Conversion of Lupeol into Dammarane Derivatives

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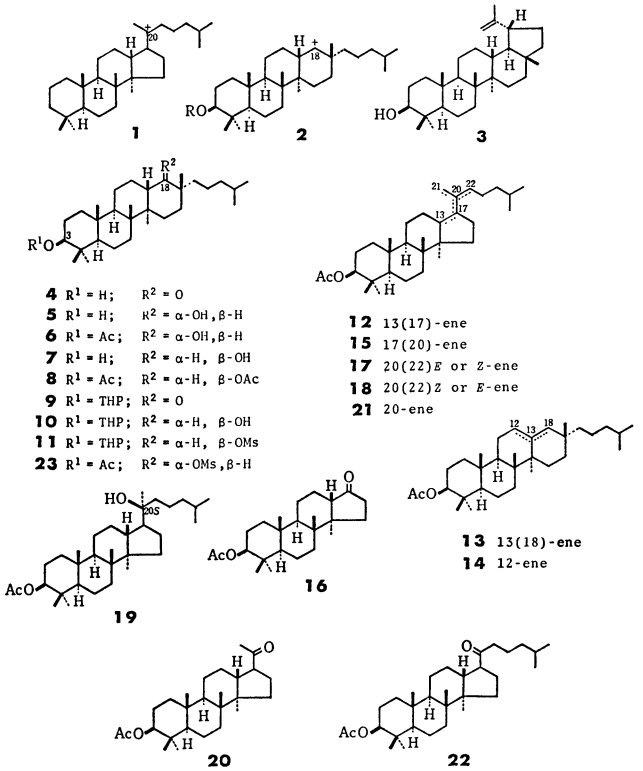
Synopsis. On treatment with potassium carbonate in aqueous dioxane, 3β-tetrahydropyranyloxybaccharan-18β-yl mesylate, prepared from lupeol, underwent D-ring contraction. The solvolytic products were hydrolyzed and acetylated to give Δ^{20}-, $\Delta^{20(22)}$-, $\Delta^{17(20)}$-, and $\Delta^{13(17)}$-dammaren-3β-yl acetates and (20*S*)-20-hydroxydammaran-3β-yl acetate together with bacchar-13(18)- and -12-en-3β-yl acetates.

It has been proposed that dammarane derivatives undergo D-ring enlargement to afford baccharane derivatives, which yield lupane derivatives by E-ring formation in succession in the biogenesis of triterpenes. In connection with a study on the behavior of C-20 cation on dammarane derivatives, such as **1**,[1] we examined reactivities of C-18[2] cation on baccharane derivatives (**2**). In this paper, a conversion of baccharane derivatives into dammarane derivatives is described. Baccharane derivatives being prepared from lupeol (**3**), this conversion constitutes a reverse transformation[3] from the biogenetic pathway described above.

3β-Hydroxybaccharan-18-one (**4**) was prepared from **3** by a known procedure.[4] Reduction of **4** with lithium aluminium hydride gave a 3β,18α-dihydroxy derivative (**5**) exclusively, which on partial acetylation afforded a 3β-monoacetate (**6**). On the other hand, Birch reduction of **4** afforded a 3β,18β-dihydroxy derivative (**7**). Although selective acetylation of the 3β-hydroxyl group of **7** was attempted under various conditions, a satisfactory selectivity was not attained; a diacetate (**8**) appeared at the early reaction stage. Protection of the 3β-hydroxyl group of **4** by tetrahydropyranylation gave a tetrahydropyranyloxy ketone (**9**), which was subjected to Birch reduction to afford a 3β-tetrahydropyranyloxy-18β-hydroxy derivative (**10**).



The mesylate (**11**; *ca.* 50 mg), prepared from **10**, was treated with potassium carbonate in boiling aqueous dioxane for 4 h and the products were treated with 10% hydrochloric acid to give a mixture of alcohols, which was acetylated. The acetylation product was separated by column chromatography into three fractions, A, B, and C. The fraction A, a mixture of unsaturated acetates, was further separated by column chromatography of silica gel impregnated with silver nitrate into five components. The first (the least polar) component was found to be a mixture of dammar-13(17)-en-3β-yl acetate (**12**) and bacchar-13(18)- and bacchar-12-en-3β-yl acetates (**13** and **14**) by comparison of their retention times with those of authentic samples[5,6] in GLC examination. The second component was shown to be a tetrasubstituted olefinic acetate by ^{1}H NMR and high resolution mass spectrum. This compound, on oxidation with ruthenium tetraoxide, afforded an octanor keto acetate (**16**),[7] showing a molecular ion at *m/e* 374. Therefore, the original acetate (**15**) is inferred to be dammar-17(20)-en-3β-yl acetate.

The third component showed an olefinic proton at δ 5.14 (1H, m), IR 1730 cm^{-1}, and a molecular ion at *m/e* 470.4221. The fourth component gave almost the same fragmentation pattern as that of the third one in the mass spectrum and showed an olefinic proton at δ 5.08 (1H, m) and a molecular ion at *m/e* 470.4106. These two compounds were found to be identical with an *E,Z*-isomeric pair of dammar-20(22)-en-3β-yl acetates (**17** and **18**), prepared from dammaranediol II monoacetate (**19**).[6] On oxidation with ruthenium tetraoxide, **17** and **18** gave the same product, hexanordammaran-20-one (**20**).[6,7]

The most polar component showed the presence of an *exo*-methylene moiety by ^{1}H NMR, IR, and a molecular ion. Spectral comparison showed that the compound was identical with dammar-20-en-3β-yl acetate (**21**),[6] prepared from **19**. Oxidation of the acetate (**21**) with ruthenium tetraoxide gave 22-nor-20-oxodammaran-3β-yl acetate (**22**).[6,7]

The fraction B was identical with baccharane-3β,18β-diyl diacetate (**8**). The fraction C was shown to be dammaranediol II monoacetate (=(20*S*)-20-hydroxydammaran-3β-yl acetate) (**19**).[6] A 20*R*-epimer was not detected in the solvolytic product.

3β-Acetoxy-18α-hydroxy derivative (**6**) was treated with mesyl chloride in a mixture of triethylamine and dichloromethane to give a mesylate (**23**), which was subjected to solvolysis under the same conditions as before. The product was found to be a mixture of bacchar-13(18)- and bacchar-12-en-3β-yl acetates (**13** and **14**)[5] by ^{1}H NMR and GLC examination.

Experimental[8]

Baccharane-3β,18α-diol (5) and 18α-Hydroxybaccharan-3β-yl Acetate (6). 3β-Hydroxybaccharan-18-one (**4**; 27 mg)[4]

was treated with $LiAlH_4$ (*ca.* 5 mg) in THF and the reaction product was worked up as usual to afford **5** as white crystals, NMR δ 3.20 (1H, m) and 3.25 (1H, br s); MS *m/e* 446 (M^+), 428, and 410. The diol (**5**) was acetylated with Ac_2O (0.1 ml) in pyridine (0.1 ml) at room temperature overnight. Usual work-up and crystallization from $CHCl_3$–MeOH gave **6** (26 mg) as white needles, mp 199—202 °C; IR (Nujol) 3560, 1720, and 1260 cm^{-1}; NMR δ 0.80—1.10 (24H), 2.03 (3H, s), 3.23 (1H, br s), and 4.47 (1H, dd-like); MS *m/e* 488 (M^+), 470, 455, 428, 413, 410, 385, 344, 189, 135 (base peak); Found: *m/e* 488.4220. Calcd for $C_{32}H_{56}O_3$: M 488.4229.

Baccharane-3β,18β-diol (7) and Baccharane-3β,18β-diyl Diacetate (8). A solution of **4** (40 mg) in THF (1 ml) and MeOH (0.1 ml) was added to Li (*ca.* 30 mg) in liquid NH_3 (3 ml) at −78 °C with stirring and the reaction mixture was kept at −33 °C for 15 min. An aqueous NH_4Cl solution was added and the solution was warmed to remove NH_3 and extracted with Et_2O. The ethereal layer was worked up to give **7** in a quantitative yield, NMR δ 0.77—1.02 (24H), 3.16 (1H, d, J=10 Hz), and 3.18 (1H, dd-like); MS *m/e* 446 (M^+), 428, 220, 207, 189, and 95 (base peak).

A solution of diol (**7**; *ca.* 40 mg) in Ac_2O (0.1 ml) and pyridine (0.1 ml) was allowed to stand overnight at room temperature. The reaction was stopped by addition of MeOH and the usual work-up was followed to give **8** (*ca.* 45 mg); mp 183—184 °C ($CHCl_3$–MeOH); IR (film) 1740 and 1245 cm^{-1}; NMR δ 0.82—1.03 (24H), 2.06 (6H, s), 4.48 (1H, dd-like), and 4.76 (1H, d, J=11 Hz); MS *m/e* 530 (M^+), 470 (base peak), 455, 410, 249, 220, 207, 202, and 189; Found: C, 76.75; H, 10.84%. Calcd for $C_{34}H_{58}O_4$: C, 76.93; H, 11.01%.

3β-Tetrahydropyranyloxybaccharan-18β-ol (10). A solution of **4** (46 mg) and 3,4-dihydro-2*H*-pyran (0.1 ml) in $CHCl_3$ (2 ml) was kept with a catalytic amount of TsOH for 1 h. After addition of an aqueous $NaHCO_3$ solution, organic layer was worked up to give a residue, which was purified by silica gel column chromatography. Elution with 5—10% EtOAc in hexane afforded **9** (50 mg), mp 183—185 °C ($CHCl_3$–MeOH); IR (KBr) 1695 cm^{-1}; MS *m/e* 528 (M^+), 444, 427, 426, 411, 388, 383, 360 (base peak), 342, 237, 223, 207, 196, and 189; Found: *m/e* 528.4530. Calcd for $C_{35}H_{60}O_3$: M 528.4540.

The ketone (**9**; 50 mg), dissolved in a mixture of THF (2 ml) and MeOH (0.1 ml), was added to Li (40 mg) in liquid NH_3 (3 ml) kept at −78 °C, and the reaction mixture was subjected to the same treatment as in the case of **7** to afford **10** (49 mg), NMR δ 0.80—1.01 (24H) and 3.07 (1H, d, J=11 Hz); MS *m/e* 530 (M^+), 446, 429, 428, 410, 395, 344, 220, 207, 189, and 85 (base peak).

Solvolysis of 3β-Tetrahydropyranyloxybaccharan-18β-yl Mesylate (11). Mesyl chloride (0.1 ml) was added to a solution of **10** (50 mg) in Et_3N (0.2 ml) and CH_2Cl_2 (1 ml) and the mixture was allowed to stand for 1 h. The usual work-up afforded a mesylate (**11**), which, without further purification, was subjected to solvolysis. The mesylate (**11**) was dissolved in a solution of K_2CO_3 in H_2O (2 ml) and dioxane (2 ml), and refluxed for 4 h. The reaction mixture was slightly acidified with 10% HCl and warmed for 10 min to complete the deprotection at C-3. The usual work-up afforded a residue, which was acetylated with Ac_2O (0.1 ml) and pyridine (0.1 ml). The reaction product was separated by silica gel (2.5 g) column chromatography into three fractions A, B, and C.

Fraction A (32 mg), eluted with 5—10% EtOAc in hexane, was further subjected to separation by column chromatography of silica gel (3 g) impregnated with $AgNO_3$ (0.5 g). Elution with 10% $CHCl_3$ in hexane gave two components. One component (*ca.* 1.2 mg) gave three peaks at t_R 18.3, 20.3, and 21.4 min in GLC analysis. These retention times were identical with those of **12**, **13**, and **14**, respectively. The other component (**15**; 1.2 mg) showed ^1H NMR δ 2.05 (3H, s) and 4.48 (1H, m); MS *m/e* 470 (M^+), 410, 357, 249, 205, 190, and 69 (base peak); Found: *m/e* 470.4077. Calcd for $C_{32}H_{54}O_2$: M 470.4121. On oxidation with RuO_4 in CCl_4, **15** affoded 17-oxooctanordammaran-3β-yl acetate (**16**); IR (KBr) 1738 cm^{-1}; MS *m/e* 374 (M^+), 314, 299, 271, 191, 190, and 189.

Elution with 33% $CHCl_3$ in hexane afforded a geometrical pair of dammar-20(22)-en-3β-yl acetates (**17** and **18**); the isomer (**17**; 3.7 mg) with a large R_f value: mp 143—144 °C, IR (KBr) 1730 and 1250 cm^{-1}; NMR δ 0.82—0.97 (24H), 2.03 (3H, s), 4.46 (1H, m), and 5.14 (1H, m); MS *m/e* 470 (M^+), 410, 344, 289, 249, 229, 220, 189, and 69 (base peak); Found: *m/e* 470.4221. Calcd for $C_{32}H_{54}O_2$: M 470.4121. The other isomer (**18**) with a small R_f value: mp 159.5—161 °C; IR (KBr) 1730 and 1250 cm^{-1}; NMR δ 0.80—0.96 (24H), 2.03 (3H, s), 4.46 (1H, m), and 5.08 (1H, m); MS *m/e* 470 (M^+), 410, 395, 344, 289, 249, 229, 220, 189, and 95 (base peak); Found: *m/e* 470.4106. Calcd for $C_{32}H_{54}O_2$: M 470.4121. Oxidation of **17** and **18** with RuO_4 in CCl_4 afforded hexanordammaran-20-one (**20**), mp 202.5—204 °C; IR (KBr) 1730, 1710, and 1250 cm^{-1}; NMR δ 0.83—0.90 (12H), 0.97 (3H, s), 2.03 and 2.11 (each 3H, s), and 4.47 (1H, dd-like); MS *m/e* 402 (M^+), 359, 342, 327, 299 (base peak), 229, 204, 191, and 189; Found: *m/e* 402.3108. Calcd for $C_{26}H_{42}O_3$: M 402.3133.

The most polar component (**21**; 9 mg) was eluted with 50% $CHCl_3$ in hexane, mp 142.5—144 °C (MeOH); IR (KBr) 1730, 1260, and 885 cm^{-1}; NMR δ 0.83—0.97 (21H), 2.03 (3H, s), 4.46 (1H, m), and 4.68 (2H, br s); MS *m/e* 470 (M^+), 410, 395, 344, 289, 249, 229, 220, 189, and 95 (base peak); Found: *m/e* 470.4055. Calcd for $C_{32}H_{54}O_2$: M 470.4121. Oxidation of **21** with RuO_4 gave 22-nor-20-oxodammaran-3β-yl acetate (**22**), IR 1740 (sh) and 1730 cm^{-1}; NMR δ 0.82—0.91 (18H), 0.98 (3H, s), 2.03 (3H, s), 2.25—2.55 (2H, m), and 4.48 (1H, m).

Solvolysis of 3β-Acetoxybaccharan-18α-yl Mesylate (23). 3β-Acetoxybaccharan-18α-ol (**6**; *ca.* 10 mg) was dissolved in Et_3N (0.1 ml) and CH_2Cl_2 (0.3 ml). The solution was treated with mesyl chloride (1 drop) and worked up to give **23**, which was subjected to solvolysis as before. The solvolytic product was a mixture of **13** (t_R=20.3 min) and **14** (t_R=21.4 min) by GLC examination.

References

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