115. Synthesis of Oncinotin-11-one, a Macrocyclic Polyamine Alkaloid from *Oncinotis tenuiloba*

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This paper presents a short synthesis of oncinotin-11-one (**11**), a minor alkaloid of *Oncinotis tenuiloba* (Apocynaceae). Based on a disconnection approach, the spermidine portion of the key intermediate **6** was constructed consecutively by simple *N*-alkylations starting from ethyl piperidine-2-carboxylate (**1**). Treatment of **6** with *in situ* lithiated 2-[(10-bromodecyl)oxy]tetrahydropyran resulted in the formation of the keto moiety under simultanous deprotection of the lactam N-atom to give the amino ketone **7** in 71% yield. Cleavage of the tetrahydro-2*H*-pyran-2-yl (Thp) portion and *Jones* oxidation of the resulting alcohol **8** gave the amino acid **9** which was cyclized. Final *N*-debenzylation of **10** provided the natural alkaloid **11**. Only two protective groups were needed in this synthesis. The reaction of *N*-alkyl-lactams with organometallic reagents is discussed.

1. Introduction. – Oncinotin-11-one[2]) (**11**) was isolated as a minor constituent from the leaves of *Oncinotis tenuiloba* STAPF accompanied by other bicyclic macrolactam alkaloids of the same structural type, representing the so-called oncinotines [1]. Since the structure of **11** (*Scheme 1*) was deduced by spectroscopic means, synthetic material was necessary to establish the structure by comparison of the spectroscopic data and chromatographic properties.

The original isolation of the parent 11-deoxo congener oncinotine has been reported in 1968 [2], and its first synthesis was completed in 1974 [3]. A more general synthetic access to oncinotine-type alkaloids was elaborated two years later, based on the typical protective-group approach commonly encountered with the preparation of polyamine alkaloids [4]. In a more recent synthesis of the structurally related inandenin-12-one, a Rh/Pd-mediated macrocyclization was chosen as the key step. Initial formation of the N(5)–C(6) bond led to an unsaturated intermediate which *in situ* underwent a second ring closure (N(5)–C(10)) affording oncinotin-12-one, but only scant experimental details were reported [5]. A different route leading to oncinotine derivatives involves the preparation of inandenin-10-one *via* ring enlargement (*Zip* reactions). Following intramolecular reductive amination, formation of the N(5)–C(10) bond finally leads to oncinotine [6]. Recently, (–)-oncinotine was synthesized in optically pure form starting from *N*-protected (*S*)-piperidine-2-acetaldehyde. Oncinotine was obtained *via* formation of the C(4)–N(5) bond by an intramolecular iminium ion cyclization [7] [8].

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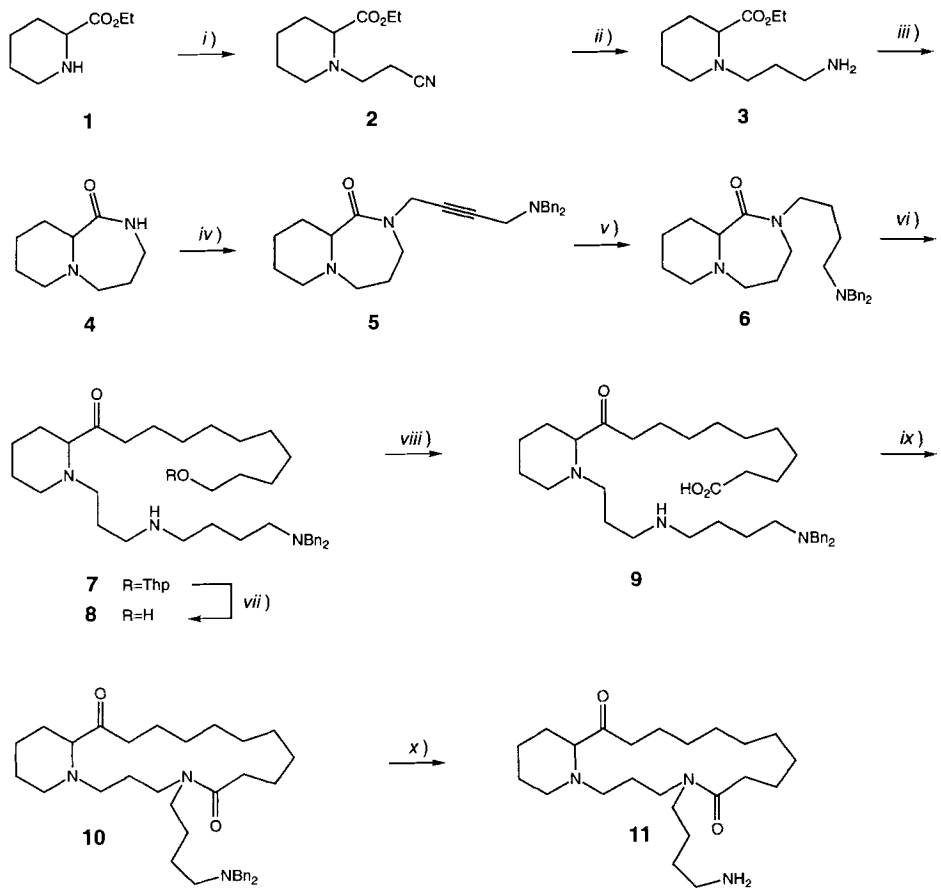
[1]) Part of the Ph. D. Thesis of *M. K.-H. D.*, Universität Zürich, 1996.

[2]) The numbering and names used in the text and schemes are in accordance with earlier publications. For systematic nomenclature, see *Exper. Part.*

Scheme 1



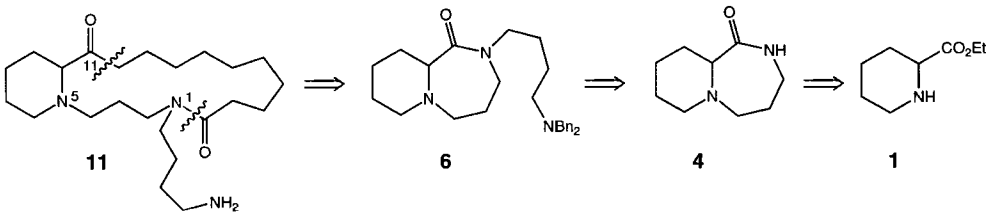
Thp = Tetrahydro-2*H*-pyran-2-yl

i) Acrylonitrile/EtOH; 75%. *ii*) 3 bar H_2/*Raney*-Ni, EtOH; 92%. *iii*) MeONa/EtOH; 67%. *iv*) *t*-BuOK, 1-chloro-4-(dibenzylamino)but-2-yne (**12**)/DMF; 68%. *v*) 1 bar H_2/Rh-C, THF; 53%. *vi*) 2-[(10-Bromodecyl)-oxy]tetrahydropyran/*t*-BuLi/Et_2O, −24 to +23°; 71%. *vii*) Pyridinium *p*-toluenesulfonate/EtOH, 55°; 90%. *viii*) *Jones* oxidation; 89%. *ix*) $SOCl_2/Et_3N$ in $CHCl_3$/benzene, 23°; 31%. *x*) H_2/Pd-C, AcOH, 55°; 98%.

Common to all syntheses is the convergent preparation of the polyamine portion by coupling selectively protected precursors the preparation of which involved several steps.

2. Results and Discussion. – In a retrosynthetic approach, the structure of oncinotin-11-one (**11**) can be reduced to the diazabicyclo[5.4.0]undecanone derivative **6** by omission of the long aliphatic chain (C(12)–C(21)) *Scheme 2*. In terms of the corresponding synthetic conversion, reaction of **6** with a 1-metallated C_{10}-synthon [9], bearing a terminal CH_2OThp portion would provide a stable primary adduct [10] which should eliminate the lactam N-atom upon hydrolysis to give the amino ketone **7**. Deprotection and oxidation

Scheme 2



of the OH group in **7** (→**9**), followed by macrocyclization, should produce the *N,N*-dibenzylated precursor **10**, which can be readily transformed into oncinotin-11-one (**11**; *Scheme 1*).

The azalactam **4** was synthesized in a three-step sequence starting from commercially available ethyl piperidine-2-carboxylate (**1**; *Scheme 1*). *N*-Cyanoethylation of **1**, followed by catalytic hydrogenation of the resulting nitrile **2**, gave ethyl 1-(3-aminopropyl)piperidine-2-carboxylate (**3**), which was cyclized to **4** by treatment with base. Although a direct conversion of related tetrahydroisoquinoline derivatives has been reported to provide the desired azalactams in a single step [11], this procedure did not work when applied to our problem. Attempted *N*-alkylation of **4** using 3-bromopropionitrile or *N*-(4-bromobutyl)phthalimid was unsuccessful, since the reagents proved to be unstable under the strongly basic conditions that were required. However, deprotonation of **4** with *t*-BuOK according to [12] and treatment of the resulting precipitate with 1-chloro-4-(dibenzylamino)but-2-yne[3]) afforded **5** in good yield. Subsequent hydrogenation (H_2/Rh-C) gave the desired key intermediate **6**. Although Rh is known to have very low hydrogenolytic activity, cleavage of the Bn_2N portion in **5** during hydrogenation is a severe problem; the major by-products formed in this reaction were 5-butyl-1,5-diazabicyclo[5.4.0]undecan-6-one and Bn_2NH. Other catalysts (Pt, Ru under protic and aprotic conditions) were unsuccessful or showed predominant hydrogenolytic cleavage of **5**.

The reaction of *Grignard* reagents with *N,N*-disubstituted carboxamides leading to ketones is well known, but severe reaction conditions are required due to the low reactivity of the carboxamides, and the formation of by-products represents a considerable problem. Therefore, the use of such reactions has been limited to only a few applications (for a rewiev, see [13]). If *N*-alkyl-lactams are treated with organomagnesium reagents, the corresponding ω-alkylamino ketones can be obtained, but usually in very poor yields [14–16].

In general, organolithium compounds are superior to their *Grignard* counterparts reacting smoothly with *N,N*-disubstituted carboxamides to give the desired ketones in good yield [17] [18]. Due to the increased nucleophilicity of the reagent and to their sterically less demanding transition states, even more bulky carboxamides can be used successfully in this reaction [19]. The analogous transformation of *N*-alkyl-lactams leading to ω-alkylamino ketones has received only little attention [20–22].

Since most derivatives of carboxylic acids are unstable to organolithium reagents, 2-[(10-bromodecyl)oxy]tetrahydropyran was chosen as the suitable C_{10} building block.

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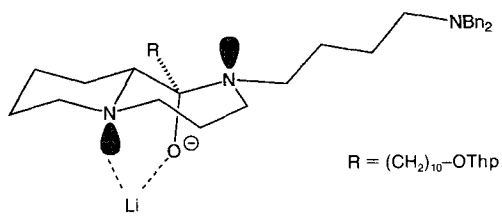
[3]) Prepared from commercially available 1-amino-4-chlorobut-2-yne and $PhCH_2Br$.

Reaction of commercially available 10-bromodecan-1-ol with 3,4-dihydro-2*H*-pyran using an acidic ion-exchange resin as catalyst gave 2-[(10-bromodecyl)oxy]tetrahydropyran in high yield.

In general, primary alkyl iodides are considered to be more suitable for the preparation of organolithium compounds by the halogen-metal interchange. This has been attributed to a pronounced halogen effect on the mechanism; but except that the yields of the metallated species are somewhat lower, the corresponding bromides can be used without further disadvantages, unless radical sensitive groups are present in the alkyl halides [23] [24].

Halogen-metal interchange was performed by treatment of 2-[(10-bromodecyl)oxy]tetrahydropyran with 2 equiv. of *t*-BuLi according to the procedure of *Bailey* and *Punzalan* [25]. Subsequent reaction of the lithiated 2-[(10-bromodecyl)oxy]tetrahydropyran with the azalactam **6** [−24°/Et_2O) leads to a primary adduct, which is probably stabilized by the formation of a five-membered chelate complex with Li^+ (see below); for an analogous explanation in a related case, see [26]. Hydrolysis of the reaction mixture finally provided the amino ketone **7** in 71% yield[4]).



Cleavage of the Thp portion using pyridinium *p*-toluenesulfonate according to [30] gave **8**, which was oxidized with *Jones* reagent to give the amino acid **9** in 80% yield (based on **7**). Macrocyclization was performed under high-dilution conditions as already described for oncinotine [3] [4] affording 31% of *N,N*-dibenzyloncinotin-11-one (**10**). Hydrogenolysis (H_2/Pt) at 55° in AcOH gave the alkaloid **11** in almost quantitative yield.

The synthetic compound **11** was identical with the natural alkaloid in all spectroscopic (IR, ^{1}H-NMR, ^{13}C-NMR, ESI-MS/MS) and chromatographic respects (TLC, HPLC) [1].

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[4]) Anhydrous $CeCl_3$ is known to favor the addition of Li reagents to C=O groups even in the presence of acidic α-H-atoms or sterical hindrance [27–29], but only reactions with aldehydes or ketones have been reported. In a single trial, $CeCl_3$ was added to the lithiated 2-[(10-bromodecyl)oxy]tetrahydropyran *ca.* 30 min before the addition of **6**, but only 16% of **7** were isolated.

Experimental Part

General. 1-Amino-4-chlorobut-2-yne·HCl was purchased from *Bachem AG*, 10-bromodecan-1-ol from *Sigma Chemical Co.*, Switzerland. Et_3N, $CHCl_3$, and benzene used in the macrocyclization of **9** were purified as described in [31]. Unless otherwise noted, *Merck* silica gel *60* (40–60 μm) was used for column chromatography (CC). TLC: Precoated silica gel *60* F_{254}, 0.2 mm (*Merck*). IR [cm^{-1}] in $CHCl_3$: *Perkin-Elmer 781*. NMR Spectra: *Bruker ARX 300* with chemical shifts in δ [ppm], coupling constants J in Hz, using the appropriate solvent as internal standard. ^{1}H-NMR Spectra were recorded at 300.1 MHz and ^{13}C-NMR spectra at 75.5 MHz in $CDCl_3$; multiple signals observed for the same C-atom are due to diastereoisomeric carboxamides (*s-cis/trans* of the $RCONR_2$ portion) [32] [33]. ESI-MS (MeOH): *Finnigan TSQ 700*; EI-MS (probe 70 eV): *Finnigan MAT 90*; CI-MS: *Finnigan MAT SSQ 700*, chemical ionization with NH_3.

Ethyl 1-(2-Cyanoethyl)piperidine-2-carboxylate (**2**). At 25° under N_2, a stirred soln. of *ethyl* piperidine-2-carboxylate (**1**; 13.60 g, 86.6 mmol) in abs. EtOH (90 ml) was treated with acrylonitrile (5.51 g, 104.0 mmol) during 50 min. After 1 h, additional acrylonitrile (5.51 g, 104.0 mmol) was added and the soln. stirred for 17 h at 25°, followed by 1 h at 45°. The solvent was evaporated *in vacuo* and the residue filtered over silica gel (400 g, Et_2O/hexane 1:1) to give 13.74 g (75%) of **2**. Colorless liquid. IR: 2940*s*, 2860*m*, 2250*w*, 1730v*s*, 1445*m*, 1375*m*, 1295*m*, 1260*w*, 1185*s*, 1130*m*, 1025*m*. ^{1}H-NMR: 4.15 (*q*, J = 6.4, 2 H); 3.25–3.21 (*t*-like *m*, 1 H); 3.02–2.84 (*m*, 2 H); 2.74–2.65 (*m*, 1 H); 2.47 (*t*, J = 7.1, 2 H); 2.40–2.33 (*m*, 1 H); 1.85–1.76 (*m*, 2 H); 1.62–1.34 (*m*, 4 H); 1.25 (*t*, J = 7.2, 3 H). ^{13}C-NMR: 172.96 (*s*, CO); 118.72 (*s*, CN); 63.55 (*d*, CH); 60.31, 51.68, 49.45, 29.12, 25.14, 21.68, 16.33 (7*t*, 7 CH_2); 14.10 (*q*, Me). EI-MS: 211 (13, $[M+1]^+$), 209 (2, $[M-1]^+$), 170 (8, $[M-CH_2CN]^+$), 137 (100, $[M-CO_2Et]^+$), 109 (3), 96 (13).

Ethyl 1-(3-Aminopropyl)piperidine-2-carboxylate (**3**). To a soln. of **2** (4.0 g, 19.0 mmol) in 220 ml of EtOH, conc. H_2SO_4 (5.0 ml) and PtO_2 (0.40 g) were added, and the mixture was hydrogenated in a *Parr* apparatus at 55 psi at r.t. After 24 h, the catalyst was filtered off (*Celite*) and the resulting soln. concentrated. After addition of H_2O (30 ml), it was basified (Na_2CO_3) and extracted repeatedly with $CHCl_3$. Drying of the org. layer (Na_2SO_4) and evaporation gave 3.77 g (92%) of **3**. Slightly yellowish oil, pure enough for the next step. An anal. sample was purified by bulb-to-bulb distillation (85°, 0.04 mbar). IR: 3270v*w*, 2940v*s*, 2860*s*, 1730v*s*, 1585*w*, 1445*m*, 1375*m*, 1263*m*, 1185*s*, 1115*m*, 1060*m*, 1025*m*, 885*w*, 855*w*. ^{1}H-NMR: 3.90 (*q*, J = 6.9, 2 H); 2.83–2.72 (*m*, 2 H); 2.47–2.43 (*t*-like *m*, 2 H); 2.36–2.27 (*m*, 1 H); 2.06–1.98 (*m*, 1 H); 1.86–1.78 (*quint.*-like *m*, 1 H); 1.57–1.27 (*m*, 8 H); 0.99 (*t*, J = 7.3, 3 H). ^{13}C-NMR: 173.77 (*s*, CO); 65.55 (*d*, CH); 60.16, 53.94, 50.42, 40.41, 30.07, 29.60, 25.11, 22.66 (8*t*, 8 CH_2); 14.12 (*q*, Me). EI-MS: 214 (6, M^+), 141 (55, $[M-CO_2Et]^+$), 98 (100, $[M-CO_2Et-C_2H_5N]^+$).

1,5-Diazabicyclo[5.4.0]undecan-6-one (**4**). A soln. of **3** (4.78 g, 22.3 mmol) in abs. EtOH (180 ml) containing NaOMe (2.41 g, 44.7 mmol) was refluxed for 1 d. The mixture was neutralized (1N aq. HCl soln.), the solvent was evaporated, and the resulting residue was taken up in H_2O (50 ml). The aq. layer was basified (1N aq. NaOH soln.) and extracted with $CHCl_3$. Drying (Na_2SO_4) and evaporation of the org. layer gave a crude product which was recrystallized from cyclohexane providing 2.52 g (67%) of **4**. Colorless needles. M.p. 128.5°. IR: 3405*m*, 3000*m*, 2940*s*, 2850*w*, 1650*s*, 1470*m*, 1430*w*, 1365*m*, 1335*w*, 1270*w*, 1140*w*, 1115*w*, 1005*w*. ^{1}H-NMR: 6.26 (br. NH); 3.60–3.49 (*m*, 1 H); 3.17–3.13 (*m*, 1 H); 3.04–2.86 (*m*, 2 H); 2.81–2.65 (*m*, 2 H); 2.35–2.27 (*m*, 1 H); 1.83–1.67 (*m*, 4 H); 1.57–1.43 (*m*, 3 H); 1.39–1.27 (*m*, 1 H). ^{13}C-NMR: 177.25 (*s*, CO); 66.86 (*d*, CH); 55.75, 52.64, 40.15, 29.06, 27.47, 26.21, 22.32 (7*t*, 7 CH_2). EI-MS: 168 (67, M^+), 140 (25), 139 (30), 124 (16), 111 (27), 98 (100), 96 (20), 83 (59), 69 (13), 55 (25).

5-[4-(Dibenzylamino)but-2-ynyl]-1,5-diazabicyclo[5.4.0]undecan-6-one (**5**). A soln. of **4** (1.675 g, 9.97 mmol) in abs. DMF (150 ml) was stirred under Ar, while *t*-BuOK (1.343 g, 11.97 mmol) was added all at once. After stirring of the microcrystalline precipitate at r.t. for 15 min, a soln. of **12** (3.110 g, 10.97 mmol) in abs. DMF (15 ml) was added during 1 h. After additional stirring for 1 h, 150 g of ice-water were added and the mixture extracted (Et_2O). The org. layer was dried (Na_2SO_4), evaporated, and the residue was purified by CC (400 g of silica gel; CH_2Cl_2/toluene/acetone 10:1:1) resulting in 2.83 g (68%) of **5**. Slightly orange oil. IR: 3000*w*, 2940*m*, 2830*m*, 1625*s*, 1475*w*, 1455*w*, 1365*m*, 1260*w*, 1170*w*, 1110*w*. ^{1}H-NMR: 7.39–7.22 (*m*, 10 arom. H); 4.42–4.26 (br. *q*-like *m*, 2 H); 4.05–3.96 (*m*, 1 H); 3.66 (*s*, 2 PhCH_2); 3.42–3.35 (*m*, 1 H); 3.29–3.26 (*s*-like *m*, 3 H); 2.95–2.88 (*m*, 1 H); 2.83–2.73 (*m*, 2 H); 2.43–2.35 (*m*, 1 H); 1.92–1.71 (*m*, 6 H); 1.62–1.56 (*m*, 2 H). ^{13}C-NMR: 173.33 (*s*, CO); 138.77 (*s*, 2 C_{ipso}); 128.88, 128.19, 127.02 (3*d*, 10 arom. CH); 80.65, 77.95 (2*s*); 68.00 (*d*, CH); 57.52, 54.69, 53.44, 45.26, 41.44, 37.28, 29.44, 27.04, 26.33, 22.76 (10*t*, 11 CH_2). ESI-MS (MeOH): 416.6 ($[M+1]^+$). EI-MS: 415 (< 2, M^+), 324 (17), 296 (6), 220 (20), 196 (47), 167 (75), 91 (100), 75 (34).

5-[4-(Dibenzylamino)butyl]-1,5-diazabicyclo[5.4.0]undecan-6-one (**6**). A suspension of 5% Rh/C (400 mg) in 250 ml of abs. THF was prehydrogenated in a low-pressure hydrogenator at r.t. and 1 atm. of H_2. A soln. of **5** (1.415 g, 3.41 mmol) in abs. THF (50 ml) was added dropwise and hydrogenation performed until H_2 absorption

ceased (≈ 10 h). The catalyst was filtered off (*Celite*), the solvent was evaporated and the residue was purified by bulb-to-bulb distillation (230–235°, $1.5 \cdot 10^{-2}$ mbar) resulting in 750 mg (53%) of **6**. Highly viscous, yellow oil. IR: 3000*m*, 2940*s*, 2860*m*, 2800*m*, 1620*s*, 1480*w*, 1450*m*, 1430*w*, 1365*m*, 1290*w*, 1170*w*, 1125*m*, 1030*w*. ^{1}H-NMR: 7.34–7.15 (*m*, 10 arom. H); 3.80–3.71 (*m*, 1 H); 3.51 (*s*, 2 PhCH_2); 3.39–3.29 (br. *m*, 1 H); 3.20–3.12 (*m*, 2 H); 3.07–2.99 (*m*, 1 H); 2.83–2.75 (*m*, 1 H); 2.73–2.61 (*m*, 2 H); 2.39 (br. *t*, *J* = 6.5, 2 H); 2.35–2.27 (*m*, 1 H); 1.86–1.65 (*m*, 4 H); 1.63–1.23 (*m*, 8 H). ^{13}C-NMR: 173.12 (*s*, CO); 139.82 (*s*, 2 C_{ipso}), 128.69, 128.06, 126.68 (3*d*, 10 arom. CH); 68.75 (*d*, CH); 58.28, 54.30, 53.82, 53.01, 48.64, 45.72, 29.56, 27.36, 26.40, 25.77, 24.34, 23.00 (12*t*, 13 CH_2). ESI-MS (MeOH): 458.4 (9, $[M + K]^+$), 442.5 (71, $[M + Na]^+$), 420.3 (100, $[M + 1]^+$). EI-MS: 329 (24), 328 (100, $[M - PhCH_2]^+$), 300 (5), 258 (8), 236 (4), 210 (30), 167 (12), 160 (7), 124 (6), 110 (11), 98 (15), 91 (48), 84 (7), 55 (3).

*1-{1-{3-{[4-(Dibenzylamino)butyl]amino}propyl}piperidin-2-yl}-11-[(tetrahydro-2*H*-pyran-2-yl)oxy]undecan-1-one* (7). *General.* All additions were performed through the rubber septum using Ar-flushed syringes which were rinsed with abs. Et_2O before use. Et_2O was freshly distilled under N_2 from dark-purple solns. of Na/benzophenone. A positive pressure of Ar was maintained within the flask during the whole procedure. Both educts were purified by bulb-to-bulb distillation and kept under Ar prior to their use.

A three-way cock (90° angles), which was connected to Ar/high vacuum and closed with a rubber septum at the top, was put on a 50-ml round-bottomed flask, equipped with a *Teflon*-coated magnetic stirring bar. The assembly was flame-dried (at 0.02 mbar) and flushed with dry Ar while cooling. The flask charged with a soln. of 2-[(10-bromodecyl)oxy]tetrahydropyran (738.5 mg, 2.30 mmol) in Et_2O (25.0 ml) using of a syringe, and cooled to −80°. A *ca.* 1.33M soln. of *t*-BuLi in pentane (3.80 ml, 5.05 mmol) was added through the septum during 1 min, and stirring was continued for additional 15 min at −80°. The cooling bath was removed and the mixture stirred for 80 min at r.t. After recooling to −24°, a soln. of **6** (482.0 mg, 1.15 mmol) in Et_2O (3.5 ml) was added during 8 min under rapid stirring. The cooling apparatus was switched off, allowing the mixture to warm up slowly to r.t. overnight. The flask was cooled in an ice bath, while sat. aq. NH_4Cl soln. (15 ml) was added dropwise and the mixture stirred for 30 min at 0–4° (still under Ar). The three-way cock and the cooling bath were removed, small amounts of H_2O were added to dissolve precipitations, and the mixture was extracted with Et_2O. The combined org. layers were evaporated and once co-evaporated with abs. toluene leaving an oily residue which was purified by CC (100 g of silica gel 15–25 μ; $CHCl_3$/MeOH/25% aq. NH_3 soln. 25:4:0.2) providing 537.7 mg (71%) of **7**. Slightly yellow, viscous oil. IR: 3385*w*, 2940*vs*, 2850*m*, 2800*w*, 1710*s*, 1600*w*, 1490*w*, 1450*m*, 1365*w*, 1240*w*, 1120*m*, 1075*m*, 1030*m*, 900*w*. ^{1}H-NMR: 7.29–7.11 (*m*, 10 arom. H); 4.50–4.48 (*t*-like *m*, 1 H); 3.84–3.74 (*m*, 1 H); 3.66 (*dt*, *J* = 9.6, 6.9, 1 H); 3.45–3.41 (*m*, 5 H); 3.31 (*dt*, *J* = 9.6, 6.7, 1 H); 3.14–3.12 (br. *m*, 1 H); 3.00–2.96 (*d*-like *m*, 1 H); 2.87–2.82 (br. *m*, 1 H); 2.77–2.62 (br. *m*, 2 H); 2.49–2.22 (*m*, 6 H); 1.83–1.61 (*m*, 8 H); 1.59–1.33 (*m*, 12 H); 1.20 (*s*-like *m*, 16 H). ^{13}C-NMR: 213.83 (*s*, CO); 139.60 (*s*, 2 C_{ipso}); 128.65, 128.08, 126.71 (3*d*, 10 arom. CH); 98.85 (*d*, OCHO); 72.53 (*d*, CH); 67.59, 62.37, 62.25, 58.20, 56.07, 52.55, 51.31, 49.42, 48.19, 40.77, 30.72, 29.66, 29.41, 29.35, 29.28, 29.24, 29.16, 26.13, 25.40, 24.47, 23.63, 23.58, 19.68 (23*t*, 27 CH_2). CI-MS: 663 ($[M + 1]^+$). EI-MS: 661.5 (< 2, $M^{+\cdot}$), 588 (9), 570 (38), 552 (9), 463 (6), 392 (49), 252 (4), 210 (10), 160 (18), 110 (13), 98 (100), 91 (60), 84 (40), 55 (9), 42 (18).

1-{1-{3-{[4-(Dibenzylamino)butyl]amino}propyl}piperidin-2-yl}-11-hydroxyundecan-1-one (**8**). A mixture of **7** (210.0 mg, 0.317 mmol), pyridinium *p*-toluenesulfonate (285.0 mg, 1.13 mmol), and 4 ml of EtOH was stirred at 55° for 2 d. The solvent was evaporated, 5% aq. $NaHCO_3$ soln. (10 ml) was added and the mixture extracted (Et_2O). The org. layer was collected, the aq. layer saturated with Na_2CO_3 and extracted further with Et_2O. The combined org. layers were evaporated and dried at $3 \cdot 10^{-3}$ mbar to give 173.5 mg (90%) of **8**. Yellow oil. IR: 3620*w*, 2930*vs*, 2855*s*, 2800*m*, 1710*s*, 1495*m*, 1455*s*, 1365*m*, 1260*w*, 1130*m*, 1030*w*, 980*w*, 910*w*. ^{1}H-NMR: 7.50–7.31 (*m*, 10 arom. H); 3.74 (*t*, *J* = 6.5, CH_2OH); 3.67 (*s*, 2 PhCH_2); 3.28 (br. *d*, *J* = 11.3, CH); 2.96 (*dd*, *J* = 10.5, 2.7, 1 H); 2.73–2.53 (*m*, 8 H); 2.50–2.43 (*m*, 1 H); 2.31–2.23 (*m*, 1 H); 2.02 (*dt*, *J* = 2.8, 11.2, 1 H); 1.90 (*m*, 16 H); 1.51–1.40 (*s*-like *m*, 14 H). ^{13}C-NMR: 213.64 (*s*, CO); 139.82 (*s*, 2C_{ipso}); 128.66, 128.03, 126.63 (3*d*, 10 arom. CH); 73.72 (*d*, CH); 62.74, 58.21, 55.19, 53.13, 51.34, 49.77, 48.55, 38.34, 32.72, 29.37, 29.25, 29.03, 27.52, 26.44, 25.64, 25.06, 24.83, 23.60, 23.51 (19*t*, 23 CH_2). ESI-MS (MeOH): 578.6 ($[M + 1]^+$). EI-MS: 578 (< 1, $M^{+\cdot}$), 561 (11), 560 (28), 487 (26), 469 (21), 403 (6), 393 (34), 380 (4), 307 (4), 282 (6), 252 (6), 210 (8), 160 (16), 124 (3), 112 (6), 98 (100), 91 (46), 84 (25).

1-{1-{3-{[4-(Dibenzylamino)butyl]amino}propyl}piperidin-2-yl}-11-oxoundecanoic Acid (**9**). A soln. of **8** (340.9 mg, 0.590 mmol) in acetone (6 ml) and H_2O (4 ml) was adjusted to pH 4 (1N aq. H_2SO_4 soln.) and refluxed. At this temp., 1.75 ml of *Jones* reagent (2.085 g of CrO_3, 30 ml of H_2O, 8.7 ml of conc. H_2SO_4) was added dropwise during 2 min. After 15 min, the dark-green soln. was cooled and $Na_2S_2O_5$ added, until the soln. became blue. Acetone was removed *in vacuo*, the mixture was basified ($NaHCO_3$) and extracted with $CHCl_3$. The org. layer was dried (Na_2SO_4), evaporated, and the residue was purified by CC (15 g of silica gel; $CHCl_3$/MeOH/25% aq. NH_3 soln. 78:19:3) to give **9** (309.0 mg, 89%). Colorless lac. IR: 2930*s*, 2850*m*, 2800*w*, 1710*s*, 1570*m*, 1490*w*, 1450*m*,

1380*m*, 1290*w*, 1120*w*. ^{1}H-NMR: 8.88 (br., COOH); 7.60–7.43 (*m*, 10 arom. H); 3.78 (*s*, 2 PhCH_2); 3.60 (br. *d*, *J* = 11.2, 1 H); 3.49 (br. *d*, *J* = 10.9, 1 H); 3.26 (br. *d*, *J* = 8.6, 1 H); 3.16–3.12 (*t*-like *m*, 2 H); 3.02–2.96 (*t*-like *m*, 1 H); 2.73–2.42 (*m*, 10 H, CH_2N); 2.12–1.73 (*m*, 16 H); 1.52–1.41 (*m*, 10 H). ^{13}C-NMR: 213.28 (*s*, CO); 180.00 (*s*, COOH); 139.65 (*s*, 2 C_{ipso}); 128.63, 128.04, 126.65 (3*d*, 10 arom. CH); 72.52 (*d*, CH); 58.11, 55.80, 52.76, 51.26, 48.42, 47.66, 40.69, 37.55, 29.90, 29.51, 29.23, 29.13, 29.08, 26.33, 24.99, 24.69, 24.47, 23.73, 23.59, 22.29 (20*t*, 22 CH_2). ESI-MS (MeOH): 592.6 (20, $[M + 1]^+$), 296.7 (100, ½ $[M + 2]^{2+}$). EI-MS: 573 (36, $[M - H_2O]^+$), 559 (4), 482 (30), 402 (11), 321 (7), 252 (11), 210 (17), 177 (11), 160 (33), 149 (14), 106 (12), 91 (100), 84 (16).

5-[4-(Dibenzylamino)butyl]-1,5-diazabicyclo[15.4.0]henicosane-6,16-dione (= *N,N-Dibenzyloncinotin-11-one*; **10**). To **9** (97.5 mg, 0.165 mmol) was added 1 ml of H_2O followed by the dropwise addition of 0.1N aq. HCl soln.; upon complete dissolution, pH was adjusted to 4 and the mixture was lyophilized. The resulting trihydrochloride was dissolved in abs. benzene (1 ml), $SOCl_2$ (1 ml) was added and the mixture allowed to stand at 23° for 1 h before the solvents were removed by lyophilization. The residue was dissolved in abs. $CHCl_3$ (15 ml), the resulting soln. diluted with abs. benzene (35 ml) and the mixture placed in a 50-ml syringe. A second syringe was charged with a soln. of abs. Et_3N (0.15 ml, 1.08 mmol) in benzene (50 ml). Using an infusion apparatus (*Precidor 5003, Infors AG*, CH), both solns. were injected under rapid stirring synchronously at 23° during 3 h through *Teflon* capillaries into a flame-dried flask containing benzene/$CHCl_3$ 9:1 (100 ml; kept under Ar). The mixture was evaporated, the residue partitioned between CH_2Cl_2/dil. aq. K_2CO_3 soln., and the aq. layer was repeatedly extracted (CH_2Cl_2). The combined org. layers were dried (Na_2SO_4), evaporated, and the residue was purified by CC (silica gel 6 g, $CHCl_3$; the product was eluted with $CHCl_3$/MeOH/25% aq. NH_3 soln. 95:5:0.2) resulting in 29.0 mg (31%) of **10**. IR 3000*w*, 2930*s*, 2800*w*, 1710*m*, 1630*s*, 1490*w*, 1450*m*, 1370*w*, 1260*w*, 1125*w*. ^{1}H-NMR: 7.29–7.12 (*m*, 10 arom. H); 3.47 (*s*, 2 PhCH_2); 3.24–2.92 (*m*, 6 H); 2.74–2.58 (*m*, 2 H); 2.40–2.31 (br. *quint.*-like *m*, 4 H); 2.30–1.98 (*m*, 6 H); 1.85 (*dt*, *J* = 3.0, 11.2, 1 H); 1.70–1.19 (*m*, 22 H). ^{13}C-NMR: 212.82, 212.36 (2*s*, CO); 172.09, 171.88 (2*s*, CON); 138.92, 138.76 (2*s*, 2 C_{ipso}); 127.72, 127.20, 127.13, 125.86, 125.74 (5*d*, 10 arom. CH); 73.40, 71.12 (2*d*, CH); 57.56, 57.36, 53.38, 52.24, 52.09, 50.71, 50.57, 46.42, 45.28, 44.49, 35.88, 31.56, 27.86, 26.82, 26.48, 26.33, 26.19, 25.95, 25.80, 25.66, 25.50, 25.00, 24.59, 24.09, 23.55, 23.50, 22.93, 22.45, 21.71 (29 signals, 22 CH_2). EI-MS: 575 (5, $[M + 1]^+$), 574 (2, M^+), 573 (6, $[M - 1]^+$), 545 (9), 484 (9), 482 (44), 456 (23), 454 (100), 210 (13), 160 (32), 124 (7), 123 (19), 122 (5), 110 (15), 98 (17), 97 (11), 96 (18), 92 (5), 91 (79), 84 (14), 83 (6), 70 (9), 69 (7), 55 (10).

5-(4-Aminobutyl)-1,5-diazabicyclo[15.4.0]henicosane-6,16-dione (= *Oncinotin-11-one*; **11**). A mixture of **10** (53.5 mg, 0.093 mmol), AcOH (20 ml) and 10% Pd/C (70 mg) was stirred in a open flask at 55° while H_2 was bubbled through with the use of a glass tube. After 1.75 h, the mixture was filtered (*Celite*), the catalyst washed with AcOH, and the combined fractions were evaporated. CC of the residue (2.5 g of silica gel; $CHCl_3$/MeOH/25% aq. NH_3 soln. 85:14:1) afforded 36 mg (98%) of **11**. Colorless lac. ^{1}H-NMR: 3.46–3.04 (*m*, 6 H); 2.85 (*dd*, *J* = 10.6, 3.0, 1 H); 2.81–2.69 (*m*, 3 H); 2.52–2.13 (*m*, 6 H); 2.00 (*dt*, *J* = 3.0, 11,2, 1 H); 1.90–1.25 (*m*, 24 H). ^{13}C-NMR: 213.63, 213.14 (2*s*, CO); 172.99, 172.82 (2*s*, CON); 74.19, 72.13 (2*d*, CH); 54.26, 54.05, 51.63, 51.53, 47.56, 46.26, 45.39, 41.77, 36.88, 32.45, 30.85, 28.77, 27.70, 27.42, 27.21, 27.08, 26.99, 26.85, 26.72, 26.58, 26.47, 25.86, 25.07, 24.98, 23.82, 23.34, 22.61, 20.84 (28 signals, 20 CH_2). For additional spectroscopic data *cf.* [1].

1-Chloro-4-(dibenzylamino)but-2-yne. 1-Amino-4-chlorobut-2-yne hydrochloride (2.324 g, 16.6 mmol) was suspended in CH_2Cl_2, and a soln. of 7.910 g of Na_2CO_3 in H_2O (20 ml) was added, followed by the addition of $PhCH_2Br$ (5.670 g, 33.2 mmol). After the mixture was refluxed for 3 h, further $PhCH_2Br$ (0.567 g, 3.23 mmol) was added and refluxing continued for 2 h. Now, H_2O was added until a clear soln. resulted, the org. layer was separated and the aq. extracted with CH_2Cl_2. The combined org. layer were re-extracted once with brine, dried (Na_2SO_4), and evaporated. CC of the residue (160 g of silica gel; toluene) gave 4.07 g (86%) of the product. Colorless oil. The basic procedure is described in [34]. ^{1}H-NMR: 7.62–7.45 (*m*, 10 arom. H); 4.44 (*t*, *J* = 2, CH_2Cl); 3.89 (*s*, 2 PhCH_2); 3.51 (*t*, *J* = 1.8, CH_2N). ^{13}C-NMR: 138.53 (*s*, 2 C_{ipso}); 128.99, 128.27, 127.15 (3*d*, 10 arom. CH); 81.92, 80.39 (2*s*), 57.56 (*t*, CH_2Cl); 41.40 (*t*, 2 PhCH_2); 30.74 (*t*, CH_2N). EI-MS: 283 (12, M^+), 248 (4), 206 (8), 194 (9), 192 (25), 91 (100), 65 (5).

2-[(10-Bromodecyl)oxy]tetrahydro-2H-pyran. The reaction was carried out according to [35]. 3,4-Dihydro-2*H*-pyrane (1.06 g, 12.60 mmol) was added to a soln. of 10-bromodecan-1-ol (1.00 g, 4.20 mmol) in abs. hexane (10 ml). After the addition of *Amberlyst H-15* (150 mg), the mixture was stirred at r.t. for 20 h. The resin was filtered off, the solvent was evaporated and the residue purified by bulb-to-bulb distillation (115–120°, $2 \cdot 10^{-2}$ mbar) to give 1.100 g (82%) of the product. Colorless oil. ^{1}H-NMR: 4.61–4.59 (*t*-like *m*, 1 H); 3.93–3.86 (*m*, 1 H); 3.79–3.72 (*m*, 1 H); 3.56–3.49 (*m*, 1 H); 3.45–3.37 (*m*, 3 H); 1.93–1.32 (*m*, 22 H). ^{13}C-NMR: 97.48 (*d*, CH); 66.29, 60.97, 32.60, 31.48, 29.44, 28.39, 28.09, 28.07, 28.00, 27.38, 26.81, 24.86, 24.17, 18.35 (14*t*, 14 CH_2). CI-MS (*i*-C_4H_{10}): 323/321 ($[M + 1]^+$). EI-MS: 321/319 (2, $[M - 1]^+$), 101 (7), 85 (100), 69 (8), 56 (20), 41 (20).

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