**8**) (170 mg) in dry dioxane (50 ml), and the mixture was stirred at 95 °C for 3 h. The cooled solution was diluted with benzene, and the organic layer was washed successively with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was filtered through silica gel (40 g) with ethyl acetate–hexane (1:4), and the eluate was concentrated and chromatographed on silica gel (35 g), with ethyl acetate–hexane (3:17) as eluant, to give the 14β-methyl Δ^8-15-ketone (**7**) (19 mg), m.p. and mixed m.p. 149—150 °C, followed by mixed fractions (40 mg), unchanged material (**8**) (85 mg), and 3-*methoxy*-14-*methyl*-14β-*estra*-1,3,5(10),6,8,11-*hexaen*-15-*one* (**9**) (25 mg), m.p. 116—118 °C (from methanol); $[\alpha]_D$ −280° (*c* 0.8); $\nu_{max.}$ 1 731 cm^{-1}; $\lambda_{max.}$ 212 (log ε 4.13), 242 (4.68), 305 (3.81), 318 (3.84), 334 (3.55), and 350 nm (3.54); $\Delta\varepsilon_{max.}$ 7.0sh (291 nm), +9.6 (298 nm), −12.4 (322 nm), and −3.6 (348 nm); δ 1.11 and 1.17 (each 3 H, s, 13β- and 14β-Me), 3.9 (3 H, s, OMe), 6.03 (1 H, d, *J* 10 Hz, 12-H), 7.08 (1 H, d, *J* 3.5 Hz, 4-H), 7.17 (1 H, q, *J* 9 and 3.5 Hz, 2-H), 7.24 (1 H, d, *J* 10 Hz, 11-H), 7.36 and 7.62 (each 1 H, d, *J* 9 Hz, 6- and 7-H), and 8.05 (1 H, d, *J* 9 Hz, 1-H) (Found: C, 82.5; H, 7.1%; M^+, 292.143. $C_{20}H_{20}O_2$ requires C, 82.15; H, 6.9%; *M*, 292.146).

Attempted Catalytic Hydrogenation of the 14α-*Methyl* Δ^8-15-*Ketone* (**6**).—To a stirred suspension of palladium on carbon (5%; 50 mg) in ethyl acetate (10 ml) equilibrated under hydrogen was added compound (**6**) (30 mg) in ethyl acetate (2 ml). Stirring was continued for 3 h after which the mixture was filtered and the filtrate was evaporated. The resulting residue was chromatographed on silica gel (10 g), with ethyl acetate–

benzene (1:9) as eluant, to give 3-*methoxy*-14-*methylestra*-1,3,5(10),6,8-*pentaen*-15-*one* (**10**) (16 mg), m.p. 209—211 °C (from methanol); $[\alpha]_D$ −14° (*c* 0.4); $\nu_{max.}$ 1 736 cm^{-1}; $\lambda_{max.}$ 234 (log ε 4.69), 269 (3.64), 279 (3.67), 290 (3.52), 321 (3.24), and 336 nm (3.32); $\Delta\varepsilon_{max.}$ −2.0 (292 nm); δ 0.87 and 1.31 (each 3 H, s, 13β- and 14α-Me), 3.94 (3 H, s, OMe), 3.08—8.0 (3 H, m, 1-, 2-, and 4-H), and 7.63 and 8.42 (each 1 H, d, *J* 9 Hz, 6- and 7-H) (Found: C, 81.9; H, 7.6%; M^+, 294. $C_{20}H_{22}O_2$ requires C, 81.6; H, 7.5%; *M*, 294). Further elution with the same solvent gave an isomeric mixture (**11**) (11 mg), $\nu_{max.}$ 1 732 cm^{-1}; *m/z* 298 (M^+), which was not further characterised.

15α-*Hydroxy*-3-*methoxy*-19-*norpregna*-1,3,5(10)-*trien*-20-*one* (**13**).—3,15α-Dihydroxy-19-norpregna-1,3,5(10)-trien-20-one (**12**) (1.48 g) in acetone (60 ml) at 25 °C was stirred in the presence of potassium carbonate (20 g) and dimethyl sulphate (5 ml) for 24 h. The mixture was filtered, and the filtrate was diluted with aqueous ammonium hydroxide and extracted with dichloromethane. Filtration of the product through silica gel with methanol–chloroform (1:99) afforded the 3-*methyl ether* (**13**) (1.35 g), m.p. 181—183 °C (from chloroform–hexane); $[\alpha]_D$ +207° (*c* 1.0); δ 0.67 (3 H, s, 13β-Me), 2.13 (3 H, s, 21-H_3), 3.77 (3 H, s, OMe), 4.17 (1 H, br m, $W_{\frac{1}{2}}$ 14 Hz, 15β-H), and 6.65—7.25 (3 H, m, 1-, 2-, and 4-H) (Found: C, 76.4; H, 8.8%; M^+, 328. $C_{21}H_{28}O_3$ requires C, 76.8; H, 8.6%; *M*, 328).

20,20-*Ethylenedioxy*-3-*methoxy*-19-*norpregna*-1,3,5(10)-*trien*-15α-*ol* (**14**).—A mixture of the 20-ketone (**13**) (1.3 g), toluene-*p*-sulphonic acid (120 mg), and ethylene glycol (8 ml) in benzene (120 ml) was slowly distilled during 6 h to give a residual volume of *ca.* 60 ml. The mixture was washed with aqueous sodium hydrogen carbonate and water and then evaporated under reduced pressure to give the 20-*acetal* (**14**) (1.35 g), m.p. 178—181 °C (from chloroform–hexane); $[\alpha]_D$ +128° (*c* 0.5); δ 0.8 (3 H, s, 13β-Me), 1.27 (3 H, s, 21-H_3), 3.73 (3 H, s, OMe), 3.82—4.05 (4 H, m, OCH_2CH_2O), *ca.* 4.08 obsc. (1 H, m, 15β-H), and 6.65—7.25 (3 H, m, 1-, 2-, and 4-H) (Found: C, 74.1; H, 8.8%; M^+, 372. $C_{23}H_{32}O_4$ requires C, 74.2; H, 8.7%; *M*, 372).

20,20-*Ethylenedioxy*-3-*methoxy*-19-*norpregna*-1,3,5(10)-*trien*-15-*one* (**15**).—The 15α-alcohol (**14**) (1.16 g) in dry dichloromethane (50 ml) at 0 °C was treated with powdered sodium acetate (0.5 g) followed by pyridinium chlorochromate (0.87 g). The mixture was stirred at 0 °C for 2 h, and the product was isolated by extraction with dichloromethane and adsorbed on silica gel (170 g). Elution with ethyl acetate–benzene (1:9) gave the 15-*ketone* (**15**) (945 mg), m.p. 175—177 °C (from acetone–methanol); $[\alpha]_D$ +82° (*c* 0.5); $\Delta\varepsilon_{max.}$ +3.14 (295 nm); δ (500 MHz) 0.87 (3 H, s, 13β-Me), 1.37 (3 H, s, 21-H_3), 1.86 (1 H, d, *J* 10.8 Hz, 14α-H), 2.2—2.4 and 2.8—3.0 (obsc. m, incl. 16α-, 16β-, and 17α-H), 3.75 (3 H, s, OMe), 3.83—4.05 (4 H, m, OCH_2CH_2O), and 6.61—7.15 (3 H, m, 1-, 2-, and 4-H) (Found: C, 74.8; H, 8.2%; M^+, 370. $C_{23}H_{30}O_4$ requires C, 74.6; H, 8.2%; *M*, 370).

Base-mediated Equilibration of the 15-*Oxo* 20-*Acetal* (**15**).—A solution of the 15-ketone (**15**) (102 mg) in methanolic 0.015M-potassium hydroxide (30 ml) was stirred at 25 °C. After 20 h, no further changes in composition could be detected (t.l.c.) and dry ice was added to the mixture, which was then concentrated under reduced pressure. The product was isolated by extraction with chloroform, and chromatographed on silica gel (10 g), with ethyl acetate–benzene (1:10) as eluant, to give 20,20-*ethylenedioxy*-3-*methoxy*-19-*nor*-14β-*pregna*-1,3,5(10)-*trien*-15-*one* (**16**) (42 mg), m.p. 167—170 °C (from benzene–hexane); $[\alpha]_D$ +91° (*c* 0.9); $\nu_{max.}$ 1 730 cm^{-1}; $\Delta\varepsilon_{max.}$ −2.41 (302 nm); δ (500 MHz) 1.33 (3 H, s, 13β-Me), 1.38 (3 H, s, 21-H_3), 2.08 (1 H, dd, *J* 9.8 and 2.5 Hz, 17α-H), 2.42 (1 H, dq, *J* 20.2, 2.5, and *ca.* 1.8 Hz, 16β-H), 2.47br (1 H, t, *J* 2 Hz, 14β-H), 2.54 (1 H, dd, *J* 20.2 and 9.8 Hz, 16α-H), 3.75 (3 H, s, 3-OMe), 3.88—4.02 (4 H, m, OCH_2CH_2O), and 6.58—7.13 (3 H, m, 1-, 2-, and 4-H) (Found: C, 74.4; H, 8.3%; M^+, 370. $C_{23}H_{30}O_4$ requires C, 74.6; H, 8.2%; *M*, 370). Further elution with the same solvent gave starting material (**15**) (41 mg).

Base-mediated Methylation of the 15-*Oxo* 20-*Acetal* (**15**).—Sodium (240 mg) was dissolved in liquid ammonia (*ca.* 130 ml; freshly distilled from sodium) and a catalytic amount of iron(III) nitrate nonahydrate was added. Following the change in colour of the medium from blue to brown, additional sodium (400 mg) was added in small portions, and the mixture was stirred until it was uniformly brown. The 15-ketone (**15**) (400 mg) in dry tetrahydrofuran (32 ml) was added, and stirring was continued for 30 min at −40 °C. The mixture was cooled to −60 °C, methyl iodide (2.4 ml) was added rapidly, and the mixture was stirred for 1 min at −60 °C. Solid ammonium chloride was added and the ammonia was evaporated through a mercury trap. The residue was diluted with water and extracted with ethyl acetate. The extract was washed twice with water, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the crystalline residue (470 mg) on silica gel (100 g), with ethyl acetate–benzene (1:19) as eluant, afforded 20,20-*ethylenedioxy*-3-*methoxy*-14,16α-*dimethyl*-19-*norpregna*-1,3,5(10)-*trien*-15-*one* (**17**) (99 mg), m.p. 195—197 °C (from benzene–hexane); $[\alpha]_D$ +64° (*c* 0.8); $\nu_{max.}$ 1 735 cm^{-1}; $\Delta\varepsilon_{max.}$ +1.11 (305 nm); δ (500 MHz) 0.94 (3 H, s, 13β-Me), 1.11 (3 H, s, 14α-Me), 1.32 (3 H, d, *J* 7.5 Hz, 16α-Me), 1.37 (3 H, s, 21-H_3), 2.28 (1 H, d, *J* 9.4 Hz, 17α-H), 2.48 (1 H, dq, *J* 9.4 and 3 × 7.5 Hz, 16β-H), 3.75 (3 H, s, OMe), 3.86—4.02 (4 H, m, OCH_2CH_2O), and 6.6—7.14 (3 H, m, 1-, 2-, and 4-H) (Found: C, 75.1; H, 8.6%; M^+, 398. $C_{25}H_{34}O_4$ requires C, 75.3; H, 8.6%; *M*, 398). Further elution with ethyl acetate–benzene (1:19) gave 20,20-*ethylenedioxy*-3-*methoxy*-14-*methyl*-19-*norpregna*-1,3,5(10)-*trien*-15-*one* (**18**) (292 mg), m.p. 212—215 °C (from benzene–hexane); $[\alpha]_D$ +70° (*c* 0.9); $\nu_{max.}$ 1 735 cm^{-1}; $\Delta\varepsilon_{max.}$ +0.77 (300 nm); δ (500 MHz) 0.94 (3 H, s, 13β-Me), 1.14 (3 H, s, 14α-Me), 1.34 (3 H, s, 21-H_3), 2.29 (1 H, dd, *J* 18.8 and 9.0 Hz, 16α-H), 2.49 (1 H, dd, *J* 18.8 and 9.0 Hz, 16β-H), 2.58 (1 H, t, *J* 9.0 Hz, 17α-H), 3.75 (3 H, s, OMe), 3.8—4.04 (4 H, m, OCH_2CH_2O), and 6.6—7.15 (3 H, m, 1-, 2-, and 4-H) (Found: C, 74.75; H, 8.4%; M^+, 384. $C_{24}H_{32}O_4$ requires C, 75.0; H, 8.4%; *M*, 384).

Wolff-Kishner Reduction of the 15-*Ketone* (**18**).—A mixture of the 15-ketone (**18**) (200 mg) and anhydrous hydrazine (95%; 6.5 ml) in diethylene glycol (16 ml) was refluxed (*ca.* 150 °C) under nitrogen for 5 h, then cooled to 25 °C. Potassium hydroxide (85%; 640 mg) was added and the mixture was boiled, allowing the hydrazine to escape, until the temperature reached 230 °C. The mixture was refluxed at 230 °C for 2.5 h, then concentrated under reduced pressure, and diluted with water. The resultant dense emulsion was acidified (M-hydrochloric acid) and then carefully neutralised with aqueous sodium hydrogen carbonate. The mixture was extracted with ethyl acetate (2 × 50 ml); t.l.c. of the solution showed the presence of two major components. The extract was treated with toluene-*p*-sulphonic acid (50 mg) for 4 h at 25 °C. Water (50 ml) and sodium hydrogen carbonate (22 mg) were added, and the organic layer was separated, dried ($MgSO_4$), and concentrated to give a syrup (172 mg), which was adsorbed on silica gel (20 g). Elution with ethyl acetate–benzene (1:9) gave 3-*methoxy*-14-*methyl*-19-*norpregna*-1,3,5(10)-*trien*-20-*one* (**21**) (92 mg) as plates from benzene–hexane, m.p. 109—110 °C, solidifying as needles, m.p. 123—124 °C; $[\alpha]_D$ +169° (*c* 0.8); $\nu_{max.}$ 1 695 cm^{-1}; δ 0.75 (3 H, s, 13β-Me), 0.97 (3 H, s, 14α-Me), 2.14 (3 H, s, 21-H_3), 3.78 (3 H, s, OMe), and 6.6—7.2 (3 H, m, 1-, 2-, and 4-H) (Found: C, 80.9; H, 9.5%; M^+, 326. $C_{22}H_{30}O_2$ requires C, 80.9; H, 9.3%; *M*, 326), followed by 3-*hydroxy*-14-*methyl*-19-*norpregna*-1,3,5(10)-*trien*-20-*one* (**22**)

(62 mg), m.p. 219—221 °C (from benzene); $[\alpha]_D$ +174° (*c* 1.0); $\nu_{max.}$ 3 585 and 1 695 cm^{-1}; δ 0.75 (3 H, s, 13β-Me), 0.97 (3 H, s, 14α-Me), 2.15 (3 H, s, 21-H_3), 5.0 (1 H, s, exch. by D_2O, OH), and 6.52—7.2 (3 H, m, 1-, 2-, and 4-H) (Found: C, 80.1; H, 8.9%; M^+, 312. $C_{21}H_{28}O_2$ requires C, 80.7; H, 9.0%; *M*, 312).

14-*Methyl*-19-*norpregn*-4-*ene*-3,20-*dione* (**23**).—A vigorously stirred suspension of the 20-ketone (**21**) (124 mg) and toluene-*p*-sulphonic acid (40 mg) in ethylene glycol (8 ml) was refluxed for 24 h at *ca.* 105 °C/10 mmHg. The mixture rapidly became homogeneous and then slowly deposited crystalline material. The mixture was cooled and aqueous sodium hydrogen carbonate was added. Extraction with benzene gave a slightly discoloured crystalline product (**19**) (138 mg), *m/z* 370 (M^+), which was shown by t.l.c. and mass spectrometry to contain *ca.* 10% unchanged 20-ketone (**21**).

The product (**19**) (124 mg) in dry tetrahydrofuran (10 ml) was added to liquid ammonia (*ca.* 100 ml; freshly distilled from sodium) containing dry t-butyl alcohol (8 ml). Lithium (350 mg) was added in small portions, and the resulting mixture was stirred at −35 °C for 5 h. Methanol (8 ml) was added, and the ammonia was allowed to evaporate. The residue was concentrated to half-volume under reduced pressure after which it was diluted with methanol (20 ml) and acidifed with concentrated hydrochloric acid at 0 °C. The resulting clear solution was stirred for 20 h at 25 °C and then concentrated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. The crystalline residue (102 mg) was chromatographed on silica gel (10 g), with ethyl acetate–benzene (1:4) as eluant, to give the 14α-*methyl compound* (**23**) (76 mg), m.p. 170—171 °C (from ethyl acetate–hexane); $[\alpha]_D$ +170° (*c* 0.8); $\lambda_{max.}$ 240 nm (log ε 4.25); $\nu_{max.}$ 1 700, 1 665, and 1 620 cm^{-1}; $\Delta\varepsilon_{max.}$ −1.75 (322 nm), +3.81 (282 nm), and +10.48 (236 nm); δ (500 MHz) 0.75 (3 H, s, 13β-Me), 0.83 (3 H, d, *J* 1.1 Hz, 14α-Me), 2.07 (3 H, s, 21-H_3), 2.86 (1 H, dd, *J* 8.8 and 8.5 Hz, 17α-H), and 5.77 (1 H, t, *J* 2.0 Hz, 4-H) (Found: C, 79.95; H, 9.7%; M^+, 314. $C_{21}H_{30}O_2$ requires C, 80.2; H, 9.6%; *M*, 314).

Acknowledgements

We thank Professor R. Wiechert, Schering A.G., Berlin for a generous gift of 3,15α-dihydroxy-19-norpregna-1,3,5(10)-trien-20-one (**12**).

References

1 Part 4: J. R. Bull, J. Floor, and M. A. Sefton, *J. Chem. Soc., Perkin Trans. 1*, 1987, 37.
2 J. R. Bull, J. Floor, and G. J. Kruger, *J. Chem. Res.*, 1979, (*S*), 224; (*M*), 2525.
3 R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *J. Chem. Soc.*, 1957, 1131.
4 P. F. Beal, U.S.P. 3 166 528 (*Chem. Abstr.*, 1965, **62**, 10495*f*); B. Bannister, U.S.P. 3 166 550 (*Chem. Abstr.*, 1965, **62**, 11880*g*).
5 G. Aranda, M. Fetizon, and N. Tayeb, *Tetrahedron*, 1985, **41**, 5661.
6 E. Toromanoff, *Tetrahedron*, 1980, **36**, 2809, and references cited.
7 J. R. Bull, *S. Afr. J. Chem.*, 1985, **38**, 155, and references cited.
8 Preliminary communication: J. R. Bull and J. Floor, *J. Chem. Soc., Chem. Commun.*, 1980, 270.
9 C. Djerassi, J. Fajkos, and A. R. Van Horn, *Steroids*, 1965, **6**, 239.
10 D. N. Kirk and W. Klyne, *J. Chem. Soc., Perkin Trans. 1*, 1976, 762; D. N. Kirk, *J. Chem. Soc., Perkin Trans. 1*, 1976, 2171.
11 D. A. Lightner, D. E. Jackman, and G. D. Christiansen, *Tetrahedron Lett.*, 1978, 4467.
12 K. Bischofberger and J. R. Bull, *Tetrahedron*, 1985, **41**, 365.
13 J. R. Bull and K. Bischofberger, *J. Chem. Soc., Perkin Trans. 1*, 1983, 2723.
14 A. R. Van Horn and C. Djerassi, *J. Am. Chem. Soc.*, 1967, **89**, 651.
15 K. Bischofberger, J. R. Bull, and A. A. Chalmers, *Magn. Reson. Chem.* submitted for publication.
16 J. F. Brunke, R. Bohm, and H. Wolf, *Tetrahedron Lett.*, 1976, 3137.
17 J. R. Bull and J. Floor, *J. Chem. Soc., Perkin Trans. 1*, 1981, 437.
18 R. Bucourt, *Top. Stereochem.*, 1974, **8**, 159.

Received 30*th June* 1986; *Paper* 6/1308