49. Synthesis of Tenuilobine, a Bis-polyamine Alkaloid from *Oncinotis tenuiloba*, and Its Transamidation to Isotenuilobine

by **Martin K.-H. Doll**[1]), **Armin Guggisberg**, and **Manfred Hesse***

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

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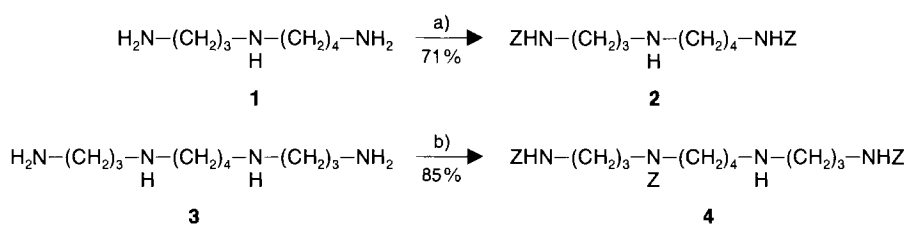
From the leaves of *Oncinotis tenuiloba* STAPF, a novel polyamine alkaloid, tenuilobine (**9**), was isolated. This paper presents the synthesis of **9**, as well as the base-catalyzed *Zip* reaction of **9**, leading to the transamidation product isotenuilobine (**10**). The structure of **10** was further confirmed by 2D-NMR correlation spectroscopy. For analytical purposes, the bis-polyamines **9** and **10** were converted into their pentaacetyl derivatives **12** and **11**, respectively, which were readily separable by reverse-phase HPLC.

1. Introduction. – Plants of the genus *Oncinotis* (Apocynaceae) are well-known for their content of polyamine alkaloids. Several different types of alkaloids have been isolated, ranging from simple monoacylated polyamines [1] to bi- or macrocyclic lactam alkaloids, all of them containing spermidine (**1**) as the basic component (*Scheme 1*). However, tenuilobine (**9**) is the first spermine derivative which was isolated from *Oncinotis* species [2]. Moreover, since **9** contains not only spermine (**3**) but spermidine (**1**) as well, this compound can be classified as a bis-polyamine alkaloid, a hitherto unknown subdivision of naturally occurring polyamine derivatives. In general, neither from plants [3] nor from animals [4], a substance was reported which contains two polyamine portions separated by an aliphatic moiety. The structure of tenuilobine (**9**) was elucidated by spectroscopic means and found to consist of hexadecanedioic acid being cross-linked with the secondary amino groups of spermidine (**1**) and spermine (**3**). To confirm these findings, we synthesized the alkaloid **9** as well as its unbranched isomer isotenuilobine (**10**), which could not be detected in the plant extract.

Scheme 1



Z = benzoyloxycarbonyl

a) ZCN in $CHCl_3$, 23°. b) 2 equiv. ZCN in $CHCl_3$; 1 equiv. ZCN/Et_3N in $CHCl_3$, 23°.

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

2. Synthesis and Discussion. – Since hexadecanedioic acid had to be linked with two different polyamines, its monomethyl ester **5** was found to be a suitable starting material for this purpose. Unfortunately, all attempts to prepare **5** from the commercially available dimethyl ester by selective monohydrolysis were unsuccessful or resulted in very low yield. This problem could be circumvented by applying a two-step sequence using 16-hydroxyhexadecanoic acid as the starting material. *Fischer* esterification, followed by oxidation of the resulting methyl 16-hydroxyhexadecanoate with chromic acid, yielded the desired monomethyl ester **5** in 92% overall yield.

The polyamines spermidine (**1**) and spermine (**3**) were converted into their di- and triprotected benzyloxycarbonyl (Z) derivatives **2** and **4**, respectively, prior to their use in the subsequent coupling reactions (*Scheme 1*). In general, the sterically less hindered NH_2 groups of spermidine (**1**) and related polyamines can be acylated selectively, when the reaction is carried out under kinetic control. Furthermore, the scope of the reaction seems to be limited to the use of sterically hindered carboxylic-acid derivatives; *e.g.* 3,4-dimethoxybenzonitrile [5] and 2-[(*tert*-butoxy)carbonyloxyimino]-2-phenylacetonitrile (Boc-ON) [6] have been used successfully for the preparation of N^1,N^8-diprotected spermidines[2]).

In our case, benzyl cyanoformate (ZCN) was chosen to prepare the corresponding N^1,N^8-bis(Z)-protected spermidine **2**, since the final removal of the Z-protecting groups proceeds very cleanly in high yield by hydrogenolysis [7]. The original procedure of *Murahashi et al.* [5] [8] using ZCN in CH_2Cl_2 was unsuccessful due to the low solubility of spermidine (**1**). When $CHCl_3$ was used instead, the desired spermidine derivative **2** was obtained in 71% yield after recrystallization. Moreover, we could extend the reaction to produce N^1,N^4,N^{12}-tris(Z)-protected spermine derivative **4** in high yield, when 3 equiv. of the reagent were added in two portions and in the presence of 3 equiv. of Et_3N.

Other reagents to produce N^1,N^8-bis(Z)-spermidine (**2**) have also been reported; *e.g.* 3-(benzyloxycarbonyl)-1,3-thiazolidine-2-thione generates **2** in 69% yield, when reacted with spermidine (**1**) [9]. Additionally, carbobenzoxyimidazole has been used for this purpose, affording 76% of **2** [10].

The most common procedure for amide formation from carboxylic acids and partially protected polyamines involves the *in situ* formation of the corresponding acid halide, which rapidly acylates the amine. This method has already been applied to the synthesis of related symmetrically cross-linked polyamines together with another procedure using phenyl bis(2-thioxo-1,3-thiazolidin-3-yl)phosphine oxide as the acyl-transfer agent [11]. Furthermore, the activated 4-nitrophenyl ester of the corresponding carboxylic acid can be used in more sensitive coupling reactions [12]. The method of *Mukaiyama* and coworkers who employed 1-methyl-2-chloropyridinium iodide as the coupling reagent [13] seemed most appropriate for our purposes. Thus, acylation of **2** with the monoester **5** furnished the intermediate **6** in 96% yield. After hydrolysis of the methyl-ester moiety in **6**, the resulting **7** was further cross-coupled with the protected spermine derivative **4** using *Mukaiyama*'s reagent at 23° to provide the all-Z-protected tenuilobine **8** in 91% yield. Final deprotection of **8** (H_2/Pd) afforded tenuilobine (**9**) in 87% yield (*Scheme 2*).

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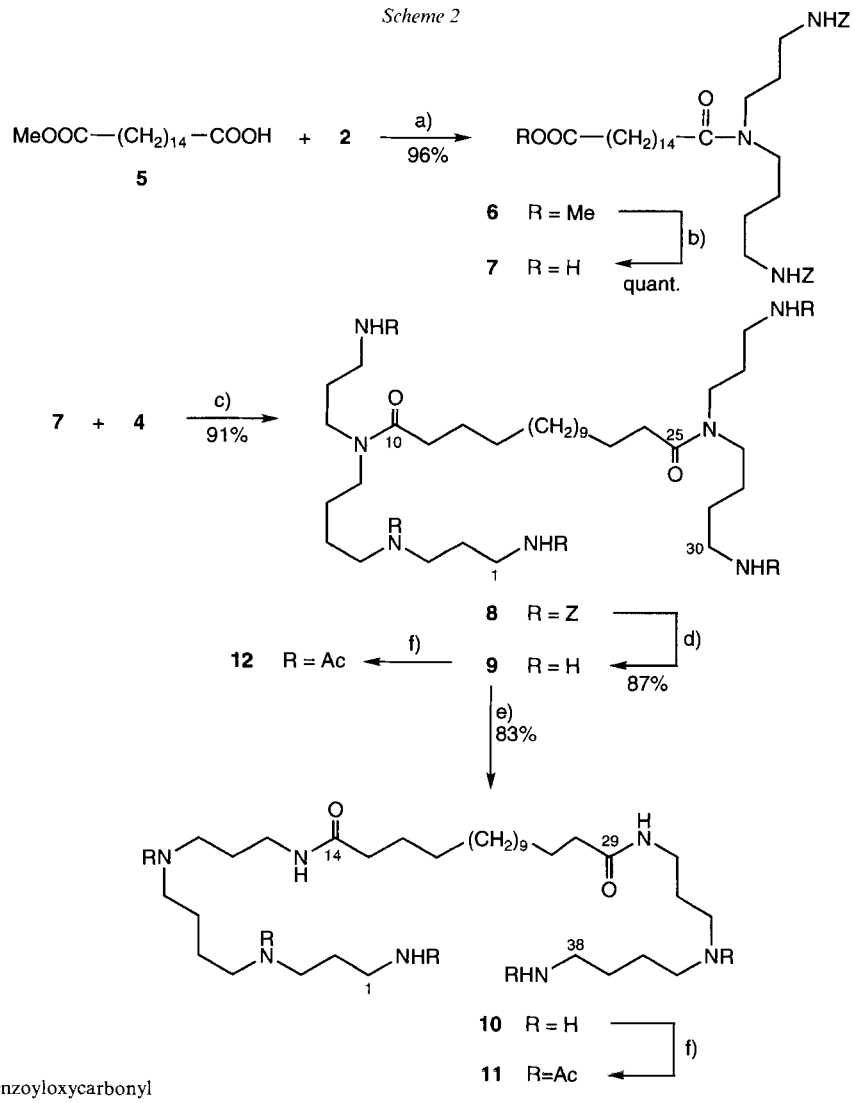
[2]) For convenience, the following atom numbering is used in the text (for systematic names, *cf.* the *Exper. Part*): $H_2NCH_2(1)CH_2CH_2(3)NH(4)CH_2CH_2CH_2CH_2(8)NH_2$ and $H_2NCH_2(1)CH_2CH_2(3)NH(4)CH_2CH_2CH_2CH_2(8)NH(9)CH_2CH_2CH_2(12)NH_2$.

Scheme 2



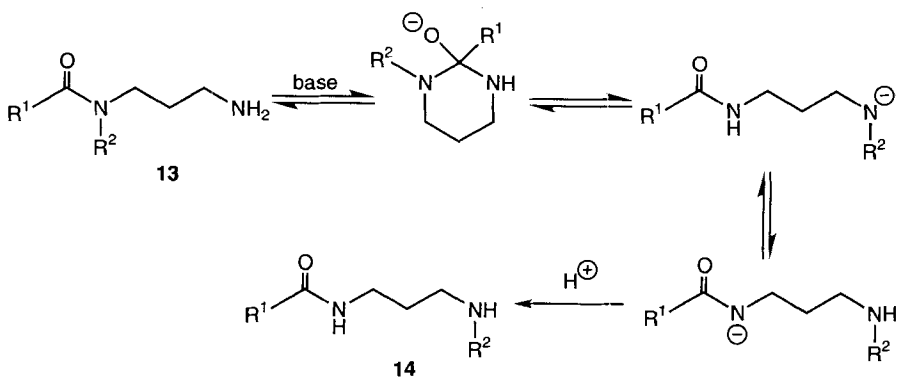
Z = benzoyloxycarbonyl

a) 1-Methyl-2-chloropyridinium iodide/Et_3N in CH_2Cl_2, reflux. b) MeOH/2N aq. NaOH, 23°. c) 1-Methyl-2-chloropyridinium iodide/Et_3N in CH_2Cl_2, 23°. d) 5% Pd/C, AcOH. e) KH/Propane-1,3-diamine (KAPA), 23°. f) Ac_2O/NaOAc, 23°.

The synthetic product **9** and the natural alkaloid were found to be identical in all respects, including their 2D-NMR spectra (^1H,^1H TOCSY) [2].

3. Transamidation. – The isomerization of *N*-(3-aminopropyl)-amides of the general structure **13** leading to their counterparts **14** is known as the *Zip* reaction [14] [15] (*Scheme 3*). In general, strongly basic or acidic conditions are required, but the reaction proceeds also thermally [16]. If R^1 and R^2 of **13** constitute a ring, then ring enlargement

Scheme 3



occurs. In this case, the analogous transamidation may also prove successful in the case of the corresponding *N*-(2-aminoethyl)- or *N*-(4-aminobutyl)-lactams, depending on the relative stability of the corresponding ring systems. However, it has been established that the reaction of the *N*-(4-aminobutyl) analogs proceeds much slower, when compared with compounds of type **13**, due to the formation of the thermodynamically favored six-membered intermediate in the latter case as compared to the seven-membered counterpart.

Therefore, tenuilobine (**9**), when treated with base, would be expected to lead to isotenuilobine (**10**) with both polyamine moieties being linked at the primary amino groups of the propanediyl portion rather than at those of the butanediyl part (*Scheme 2*). To examine this expectation, **9** was treated with KAPA (KH/propane-1,3-diamine) at 23° (30 min), and, indeed, the structure of the resulting product was unambiguously established as **10** by 2D-NMR techniques.

With respect to C(10) (δ 180.44) in the $^1H,^{13}C$-HMBC spectrum of **10**, cross-peaks were observed only for H–C(8) (δ 3.37), H–C(11) (δ 2.34), and H–C(12) (δ 1.66). The assignment of the signals was further supported by their chemical shifts. Additional $^1H,^1H$-TOCSY experiments revealed cross-peaks between H–C(8), H–C(7) (δ 2.02), and H–C(6) (δ 3.16) as well as between H–C(11), H–C(12), and H–C(13–22) (δ 1.37), respectively, indicating the presence of the $RCH_2CH_2CONH(CH_2)_3NHR'$ portion in the molecule as expected from the *Zip* reaction.

It should be noted that transamidation occurs even during storage of pure **9** at 4° (5 months), as it was also the case for pyridine solutions (4°, 4 weeks). Examination of such samples using TLC[3]) revealed the formation of an intermediate (*ca.* 20%, R_f 0.20) accompanied only by a trace of **10** (< 5%, R_f 0.16). Unchanged tenuilobine (**9**) was still predominant (*ca.* 80%, R_f 0.27). Although it is not clear whether the intermediate consists of a mixture of the two possible partly transamidated isomers of **9**, or if it is exclusively one of them, it can be stated, that the transamidation **9** → **10** proceeds stepwise rather than synchronously.

Surprisingly, the ESI-MS/MS spectra of **9** and **10** are identical with respect to the observed fragment ions, except their relative intensities. This might be due to a thermally

[3]) *Polygram® SIL N-HR/UV$_{254}$, Macherey-Nagel*; $CHCl_3$/MeOH/25% aqueous NH_3 solution 6:3:1.

promoted rearrangement of **9** during MS measurement, in the same manner as discussed above. Unfortunately, no direct comparison of the NMR spectra of **9** and **10** was possible, since the latter was hardly soluble in (D_5)pyridine, and D_2O had to be used as solvent[4]).

For HPLC purposes, **9** and its transamidated isomer **10** were converted into their pentaacetyl derivatives **12** and **11**, respectively, which could be easily distinguished using reverse-phase conditions (*cf. Exper. Part*). Additionally, coinjection of **12** together with the pentaacetyl derivative of the alkaloid isolated from natural sources demonstrated the identity of the samples, and the absence of **11** in the acetylated extract showed that **10** is not a natural product. This has been already shown using a different system of chromatography [2].

The financial support from the *Swiss National Science Foundation* is greatly appreciated. Thanks are due to Dr. *D. Nanz* and Mr. *D. Rentsch* for recording 2D-NMR spectra and helpful discussions, and Dr. *E. Reder* and Mr. *L. Bigler* for measuring the mass spectra. Technical assistance by Ms. *C. Sprenger* is gratefully acknowledged.

Experimental Part

General. For the slow addition of ZCN, an infusion pump (*Precidor 5003*, *Infors AG*, Switzerland) was used. Column chromatography (CC): *Merck* silica gel *60* (40–60 μ). IR (cm^{-1}): in $CHCl_3$, *Perkin-Elmer 781*. 1D-NMR Spectra: *Bruker AMX-600*, *Bruker AM 400*, and *Bruker ARX 300* with chemical shifts δ in ppm, coupling constants J in Hz, using the appropriate solvent as internal standard. Unless stated otherwise, ^{1}H-NMR: at 300.1 MHz. ^{13}C-NMR: at 75.5 MHz in $CDCl_3$. 2D-NMR (D_2O): *Bruker AMX-600*; TOCSY (mixing time 150 ms) and HMBC (J selected for 9 Hz) [19]. ESI-MS: *Finnigan TSQ 700* mass spectrometer; for MS/MS, Ar (2.5 mtorr) was used as collision gas.

Methyl 16-Hydroxyhexadecanoate. An ethereal soln. of CH_2N_2 (freshly prepared) was added dropwise to a stirred soln. of 16-hydroxyhexadecanoic acid (1.0 g, 36.7 mmol) in MeOH (25 ml), until a slightly yellow color persisted. Evaporation of the solvent *in vacuo* left 1.0 g (95%) of the product. M.p. 54.7–55.1° (recrystallized from MeOH/cyclohexane/pentane). ^{1}H-NMR: 3.59 (*s*, Me); 3.57 (*t*, J = 6.7, CH_2OH); 2.23 (*t*, J = 7.5, CH_2CO_2Me); 1.57–1.30 (*m*, 2 CH_2); 1.19 (*s*-like *m*, 11 CH_2).

15-(Methoxycarbonyl)pentadecanoic Acid (**5**). An aq. soln. of chromic acid (9.41 ml, prepared from 2.085 g of CrO_3, 30 ml of H_2O, and 8.7 ml of H_2SO_4) was added over 20 min to a stirred soln. of methyl 16-hydroxyhexadecanoate (907.3 mg, 3.2 mmol) in acetone (50 ml) and stirring was continued for 3 h. After addition of H_2O (15 ml), the acetone was evaporated *in vacuo*, $Na_2S_2O_5$ was added and the aq. soln. extracted with Et_2O. The combined Et_2O layers were re-extracted once (H_2O), dried (Na_2SO_4), and evaporated: 926.8 mg (97%) of **5**. M.p. 68.7–71.9°. ^{1}H-NMR: 3.66 (*s*, Me); 2.34 (*t*, J = 7.5, CH_2CO_2H); 2.30 (*t*, J = 7.6, CH_2CO_2Me); 1.67–1.58 (*m*, 2 CH_2); 1.35–1.25 (*m*, 10 CH_2).

Benzyl N-{*[8-(Benzyloxycarbonyl)amino]-4-azaoctyl*}*carbamate* (**2**). A soln. of *spermidine* (**1**) (3.56 g, 24.5 mmol) in $CHCl_3$ (230 ml; purified on *ICN* Alumina **B**, activity 1) was stirred under N_2 at 23°. During 6 h, a soln. of $PhCH_2OCOCN$ (7.9 g, 49.02 mmol) in $CHCl_3$ (80 ml) was added, and stirring was continued for 16 h. Evaporation of the solvent and recrystallization of the residue (acetone/hexane) yielded 7.17 g (71%) of **2**. M.p. 105.9–107.5°. IR: 3450*m*, 2940*m*, 1712*s*, 1511*s*, 1455*w*, 1260*m*, 1025*w*. ^{1}H-NMR: 7.27–7.19 (*m*, 10 arom. H); 5.49, 5.20 (br. 2*s*, 2 NHCO); 5.00 (*s*, 2 PhCH_2); 3.21–3.15, 3.11–3.07 (2 *q*-like *m*, 2 CH_2NHCO); 2.57 (*t*, J = 6.4, CH_2NH); 2.52–2.48 (*t*, J = 6.2, CH_2NH); 1.61–1.52 (*quint.*-like *m*, CH_2); 1.48–1.39 (*m*, 2 CH_2). ^{13}C-NMR: 155.47 (*s*, 2 CO); 135.72 (*s*, 2 C_{ipso}); 127.47, 127.02 (2*d*, 10 arom. CH); 65.50 (*t*, 2 PhCH_2); 48.32, 46.74, 39.90, 38.89, 28.54, 26.77, 26.30 (7*t*, 7 CH_2). ESI-MS ($CHCl_3$/MeOH 2:1): 850.0 (42, $[2M + Na]^+$), 828.1 (9, $[2M + 1]^+$), 436.2 (100, $[M + Na]^+$), 414.5 (64, $[M + 1]^+$). ESI-MS/MS (of *m/z* 414.5, −20 eV): 414.4 (15), 306.5 (3), 181.2 (7), 148.3 (13), 91.4 (100, $[C_6H_5CH_2]^+$), 72.6 (4).

Dibenzyl N,N-*[4-(Benzyloxycarbonyl)-4,9-diazadodecane-1,12-diyl]bis[carbamate]* (**4**). A soln. of *spermine* (**3**; 5.0 g, 24.7 mmol) in $CHCl_3$ (250 ml, purified as described for **2**) was stirred under Ar at 23°. To this soln.

[4]) Although the NMR spectra of **10** were well resolved in D_2O, attempts to record the spectra of **9** in the same solvent resulted in extremely broad signals.

$PhCH_2OCOCN$ (8.0 g, 49.6 mmol) in $CHCl_3$ (120 ml) was added during 3 h and stirring was continued overnight. After the addition of Et_3N (7.48 g, 74.05 mmol), additional $PhCH_2OCOCN$ (4.18 g, 25.94 mmol) in $CHCl_3$ (70 ml) was added within 2 h and stirring was continued for 20 h. Evaporation of the solvent and CC of the residue ($CHCl_3$/MeOH/25% aq. NH_3 soln. 90:10:0.5) gave 12.74 g (85%) of **4**. Brownish, viscous oil. IR: 3450*m*, 2940*m*, 1710*s*, 1512*s*, 1240*s*, 1140*m*, 695*m*. ^{1}H-NMR: 7.34–7.28 (*m*, 15 arom. H); 5.63–5.56 (br. *m*, 2 NHCO); 5.10–5.08 (*d*-like *m*, 3 $PhCH_2$); 3.27–3.16 (br. *m*, 4 CH_2NHCO); 2.62–2.52 (br. *m*, 2 CH_2NH); 1.75–1.42 (br. *m*, 4 CH_2). ^{13}C-NMR (100 mg in 0.6 ml): 156.60, 156.45 (2*s*, 3 CO); 136.69 (*s*, 3 C_{ipso}); 128.45, 128.38, 128.19, 127.92, 127.77, 126.80 (6*d*, 15 arom. CH); 67.07, 66.40 (2*t*, 3 $PhCH_2$); 49.09, 47.32, 46.58, 44.14, 39.48, 38.15, 37.69, 29.18, 28.03, 26.70, 26.19, 25.59 (12*t*, CH_2). ESI-MS (MeOH + 1% TFA): 1211.9 (12, $[2M + 1]^+$), 606.6 (100, $[M + 1]^+$). ESI-MS/MS (of *m/z* 606.3, −20 eV): 606.5 (79), 562.3 (9), 353.7 (9), 263.7 (43), 112.2 (11), 91.1 (100, $[C_6H_5CH_2]^+$), 84 (9).

Methyl 15-{{{4-[(Benzyloxycarbonyl)amino]butyl}{3-[(benzyloxycarbonyl)amino]propyl}amino}carbonyl}pentadecanoate (**6**). To a suspension of 1-methyl-2-chloropyridiniumiodide (307 mg, 1.2 mmol) in abs. CH_2Cl_2 (10 ml) were added **5** (300 mg, 1.0 mmol) and Et_3N (243 mg, 2.4 mmol), and the mixture was stirred under Ar at 23°. After dropwise addition of a soln. of **2** (517 mg, 1.3 mmol) in CH_2Cl_2 (5 ml), the mixture was refluxed for 1.5 h and stirred at 23° overnight. The solvent was evaporated, the residue taken up in CH_2Cl_2 (50 ml), and the soln. extracted with 0.5N aq. HCl soln. and with brine. Drying of the org. layer (Na_2SO_4), evaporation of the solvent, and CC (CH_2Cl_2/MeOH 49:1) of the residue yielded 670.4 mg (96%) of **6**. IR: 3450*m*, 2925*s*, 2855*m*, 1718*s*, 1625*s*, 1510*s*, 1240*s*, 1140*w*, 1015*w*. ^{1}H-NMR (400.1 MHz): 7.27–7.21 (*m*, 10 arom. H); 5.77 (br., NH); 5.08–5.00 (*d*-like *m*, 2 $PhCH_2$); 4.93 (br., NH); 3.58 (*s*, Me); 3.31–3.28 (*m*, CH_2NHCO); 3.21–3.11 (*m*, $(CH_2)_2NCO$); 3.05–3.00 (*m*, CH_2NHCO); 2.24–2.17 (*m*, CH_2CO_2Me, CH_2CON); 1.67–1.42 (br. *m*, 5 CH_2); 1.20–1.17 (*m*, 10 CH_2). ^{13}C-NMR (100.6 MHz): 174.19, 173.55 (2*s*, CO_2Me, CON); 156.46 (*s*, 2 NHCO); 136.77 (*s*, 2 C_{ipso}); 128.39, 128.28, 128.00, 127.92, 127.84 (5*d*, 10 arom. CH); 66.52, 66.21 (2*t*, 2 $PhCH_2$); 51.23 (*s*, Me); 47.24, 45.33, 45.15, 42.12, 40.29, 38.52, 37.61, 33.95, 32.95, 29.46, 29.36, 29.08, 28.98, 27.72, 27.34, 27.08, 25.95, 25.43, 25.31, 24.80, 24.78 (21*t*, 21 CH_2). ESI-MS ($CHCl_3$/MeOH 2:1 + 5% TFA): 1392.5 (36, $[2M + 1]^+$), 718.6 (23, $[M + Na]^+$), 696.5 (100, $[M + 1]^+$), 588.6 (26), 480.5 (16). ESI-MS/MS (of *m/z* 696.5, −15 eV): 696.5 (20), 652.4 (42), 588.5 (27), 544.3 (37), 480.5 (100), 448.3 (46), 437.0 (29), 198.2 (45).

15-{{{4-[(Benzyloxycarbonyl)amino]butyl}{3-[(benzyloxycarbonyl)amino]propyl}amino}carbonyl}pentadecanoic Acid (**7**). To a soln. of **6** (620.4 mg, 0.89 mmol) in MeOH (15 ml) was added 2N aq. NaOH soln. (2.4 ml) at 23°. After stirring for 24 h, acidification (pH 5) with 2N aq. HCl soln. and evaporation of the solvents, the residue was taken up in $CHCl_3$ and filtered to remove NaCl. Evaporation of the filtrate yielded **7** in quant. yield. Colorless lac. IR: 3450*m*, 2930*s*, 2860*m*, 1711*s*, 1625*s*, 1510*s*, 1235*s*, 1140*w*, 1015*w*. ESI-MS (MeOH): 720.8 (12, $[M + K]^+$), 704.8 (100, $[M + Na]^+$).

Dibenzyl N,N-{*26-(3-Aminopropyl)-4-(benzyloxycarbonyl)-9-{3-[(benzyloxycarbonyl)amino]propyl}-10,25-dioxo-4,9,26-triazatricosane-1,30-diyl}bis[carbamate]* (**8**). A mixture of **7** (627.3 mg, 0.92 mmol), 1-methyl-2-chloropyridinium iodide (282.0 mg, 1.1 mmol), and Et_3N (223.0 mg, 2.2 mmol) in CH_2Cl_2 (30 ml) was stirred under Ar at 23°. A soln. of **4** (690 mg, 1.14 mmol) in CH_2Cl_2 (10 ml) was added dropwise and stirring was continued for 16 h. The solvent was evaporated, CH_2Cl_2 (100 ml) was added and the soln. washed with 0.5N aq. HCl soln. (2 × 50 ml) and 5% aq. Na_2CO_3 soln. Drying (Na_2SO_4) and evaporation of the org. layer left 1.4 g of crude material, which afforded, after CC ($CHCl_3$/MeOH 98:2), 1.065 g (91%) of colorless, oily **9**. IR: 3450*w*, 2930*m*, 2860*w*, 1715*s*, 1628*m*, 1512*s*, 1260*s*, 1090*m*, 1015*m*. ^{1}H-NMR: 7.33–7.28 (*m*, 25 arom. H); 5.10–5.08 (*m*, 5 $PhCH_2$); 3.38–3.09 (br. *m*, 10 CH_2N); 2.28–2.23 (*m*, 2 CH_2CON); 1.71–1.48 (br. *m*, 9 CH_2); 1.26–1.24 (*m*, 10 CH_2). ^{13}C-NMR (100 mg in 0.6 ml): 173.72, 173.00 (2*s*, 2 CH_2CON); 156.57 (*s*, NCO_2); 136.85, 136.55 (2*s*, 5 C_{ipso}); 128.50, 128.47, 128.41, 127.95 (4*d*, 25 arom. CH); 67.31, 66.67, 66.37 (3*t*, 5 $PhCH_2$); 47.38, 46.47, 45.37, 45.16, 44.26, 42.27, 40.40, 38.60, 37.74, 33.07, 29.61, 29.50, 28.91, 27.84, 27.48, 26.06, 25.58 (17*t*, CH_2). ESI-MS ($CHCl_3$/MeOH 2:1): 1292.2 (100, $[M + Na]^+$), 657.4 (13, $½[M + 2Na]^{2+}$).

N^1-(4-Aminobutyl)-N^1,N^{16}-bis(3-aminopropyl)-N^{16}-{4-[(3-aminopropyl)amino]butyl}hexadecanediamide (= *Tenuilobine*; **9**). To a soln. of **8** (463 mg, 0.36 mmol) in AcOH (100 ml) was added 5% Pd/C (150 mg), and the mixture was hydrogenated in a *Parr* apparatus (3.5 bar, 16 h). Evaporation and CC of the residue ($CHCl_3$/MeOH/25% aq. NH_3 soln. 5:3:1) gave 190 mg (87%) of **9**. Colorless oil. ^{13}C-NMR (150.9 MHz, (D_5)pyridine): 172.53, 172.34 (2*s*, 2 CO); 50.07, 49.94, 48.41, 48.35, 47.79, 45.74, 45.70, 42.97, 42.93, 42.29, 42.22, 41.00, 39.74, 39.65, 34.14, 34.00, 33.29, 33.24, 32.16, 31.48, 31.25, 29.98, 29.92, 29.88, 27.94, 27.74, 27.39, 26.98, 26.19, 26.07, 25.72, (32*t*, CH_2). For additional spectroscopic data *cf.* [2].

N^1-(4-Acetamidobutyl)-N^1,N^{16}-bis(3-acetamidopropyl)-N^{16}-{4-[(3-acetamidopropyl)(acetyl)amino]butyl}hexadecanediamide (**12**). Acetylation of **9** was performed as described in [2]. ^{13}C-NMR (70 mg in 0.6 ml): 173.77, 173.66, 172.97 (3*s*, 2 CH_2CON); 171.03, 170.84, 170.66, 170.40, 170.32 (5*s*, 5 MeCO); 48.17, 47.40, 46.41, 44.73,

42.34, 42.25, 38.60, 36.88, 35.99, 35.90, 32.99, 29.40, 29.31, 29.12, 27.29, 26.90, 26.29, 26.07, 25.78, 25.48, 25.36, 24.88, 23.14, 22.93, 21.31 (25*t*, CH_2). For additional spectroscopic data see [2].

1,38-Diamino-5,9,26,30,35-pentaazaoctatriacontane-10,25-dione (= *Isotenuilobine*; **10**). A suspension of KH (600 mg, 15 mmol) in propane-1,3-diamine (5 ml) was stirred at 23° under Ar, until H_2 evolution ceased. A soln. of **9** (51.4 mg, 0.086 mmol) in a small amount of propane-1,3-diamine was added dropwise and stirring was continued for 30 min. The mixture was carefully dropped into 0.3N aq. HCl soln. (15 ml) and the solvents were removed *in vacuo*. The residue was taken up in H_2O, basified (K_2CO_3), and extracted with $CHCl_3$. Drying of the org. layer (Na_2SO_4), evaporation, and CC ($CHCl_3$/MeOH/25% aq. NH_3 soln. 5:3:1) yielded 42.6 mg (83%) of **10**. Colorless oil. IR (KBr): 3335*s*, 2920*s*, 2485*m*, 1652*s*, 1531*s*, 1460*s*, 1405*s*, 1265*w*, 1170*w*, 1055*w*, 725*w*. ^{1}H-NMR (600.1 MHz, D_2O): 3.37 (*t*, J = 6.7, CH_2NHCO); 3.28–3.25 (*t*-like *m*, CH_2NH_2); 3.24–3.13 (*m*, 7 CH_2N); 2.34 (*t*, J = 7.5, 2 CH_2CO); 2.23–1.17 (*m*, CH_2); 2.02–1.98 (*quint.*-like *m*, 2 CH_2); 1.91–1.83 (*m*, 4 CH_2); 1.68–1.65 (*m*, 2 CH_2); 1.38–1.36 (*m*, 10 CH_2). ^{13}C-NMR (150.9 MHz, D_2O): 180.44 (*s*, 2 CO); 50.01, 49.96, 49.91, 48.15, 48.13, 47.54, 41.80, 39.56 (8*t*, 8 CH_2); 38.98, 38.77 (2*t*, 4 CH_2); 31.94, 31.90, 31.78, 31.53, 31.39, 28.64, 28.39 (7*t*, 14 CH_2); 26.91, 26.73, 25.81 (3*t*, 3 CH_2); 25.78 (*t*, 2 CH_2). ESI-MS (MeOH/H_2O 1:1): 598.9 (31, $[M + 1]^+$), 300.1 (61, $½[M + 2]^{2+}$), 200.3 (100, $½[M + 3]^{3+}$). ESI-MS/MS (of *m/z* 68.9, −25 eV): 599.1 (66), 581.1 (12), 525.4 (35), 508.1 (37), 454.1 (29), 436.7 (38), 383.1 (35), 365.2 (45), 307.6 (15), 129.2 (100), 112.1 (26), 72.4 (7).

5,30,35-Triacetyl-1,38-bis(acetylamino)-5,9,26,30,35-pentaazaoctatriacontane-10,25-dione (**11**). A sample of **10** was peracetylated as described in [2]. ESI-MS (MeOH): 830.9 (52, $[M + Na]^+$), 427.0 (100, $½[M + 2Na]^{2+}$).

HPLC-Separation of **11** *and* **12**. *MN Nucleosil 100-5C$_8$* (200-8-4), MeOH/H_2O (58:42; flow 1.5 ml/min), UV detection at 225 nm: t_R 22.8 min for **11** and 25.4 min for **12** with $R \approx 0.87$.

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