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Studies on the Constituents of Asclepiadaceae Plants. LI.[1] Oxidation at the 18-Methyl Group of C/D-*cis*-Pregnane Type Steroids and ^{13}C-Nuclear Magnetic Resonance Spectra of 18-Oxygenated Pregnanes and Related Compounds

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Four 18-oxygenated pregnane-type steroids; 18,20-epoxypregn-5-en-3β-ol acetate (III), 18,20-epoxy-isolineolon cyclic sulfite (VIII), 18,20-epoxy-deacyl condurangogenin C (XVIII), and 18,20-epoxy-20-epideacyl condurangogenin C (XXI) were synthesized, and their structures were established by chemical and spectral studies.

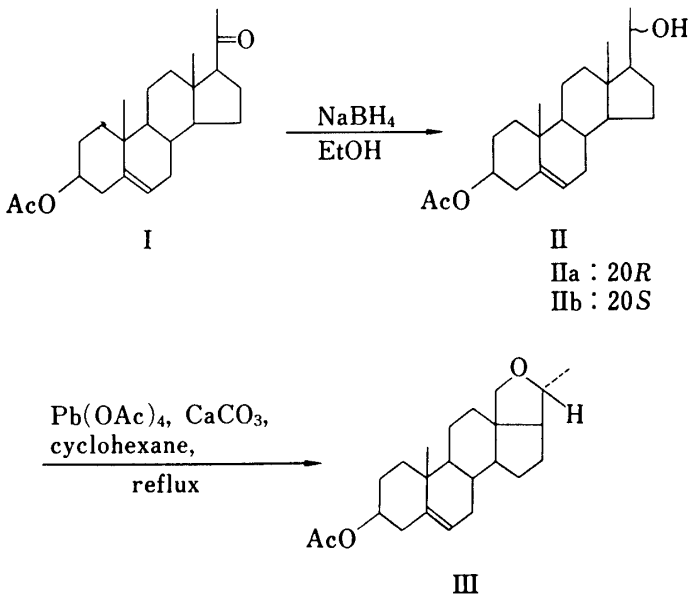
A remarkable difference in ^{13}C-nuclear magnetic resonance chemical shifts between 20*R*- and 20*S*-hydroxy-C/D-*cis*-pregnane-type steroids was found.

Keywords——18,20-epoxide; lead tetraacetate; hypoiodite reaction; catalytic hydrogenation; ^{13}C-NMR; 20-hydroxy-C/D-*cis*-pregnane type steroids; steric shift; the configuration at C-20

In order to confirm the structure of condurangogenin B (X),[2] which is the aglycone of the antitumor-active compound condurangoglycoside B_0 (IX),[2] the hypoiodite reaction[3] of condurangogenin C 3-acetate (XIII)[4] and some preliminary experiments were carried out.

To find suitable conditions for oxidation at the 18-methyl group, pregn-5-ene-3,20-diol 3-monoacetate (II) was prepared from pregnenolone acetate (I). It is well known that sodium borohydride ($NaBH_4$) reduction of the C-20 ketone of C/D *cis* pregnane gives the 20*R*-alcohol as the major product.[5] In the present case, the ratio of the 20*R*- and 20*S*-alcohols of II was found to be *ca.* 16:1 (Chart 1).

On oxidation of II in the presence of lead tetraacetate ($Pb(OAc)_4$), the 18,20-epoxide (III) was formed exclusively in 16.7% yield.[6] In the ^{1}H-NMR spectrum of III, AB type doublet signals appeared at δ 3.46 and 3.74 (1H each, d, J=10 Hz), suggesting that oxidation had

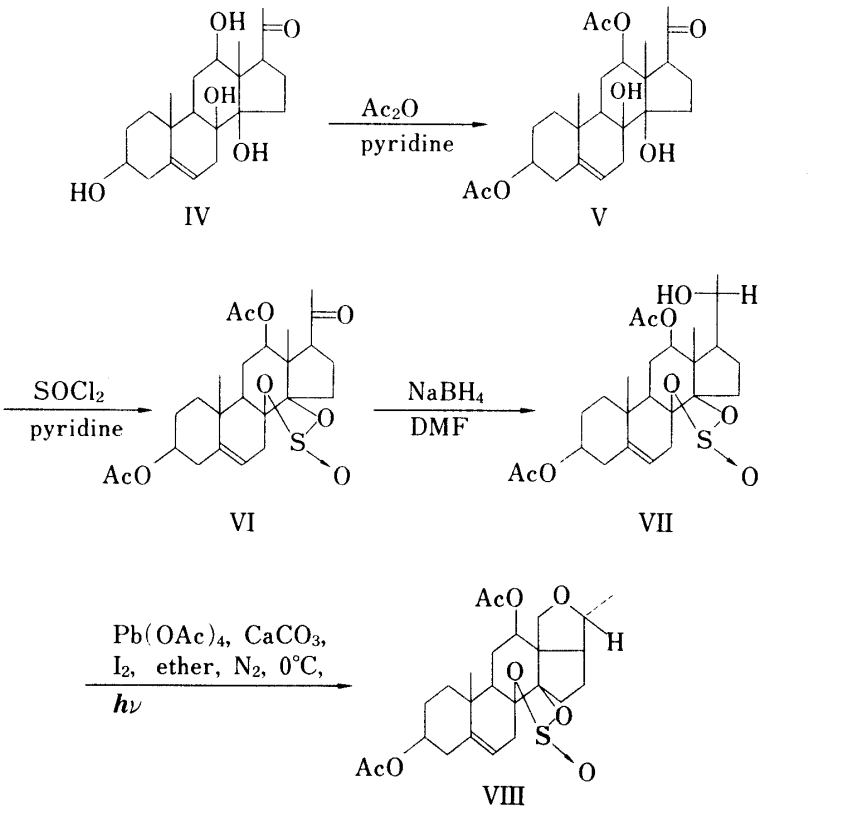


I II IIa : 20*R* IIb : 20*S* III

Chart 1

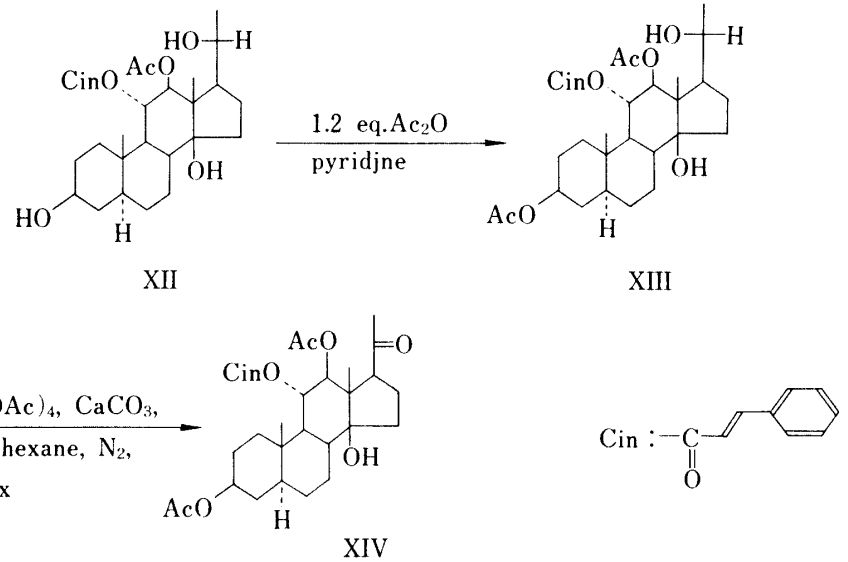
occurred at the 18-methyl group, and this was supported by the ^{13}C-NMR signal at δ 71.3 (triplet). The configuration at C-20 in III was deduced to be *R*, since the content of the 20*R*-alcohol was more than 90% in II (Chart 1).

As another preliminary experiment on the oxidation of the 18-methyl group, isolineolon (IV),[7] which is one of the C/D-*cis*-pregnane type steroids, was adopted as a model compound. After acetylation of IV, isolineolon 3,12-diacetate (V) was reacted with thionyl chloride ($SOCl_2$) to give a cyclic sulfite (VI).[8] Two signals assignable to C-8 and C-14 were observed as singlets at δ 88.8 and 105.5, respectively. On treatment of VI with $NaBH_4$, the 20*R*-alcohol (VII) was obtained in 40.4% yield as the sole product due to the bulkiness of the cyclic



IV V VI VII VIII

Chart 2



XII XIII XIV

Chart 3

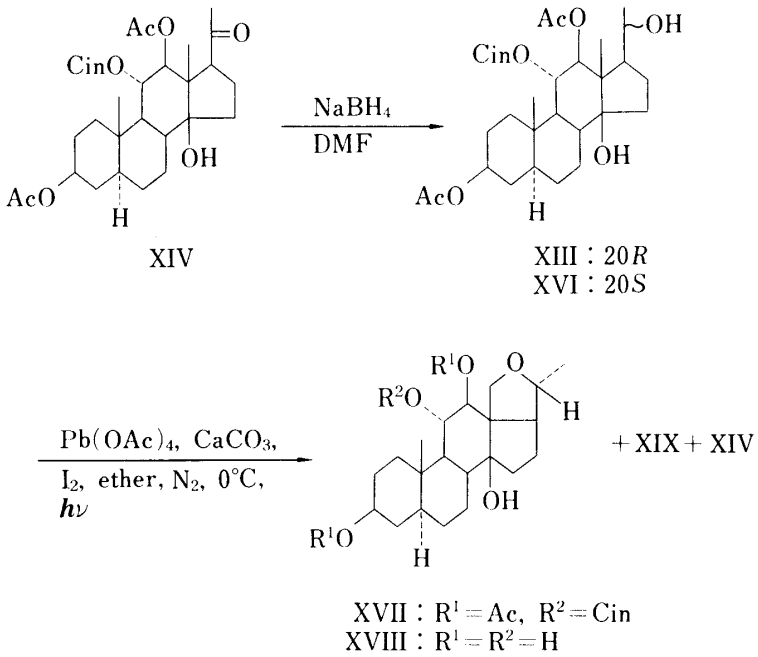
sulfite group (Chart 2).

The hypoiodite reaction[3] of VII gave an 18,20-epoxide (VIII) in 1.9% yield (Chart 2). The AB type ^{1}H-NMR doublet signals at δ 3.54 and 4.11 (1H each, d, J=10 Hz) and the ^{13}C-NMR signal at δ 70.0 (t) indicated that oxidation had occurred at the 18-methyl group. The configuration at C-20 in VIII was considered to be the same as that of VII.

Next, condurangogenin C (XII) was treated with 1.2 molar equivalents of acetic anhydride (Ac_2O) in pyridine to furnish the 3-acetate (XIII) in 33.0% yield, and XIII was crystallized from MeOH as colorless platelets; this product is the first crystalline derivative of XII. Oxidation of XIII with $Pb(OAc)_4$ under reflux in cyclohexane yielded condurangogenin A 3-acetate (XIV) in 91.0% yield as colorless needles from MeOH.

On reduction of XIV with $NaBH_4$, the product was a mixture of XIII and its C-20 epimer (XVI) in a ratio of *ca.* 4 : 1 as determined by high performance liquid chromatography (HPLC). Thus, the C-20 configuration of condurangogenin C (XII) was estimated to be *R* (Chart 4).

The hypoiodite reaction of this mixture provided the 18,20-epoxide (XVII) in 16.9% yield, with minor products conduranogenin B 3-acetate (XIX) and XIV as determined by TLC analysis (Chart 4). Condurangogenin C 18,20-epoxide (XVII) showed AB type doublet signals at δ 3.96 and 4.11 (1H each, d, J=9 Hz) in its ^{1}H-NMR and a signal at δ 65.3 (t) in its ^{13}C-NMR spectra, which indicated that oxygenation had occurred at the 18-methyl group. Takase *et al.* and we have described the hypoiodite reaction of XVII to yield XIX in a joint report.[9] These results establish not only the C-20*R* configuration in XII but also the ketalic structure and the ester linkages of X. On saponification of XVII, a deacyl derivative (XVIII) was obtained; this showed no absorption due to ester-carbonyl groups in its infrared (IR) spectrum (Chart 4).



XIV

XIII : 20*R*
XVI : 20*S*

XVII : R^1=Ac, R^2=Cin
XVIII : R^1=R^2=H

Chart 4

On the other hand, catalytic hydrogenation of condurangogenin B 3-acetate (XIX) over platinum dioxide (PtO_2) in 90% acetic acid (AcOH) followed by saponification gave the perhydro derivative (XXI) *via* the perhydrogenated ester (XX). This deacyl derivative (XXI) was considered to be the 20*S* epimer of XVIII on the basis of elemental analysis, and the mass, IR, ^{1}H-NMR and ^{13}C-NMR spectra (Chart 5).

Howard *et al.* reported that acidification of ketals results in the establishment of an equilibrium mixture whose components are ketal, unsaturated ether, and alcohol (Equation 1 in

Fig. 1).[10] There should be a similar equilibrium of condurangogenin B (X) (Equation 2). The hydrogenation of X might occur from the *re* face of the intermediate B so that the configuration of XX was anticipated as 20*S*, and this was supported by the fact that when the 3,11,12-triacetate (XXII) was treated for 2.5 h under the conditions described for the hypoiodite reaction of XVI, no ketal compound corresponding to XXIV was detected on TLC (Chart 5).

A striking difference in ^{13}C-NMR chemical shifts between XVIII and XXI was observed in the carbon signals for the D-ring (Table I). The upfield shift of the signals from the 20*S*-compound (XXI) was considered to be due to the steric shift[10] resulting from fixation of the 21-methyl group onto the D-ring.

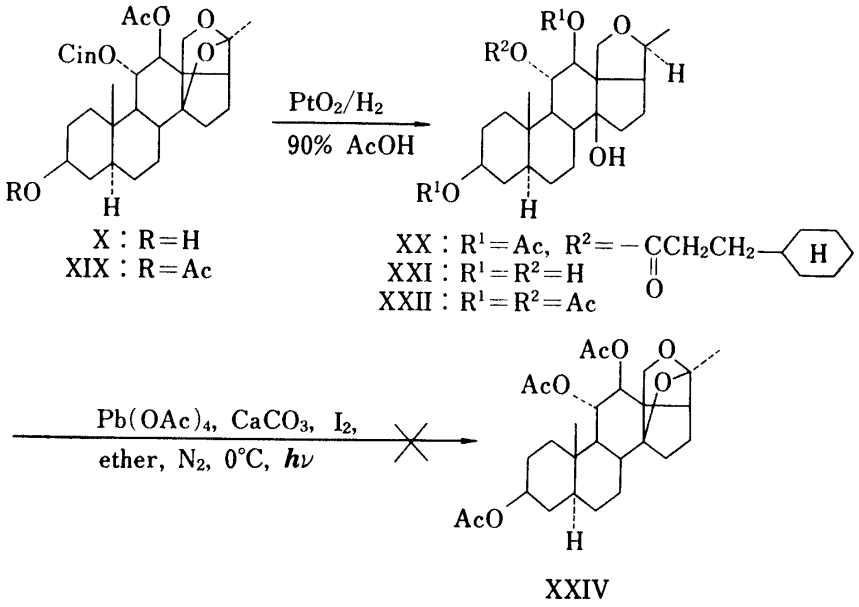


Chart 5

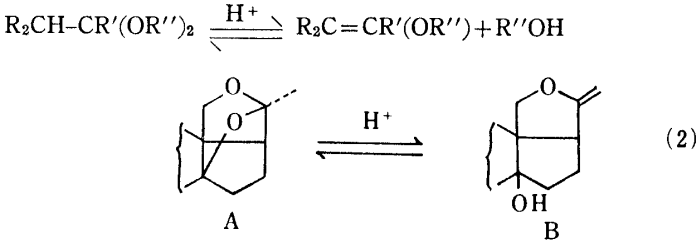


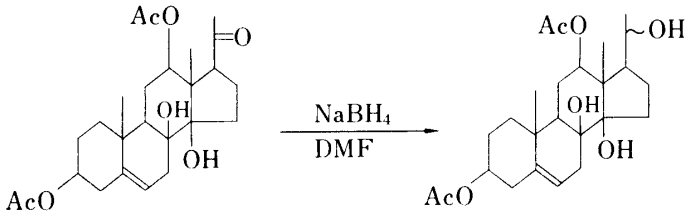
Fig. 1

TABLE I. ^{13}C-NMR Chemical Shifts

	XVIII	XXI		XVIII	XXI
C-1	39.8	39.7	C-11	74.9	74.6
C-2	32.9	32.8	C-12	77.0	76.7
C-3	70.5	70.6	C-13	66.5	64.3
C-4	39.8	39.9	C-14	83.1	83.9
C-5	45.9	45.9	C-15	36.9	35.7
C-6	29.9	29.9	C-16	24.9	22.9
C-7	28.5	29.0	C-17	57.1	52.8
C-8	43.3	43.0	C-18	65.9	66.6
C-9	51.9	52.4	C-19	12.3	12.3
C-10	38.0	38.0	C-20	82.8	77.6
			C-21	20.4	15.7

δ in pyridine-d_5 at 80°C.

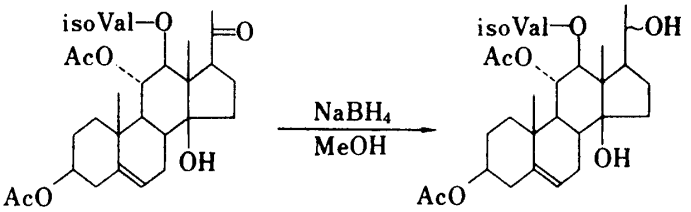
In the ^{13}C-NMR spectrum of a mixture of the 20*R*- and 20*S*-alcohols (XIII and XVI, respectively) the signals ascribable to the 20*S* alcohol could be distinguished clearly from those of the 20*R*-counterpart by comparison of the spectrum with that of the 20*R*-alcohol (XIII). A remarkable difference was observed in their carbon chemical shifts, especially in those assignable to C-16 and C-20. Similar differences were observed in two other pairs (Va and Vb,



V

Va : 20*R*
Vb : 20*S*

Chart 6



XXV

XXVIa : 20*S*
XXVIb : 20*R*

isoVal : $-\overset{\overset{O}{\|}}{C}CH_2CH(CH_3)_2$

Chart 7

TABLE II. ^{13}C-NMR Chemical Shifts

	XIII[a)]	XVI[a)]	Va	Vb	XXVIb	XXVIa	IIa	IIb
C-1	37.2	37.4	38.3	38.3	38.4	38.4	38.4	38.5
C-2	27.9	27.9	27.5	27.5	28.1	28.1	28.0	28.1
C-3	71.3	71.3	74.0	74.0	73.4	73.4	73.9	74.0
C-4	34.3	34.3	38.5	38.6	38.8	38.6	37.1	37.2
C-5	44.5	44.4	137.8	137.7	138.8	138.3	139.7	139.9
C-6	28.8	28.8	120.3	120.5	123.5	123.5	122.5	122.8
C-7	27.7	27.8	35.6	36.0	28.1	28.1	32.2	32.1
C-8	39.4	39.2	74.0	73.8	37.3	37.1	31.9	31.8
C-9	49.8	50.3	45.0	44.8	47.9	47.8	50.4	50.3
C-10	37.5	37.4	37.4	37.3	39.2	39.1	36.8	36.8
C-11	72.9	72.9	24.5	24.6	72.0	72.3	21.2	21.0
C-12	78.9	78.8	78.4	77.5	78.7	78.2	40.0	39.1
C-13	53.5	53.3	54.0	53.4	54.0	53.6	42.7	41.6
C-14	83.7	82.7	85.8	85.3	83.2	82.3	58.7	59.2
C-15	32.6	32.9	35.8	36.0	33.6	34.0	26.1	26.5
C-16	26.4	18.1	26.9	18.8	26.5	18.6	24.9	24.5
C-17	51.3	50.9	53.1	51.9	52.4	51.8	56.4	56.8
C-18	11.9	10.3	12.3	11.8	12.2	10.7	12.4	12.6
C-19	12.2	12.2	18.2	18.1	19.2	19.2	19.3	19.3
C-20	71.6	65.3	70.6	65.3	70.3	64.7	69.4	68.9
C-21	23.0	22.1	23.4	22.4	23.7	22.7	24.4	24.8

a) δ in chloroform-*d*; others, δ in pyridine-d_5.

XXVIa and XXVIb) with C/D-*cis* juncture derived from isolineolon diacetate (V) and drevogenin A 3-acetate (XXV)[12a,b] while a pair (IIa and IIb) with C/D-*trans* juncture derived from pregnenolone acetate (I) showed minor differences (Table II).

In the 20-hydroxy-C/D-*cis*-pregnane type steroids, the free rotation of the side-chain is considered to be restricted by steric hindrance among the C-18 methyl, C-21 methyl and 20-hydroxyl groups on the basis of a CPK model (Fig. 2). Therefore the C-21 methyl group in 20*S*-alcohols of C/D-*cis* pregnane type steroids are close to the plane of the D-ring, resulting in upfield shifts of the C-20 resonances (steric shift).[11]

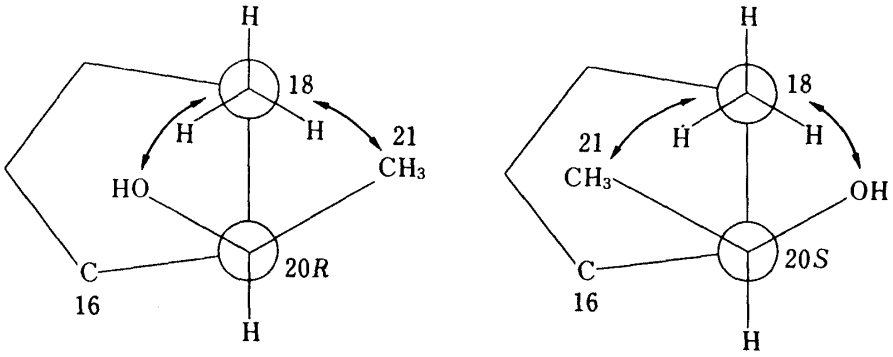


Fig. 2

These results suggest that the application of ^{13}C-NMR to 20-hydroxy-C/D-*cis*-pregnane type steroids will be a more useful and simpler method for investigation of the C-20 configuration than procedures involving the measurement of circular dichroism or optical rotatory dispersion of their derivatives with a suitable chromophore.[5]

Experimental

Melting points were taken on a Kofler hot stage and are uncorrected. Optical rotations were measured with JASCO DIP-4 digital polarimeter at room temperature. IR spectra were recorded with JASCO A-102 and IRA-2 grating infrared spectrophotometers. Ultraviolet (UV) spectra were taken on a Shimadzu UV-220 double-beam spectrophotometer. Electron impact mass spectra (EI-MS) were obtained with a JEOL JMS-D300. Field desorption mass spectra (FD-MS) were taken on a JEOL JMS-OISG-2. ^{1}H- and ^{13}C-NMR spectra were recorded with JEOL FX-100, FX-200, and FX-500 spectrometers, and tetramethylsilane (TMS) was used as an internal standard for spectra run in chloroform-*d* ($CDCl_3$) or pyridine-d_5.

Pregn-5-ene-3,20-diol 3-Monoacetate (II)——$NaBH_4$ (0.5 g) was added to a solution of pregnenolone acetate (I) (1.04 g) in 10 ml of EtOH. The solution was stirred for 0.5 h at room temperature, then treated with cold 2 N HCl, and extracted with ether. The combined extracts were washed with 5% $NaHCO_3$ and saturated NaCl successively, dried over anhydrous sodium sulfate (Na_2SO_4), and concentrated. The crude product was subjected to column chromatography on silica gel, and recrystallization of the eluted material from MeOH gave II (0.90 g) as colorless needles. mp 157—163°C. *Anal.* Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.58; H, 9.99. IR ν_{max}^{Nujol} cm^{-1}: 3500, 1750. EI-MS *m/z*: 342 (M^+-H_2O), 313, 300, 282, 267, 253. ^{1}H-NMR (in $CDCl_3$) δ: 0.80 (3H, s, 18-Me), 1.05 (3H, s, 19-Me), 1.17 (3H, d, $J=7$ Hz, 21-Me), 2.06 (3H, s, Ac), 3.74 (1H, m, 20-H), 4.60 (1H, m, 3α-H), 5.40 (1H, br d, $J=4$ Hz, 6-H). ^{13}C-NMR data are listed in Table II.

Separation of II——The 20-epimers of pregn-5-ene-3,20-diol 3-monoacetate (II) were separated by column chromatography on silica gel, and recrystallization of the products from MeOH gave the 20*R*-alcohol (IIa) and 20*S* alcohol (IIb); the ratio of IIa and IIb was *ca.* 16: 1.

20*R*-Pregn-5-ene-3,20-diol 3-Monoacetate (IIa)——Colorless needles. mp 166.5—168°C. $[\alpha]_D$ −66.7° ($c=3.03$, $CHCl_3$). *Anal.* Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.61; H, 10.03. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430, 1720, 1250. EI-MS *m/z*: 300 (M^+-AcOH, base peak), 285, 282, 267. ^{1}H-NMR (in $CDCl_3$) δ 0.77 (3H, s, 18-Me), 1.03 (3H, s, 19-Me), 1.16 (3H, d, $J=7$ Hz, 21-Me), 2.03 (3H, s, Ac), 3.74 (1H, br q, $J=7$ Hz, 20-H), 4.62 (1H, m, 3α-H), 5.39 (1H, br d, $J=5$ Hz, 6-H). ^{13}C-NMR data are listed in Table II.

20*S*-Pregn-5-ene-3,20-diol 3-Monoacetate (IIb)——Colorless platelets. mp 142.5—143.5°C. $[\alpha]_D$ −69.0° ($c=0.60$, $CHCl_3$). *Anal.* Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 75.79; H, 9.96. IR

$\nu_{max}^{CHCl_3}$ cm^{-1}: 3440, 1720, 1250. EI-MS *m/z*: 300 ($M^+ - AcOH$, base peak), 285, 282, 267. ^{1}H-NMR (in $CDCl_3$) δ: 0.68 (3H, s, 18-Me), 1.02 (3H, s, 19-Me), 1.25 (3H, d, $J=7$ Hz, 21-Me), 2.03 (3H, s, Ac), 3.72 (1H, m, 20-H), 4.60 (1H, m, 3α-H), 5.38 (1H, br d, $J=5$ Hz, 6-H). ^{13}C-NMR data are listed in Table II.

18,20-Epoxy-pregn-5-en-3β-ol 3-Acetate (III)——A mixture of II (200 mg), freshly prepared $Pb(OAc)_4$ (1.0 g) and calcium carbonate ($CaCO_3$) (300 mg) in cyclohexane (25 ml) was refluxed and stirred for 24 h. The reaction mixture was filtered and the filtrate was treated with 5% potassium iodide (KI), 10% sodium sulfite (Na_2SO_3), and water successively, then dried over Na_2SO_4. Evaporation of the solvent yielded 270 mg of products, which were separated by column chromatography. Recrystallization of the desired material from MeOH gave III (33.1 mg) as colorless platelets. mp 132.5—134.5°C. $[\alpha]_D$ −62.5° ($c=2.32$, $CHCl_3$). *Anal.* Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.96; H, 9.33. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1250, 1080. EI-MS *m/z*: 298 ($M^+ - AcOH$, base peak), 283 ($M^+ - AcOH$, CH_3). ^{1}H-NMR (in $CDCl_3$) δ: 0.98 (3H, s, 19-Me), 1.22 (3H, d, $J=6$ Hz, 21-Me), 2.04 (3H, s, Ac), 3.46 (1H, d, $J=10$ Hz, 18-H), 3.68 (1H, m, 20-H), 3.74 (1H, d, $J=10$ Hz, 18-H), 4.56 (1H, m, 3α-H), 5.34 (1H, m, 6-H). ^{13}C-NMR (in pyridine-d_5) δ: 38.3 (t, C-1), 28.0 (t, C-2), 73.8 (d, C-3), 37.1 (t, C-4), 139.6 (s, C-5), 122.2 (d, C-6), 32.3 (t, C-7), 32.4 (d, C-8), 49.6 (d, C-9), 37.1 (s, C-10), 23.3 (t, C-11), 36.7 (t, C-12), 55.3 (s, C-13), 55.3 (d, C-14), 26.3 (t, C-15), 33.5 (t, C-16), 55.2 (d, C-17), 71.3 (t, C-18), 19.2 (q, C-19), 84.2 (d, C-20), 21.5 (q, C-21), 21.2 (q, Ac), 169.8 (s, Ac).

Isolineolon 3,12-Diacetate (V)——Isolineolon (IV) (0.66 g) was acetylated in the usual manner and gave V (0.75 g) as a powder. mp 71—76°C. $[\alpha]_D$ +45.2° ($c=1.04$, $CHCl_3$). *Anal.* Calcd for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 66.40; H, 8.03. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3340, 1725, 1695. EI-MS *m/z*: 388 ($M^+ - AcOH$), 370 ($M^+ - AcOH$, H_2O), 328 ($M^+ - 2AcOH$), 310, 295, 269, 251, 208. ^{1}H-NMR (in $CDCl_3$) δ: 1.17 (3H, s, 19-Me), 1.20 (3H, s, 18-Me), 2.03 (3H, s, Ac), 2.14 (3H, s, Ac), 2.23 (3H, s, 21-Me), 3.08 (1H, m, 17α-H), 4.60 (1H, m, 3α-H), 4.66 (1H, dd, $J=5$, 7 Hz, 12α-H), 5.40 (1H, m, 6-H).

Cyclic Sulfite of Isolineolon Diacetate (VI)——$SOCl_2$ (6 ml) was added to a solution of (564.6 mg) in 20 ml of pyridine at −22°C and the mixture was allowed to stand for 0.5 h, then at 0°C for 5 h, and at room temperature for 1 h successively. The resulting solution was treated with ice-water, and extracted with $CHCl_3$. The combined extracts were washed with 2 N HCl and 5% $NaHCO_3$, dried over Na_2SO_4, and concentrated. The crude products were subjected to column chromatography on silica gel, and recrystallization of the desired material from acetone–hexane gave VI (545.1 mg) as colorless prisms. mp 215—217°C. $[\alpha]_D$ +26.6° ($c=1.97$, $CHCl_3$). *Anal.* Calcd for $C_{25}H_{34}O_8S$: C, 60.71; H, 6.93; S, 6.48. Found: C, 60.70; H, 6.99; S, 6.61. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 1650, 1250, 1030. EI-MS *m/z*: 434 ($M^+ - AcOH$), 370 ($M^+ - AcOH$, SO_2), 353, 342, 327. ^{1}H-NMR (in $CDCl_3$) δ: 1.04 (3H, s, 19-Me), 1.20 (3H, s, 18-Me), 2.04 (3H, s, Ac), 2.17 (3H, s, Ac), 2.20 (3H, s, 21-Me), 2.87 (1H, t, $J=8$ Hz, 17α-H), 3.09 (1H, dd, $J=7$, 10 Hz, 7β-H), 4.65 (1H, m, 3α-H), 4.65 (1H, dd, $J=6$, 7 Hz, 12α-H), 5.85 (1H, br d, $J=6$ Hz, 6-H). ^{13}C-NMR (in pyridine-d_5) δ: 38.4 (t, C-1), 27.3 (t, C-2), 73.6 (d, C-3), 38.0 (t, C-4), 138.7 (s, C-5), 118.1 (d, C-6), 34.4 (t, C-7), 88.8 (s, C-8), 45.9 (d, C-9), 37.8 (s, C-10), 26.3 (t, C-11), 78.5 (d, C-12), 52.8 (s, C-13), 105.5 (s, C-14), 35.8 (t, C-15), 23.1 (t, C-16), 59.1 (d, C-17), 14.5 (q, C-18), 18.2 (q, C-19), 207.7 (s, C-20), 31.6 (q, C-21), 21.1 (q, Ac), 21.1 (q, Ac), 169.7 (s, Ac), 170.2 (s, Ac).

Reduction of VI with $NaBH_4$——$NaBH_4$ (0.3 g) was added to a solution of VI (0.8 g) in 5 ml of DMF and the solution was stirred for 2 h at room temperature. The resulting solution was treated in the manner described for II. The crude products were subjected to column chromatography on silica gel, and recrystallization of the desired material from MeOH gave VII (321.7 mg) as colorless prisms. mp 208.5—210.5°C. $[\alpha]_D$ +87.4° ($c=1.0$, $CHCl_3$). *Anal.* Calcd for $C_{25}H_{36}O_8S$: C, 60.46; H, 7.31; S, 6.46. Found: C, 60.57; H, 7.39; S, 6.33. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550, 1725, 1250, 1030. EI-MS *m/z*: 436 ($M^+ - AcOH$), 418 ($M^+ - AcOH$, H_2O), 388 ($M^+ - AcOH$, SO), 372 ($M^+ - AcOH$, SO_2), 355, 337. ^{1}H-NMR (in $CDCl_3$) δ: 1.17 (3H, d, $J=7$ Hz, 21-Me), 1.22 (3H, s, 19-Me), 1.27 (3H, s, 18-Me), 2.04 (3H, s, Ac), 2.10 (3H, s, Ac), 3.02 (1H, dd, $J=6$, 11 Hz, 7β-H), 3.74 (1H, m, 20-H), 4.50 (1H, dd, $J=6$, 4 Hz, 12α-H), 4.60 (1H, m, 3α-H), 5.41 (1H, br d, $J=4$ Hz, 6-H).

Hypoiodite Reaction of VII——A mixture of VII (323.0 mg), freshly prepared $Pb(OAc)_4$ (1.5 g), $CaCO_3$ (240 mg), iodine (I_2) (303.1 mg), and dry ether (16 ml) was irradiated under nitrogen using a tungsten lamp at 0°C for 2 h. The reaction mixture was passed through a short column of celite. The eluate was treated with 5% sodium thiosulfate solution ($Na_2S_2O_3$) and water successively, then dried over Na_2SO_4. Evaporation of the solvent yielded 331.7 mg of residue. The products were subjected to column chromatography on silica gel, and recrystallization of the desired material from ethyl acetate (AcOEt) gave VIII (6.0 mg) as colorless prisms. mp 259—260°C. $[\alpha]_D$ +41.8° ($c=0.57$, $CHCl_3$). *Anal.* Calcd for $C_{25}H_{34}O_8S$: C, 60.71; H, 6.93; S, 6.48. Found: C, 60.50; H, 7.06; S, 6.03. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1243, 1030. EI-MS *m/z*: 370 ($M^+ - AcOH$, SO_2), 310 ($M^+ - 2AcOH$, SO_2). ^{1}H-NMR (in $CDCl_3$) δ: 1.16 (3H, s, 19-Me), 1.19 (3H, d, $J=8$ Hz, 21-Me), 2.04 (3H, s, Ac), 2.12 (3H, s, Ac), 3.08 (1H, dd, $J=12$, 6 Hz, 7β-H), 3.54 (1H, d, $J=10$ Hz, 18-H), 3.72 (1H, br q, $J=8$ Hz, 20-H), 4.11 (1H, d, $J=10$ Hz, 18-H), 4.62 (2H, m, 3α-H, 12α-H), 5.40 (1H, br d, $J=6$ Hz, 6-H). ^{13}C-NMR (in $CDCl_3$) δ: 37.7 (t, C-1), 35.1 (t, C-2), 73.5 (d, C-3), 38.6 (t, C-4), 138.6 (s, C-5), 117.7 (d, C-6), 27.2 (t, C-7), 87.7 (s, C-8), 46.5 (d, C-9), 38.6 (s, C-10), 25.6 (t, C-11), 74.1 (d, C-12), 64.8 (s, C-13), 103.8 (s, C-14), 38.6 (t, C-15), 25.6 (t, C-16), 56.1 (d, C-17), 70.0 (t, C-18), 18.3 (q, C-19), 82.6 (d, C-20), 19.5 (q, C-21), 21.4 (q, Ac), 21.6 (q, Ac), 170.3 (s, Ac), 170.7 (s, Ac).

Condurangogenin C 3-Acetate (XIII)——Ac_2O (0.29 ml) was added to a solution of condurangogenin C (XII) (1.36 g) in 1 ml of dry pyridine. The solution was kept at room temperature for 24 h, then worked

up in the usual manner. The products were subjected to column chromatography on silica gel, and recrystallization of the eluate from MeOH gave XIII (482.7 mg) as colorless platelets. mp 144—147°C. $[\alpha]_D$ +24.9° (c=1.02, $CHCl_3$). *Anal.* Calcd for $C_{34}H_{46}O_8$: C, 70.08; H, 7.96. Found: C, 69.20; H, 7.98. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1730, 1640. UV λ_{max}^{EtOH} nm (log ε): 280.8 (4.34), 223.2 (4.16), 218.7 (4.18). EI-MS m/z: 564 (M^+-H_2O), 522 (M^+—AcOH), 520, 504, 494, 416, 392, 390, 131 (base peak). ^{1}H-NMR (in $CDCl_3$) δ: 0.98 (3H, s, 19-Me), 1.20 (3H, d, J=7 Hz, 21-Me), 1.33 (3H, s, 18-Me), 1.84 (3H, s, Ac), 2.00 (3H, s, Ac), 3.48 (1H, s, 14-OH disappeared on addition of D_2O), 3.80 (1H, br d, J=7 Hz, 20-H), 4.60 (1H, m, 3α-H), 4.84 (1H, d, J=9 Hz, 12α-H), 5.32 (1H, t, J=9 Hz, 11β-H), 6.40 (1H, d, J=16 Hz, Cin), 7.10—7.60 (5H, m, Cin), 7.70 (1H, d, J=16 Hz, Cin).

Condurangogenin A 3-Acetate (XIV)——A mixture of XIII (200.9 mg) freshly prepared $Pb(OAc)_4$ (1.12 g), $CaCO_3$ (220 mg), and cyclohexane (20 mg) was refluxed under nitrogen for 24 h, then passed through a short column of celite. The eluate was treated with 5% KI and 10% Na_2SO_3 successively, and dried over Na_2SO_4. After evaporation of the solvent, the products were separated by column chromatography, and recrystallization of the desired material from MeOH gave XIV (182.0 mg) as colorless needles. mp 154—156°C. $[\alpha]_D$ +122.1° (c=1.36, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3410, 3050, 3000, 1730, 1700, 1640. UV λ_{max}^{EtOH} nm (log ε): 281.5 (4.30), 223.2 (4.04), 218.0 (4.08). EI-MS m/z: 580.3046 (M^+, Calcd for $C_{34}H_{44}O_8$: 580.3036), 562 (M^+-H_2O), 552, 518, 432, 404, 372, 131 (base peak). ^{1}H-NMR (in $CDCl_3$) δ: 0.97 (3H, s, 19-Me), 1.10 (3H, s, 18-Me), 1.84 (3H, s, Ac), 2.00 (3H, s, Ac), 2.13 (3H, s, 21-Me), 3.06 (1H, m, 17α-H), 4.45 (1H, s, 14-OH), 4.60 (1H, m, 3α-H), 4.85 (1H, d, J=9 Hz, 12α-H), 5.32 (1H, t, J=9 Hz, 11β-H), 6.45 (1H, d, J=16 Hz, Cin), 7.10—7.65 (5H, m, Cin), 7.70 (1H, d, J=16 Hz, Cin).

$NaBH_4$ Reduction of XIV——$NaBH_4$ (0.7 g) was added to a solution of XIV (1.81 g) in 20 ml of DMF, and the mixture was stirred for 0.5 h at room temperature. The resulting solution was treated in the manner described for II. The crude products were subjected to column chromatography on silica gel, and recrystallization of the desired material from MeOH gave a mixture of XIII and its C-20 epimer (XVI) as colorless platelets. It was found that this mixture consists of *ca.* 80% of XIII by HPLC analysis (mobile phase, MeOH–H_2O=5: 1; μ-BONDAPAK C-18, 7.8 mmφ×300 mm). mp 141—147.5°C. $[\alpha]_D$ +41.8° (c=1.77, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3360, 1725, 1635. EI-MS m/z: 564 (M^+-H_2O), 522 (M^+—AcOH), 520, 504, 416, 392, 390, 131 (base peak). ^{1}H-NMR (in $CDCl_3$) δ: 0.99 (3H, s, 19-Me), 1.21 (3H, d, J=7 Hz, 21-Me), 1.34 (3H, s, 18-Me), 1.85 (3H, s, Ac), 2.02 (3H, s, Ac), 3.28 (1H, br s, 14-OH), 3.82 (1H, br d, J=7 Hz, 20H), 4.62 (1H, m, 3α-H), 4.83 (1H, d, J=10 Hz, 12α-H), 5.34 (1H, t, J=10 Hz, 11β-H), 6.42 (1H, d, J=16 Hz, Cin), 7.10—7.64 (5H, m, Cin), 7.72 (1H, d, J=16 Hz, Cin). ^{13}C-NMR data are listed in Table II.

18,20-Epoxy-condurangogenin C (XVII)——A mixture of XIII and XVI (535.5 mg), freshly prepared $Pb(OAc)_4$ (2.0 g), $CaCO_3$ (441.3 mg), I_2 (603.4 mg), and dry ether (16 ml) was irradiated under nitrogen using a tungsten lamp at 0°C for 0.5 h. The reaction mixture was treated in the manner described for VIII. The products showed a main spot with *Rf* 0.22 and two minor spots with *Rf* 0.61 and 0.15 on a thin layer chromatogram (Merck SILICA GEL 60F-254 precoated; acetone: benzene=1: 6 solvent system). The minor products were identified as condurangogenin A acetate (XIV) (less mobile spot) and condurangogenin B acetate (XIX) (more mobile spot) by comparison with authentic samples. The main product was separated by column chromatography, and XVII was obtained as a powder. mp 100—106°C. $[\alpha]_D$ +18.4° (c=1.0, $CHCl_3$). *Anal.* Calcd for $C_{34}H_{44}O_8$: C, 70.32; H, 7.64. Found: C, 70.32; H, 7.48. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460, 1720, 1640. UV λ_{max}^{EtOH} nm (log ε): 281.8 (4.79), 223.3 (4.56), 218.3 (4.60). EI-MS m/z: 562 (M^+-H_2O), 502 (M^+-H_2O, AcOH), 459 (M^+—Cin), 442, 431, 414, 372, 354, 131 (base peak). ^{1}H-NMR (in $CDCl_3$) δ: 0.92 (3H, s, 19-Me), 1.07 (3H, d, J=7 Hz, 21-Me), 1.87 (3H, s, Ac), 2.00 (3H, s, Ac), 2.90 (1H, br s, 14-OH), 3.85 (1H, m, 20-H), 3.96 (1H, d, J=9 Hz, 18-H), 4.11 (1H, d, J=9 Hz, 18-H), 4.61 (1H, m, 3α-H), 4.94 (1H, t, J=10 Hz, 11β-H), 5.12 (1H, d, J=10 Hz, 12α-H), 6.44 (1H, d, J=15 Hz, Cin), 7.05—7.65 (5H, m, Cin), 7.72 (1H, d, J=15 Hz, Cin).

18,20-Epoxy-deacyl Condurangogenin C (XVIII)——A mixture of XVII (43.3 mg) in 5% potassium hydroxide (KOH)–MeOH was refluxed for 2 h. The solution was diluted with water (5 ml), concentrated *in vacuo* to 5 ml, and extracted exhaustively with ether. The ether was evaporated off and the residue was separated by column chromatography. Recrystallization of the desired product from MeOH–acetone gave XVIII (16.0 mg) as colorless prisms. mp 266—269°C. $[\alpha]_D$ −9.4° (c=0.36, MeOH). *Anal.* Calcd for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35. Found: C, 67.06; H, 9.22. IR ν_{max}^{Nujol} cm^{-1}: 3450, 3300. EI-MS m/z: 348 (M^+-H_2O, base peak), 330 (M^+-2H_2O), 315, 312. ^{1}H-NMR (in pyridine-d_5 at 80°C) δ: 1.01 (3H, s, 19-Me), 1.14 (3H, d, J=6 Hz, 21-Me), 2.69 (1H, q, J=6 Hz, 20-H), 3.48 (1H, t, J=9 Hz, 11β-H), 3.64 (1H, d, J=9 Hz, 12α-H), 3.82 (1H, m, 3α-H), 4.35 (1H, d, J=8 Hz, 18-H), 4.52 (1H, d, J=8 Hz, 18-H). ^{13}C-NMR data are listed in Table I.

Hydrogenation of Condurangogenin B 3-Acetate (XIX)——Condurangogenin B (X) (294.8 mg) was acetylated in the usual manner and then hydrogenated over a PtO_2 catalyst (100 mg) in 90% AcOH (20 ml) at room temperature for 2.5 h. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give XX (206.0 mg) as a powder. mp 73—80°C. $[\alpha]_D$ +16.7° (c=1.46, $CHCl_3$). *Anal.* Calcd for $C_{34}H_{52}O_8$: C, 69.36; H, 8.90. Found: C, 68.98; H, 8.72. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3470, 1730, 1250, 1025. EI-MS m/z: 570 (M^+-H_2O), 542, 510. ^{1}H-NMR (in $CDCl_3$) δ: 0.88 (3H, s, 19-Me), 1.19 (3H, d, J=7 Hz, 21-Me), 1.94 (3H, s, Ac), 2.00 (3H, s, Ac), 3.59 (1H, br d, J=

7 Hz, 17α-H), 3.66 (1H, d, $J=8$ Hz, 18-H), 3.70 (1H, br q, $J=7$ Hz, 20-H), 4.05 (1H, d, $J=8$ Hz, 18-H), 4.60 (1H, m, 3α-H), 4.83 (1H, t, $J=7$ Hz, 11β-H), 5.02 (1H, d, $J=7$ Hz, 12α-H).

18,20-Epoxy-20-epideacyl Condurangogenin C (XXI)——Condurangogenin B perhydro derivative (XX) (128.8 mg) was treated in the manner described for XVIII to give XXI (35.7 mg) as colorless needles. mp 279—281°C. $[\alpha]_D$ +24.0° ($c=0.1$, MeOH). *Anal.* Calcd for $C_{21}H_{34}O_5 \cdot H_2O$: C, 65.59; H, 9.44. Found: C, 65.90; H, 9.80. IR ν_{max}^{Nujol} cm^{-1}: 3450, 3300. EI-MS *m/z*: 348 (M^+-H_2O), 330 (M^+-2H_2O), 312, 304 (base peak), 286. FD-MS *m/z*: 367 (M^++1), 348 (M^+-H_2O, base peak). ^{1}H-NMR (in pyridine-d_5 at 80°C) δ: 1.05 (3H, s, 19-Me), 1.11 (3H, d, $J=7$ Hz, 21-Me), 2.40 (1H, m, 15α-H), 2.70—3.20 (3H, m, 15β-H, 8-H, 17α-H), 3.50 (1H, t, $J=9$ Hz, 11β-H), 3.78 (1H, d, $J=9$ Hz, 12α-H), 3.80 (1H, m, 3α-H), 4.14 (1H, br q, $J=7$ Hz, 20-H), 4.16 (1H, d, $J=8$ Hz, 18-H), 4.26 (1H, d, $J=8$ Hz, 18-H). ^{13}C-NMR data are listed in Table I.

18,20-Epoxy-20-epicondurangogenin C 3,11,12-Triacetate (XXII)——18,20-Epoxy-20-epideacyl condurangogenin C (XXI) (12.0 mg) was acetylated in the usual manner to give XXII (11.8 mg) as a powder. mp 82—90°C. $[\alpha]_D$ +18.0° ($c=0.6$, $CHCl_3$). *Anal.* Calcd for $C_{27}H_{40}O_8 \cdot H_2O$: C, 63.51; H, 8.29. Found: C, 63.60; H, 7.92. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440, 1740, 1240, 1020. EI-MS *m/z*: 474 (M^+-H_2O), 414 (M^+-H_2O, AcOH), 372 (M^+-2AcOH), 354, 312. ^{1}H-NMR (in $CDCl_3$) δ: 0.89 (3H, s, 19-Me), 1.20 (3H, d, $J=7$ Hz, 21-Me), 1.97 (3H, s, Ac), 2.01 (3H, s, Ac), 2.04 (3H, s, Ac), 3.54 (1H, s, 14-OH), 3.65 (1H, d, $J=10$ Hz, 18-H), 3.78 (1H, br q $J=7$ Hz, 20-H), 4.05 (1H, d, $J=10$ Hz, 18-H), 4.62 (1H, m, 3α-H), 4.84 (1H, t, $J=9$ Hz, 11β-H), 5.04 (1H, d, $J=9$ Hz, 12α-H).

Deacyl Condurangogenin B 3,11,12-Triacetate (XXIV)——Condurangogenin B (X) (122.8 mg) was treated in the manner described for XVIII to give the deacyl derivative (XXIII) (44.2 mg), and 22.2 mg of XXIII was acetylated in the usual manner. The product was purified by column chromatography on silica gel, and recrystallization from hexane-acetone gave XXIV (20.8 mg) as colorless prisms. mp 181.5—184°C. $[\alpha]_D$ +5.1° ($c=1.11$, $CHCl_3$). *Anal.* Calcd for $C_{27}H_{38}O_8$: C, 66.10; H, 7.81. Found: C, 65.94; H, 7.83. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1725, 1245. EI-MS *m/z*: 490 (M^+), 462 ($M^+-CH_2CH_2$), 402 ($M^+-CH_2CH_2$, AcOH), 370 (M^+-2AcOH), 310 (M^+-3AcOH), 250 (M^+-4AcOH). ^{1}H-NMR (in $CDCl_3$) δ: 1.00 (3H, s, 19-Me), 1.40 (3H, s, 21-Me), 1.96 (3H, s, Ac), 2.03 (3H, s, Ac), 2.04 (3H, s, Ac), 3.86 (1H, d, $J=9$ Hz, 18-H), 4.08 (1H, d, $J=9$ Hz, 18-H), 4.58 (1H, m, 3α-H), 5.02 (1H, t, $J=9$ Hz, 11β-H), 5.06 (1H, d, $J=9$ Hz, 12α-H).

Attempted Conversion of XXII into XXIV——A mixture of XXII (50.9 mg), freshly prepared $Pb(OAc)_4$ (0.25 g), $CaCO_3$ (40 mg), I_2 (50 mg), and dry ether (3 ml) was irradiated under nitrogen using a tungsten lamp at 0°C for 2.5 h, but no product corresponding to XXIV was detected on TLC.

$NaBH_4$ Reduction of V——Isolineolone 3,12-diacetate (V) (119.6 mg) was treated in the manner described for XVI. The products were separated by column chromatography on silica gel to give the 20*R*-alcohol (Va) (31.4 mg) and the 20*S*-alcohol (Vb) (19.6 mg). 20*S*-Hydroxy-isolineolone 3,12-diacetate (Vb), powder. mp 99—106°C. $[\alpha]_D$ +15.8° ($c=0.48$, $CHCl_3$). *Anal.* Calcd for $C_{25}H_{38}O_7$: C, 66.64; H, 8.50. Found: C, 66.32; H, 8.48. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350, 1725, 1660, 1250. EI-MS *m/z*: 390 (M^+-AcOH), 372, 354, 330, 315, 312, 297. ^{1}H-NMR (in $CDCl_3$) δ: 1.13 (3H, d, $J=6$ Hz, 21-Me), 1.20 (3H, s, 19-Me), 1.26 (3H, s, 18-Me), 2.03 (3H, s, Ac), 2.07 (3H, s, Ac), 3.97 (1H, br q, $J=6$ Hz, 20-H), 4.23 (1H, m, 3α-H), 4.60 (1H, dd, $J=8$, 4 Hz, 12α-H), 5.42 (1H, m, 6-H). ^{13}C-NMR data are listed in Table II. 20*R*-Hydroxy-isolineolon 3,12-diacetate (Va), colorless needles. mp 219—221°C. $[\alpha]_D$ +10.4° ($c=1.23$, $CHCl_3$). *Anal.* Calcd for $C_{25}H_{38}O_7$: C, 66.64; H, 8.50. Found: C, 66.81; H, 8.40. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350, 1725, 1250. EI-MS *m/z*: 390 (M^+-AcOH), 372, 354, 330, 315, 312, 297. ^{1}H-NMR (in $CDCl_3$) δ: 1.20 (3H, s, 19-Me), 1.26 (3H, d, $J=6$ Hz, 21-Me), 1.41 (3H, s, 18-Me), 2.04 (3H, s, Ac), 2.10 (3H, s, Ac), 3.84 (1H, dq, $J=6$, 3 Hz, 20-H), 4.58 (1H, m, 3α-H), 4.58 (1H, dd, $J=7$, 5 Hz, 12α-H), 5.42 (1H, m, 6-H). ^{13}C-NMR data are listed in Table II.

Reduction of Drevogenin A Acetate (XXV)——$NaBH_4$ (50 mg) was added gradually to a solution of 83.2 mg of drevogenin A acetate (XXV) in 10 ml of MeOH, and the mixture was stirred for 1 h, then poured into water and extracted with three portions of ether. The ethereal solution was washed successively with water, 2 N HCl, 5% $NaHCO_3$ solution and brine, then dried over anhydrous Na_2SO_4. After evaporation of the solvent *in vacuo*, the residue (82.0 mg) was chromatographed on a silica gel column with 50% ethyl acetate in *n*-hexane to give the 20-epimer XXVIa and XXVIb. XXVIa: powder 11.3 mg, $[\alpha]_D$ −8.5° ($c=0.46$, $CHCl_3$). ^{1}H-NMR (in $CDCl_3$) δ: 0.94 (6H, d, $J=6$ Hz, Isoval-di Me), 1.10 (3H, d, $J=6.3$ Hz, 21-Me), 1.14 (3H, s, 19-Me), 1.15 (3H, s, 18-Me), 1.95, 2.05 (3H, each s, Ac), 3.85 (1H, dq, $J=2$ and 6 Hz, 20-H), 4.53 (1H, m, 3α-H), 4.77 (1H, d, $J=10$ Hz, 12α-H), 5.36 (1H, t, $J=10$ Hz, 11β-H). ^{13}C-NMR data are listed in Table II. XXVIb: powder, 24.9 mg $[\alpha]_D$ −4.2° ($c=1.17$, $CHCl_3$), MS *m/z*: 474 (M^+-AcOH), 396 (M^+-2AcOH, H_2O). ^{1}H-NMR (in $CDCl_3$) δ: 0.97 (6H, d, $J=6$ Hz, Isoval-di Me), 1.15 (3H, s, 19-Me), 1.24 (3H, d, $J=6$ Hz, 20-H). 1.29 (3H, s, 18-Me), 1.95, 2.02 (3H each, s, Ac), 3.85 (1H, dq, $J=2$ and 6 Hz, 20-H), 4.50 (1H, m, 3α-H), 4.77 (1H, d, $J=10$ Hz, 12α-H), 5.36 (1H, t, $J=10$ Hz, 11β-H), ^{13}C-NMR data are listed in Table II.

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