126. Synthesis of 12-Methyl-13-tridecanolide

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Dedicated to Professor Dr. *Bogdan Kurtev*, Sofia, on the occasion of his 70th birthday

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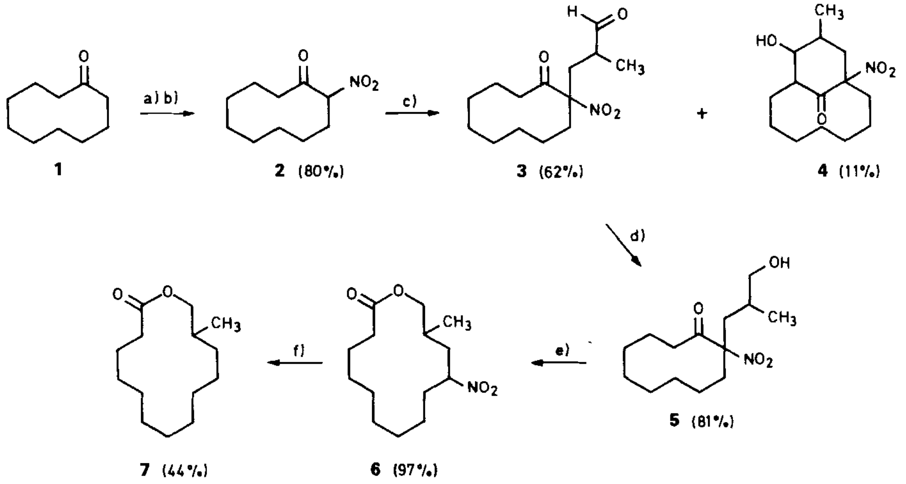
The title compound was prepared from 2-nitrocyclodecanone (**2**). Compound **2** was treated with 2-methylpropenal to give the *Michael*-addition product **3** which was reduced to the alcohol **5** and the latter ring-enlarged with Bu_4NF to 12-methyl-10-nitro-13-tridecanolide (**6**) followed by reductive elimination of the NO_2 group by Bu_3SnH.

The 12-methyl-13-tridecanolide (**7**) is a volatile constituent of the root oil of *Angelica archangelica* L. [1] and was synthesized by *Voss* and *Gerlach* [2] in its racemic form.

In the course of our investigations in the field of macrolides, we have synthesized **7** starting from cyclodecanone (**1**) in an overall yield of 17% *(Scheme)*. Nitration of **1** *via* its enol acetate was performed according to [3] with NH_4NO_3 and $(CF_3CO)_2O$ [4] to give

Scheme



a) $CH_2=C(CH_3)OCOCH_3$, TsOH, 31 h, reflux. b) NH_4NO_3, $(CF_3CO)_2O$, 1 h, 20°, $CHCl_3$. c) $CH_2=C(CH_3)CHO$, Bu_3P, i-PrOH, 30 min, 20°. d) $NaBH_4$, MeOH, 0°. e) Bu_4NF, THF, 20°, 15 min. f) Bu_3SnH, α,α'-azoisobutyronitrile, toluene, reflux.

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[1] Part of the thesis of *St. St.*, guest of the Institute of Organic Chemistry, Bulgarian Academy of Sciences, Sofia.

2-nitrocyclodecanone (**2**) in a yield of 80%. Treatment of **2** with 2-methylpropenal in the presence of catalytic amounts of Bu_3P in i-PrOH gave the desired *Michael* adduct **3** (62%) besides its aldol-reaction product 10-hydroxy-11-methyl-1-nitrobicyclo[7.3.1]tridecan-13-one (**4**; 11%). Several other reaction conditions were tried, but either no reaction was observed ($(C_6H_5)_3P$, 0.1–1 equiv./24 h) or besides unreacted **2**, both products were isolated (*e.g.* using catalysts like Bu_4NF, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or *Triton B*). The spontaneous formation of **4** to a large extent was observed during chromatography of **3** on silica gel or in solutions of **3** in $CHCl_3$, Et_2O, or acetone. The synthesis of pure **4** in a yield of 90% was possible using similar conditions as in the synthesis of **3**, but with benzene instead of i-PrOH as solvents. In contrast to similar *Michael* reactions [5], the high tendency of **3** to form the cyclized aldol product is remarkable. This may be dependent on the 10-membered cycloketone or the additional Me group in the side chain, but we have not investigated both points until now.

Reduction of **3** with $NaBH_4$ gave the alcohol **5** together with 8% of the bicyclic ketone **4** and small amounts of the ring-enlargement product 12-methyl-10-nitro-13-tridecanolide (**6**). The latter was prepared in quantitative yield by treating **5** in dry THF with Bu_4NF. Compounds **3**, **4**, and **5** are mixtures of diastereoisomers while **6** is pure. The reductive elimination of the NO_2 group with Bu_3SnH was done using modified reaction conditions of *Ono et al.* [6]. But even then, the yield of 12-methyl-13-tridecanolide (**7**) was rather low (44%). The synthetic material was identified with the natural **7** on the basis of the published data.

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Experimental Part

General. All solvents and reagents are from *Fluka*, except 2-methyl-2-propenal *(Aldrich)*, and used without further purification, except THF which was destilled over $LiAlH_4$. Bu_4NF was dried (6 h/60°/0.005 Torr) and used as 10% soln. in THF. M.p.: *Mettler FP-5;* uncorrected. Unless otherwise specified: IR spectra: *Perkin-Elmer 297;* $CHCl_3$ soln.; in cm^{-1}. ^1H- (200 MHz) and ^{13}C-NMR (50 MHz): *Varian XL-200;* $CDCl_3$ soln. with TMS as internal standard; chemical shifts (δ) in ppm, coupling constants J in Hz. CI-MS: *MAT 112 S*, reactant gas 2-methylpropane. TLC: silica gel alu foils *(Merck, 60 F_{254})*. Flash chromatography: silica gel *60 PF_{254} (Merck)*. Solns. were dried over anh. $MgSO_4$.

1. *2-Nitrocyclodecanone* (**2**). 1.1. *1-Cyclodecen-1-yl Acetate.* It was synthesized from cyclodecanone (**1**) according to [3] as colourless oil (86%). B.p. 72°/0.15 Torr. $n_D^{22} = 1.4801$ ([3]: $n_D^{25} = 1.4805$). IR: 2930*s*, 2860*m*, 1742*s*, 1695*m*, 1472*w*, 1445*w*, 1370*m*, 1240*s*, 1170*w*, 1155*w*, 1130*m*, 1060*m*, 1020*w*, 920*w*. IR (film): 2920*w*, 2855*m*, 1755*s*, 1685*w*, 1475*w*, 1445*w*, 1368*m*, 1235*m*, 1205*s*, 1165*w*, 1150*w*, 1138*m*, 1070*m*, 1015*w*, 915*w*. ^1H-NMR: 5.22 (*t*, J = 8,0, 0.5 H–C(2)); 5.12 (*t*, J = 8.8, 0.5 H–C(2)); 2.48–2.00 (*m*, 7 H), therein at 2.16 (*d*, J = 11.8, CH_3); 1.43 (br. *s*, 12 H). CI-MS: 197 ($[M + 1]^+$). Anal. calc. for $C_{12}H_{20}O_2$ (196.292): C 73.43, H 10.27; found: C 73.58, H 10.13.

1.2. *2-Nitrocyclodecanone* (**2**). To a soln. of 7.0 g (36 mmol) of the enol acetate (see *1.1*) and 3.04 g (38 mmol) of NH_4NO_3 in 30 ml of $CHCl_3$ were added dropwise under stirring 20 ml (144 mmol) of $(CF_3CO)_2O$ at 20° and stirred for 1 h [4]. The soln. was diluted with CH_2Cl_2 (100 ml) and poured into ice/H_2O (100 ml) and the aq. layer separated and extracted with CH_2Cl_2. The org. layers were washed with cold 1% aq. $NaHCO_3$ soln. (100 ml), H_2O (100 ml), and brine (100 ml), dried, and evaporated. The residue was bulb-to-bulb destilled (105–100°/0.2 Torr): 6,645 g (93%) of **2** yellow oil. $n_D^{22} = 1.5200$ ([7]: $n_D^{20} = 1.5191$). IR: 2940*s*, 2875*m*, 1730*m*, 1698*m*, 1590*s*, 1558*s*, 1510*m*, 1475*m*, 1450*m*, 1398*s*, 1345*m*, 1330*m*, 1315*m*, 1285*m*, 1190*m*, 1110*m*, 1095*m*, 860*w*. IR (film): 2938*s*, 2864*m*, 1729*m*, 1592*s*, 1558*s*, 1515*m*, 1475*m*, 1450*m*, 1396*s*, 1340*m*, 1330*m*, 1310*m*, 1215*m*, 1190*m*, 1110*m*, 1095*m*, 870*w*. ^1H-NMR: 5.41–5.34 (*dd*, J = 9.4, 4.2, H–C(2)); 2.90–2.63 (*m*, 3 H); 2.57–2.20 (*m*, 1 H); 2.00–1.20 (*m*, 12 H). CI-MS: 200 ($[M + 1]^+$). Anal. calc. for $C_{10}H_{17}NO_3$ (199.254): C 60.30, H 8.54, N 7.09; found: C 60.20, H 8.62, N 6.99.

2. *2-Methyl-3-(1'-nitro-2'-oxocyclodecyl)propanal* (**3**). To a soln. of 1.99 g (10 mmol) of **2** and 1.00 g (13 mmol) of 2-methyl-2-propenal in 12 ml of i-PrOH at 20°, 0.224 g (0.11 mmol) of Bu_3P (10% (*v*/*v*) soln. in i-PrOH) were added dropwise under Ar during 5 min. After 30 min stirring at 20°, the reaction was stopped by adding 467 mg (3.3 mmol) of MeI and stirred for 5 min. The solvent was evaporated, the residue dissolved in Et_2O, washed with H_2O, dried, and evaporated. GC analysis of the crystalline residue: **3** (80%), **4** (11%). Recrystallization from hexane/Et_2O 3:1: 1.68 g (62%) of **3**, colourless needles. M.p. 51–52°. IR: 3415*m*, 2925*s*, 2810*w*, 2710*w*, 1730*s*, 1545*s*, 1468*m*. IR (KBr): 2925*m*, 2805*w*, 2710*w*, 1735*s*, 1545*s*, 1468*m*, 1360*w*, 1090*w*. ^{1}H-NMR (diastereoisomeric mixture *ca.* 6:1): 9.63, 9.54 (2 *d*, *J* = 1.0, 2.0, CHO); 3.03–2.86 (*m*, 2 H–C(3)); 2.69–2.11 (*m*, 4 H); 1.93, 1.85 (*dd*, *J* = 15.5, 4.2, H–C(2)); 1.74–1.26 (*m*, 12 H); 1.18 (*d*, *J* = 7.2, CH_3). ^{13}C-NMR (diastereoisomeric mixture): 202.4, 202.2 (2 *s*, CO); 201.9, 201.7 (2 *d*, CHO); 99.8 (*s*, C(1')); 41.8, 41.6 (2 *d*, C(2)); 35.4, 35.2, 34.7, 33.9, 31.2, 30.3, 25.4, 25.24, 25.19, 24.5, 24.3, 24.1, 22.9, 22.7, 19.9, 19.5 (16 *t*); 15.5, 15.1 (2 *q*, CH_3). CI-MS: 270 ($[M + 1]^+$). Anal. calc. for $C_{14}H_{23}NO_4$ (269.346): C 62.45, H 8.55, N 5.20; found: C 62.32, H 8.70, N 5.06.

3. *10-Hydroxy-11-methyl-1-nitrobicyclo[7.3.1]tridecan-13-one* (**4**). To a mixture of 200 mg (1 mmol) of **2** and 84 mg (1.2 mmol) of 2-methyl-2-propenal in 1.5 ml of dry benzene, 60 mg (0.3 mmol) of Bu_3P (as 10% (*v*/*v*) soln. in dry benzene) were added dropwise during 5 min. After 20 min stirring at 20°, it was worked up. The residue was purified by flash chromatography (hexane/Et_2O 1:1): 245 mg (90%) of **4**. M.p. 111.5–112.5°. IR: 3610*w*, 2930*s*, 2880*m*, 1730*s*, 1550*s*, 1472*m*, 1445*w*, 1350*w*, 1065*w*, 1040*w*. IR (KBr): 3540*w*, 2930*s*, 2875*m*, 1725*s*, 1545*s*, 1470*m*, 1460*m*, 1445*m*, 1352*m*, 1065*w*, 1035*m*, 1025*m*, 948*w*, 860*w*, 850*w*, 840*w*, 815*w*, 715*s*, 640*w*. ^{1}H-NMR (diastereoisomeric mixture): 3.90–3.84 (*m*, H–C(10)); 3.26–3.17 (*m*, H–C(9)); 2.71–1.09 (*m*, 21 H), therein at 1.58 (*s*, OH, exchangeable with D_2O) and at 1.22, 1.15, 1.11 (3 *d*, *J* $\approx$ 6.4, CH_3). ^{13}C-NMR: 204.6 (*s*, CO); 98.7, 98.5, 98.4 (3 *s*, C(1)); 80.6, 80.5, 79.4 (3 *d*, C(10)); 53.4, 51.4, 49.5 (3 *d*, C(9)); 41.6, 40.8, 40.2 (3 *t*); 37.5, 36.4, 35.4 (3 *d*, C(11)); 35.3, 34.6, 33.3, 26.4, 26.3, 26.1, 26.0, 24.5, 24.4, 23.8, 23.5, 23.3, 22.2, 22.1, 21.9, 21.3, 21.2, 21.0, 20.6, 20.5, 20.4 (21 *t*); 19.6, 17.4, 16.5 (3 *q*, CH_3). CI-MS: 270 ($[M + 1]^+$). Anal. calc. for $C_{14}H_{23}NO_4$ (269.346): C 62.45, H 8.55, N 5.20; found: C 62.19, H 8.42, N 5.43.

4. *2-Nitro-2-(2'-methyl-3'-hydroxypropyl)cyclodecan-1-one* (**5**). To a soln. of 1.70 g (6.32 mmol) of **3** in 32 ml of MeOH, 0.12 g (3.16 mmol) of $NaBH_4$ were added at 0° in small portions and stirred afterwards at 0° for 30 min. Then, the mixture was given into 0.5% aq. HCl (till pH *ca.* 1), extracted with Et_2O, the org. phase washed with H_2O, dried, and evaporated, and the residue purified by flash chromatography (hexane/Et_2O 2:1): 40 mg (2.4%) of **6** (fast running), 140 mg (8.3%) of **4**, and 1.38 g (81.2%) of **5**, m.p. 76–77° (hexane/Et_2O 4:1). IR: 3610*w*, 2935*m*, 2870*m*, 1725*m*, 1595*s*, 1470*m*, 1360*w*, 1035*m*. IR (KBr): 3310*m*, 2935*m*, 2870*m*, 1720*m*, 1590*s*, 1470*m*, 1360*w*, 1035*m*. ^{1}H-NMR (diastereoisomeric mixture *ca.* 8:1): 3.45–3.29 (*m*, 2 H–C(3')); 2.95–2.79 (*m*, H–C(2')); 2.63–1.23 (*m*, 12 H), therein at 1.70 (*s*, OH, exchangeable with D_2O) and at 0.96, 0.80 (2 *d*, *J* = 6.8, 6.8, CH_3). ^{13}C-NMR: 203.3 (*s*, CO); 100.9 (*s*, C(2)); 68.2, 67.1 (2 *t*, C(3')); 37.4, 36.7, 35.3, 34.7 (4 *t*); 31.4, 31.2 (2 *d*, C(2')); 31.3, 29.4, 25.5, 25.3, 24.5, 24.4, 24.2, 24.1, 22.8, 22.7, 19.8, 19.6 (12 *t*); 18.7, 16.2 (2 *q*, CH_3). CI-MS: 272 ($[M + 1]^+$). Anal. calc. for $C_{14}H_{25}NO_4$ (271.362): C 61.96, H 9.29, N 5.16; found: C 61.78, H 9.07, N 5.09.

5. *12-Methyl-10-nitro-13-tridecanolide* (**6**). To a soln. of 850 mg (3.14 mmol) of **5** in 25 ml of dry THF, 95 mg (0.314 mmol) of Bu_4NF under Ar were added. After 15 min stirring at 20°, the reaction was stopped by passing the mixture through a short column. The resulting oil crystallized: 850 mg. After recrystallization from hexane/Et_2O 5:1, 820 mg (96.5%) of **6** as colourless prisms were obtained. M.p. 50.5–50.8°. IR: 2940*s*, 2860*m*, 1730*s*, 1550*s*, 1460*m*, 1378*m*, 1150*m*. IR (KBr): 2940*s*, 2860*m*, 1730*s*, 1550*s*, 1465*m*, 1450*m*, 1375*m*, 1340*m*, 1310*m*, 1290*m*, 1260*m*, 1245*m*, 1230*m*, 1150*m*, 1100*m*, 1000*m*. ^{1}H-NMR: 4.74–4.60 (*m*, H–C(10)); 4.35–4.27 (*dd*, *J* = 11.6, 2.8, H–C(13)); 3.83–3.75 (*dd*, *J* = 11.4, 5.6, H–C(13)); 2.56–2.28 (*m*, 2 H–C(2)); 2.04–1.20 (*m*, 11 H); 1.03 (*d*, *J* = 6.6, CH_3). ^{13}C-NMR: 173.5 (*s*, CO); 84.6 (*d*, C(10)); 66.9 (*t*, C(13)); 34.8, 34.0, 32.4 (3 *t*); 29.5 (*d*, C(12)); 25.5, 25.4, 25.2, 24.0, 23.7, 22.6 (6 *t*); 17.8 (*q*, CH_3). CI-MS: 272 ($[M + 1]^+$). Anal. calc. for $C_{14}H_{25}NO_4$ (271.362): C 61.96, H 9.29, N 5.16; found: C 61.83, H 9.42, N 5.19.

6. *(±)-12-Methyl-13-tridecanolide* (**7**). To a soln. of 3.66 ml (13.8 mmol) of Bu_3SnH in 3 ml of dry toluene, a soln. of 747 mg (2.76 mmol) of **6** and 410 mg (2.5 mmol) of α,α'-azoisobutyronitrile in 5 ml of dry toluene was added dropwise during 30 min under Ar and reflux. After additional 10 min boiling, the mixture was cooled and chromatographed (hexane/toluene 1:1): 291 mg (47%) of **7**, yellow oil with musk-like odor which was bulb-to-bulb destilled (b.p. 100°/0.005 Torr; [2]: b.p. 90°/0.005 Torr): 271 mg (43.8%). IR: 2915*s*, 2860*s*, 1720*s*, 1460*m*, 1445*m*, 1375*w*, 1340*w*, 1255*m*, 1240*m*, 1165*m*, 1150*m*, 1107*w*, 1060*w*, 1007*w*. IR (film): 2920*s*, 2850*s*, 1735*s*, 1460*m*, 1440*m*, 1375*w*, 1340*w*, 1235*m*, 1170*m*, 1148*m*, 1105*w*, 1060*w*, 1005*w*. ^{1}H-NMR: 4.23–4.16 (*dd*, *J* = 10.8, 3.4, H–C(13)); 3.75–3.65 (*dd*, *J* = 10.8, 8.4, H–C(13)); 3.50–2.26 (*m*, 2 H–C(2)); 1.86–0.91 (*m*, 22 H), therein at 0.92 (*d*, *J* = 6.8, CH_3). ^{13}C-NMR: 173.9 (*s*, CO); 68.0 (*t*, C(13)); 34.2 (*t*); 31.8 (*d*, C(12)); 30.1, 26.2, 26.1, 25.7, 25.6, 24.6, 24.0, 23.7,

22.4 (9 *t*); 16.7 (*q*, CH_3). CI-MS: 227 ($[M + 1]^+$). EI-MS (> 10 rel %): 226 (10, $M^{+\cdot}$), 208 (14, $[M - 18]^+$), 153 (13), 125 (10), 124 (13), 112 (14), 111 (23), 110 (17), 109 (10), 98 (40), 97 (34), 95 (21), 85 (17), 84 (39), 83 (43), 82 (31), 81 (29), 73 (11), 72 (19), 71 (20), 70 (38), 68 (26), 67 (22), 57 (62), 56 (89), 55 (100), 54 (12), 43 (55), 42 (30), 41 (94). Anal. calc. for $C_{14}H_{26}O_2$ (226.362): C 74.34, H 11.50; found: C 73.95, H 11.40.

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