Acta Chemica Scandinavica B 31 (1977) 231—234

Triterpenes. BF_3 Catalysed Rearrangement of 3β,28-Diacetoxy-18(α or β),19(α or β)-epoxylupane. A Novel Route to Baccharane Derivatives

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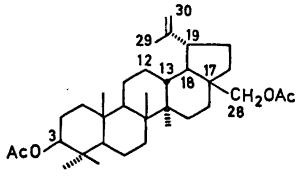
Both the 3β,28-diacetoxy-18α,19α-epoxylupane (*4a*) and the corresponding 18β,19β-isomer (*3a*) gave 3β,28-diacetoxy-18,19-secolup-13(18)-en-19-one (*5a*) on treatment with BF_3-etherate. 18β,19β-Epoxy isomer (*3a*) gave, in addition, 3β,28-diacetoxy-lupa-12,18-diene (*6*). The baccharane derivative *5a* was also synthesized *via* another route. The stereochemistry of the isomeric 18,19-epoxy-lupane derivatives *3* and 4 is discussed.



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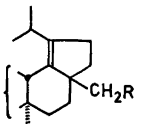

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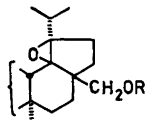
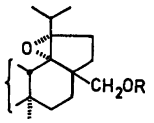
b R=H



3a R=Ac
b R=H
c R=$COCF_3$



4a R=Ac
b R=H
c R=$COCF_3$

The rather rare tetracyclic triterpenes with a six-membered D-ring include the baccharane series, the parent hydrocarbon of which has been shown to be 18,19-secolupane.[1,2] In this communication we report a novel route to a polyfunctional baccharane derivative starting from lupane derivatives. Nomenclature based on the lupane skeleton is applied throughout.

Betulin diacetate (*1*) can be transformed to its Δ^{18}-isomer (*2a*), either through successive dehydrogenation and hydrogenation steps,[3,4] or *via* acid catalysed double-bond migration.[5] On epoxidation of *2a*, both *m*-chloroperbenzoic acid and performic acid give as the main product the same epoxide isomer; only a few percent of the other epoxide isomer was formed. Treatment of *2a* with ozone yields only the epoxide obtained as a minor product from the peracid epoxidation. Epoxidation of triterpenes with peracids usually occurs by attack from the α-side, on account of steric hindrance due to methyl groups on the β-side. When considering oxidative attack of the double bond in compound *2a*, it is difficult to conclude from Dreiding models, however, which side is the less hindered. The ^1H NMR spectra of the epoxides show different chemical shifts for the protons at the acetoxy carbon C-28. In the epoxide obtained with peracids the C-28 protons have higher δ-values (in *3a* doublets at δ 3.80 and 4.50) and are magnetically more different than those of the epoxide produced by ozone (in *4a* doublets at δ 3.74 and 4.20). This difference can be explained by hindered rotation about the C-17 – C-28 axis and the influence of the magnetic anisotropy of a β-epoxy oxygen, thus indicating the β-epoxy structure *3* for the main epoxide produced by peracid and the α-epoxy structure *4* for the epoxide obtained by treatment with ozone.

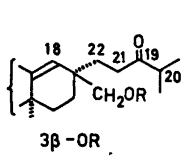
Further information was sought from the NMR shift reagent spectra of epoxides *3c* and *4c*, where hydroxy groups are protected as

trifluoroacetates. The $Eu(DPM)_3$ or $Eu(fod)_3$ induced shifts in the spectrum of the presumed β-epoxide agree with the β-structure *3c* but they do not strictly exclude the possibility of the α-structure *4c*. As to the presumed α-epoxide *4c*, the induced shifts are so small that it is evident that Eu-reagent does not form a dipolar complex with the epoxy oxygen thus preventing clear deductions.

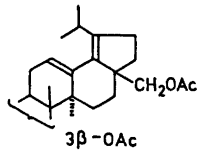
Both epoxides are highly resistant toward anionic species (HO^-, H^-, several R^-, *etc.*) and attempted determination of the stereostructure of the epoxides with chemical methods based on these reagents failed.

Results from X-ray crystallographic measurements,[6] however, confirmed the assumption that the epoxide obtained with peracids has β-epoxy structure *3* and thus the epoxide produced by ozone the α-epoxy structure *4*.

The reason for different stereochemical outcome of ozone and peracid epoxidation is not clear. Any directive effect of C-28 oxygen function is excluded as the corresponding Δ^{18}-lupane derivative *2b*, lacking C-28 oxygen, similarly gives different epoxides as main products when treated with ozone [8] and peracid.[7] The different stereochemistry may be due to the fact that ozone is diradical [8] and peracid ionic in character.



5a R = Ac
b R = $COCF_3$



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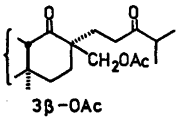

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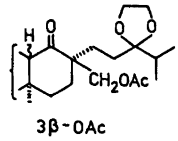

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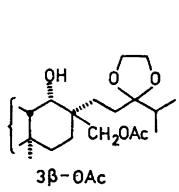
Both epoxides *3a* and *4a* rearrange to the baccharane derivative *5a* on treatment with BF_3-etherate in benzene, and the β-epoxide *3a* gives, in addition, as a minor product, the conjugated diene *6*. The double-bond structure of the latter *6* is confirmed by the formation of Diels-Alder adduct *10*. *5a* is reduced to the methylene compound *12 via* formation of the thioacetal *11* followed by Raney-Ni desulfurisation. The $Eu(DPM)_3$ induced shifts to lower field in ^1H NMR spectrum of the trifluoroacetate derivative *5b* are in the expected order: protons at C-22 (2 H, tr, $J = 8$ Hz) $\simeq$ at C-20 (1 H, m) > at C-21 (2 H, tr, $J = 8$ Hz) > at C-29 and C-30 (6 H, d, $J = 7$ Hz).



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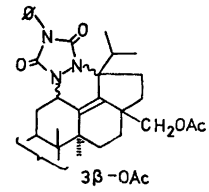

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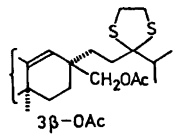

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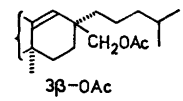

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The baccharane derivative *5a* was also synthetised *via* an independent route. Oxidation of the double bond in *2a* with $RuO_2 - NaIO_4$ results in the diketone *7*, the side chain carbonyl of which is selectively protected as an ethylene acetal to give the ketoacetal *8*. $NaBH_4$ reduction of *8* gave a mixture of compounds, among them the hydroxy acetal *9*. The 13βH,-18αOH-structure follows from the 4 Hz half-height width of the broad singlet of 18βH at δ 3.33. Dehydration of hydroxy acetal *9* in HMPT and subsequent regeneration of the side chain carbonyl at C-19 produces the baccharane derivative *5a*, identical (TLC, m.p., $[\alpha]_D$, IR, ^1H NMR, and MS) with the compound *5a* obtained from the BF_3-catalysed rearrangement of epoxides *3a* and *4a*.

EXPERIMENTAL

Melting points are uncorrected. ^1H NMR spectra were recorded on a Jeol JNM – PMX 60 spectrometer, the spectra with shift reagent in CS_2 and others in $CDCl_3$ (unless stated otherwise) and related to internal TMS, the IR

spectra on a Perkin-Elmer 125 spectrometer using KBr pellets, mass spectra on a Perkin-Elmer 270 B mass spectrometer, specific rotations in $CHCl_3$ solution on a Perkin-Elmer 141 polarimeter, and elemental analyses with a F & M 185 CHN analyser.

Derivatives of 18β,19β-epoxylupane 3a, 3b *and* 3c. (a) 3β,28-Diacetoxy-lup-18-ene [3,5] (*2a*) was epoxidised with *m*-chloroperbenzoic acid, as described earlier,[5] to 3β,28-diacetoxy-18β,19β-epoxylupane (*3a*) m.p. 222–223 °C (EtOH), $[\alpha]_D$ +25° (*c* 1.0). (Ref. 5, m.p. 222 °C, $[\alpha]_D$ +25.5°). δ 4.50 (1 H, m, 3αH), 4.50 and 3.80 (à 1 H, d, 11 Hz, AB system of C-28 protons). X-Ray crystallographic data will be published [6] later. A small amount (about 5 % from *3a*) of 3β,28-diacetoxy-18α,19α-epoxylupane (*4a*), characterised below, was also obtained.

(b) 3β,28-Diacetoxy-lup-18-ene (*2a*) (0.2 g), CH_2Cl_2 (3 ml), EtOAc (5 ml), HCO_2H (2 ml), and 30 % H_2O_2 (1 ml) were stirred for 1 h at room temperature. The mixture was washed with water, $NaHCO_3$-solution, dried, and the solvent evaporated. Crystallisation from Et_2O–MeOH gave 3β,28-diacetoxy-18β,19β-epoxylupane (*3a*) (0.17 g) with physical constants as above.

Hydrolysis of *3a* (1.0 g) with KOH (1.0 g) in boiling EtOH (30 ml) for 1 h, work up, and chromatography on silica plates ($CHCl_3$-EtOAc 9:1 eluent), and crystallisation from EtOH gave 3β,28-dihydroxy-18β,19β-epoxylupane (*3b*) (0.75 g), m.p. 245 °C, $[\alpha]_D$ +29° (*c* 1.04). Reacetylation in boiling Ac_2O gave the starting epoxide *3a*.

3β,28-Dihydroxy-18β,19β-epoxylupane (*3b*) (1.0 g) in CH_2Cl_2 (20 ml) and $(CF_3CO)_2O$ (1.0 ml) was allowed to stand for 15 min at room temperature. Most of the solvent was evaporated under reduced pressure. The residue crystallised from EtOH resulting in 3β,28-di(trifluoroacetoxy)-18β,19β-epoxylupane (*3c*) (0.5 g), m.p. 124 °C, $[\alpha]_D$ +23° (*c* 1.28); M+ 650; ν 1775, 1225, 1160, 950, 870, 775, 730, 655; δ 4.58 (1 H, m, 3αH), 4.46 and 4.15 (à 1 H, d, 11 Hz, AB system of C-28 protons), 1.05 and 1.00 (à 3 H, d, 7 Hz, methyls of isopropyl group), 1.12, 1.06, 0.94 (à 3 H, s), 0.86 (6 H, s).

Derivatives of 18α,19α-epoxylupane 4a, 4b *and* 4c. 3β,28-Diacetoxy-lup-18-ene (*2a*) (1.0 g) in EtOAc–CH_2Cl_2 (1:1, 50 ml) was ozonised at −75 °C until the solution remained faintly blue. Excess ozone was driven off with a stream of nitrogen and the solution allowed to reach room temperature. Evaporation of the solvent, chromatography on silica plates ($CHCl_3$ eluent), and crystallisation from EtOH gave 3β,28-, diacetoxy-18α,19α-epoxylupane (*4a*) (0.7 g), m.p. 210 °C, $[\alpha]_D$ +36.6° (*c* 1.02); M+ 542; δ 4.44 (1 H, m, 3αH), 4.20 and 3.74 (à 1 H, d, 11 Hz, AB system of C-28 protons), 2.02 and 1.98 (à 3 H, s, acetyl groups), 1.10–0.85 (group of 7 Me). Anal. $C_{34}H_{54}O_5$: C, H.

Hydrolysis of *4a* (1.0 g) as the corresponding β-epoxide *3a* above gave 3β,28-dihydroxy-18α,19α-epoxylupane (*4b*) (0.5 g) crystallised from Et_2O–MeOH m.p. 214 °C, $[\alpha]_D$ +22.6° (*c* 1.0). Reacetylation in boiling Ac_2O gave the starting diacetate *4a*.

3β,28-Di(trifluoroacetyl)-18α,19α-epoxylupane (*4c*) was prepared as the corresponding β-epoxy derivative *3c* above. Crystallisation from MeOH–Et_2O gave m.p. 225 °C, $[\alpha]_D$ +30° (*c* 1.0); M+ 650; ν 1770, 1210, 1155, 920, 875, 775, 730; δ 4.74 (1 H, m, 3αH), 4.59 and 4.05 (à 1 H, d 11 Hz, AB system of C-28 protons), 1.15–0.89 (group of 7 Me).

BF_3-catalysed rearrangement of 3β,28-diacetoxy-18β,19β-epoxylupane (3a) *and trifluoroacetate* 3c. 3β,28-Diacetoxy-18β,19β-epoxylupane (*3a*) (0.5 g) in dry benzene (30 ml) and BF_3-etherate (1 ml) was allowed to stand for 20 min at room temperature. The reaction was interrupted by addition of methanol (5 ml) and the mixture washed with water and $NaHCO_3$-solution, dried and the solvent evaporated. Chromatography on silica plates ($CHCl_3$–light petroleum, b.p. 60–80 °C, 3:1 eluent) gave two compounds. The less polar 3β,28-diacetoxy-lupa-12,18-diene (*6*) crystallised from EtOH (30 mg), m.p. 140 °C, $[\alpha]_D$ +220° (*c* 1.03). (Ref. 4, m.p. 140–143 °C, $[\alpha]_D$ +219 °.) λ_{max} (EtOH) 234 nm (ε 7600); M+ 524; ν 3020, 1730, 1240; δ (CCl_4) 5.35 (1 H, br. tr, 3 Hz, C-12 vinyl proton), 4.45 (1 H, m, 3αH), 3.28 (2 H, AB quart, 11 Hz, C-28 protons), 1.05–0.89 (group of 7 Me).

The more polar 3β,28-diacetoxy-18,19-secolup-13(18)-en-19-one (*5a*) crystallised from EtOH (0.35 g), m.p. 115 °C, $[\alpha]_D$ −34.8° (*c* 1.15); M+ 542; ν 1730, 1710, 1240; δ (CCl_4) 4.93 (1 H, br. s, C-18 vinyl proton), 4.40 (1 H, m, 3αH), 3.79 (2 H, AB quart, 11 Hz, C-28 protons), 2.00 and 1.96 (à 3 H, s, acetyl methyls), 1.12 (6 H, s), 1.00–0.80 (group of 5 Me). Anal. $C_{34}H_{54}O_5$: C, H.

Similar treatment of 3β,28-di(trifluoroacetoxy)-18β,19β-epoxylupane (*3c*) (1.0 g) with BF_3-etherate gave 3β,28-di(trifluoroacetoxy)-18,19-secolup-13(18)-en-19-one (*5b*) (0.7 g), m.p. 125 °C (from EtOH), $[\alpha]_D$ −24.8° (*c* 1.25); ν 1775, 1710, 1220, 1160.

BF_3-catalysed rearrangement of 3β,28-diacetoxy-18α,19α-epoxylupane (4a). The treatment with BF_3-etherate of 3β,28-diacetoxy-18α19α-epoxylupane (*4a*) as the β-epoxide *3a* above resulted in quantitatively 3β,28-diacetoxy-18,19-secolup-13(18)-en-19-one (*5a*) identical with the compound *5a* obtained from the β-epoxide *3a*.

Diels-Alder adduct (10). 3β,28-Diacetoxy-lupa-12,18-diene (*6*) (0.1 g) and 4-phenyl-1,2,4-triazoline-3,5-dione (50 mg) in dry benzene (10 ml) were allowed to stand overnight. The solvent was evaporated and the residue chromatographed on silica plates ($CHCl_3$ eluent). Crystallisation from EtOH gave adduct *10* (60 mg), m.p. 160 °C decomp., $[\alpha]_D$ +162° (*c* 0.56); ν 1730, 1690; δ (CCl_4) 7.40 (5 H, m, phenyl), 4.65 (2 H, m, 3αH and C-12 proton), 3.95 (2 H, br. s, C-28 protons), 2.04 and 2.00

(à 3 H, s, acetyl methyls), 1.12–0.85 (group of 7 Me). Anal. $C_{40}H_{57}N_3O_6$: C, H, N.

Reduction of 3β,28-diacetoxy-18,19-secolup-13(18)-en-19-one (5a). 3β,28-Diacetoxy-18-19-secolup-13(18)-en-19-one (*5a*) (0.5 g), ethane-1,2-dithiol (2.0 g), and BF_3-etherate (0.3 ml) was allowed to stand for 15 min at room temperature, methanol (15 ml) was added and the precipitated thioacetal *11* (0.3 g) m.p. 160 °C, $[\alpha]_D$ −29° (*c* 1.0), refluxed with Raney-Ni in EtOH for 1 h. The Raney-Ni was filtered off, the solvent evaporated and the residue chromatographed on silica plates ($CHCl_3$-light petroleum, b.p. 60–80 °C, 3:1 eluent). Crystallisation from Et_2O-MeOH gave 3β,28-diacetoxy-18,19-secolup-13(18)-ene (*12*) (0.16 g), m.p. 90 °C, $[\alpha]_D$ −40° (*c* 1.47); *ν* 3020, 1735, 1265, 1245, 756; *δ* 5.00 (1 H, br. s, C-18 vinyl proton), 4.50 (1 H, m, 3αH), 3.88 (2 H, AB quart, 11 Hz, C-28 protons), 2.05 (6 H, s, acetyl methyls), 0.95–0.80 (group of 7 Me). Anal. $C_{34}H_{56}O_4$: C, H.

3β,28-Diacetoxy-18,19-secolupan-18,19-dione (7). 3β,28-Diacetoxy-lup-18-ene (*2a*) (1.0 g) in CCl_4 (30 ml), $NaIO_4$ (1.0 g) in water (20 ml), and a catalytic amount of RuO_2 was shaken vigorously for 20 h. The water layer was removed and the CCl_4 phase washed with water, added MeOH (1 ml), dried, and chromatographed on a short silica column ($CHCl_3$-light petroleum, b.p. 60–80 °C, 2:1 eluent). Crystallisation from EtOH gave 3β,28-diacetoxy-18,19-secolupan-18,19-dione (*7*) (0.8 g), m.p. 166 °C, $[\alpha]_D$ +38.7° (*c* 1.2); M+ 588; *ν* 1740, 1720, 1705, 1250; *δ* 4.45 (1 H, m, 3αH), 4.44 and 3,95 (à 1 H, d, 11 Hz, AB system of C-28 protons), 3.9–2.2 (4 H, m), 2.03 (6 H, s, acetyl methyls), 1.15–0.8 (group of 7 Me). Anal. $C_{34}H_{54}O_6$: C, H.

3β,28-Diacetoxy-18,19-secolupan-18,19-dione 19-ethylene acetal (8). 3β,28-Diacetoxy-18,19-secolupan-18,19-dione (*7*) (1.0 g), ethylene glycol (5 ml), *p*-toluenesulfonic acid (0.1 g), and benzene (50 ml) were refluxed for 4 h and water removed from the condensed azeotrope. The mixture was washed with $NaHCO_3$-solution, dried, and the solvent evaporated. Crystallisation from Et_2O-MeOH gave 3β,28-diacetoxy-18,19-secolupan-18,19-dione 19-ethylene acetal (*8*) (0.6 g), m.p. 192 °C, $[\alpha]_D$ +43° (*c* 1.0); M+ 602; *δ* 4.43 (1 H, m, 3αH), 4.42 and 3.90 (à 1 H, d, 11 Hz, AB system of C-28 protons), 3.87 (4 H, s, ethylene acetal protons). Anal. $C_{36}H_{58}O_7$: C, H.

3β,28-Diacetoxy-18α-hydroxy-18,19-secolupan-19-one ethylene acetal (9). 3β,28-Diacetoxy-18,19-secolupan-18,19-dione 19-ethylene acetal (*8*) (1.0 g) in EtOH (50 ml) and $NaBH_4$ (0.5 g) was stirred for 1 h. Benzene (50 ml) was added and the solution washed with water, dried, and the solvent evaporated. The reaction mixture consisting of several compounds was chromatographed on silica plates ($CHCl_3$ + 2 % EtOAc eluent). The least polar main component 3β,28-diacetoxy-18α-hydroxy-18, 19-secolupan-19-one ethylene acetal (*9*) crystallised from EtOH (0.2 g), m.p. 163 °C, $[\alpha]_D$ +10.8° (*c* 1.02); M+ absent, M+ − 43 561; *ν* 3500, 1730, 1240; *δ* 4.40 (1 H, m, 3αH), 4.1–3.7 (6 H, m, C-28 and 19-ethylene acetal protons), 3.33 (1 H, br. s, half-height width 4 Hz, C-18βH). Anal. $C_{36}H_{60}O_7$: C, H.

3β,28-Diacetoxy-18,19-secolup-13(18)-en-19-one (5a) via dehydration. 3β,28-Diacetoxy-18α-hydroxy-18,19-secolupan-19-one ethylene acetal (*9*) (0.2 g) in hexamethylphosphoric triamide (3 ml) was heated for 10 min at 240 °C. To the cooled mixture was added benzene (30 ml), washed with water and 1 M H_2SO_4. Benzene was evaporated and the partially hydrolysed acetal was dissolved in acetone and 1 M H_2SO_4 added. The mixture was stirred for 2 h, worked up, and chromatographed on silica plates ($CHCl_3$ eluent). Crystallisation from Et_2O-MeOH gave 3β,28-diacetoxy-18,19-secolup-13(18)-en-19-one (*5a*) (0.1 g) identical with the product from the BF_3-rearrangement above.

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Received September 2, 1976.