

162. Synthesis of 14-Membered Lactones from Cyclooctanone

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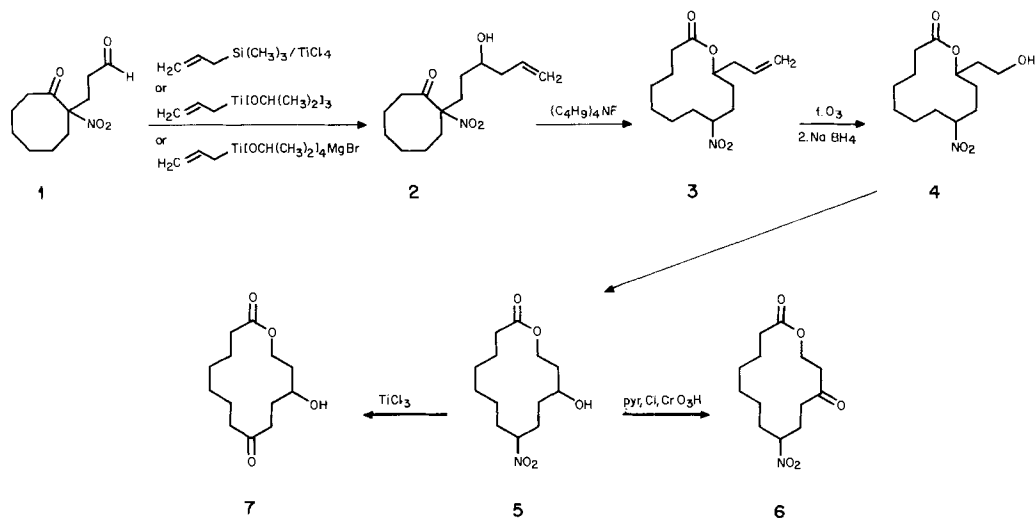
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Summary

As shown in the *Scheme*, 3-(1-nitro-2-oxocyclooctyl)propanal (**1**) prepared earlier from cyclooctanone was converted into the 14-membered lactones **6** and **7**. The aldehyde **1** was submitted to allylation to give **2** using allyltitanium or allylsilicon reagents. After lactonization and transformation of the C,C-double bond to an alcohol, **4** was transactonized under acidic conditions to form **5**, from which **6** and **7** were prepared.

In two previous papers we have reported the synthesis of 6-nitro-9-decanolide [1] and 8-nitro-11-dodecanolide [2] by one-step ring enlargement reactions using 2-nitrocyclohexanone and 2-nitrocyclooctanone, respectively, as starting materials. In this paper we report the synthesis of 8-nitro-11-oxo-13-tridecanolide (**6**) and 11-hydroxy-8-oxo-13-tridecanolide (**7**) by a two stage *zip* reaction.

Scheme



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The methylation of 3-(1-nitro-2-oxocyclooctyl)propanal (**1**) with $\text{CH}_3\text{Ti}[\text{OCH}(\text{CH}_3)_2]_3$ to yield 2-nitro-2-(3-hydroxybutyl)cyclooctanone was reported earlier [2]. To introduce a hydroxylated alkyl substituent at the aldehyde C-atom in **1**, attempts were made to use *O*-protected titanium reagents such as 3-(*tert*-butyl)dimethylsilyloxypropyl- and 3-(tetrahydropyran-2-yl)oxypropyltitanium triisopropoxide. However, under various reaction conditions no product was obtained. Titanium reagents containing additional O-atoms at the alkyl substituent(s) do not seem to be sufficiently reactive. Similar results have also been reported [3].

On the basis of these negative results, an indirect route was used. Treatment of **1** with allyltrimethylsilane [4] in the presence of TiCl_4 in dry CH_2Cl_2 at -65° gave in quantitative yield the desired 2-(3-hydroxy-5-hexenyl)-2-nitrocyclooctanone (**2**), see *Scheme*. The same product was obtained using $\text{CH}_2=\text{CH}-\text{CH}_2-\text{Ti}[\text{OCH}(\text{CH}_3)_2]_3$ in THF in 57.8% yield and allylmagnesium bromide/ $\text{Ti}[\text{OCH}(\text{CH}_3)_2]_4$ complex in THF in approx. 50% yield. The reaction product **2** is an oil which seems to be a diastereomeric mixture, judged by its complex $^1\text{H-NMR}$ spectrum.

To protect the OH-group against oxidation in a later step, the ring enlargement reaction of **2** to 8-nitro-13-tetradecen-11-olide (**3**) was achieved in the presence of tetrabutylammonium fluoride (TBAF) in THF. The yield was 85% with respect to **1**. Again compound **3** is an oily diastereomeric mixture ($^1\text{H-NMR}$ evidence) with a ratio of nearly 3:2 of the two components. The conversion of the vinyl group into a primary OH-group was achieved with O_3/MeOH followed by NaBH_4 reduction. The yield of the diastereomeric mixture ($^1\text{H-NMR}$: ratio of the two components nearly 3:2) 13-hydroxy-8-nitro-11-tridecanolide (**4**) was 75%. The transformation of the 12-membered **4** to the 14-membered 11-hydroxy-8-nitro-13-tridecanolide (**5**) was not performed in the presence of catalytical amounts of TBAF (0.2 equiv.) in THF, but **5** was obtained under acidic conditions. (\pm)-Camphor-10-sulfonic acid in CH_2Cl_2 converted **4** to a mixture of **4** and **5**, which was oxidized without purification by pyridinium chlorochromate [5] to the crystalline 8-nitro-11-oxo-13-tridecanolide (**6**, $\text{C}_{13}\text{H}_{21}\text{NO}_5$, m.p. $70.5\text{--}72.0^\circ$) in a yield of 64% (from **4**). Compound **6** shows in the IR spectrum the lactone and carbonyl absorption at 1720 and the nitro absorption at 1545 cm^{-1} . Its $^{13}\text{C-NMR}$ spectrum exhibits the expected 13 resonances and its molecular weight was determined by chemical-ionization mass spectrometry (methylpropane) as 272 [$M + \text{H}$] $^+$. To confirm the synthesis and the spectral assignments of **6** its structure was proved by X-ray analysis. In the *Figure* the stereoprojection of **6** is given [6]. The mixture **4/5** was converted by TiCl_3 into the crystalline 11-hydroxy-8-oxo-13-tridecanolide (**7**) in 54% yield (from **4**).

It is noteworthy to mention that the alkylation of **1** with the allyltitanium reagent proceeds in a regiospecific manner [7]. It is not quite clear whether the resulting alcohol **2** is a diastereomeric mixture. Further experiments are necessary. As mentioned above, the transformation of **4** into **5** in reasonable yield was only possible using acidic reaction conditions. The driving force of the ring enlargement reaction **2** to **3** seems to depend on the steric release (medium-to-nearly-large ring) and the formation of the nitronate anion. In case of the ring enlargement of **4**, steric factors may only marginally influence this reaction.

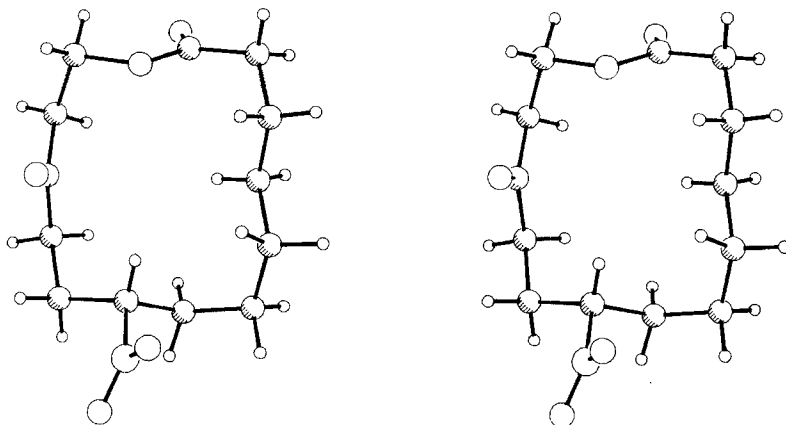


Figure. Stereoprojection of 6

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Experimental Part

General. All reactions were conducted under Ar-atmosphere. Chemical-ionization mass spectrometry was carried out with methylpropane; column chromatography on silicic acid (*Mallinckrodt*, 100 mesh). UV and I_2 were used for detection on TLC. Unless otherwise specified: IR spectra as film in cm^{-1} ; $^1\text{H-NMR}$ spectra in CDCl_3 at 90 MHz; $^{13}\text{C-NMR}$ spectra in CDCl_3 with *Varian XL 100*; δ in ppm, J in Hz, standard tetramethylsilane = 0 ppm. Mass spectra in m/z (> 5% relative intensity). Solutions were dried over anhydrous MgSO_4 .

2-(3-Hydroxy-5-hexenyl)-2-nitro-cyclooctanone (**2**). - 1) To a mixture of 3-(1-nitro-2-oxocyclooctyl)propanal (**1**) [2] (2.26 g, 0.01 mol) and dry CH_2Cl_2 (60 ml) was added dropwise TiCl_4 (3.80 g, 0.02 mol) at -65° . After stirring for 5 min, allyltrimethylsilane (2.60 g, 0.02 mol) [4] was added dropwise at the same temp. and stirred for an additional 20 min, and was then acidified with aq. HCl (1N, 20 ml). The mixture was extracted with CH_2Cl_2 , the extract washed with aq. 1N HCl, H_2O , sat. aq. NaCl and then dried. The solvent was removed under reduced pressure to give **2** as a residual oil (2.70 g, quantitative), which was used for the next reaction without purification. An analytical sample (oil) of **2** was obtained by column chromatography (benzene/hexane/ CH_2Cl_2 10:7:3). IR: 3550 (sh), 3400, 3070, 1720, 1640, 1542, 920. $^1\text{H-NMR}$: 6.01–5.63 (*m*, 1H); 5.23–4.97 (*m*, 2H); 3.83–3.50 (*m*, 1H); 2.9–1.0 (*m*, 19H). MS: 269 (M^+ , 0), 228 (9), 197 (5), 182 (41), 181 (13), 139 (10), 137 (6), 135 (10), 121 (8), 113 (9), 111 (7), 109 (14), 107 (7), 97 (13), 95 (20), 93 (16), 91 (9), 85 (9), 84 (8), 83 (29), 82 (6), 81 (42), 80 (5), 79 (20), 77 (7), 71 (10), 70 (5), 69 (33), 68 (10), 67 (70), 57 (16), 56 (7), 55 (68), 54 (11), 53 (18), 44 (6), 43 (30), 42 (15), 41 (100), 40 (8). Anal. calc. for $\text{C}_{14}\text{H}_{23}\text{NO}_4$ (269.35): C 62.43, H 8.61, N 5.20; found: C 62.61, H 8.47, N 5.46.

2) To a stirred mixture of chlorotriisopropoxytitanium (2.6 g, 0.01 mol) and dry THF (20 ml), a solution of allylmagnesium bromide in THF [prepared from allyl bromide (1.32 g, 0.011 mol), an excess of Mg-turnings and dry THF (40 ml)], at -65° was added. After stirring for 2 h at the same temp., a solution of **1** (0.57 g, 0.0025 mol) in dry THF (10 ml) was added dropwise and the resulting mixture was stirred for 2 h at -40° and 2 h at -5° . Then the mixture was poured into aq. HCl (1N, 100 ml), extracted with Et_2O , the extract washed with aq. HCl (1N), H_2O , sat. aq. NaCl, and dried. The solvent was removed under reduced pressure to give a residue, which was purified by column chromatography (benzene/hexane/ CH_2Cl_2 10:7:3) to yield **2** (0.39 g, 57.8%) as an oil.

3) To a stirred mixture of titanium tetraisopropoxide (2.84 g, 0.01 mol) and dry THF (20 ml) at 65° was added a solution of allylmagnesium bromide in THF [prepared from allyl bromide (1.32 g, 0.011 mol), an excess of Mg-turnings and dry THF (40 ml)] [8]. After stirring for 1 h at the same temp., a solution of **1** (0.57 g, 0.0025 mol) in dry THF (10 ml) was added dropwise and the resulting mixture was stirred (1 h at -40° , 1 h at 0°). TLC showed that **2** was formed ($\approx 50\%$ yield), no isolation was attempted.

8-Nitro-13-tetradecen-11-olide (3). To a stirred solution of crude **2** (2.70 g, ≈ 0.01 mol) in dry THF (40 ml) were added anh. TBAF (0.52 g, 0.002 mol) and molecular sieve (3Å, 0.20 g) at r.t. and stirred for 24 h at r.t. The mixture was then poured into H₂O, acidified with AcOH and extracted with Et₂O. The extract was washed with H₂O and sat. aq. NaCl, and dried. The solvent was removed under reduced pressure to give a residue, which was purified by column chromatography (benzene/hexane 10:7) to afford **3** (2.28 g, 85% from **1**) as an oil. IR: 3070, 1730, 1640, 1545, 920; in CHCl₃: 1720, 1640, 1542, 920. ¹H-NMR (diastereomeric mixture): 5.97–5.47 (*m*, 1H); 5.23–4.73 (*m*, ≈ 3.6 H); 4.5 (quint., *J* = 6.0, ≈ 0.4 H); 2.50–1.20 (*m*, 18H). MS: 269 (*M*⁺, 0), 229 (5), 228 (26), 223 (6), 222 (6), 179 (8), 154 (7), 135 (9), 133 (6), 123 (7), 121 (8), 119 (6), 111 (8), 109 (18), 107 (9), 105 (5), 98 (7), 97 (12), 95 (24), 94 (12), 93 (17), 91 (6), 85 (10), 84 (7), 83 (19), 81 (37), 80 (21), 79 (27), 71 (20), 70 (6), 69 (37), 68 (11), 67 (47), 57 (15), 56 (7), 55 (62), 54 (10), 53 (10), 43 (19), 42 (12), 41 (100). Anal. calc. for C₁₄H₂₃NO₄ (269.35): C 62.43, H 8.61, N 5.20; found: C 62.35, H 8.88, N 5.32.

13-Hydroxy-8-nitro-11-tridecanolide (4). A stream of O₃/O₂ was passed through a solution of **3** (1.0 g, 3.7 mmol) in dry MeOH (70 ml) at -78° until the mixture was light blue. Then the mixture was purged with N₂ to remove excess O₃, treated with NaBH₄ (0.5 g, 0.013 mol) at -78° and slowly warmed up to r.t. After stirring overnight, the mixture was poured into H₂O, acidified with AcOH, and extracted with Et₂O. The extract was washed with H₂O and sat. aq. NaCl-solution and dried. The solvent was removed under reduced pressure to give a residue, which was purified by column chromatography (Merck, silica gel, CH₂Cl₂/acetone 20:1) to afford **4** (0.76 g, 75%) as an oil. IR: 3440, 1730, 1550. ¹H-NMR (diastereomeric mixture): 5.47–5.13 (*m*, 1H); 5.07–4.73 (*m*, ≈ 0.6 H); 4.70–4.33 (*m*, ≈ 0.4 H); 3.85–3.40 (*m*, CH₂–OH); 2.8–1.0 (*m*, 19H). MS: 273 (*M*⁺, 0), 209 (5), 135 (11), 133 (7), 123 (6), 121 (7), 119 (5), 111 (5), 109 (19), 107 (13), 105 (5), 98 (6), 97 (15), 96 (6), 95 (38), 94 (7), 93 (20), 91 (9), 85 (16), 84 (7), 83 (19), 82 (8), 81 (59), 80 (8), 79 (22), 73 (18), 71 (41), 70 (9), 69 (44), 68 (15), 67 (68), 57 (26), 56 (9), 55 (100), 54 (21), 53 (12), 45 (11), 43 (34), 42 (17), 41 (92). CI–MS: 274 ([*M* + 1]⁺, 100), 256 (43), 243 (58), 227 (30), 225 (23), 209 (56). Anal. calc. for C₁₃H₂₃NO₅ (273.34): C 57.13, H 8.48, N 5.12; found: C 56.76, H 8.38, N 5.04.

11-Hydroxy-8-nitro-13-tridecanolide (5). To a mixture of **4** (1.36 g, 4.9 mmol) in dry CH₂Cl₂ (50 ml) was added (±)-camphor-10-sulfonic acid (30 mg, 0.13 mmol). After stirring for 50 h at r.t., the mixture was washed with 5% aq. NaHCO₃, H₂O and sat. aq. NaCl and dried. The solvent was removed under reduced pressure to give a mixture (1.36 g) of **4** and **5**, which was submitted to the next reaction without purification.

8-Nitro-11-oxo-12-tridecanolide (6). To a suspension of pyridinium chlorochromate [5] (1.62 g, 7.5 mmol) in dry CH₂Cl₂ (9 ml) was added rapidly a solution of crude **5** (1.36 g) in dry CH₂Cl₂ (10 ml). The mixture was stirred for 1.5 h at r.t. and then diluted with dry Et₂O (50 ml). The supernatant liquid was decanted from the black gum. The gum was washed three times with Et₂O. The combined org. solutions were passed through a short silica gel column and the solvent was removed under reduced pressure to give an oil, which was crystallized from Et₂O/hexane (2:1) to give **6** (0.86 g, 64% from **4**) as colorless crystals. M.p. 70.5–72.0°. IR (CHCl₃): 1720, 1545. ¹H-NMR: 4.73–4.33 (*m*, 3H); 3.1–1.0 (*m*, 18H). ¹³C-NMR: 205.7, 172.7, 84.8, 59.2, 41.3, 38.0, 33.9, 28.7, 26.4, 25.7, 25.0, 24.0, 22.6. CI–MS: 272 ([*M* + 1]⁺, 20), 256 (8), 254 (8), 225 (100), 224 (25), 207 (68). Anal. calc. for C₁₃H₂₁NO₅ (271.32): C 57.55, H 7.80, N 5.16; found: C 57.28, H 7.94, N 5.06.

11-Hydroxy-8-oxo-13-tridecanolide (7). Crude **5** (1.1 g) was dissolved in a methanolic solution (30 ml) of MeONa (0.27 g, 5 mmol). After stirring for 5 min, a mixture of TiCl₃ (2.5 g, 16 mmol), NH₄OAc (7.5 g, 0.1 mol) and H₂O (34 ml) was added rapidly at r.t. and stirring was continued for 40 min [9]. Then the mixture was extracted with Et₂O, the extract washed with H₂O and sat. aq. NaCl and dried. The solvent was removed under reduced pressure to give a residue, which was purified by column chromatography (Merck, silica gel, CH₂Cl₂/acetone 30:1) followed by crystallization from Et₂O to give **7** (0.52 g, 54% from **4**) as colorless crystals. M.p.: 81.0–82.0°. IR (in CHCl₃): 3490, 1710. ¹H-NMR: 4.60–3.83 (*m*, 2H); 3.60–3.13 (*m*, 1H); 2.9–0.9 (*m*, 19H). ¹³C-NMR: 211.4, 173.5, 64.8, 60.0, 40.4, 38.4, 35.3, 33.2, 31.6, 26.9 (2 C), 24.5, 22.1. MS: 242 (*M*⁺, 2), 225 (9), 224 (50), 206 (5), 197 (5), 196 (6), 195 (5), 186 (6), 185 (19), 182 (7), 172 (6), 171 (5), 168 (12), 167 (9), 157 (27), 155 (28), 154 (19), 152 (6), 151 (5), 141 (7), 140 (17), 139 (27), 138 (5), 137 (11), 136 (7), 131 (8), 130 (14), 128 (8), 127 (7), 126 (23), 125 (9), 124 (7), 123 (17), 122 (8), 121 (11), 115 (7), 114 (6), 113 (61), 112 (38), 111 (74), 110 (38), 109 (43), 108 (11), 107 (5), 101 (9), 100 (16), 99 (5), 98 (19), 97 (50), 96 (14), 95 (31), 94 (14), 93 (12), 91 (7), 89 (5), 88 (5), 85 (26), 84 (35), 83 (42), 82 (19), 81 (18), 80 (5), 79 (12), 77 (6), 73 (9), 72 (16), 71 (90), 70 (29), 69 (56), 68 (98), 67 (57), 66 (5), 65 (5), 59 (7), 58 (20), 57 (41), 56 (20), 55 (100), 54 (9), 53 (15). Anal. calc. for C₁₃H₂₂O₄ (242.32): C 64.44, H 9.15; found: C 64.35, H 9.27.

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