

# Triterpenes. The Synthesis of Novel 18 $\beta$ H,19 $\beta$ -Substituted Lupane Derivatives

ELIAS SUOKAS and TAPIO HASE

Department of Chemistry, Helsinki University of Technology, SF-02150 Otaniemi, Finland

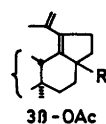
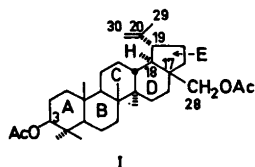
Catalytic hydrogenation of the conjugated diene (II), obtained from betulin diacetate (I) by mercuric acetate dehydrogenation, has been shown to proceed *via* 1,2- and 1,4-addition to compounds (IVb) and (VIIa). The latter is capable of further hydrogenation to (VIb). Acid catalysed isomerisation of (VIIIa) gives a novel isomer (XII) of betulin diacetate (I).

Betulin diacetate (I) gives on dehydrogenation with mercuric acetate the conjugated diene (II).<sup>1,2</sup> Analogously<sup>3</sup> to the corresponding lupane

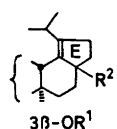
derivative (III), the hydrogenation of (II) with PtO<sub>2</sub>-catalyst gives a mixture of the dihydro diacetate (IVb) with an endo double bond in ring E, and a tetrahydro diacetate of unknown stereochemistry at C-18 and C-19, differing from dihydrobetulin diacetate (V). For this compound we now present formula (VIb), which follows from the results outlined below.

The hydrogenation of diene (II) in the presence of Pd/BaSO<sub>4</sub>-catalyst gives quantitatively the 1,4-addition product with the double bond exo to ring E. The stereochemistry at C-18 is determined from the reactions presented below and is found to be 18 $\beta$  H as in formula (VIIa). Ozonisation of the exo double bond in compound (VIIa) and reduction of the ozonide with (MeO)<sub>3</sub>P under neutral conditions gives a five membered ring ketone, which has a large positive value of molecular ellipticity [ $\theta$ ]<sub>313</sub> + 6270° indicating<sup>4</sup> a 18 $\beta$ H-structure for the ketone (VIIIa). The m.p., [ $\theta$ ], and [ $\alpha$ ]<sub>D</sub> are in agreement with values reported for the compound (VIIIa).<sup>5-7</sup>

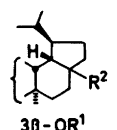
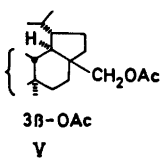
Acid catalysed isomerisation of the exo double bond in the diacetate (VIIa) gives another diacetate having an isopropenyl side chain and being different from betulin diacetate (I). Ozonolysis of the terminal methylene group gives a 19-acetyl derivative, which does not epimerise even under alkaline hydrolysis. It is known<sup>5</sup> that the 18 $\alpha$ H,19 $\alpha$ Ac-isomer (IX)<sup>5,8</sup> is stable as such and this side chain will be base epimerised into the unknown 18 $\alpha$ H,19 $\beta$ Ac-isomer only under special circumstances involving further reaction with the 17 $\beta$ -CH<sub>2</sub>OH group to give the hemiacetal (X).<sup>5</sup> As the new 19-acetyl compound is different from the stable



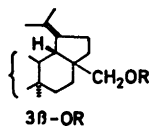
II R = -CH<sub>2</sub>OAc  
III R = -CH<sub>3</sub>



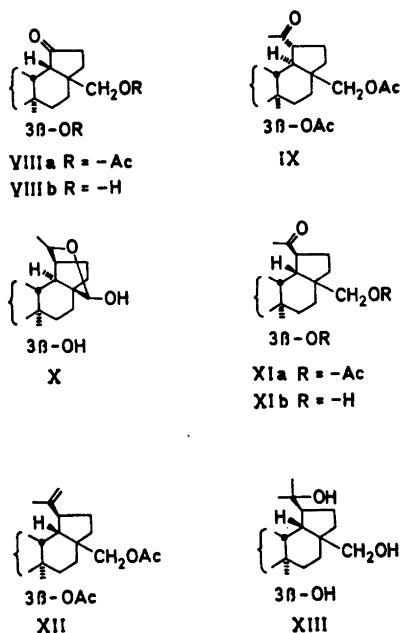
IVa R<sup>1</sup> = -H, R<sup>2</sup> = -CH<sub>2</sub>OH  
IVb R<sup>1</sup> = -Ac, R<sup>2</sup> = -CH<sub>2</sub>OAc  
XIV R<sup>1</sup> = -Ac, R<sup>2</sup> = -CH<sub>3</sub>



VIa R<sup>1</sup> = -H, R<sup>2</sup> = -CH<sub>2</sub>OH  
VIb R<sup>1</sup> = -Ac, R<sup>2</sup> = -CH<sub>2</sub>OAc  
XVII R<sup>1</sup> = -Ac, R<sup>2</sup> = -CH<sub>3</sub>



VIIa R = -Ac  
VIIb R = -H



18 $\alpha$ H,19 $\alpha$ Ac-isomer and *tert*-BuO<sup>⊖</sup> only hydrolyses it, and does not give the hemiacetal (X), which should be formed from the 18 $\alpha$ H,19 $\beta$ Ac-isomer, the stereochemistry at C-18 must be 18 $\beta$ H. This stereochemistry also applies to the preceding isopropenyl compound. The CD curve of the new 19-acetyl derivative ( $[\theta]_{281} - 3990^\circ$ ) gives the 19 $\beta$ -acetyl stereochemistry for the compound, when the octant rule projection is drawn with the least hindered conformation as in Fig. 1.<sup>4</sup> The large  $[\theta]$  value indicates hindered rotation about the C-19/C-20 axis and is caused mainly by the hydrogens at C-12. According to Dreiding models the corresponding 18 $\beta$ H,19 $\alpha$ Ac-derivative would be highly crowded and hardly

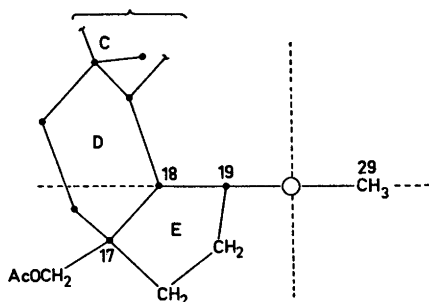
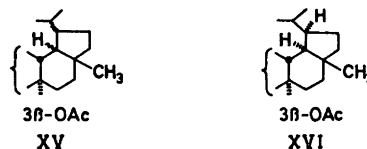


Fig. 1.

capable of resisting epimerisation. For the reasons given above we present the 18 $\beta$ H,19 $\beta$ Ac-structure (XIa) for the new acetyl compound and correspondingly the 19 $\beta$ -isopropenyl side chain structure (XII) for its precursor, an isomer of betulin diacetate (I).

The treatment of the 19 $\beta$ -acetyl compound (XIa) with methylolithium gave the triol (XIII), which on reacylation lost a molecule of water and gave mainly the terminal methylene compound (XII) and a small amount of the tetrasubstituted exo double bond compound (VIIa). This reaction and the ozonolysis of (VIIa) to the ketone (VIIIa) indicates that C-18 does not become involved in the acid catalysed isomerisation of the tetrasubstituted exo double bond compound (VIIa) and thus the 18 $\beta$ H-structure is correct for the compound (VIIa).

Hydrogenation of the terminal methylene in the 19 $\beta$ -isopropenyl compound (XII) gave a dihydro derivative, identical with the tetrahydro compound from the hydrogenation of the diene (II) (IR, <sup>1</sup>H NMR, mixed m.p.,  $[\alpha]_D$ , mass spectra, TLC). These hydrogenation products therefore have the 18 $\beta$ H,19 $\beta$ -isopropyl structure (VIb). Hydrogenation of the lupane derivative (III) with PtO<sub>2</sub>-catalyst has been reported<sup>3</sup> to give a mixture of the dihydro compound (XIV) and tetrahydro compound (XV). Because the amount of the tetrahydro compound (XV) does not increase with a prolonged reaction time, it was assumed<sup>3</sup> that (XIV) and (XV) must be



formed *via* different routes. However, it has been suggested<sup>4</sup> that the tetrahydro compound (XV) is formed by addition of hydrogen from the  $\alpha$ -face to the dihydro compound (XIV), a mechanism which leads to 18 $\alpha$ H,19 $\beta$ -isopropyl structure (XVI). The hydrogenation of the betulin derived diene diacetate (II) under the same reaction conditions with PtO<sub>2</sub>-catalyst gives similar two compounds (IVb) and (VIb) and the amount of the tetrahydro derivative (VIb) does not increase during extended reaction time. Because the tetrahydro compound (VIb) has *trans*-hydrogens at C-18 and C-19 it

cannot be formed *via cis*-addition of hydrogen to dihydro compound (IVb). Instead its formation by the addition of hydrogen from  $\alpha$ -face to the 1,4-addition product (VIIa) is possible, and, indeed, the hydrogenation of the exo double bond compound (VIIa) with  $\text{PtO}_2$ -catalyst gave the same tetrahydro compound (VIb) as obtained from the diene (II) under the same conditions. Thus the hydrogenation of diene (II) with  $\text{PtO}_2$ -catalyst in  $\text{EtOAc-AcOH}$  solution gives first both the dihydro compound (IVb) and dihydro compound (VIIa). The former resists further hydrogenation while the latter gives the tetrahydro compound (VIb).

Finally, we note that the *cis*-structure (XVI) assigned,<sup>2</sup> without proof, to the tetrahydro derivative from the diene (III), should probably be replaced by the *trans*-structure (XVII), in view of our results in the betulin series (*i.e.*, II  $\rightarrow$  VIb).

## EXPERIMENTAL

Melting points are uncorrected.  $^1\text{H}$  NMR spectra were recorded on a Varian A-60 spectrometer in  $\text{CDCl}_3$  (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, CD curves in dioxane solution on a Cary 61 spectrorotameter, specific rotations in  $\text{CHCl}_3$  solution (unless stated otherwise) on a Perkin-Elmer 141 polarimeter, and elemental analyses with a F&M 185 CHN-analyser.

The typical values for the hydroxy- or acetoxy-,  $3\alpha\text{H}$ , and  $17\beta\text{-CH}_2$ -groups, present in all the synthesised compounds, are omitted from the spectral data.

**Hydrogenation of  $3\beta,28$ -diacetoxy-lupa-18,20-(30)-diene (II).** (a) *With  $\text{PtO}_2$ -catalyst.*  $3\beta,28$ -Diacetoxy-lupa-18,20(30)-diene (II)<sup>1,2</sup> (3 g) and  $\text{PtO}_2$ -catalyst (0.6 g) in  $\text{EtOAc-AcOH}$  (1:1, 170 ml) were shaken for 20 h under hydrogen at room temperature and normal pressure. After that, the reaction mixture contained, according to TLC, two compounds at ratio of about 3:7, which does not change on prolonged reaction time. The catalyst was filtered off and the solvent removed. For better resolution of the two compounds the reaction mixture was hydrolysed by refluxing in  $\text{KOH/EtOH}$  for 1 h, worked up, and chromatographed on silica plates impregnated with 10%  $\text{AgNO}_3$ .

The less polar  $3\beta,28$ -dihydroxy- $18\beta(\text{H}),19\alpha(\text{H})$ -lupane (VIa) (0.4 g), recrystallised from  $\text{EtOH}$ , had m.p.  $255^\circ\text{C}$ ,  $[\alpha]_{\text{D}} + 11^\circ$  (*c* 1.45),  $^1\text{H}$  NMR ( $\text{CDCl}_3\text{-CS}_2$ )  $\delta$  0.68–0.95 (7 Me groups), (Found: C 81.29; H 11.87. Calc. for  $\text{C}_{30}\text{H}_{52}\text{O}_2$ : C

81.02; H 11.79). Diacetate (VIb), from (VIa) by refluxing 10 min in  $\text{Ac}_2\text{O}$ , had m.p.  $210^\circ\text{C}$  ( $\text{Ac}_2\text{O}$ ),  $[\alpha]_{\text{D}} + 20^\circ$  (*c* 1.5),  $\text{M}^+ 528$ .

The more polar  $3\beta,28$ -dihydroxy-lup-18-ene (IVa) (1.6 g), recrystallised from  $\text{EtOH}$ , had m.p.  $220^\circ\text{C}$ ,  $[\alpha]_{\text{D}} - 24^\circ$  (*c* 1.1),  $\delta$  0.75–1.05 (7 Me groups), 2.05–2.5 (3H, m), 3.0–3.8 (4H, m). (Found: C 81.33; H 11.60. Calc. for  $\text{C}_{30}\text{H}_{50}\text{O}_2$ : C 81.39; H 11.38). Diacetate (IVb) m.p.  $211^\circ\text{C}$ ,  $[\alpha]_{\text{D}} + 15^\circ$  (*c* 1.5),  $\delta$  0.82–1.05 (7 Me groups).

(b) *With  $\text{Pd/BaSO}_4$ -catalyst.*  $3\beta,28$ -Diacetoxy-lupa-18,20(30)-diene (II)<sup>1,2</sup> (2 g) and 10%  $\text{Pd/BaSO}_4$ -catalyst (0.4 g) in  $\text{EtOAc}$  (140 ml) were shaken for 17 h under hydrogen at room temperature and normal pressure. Only one compound resulted according to TLC. Catalyst was filtered off and the solvent evaporated. Crystallisation from  $\text{EtOH}$  yielded  $3\beta,28$ -diacetoxy- $18\beta(\text{H})$ -lup-19(20)-ene (VIIa), (1.8 g), m.p.  $197^\circ\text{C}$ ,  $[\alpha]_{\text{D}} - 19^\circ$  (*c* 1.15),  $\text{M}^+ 526$ ,  $\delta$  0.83–0.95 (5 Me groups), 1.68 (2 Me, s), 2.2–2.6 (3H, m). (Found: C 77.69; H 10.58. Calc. for  $\text{C}_{30}\text{H}_{50}\text{O}_4$ : C 77.52; H 10.33). Hydrolysis with  $\text{KOH/EtOH}$  gave the diol (VIIb), m.p.  $177^\circ\text{C}$ ,  $[\alpha]_{\text{D}} - 36^\circ$  (*c* 1.21),  $\delta$  0.75–0.95 (5 Me groups), 1.70 (2 Me, s), 2.15–2.6 (3 H, m).

**Ozonolysis of  $3\beta,28$ -diacetoxy- $18\beta(\text{H})$ -lup-19(20)-ene (VIIa).**  $3\beta,28$ -Diacetoxy- $18\beta(\text{H})$ -lup-19(20)-ene (VIIa) (1 g) in  $\text{EtOAc-CH}_2\text{Cl}_2$  (1:1, 75 ml) was ozonised at  $-75^\circ\text{C}$  until the solution remained slightly blue. Excess ozone was driven off with a nitrogen stream and the ozonide reduced with  $(\text{MeO})_2\text{P}$ . The mixture contained (TLC) one major and several minor components. The major component was separated by chromatography on silica plates with  $\text{CHCl}_3$  eluent. Recrystallisation from  $\text{EtOH}$  gave  $3\beta,28$ -diacetoxy-20,29,30-trisnor- $18\beta(\text{H})$ -lupan-19-one (VIIIa) (0.35 g), m.p.  $250^\circ\text{C}$ ,  $[\alpha]_{\text{D}} + 31^\circ$  (*c* 1.12) (Ref. 5, m.p.  $250$ – $253^\circ\text{C}$ ,  $[\alpha]_{\text{D}} + 35.5^\circ$ ),  $[\theta]_{\text{D},513} + 6270^\circ$ ,  $\nu_{\text{max}}$  1730,  $\delta$  0.70–0.98 (5 Me groups), 4.05–4.35 (2 H, m). Hydrolysis in  $\text{KOH/EtOH}$  gave the diol (VIIIb) m.p.  $263^\circ\text{C}$  ( $\text{EtOH}$ ),  $[\alpha]_{\text{D}} + 31^\circ$  ( $\text{THF}$ , *c* 1.13) (Ref. 7, m.p.  $254$ – $6^\circ\text{C}$ ,  $[\alpha]_{\text{D}} + 40.5^\circ$   $[\theta]_{\text{D},513} + 7260^\circ$ ),  $\nu_{\text{max}}$  1730. Reactylation of VIIIb with  $\text{Ac}_2\text{O}$  gave (VIIIa).

**Isomerisation of  $3\beta,28$ -diacetoxy- $18\beta(\text{H})$ -lup-19(20)-ene (VIIa).**  $3\beta,28$ -Diacetoxy- $18\beta(\text{H})$ -lup-19(20)-ene (VIIa) (1.5 g) and *p*-toluenesulfonic acid (0.2 g) in  $\text{AcOH}$  (150 ml) were refluxed for 1.5 h. Reaction mixture contained, according to TLC, starting material and a less polar compound. Chromatography on silica impregnated with 10%  $\text{AgNO}_3$  with light petroleum (b.p.  $60$ – $80^\circ\text{C}$ )-benzene (3:1) eluent gave  $3\beta,28$ -diacetoxy- $18\beta(\text{H}),19\alpha(\text{H})$ -lup-20(30)-ene (XII). Recrystallisation from  $\text{EtOH}$  gave (0.6 g) m.p.  $174^\circ\text{C}$ ,  $[\alpha]_{\text{D}} + 6^\circ$  (*c* 1.04),  $\nu_{\text{max}}$  3080, 1640, 885,  $\delta$  0.85 (5 Me groups), 0.99, 1.07, 1.70 ( $\delta$  1 Me, s), 2.9 (1 H, m), 4.7 (2 H, br.d. 6 Hz). (Found: C 77.96; H 10.33. Calc. for  $\text{C}_{30}\text{H}_{50}\text{O}_4$ : C 77.52; H 10.33).

**Ozonolysis of  $3\beta,28$ -diacetoxy- $18\beta(\text{H}),19\alpha(\text{H})$ -lup-20(30)-ene (XII).**  $3\beta,28$ -Diacetoxy- $18\beta(\text{H}),19\alpha(\text{H})$ -lup-20(30)-ene (XII) (0.35 g) in

$\text{CHCl}_3$ - $\text{CH}_2\text{Cl}_2$  solution (1:1, 50 ml) was ozonised at  $-75^\circ\text{C}$  until slightly blue. Unreacted ozone was driven off with nitrogen and the ozonide reduced with  $(\text{MeO})_3\text{P}$ . Chromatography and recrystallisation from EtOH gave  $3\beta,28$ -diacetoxy-30-nor-18 $\beta$ (H),19 $\alpha$ (H)-lupan-20-one (XIa) (0.15 g), m.p.  $207^\circ\text{C}$ ,  $[\alpha]_{\text{D}} +27^\circ$  (c 1.25),  $[\theta]_{281} -3990^\circ$ ,  $\nu_{\text{max}}$  1725,  $\delta$  0.83 (3 Me groups), 0.79 (2 Me groups), 2.17 (1 Me, s), 3.1 (1 H, m). (Found: C 74.95; H 9.94. Calc. for  $\text{C}_{33}\text{H}_{52}\text{O}_6$ : C 74.96; H 9.91). Hydrolysis with KOH/EtOH gave the diol (XIb) m.p.  $234^\circ\text{C}$  (EtOH),  $[\alpha]_{\text{D}} +22^\circ$  (c 1.0),  $\nu_{\text{max}}$  1695, 1355,  $\delta$  0.75–0.97 (5 Me groups), 2.17 (1 Me, s). Compound (XIa) does not react on standing for 3 h in AcOH-TsOH solution, and refluxing (XIa) in *tert*-BuOH with *tert*-BuO $^-$ K $^+$  only hydrolyses (XIa) to (XIb).

*Methylation of 3 $\beta,28$ -diacetoxy-30-nor-18 $\beta$ (H),19 $\alpha$ (H)-lupan-20-one (XIa).*  $3\beta,28$ -Diacetoxy-30-nor-18 $\beta$ (H),19 $\alpha$ (H)-lupan-20-one (XIa) (0.25 g) in abs. ether (50 ml) was purged with a nitrogen stream, cooled to  $-75^\circ\text{C}$  and 1 ml of methyllithium (2 M-solution in ether) was added. The reaction mixture was allowed to warm slowly to room temperature, washed with water, dil.  $\text{H}_2\text{SO}_4$ ,  $\text{NaHCO}_3$ , and dried. Chromatography on silica plates gave two compounds. The less polar compound was found to be hydrolysed starting material,  $3\beta,28$ -dihydroxy-30-nor-18 $\beta$ (H),19 $\alpha$ (H)-lupan-20-one (XIb), and the major component was  $3\beta,20,28$ -trihydroxy-18 $\beta$ (H),19 $\alpha$ (H)-lupane (XIII), crystallised from EtOH (0.13 g), m.p.  $220^\circ\text{C}$ ,  $[\alpha]_{\text{D}} -4^\circ$  (c 0.87),  $\delta$  0.75–1.20 (7 Me groups). Acetylation of (XIII) by refluxing in  $\text{Ac}_2\text{O}$  for 10 min gave approximately 1:9 mixture of diacetates (VIIa) and (XII) resulting from dehydration and acetylation reactions, respectively.

*Hydrogenation of 3 $\beta,28$ -diacetoxy-18 $\beta$ (H),19 $\alpha$ (H)-lup-20(30)-ene (XII) and 3 $\beta,28$ -diacetoxy-18 $\beta$ (H)-lup-19(20)-ene (VIIa).* Both diacetates (XII) and (VIIa) were hydrogenated as the diene diacetate (II) above with  $\text{PtO}_2$ -catalyst. Both reactions gave only one compound on TLC and both were identical (m.p., mixed m.p.,  $[\alpha]_{\text{D}}$ , IR,  $^1\text{H}$  NMR, TLC, mass spectra) with the tetrahydro compound (VIb) from the hydrogenation of the diene (II).

## REFERENCES

- Allison, J. M., Lawrie, W., McLean, J. and Taylor, G. R. *J. Chem. Soc.* (1961) 3353.
- Adhikary, S. P., Lawrie, W. and McLean, J. *J. Chem. Soc. C* (1970) 1030.
- Baddeley, G. V., Simes, J. H. and Watson, T. G. *Tetrahedron* 26 (1970) 3799.
- Crabbe, P. *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*, Holden-Day, San Francisco 1965.
- Vystrčil, A. and Buděšínský, M. *Collect. Czech. Chem. Commun.* 35 (1970) 295.
- Djerassi, C. and Hodges, R. *J. Amer. Chem. Soc.* 78 (1956) 3534.
- Baddeley, G. V., Eade, R. A., Ellis, J., Harper, P. and Simes, J. J. H. *Tetrahedron* 25 (1969) 1643.
- Ružička, L. and Rey, E. *Helv. Chim. Acta* 25 (1942) 171.

Received March 8, 1974.