Pergamon

Tetrahedron Letters, Vol. 37, No. 29, pp. 5187-5190, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01047-7

Ruthenium Tetroxide Oxidation of 3β-Acetoxy-28-hydroxy-18-lupene to Tricyclic Products

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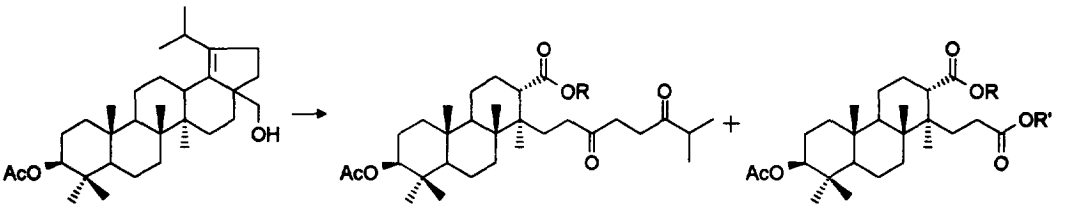
Abstract: By gradual addition 3β-acetoxy-28-hydroxy-18-lupene with stirring at ~50°C EtOAc-H_2O biphase system, containing F_3CCOOH and RuO_4, regenerated *in situ* from $RuO_2 \cdot xH_2O$ and $NaIO_4$, satisfactory yields of 3β-acetoxy-28-nor-17,18;18,19-disecolupan-17,19-dion-18-oic acid and 3β-acetoxy-19,20,21,22,28,29,30-heptanor-17,18-secolupan-17,18-dioic acid were obtained.

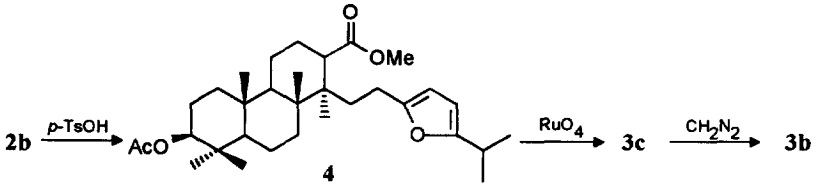
E. Suokas and T. Hase developed a simple and effective conversion of betulin diacetate to 3β,28-diacetoxy-18-lupene,[1] by action of a HBr-Ac_2O-AcOH mix in dry benzene. Ruthenium tetroxide oxidation of the 18-lupene to 3β,28-diacetoxy-18,19-secolupane was carried out by vigorous stirring at room temperature in a biphase solvent system H_2O-CCl_4 under catalytic conditions using a catalytic amount of $RuO_2 \cdot xH_2O$ in combination with a $NaIO_4$ excess, which serves to generate RuO_4 from dioxide *in situ*.[2] It was shown[3] that ruthenium tetroxide oxidation of α-amino acids cyclic derivatives to corresponding lactams proceeds 5-7 times as fast in EtOAc-H_2O biphase solvent system than in H_2O-CCl_4 system. We have successfully applied this solvents system to RuO_4 oxidation of 18-lupene and 18,19-secolupane derivatives.[4] By the oxidation of 3β,28-dihydroxy-18-lupene[1,4] in these conditions and subsequent acetylation of the product we obtained 3β-acetoxy-28-nor-18,19-secolupan-18,19-dione.[5,6]

By research into the RuO_4 oxidation of 3β-acetoxy-28-hydroxy-18-lupene[7] **1**, we have found out, that with an increase of reaction time, two more polar products were formed as traces (by TLC on Silufol) besides 3β-acetoxy-28-nor-18,19-secolupane-18,19-dione as a major product. We developed reaction conditions in which these compounds became major products, and identified them as tricyclic compounds **2a** and **3a**, on the base of MS, NMR ^1H and ^{13}C spectra.. All the new compounds described in this letter were characterized by spectral data: MS, IR, and ^1H NMR[8-10] and ^{13}C NMR (Table).



1 **2a** R=H; **2b** R=Me; **3a** R=R'=H; **3b** R=R'=Me; **3c** R=Me; R'=H

Method of RuO_4 oxidation 3β-acetoxy-28-hydroxy-18-lupene 1. Into vigorously stirred at 50°C mixture of 5 g $NaIO_4$, 200 ml water, 100 ml EtOAc, and 0.1 ml (~1.3 mmol) F_3CCOOH 223 mg (~1.3 mmol) $RuO_2 \cdot xH_2O$ was added, and then solution of 1.910 g (~3.94 mmol) lupene **1** in 120 ml EtOAc was added by drops over a 5 h period. Then the reaction mixture was further stirred for 30 h at 50°C with further addition of 5 g $NaIO_4$ by small portions as the reaction proceeded. Then the EtOAc layer was separated, water phase was extracted by EtOAc, combined organic layers were treated by 1 ml *iso*-PrOH, filtered over the tight Shott filter, decolourized by stirring with $Na_2S_2O_3$ aqueous solution, separated, dried over Na_2SO_4, and evaporated *in vacuo* to dryness. The residue was separated by column chromatography on silica gel (eluent $CHCl_3$) and two major products were obtained: 1.15 g (2,217 mmol, 56.3%) of 3β-acetoxy-28-nor-17,18;18,19-disecolupane-18,19-dione-10-oic acid **2a**[8], and 0.29 g (0.665 mmol, 16.9%) 3β-acetoxy-19,20,21,22,28,29,30-heptanor-17,18-secolupan-17,18-dioic acid **3a**[9]. Acids **2a**, and **3a** were treated by CH_2N_2 in ether and methyl ester **2b**[8] and dimethyl ester **3b**[9] were obtained, respectively.



Reaction of compound 2b with *p*-TsOH in benzene. A mixture of 958 mg (1.798 mmol) ester **2b** and 90 mg (0.473 mmol) *p*-TsOH·H_2O in 60 ml dry benzene was refluxed for 10 h with the removal of the water formed. The cooled reaction mixture was washed with the saturated aqueous $NaHCO_3$, dried over Na_2SO_4, evaporated *in vacuo*, and separated by column chromatography (silica gel, hexane-acetone, 15:1). Thus 327 mg (0.635 mmol, 35.3%) furan derivative **4**[10] were obtained.

RuO_4 oxidation of compound 4. A mixture of 807 mg (1.568 mmol) compound **4**, 50 ml EtOAc, 30 ml water, and 12 mg (~0.072 mmol) $RuO_2 \cdot xH_2O$ was stirred for 9 h with the addition of 2.3 g (10.5 mmol) $NaIO_4$ by small portions as the reaction proceeded. The EtOAc layer was separated, filtered, washed with brine containing $Na_2S_2O_3$, dried (Na_2SO_4), and evaporated. The residue, 694 mg, separated by column chromatography (silica gel, hexane-acetone, 2:1), afforded pure 18-methyl ester of 3β-acetoxy-19,20,21,22,28,29,30-heptanor-17,18-secolupan-17,18-dioic acid **3c**[9]. Compound **3c** treated by the CH_2N_2 in ether, afforded dimethyl ester **3b**[9], identical to the one obtained from acid **3a**.

Table. The ^{13}C NMR (62.9 MHz, $CDCl_3$+TMS) chemical shifts of compounds **1-4**, δ_C

C	1	2a	2b	3a	3b	3c	4
1	38.7	38.6	39.0	38.9	38.9	38.8	38.9
2	23.8	23.7	23.9	23.8	23.9	23.8	24.0
3	80.9	80.6	80.8	80.9	80.8	80.8	80.9
4	37.9[a]	37.8[a]	38.0[a]	38.0[a]	38.0[a]	37.9[a]	38.0[a]
5	55.6	55.4	55.7	55.6	55.7	55.5	55.7
6	18.3	18.2	18.4	18.4	18.5	18.3	18.5
7	34.4	34.0	34.4	34.4	34.4	34.2	34.5
8	41.0	42.3	42.6	42.5[b]	42.4[b]	42.3[b]	42.4[b]
9	51.1	51.0	51.3	51.1	51.2	51.0	51.1
10	37.2[a]	37.3[a]	37.6[a]	37.6[a]	37.6[a]	37.5[a]	37.6[a]
11	21.6	20.2	20.5	20.4	20.5	20.3	20.5
12	28.4	26.2	26.5	26.3	26.4	26.2	26.5
13	40.7	48.1	48.5	48.4	48.5	48.3	48.6
14	43.7	42.3	42.6	42.6[b]	42.6[b]	42.5[b]	42.9[b]
15	28.4	29.1	29.3	30.4[c]	30.8	30.4	34.5
16	32.8	33.7	33.9	30.9[c]	30.8	30.4	34.5
17	54.4	212.7	212.6	179.7	174.4	178.3	159.9
18	133.8	180.2	176.3	181.7	176.2	176.1	176.4
19	144.7	209.1	209.0	-	-	-	154.9
20	26.8	40.7	41.0	-	-	-	28.1
21	29.8	36.0	36.3	-	-	-	104.4
22	35.1	39.3	39.4	-	-	-	102.9
23	28.0	27.9	28.1	28.1	28.1	28.0	28.0
24	16.8	15.8	16.0	16.1	16.0	15.8	16.0
25	16.6	16.4	16.7	16.6	16.6	16.5	16.7
26	16.6	16.4	16.7	16.6	16.6	16.5	26.7
27	15.5	13.6	13.8	13.6	13.5	13.4	13.5
28	66.4	-	-	-	-	-	-
29	22.0	18.2	18.4	-	-	-	21.4
30	22.0	18.2	18.4	-	-	-	21.4
3-OO$\underline{C}$CH$_3$	170.6	170.5	170.6	170.8	170.6	170.6	170.6
3-OOC$\underline{C}$H$_3$	21.2	21.0	21.3	21.3	21.3	21.2	21.4
18-O$\underline{C}$H$_3$			51.3		51.3	51.3	51.1
17-O$\underline{C}$H$_3$					51.5		

[a-c]:Assignments may be reversed.

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8. **2a**: m. p. 141-145° C (hexane -acetone), $[\alpha]_D^{20}$+12.0° (*c* 1, $CHCl_3$), MS, *m/z*: 518 (M^+); IR ($CHCl_3$) ν_{max}: 3500-3100, ~3000, 2950, 1715, 1702, 1686, 1674, 1643, 1624, 1558, 1542, 1530, 1484, 1462,1441, 1363, 1254, 1122 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ_H: 0.84 (3H, s, 24-H), 0.85 (3H, s, 23-H), 0.87 (3H, s, 25-H), 1.00 (3H, s, 26-H), 1.07 (3H, s, 27-H), 1.11 (6H, d, *J*=7.0 Hz, 29-H, 30-H), 2.05 (3H, s, Me of 3-OAc), 4.48 (1H, dd, *J*=10.4 Hz, *J*=5.2 Hz, 3α-H), 1.1-1.9, 2.4-2.8 (the rests H).
   2b: m. p. 133-136° C (ethanol), $[\alpha]_D^{20}$ +8.1° (*c* 1, $CHCl_3$), MS, *m/z*: 532 (M^+); IR ($CHCl_3$) ν_{max}: 2990, 2940, 2860, 1702, 1362, 1252, 1159, 1021 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ_H: 0.84 (3H, s, 24-H), 0.85 (3H, s, 23-H), 0.86 (3H, s, 25-H), 0.99 (3H, s, 26-H), 1.02 (3H, s, 27-H), 1.11 (6H, d, *J*=6.8 Hz, 29-H, 30-H), 2.04 (3H, s, Me of 3-OAc), 3.64 (3H, s, 18-OMe), 4.48 (1H, dd, *J*=10.5 Hz, *J*=5.2 Hz, 3α-H), 1.1-1.9, 2.05-2.8 (the rests H).
9. **3a**: m. p, 246-248°C (hexane-acetone) $[\alpha]_D^{20}$ -4.7° (*c* 0.42, $CHCl_3$), IR ($CHCl_3$) ν_{max}: 3500, 3400, ~2991, 2936, 2859, 1702, 1460,1444, 1411, 1389, 1367, 1246, 1202, 1142, 1021 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ_H: 0.84 (3H, s, 24-H), 0.86 (3H, s, 23-H), 0.87 (3H, s, 25-H), 1.00 (3H, s, 26-H), 1.09 (3H, s, 27-H), 2.05 (3H, s, Me of 3-OAc),2.23 (2H, m), 2.65 (1H, dd, *J*=11.0 Hz, *J*=5.5 Hz, 13β-H), 4.48 (1H, dd, *J*=10.5 Hz, *J*=5.4 Hz, 3α-H), 1.1-2.0 (the rests H).
   3b: m. p. 140-144°C (ethanol, first m. p. ~70°), $[\alpha]_D^{20}$ +12.2° (*c* 1, $CHCl_3$), MS, *m/z*: 464 (M^+) IR ($CHCl_3$) ν_{max}: 2996, 2936, 2859, 1713, 1367, 1246, 1164, 1021 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ_H: 0.84 (3H, s, 24-H), 0.85 (3H, s, 23-H), 0.87 (3H, s, 25-H), 0.99 (3H, s, 26-H), 1.03 (3H, s, 27-H), 2.05 (3H, s, Me of 3-OAc), 2.62 (1H, dd, *J*=11.5 Hz, *J*=4.8 Hz, 13β-H), 3.63 (3H, s, 17-OMe), 3.65 3H, s, 18-OMe), 4.48 (1H, dd, *J*=10.7 Hz, *J*=5.4 Hz, 3α-H), 1.1-2.3 (the rests H).
   3c: m. p. 180-184°C (ethanol), $[\alpha]_D^{20}$ +10.6° (*c* 1, $CHCl_3$), MS, *m/z*: 450 (M^+) IR ($CHCl_3$) ν_{max}: 3660, 3000, 2996, 2936, 2865, 1713, 1367, 1252 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ_H: 0.84 (3H, s, 24-H), 0.86 (3H, s, 23-H), 0.87 (3H, s, 25-H), 1.00 (3H, s, 26-H), 1.05 (3H, s, 27-H), 2.05 (3H, s, Me of 3-OAc), 2.63 (1H, dd, *J*=11.2 Hz, *J*=4.8 Hz, 13β-H), 3.64 (3H, s, 18-OMe), 4.48 (1H, dd, *J*=10.6 Hz, *J*=5.0 Hz, 3α-H), 0.8-2.2 (the rests H).
10. **4**: m. p. 96-99°C (ethanol), $[\alpha]_D^{20}$ +4.4° (*c* 1, $CHCl_3$), MS, *m/z*: 514 (M^+) IR ($CHCl_3$) ν_{max}: 2950, 2930, 2870, 2850, 1722, 1600, 1466, 1448,1432, 1370, 1252, 1214, 1158 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ_H: 0.84 (3H, s, 24-H), 0.86 (3H, s, 23-H), 0.87 (3H, s, 25-H), 0.99 (3H, s, 26-H), 1.11 (3H, s, 27-H), 1,21 (6H, d, *J*=6.8 Hz, 29-H, 30-H), 2.04 (3H, s, Me of 3-OAc), 2.18 (1H, m, *J*=14 Hz, *J*=12 Hz, *J*=4 Hz), 2.44 (1H, m, *J*=14 Hz, *J*=12 Hz, *J*=5.5 Hz) 2.65 (1H, dd, *J*=12 Hz, *J*=4.5 Hz, 13β-H), 2.87 (1H, m, *J*=6.8 Hz, 20-H), 3.63 (3H, s, 18-OMe), 4.48 (1H, dd, *J*=10.5 Hz, *J*=5.5 Hz, 3α-H), 5.89 (2H, q, *J*=3.2 Hz, 21-H, 22-H), 1.2-1.9 (the rests H).

(*Received in UK* 28 *January* 1996; *revised* 25 *April* 1996; *accepted* 24 *May* 1996)