Triterpenes. BF₃ Catalysed Rearrangement of 3β,28-Diacetoxy-18(α or β),19(α or β)-epoxy lupane. A Novel Route to Baccharane Derivatives

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Both the 3β,28-diacetoxy-18β,19α-epoxy lupane (4α) and the corresponding 18β,19β-isomer (3α) gave 3β,28-diacetoxy-18,19-secolup-13(18)-ene-19-one (5α) on treatment with BF₃-etherate. 18β,19β-Epoxy isomer (3α) gave, in addition, 3β,28-diacetoxy-lup-12,18-diene (6). The baccharane derivative 5α was also synthesized via another route. The stereochemistry of the isomeric 18,19-epoxy-lupane derivatives 3 and 4 is discussed.

Betulin diacetate (1) can be transformed to its Δ₁⁴-isomer (2α), either through successive dehydrogenation and hydrogenation steps, or via acid catalysed double-bond migration. On epoxidation of 2α, 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 2α 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 2α, 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 3α doublets at δ 3.80 and 4.50) and are magnetically more different than those of the epoxide produced by ozone (in 4α 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 3c, 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, 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 4ß-lupane derivative 2b, lacking C-28 oxygen, similarly gives different epoxides as main products when treated with ozone and peracid. The different stereochemistry may be due to the fact that ozone is diradical and peracid ionic in character.

Both epoxides 3a and 4a rearrange to the baccharane derivative 5a on treatment with BF₃-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 thiaocetal 11 followed by Raney-Ni desulfurisation. The Eu(DPM)₃ induced shifts to lower field in ¹H NMR spectrum of the trifluoroacetate derivative 1b are in the expected order: protons at C-22 (2 H, tr, J = 8 Hz) ≥ 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).

The baccharane derivative 5a was also synthesised via an independent route. Oxidation of the double bond in 2a with RuO₄ – NaIO₄ results in the diketone 7, the side chain carbonyl of which is selectively protected as an ethylene acetal to give the ketoacetal 8. NaBH₄ reduction of 8 gave a mixture of compounds, among them the hydroxy acetal 9. The 13ßH₁₈αOH-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., [α]D, IR, ¹H NMR, and MS) with the compound 5a obtained from the BF₃-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 CS₂ and others in CDCl₃ (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 CHCl₃ solution on a Perkin-Elmer 141 polarimeter, and elemental analyses with a F & M 185 CHN analyser.

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

(b) 3β,28-Diaceatoxy-lup-18-ene 2a) (0.2 g), CH₂Cl₂ (3 ml), EtOAc (6 ml), HCO₂H (2 ml), and 30% H₂O₂ (1 ml) were stirred for 1 h at room temperature. The mixture was washed with water, NaHCO₃-solution, dried, and the solvent evaporated. Crystallisation from Et₂O–MeOH gave 3β,28-diaceatoxy-18β,19β-epoxy-18-lup-18-ene (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 (CHCl₃-EtOAc 9:1 eluent), and crystallisation from EtOH gave 3β,28-dihydroxy-18β,19β-epoxy-lup-3a (0.75 g), m.p. 245°C, [α]D +29° (c 1.04). Reactecylation in boiling Ac₂O gave the starting epoxide 3a.

3β,28-Dihydroxy-18β,19β-epoxy-lup-3a (3b) (1.0 g) in CH₂Cl₂ (20 ml) and (CF₃CO)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-epoxy-lup-3a (3c) (0.5 g), m.p. 124°C, [α]D +25° (c 1.28); M+ 560; ν 1775, 1225, 1160, 950, 870, 775, 730, 655; δ 4.58 (1 H, m, 3H), 4.46 and 4.15 (1 H, d, 11 Hz, AB system of C-28 protons), 1.05 and 1.00 (3 H, d, 7 Hz, methyls of isopropyl group), 1.12, 1.06, 0.94 (3 H, s), 0.86 (6 H, s).

Derivatives of 18α,19α-epoxy-lup-3a, 4a and 4c. 3β,28-Diaceatoxy-lup-18-ene 2a) (1.0 g) in EtOAc–CH₂Cl₂ (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 (CHCl₃ eluent), and crystallisation from EtOH gave 3β,28-diaceatoxy-18α,19α-epoxy-lup-3a) (0.7 g), m.p. 210°C, [α]D +36.6° (c 1.02); M+ 542; δ 6.44 (1 H, m, 3H), 4.20 and 3.74 (1 H, d, 11 Hz, AB system of C-28 protons), 2.02 and 1.98 (3 H, s, acetyl groups), 1.10–0.85 (group of 7 Me).

Hydrolysis of 4a (1.0 g) as the corresponding epoxy-3a gave 3β,28-dihydroxy-18α,19α-epoxy-lup-3a) (0.5 g) crystallised from Et₂O–MeOH m.p. 214°C, [α]D +22.6° (c 1.0). Reactecylation in boiling Ac₂O gave the starting diaceatoxy 4a.

3β,28-Di-(trifluoroacetoxy)-18α,19α-epoxy-lup-3a) (4c) was prepared as the corresponding β-epoxy derivative 3c above. Crystallisation from MeOH–Et₂O gave m.p. 225°C, [α]D +30° (c 1.0); M+ 650; ν 1770, 1210, 1155, 920, 875, 775, 730; δ 4.74 (1 H, m, 3H), 4.50 and 4.05 (1 H, d, 11 Hz, AB system of C-28 protons), 1.15–0.89 (group of 7 Me).

BF₃-catalysed rearrangement of 3β,28-diaceatoxy-18β,19β-epoxy-lup-3a) (3a) and trifluoroacetoxy 3c. 3β,28-Diaceatoxy-18β,19β-epoxy-lup-3a) (0.5 g) in dry benzene (30 ml) and BF₃-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 NaHCO₃-solution, dried and the solvent evaporated. Chromatography on silica plates (CHCl₃–light petroleum, b.p. 60–80°C, 3:1 eluent) gave two compounds. The less polar 3β,28-diaceatoxy-lup-12,18-diene (6) crystallised from EtOH (50 mg), m.p. 140–143°C, [α]D +220° (c 1.00). (Ref. 4, m.p. 140–143°C, [α]D +219° λ) (EtOH) 234 nm (ε 7000); M+ 524; ν 3020, 1730, 1240; δ (CCl₃) 5.35 (1 H, br. tr, 3 Hz, C-12 vinyl proton). 4.45 (1 H, m, 3H), 3.28 (2 H, AB quart, 11 Hz, C-28 protons), 1.05–0.89 (group of 7 Me).

The more polar 3β,28-diaceatoxy-18,19-seco-lup-13(18)-ene-19-one (5a) crystallised from EtOH (0.35 g), m.p. 115°C, [α]D –34.8° (c 1.15); M+ 542; ν 1730, 1710, 1240; δ (CCl₃) 4.93 (1 H, br. s, C-18 vinyl proton), 4.40 (1 H, m, 3H), 3.79 (2 H, AB quart, 11 Hz, C-28 protons), 2.00 and 1.96 (3 H, s, acetyl methyl), 1.12 (6 H, s), 1.00–0.80 (group of 5 Me). Anal. C₂₄H₃₂O₄C: H.

Similar treatment of 3β,28-di-(trifluoroacetoxy)-18β,19β-epoxy-lup-3a) (3c) (1.0 g) with BF₃-etherate gave 3β,28-di-(trifluoroacetoxy)-18,19-seco-lup-13(18)-en-19-one (5b) (0.7 g), m.p. 125°C (from EtOH), [α]D –24.8° (c 1.25); ν 1775, 1710, 1220, 1160.

BF₃-catalysed rearrangement of 3β,28-diaceatoxy-18α,19α-epoxy-lup-3a) (4a). The treatment with BF₃-etherate of 3β,28-diaceatoxy-18α,19α-epoxy-lup-3a) as the β-epoxide 3a above resulted in quantitatively 3β,28-diaceatoxy-18α, 19-seco-lup-13(18)-en-19-one (5a) identical with the compound 5a obtained from the β-epoxide 3a.

Diels-Alder adduct (10). 3β,28-Diaceatoxy-lup-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 (CHCl₃ eluent). Crystallisation from EtOH gave adduct 10 (60 mg), m.p. 180°C dec., [α]D +162° (ε 0.56); ν 1730, 1690; δ (CCl₃) 7.40 (5 H, m, phenyl), 4.65 (2 H, m, 3aH and C-12 proton), 3.95 (2 H, br. s, C-28 protons), 2.04 and 2.00.

(à 3 H, s, acetyl methyl), 1.12 – 0.85 (group of 7 Me). Anal. C₇H₅NO₄; C, H, N.

Reduction of 3,28-Diacetoxy-18,19-secolupan-13(18)-en-19-one (5a). 3,28-Diacetoxy-18,19-secolupan-13(18)-en-19-one (5a) (0.5 g), ethane-1,2-dithiol (2.0 g), and BF₃-etherate (0.3 ml) was allowed to stand for 15 min at room temperature, methanol (15 ml) was added and the precipitated thioacetal II (0.3 g) m.p. 160°C, [α]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 (CHCl₃-light petroleum, b.p. 60 – 80°C, 3:1 eluent). Crystallisation from Et₂O-MeOH gave 3,28-Diacetoxy-18,19-secolupan-13(18)-en-19-one (12) (0.16 g), m.p. 90°C, [α]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, 3xH), 3.88 (2 H, AB quartet, 11 Hz, C-28 protons), 2.05 (6 H, s, acetyl methyls), 0.95 – 0.80 (group of 7 Me). Anal. C₇H₅NO₄; C, H.

3,28-Diacetoxy-18,19-secolupan-18,19-dione (7). 3,28-Diacetoxy-lup-18-ene (2a) (1.0 g) in CCl₄ (30 ml), NaIO₄ (1.0 g) in CCl₄ (20 ml), and a catalytic amount of RuO₄ was shaken vigorously for 20 h. The water layer was removed and the CCl₄ phase washed with water, added MeOH (1 ml), dried, and chromatographed on a short silica column (CHCl₃-light petroleum, b.p. 60 – 80°C, 2:1 eluent). Crystallisation from Et₂O gave 3,28-Diacetoxy-18,19-secolupan-18,19-dione (7) (0.8 g), m.p. 166°C, [α]D + 58.7° (c 1.2); M⁺ 588; ν 1740, 1720, 1705, 1250; δ 4.45 (1 H, m, 3xH), 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. C₇H₅NO₄; C, H.

3,28-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 azetrop. The mixture was washed with NaHCO₃ solution, dried, and the solvent evaporated. Crystallisation from Et₂O-MeOH gave 3,28-Diacetoxy-18,19-secolupan-18,19-dione (7) (0.6 g), m.p. 192°C, [α]D + 45° (c 1.0); M⁺ 562; δ 4.43 (1 H, m, 3xH), 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. C₇H₅NO₄; C, H.

3,28-Diacetoxy-18α-hydroxy-18,19-secolupan-19-one ethylene acetal (9). 3,28-Diacetoxy-18,19-secolupan-18,19-dione 19-ethylene acetal (8) (1.0 g) in EtOH (50 ml) and NaBH₄ (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 (CHCl₃ + 2 % EtOAc eluent). The least polar main component 3,28-Diacetoxy-18α-hydroxy-18,19-secolupan-19-one ethylene acetal (9) crystallised from EtOH (0.2 g), m.p. 163°C, [α]D + 10.8° (c 1.02); M⁺ absent, M⁺ 43661; ν 3500, 1730, 1240; δ 4.40 (1 H, m, 3xH), 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. C₇H₅NO₄; C, H.

3,28-Diacetoxy-18,19-secolupan-13(18)-en-19-one (5a) via dehydration. 3,28-Diacetoxy-18α-hydroxy-19,19-secolupan-19-one ethylene acetal (9) (0.2 g) in hexamethyldisiloxane (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 H₂SO₄. Benzene was evaporated and the partially hydrolysé acetal was dissolved in acetone and 1 M H₂SO₄ added. The mixture was stirred for 2 h, worked up, and chromatographed on silica plates (CHCl₃ eluent). Crystallisation from Et₂O-MeOH gave 3,28-Diacetoxy-18,19-secolupan-13(18)-en-19-one (5a) (0.1 g) identical with the product from the BF₃-rearrangement above.

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