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STUDIES ON OXIDATION OF TRITERPENOIDS: PART VII. TRANSFORMATION OF OLEANANE AND URSANE SKELETONS TO 11α,12α-OXIDOTRITERPENOIDS WITH HYDROGEN PEROXIDE AND SELENIUM DIOXIDE AND THEIR CARBON - 13 NMR DATA.

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Abstract - Hydrogen peroxide-selenium dioxide in t-butanol has been found to be a good reagent for the preparation of 11α,12α, -oxidotriterpenoids of oleanane and ursane skeletons; whereas α-amyrin and β-amyrin acetates furnished 11α,12α-epoxyurs-14-en-3β-yl acetate (4c) and 11α,12α-epoxytaraxer-14-en-3β-yl acetate (4g) respectively, uvaol and ursolic acid/methyl ester gave 11α,12α-epoxyurs-28→13-olide-3β-ol (5d); erythrodiol (3c) and oleanolic acid (3b)/methyl ester (3d) afforded 11α,12α-epoxy-oleanan-28→13-olide-3β-ol (5); olean-12-en-2α,3β,28-yl triacetate (3j) on similar reaction furnished 11α,12α-epoxytaraxer-14-en-3β-ol-2α,28-yl diacetate (4d) and 11α,12α-epoxytaraxer-14-en-2α,3β-diol-28-yl acetate (4g).

The isolation of a nor-triterpenoid peroxide - baccatin (1) has been reported[1] from this laboratory. The compound 1 has been assumed to be formed biogenetically from another triterpenoid acid - sebiferenic acid[2] 2 present in the same plant. In order to prepare 1 and 2 from a triterpenoid of known structure, cratagolic acid 3g was chosen for the purpose, which demanded isomerization of the double bond from thermodynamically stable C-12-13 position to less stable position C-14-15. E. J. Corey et al[3] reported the transformation of β-amyrin (3) to 11α,12α-epoxytaraxer-14-en-3β-ol 4 by photoexidation and by chemical methods which involved hydroxylation of C-11 methylene followed by oxidation with hydrogen peroxide in presence of p-toluene sulfonic acid/selenium dioxide. The photochemical oxidations of oleanolic acid 3b and erythrodiol 3c have been studied by I. Kitagawa et al[4] to furnish 11α,12α-epoxyoleanan-28→13-olide-3β-ol 5 and 11α,12α-epoxy-oleanan-13→28-oxo-3β-ol 5a. The presence of a C-17 carboxyl group has been

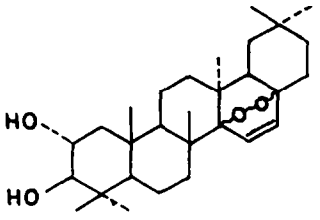
demonstrated to be essential for the formation of 11α,12α-epoxy system in the oxidation of oleanene and ursene triterpenoids with hydrogen peroxide in presence of acetic acid by Mazumder et al[5].

As the earlier methods [4,5] mentioned above were found to be unsuitable which involved lactonization of the C-17 carboxyl group, we attempted an alternative method the study of which is the subject matter of the present communication.

It is well known that selenium dioxide is a good reagent for allylic oxidation.[6] We assumed that if selenium dioxide is used as the oxidizing reagent along with hydrogen peroxide the initially formed organo-selenic acid would form hydroperoxide which would subsequently yield the 11α,12α-epoxide with simultaneous migration of the double bond to the taraxerene system. In order to test the applicability of this assumption the first compound that was examined was β-amyrin acetate 3a. The product obtained after refluxing a solution of 3a with selenium dioxide and hydrogen peroxide in t-butanol for 60 h afforded two compounds which were separated by column chromatography (CC). The first compound, $C_{32}H_{50}O_3$, m.p. 307-08°C; M^+ 482; IR 1735, 1260 (OAc), 880 (epoxy), 820 (>C=C<$_H$) cm^{-1}; ^1H NMR showed the presence of eight tertiary methyl between δ 0.82 to 1.10, the acetoxy methyl at 2.06, two protons that appeared at 2.80 and 3.11 as doublet (J = 5 Hz) and triplet (J = 5 Hz) respectively clearly showed the formation of epoxide at C-11-12 position; the doublet of a doublet at 4.52 was due to proton geminal to the acetoxy group at C-3 position and the doublet of a doublet at 5.55 (J = 3, 10 Hz) integrated for one proton was assigned to the olefinic proton at C-15. The ^{13}C NMR signals (Table 1) also showed the presence of two additional doublets at 53.5 and 54.6 ppm which have been assigned to C-12 and C-11 carbons bearing the oxirane ring system. Thus from spectral analysis structure 4a has been assigned . The polar compound was analysed for $C_{30}H_{48}O_2$, M^+ 440, m.p. 285-6°C; IR 3500 (OH), 880 (epoxide), 820 (>C=CH-) cm^{-1}; it was established to be the alcohol 4 by preparation of its acetate (Py-Ac_2O) which was found to be identical with 4a . Similar reaction on α-amyrin acetate 3l also furnished the 11α,12α-epoxy-urs-14-en-3β-yl acetate 4c and its corresponding hydroxy derivative 4b .

Encouraged by this finding we repeated the reaction on acetyl oleanolic acid 3k which also furnished two compounds, the less polar was analysed for $C_{32}H_{48}O_5$, M^+ 512; m.p. 293-94°C, IR 1765 (γ-lactone), 1720, 1240 (-OAc), 880 (epoxide) cm^{-1}; it did not respond to TNM test for unsaturation. The spectral data (^1H and mass) have been found to be identical with 11α,12α-epoxy-oleanan-28$\rightarrow$13-olide-3β-yl acetate 5b reported earlier[4]. The ^{13}C NMR signals (Table 1) has been found to be assignable to the structure 5b . The more polar fraction was analysed for $C_{30}H_{46}O_4$ M^+ 470, m.p. 269-70°C, IR 3530 (OH), 1770 (γ-lactone), 880 (epoxide) cm^{-1}; its acetate derivative (Py-Ac_2O) has been found to be identical with 5b , thus the

alcohol is established to be 5.



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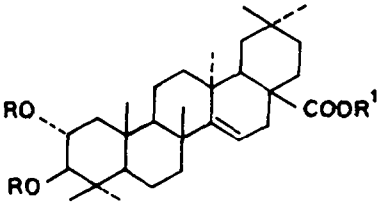
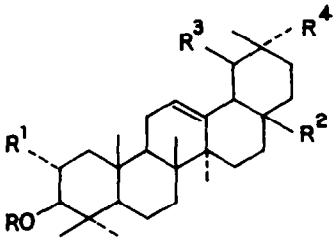
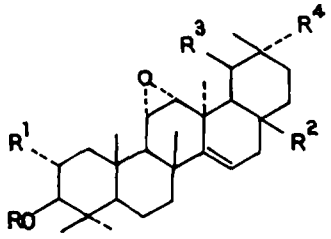


2, R = R¹ = H
2a, R = Ac, R¹ = Me

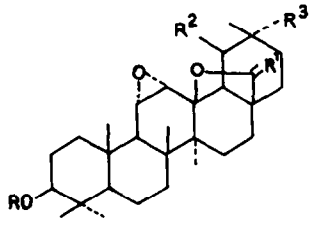


3, R=R¹=R³=H, R²=R⁴=Me
3a, R=Ac, R¹=R³=H, R²=R⁴=Me
3b, R=Ac, R¹=R³=H, R²=COOH, R⁴=Me
3c, R=R¹=R³=H, R²=CH_2OH, R⁴=Me
3d, R=Ac, R¹=R³=H, R²=COOMe, R⁴=Me
3e, R=Ac, R¹=R⁴=H, R²=COOMe, R³=Me
3f, R=R¹=R⁴=H, R²=CH_2OH, R³=Me
3g, R=R³=H, R¹=OH, R²=COOH, R⁴=Me
3h, R=R³=H, R¹=OH, R²=COOMe, R⁴=Me
3i, R=R³=H, R¹=OH, R²=CH_2OH, R⁴=Me
3j, R=Ac, R¹=OAc, R²=CH_2OAc, R³=H, R⁴=Me
3k, R=Ac, R¹=R³=H, R²=COOH, R⁴=Me
3l, R=Ac, R¹=R⁴=H, R²=R³=Me



4, R=R¹=R³=H, R²=R⁴=Me
4a, R=Ac, R¹=R³=H, R²=R⁴=Me
4b, R=R¹=R⁴=H, R²=R³=Me
4c, R=Ac, R¹=R⁴=H, R²=R³=Me
4d, R=R³=H, R¹=OAc, R²=CH_2OAc, R⁴=Me
4e, R=R³=H, R¹=OH, R²=CH_2OAc, R⁴=Me
4f, R¹=R³=H, R=Ac, R²=COOMe, R⁴=Me
4g, R¹=R⁴=H, R=Ac, R=Ac, R²=COOMe, R³=Me.

Next we ventured our attempt of preparing the epoxy esters 4f/4g from methyl esters 3d/3e respectively with the hope that the carbomethoxy group would not be involved during epoxidation with SeO_2-H_2O_2. But to our surprise methyl acetyl oleanolate 3d on treatment with the reagent formed lactones 5 and 5b. Oxidation of methyl acetyl ursolate 3e with SeO_2-H_2O_2 formed 11α,12α-epoxy-urs-28→13-olide-3β-yl acetate 5c and its corresponding alcohol 5d which were identified by spectral analysis. Similar reactions on erythrodiol 3c and uvaol 3f also formed 5 and 5d respectively, instead of forming the corresponding oxide 5a and 5e.



5, R=R²=H, R¹=O, R³=Me
5a, R=R²=H, R¹=H_2, R³=Me
5b, R=Ac, R¹=O, R²=H, R³=Me
5c, R=Ac, R¹=O, R²=Me, R³=H
5d, R=R³=H, R¹=O, R²=Me
5e, R=R³=H, R¹=H_2, R²=Me

As it is now evident that the epoxidation of C-11-12 position is accompanied by lactonization in cases where there is a functional group like COOH/COOMe/CH_2OH at the C-17 position of the oleanene/ursene derivatives, we thought of carrying out the reaction on compounds with a CH_2OAc functional group at C-17 position of oleanene/ursene derivatives, on the assumption that the carbonium ion formed at C-13 position during epoxidation would not be able to undergo electrophillic attack on the oxygen atom of the acetoxyl group. This assumption has been found to be true in the following case:

Methyl cratagolate 3h was reduced with LAH to olean-12-en-2α,3β,28-triol 3i which was acetylated to its triacetate 3j. The triacetate 3j was subjected to oxidation with SeO_2-H_2O_2 when two compounds were separated by CC. The first compound separated was $C_{34}H_{52}O_6$, m.p. 295-96°C, M^+ 556, IR 3400, 1750, 1720, 1280, 1240, 880, 820 cm^{-1}; TNM developed a yellow colouration. Thus from above, the presence of hydroxyl, two acetoxyl, an epoxy ring and a trisubstituted olefinic groups were suggested, which were proved by ^1H NMR data: seven tertiary methyls appeared as singlets in the region δ 0.77 to 1.19, two acetoxy methyls at 2.05 and 2.08, the two oxirane protons at C-12 and C-11 as doublet and triplet at 2.80 and 3.13 respectively; the axial proton geminal to the hydroxyl group at C-3 appeared as a doublet at 3.22; the two protons that appeared as ABq (J = 10 Hz) centered at 3.71 were assigned to the methylene protons bearing acetoxyl group at C-28; the doublet of a triplet (J = 2 and 10 Hz) at 5.03 was due to the proton at C-2 with an equatorial acetoxyl group; the olefinic proton at C-15 appeared as a dd (J = 2 and 10 Hz) centered at 5.47 ppm. Thus from ^1H NMR, the diacetate has been established as 11α,12α-epoxy-taraxer-14-en-3β-ol-2α,28-yl diacetate 4d .

The second compound was analysed for $C_{32}H_{50}O_5$, M^+ 514, m.p. 266-67°C; IR: 3200-3600(br, OH), 1720, 1250 (-OAc), 880 (epoxy), 820 (>C=CH-) cm^{-1}; ^1H NMR showed the presence of seven tertiary methyls between δ 0.87 to 1.16, an acetoxy methyl at 2.04, the doublet (J= 5 Hz) at 2.80, a triplet (J = 5 Hz) at 3.13 were due to one proton each attached to C-12 and C-11 with oxirane ring, the doublet (J=10 Hz) at 3.03 was due to axial proton geminal to the hydroxyl group at C-3, the two protons that appeared as ABq centered at 3.72 (J = 14 Hz) were due to methylene protons at C-28 geminal to acetoxyl group, a proton that existed as a doublet of a triplet (J = 4 and 12 Hz) at 3.79 was due to the axial proton at C-2 bearing a hydroxyl group and the C-15 olefinic proton appeared as usual at 5.46 ppm. Thus from spectral data the compound has been designated as 11α,12α-epoxy-taraxer-14-en-2α,3β-diol-28-yl acetate 4e. ^{13}C NMR signals of the epoxides 4a, 4d, 4e and 5c have been assigned satisfactorily as depicted in Table - 1.

Thus from the above findings it may be concluded that (i) the reaction is analogous to photochemical oxidation[3,4] in the formation of 11,12-epoxide of oleanene and ursene skeletons,(ii) the C-17 methyl esters also generate lactone rings as

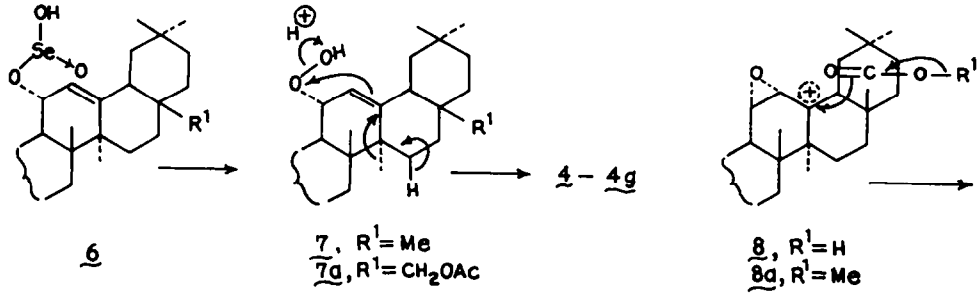
well as the $-CH_2OH$ group, (iii) the primary acetate at C-28 position remains intact whereas the secondary acetate at C-3 undergoes hydrolysis during the reaction and (iv) the acetate group allows smooth isomerization of the double bond from C-12(13) position to C-14(15) position.

Table 1

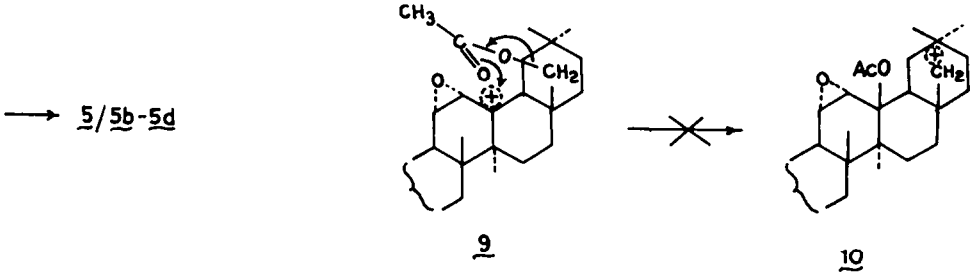
^{13}C NMR shifts assignments (δ) of 4a, 4d, 4e, and 5c ($CDCl_3$ as solvent with internal TMS) compared with those of 3a and 2a.

Carbon	3a[7]	4a	5c	2a[2]	4d	4e
1	38.2	38.2 t	37.6 t	43.2	43.3 t	46.3 t
2	23.6	23.2 t	22.7 t	70.0	72.6 d	68.7 d
3	80.7	80.7 d	80.4 d	80.6	80.8 d	83.9 d
4	37.6	37.6 s	37.8 s	39.3	39.0 s	39.0 s
5	55.3	58.2 s	56.2 s	55.2	57.9 s	57.9 s
6	18.3	18.8 t	17.5 t	18.6	18.7 t	18.8 t
7	32.6	33.1 t	31.4 t	35.5	32.7 t	32.7 t
8	39.7	38.9 s	41.4 s	38.9	38.7 s	38.9 s
9	47.6	51.8 d	51.3 d	49.1	51.6 d	51.7 d
10	36.8	36.5 s	36.3 s	38.9	37.7 s	37.8 s
11	23.4	54.6 d	54.6 d	17.4	54.5 d	54.6 d
12	121.5	53.5 d	54.5 d	31.7	53.5 d	53.5 d
13	144.9	37.6 s	89.0 s	37.3	37.4 s	37.4 s
14	41.7	157.1 s	41.3 s	160.1	157.6 s	157.7 s
15	28.3	118.9 d	26.6 t	116.8	118.1 d	118.0 d
16	26.2	37.9 t	23.2 t	31.0	31.3 t	31.3 t
17	32.5	35.4 s	45.1 s	51.3	39.0 s	39.1 s
18	47.2	48.1 d	60.6 d	41.9	44.0 d	44.0 d
19	46.8	40.2 t	40.2 d	40.8	40.1 t	40.2 t
20	31.1	28.7 s	37.5 d	29.2	28.5 s	28.5 s
21	34.8	35.2 t	30.5 t	33.8	35.6 t	35.6 t
22	37.1	36.5 t	31.3 t	32.1	28.5 t	28.5 t
23	28.1	27.9 s	27.7 q	29.7	28.3 q	28.4 q
24	16.8	17.0 s	17.2 q	17.5	17.9 q	18.1 q
25	15.7	16.5 q	16.3 q	16.5	16.5 q	16.6 q
26	16.8	29.9 q	16.2 q	18.6	29.7 q	29.7 q
27	26.0	30.2 q	19.5 q	26.1	27.1 q	27.2 q
28	27.0	27.0 q	179.2 s	178.3	65.7 t	65.7 t
29	33.4	33.6 q	17.3 q	33.3	33.6 q	33.6 q
30	23.6	19.5 q	21.3 q	22.4	20.0 q	20.0 q
2 $-OCOCH_3$				20.7	21.3 q	
2 $-OCOCH_3$				170.6	171.0 s	
3 $-OCOCH_3$		21.3 q	21.3 q	21.0		
3 $-OCOCH_3$		170.8 s	170.9 s	170.3		
28 $-OCOCH_3$					21.0 q	21.0 q
28 $-OCOCH_3$					171.0 s	171.5 s

Discussion of the reaction mechanism: It is evident from the results discussed above that selenium dioxide initially oxidises the allylic C-11 methylene to the intermediate organoselenic acid 6 which forms the hydroperexide 7 in all cases of compounds of oleanene and ursene derivatives having double bonds at C-12(13) position. The hydroperexide 7 would undergo in presence of acid (selenic acid) a concerted elemination of a molecule of water with migration of double bond to C-14(15) position or a carbonium ion may be formed at C-13 position prior to the formation of double bond at C-14(15) position. In the case of oleanolic acid/ methyl ester and ursolic acid/methyl ester the suitably situated carbonyl group at C-28 position acts as a nucleophile on the intermediate carbonium ion 8/8a forming lactone derivatives in preference to the taraxerene derivatives. On the other



6 7, R^1=Me; 7a, R^1=CH_2OAc 8, R^1=H; 8a, R^1=Me



9 10

hand, the acetyl derivative at C-28 (or C-17-CH_2OAc) 9 which also carries a carbonyl group would also be expected to give a product formed from analogous carbonium ion 9 to yield a rearranged intermediate 10. As no such rearranged product was obtained it may be definitely due to non-proximity of the acetate carbonyl group from the site of the carbonium ion. Thus the triacetate 3j furnishes the taraxerene derivatives 4d and 4e where the functional group at C-28 is not involved in the reaction. The formation of lactones 5 and 5b and 5c and 5d from the methyl esters of oleanolic acid 3d and ursolic acid 3e respectively must proceed via the intermediate 8 setting free the methyl carbonium ion. We have encountered such lactonization of methyl esters during bromination of methyl esters of triterpenoid C-17 carboxylic acids[8].

EXPERIMENTAL

M.ps are uncorrected. Petroleum ether (PE) used had b.p. 60-80°C. ^1H NMR spectra (internal TMS):in $CDCl_3$, Bruker WH-400; ^{13}C NMR spectra (off resonance, internal TMS): in $CDCl_3$, Bruker WH-270, with DEPT program; IR spectra: Beckman IR-20 (Nujol); MS: Varian Mat 711 (70eV). Column chromatography was performed over silica gel. All organic solns after work-up were dried over Na_2SO_4.

General oxidation procedure: A soln of triterpenoid (0.5 g) in t-BuOH (100 ml) was refluxed with SeO_2 (0.2 g) and H_2O_2 (3 ml) for 60 h. The completion of the reaction was indicated by deposition of black selenium metal. After recovery of the solvent by distillation, the residue was extracted with ether and washed with water. The solvent was removed by distillation and the residue (0.5 g) chromatographed. Elution of the chromatogram with solvent mixtures of different polarities was performed and the residue obtained by removal of solvent mixture of same polarity and same Rf value in TLC were combined together and crystallized.

Oxidation of β-amyrin acetate (3a): 3a (0.5 g) was oxidized with SeO_2 (0.2 g) and H_2O_2 (3 ml) in t-BuOH and worked-up as detailed above. The chromatogram on elution with PE-benzene (4:1) furnished 4a (0.3 g) which on crystallization with $CHCl_3$-MeOH furnished 4a of m.p. 307-08°C; m/z: 482 (M^+), 468, 390, 343, 283, 259, 231, 205, 189, 175, 135, 108 (base), 95, 81, 69; ^1H NMR: δ 0.82, 0.86, 0.87, 0.90, 0.97, 1.00, 1.08, 1.10 (8s, 8 Me), 2.05 (s, -OAc), 2.79 + 2.80 (d, 1H, J = 5 Hz), 3.10 + 3.11 + 3.12 (t, 1H, J = 5 Hz), 4.52 (dd, 1H, H-C-3-OAc), 5.55 (dd, 1H, J = 3, 10 HZ) (Found: C, 79.40; H, 10.42 Calcd for $C_{32}H_{50}O_3$: C, 79.62; H, 10.44%). Further elution with PE-benzene (2:3)eluted 4 (0.25 g) that crystallised from $CHCl_3$-MeOH, m.p. 284-85°C, m/z: 440 (M^+), 425, 407, 389, 300, 257, 203, 189, 150, 133, 108 (base); acetylation with Py-Ac_2O gave a compound identical (m.m.p., co-IR and co-TLC) with 4a.

Oxidation of α-amyrin acetate (3e): A mixture of 3e (0.5 g), SeO_2 (0.2 g) and H_2O_2 (3 ml) in t-BuOH (100 ml) was refluxed for 60 h. after usual work-up the residue (o.5 g) was chromatographed. PE eluted a solid (0.2 g), m.p. 224-25°C identical (m.m.p. and co-IR) with starting material 3e. Further elution with PE-benzene (4:1) furnished a solid (0.2 g) which on crystallisation from $CHCl_3$-MeOH furnished 5c of m.p. 213-14°C, (Lit[3] m.p. 214-15°C), m/z: 482 (M^+), 468, 408, 390, 343, 283, 259, 231, 205, 189, 108 (base). Further elution with PE-benzene (2:3) afforded (0.1 g) 4b, m.p. 245-46°C, (Lit[3] m.p. 249-50°C); IR 3450 (OH), 880 (epoxide), 820 (>C=CH-) cm^{-1}; TNM: yellow colour; m/z: 440 (M^+), 425, 407, 389, 300, 203, 189, 108 (base); acetylation with Py-Ac_2O gave 4c (identified by m.m.p. and co-TLC).

Oxidation of acetyl oleanolic acid (3k): The residue (0.45 g) obtained after oxidation of 3k (0.5 g) with SeO_2 (0.2g) and H_2O_2 (3ml) in t-BuOH (100 ml) and usual work-up (see general procedure) was chromatographed. Elution with PE-benzene (3:2) furnished 5b (0.3 g) was crystallised from $CHCl_3$-MeOH, m.p. 293-94°C (Lit.[4] 300 C), IR 1765 (γ-lactone), 1720, 1240 (acetate), 880 (epoxide) cm^{-1}; m/z: 512 (M^+), 496, 452, 436, 315, 300, 277, 263, 218, 205, 189, 43 (base); ^1H NMR: δ 0.87, 0.92, 1.00, 1.05, 1.07, 1.10, 1.11 (7s, 7 Me), 2.06 (s, -OAc), 2.98 (d, 1H, 4.5 Hz), 3.13 (t, 1H, J = 5 Hz), 4.53 (m, 1H, H-C-3-OAc). Further elution with PE-benzene (1:9) afforded 5 (0.1 g) crystallized from $CHCl_3$-MeOH, m.p. 269-70°C (Lit.[4] m.p. 269-71.5°C), IR 3530, 1770, 880 cm^{-1}; m/z: 470 (M^+), 455, 452, 207, 189, 95 (base); Ac_2O-Py gave an acetate identical with 5b (m.m.p. and co-IR).

Oxidation of methyl acetyloleanolate 3d: The residue obtained after oxidation (general procedure) of 3d was chromatographed. PE-benzene (3:2) eluted a solid that crystallised from $CHCl_3$-MeOH, m.p. 292-93°C; IR 1765, 1720, 1240, 880 cm^{-1} which was found identical (m.m.p. and co-IR) with 5b. Further elution with PE-benzene (1:9) furnished solid, m.p. 269-70°C, IR 3530, 1770, 880 cm^{-1} that was found identical with 5.

Oxidation of methyl acetylursolate 3e: The residue obtained after oxidation of 3e (see general procedure) was chromatographed. Elution of the column with PE-benzene (3:2) furnished 5c (0.3 g) crystallised from $CHCl_3$-MeOH, m.p. 281-82°C, IR 1775, 1740, 1250, 885 cm^{-1}; m/z: 512 (M^+), 497, 484, 468, 452, 316, 300, 278, 277, 263, 249, 231, 217, 205, 204, 203, 189 (base); ^1H NMR: δ 0.87, 0.88, 1.06, 1.08, 1.19 (5s, 5-Me), 0.90 and 1.22 (2d, 2-Me, J = 6.5 Hz), 2.00 (s, -Ac), 2.94 (d, 1H, J = 4 Hz, -C-12-H), 3.18 (dd, 1H, J = 3.5 Hz, -O-C-11-H, 4.53 (m, 1H, H-C-3-OAc. Further elution with benzene gave solid 5d (0.1 g), m.p. 295-96°C; IR 3300, 1775, 885 cm^{-1}; acetylation with Ac_2O-Py afforded an acetate identical with 5c.

Oxidation of erythrodiol 3c: On CC of the residue obtained on oxidation of 3c (see general procedure) benzene eluted a single compound 5, m.p. 266-67°C; IR 3530, 1770, 880 cm^{-1}; Ac_2O-Py furnished an acetate identical (m.m.p. and co-IR) with 5b.

Oxidation of Uvaol 3f: The residue of the oxidation product (see general procedure) of 3f on CC afforded a solid 5d on elution with benzene, m.p. 292-93°C IR 3300, 1770, 885 cm^{-1}; Ac_2O-Py furnished an acetate identical with 5c.

Preparation 3j from methyl cratagolate 3h and oxidation of 3j: A soln of 3h (1 g) dissolved in dioxan (150 ml) was refluxed with LAH for 4 h. Excess LAH was destroyed with a saturated soln of Na_2SO_4 and the product was extracted with a large amount of ether. The solvent was removed and the crude triol 3i (0.8 g), IR 3300-3600 cm^{-1} was acetylated with Ac_2O-Py. The triacetate 3j (0.7 g), m.p. 179-80°C, IR 1720-1750, 1240-1250, 820 cm^{-1} was oxidised with SeO_2 and H_2O_2 as detailed in the general procedure. Elution of the chromatogram with PE-benzene (1:1) furnished 4d (0.3 g) crystallised from $CHCl_3$-MeOH, m.p. 295-96°C, IR 3400, 1750, 1720, 1280, 1240, 880, 820, cm^{-1}; m/z: 556 (M^+), 496, 478, 454, 436, 421, 405, 403, 349, 256, 229, 202, 187, 134, 120, 107, 43 (base); ^1H NMR: δ 0.77, 0.81, 0.87, 0.93, 0.96, 0.98, 1.19 (7s, 7 Me), 2.05, 2.08 (2s, 2x -OAc), 2.80 (d, 1H, J = 5 Hz 12-HC-O-), 3.13 (t, 1H, J = 5 Hz, 11-HC-O-), 3.22 (d, 1H, J = 10 Hz, 3-HC-OH), 3.7 (ABq, J = 15 Hz, 28-CH_2-OAc), 5.03 (d of t, 1H, 2-CH-OAc, J = 5, 10 Hz), 5.47 (dd, 1H, J = 2, 10 Hz) (Found: C, 73.20; H, 9.22. Calc for $C_{34}H_{52}O_6$: C, 73.35; H, 9.41 %).

Further elution with benzene-EtOAc (4:1) afforded 4e (0.2 g), crystallised from $CHCl_3$-MeOH, m.p. 266-67°C, IR 3200-3600 (OH), 1720, 1250 (OAc), 880 (C=CH), cm^{-1}; m/z : 514 (M^+), 472, 454 (base), 439, 421, 317, 255, 230, 201, 187, 135, 108, 69, 55; ^1H NMR: δ 0.87 (s, 2xMe), 2.04 (s, OAc), 2.80(d, 1H, J = 5 Hz, -O-C-12 H), 3.03 (d, 1H, J = 10 Hz, HO-C-3 H), 3.13 (t, 1H, J = 5 Hz, -O-C-11 H), 3.72 (ABq, 2H, 28-CH_2-OAc, J = 14 Hz), 3.79 (dt, 1H, J = 4, 12 Hz, HO-C-2 H) and 5.46 (dd, 1H, C=C-15H) ppm).(Found: C, 74.30; H, 9.65. Calc for $C_{32}H_{50}O_5$: C, 74.67; H, 9.79%).

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