Tetrahedron Vol. 39, No. 17, pp. 2819 to 2824, 1983
Printed in Great Britain.

0040-4020/83 $3.00+.00

ACTION OF HYDROGEN PEROXIDE ON OLEAN-12,15-DIEN-3,11-DIOL: PREPARATION OF C-NOR-TRITERPENE LACTONES

B. P. PRADHAN,* M. M. MUKHERJEE and D. K. CHAKRABERTI
Department of Chemistry, University of North Bengal, Dist. Darjeeling—734 430, India

and

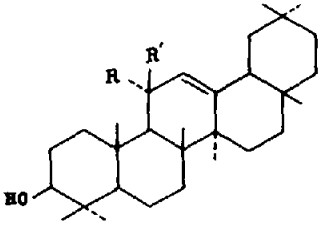
J. N. SHOOLERY
Varian Associates, Palo Alto, California, U.S.A.

(*Received in UK 19 April 1982*)

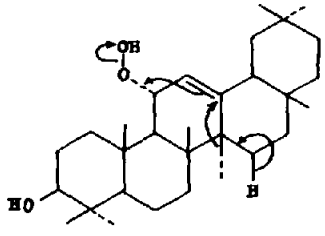
Abstract—Treatment of olean-12,15-dien-3,11-diol with hydrogen peroxide containing p-toluenesulphonic acid furnished two isomeric γ-lactones identified as 3β-acetates of C-12-nor-olean-15-en-13α-carb→19α-olide and C-12-nor-olean-18(19)-en-13β-carb→15β-olide.

E. J. Corey *et al.*[1] synthesised epoxytaraxerol **2** from both the olean - 12 - en - 3β,11β - diol **1a** and olean - 12 - en - 3β,11α - diol **1b** and suggested that the formation of the same epoxide **2** from the isomeric (C-11) diols must proceed by C-11–O bond cleavage with the formation of the same C-11,12,13 allylic cation which then forms the hydroperoxide **3**. This **3** in turn undergoes O–O fission and carbon rearrangement to afford **2**.

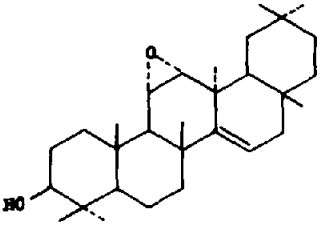
Treatment of taraxeryl acetate **8** with NBS afforded **9**,



1a, R=H, R'= OH
1b, R=OH, R'= H



3



2

Chart I

that would undergo nucleophilic attack by OH^- ion producing a 16-hydroxytaraxerol derivative or to produce a cation at C-8 by migration of C-8–Me to C-14 position which was expected to eliminate a C-7 proton to give multiflorenol derivative **7**; but in actual practice, the findings were widely different from those expected and are discussed below:

This type of reaction under identical conditions was carried out on the diol **4** synthesised from taraxeryl acetate with a view to producing the allylic cation **5**. The intermediate **5** would further isomerize either to produce the allylic cation **6** by migration of C-15–16 double bond $C_{32}H_{51}O_2Br$ (M^+ 548, Br 81) m.p. 180–82°, $[\alpha]_D$ +47.4°, ν_{max} 1720, 1250 ($-OCOCH_3$); ^1H NMR: δ 5.3 (m, 1H, >C=C<H), 4.53 (m, 1H, H–C–O–$COCH_3$), 4.3 (m, 1H, H–C–Br), 2.09 (s, 3H, –O–$COCH_3$) ppm. Treatment of **9**

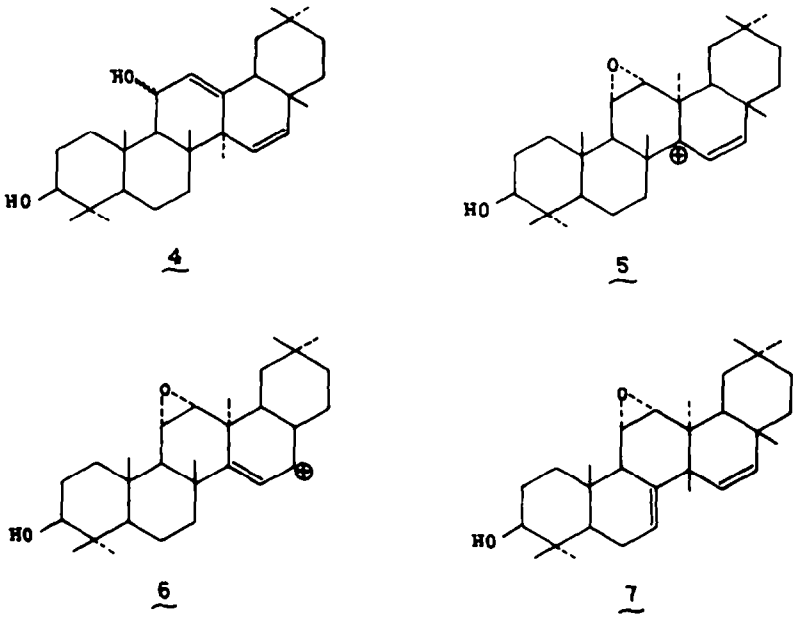


Chart II

with sodium dichromate and acetic acid furnished 11 - oxo - 15 - bromo - β - amyrenyl acetate[2] **10** $C_{32}H_{49}O_3Br$, m.p. 240–41°, $[\alpha]_D + 88°$, λ_{max} 249 nm; ν_{max} 1725, 1250 ($-OCOCH_3$), 1680 ($-C=C-C=O$) cm^{-1}. Attempts to dehydrobrominate **10** with dimethyl aniline/collidine gave the starting compound **10**. A reverse route was followed to prepare the 11 - oxo - 12,15 - diene by dehydrobrominating **9** which furnished compound **11**, $C_{32}H_{50}O_2$, m.p. 199–200°, $[\alpha]_D + 42°$; no UV absorption between 220–300 nm; ν_{max} 1730, 1240 ($-OCOCH_3$), 1650, 890, 750 ($>C=C<$), 820 ($>C=C<_{H}$) cm^{-1}; NMR: 5.2–5.6 (m, 3H, vinyl protons), 4.5 (m, 1H, H–C–$OCOCH_3$), 2.08 (s, 3H, $-O-COCH_3$), 0.8–1.2 (8-t-CH_3) ppm. The diene **11** was oxidised to give the desired 11-oxo-12,15-diene **12**, $C_{32}H_{48}O_3$, m.p. 243–45°, $[\alpha]_D + 28.6°$, λ_{max} 244 nm; ν_{max} 1730, 1240 ($-O-COCH_3$), 1660 ($C=C-C=O$), 1650, 890, 750

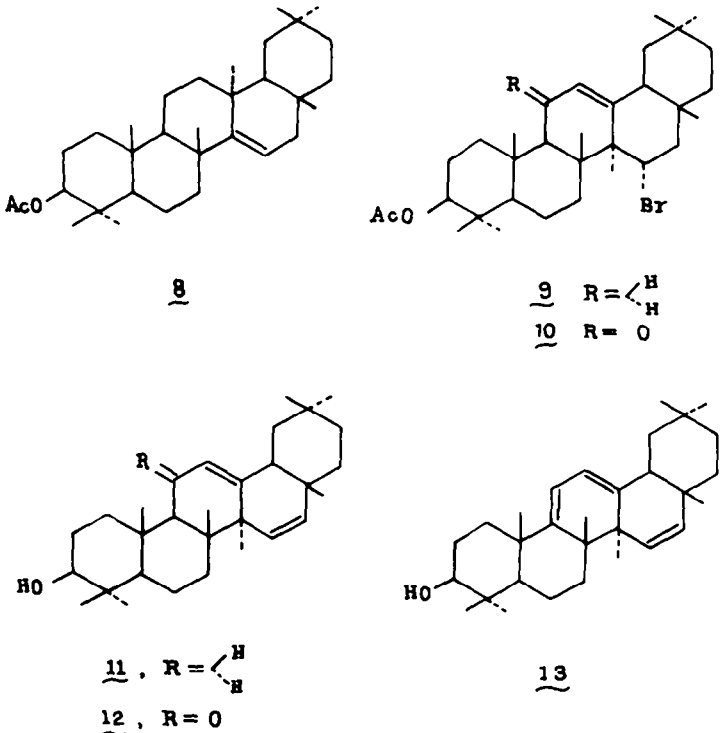


Chart III

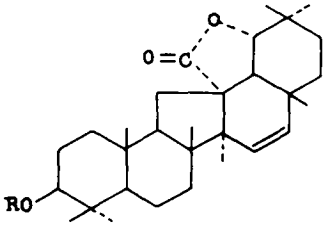
(), 820 () cm^{-1}. LAH reduction of the 11-oxo-diene **12** furnished a diene-diol **4**, $C_{30}H_{48}O_2$, m.p. 198–200°, ν_{max} 3460 (–OH), 820 () cm^{-1}; purification of the diol by chromatography yielded a homoannular diene **13**, $C_{30}H_{46}O$, m.p. 189–90°, λ_{max} 276 nm.

The diol **4** was directly treated with hydrogen peroxide containing p-toluenesulphonic acid following the procedure adopted by Corey *et al.*[1] The product furnished two compounds (**14** and **16**) of the same molecular formula $C_{30}H_{46}O_3$. The compound **14**, m.p. 240–41° showed IR bands at 3520 (–OH), 1775 (γ-lactone), 1650, 890, 870, 750 () cm^{-1}. Acetylation of **14** furnished the acetate **15** $C_{32}H_{48}O_4$, m.p. 215–16°; ν_{max} 1780 (γ-lactone), 1720, 1250 (–$OCOCH_3$), 1650, 890, 870, 750 () cm^{-1}. The formation of the lactone has thus been proved by the IR spectrum of the alcohol **14** and its acetate **15**. The structure **14** has been conclusively established from mass, ^1H and ^{13}C NMR spectra of the compound **15**.

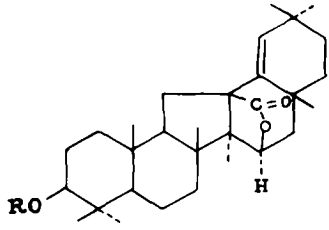
^1H NMR of **15** showed the presence of eight tertiary Me- groups between 0.5 and 1.5 ppm, the acetoxy Me-group at 2.05 ppm, the proton geminal to the lactonic O at 4.72 ppm as a doublet (J = 7.3 Hz), and the *cis*-disubstituted olefinic protons appeared at 5.27 ppm as an AB quartet (J = 10 Hz). Irradiation at 4.72 ppm gave a singlet at 1.7 ppm showing the proton at 1.73 ppm to be coupled to the one at 4.72 ppm with J = 7.5 Hz and weakly to other protons. Again irradiation at 1.73 ppm at a fairly low level gave a sharp line at 4.72 ppm which was a doublet otherwise. Hence the doublet at 4.72 ppm arises due to a single proton adjacent to the lactonic O that couples with the proton at 1.73 ppm. The multiplet at 4.5 ppm collapses to a broad singlet suggesting the presence of a proton at C-3 coupled with protons at C-2. The absence of any peaks between 2.2 and 3.5 ppm shows that the C-α to the lactonic –CO– possesses no proton. The above observations could be explained if the lactone –CO– group is attached to the C-13 position and the γ-lactone ring is formed with the C-19 carbon with a geminal β-H that has a single neighbouring β-axial proton at C-18 position, thus establishing the structure of **14**. This structure is corroborated by the ^{13}C NMR and mass (Experimental) spectra.

The compound **16** had m.p. 256–57° and showed IR absorptions at 3525 (OH), 1780 (γ-lactone), 820 () cm^{-1}. ^1H NMR showed a singlet at 5.3 ppm for the vinyl proton, a multiplet at 4.8 ($W_{1/2}$ = 20 Hz) ppm for the proton geminal to the lactonic oxygen which may have two neighbouring protons, a triplet at 3.23 ppm ($W_{1/2}$ = 20 Hz) for the proton geminal to the OH at C-3 present as an axial proton.[3] Acetylation of **16** gave the acetate **17**, $C_{32}H_{48}O_4$ m.p. 228–29°; ν_{max} 1780 (γ-lactone), 1715, 1250 (acetate), 820 (trisubstituted double bond) cm^{-1}. The mass spectrum of **17** was essentially identical with those of **15**.

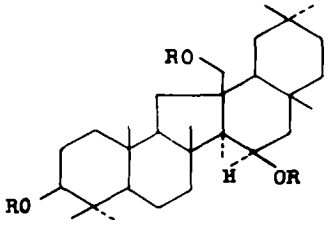
The ^1H NMR of **17** showed a multiplet at 4.8 ($W_{1/2}$ = 7 Hz) ppm (integrated for one proton) showing that the proton geminal to the lactonic O is equatorial which couples with axial and equatorial protons; the multiplet at 4.5 ppm was due to C-3 proton, the singlet at 5.3 ppm was due to C-19 olefinic proton. The absence of any peaks in the region 2.2–3.5 ppm showed that the lactone –CO– has no α-H as in **15**, and hence should be attached to the same carbon (C-13). The absence of AB quartet for the *cis* C-15–16 olefinic protons present in **4** indicated



14, R = H
15, R = CH_3CO



16, R = H
17, R = CH_3CO



18, R = H
19, R = CH_3CO

Chart IV

that this double bond must be involved in the formation of lactone **16** and the lactonic O should be attached to C-15 with an α-equatorial geminal proton that couples with C-16 protons. The structure **16** thus assigned to the lactone explains all the IR and NMR peaks.

LAH reduction of the lactone **16** afforded a triol **18** $C_{30}H_{50}O_3$ m.p. 280–82°, acetylation of which gave a triacetate **19**, $C_{36}H_{56}O_6$, m.p. 190–93°, ν_{max} 1735–40, 1250–40 (acetate groups), 820 cm^{-1}. ^1H NMR of the triacetate **19** showed peaks at 0.85–1.2 (eight t-Me groups), 2.05 (two acetoxyl Me- groups), 2.1 (one acetoxyl Me-), 3.65 ($J = 11$ Hz, AB-quartet for two methylene protons geminal to the acetate group), 4.45 (a multiplet for the proton at C-3 geminal to the acetate), 5.2 ($J = 8$ Hz, a doublet split into a multiplet for C-15-proton geminal to the acetate) and at 5.3 (a singlet for the C-19 vinyl proton which has no neighbouring proton) ppm.

Mechanism. Contrary to the formation of the proposed intermediates **5** or **6** the double bond at C-12–13 is pushed, during the formation of the epoxide **I-2**, from the hydroperoxide **I-1** towards ring E (to form a germanicol derivative) rather than to ring B or D due to the presence of double bond at C-15–16 position. Under the reaction condition the epoxide **I-2** is unstable due to the conformational strain caused by the double bonds at C-15–16 and C-18–19 positions and hence undergoes epoxide ring opening in presence of acid forming carbonium ion **I-4** probably by 1,3-hydride shift from C-13 to C-11 as shown in **I-3**. The intermediate carbonium ion **I-4** undergoes ring contraction producing the isomeric cations **I-5** and **I-5'** which in turn lose a proton to form isomeric aldehydes **I-6** and **I-6'** respectively. These aldehydes get oxidised in presence of hydrogen peroxide to the corresponding α and β carboxylic acids at C-13 positions.

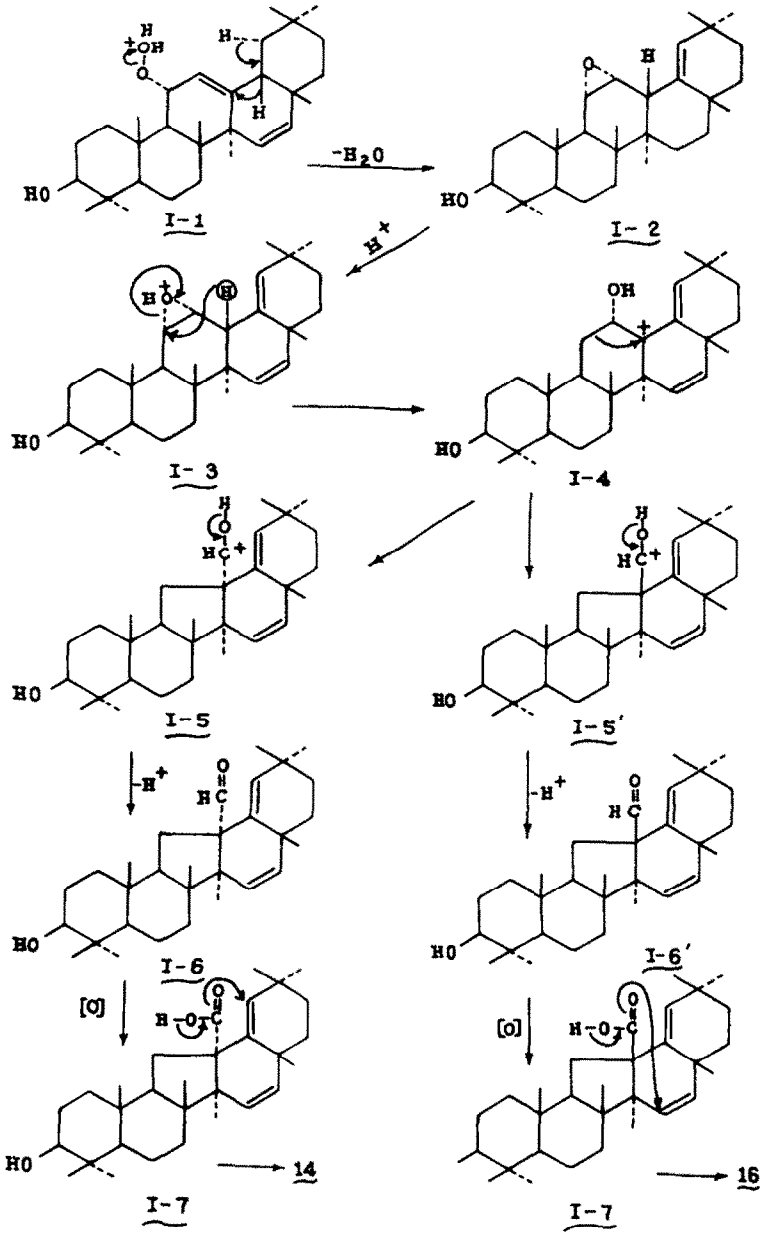


Chart V

The α-carboxyl group in **I-7** being at proximity to the double bond at C-18–19, undergoes lactonization furnishing the γ-lactone **14**, whereas the inetermediate **I-7'** having its carboxyl group in the β-position is at proximity to the C-15–16 double bond, lactonizes forming **16**. The Dreiding model of the lactones **14** and **16** showed that the lactones are strain free, thus stabilising the molecules. This is perhaps the first report on the formation of a lactone with the carbon skeleton rearrangement in ring C of a triterpenoid with hydrogen peroxide in presence of p-toluenesulphonic acid.

EXPERIMENTAL

M.ps are uncorrected. Petroleum used had b.p. 60–80°. All the rotations were determined in $CHCl_3$ at 1–2% solns. The ^1H NMR spectra were recorded with Varian A-60, T-60, FT-80A and XL-100 NMR spectrometers using $CDCl_3$ containing TMS as internal reference. All the UV spectra were determined in 95% ethanol and IR in nujol. Column chromatography were done on neutral alumina deactivated with 10% aqueous acetic acid (4 ml/100 g of alumina).

Oxidation of taraxeryl acetate **8** *with NBS in DMSO*

Preparation of 15-*bromo-β-amyrin acetate* **9**. To a soln of **8** (1 g) in $CHCl_3$ (50 ml) and DMSO (25 ml), was added NBS (1 g) in portions and kept in dark for 14 hr. The mixture was filtered and the filtrate extracted with $CHCl_3$, washed with water and dried ($NaSO_4$). Removal of the solvent and chromatography of the residue furnished **9** (0.9 g), m.p. 180–82°, $[\alpha]_D + 47.4°$. (Found: C, 70; H, 9.1. $C_{32}H_{51}O_2Br$ requires: C, 70.23; H, 9.3%.) Beilstein test for halogen—positive.

Oxidation of 15-*bromo-β-amyrin acetate* **9**

Preparation of 11-*oxo*-15-*bromo-β-amyrin acetate* **10**. To a refluxing soln of **9** (1 g) in benzene (40 ml) was added slowly a soln of $Na_2Cr_2O_7$ (1 g) in glacial AcOH (30 ml) with stirring while maintaining the temp at 70°. After the addition was complete the stirring was continued for 24 hr, maintaining the temp at 80–85°. At the end it was cooled and rectified spirit (5 ml) was added. The soln was concentrated to 1/3rd volume and poured into ice cold water. The ppt was filtered off, washed and crystallization from $CHCl_3$–MeOH gave **10** (0.75 g) m.p. 240–41°, $[\alpha]_D + 89°$. (Found: C, 68.2; H, 8.6. $C_{32}H_{49}O_3Br$ requires: C, 68.4; H, 8.7%.) Beilstein test—positive.

Attempted dehydrobromination of 11-*oxo*-15-*bromo-β-amyrin acetate* **10**

(a) *With dimethyl aniline.* Compound **10** (0.5 g) was refluxed with dimethylaniline (75 ml) for 6 hr. The mixture was cooled, acidified with HCl (6 N) and then extracted with ether. Removal of the solvent and chromatography of the residue furnished an eluate (with petroleum at eluent) which on crystallization with $CHCl_3$–MeOH afforded the starting **10**, m.p. (m.m.p.) 240–41°, Beilstein test—positive.

(b) *With s-collidine.* Compound **10** (0.2 g) was refluxed with s-collidine (15 ml) for 18 hr at 180° in an oil bath. Working up the mixture in the usual method gave back **10**, m.p. (m.m.p.) 240°, Beilstein test—positive.

Dehydrobromination of 15-*bromo-β-amyrin acetate* **9**

Preparation of olean - 12,15 - dien - 3 - β - yl acetate **11**. Acetate **9** (0.2 g) was refluxed with distilled dimethylaniline (30 ml) for 6 hr. The mixture was diluted with water, acidified with aq HCl and extracted with ether. The ether was distilled off and the residue chromatographed. Petroleum eluted a solid which on crystallization ($CHCl_3$–MeOH) gave **11**, m.p. 199–200°, $[\alpha]_D +$ 42°. (Found: C, 81.9; H, 10.8. $C_{32}H_{50}O_2$ requires: C, 82.35; H, 10.8%.) UV—no absorption in the region 220–300 nm. Beilstein test—negative.

Oxidation of olean-12,15-dien-3-β-yl acetate **11**

Preparation of 11 - *oxo* - *olean* - 12,15 - *dien* - 3 - β - *yl acetate* **12**. A soln of $Na_2Cr_2O_7$ (4 g) in glacial AcOH (100 ml) was added slowly during a period of 1 hr to a vigorously stirred soln of olean - 12,15 - dien - 3 - β - yl acetate (4 g) in refluxing benzene (50 ml). The mixture was refluxed for 24 hr and then cooled. Excess of dichromate was decomposed with EtOH (50 ml). The soln was concentrated to 1/3rd volume and the contents poured into ice cold water, extracted with ether, washed with water and dried (Na_2SO_4). Removal of the solvent and chromatography of the residue furnished a solid on elution with petroleum: φH (3:2). The solid on crystallization ($CHCl_3$–MeOH) gave **12**, m.p. 243–45°, $[\alpha]_D + 28.8°$, λ_{max} 244 (ε, 11,376) nm, ^1H NMR: δ 0.82–1.04 (8 t-Me protons), 2.03 (s, 3H, $-OCOCH_3$), 2.23 (dd, 1H, C-18β-H), 2.42 (s, 1H, C-9α-H), 2.82 (t of d, 1H, C-1β-H),[4] 4.5 (t, 1H, H–C–3–O–CO–), 5.38 (s, 2H, 2 vinyl H), and 5.64 (s, 1H, 1 vinyl H) ppm. (Found: C, 79.86; H, 9.95. $C_{32}H_{48}O_3$ requires: C, 79.95; H, 10.06%.)

LAH reduction of 11 - *oxo* - *olean* - 12,15 - *dien* - 3 - β - *yl acetate* **12**

Preparation of olean - 12,15 - dien - 3,11 - diol **4**. A soln of **12** (2.5 g) in dry benzene (30 ml) and dry ether (70 ml) was refluxed with LAH (5 g) for 6 hr followed by stirring at room temp for another 12 hr. Excess LAH was destroyed by adding water dropwise at r.t. The etherial layer was separated and the aqueous layer was extracted with ether and the two ether soln were mixed, washed with water and dried (Na_2SO_4). The ether was removed and the residue yielded **4** (4.5 g), m.p. 198–200°, ν_{max} 3460, 1650, 890, 860, 820, 750 cm^{-1} (TLC single spot).

Compound **4** (0.2 g) was absorbed in a column of deactivated alumina (10 g) and elution with petroleum: φH (3:2) furnished **13** m.p. 189–90°, λ_{max} 276 nm, m/e 422 (M^+). (Found: C, 84.8; H, 11.30. $C_{30}H_{46}O$ requires: C, 85.25; H, 10.97% (TLC homogenous).)

Treatment of olean - 12,15 - dien - 3,11 - diol **4** *with* H_2O_2–*p*TsOH

Isolation of **14** *and* **16**. To a soln of **4** (1.9 g) in CH_2Cl_2 (100 ml) was added a soln (80 ml) prepared by mixing p-TsOH (3 g) and 30% H_2O_2 (5 ml) in t-BuOH (80 ml). The mixture was stirred slowly for 24 hr and then poured into water. It was then extracted with CH_2Cl_2, washed with water, dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue (1.5 g) was absorbed in an alumina column. Elution with benzene yielded a mixture of **14** and **16**, (Rf **14** = 49; **16** = 46 in EtOAc). The mixture was repeatedly crystallized from $CHCl_3$–MeOH when **14** (0.3 g) separated as the less soluble part. Further purification by crystallization from $CHCl_3$–MeOH afforded pure **14**, m.p. 240–41°, no UV absorption in the region 220–300 nm. (Found: C, 78.94; H, 9.89. $C_{30}H_{46}O_3$ requires: C, 79.25; H, 10.20%.)

Acetylation of lactone **14**. **14** (0.1 g) was heated with a mixture of Py (2 ml) and Ac_2O (2 ml) for 4 hr. The mixture was then poured into ice cold water and then filtered. The residue was washed with water and dried under suction. Crystallization of the solid furnished **15**, m.p. 215–16°; *m/e* 496 (M^+). 468 (M^+–CO), 452 (M^+–CO_2), 436 (M^+–AcOH), 421, 408, 392, 372, 313, 300, 269, 257, 244, 231, 217, 218, 206, 203, 191, 189, 187, 175, 171, 161, 147, 135; ^{13}C NMR (multiplicity): 175.5(*s*), 170.5(*s*), 132.75(*d*), 132.5(*d*), 82.0(*d*), 80.0(*d*), 75.8(*s*), 67.5(*d*), 55.75(*d*), 51.75(*d*), 45.25(*s*), 42.0(*s*), 38(3*t*, 1*s*), 36.8(*s*), 35.75(*t*), 34.8(*t*), 34.2(*s*), 32.8(*q*), 30.25(*s*), 29.0(*q*), 28.0(*q*), 25.0(*q*), 23.75(*q*), 23.5(*t*), 22.75(*q*), 21.25(*q*), 19.75(*t*), 18.6(*q*), 16.25(*q*) ppm. (Found: C, 77.25; H, 9.85. $C_{32}H_{48}O_4$ requires: C, 77.36; H, 9.74%.)

Isolation of lactone **16**. The more soluble fraction was crystallized twice and the purer product was isolated from the filtrate. Concentration of the filtrate gave **16** (0.2 g), m.p. 256–57°; *m/e* 454 (M^+), 436 (M^+–H_2O), 426 (M^+–CO), 410 (M^+–CO_2), 408, 392, 313, 269, 231, 205, 189, 187, 171. (Found: C, 79.45; H, 9.76. $C_{30}H_{46}O_3$ requires: C, 79.25; H, 10.20%.)

Acetylation of lactone **16**. **16** (0.01 g) was heated with Py (1 ml) and Ac_2O (1 ml) for 4 hr. The mixture on usual work up and crystallization from $CHCl_3$–MeOH gave the acetate **17**, m.p. 228–29°, *m/e* 496 (M^+), 468 (M^+–CO), 452 (M^+–CO_2), 436 (M^+–AcOH), 408, 392, 372, 313, 269, 257, 256, 217, 206, 203, 191, 189, 187, 171, 161, 147, 135. (Found: C, 77.38; H, 9.94. $C_{32}H_{48}O_4$ requires: C, 77.30; H, 9.74.)

LAH reduction of lactone **16**. A soln of 16 (0.2 g) dissolved in dry ether (50 ml) was refluxed with LAH 90.4 g) for 4 hr. Excess of LAH was decomposed with a saturated soln of Na_2SO_4 and the product extracted with ether (200 ml), washed with water and dried (Na_2SO_4). The solvent was distilled off and the residue when recrystallized from acetone furnished the triol **18** (0.15 g), m.p. 280–82° (TLC single spot). (Found: C, 78.42; H, 10.84. $C_{30}H_{50}O_3$ requires: C, 78.55; H, 10.99%.)

Acetylation of triol **18**—*preparation of triacetate* **19**. A mixture of 18 (0.12 g) in dry Py (2.0 ml) and Ac_2O (2.0 ml) was kept over a water bath for 12 hr. The mixture was poured into cold water when a solid which separated out was washed with water and dried under suction. It was then crystallized from $CHCl_3$–MeOH to afford the triacetate **19** (0.1 g), m.p. 190–93° (TLC-single spot); m/e 584 (M^+), 524 (M^+–AcOH), 432, 464 (M^+–2AcOH), 459, 389, 358, 343, 340, 269, 249, 215, 204, 189, 187; ^{13}C NMR (multiplicity): 170.5(*s*), 170.2(*s*), 170(*s*), 155.5(*s*), 122(*d*), 80.5(*d*), 78.5(*d*), 76.0(*t*), 55.5(*d*), 50.0(*d*), 46.8(*s*), 41.5(*s*), 39.5(*t*), 38.2(*s*), 38.0(*t*), 37.8(*s*), 37.5(*s*), 34.0(*t*), 33.9(*t*), 33.5(*t*), 32.0(*s*), 31.5(*t*), 31.0(*q*), 29.5(*q*), 28.0(*q*), 25.5(*q*), 23.8(*t*), 23.5(*q*), 22.5(*q*), 21.5(3*q*), 18.5(*t*), 16.0(*q*), 15.5(*q*) ppm. (Found: C, 73.50; H, 9.85. $C_{36}H_{56}O_6$ requires: C, 73.93; H, 9.65%.)

Acknowledgement—The authors' thanks are due to Dr. A. Duffield, University of New South Wales for the mass spectra; to Dr. S. K. Sengupta, East India Pharmaceutical Works Ltd. Calcutta for the optical rotations. Two of us (M. M. Mukherjee and D. K. Chakrabarti) are grateful to U.G.C. for the financial assistance.

REFERENCES

[1]I. Ageta, E. J. Corey, A. G. Hortmann, J. Klien, S. Proskow and J. J. Ursprung, *J. Org. Chem.* **30**, 1698 (1965).
[2]K. Chattopadhyay, D. R. Misra and H. N. Khastgir, *Indian J. Chem.* **14B**, 403 (1976).
[3]L. M. Jackman and S. Sternhell, *Application of Nuclear Magnetic Spectroscopy in Organic Chemistry*, 2nd Edn. Pergamon Press, Oxford (1969).
[4]H. S. Bhacca and D. H. Williams, *Application of NMR Spectroscopy in Organic Chemistry*. Holden-Day, New York (1964).