Tetrahedron Vol. 43, No. 16, pp. 3827 to 3838, 1987
Printed in Great Britain.

0040–4020/87 $3.00 + .00

HIGHER ISOPRENOIDS — XIX[a]

GUGGULSTERONES TO DEXAMETHASONE

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(*Received in UK* 9 *June* 1987)

Abstract — Guggulsterones (*E*- and *Z*-pregna-4,17(20)-diene-3,16-dione), which constitute some 2% of the gum-resin from *Commiphora mukul*, have obvious functionality suitable for elaboration into clinically useful steroidal drugs. In an effort to demonstrate this potential, guggulsterone mixture has been converted into 21-acetoxy-17α-hydroxy-16α-methylpregn-4-ene-3,20-dione, which has been earlier transformed into the well-known corticosteroid dexamethasone (9α-fluoro-16α-methyl-11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione)

Bulk of therapeutically useful steroids continue to be made from natural steroidal raw materials such as diosgenin, sterols and bile acids. Of these, diosgenin had till recently occupied a place of preeminence, but has become less important with the commercialization of fermentation of cholesterol and sitosterol to androstenedione and androstadienedione. However, 16-dehydropregnenolone (1), obtainable from diosgenin by Marker degradation, has some obvious advantages for the manufacture of C_{21} steroids, such as corticosteroids and continues to be exploited towards that end.[1-3] The discovery of occurrence of pregnane derivatives, *Z*- and *E*-pregna-4,17(20)-diene-3,16-diones (*Z*- and *E*-guggulsterones; 2, 3)[4], to the extent of some 2% in the gum-resin from *Commiphora mukul* (Hook. ex Stocks)Engl., prompted us to explore this material as a possible useful steroidal raw material, especially since this gum resin is a commercial product in India. The tree *Commiphora mukul* grows wild in the semi-arid regions of India and the annual production of its gum-resin (*guggulu* in Sanskrit) has been estimated (1975) at around 400 tonnes.[5]

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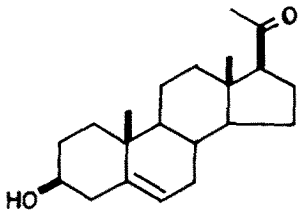
[a] Part XVIII, Indian J. Chem. 22B, 989 (1983)
[b] MRC Communication No. 58
[c] Abstracted from the Ph.D. Theses of S. Swaminathan (1985) and R.K. Bakshi (1983), M.S. University, Baroda



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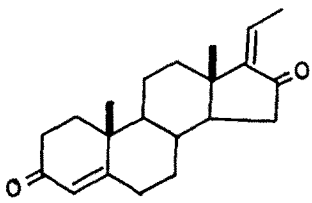

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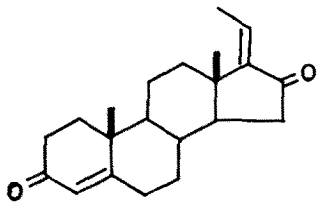

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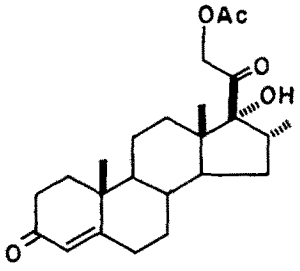
Structure of guggulsterone(s) is well-suited for elaboration into a host of C_{21} steroidal drugs. However, its oxygen function at C-16 confers on it a special advantage for transformation into compounds with additional functionality at C-16. In an effort to demonstrate this potential, guggulsterone mixture (*Z* and *E*) has been elaborated into 21-acetoxy-17α-hydroxy-16α-methylpregn-4-ene-3,20-dione (4). This compound has been earlier[6] converted into its 1-dehydro derivative (5), an intermediate in the Oliveto synthesis[7] of dexamethasone (6; 9α-fluoro-16α-methyl-11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione). Dexamethasone is a reputed glucocorticoid.[8]



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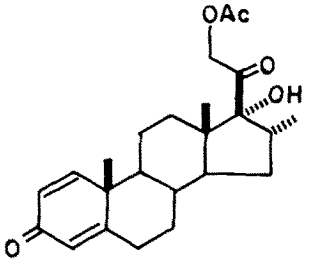

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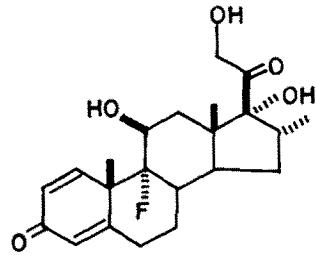

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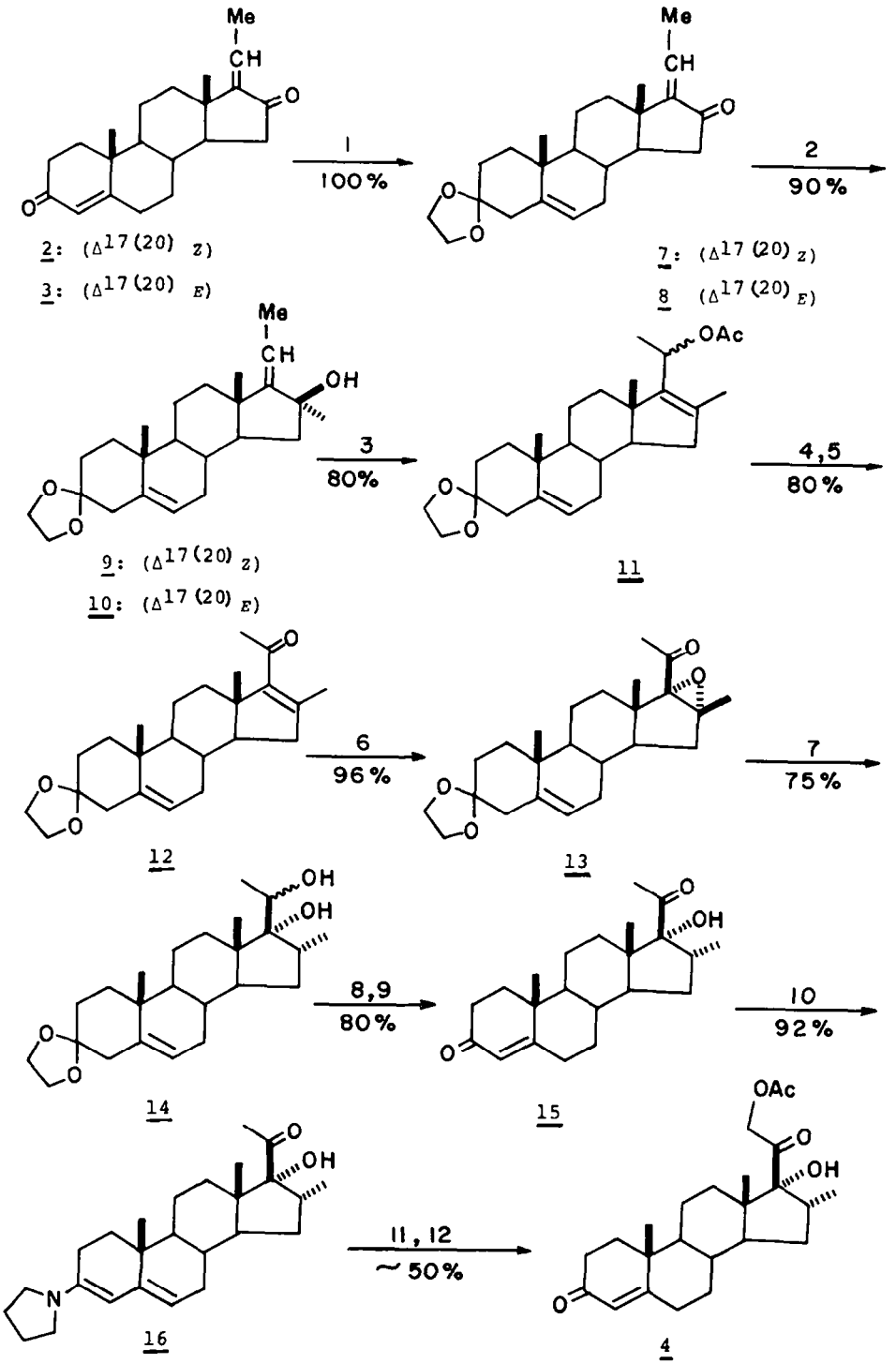
Fig. 1 depicts the route finally developed, after considerable experimentation, for the targeted conversion : guggulsterones (2, 3) to 4. The overall yield is ∿16%.

The first step called for selective protection of the C-3 carbonyl, so that C-16 carbonyl could then be manipulated in the desired manner. Though, there was little information available in the literature regarding the relative reactivities of the 3-keto-4-ene and 16-keto-17(20)-ene systems, the C-3 carbonyl, being less hindered, was expected to be more reactive.[9] Keeping in view the subsequent requirements, protection through ketalization appeared most appropriate, and trans-ketalization being more selective,[10] offered the best possibility. In practice, reaction of guggulsterones with 2-ethyl-2-methyl-1,3-dioxolan in presence of *p*-toluenesulfonic acid (*p*-TSA), under suitable conditions, furnished the required dioxolan mixture (7, 8) in 84% yield (∿100% based on unrecovered starting material).



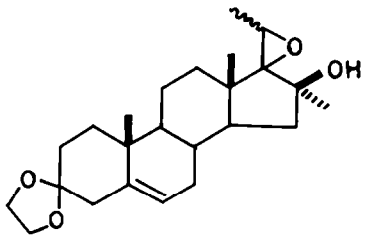
Reagents : 1. 2-Ethyl-2-methyl-1,3-dioxolan, *p*-TSA
2. MeLi, TMEDA
3. Ac_2O, AcOH, CH_2Cl_2, *p*-TSA
4. 5% KOH-EtOH
5. Pyridinium chlorochromate
6. H_2O_2 aq, NaOH aq
7. LAH, THF
8. DMSO, $(COCl)_2$
9. MeCOMe, *p*-TSA
10. Pyrrolidine, *i*-PrOH
11. EtOH-HCl; Br_2-EtOH
12. KOAc, MeCOMe

Fig. 1. Transformation of guggulsterones into 21-acetoxy-17α-hydroxy-16α-methylpregn-4-ene-3,20-dione

It was found that during this reaction isomerization of $\Delta^{17(20)}$ also occurred. Thus, though the starting guggulsterone mixture consisted of approx. 3:1 of 2 and 3, the product contained 7 and 8 in the ratio of ~1:1. This isomerization, which is unexceptional, was confirmed by carrying out the reaction with pure *Z*-guggulsterone (2), when again ~1:1 mixture of 7 and 8 were obtained. This mixture of dioxolanes (7,8) was used as such in the next step, though for characterization purposes pure 7 and 8 were obtained by chromatography. Identification of 7 and 8 is based on their ^{1}H-NMR spectra: because of the deshielding effect[11] of the C-16 carbonyl the *syn*-substituent at C-20 would suffer a down-field shift; thus the compound with δC-20 Me at 2.05 ppm (other isomer, 1.86 ppm) and δC-20 H at 5.68 ppm (other isomer, 6.45 ppm) has been assigned the *Z*-configuration (7).

The next step was aimed at introduction of C-16 methyl through an organometallic reagent. Configuration of methyl at C-16 is unimportant as chirality at this centre would be lost in the next step. Preliminary experiments with MeMgI in ether or tetrahydrofuran (THF) showed that the reaction was sluggish and remained incomplete even after refluxing for 24 hr: yield of 9/10 being 22% and 40% respectively for ether and THF. As expected, methyllithium proved more reactive. Its reaction with *E*-ketal (8) was complete in 4 hr, though *Z*-ketal (7), because of increased steric hindrance, gave the required alcohol 9 in 75% yield after a reaction period of 15 hr. However, the addition of methyllithium to both 7 and 8 could be accelerated in presence of tetramethylethylenediamine (TMEDA), which is known to activate alkyllithium reagents.[12] Thus, the reaction of 7/8 with methyllithium under these conditions was essentially complete in 3 hr to furnish 9/10 in 90% yield. The 16α-configuration assigned to the incoming methyl group is based on mechanistic considerations and analogies from literature.[13]

Suitable allylic tertiary alcohols have been converted by chromium (VI) oxidants to α,β-olefinic aldehydes (ketones) through *in situ* 1,3-transposition followed by oxidation.[14-17] However, in an effort to convert 9/10 directly into 12 by such an oxidation, the expected reaction did not occur with Jones reagent[15] or pyridinium chlorochromate[16b] or 3,5-dimethylpyrazole-CrO_3 complex.[17] The last two reagents furnished complex, difficult-to-separate mixtures, while from Jones oxidation reaction a product (in ~35% yield) formulated as a mixture of 17,20-epoxy compounds (17), could only be obtained. However, the desired conversion could be effected by a two-step process. The alcohol mixture (9, 10), on exposure to acetic anhydride, acetic acid in CH_2Cl_2 in presence of *p*-TSA,[18] furnished the rearranged acetate 11 (along with some deketalized product). Saponification of 11 followed by oxidation with pyridinium chlorochromate gave the required ketone 12. Another sample of 12 was prepared by ketalization of the known 16-methylpregna-4,16-diene-3,20-dione (18).[19] The two preparations were identical in all respects.



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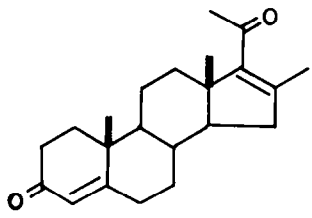

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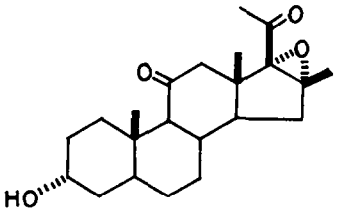
The next objective called for a sequence of reactions permitting stereospecific introduction of 17α-OH function while ensuring α-configuration for the C-16 methyl. Epoxidation of 12 followed by reductive oxirane ring-cleavage appeared as the logical choice of reactions. Epoxidation with alkaline H_2O_2[20,21] should attack only Δ^{16} and since the attack would preferentially proceed from the less-hindered α-face of the steroid molecule,[21,22] the product should be 13. In practice, oxidation with alkaline H_2O_2 in CH_2Cl_2-EtOH furnished 16,17-epoxide (in 96% yield) which, in view of the above remarks, was formulated as 13. The course of the reaction is best followed by IR spectrophotometry (change of $\nu^{C=O}$ from 1658 cm^{-1} to 1695 cm^{-1}). In spite of a negative report[21] on the attempted ring-opening of the oxirane in the closely related compound 19 with LAH, we decided to investigate this reaction with our epoxide 13. LAH reduction in refluxing ether resulted in reduction of C-20 carbonyl only. However, ultimately it was found that when this reaction was carried out in refluxing THF and excess of LAH, the desired reaction occurred to give a diol in a yield of 75%. It is obvious that the hydride attack must have occurred from the β-face, but the question of regiospecificity remains. In principle, the hydride attack can take place at either of the two positions C-16, C-17, though C-16 position being less hindered, was expected to be preferred. In fact, LAH reduction of 16,17-α-epoxypregnanes is known[23] to give 17-α-ols. Furthermore, it is reasonable to assume that the C-20 carbonyl is first rapidly reduced and the oxirane cleavage of the resulting epoxyalcohol then occurs. It has been postulated[24] that regioselectivity in the ring-opening in certain epoxyalcohols is best explained by invoking a six-membered transition state. Thus, in the present case such a situation (cf 20) would lead to delivery of hydride at C-16 leading specifically to the diol 14. Stereochemistry at C-20 is unimportant, as it will be destroyed at the next stage. Structure 14 is supported by its electron impact-induced fragmentation; it undergoes cleavage typical of α-glycols,[4,25] as shown in 21. Its ^{1}H-NMR spectrum displays a 3H doublet at δ0.95 ppm (J = 7 Hz) expected of secondary methyl at C-16.



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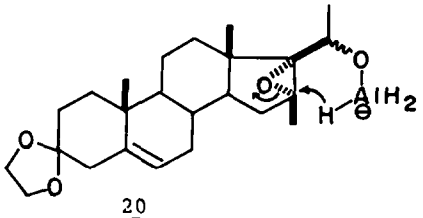

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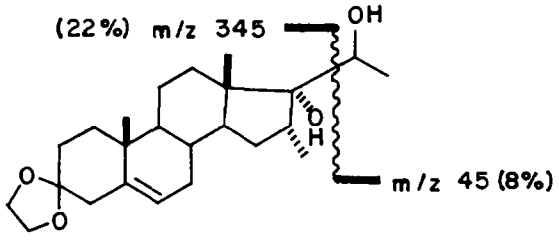

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Oxidation of 14 with DMSO-oxalyl chloride[26] furnished in over 80% yield the corresponding C-20 ketone. The latter on ketal cleavage gave the hydroxydiketone 15. This compound has been earlier prepared[6] from 3β,17α-dihydroxy-16α-methylpregn-5-en-20-one.

Final objective, namely hydroxylation of 15 at C-21, required a lot of exploratory studies. Procedure finally worked out successfully is depicted in Fig. 1 and exploits the fact that the 4-en-3-one system in a 17α-hydroxy-20-keto-pregnane can be preferentially protected through its enamine with pyrrolidine and C-21 brominated under the usual acidic conditions.[27,28] Thus, the dienamine 16[28] obtained in 92% yield was converted into its eniminium chloride and brominated, and the resulting product hydrolysed (20% $KHCO_3$aq) to get 21-bromo-17α-hydroxy-16α-methylpregn-4-ene-3,20-dione. The latter compound, without isolation was treated with KOAc in refluxing acetone to get the known[6] 21-acetoxy-17α-hydroxy-16α-methyl-pregn-4-ene-3,20-dione (4).

EXPERIMENTAL

All m.ps are uncorrected. Pet. ether refers to light petroleum fraction b.p. 60-80°. Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately prior to use.[29] Dimethyl sulphoxide was distilled from CaH_2 under reduced pressure and kept over 4A molecular sieves. Acetone was refluxed over $KMnO_4$ and then distilled from anhyd. K_2CO_3. All solvent extracts were finally washed with brine and dried (Na_2SO_4).

Silica gel for chromatography (-100, + 200 mesh) was washed with hot water till sulphate-free, dried and activated at 125-130° for 6 hr and standardized.[30] TLC was carried out on silica gel layers (0.25 mm) containing 15% gypsum and activated at 110-115° (2 hr); visualization: 1% vanillin in 30% H_3PO_4 aq spray followed by heating ~100°/5 min. Course of all reactions and chromatographies was followed by TLC.

The following instruments were used for spectral/analytical data: Schmidt + Haensch electronic polarimeter model Polatronic 1; Perkin-Elmer model 781 Infrared Spectrophotometer; Perkin-Elmer model 402 Ultraviolet Spectrophotometer; Perkin-Elmer model R32 (90 MHz) NMR Spectrometer: Varian Mat CH7 Mass Spectrometer (70 eV, direct inlet system); Hewlett-Packard Model 185B C,H,N Analyzer. All optical rotations were measured in $CHCl_3$ soln unless stated otherwise. All ^{1}H-NMR spectra were recorded in $CDCl_3$ with TMS as internal reference; signals are reported in ppm (δ); while citing ^{1}H-NMR data, following abbreviations have been used: s (singlet), d(doublet), t(triplet), q(quartet), m(multiplet), b(broad). While summarising mass spectral data, besides the molecular ion, nine other most important ions (m/z) are reported with nine other most important ions (m/z) are reported with their relative intensities.

3,3-Ethylenedioxypregna-5,17(20)-dien-16-ones (7,8)

A mixture of *z*- and *E*-guggulsterones (2,3; m.p. 140-170°; 900 mg), *p*-toluenesulfonic acid (*p*-TSA) (20 mg), and 2,2-ethylenedioxybutane (16 ml) was heated at 110° (bath temp.) and 2-butanone (mixed with some 2,2-ethylenedioxybutane) slowly stripped off (6 ml) during 6 hr. At the end of this period, the reaction mixture was cooled, *p*-TSA neutralized by stirring with 5% Na_2CO_3 aq (10 ml) for 15 min at 20°. The organic material was taken up in EtOAc (20 ml), washed with water, dried and freed of solvent to give a residue (980 mg) which was chromatographed over SiO_2-gel/IIA (2.5 cm x 40 cm). Elution was carried out with pet. ether containing 5% EtOAc. After rejecting 50 ml of first eluates (10 mg of material), the next 25 ml x 8 of solvent eluted 450 mg of 7. The next 25 ml x 2 of eluate gave a mixture of 7 and 8 (80 mg). This was followed by compound 8 (400 mg, 25 ml x 8). Finally, last 25 ml x 4 eluted 35 mg of guggulsterone mixture (1:1).

z-Isomer (7). The product was recrystallized from ethyl acetate-pet ether to afford leaflets, m.p. 176-178°, $[\alpha]_D$ + 38.5°. λ_{max}^{EtOH} 245 nm, ε = 11400. IR (Nujol): 1710, 1640, 1420, 1360, 1340, 1310, 1261, 1230, 1100 cm^{-1}. ^{1}H-NMR: Me (3H singlets at 0.94, 1.07 ppm), Me-CH=C (3H, d, 2.05 ppm, J = 7Hz), OCH_2CH_2O (4H, s, 3.89 ppm), CH=C (1H, m, 5.2-5.35 ppm; 1H, q, 5.68 ppm, J = 7 Hz). Mass: m/z 356 (M^+, 67%), 91(100%), 135(33%), 119(49%), 105(62%), 93(43%), 86(40%), 79(70%), 77(52%), 67(36%). (Found: C, 77.60; H, 8.85. $C_{23}H_{32}O_3$ requires: C, 77.49; H, 9.05%).

E-Isomer (8). Recrystallization of this material furnished leaflets, m.p. 207-208°, $[\alpha]_D$ + 45.5°. λ_{max}^{EtOH} 245 nm, ε = 13,500. IR (Nujol): 1721, 1648, 1429, 1320, 1300, 1270, 1248, 1195, 1131, 1102, 1008, 942, 865 cm^{-1}. ^{1}H-NMR: Me (3H singlets at 1.06, 1.09 ppm), Me-CH=C (3H, d, 1.86 ppm, J = 7Hz), OCH_2CH_2O (4H, s, 3.91 ppm), CH=C (1H, m, 5.2-5.4 ppm; 1H, q, 6.45 ppm, J = 7 Hz). Mass: m/z 356 (M^+, 20%), 55 (100%), 119(19%), 105(30%), 100(94%), 93(20%), 91(46%), 86(19%), 79(32%), 77(25%). (Found:C, 77.50, H, 8.92; $C_{23}H_{32}O_3$ requires: C, 77.49; H, 9.05%).

3,3-Ethylenedioxy-16α-methylpregna-5,17(20)-dien-16-ols (9,10)

To a soln of ketals 7 and 8 (3.56 g, 0.01 mole) in dry ether (200 ml) was added TMEDA (4 ml), and a soln of MeLi in ether (0.280 g in 10 ml ether; 0.013 mol) introduced, with stirring, at room temp. (25°) under anhydrous conditions and under a blanket of N_2. The reaction mixture was stirred at room temp. for a total of 3hr, and then worked up by addition of ice-cold satd. NH_4Cl aq (35 ml) and extraction with ether. Removal of solvent gave a material (3.65 g) which was chromatographed on SiO_2-gel/II; 5% EtOAc in pet. ether eluted the required product (9 + 10, m.p. 140-145°; 3.35 g), which was used as such in the next step.

For characterization purposes pure 9 and 10 were prepared from pure 7 and 8 respectively.

z-Isomer (9). A soln of *z*-ketal 7 (500 mg) in anhyd. ether (40 ml) was reacted with MeLi (37 mg in 2 ml ether) as above (no TMEDA) and worked up after 15 hr stirring to get a product (530 mg) which was chromatographed over SiO_2-gel/II (1.5 cm x 30 cm). Elution was carried out with 5% EtOAc in pet. ether (10 ml cuts). First eluates (100 ml) gave unchanged starting material (105 mg). After rejecting the intercut (50 ml; 40 mg of mixture), the next 300 ml eluted 314 mg of pure 9, which was recrystallised from EtOAc-pet. ether, m.p. 149-151°, $[\alpha]_D$ + 34.4°(EtOH). IR (Nujol):

3500, 1315, 1258, 1140, 1095, 1085, 1020, 945, 865, 820, 800 cm^{-1}. ^{1}H-NMR: Me (3H singlets at 0.91, 1.02, 1.41 ppm), Me-CH=C (3H, d, 1.82 ppm, J = 7Hz), OCH_2CH_2O (4H, s, 3.89 ppm), CH=C (2H, m, 5.1-5.42 ppm). Mass: m/z 372 (M^+, 46%), 100(100%), 133(16%), 119(23%), 105(29%), 93(20%), 91(35%), 79(23%), 55(73%), 43(65%). (Found: C, 77.48; H, 9.90. $C_{24}H_{36}O_3$ requires: C, 77.37; H, 9.74%).

E-Isomer (10). A similar reaction of *E*-ketal 8 (450 mg) in dry ether (40 ml) with MeLi (32 mg in 2 ml ether) for 4 hr furnished a product (500 mg) which on chromatography as above gave, besides the starting ketal (10 mg), 393 mg of the desired product 10, recrystallized from EtOAc-pet. ether, m.p. 171-173°, $[\alpha]_D$ + 76.6°(EtOH). IR (Nujol): 3492, 2860, 1348, 1272, 1260, 1240, 1200, 1160, 1141, 1080,1040, 1021, 950, 932, 878, 821, 804 cm^{-1}. ^{1}H-NMR: Me (3H singlets at 1.07, 1.10, 1.31ppm), Me-CH=C (3H,d,1.74 ppm, J = 7 Hz), OCH_2CH_2O (4H, s, 3.95 ppm), CH=C (2H,m,5.3-5.7 ppm). Mass: m/z 372(M^+, 38%), 100(100%), 119(23%), 105(30%), 93(20%), 91(37%), 79(26%), 55 (85%), 43(75%), 41(28%). (Found: C, 77.38, H, 9.87; $C_{24}H_{36}O_3$ requires: C, 77.37; H,9.74%).

Oxidation of ketal alcohols (9,10) with Jones reagent: isolation of 3,3-ethylenedioxy-17,20-epoxy-16α-methylpregn-5-en-16-ols (17)

To a mixture of ketal alcohols 9 and 10 (88 mg, 0.24 mmole) in acetone (20 ml) at -15°, Jones reagent[31] (0.1 ml) was added and the reaction mixture stirred at that temp. for 5 min. Usual work up gave a product (82 mg) which was chromatographed over SiO_2-gel/II (10 g) using 5% EtOAc in pet. ether as eluant. First 50 ml eluted a product (foam, 40 mg) characterized as 17. IR (Nujol): 3520, 2850, 1319,1300, 1260, 1240, 1204, 1158, 1135, 1095, 1082, 1045, 1020, 1005, 980, 942, 902, 865, 820, 800 cm^{-1}. ^{1}H-NMR: Me (9H, bs, 1.0 ppm; 3H, s, 1.12 ppm), OCH_2CH_2O (4H, s, 3.92 ppm), CH=C (1H, m, 5.4 ppm). (Found: C, 74.15, H, 9.21; $C_{24}H_{36}O_4$ requires: C, 74.19; H, 9.34%).

3,3-Ethylenedioxy-16-methylpregna-5,16-diene-20-acetate (11)

To a cooled (-10°) soln of anhydrous acetic acid (15 ml), and acetic anhydride (freshly distilled over P_2O_5; 5 ml) in CH_2Cl_2 (20 ml) containing *p*-TSA (150 mg), ketal alcohol (9,10) mixture (3.0 g, 0.008 mole) was added (5 min) with stirring. After stirring for another 12-15 min, the contents were poured onto a mixture of crushed ice (~100 g) and 15% Na_2CO_3 aq (~0°, 100 ml). The organic layer was separated, the aq phase extracted with CH_2Cl_2 (50 ml x 3) and the combined extract washed with 5% Na_2CO_3 aq (50 ml x 2), water and dried. Removal of solvent furnished a product (295 mg) which was chromatographed over SiO_2-gel/II (90 g);elution was carried out with 5% EtOAc in pet. ether (25 ml cuts). After rejecting the first eluates (50 ml; 50 mg product), the next 250 ml eluted the required acetate 11 (1.82 g, m.p. 105-110°). The next 100 ml gave a mixture (75 mg), while the last 250 ml yielded (750 mg) essentially deketalized product corresponding to acetate 11.

The required acetate (11; apparently 1:1 mix. of C-21 acetates) showed the following spectral characteristics. IR (Nujol): 1736, 1240, 1202, 1100, 1062, 1049, 1020, 950, 908, 860 cm^{-1}. ^{1}H-NMR: Me (3H, two singlets at 0.88 and 0.92 ppm; 3H, s, 1.08 ppm; 3H, d, 1.38 ppm, J = 7Hz), Me-C=C (3H, two singlets at 1.74 and 1.76 ppm), $OCOCH_3$ (3H, s, 2.02 ppm), OCH_2CH_2O (4H, s, 3.94 ppm), CH=C (1H, m, 5.27-5.44 ppm), CHOAc (1H, m, 5.45-5.88 ppm). Mass: m/z 413 (M^+-1, 12%), 55(100%), 119(37%), 105(66%), 100(94%), 91(72%), 79(54%), 77(40%), 67(24%), 45(49%). (Found: C, 75.41; H, 9.20; $C_{26}H_{38}O_4$ requires: C, 75.32; H, 9.24%).

The deketalized fraction was best again ketalized in the usual manner to get more of 11.

3,3-Ethylenedioxy-16-methylpregna-5,16-dien-20-ol

The above acetate (11; 750 mg, 1.8 mmole) and 5% KOH-EtOH (50 ml) were refluxed (4 hr) and worked up as usual to get the deacetylated derivative (730 mg, m.p. 154-157°), which was used as such for the next step. A small sample was crystallised from EtOAc-pet.ether, m.p. 157-159°. IR (Nujol): 3498, 1452, 1422, 1318, 1300, 1265, 1232, 1205, 1140, 1100, 1020, 995, 952, 870, 812 cm^{-1}. ^{1}H-NMR: Me (3H, two singlets at 0.89 and 0.91 ppm; 3H, s, 1.05; 3H, d, 1.35 ppm, J = 7Hz), Me-C=C (3H, two singlets at 1.72 and 1.77 ppm), OCH_2CH_2O (4H, s, 3.92 ppm), CHOH (1H, m, 4.40-4.80 ppm), CH=C (1H, m, 5.20, 5.45 ppm). Mass: m/z 372(M^+, 74%), 100(100%), 357(47%), 327(51%), 119(33%), 105(46%), 93(39%), 91(50%), 79(42%), 55(66%).

3,3-Ethylenedioxy-16-methylpregna-5,16-dien-20-one (12)

(a) Above alcohol (136 mg, 0.365 mmole) in CH_2Cl_2 (15 ml) was treated with pyridinium chlorochromate[32] (136 mg) at room temp. (~30°) for 1 hr and worked up with ether in the usual manner. Solvent removal gave a product (197 mg), which was filtered through a bed of SiO_2-gel/II (10 g) using 5% EtOAc in pet. ether as solvent. This material, thus obtained, was recrystallized from EtOAc to give a white crystalline solid, m.p. 214-216°, $[\alpha]_D$ + 55.1°. IR ($CHCl_3$): 1662, 1600, 1450, 1428, 1375, 1360, 1330, 1220, 1125, 1100, 1020, 950, 860 cm^{-1}. ^{1}H-NMR: Me (3H singlets at 0.98 and 1.06 ppm), Me-C=C (3H, s, 2.02 ppm), MeCO (3H, s, 2.22 ppm), OCH_2CH_2O (4H, s, 3.87 ppm), CH=C (1H, m, 5.15-5.37 ppm). Mass: m/z 370(M^+, 19%), 43(100%), 119(16%), 105(27%), 100(50%), 93(15%), 91(34%), 79(20%), 55(66%), 41(16%). (Found: C, 77.79; H, 9.22; $C_{24}H_{34}O_3$ requires: C, 77.80; H, 9.25%).

(b) From 16-methylpregna-4,16-diene-3,20-dione. A mixture of this dione[19] (3.0 g, 9.2 mmole), *p*-TSA (110 mg) and 2,2-ethylenedioxybutane (60 ml) was heated (110°, bath temp.) with distillation of 2-butanone exactly as already described for 7, 8. The product (3.3 g), thus obtained, was chromatographed over Al_2O_3/II (2 cm x 67.5 cm), while eluting with 5% EtOAc in pet. ether (100 ml cuts). After rejecting the first 300 ml of eluate (585 mg of product), the next 700 ml eluted the required product (1.73 g, m.p. 213-215°), which was recrystallised from EtOAc, m.p. 214-216°, identical in all respects (m.p., mixed m.p., IR, ^{1}H-NMR) with the product described under (a). Last 500 ml of eluate gave 550 mg of starting dione.

3,3-Ethylenedioxy-16α,17α-epoxy-16β-methylpregn-5-en-20-one (13)

To a soln of the above enone (12; 4.8 g, 0.013 mole) in CH_2Cl_2 (30 ml) and 95% EtOH (150 ml) was added 30% H_2O_2 aq (22.23 ml; 6.61g, 0.19 mole) and 10% NaOH aq (15.4 ml; 1.54 g, 0.0387 mole) at room temp (25-32°), with manual mixing. The clear, homogenous reaction mix was set aside at room temp for 48 hr (by this time $\nu_{C=O}$ had steadily shifted from 1658 cm^{-1} to 1695 cm^{-1}, indicating thereby the disappearance of the starting enone). At the end of this period the reaction mixture was diluted with water (700 ml) and extracted with CH_2Cl_2 (60 ml x 3). The combined organic phase was washed with water (100 ml x 2) and dried. On solvent removal, a solid (5.0 g, m.p. 176-178°) was obtained, which was recrystallised from EtOAc, m.p. 182-184° (4.8 g). IR (KBr): 3400, 1695, 1452, 1442, 1422, 1380, 1370, 1360, 1315, 1305, 1260, 1230, 1138, 1098, 1060, 1022, 978, 968, 942, 888, 862, 820, 810 cm^{-1}. ^{1}H-NMR: Me (3H singlets at 1.03, 1.03, 1.41 ppm), MeCO (3H, s, 2.19 ppm), OCH_2CH_2O (4H, s, 3.93 ppm), CH=C (1H, m, 5.25-5.40 ppm). (Found: C, 74.53; H, 8.76; $C_{24}H_{34}O_4$ requires: C, 74.57; H, 8.87%).

3,3-Ethylenedioxy-16α-methylpregn-5-ene-17α,20ξ-diol (14)

To a stirred and refluxing soln of LAH (807 mg, 0.021 mole) in THF (80 ml) was added a soln of the above epoxide (4.082 g, 0.011 mole) in THF (40 ml) dropwise (40 min) and the reaction continued for another 7 hr. The reaction mixture was next cooled (0°), moist ether (20 ml), followed by 20% Rochelle salt aq soln (200 ml, cold) added, and the granular ppt filtered, washed with ether (20 ml). Ether phase was separated, the aq part extracted with ether (35 ml x 3), and the combined extracts washed with water and dried. Solvent was flashed off to get a product (4.2 g), which was chromatographed over SiO_2-gel/II (3 cm x 70 cm; 125 g). Elution was carried out with 15% EtOAc in pet. ether (100 ml cuts). First 100 ml eluted (150 mg) a complex mixture which was discarded. Next 2500 ml gave the required product (2.9 g), which was crystallised from MeOH aq, m.p. 157-173°C (mix. of C-20 epimers?) {Last fraction (500 ml) yielded a product (800 mg) consisting of some three compounds, not readily separable and hence was not investigated further}. IR (KBr): 3450, 1450, 1380, 1368, 1260, 1200, 1130, 1095, 1082, 1012, 995, 950, 890, 878, 860 cm^{-1}. ^{1}H-NMR: Me (3H singlets at 0.84, 1.00 ppm), MeCH- (3H, d, 0.95 ppm, J=7Hz), MeCHOH (3H, d, 1.16 ppm, J = 8Hz), CHOH (1H, m, 3.8-4.1 ppm), OCH_2CH_2O (4H, s, 3.89 ppm), CH=C (1H, m, 5.3 ppm). Mass: m/z 390 (M^+, 30%), 99(100%), 345 (22%), 327(9%), 100(28%), 55(23%), 45(8%), 43(12%). (Found: C, 71.28; H, 9.71; $C_{24}H_{38}O_4H_2O$ requires: C, 70.55; H, 9.87%).

3,3-Ethylenedioxy-17α-hydroxy-16α-methylpregn-5-en-20-one

To a stirred soln of oxalyl chloride (0.48 ml, 0.5796 g, 0.0045 mole) in dry CH_2Cl_2 (8 ml), chilled to -60°, was introduced a soln of DMSO (0.64 ml, 0.703 g, 0.009 mole) in CH_2Cl_2 (2 ml) dropwise over a period of 5 min, while keeping the temp below -58°. The whitish soln was stirred for 40 min at -60°, and at the end of this period a soln of the above diol (1.1126g, 0.0028 mole) in CH_2Cl_2 was added dropwise over a 10 min period, while maintaining the temp. at ~-60°. After stirring at this temp for 1 hr, triethylamine (2 ml) was added and the reaction mixture

stirred for another 1 hr at this temp., after which it was allowed to warm to room temp., diluted with water (20 ml) and the organic phase separated. The aq phase was extracted with CH_2Cl_2 (6 ml x 2), the combined extracts washed with water (15 ml x 4) and dried. Solvent was flashed off to get a product (1.094 g), which was passed through a column of SiO_2-gel/II (1.2 cm x 12 cm; 15 g), using 5% EtOAc in pet. ether as the solvent. After rejecting the first 100 ml of eluate, the required product was collected from the subsequent eluates. This material was crystallised from EtOAc, m.p.210-213°, yield 0.95g. IR (Nujol): 3485, 1705, 1428, 1350, 1335, 1310, 1265, 1238, 1223, 1208, 1195, 1140, 1128, 1115, 1105, 1088, 1065, 1035, 1005, 970, 955, 922,878, 862, 820, 796, 740, 696 cm^{-1}. ^{1}H-NMR: Me (3H singlets at 0.80, 1.03 ppm), MeCH (3H, d, 0.91ppm, J = 8Hz), MeCO (3H, s, 2.23 ppm), OCH_2CH_2O (4H, s, 3.92 ppm), CH=C (1H, m, 5.35 ppm). Mass: m/z 388 (M^+, 22%), 99(100%), 345(15%), 327(7%), 100(24%), 43(18%). (Found: C, 74.83; H, 9.38; $C_{24}H_{36}O_4$ requires: C, 74.19; H,9.34%).

17α-Hydroxy-16α-methylpregn-4-ene-3,20-dione(15)

The above ketone (1.2 g, 0.003 mole) in acetone (30 ml) containing a trace of *p*-TSA was left at room temp.(25-30°) overnight (15 hr). Water (4 ml) was added, acetone flashed off, residue diluted further with water (30 ml) and filtered, dried and crystallised from EtOAc, m.p. 182-184°, yield ~100% (Lit.[6]: m.p. 182-184°). IR (KBr): 3460, 1710, 1665, 1615, 1460, 1440, 1360, 1340, 1285, 1275, 1240,1220, 1200,1150, 1130, 1000, 970, 955, 925, 900, 888 cm^{-1}. ^{1}H-NMR: Me (3H singlets at 0.80, 1.17 ppm), MeCH (3H, d, 0.89 ppm, J = 8Hz), MeCO (3H, s, 2.21 ppm), CH=C (1H, s, 5.70 ppm). (Found: C, 77.07; H, 9.53; $C_{22}H_{32}O_3$ requires: C, 76.70;H, 9.36%).

21-Acetoxy-17α-hydroxy-16α-methylpregn-4-ene-3,20-dione (4)

A mixture of the above diketone (15; 641 mg, 0.0018 mole) isopropanol (22 ml) and pyrrolidine (1 ml, 0.021 mole) was refluxed (N_2) and slowly distilled over a period of 1 hr to collect ~5 ml of distillate (comprising of H_2O, isopropanol and pyrrolidine). The residue was cooled to ~40° and the remaining isopropanol and pyrrolidine removed under suction. The yellowish solid residue was collected, washed with pet. ether and dried to get a material (16[28]; 694 mg), m.p. 120-160° (dec.) ^{1}H-NMR: Me (3H singlets at 0.82. 1.0 ppm), MeCH (3H, d, 0.89 ppm, J = 8Hz), MeCO (3H, s, 2.22 ppm), N-CH_2 (4H, m, 3.12 ppm), CH=C (1H, s, 4.78 ppm; 1H, m, 5.0 ppm). This material was used as such in this next step.

To a stirred suspension of the dienamine 16 (620 mg, 0.0015 mole) in EtOH (17 ml) was introduced EtOH-HCl (3 ml, 0.26 g HCl per ml of soln) at room temp. (~26°). A soln of bromine (295 mg, 0.0018 mole) in EtOH (4.5 ml) was made at -60° immediately prior to use. This soln was, next, added dropwise to the above eniminium salt soln at a rate that this bromine colour never persisted for more than a few seconds (~5 min total time). After stirring the reaction mixture for another half an hr, ethanol and gases were removed under reduced press at <40°. The residue was triturated with ether and the pptd solid collected. This solid was redissolved in EtOH, 20% $KHCO_3$ aq (5 ml) added and the mixture stirred for 1 hr. Alcohol was then removed under vacuo and the residue treated with water (70 ml) and the pptd solid (600 mg) collected after several hr. ^{1}H-NMR: $COCH_2Br$ (2H, ABq, 4.2 ppm, J = 14 Hz).

The above crude bromide (574 mg, 0.0013 mole, KOAc (720 mg, 0.0073 mole) and dry acetone were mixed and refluxed (N_2) with stirring for 2 hr. At the end of this period water (4 ml) was added, most of acetone distilled off (reduced press), the residue diluted with H_2O (25 ml) and the mixture left as such overnight. The pptd material (brownish) was collected by filtration, dried and passed through a short bed of SiO_2-gel/II to get a white solid (320 mg), which was crystallized from MeOH, m.p. 158-160° (Lit.[6]: m.p. 158-160.5°). IR (Nujol): 3420,1750, 1730,1666, 1611,1410, 1245, 1138, 1080, 1070, 1025, 920, 870 cm^{-1}. ^{1}H-NMR: Me (3H singlets at 0.79, 1.18 ppm), MeCH (3H, d, 0.92 ppm, J = 8Hz), MeCOO (3H, s, 2.14 ppm), CH_2OAc (2H, ABq, 4.9 ppm, J = 17Hz), CH=C (1H, s, 5.73 ppm).

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