127. Cyclopentenone Annulation of 2-Oxocycloalkane-1-carbonitriles

by **Vassil I. Ognyanov**[1]) and **Manfred Hesse***

Organisch-chemisches Institut der Universität Zürich, Winterthurerstrasse 190, CH–8057 Zürich

(11.VI.87)

Phase-transfer alkylation of the 2-oxocycloalkane-1-carbonitriles **1a** and **1b** with ethyl 4-bromo-3-methoxy-2-butenoate (**2**), followed by deprotection and base-catalyzed cyclization gave the annulated cyclopentenones **5a** and **5b**, respectively, in high overall yields *(Scheme 1)*. Stereoselective catalytic hydrogenation of **5b** followed by de-ethoxycarbonylation afforded 14-oxo-*cis*-bicyclo[10.3.0]pentadecane-1-carbonitrile (**7**). Treatment of **7** with $LiN(i\text{-}Pr)_2$ in THF gave the known synthetic muscone precursor **8** *(Scheme 2)*. The tricyclo[10.4.0.$0^{1,15}$]hexadecan-14-one (**14**) was prepared from **7** in 5 steps by a reaction sequence proceeding without affecting the chiral centres *(Scheme 2)*. The structure of **14** was established by X-ray structure analysis *(Figure)*.

During the course of our studies on the zip reaction, we have shown that the CN group can be used as a good anion stabilizer in the ring enlargement of cycloalkanones [1–3].

The results obtained in the case of the carbon zip reaction [3] were strongly dependent on the ring size of the cycloalkanone and on the length of the alkyl-carboxylate side chain used. With this method, good yields of the C_3 ring enlargement were observed only for the 8-membered oxo-carbonitrile. On the other hand, we have shown [4] that *Michael* adducts of 2-nitrocycloalkanones with 3-oxo-4-pentenoates rearrange smoothly into compounds enlarged by 4 C-atoms. In this case, the side chain used had a C-nucleophilic centre, twice activated by carbonyl and alkoxycarbonyl functions. Thus, it seemed reasonable to find a way for introducing a similarly activated side chain into position 1 of 2-oxocycloalkane-1-carbonitriles which could serve for the preparation of compounds enlarged by three C-atoms. Therefore, we decided to use ethyl 4-bromo-3-methoxy-2-butenoate (**2**) [5] as an alkylating agent which is an γ-electrophilic equivalent of ethyl 3-oxobutyrate [6].

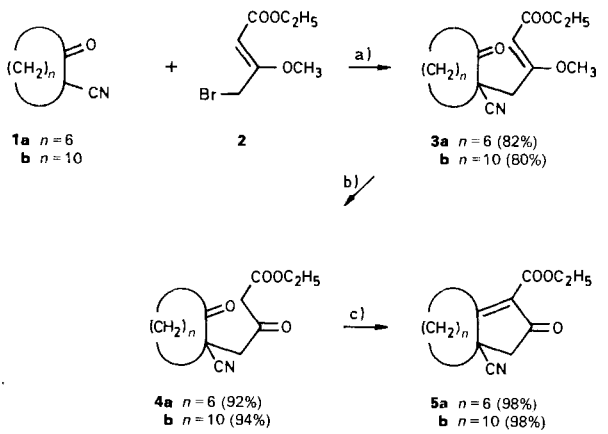
The alkylated compounds **3a, b** were obtained in high yields from **2** and the 2-oxocycloalkane-1-carbonitriles **1a, b** [7] under the conditions of phase-transfer catalysis ($Bu_4NHSO_4/CH_2Cl_2/2N$ aq. NaOH; *Scheme 1*). Deprotection of the enol-ether function in **3a, b** with CF_3COOH provided the desired β-keto esters **4a** and **4b** in 92 and 94% yield, respectively[2]).

All attempts to convert **4a** or **4b** into a ring-enlarged compound under different conditions ($LiN(i\text{-}Pr)_2$/THF at $-40\rightarrow20°$; *t*-BuOK/THF/0°; Bu_4NF/THF/20°; $KHCO_3$/CH_3OH/20°) failed. The only isolable products were the corresponding annulated cyclo-

[1]) On leave from the Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, 1113 Sofia, Bulgaria.

[2]) An analogous alkylation of β-keto esters with methyl 4-bromo-3-methoxy-2-butenoate and Na sand in Et_2O, followed by deprotection with CF_3COOH was already described [8].

Scheme 1



a) Bu_4NHSO_4/2N aq. NaOH/CH_2Cl_2;
b) CF_3COOH/CCl_4;
c) Bu_4NOH/CH_2Cl_2.

pentenones **5a, b**, obtained in almost quantitative yields when a catalytic amount of Bu_4NOH in CH_2Cl_2 was used as a base *(Scheme 1)*[3]).

This result is in contrast to the rearrangement of 2-nitrocycloalkanones possessing a β-keto ester side chain homologous to that in **4a, b** [4]. A bicyclic compound similar to **5a, b** was obtained only in the case of the 5-membered nitro ketone, while the 8- and 12-membered nitro ketones gave products of C_4 ring enlargement. On the other hand, we have shown [3] that a C_3 ring enlargement can be realized with an oxo-carbonitrile analogous to **4a**, having a side chain activated only with an alkoxycarbonyl function. In the present work, the unsuccessful ring enlargement of **4a, b** is probably due to the weaker electron-attracting ability of the CN group, leading to the irreversible formation of the products **5a, b** of aldol condensation.

The ease of the preparation of the bicycles **5a, b** prompted us to try their conversion into medium sized ring compounds. Thus, the catalytic hydrogenation of **5b** with 5% Pd/C in MeOH occurred stereoselectively[4]) to give the *cis*-diastereoisomeric mixture **6** as a main product together with its enolic form **6'**. The 1,12-*cis*-configuration of **6** was deduced from the X-ray structure of compound **14**, prepared from **6** by a sequence proceeding without affecting the chiral centres C(1) and C(12) *(Scheme 2)*.

De-ethoxycarbonylation of **6** with NaI/AcOH/diglyme [8] gave the bicyclic oxo-carbonitrile **7** in the form of its 1,12-*cis*-diastereoisomer. Further treatment of **7** with $LiN(i\text{-}Pr)_2$/THF/$-78 \rightarrow 50°$ afforded the known [12] synthetic muscone precursor **8**[5]) and the thermodynamically more stable 1,12-*trans*-diastereoisomer **9** in 50 and 35% yield, respectively. It could be assumed that the isomerization of **7** into **9** probably occurred through a *Michael*-type addition of a CN anion to the initially formed α,β-unsaturated ketone **8** *(Scheme 2)*.

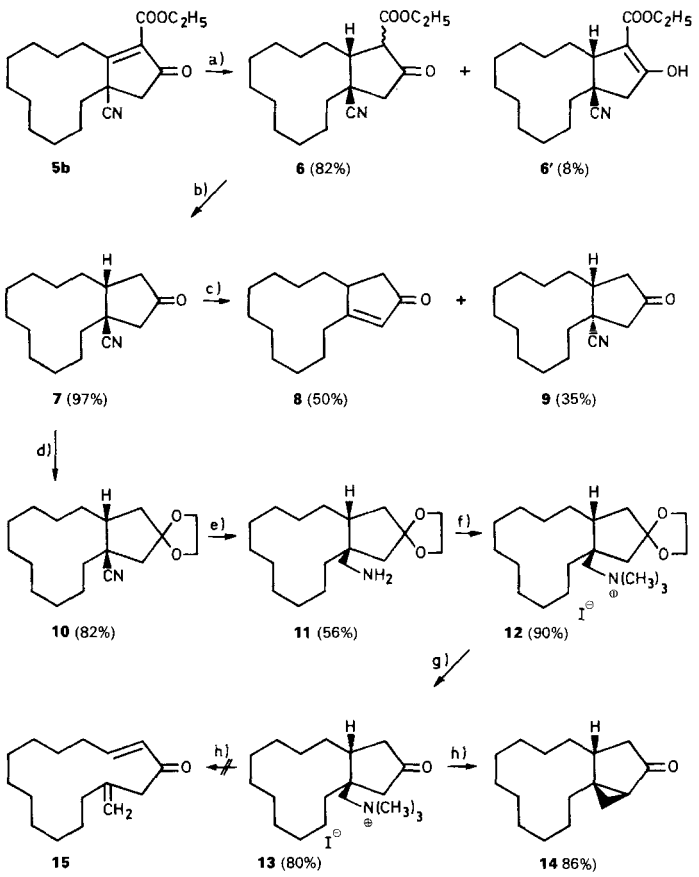
---

[3]) For recent variants of cyclopentenone annulation, see [6] [8–11].

[4]) A stereoselective hydrogenation of an analogue to **5b**, a cyclopentenone, is described in [8].

[5]) A high-yield conversion of **8** into the naturally occurring 15-membered cyclic ketones muscone and exaltone was published [12].

Scheme 2



a) H_2/Pd/C/MeOH/0°; b) NaI/AcOH/diglyme; c) Li(i-Pr)$_2$N/THF; d) $HOCH_2CH_2OH$/TsOH/C_6H_6; e) H_2/Rh/Al_2O_3/NH_3/EtOH; f) CH_3I/$KHCO_3$/MeOH; g) $(HOOC)_2$/SiO_2/CH_2Cl_2; h) *Amberlyst A 26*, $F^{\ominus}$-form/THF.

In [13], we described the synthesis of a methylidene lactone from a 1-oxocycloalkane-2-carbonitrile derivative by means of a ring-enlargement reaction assisted with a heterolytic fragmentation [14–16]. As a main step, a *Hofmann*-type elimination of a quaternary ammonium salt derived from a CN group was utilized. Thus, it seemed reasonable to try the enlargement of the bicyclic oxo-carbonitrile **7** into the exocyclic methylidene ketone **15** by using a similar fragmentation process. The protected carbonitrile **10** was prepared from **7** and ethylene glycol in 82% yield. Catalytic hydrogenation of the CN group in **10** was carried out with H_2/Rh/Al_2O_3 in 10% NH_3 in EtOH [17]. The corresponding amine **11**, obtained in 56% yield, was further subjected to an exhaustive *Hofmann* methylation to give the quaternary ammonium iodide **12** in 90% yield. Cleavage of the acetal function in **12** on wet SiO_2 [18] afforded the ketone **13** in 80% yield. From the structure of **13** is seen that β-elimination of a quaternary ammonium salt is impossible to occur due to the

absence of a β-proton. Therefore, it could be expected that abstraction of a proton in α-position to the carbonyl group will lead to the product **14** of γ-elimination or to the desired fragmentation product **15**. For proton abstraction, we used fluoride ions [19]. Thus, treatment of the quaternary ammonium iodide **13** with a F-anion exchange resin in boiling THF afforded directly the tricyclus **14** in 86% yield. No traces of the ring-enlarged compound **15** could be detected *(Scheme 2)*. The structure assignment of **14** was supported by spectral data as well as by X-ray structure analysis *(Figure)*. Attempts for ring enlargement of the quaternary ammonium iodide **12** by F-anion exchange and further pyrolysis were unsuccessful.

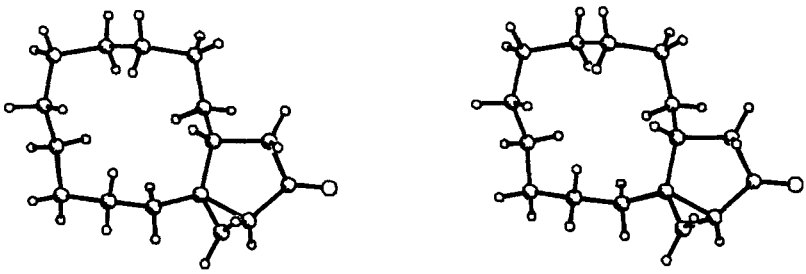


Figure. *Stereoprojection of Tricyclo[10.4.0.0^{4,15}]hexadecan-14-one* (**14**)

This work was supported by the *Swiss National Science Foundation* which is thankfully acknowledged. We thank Dr. *R. Prewo* for X-ray structure determination, Dr. *A. Lorenzi-Riatsch* for mass spectra, and Dr. *R. Kunz* for ^{13}C-NMR spectra.

Experimental Part

General. If not otherwise mentioned, the following conditions were used: before evaporation, org. solns. were dried (Na_2SO_4). Flash chromatography: silica gel *60 PF_{254}* for prep. TLC chromatography, *Merck*. M.p.: *Mettler-FP-52* apparatus. IR (cm^{-1}): in $CHCl_3$ on *Perkin-Elmer 297*. ^{1}H-NMR: *Varian XL-200* at 200 MHz in $CDCl_3$; δ in ppm, J in Hz; tetramethylsilane as internal standard (= 0 ppm). ^{13}C-NMR: *Varian XL-200* at 50 MHz. EI-MS: *Varian MAT 112S; m/z* (rel. intensity 5%). CI-MS: *Varian MAT 112* (2-methylpropane).

1. *Ethyl 4-(1-Cyano-2-oxocyclooctyl)-3-methoxy-2-butenoate* (**3a**) *and Ethyl 4-(1-Cyano-2-oxocyclododecyl)-3-methoxy-2-butenoate* (**3b**). To a soln. of **1a** or **1b** (10 mmol), **2** (2.45 g, 11 mmol), and Bu_4NHSO_4 (*Fluka;* 0.37 g, 1.1 mmol) in CH_2Cl_2 (20 ml), 2N aq. NaOH (6.1 ml, 12.2 mmol) was added within 3 min under stirring. After 1 h stirring at 20°, the org. layer was evaporated, the residue dissolved in Et_2O (50 ml), and the org. layer washed with H_2O and sat. NaCl soln., dried, and evaporated. The residue was chromatographed (45 g of silica gel, Et_2O/hexane 1:2) or crystallized from EtOH to give **3a** (2.41 g, 82.4%) or **3b** (2.80 g, 80.3%).

Data of **3a**: Oil. IR: 2240, 1712, 1632. ^{1}H-NMR: 5.16 (*s*, H–C(2)); 4.14 (*q*, J = 7, CH_3CH_2O); 3.63 (*s*, CH_3O); 3.70, 3.33 (*AB*, J = 15, 2 H–C(4)); 2.82–2.48 (*m*, 2 H); 2.40–2.20 (*m*, 13 H), therein at 1.28 (*t*, J = 7, CH_3CH_2O). ^{13}C-NMR: 208.1 (CO); 168.2 (COO); 167.0 (C(3)); 119.0 (CN); 94.1 (C(2)); 59.8 (CH_3CH_2O); 55.7 (CH_3O); 53.3 (C(1)); 37.7, 35.2, 28.2, 26.2, 24.5, 24.4, 24.2 (7 CH_2); 14.2 (CH_3CH_2O). CI-MS: 294 ([M + 1]$^+$), 248. Anal. calc. for $C_{16}H_{23}NO_4$ (293.36): C 65.50, H 7.90, N 4.77; found: C 65.43, H 7.90, N 4.63.

Data of **3b**: M.p. 85–87° (EtOH). IR: 2240, 1710, 1636. ^{1}H-NMR: 5.15 (*s*, H–C(2)); 4.13 (*q*, J = 7, CH_3CH_2O); 3.63 (*s*, CH_3O); 3.70, 3.36 (*AB*, J = 15, 2 H–C(4)); 2.96–2.68 (*m*, 2 H); 2.16–1.16 (*m*, 21 H), therein at 1.28 (*t*, J = 7, CH_3CH_2O). ^{13}C-NMR: 202.7 (CO); 169.1 (COO); 167.1 (C(3)); 119.7 (CN); 93.5 (C(2)); 59.7 (CH_3CH_2O); 55.8 (CH_3O); 52.9 (C(1)); 35.6, 34.7, 26.3, 26.2, 23.5, 22.9, 22.6, 22.5, 22.3, 21.3, 20.0 (11 CH_2); 14.2

(CH_3CH_2O). CI-MS: 350 ($[M + 1]^+$), 304. Anal. calc. for $C_{20}H_{31}NO_4$ (349.47): C 68.73, H 8.94, N 4.01; found: C 68.36, H 8.89, N 3.90.

2. *Ethyl 4-(1-Cyano-2-oxocyclooctyl)-3-oxobutanoate* (**4**) *and Ethyl 4-(1-Cyano-2-oxocyclododecyl)-3-oxobutanoate* (**4b**). To a soln. of **3a** or **3b** (10 mmol) in CCl_4 (5 ml), CF_3COOH (*Fluka;* 1.53 ml, 20 mmol) was added. After 2.5 h stirring under reflux, the solvent was evaporated and the residue chromatographed (45 g of silica gel, Et_2O/hexane 2:1) or crystallized from EtOH to give **4a** (2.57 g, 92.2%) and **4b** (3.15 g, 94%), respectively.

Data of **4a**: Oil. IR: 2240, 1744, 1718. ^{1}H-NMR: 4.20 (*q*, J = 7, CH_2O); 3.60–3.20 (*m*, 4 H), therein at 3.54 (*A* of *AB*, J = 18, H–C(4)) and at 3.44 (*s*, 2 H–C(2)); 3.07 (*B* of *AB*, J = 18, H–C(4)); 2.68–2.30 (*m*, 2 H); 2.20–1.44 (*m*, 9 H); 1.29 (*t*, J = 7, CH_3). ^{13}C-NMR: 208.5 (CO); 198.1 (C(3)); 166.2 (COO); 120.6 (CN); 61.6 (CH_3CH_2O); 51.6 (CH_2); 48.5 (C(1)); 48.3, 41.2, 40.3, 27.8, 25.0, 24.7, 22.8 (7 CH_2); 13.9 (CH_3CH_2O). CI-MS: 280 ($[M + 1]^+$), 262, 234.

Data of **4b**: M.p. 107–108° (EtOH). IR: 2240, 1726. ^{1}H-NMR: 4.22 (*q*, J = 7, CH_3CH_2O); 3.48, 3.45 (*AB*, J = 15, 2 H–C(2)); 3.47, 2.94 (*AB*, J = 18, 2 H–C(4)); 3.32–2.74 (*m*, 3 H); 2.24–0.80 (*m*, 20 H), therein at 1.29 (*t*, J = 7, CH_3CH_2O). ^{13}C-NMR: 202.5 (CO); 198.0 (C(3)); 166.3 (COO); 120.4 (CN); 61.6 (CH_3CH_2O); 49.0 (C(1)); 48.6, 46.5, 36.4, 34.7, 26.2, 26.1, 23.6, 22.4, 22.3, 22.2, 21.0, 20.3 (12 CH_2); 13.9 (CH_3CH_2O). CI-MS: 336 ($[M + 1]^+$), 318, 291. Anal. calc. for $C_{19}H_{29}NO_4$ (335.44): C 68.03, H 8.71, N 4.17; found: C 68.00, H 8.65, N 3.99.

3. *Ethyl 1-Cyano-10-oxobicyclo[6.3.0]undec-8-ene-9-carboxylate* (**5a**) *and Ethyl 1-Cyano-14-oxobicyclo[10.3.0]pentadec-12-ene-13-carboxylate* (**5b**). To a soln. of **4a** or **4b** (10 mmol) in CH_2Cl_2 (30 ml), a 40% aq. soln. of Bu_4NOH (*Fluka;* 0.65 ml, 1 mmol) was added. After 8 h stirring at 20°, the mixture was filtered through silica gel (30 g, CH_2Cl_2) to give **5a** (2.56 g, 98%) or **5b** (3.10 g, 98%).

Data of **5a**: Oil. IR: 2232, 1744, 1722, 1642. ^{1}H-NMR: 4.35 (*q*, J = 7, CH_3CH_2O); 3.35 (*A* of ABX_2, J_{AB} = 13, J_{AX} = 5, 1 H–C(7)); 3.01 (*A* of *AB*, J = 18, 1 H–C(11)); 2.84–2.44 (*m*, 3 H), therein at 2.68 (*B* of *AB*, J = 18, 1 H–C(11)); 2.20–1.14 (*m*, 12 H), therein at 1.36 (*t*, J = 7, CH_3CH_2O). ^{13}C-NMR: 197.3 (CO); 182.3 (C(8)); 161.9 (COO); 134.5 (C(9)); 120.4 (CN); 61.4 (CH_3CH_2O); 45.0 (CH_2); 44.3 (C(1)); 34.0, 28.8, 28.5, 26.0, 24.3, 22.1 (6 CH_2); 14.0 (CH_3CH_2O). CI-MS: 262 ($[M + 1]^+$), 248, 235, 216.

Data of **5b**: Oil. IR: 2240, 1746, 1724, 1640. ^{1}H-NMR: 4.50–4.14 (*m*, *AB* of ABX_3, CH_3CH_2O); 3.64 (*A* of ABX_2, J_{AB} = 39, J_{AX} = 5, 1 H–C(11)); 3.48 (*t*, J = 6, 0.5 H); 3.20–2.58 (*m*, 4.5 H), therein at 2.94 and 2.68 (*AB*, J = 18, 2 H–C(15)); 2.42–0.80 (*m*, 19 H), therein at 1.36 (*t*, J = 7, CH_3CH_2O). ^{13}C-NMR: 197.6 (CO); 174.9 (C(12)); 162.9 (COO); 137.2 (C(2)); 120.5 (CN); 61.7 (CH_3CH_2O); 44.8 (C(1)); 44.5, 35.6, 31.6, 27.7, 25.3, 24.6, 24.4, 24.3, 23.1, 22.0, 19.0 (11 CH_2); 14.0 (CH_3CH_2O). CI-MS: 318 ($[M + 1]^+$), 304, 291, 272.

4. *Ethyl 1-Cyano-14-oxo-*cis*-bicyclo[10.3.0]pentadecane-13-carboxylate* (**6**) *and Ethyl 1-Cyano-14-hydroxy-*cis*-bicyclo[10.3.0]pentadec-13-ene-13-carboxylate* (**6'**). A mixture of **5b** (3.17 g, 10 mmol) and 5% Pd/C (*Fluka;* 0.38 g) in MeOH (30 ml) was stirred under H_2 at 0° for 4 h. The catalyst was filtered off, the solvent evaporated, and the residue chromatographed (45 g of silica gel, Et_2O/hexane 1:2) to give 2.87 g of colourless oil. Crystallization from EtOH afforded **6'** (0.26 g, 8.4%). Evaporation of the mother liquor gave **6** (2.6 g, 81.6%).

Data of **6**: Oil. IR: 2236, 1762, 1728, 1660, 1620. ^{1}H-NMR: 4.24 (2 *q*, shifted by 1 Hz each, J = 7, CH_3CH_2O); 3.30–2.50 (*m*, 4 H); 2.22–1.10 (*m*, 23 H). ^{13}C-NMR: 205.6 (CO); 168.7 (COO); 122.0 (CN); 61.9 (CH_3CH_2O); 61.2 (C(13)); 45.9 (CH_2); 42.6 (C(1)); 40.8 (C(12)); 29.2, 27.2, 25.6, 25.4, 25.3, 24.4, 22.6, 22.0, 21.8, 18.4 (10 CH_2); 14.0 (CH_3CH_2O). Ester **6** is a mixture of two diastereoisomers and traces of **6'**: the intensities of the NMR signals of the second diastereoisomer is less than 40% compared with the main signal. EI-MS: 319 (24, $M^{+\cdot}$), 273 (38), 246 (17), 202 (14), 188 (15), 175 (14), 162 (10), 149 (12), 135 (17), 130 (14), 121 (14), 115 (24), 109 (21), 105 (22), 95 (36), 81 (51), 67 (36), 55 (69), 41 (100). Anal. calc. for $C_{19}H_{29}NO_3$ (319.44): C 71.44, H 9.15, N 4.38; found: C 71.57, H 9.04, N 4.24.

Data of **6'**: M.p. 69.5–71.5°. IR (KBr): 3420, 2232, 1658 (br.), 1622. ^{1}H-NMR: 10.5 (br. *s*, OH, exchangeable with D_2O); 4.40–4.10 (*m*, ABX_3, CH_3CH_2O); 3.08 (*t*, J = 5, H–C(12)); 2.70, 2.68 (*AB*, J = 17, 2 H–C(15)); 2.00–1.10 (*m*, 23 H), therein at 1.32 (*t*, J = 7, CH_3CH_2O). ^{13}C-NMR: 171.8 (C(14)); 169.0 (COO); 125.1 (CN); 106.3 (C(13)); 60.3 (CH_3CH_2O); 46.1 (C(12)); 44.9 (C(1)); 42.0, 30.9, 28.1, 26.2, 25.9, 25.6, 25.4, 24.7, 24.1, 23.9, 23.1 (11 CH_2); 14.2 (CH_3CH_2O). CI-MS: 320 ($[M + 1]^+$), 274. Anal. calc. for $C_{19}H_{29}NO_3$ (319.44): C 71.44, H 9.14, N 4.38; found: C 71.43, H 9.14, N 4.42.

5. *14-Oxo-*cis*-bicyclo[10.3.0]pentadecane-1-carbonitrile* (**7**). A mixture of **6** (3.19 g, 10 mmol), NaI (15 g), and AcOH (2.5 ml) in diglyme (25 ml) was stirred under reflux for 1 h. After cooling, H_2O (120 ml) was added and the org. layer extracted with AcOEt (3 × 120 ml). The combined org. extracts were washed with sat. NaCl soln., 5% aq. soln. of $Na_2S_2O_3$, sat. NaCl soln., and dried. After evaporation, the residue was chromatographed (45 g of silica gel, Et_2O/hexane 1:2) to give **7** (2.39 g, 97%) as an oil. IR: 2232, 1750. ^{1}H-NMR: 2.84–2.50 (*m*, 3 H); 2.27, 2.22

(*AB*, J = 9, 2 H–C(15)); 2.1–1.20 (*m*, 20 H). ^{13}C-NMR: 213.1 (CO); 123.8 (CN); 47.2, 44.5 (2 CH_2); 44.0 (C(1)); 41.2 (C(12)); 30.3, 25.9, 25.1, 25.0, 24.7, 24.0, 23.6, 23.3, 23.2, 21.4 (10 CH_2). EI-MS: 247 (49, $M^{+\cdot}$), 219 (21), 204 (30), 190 (29), 176 (26), 162 (27), 148 (38), 134 (29), 122 (22), 109 (26), 95 (40), 81 (64), 67 (41), 55 (75), 41 (100).

6. *Bicyclo[10.3.0]pentadec-12-en-14-one* (**8**) *and* trans-*14-Oxobicyclo[10.3.0]pentadecane-1-carbonitrile* (**9**). A soln. of Li(i-Pr)$_2$N (4.2 mmol) in abs. THF (10 ml) was added within 10 min to a soln. of **7** (0.88 g, 3.56 mmol) in abs. THF (10 ml) at –78° with stirring under Ar. The mixture was warmed up to 20° within 30 min, then heated at 50° for 15 min and quenched with AcOH (1 ml) at 0°. After evaporation of THF, the residue was dissolved in CH_2Cl_2 (50 ml), washed with H_2O, sat. NaCl soln., and dried. After evaporation, two products were isolated by chromatography (40 g of silica gel, Et_2O/hexane 1:2): **9** (fast running, 0.31 g, 35.2%) and **8** (0.39 g, 49.8%).

Data of **8**: M.p. 95–96° (EtOH; [12]: 95–97° (EtOH)). IR: 1684, 1610. ^{1}H-NMR: 6.01 (*s*, H–C(13)); 3.10–2.10 (*m*, 5 H); 2.00–1.16 (*m*, 18 H). ^{13}C-NMR: 209.4 (CO); 185.4 (C(12)); 129.8 (C(13)); 42.0 (C(1)); 40.5, 28.2, 27.4, 25.3, 25.1, 24.2, 23.8, 23.0, 22.9, 22.6, 19.4 (11 CH_2). CI-MS: 221 ([M + 1]$^+$). Anal. calc. for $C_{15}H_{24}O$ (220.35): C 81.76, H 10.97; found: C 81.55, H 10.90.

Data of **9**: M.p. 96–98° (EtOH). IR: 2232, 1750. ^{1}H-NMR: 2.76–1.76 (*m*, 7 H), therein at 2.58 and 2.44 (*AB*, J = 18, 2 H–C(15)); 1.64–1.06 (*m*, 18 H). ^{13}C-NMR: 212.1 (CO); 122.5 (CN); 46.2 (CH_2); 44.2 (C(1)); 43.4 (CH_2); 37.2 (C(12)); 29.2, 27.0, 25.6, 25.5, 24.6, 22.1, 22.0, 21.8, 21.7, 18.4 (10 CH_2). CI-MS: 248 ([M + 1]$^+$), 221. Anal. calc. for $C_{16}H_{25}NO$ (247.38): C 77.68, H 10.18, N 5.66; found: C 77.85, H 10.12, N 5.69.

7. *14,14-(Ethylenedioxy)*-cis-*bicyclo[10.3.0]pentadecane-1-carbonitrile* (**10**). A soln. of **7** (2.47 g, 10 mmol) and ethylene glycol (*Fluka;* 2.11 g, 34 mmol) in C_6H_6 (10 ml) containing TsOH (0.19 g, 1 mmol) was heated under reflux overnight, with azeotropic removal of H_2O. The mixture was cooled, washed with 10% aq. soln. of $NaHCO_3$ and H_2O, then dried. After evaporation of the solvent, the residue was chromatographed (45 g of silica gel, Et_2O/hexane 1:2) and crystallized from EtOH to give **10** (2.40 g, 81.6%). M.p. 77–79° (EtOH). IR: 2238. ^{1}H-NMR: 4.05–3.74 (*m*, OCH_2CH_2O); 2.48–2.16 (*m*, 3 H); 2.04–1.80 (*m*, 2 H); 1.80–1.12 (*m*, 20 H). ^{13}C-NMR: 124.6 (CN); 115.6 (C(14)); 64.4 (OCH_2); 64.2 (OCH_2); 48.0 (CH_2); 45.4 (C(1)); 43.7 (C(12)); 24.4, 29.9, 26.0, 25.1, 25.0, 24.8, 24.5, 24.3, 23.9, 23.2, 22.1 (11 CH_2). EI-MS: 291 (11, $M^{+\cdot}$), 194 (10), 181 (10), 167 (15), 138 (28), 125 (68), 113 (31), 99 (86), 86 (100), 55 (25), 41 (47). Anal. calc. for $C_{18}H_{29}NO_2$ (291.43): C 74.18, H 10.03, N 4.80; found: C 74.22, H 9.81, N 4.70.

8. *14,14-(Ethylenedioxy)*-cis-*bicyclo[10.3.0]pentadecane-1-methylamine* (**11**). A soln. of **10** (1.68 g, 5.8 mmol) in THF (40 ml) was mixed with 5% NH_3/EtOH (40 ml). After addition of 5% Rh/Al_2O_3 (*Fluka;* 1.156 g), the mixture was hydrogenated in a *Parr* shaker under 3 atm H_2 for 80 h. The soln. was filtered from the catalyst, the solvent evaporated, and the residue chromatographed (20 g of silica gel, CH_2Cl_2/MeOH 9:1) to give **10** (fast running, 0.5 g, 30%) and **11** (0.95 g, 56%) as an oil. IR: 3390 (br.), 1605. ^{1}H-NMR: 4.04–3.78 (*m*, OCH_2CH_2O); 2.68, 2.65 (*AB*, J = 13, CH_2N); 2.22–0.98 (*m*, 27 H), therein at 1.86 (br. *s*, NH_2, exchangeable with D_2O). ^{13}C-NMR: 117.3 (C(14)); 63.9 (OCH_2); 63.8 (OCH_2); 49.2 (C(1)); 45.7, 44.5, 42.4, 42.2 (4 CH_2); 42.1 (C(12)); 29.7, 27.1, 26.3, 26.2, 25.2, 24.0, 23.9, 20.2 (8 CH_2). CI-MS: 296 ([M + 1]$^+$).

9. {*[14,14-(Ethylendioxy)*-cis-*bicyclo[10.3.0]pentadecan-1-yl]methyl}trimethylammonium Iodide* (**12**). To a soln. of **11** (0.68 g, 2.3 mmol) and CH_3I (*Fluka;* 12.58 g, 82 mmol) in MeOH (32 ml) was added $KHCO_3$ (2.50 g, 25 mmol) and stirred for 36 h at 20°. After evaporation of the solvent, the residue was washed with $CHCl_3$ (3 × 30 ml), the combined $CHCl_3$ extract evaporated, and the resulting solid crystallized from CH_3COCH_3/MeOH to give **12** (0.96 g, 90%). M.p. 196° (dec.). IR: 2944, 1480. ^{1}H-NMR: 4.04 (*m*, OCH_2CH_2O); 3.62–3.44 (*m*, 11 H); 2.40–0.94 (*m*, 25 H). ^{13}C-NMR: 116.1 (C(14)); 70.5 (CH_2N); 64.3 (OCH_2); 64.2 (OCH_2); 56.6 (C(12)); 49.5 (C(1)); 45.7 (CH_2); 44.8 ((CH_3)$_3$N); 41.7, 32.5, 27.1, 26.4, 26.3, 26.0, 25.5, 24.3, 24.2, 23.8, 20.9 (11 CH_2). CI-MS: 324 ([M – CH_3I + 1]$^+$), 279, 142. Anal. calc. for $C_{21}H_{40}INO_2$ (465.46): C 54.19, H 8.66, N 3.01; found: C 54.12, H 8.44, N 3.11.

10. *[(14-Oxo-*cis-*bicyclo[10.3.0]pentadecan-1-yl)methyl]trimethylammonium Iodide* (**13**). To a stirred suspension of silica gel (silica gel *60, Merck*, for column chromatography, 70–230 mesh; 3 g) in CH_2Cl_2 (8 ml) was added dropwise 10% aq. soln. of $(COOH)_2$ (0.3 ml). After 10 min, **12** (0.93 g, 2 mmol) was added and stirring continued for 12 h at 20°. The solid phase was separated by filtration and washed with $CHCl_3$/MeOH 9:1 (3 × 30 ml). Evaporation of the solvent and crystallization of the residue from CH_3COCH_3/MeOH gave **13** (0.67 g, 80%). M.p. 224° (dec.). IR: 1750. ^{1}H-NMR: 4.12–3.40 (*m*, 11 H); 3.06–2.02 (*m*, 5 H); 2.02–1.00 (*m*, 20 H). ^{13}C-NMR: 215.3 (CO); 71.4 (CH_2N); 56.3 ((CH_3)$_3$N); 50.1 (CH_2); 47.2 (C(1)); 43.5 (C(12)); 41.8, 33.5, 27.1, 26.8, 26.0, 25.8, 25.7, 24.2, 24.0, 23.7, 20.9 (11 CH_2). CI-MS: 280 ([M – CH_3I + 1]$^+$), 235, 142. Anal. calc. for $C_{19}H_{36}INO$ (421.40): C 54.15, H 8.61, N 3.32; found: C 54.26, H 8.42, N 3.28.

11. *Tricyclo[10.4.0.0^{1,15}]hexadecan-14-one* (**14**). A mixture of **13** (0.42 g, 1 mmol) and *Amberlyst-A 26* (F^--form, 3 g; *Fluka*) in THF (10 ml) was refluxed for 1 h. The solvent was filtered, evaporated, and the residue recrystallized from MeOH to give **14** (0.20 g, 86%). M.p. 84–85° (MeOH). IR: 1710. ^{1}H-NMR: 2.40–2.06 (*m*, 3 H); 1.98–0.80 (*m*, 23 H). ^{13}C-NMR: 214.4 (CO); 39.8 (CH_2); 37.5 (C(1)); 36.9, 34.8, 28.8, 28.6, 26.1, 24.6, 24.2, 24.0, 23.7, 23.6, 23.2, 23.1, 20.2 (13 CH_2). CI-MS: 235 ([M + 1]$^+$). Anal. calc. for $C_{16}H_{26}O$ (234.38): C 81.99, H 11.18; found: C 81.71, H 10.95. This substance was used for X-ray structure determination after crystallization from i-PrOH.

REFERENCES

[1] B. Milenkov, M. Süsse, M. Hesse, *Helv. Chim. Acta* **1985,** *68,* 2115.
[2] B. Milenkov, M. Hesse, *Helv. Chim. Acta* **1987,** *70,* 308.
[3] M. Süsse, J. Hájiček, M. Hesse, *Helv. Chim. Acta* **1985,** *68,* 1986.
[4] Y. Nakashita, M. Hesse, *Helv. Chim. Acta* **1983,** *66,* 845.
[5] C. Piantadosi, V. G. Sculason, *J. Pharm. Sci.* **1964,** *53,* 902.
[6] L. A. Paquette, G. D. Annis, H. Schostares, J. F. Blount, *J. Org. Chem.* **1981,** *46,* 3768.
[7] B. Föhlisch, R. Herter, E. Wolf, J. J. Stezowski, E. Eckle, *Chem. Ber.* **1982,** *115,* 355.
[8] K. Kojima, S. Amemiya, H. Suemune, K. Sakai, *Chem. Pharm. Bull.* **1985,** *33,* 2750.
[9] B. M. Trost, D. P. Curran, *J. Am. Chem. Soc.* **1980,** *102,* 5699.
[10] E. Piers, B. Abeysekera, J. R. Scheffer, *Tetrahedron Lett.* **1979,** *35,* 3279.
[11] H. J. Altenback, *Angew. Chem. Int. Ed.* **1979,** *18,* 940.
[12] J. Tsuji, T. Yamada, I. Shimizu, *J. Org. Chem.* **1980,** *45,* 5209.
[13] B. Milenkov, A. Guggisberg, M. Hesse, *Tetrahedron Lett.* **1987,** *28,* 315.
[14] D. Sternbach, M. Shibuya, F. Jaisli, M. Bonetti, A. Eschenmoser, *Angew. Chem.* **1979,** *91,* 672.
[15] C. A. Grob, *Angew. Chem.* **1969,** *81,* 543.
[16] C. A. Grob, P. W. Schiess, *Angew. Chem.* **1967,** *79,* 1.
[17] M. Freifelder, *J. Am. Chem. Soc.* **1960,** *82,* 2386.
[18] F. Huet, A. Lechevallier, M. Pellet, J. M. Conia, *Synthesis* **1978,** 63.
[19] M. Hesse, *Fortschr. Chem. Forsch.* **1967,** *8,* 608.