# The Syntheses of Cyclic Spermine Alkaloids: Analogues of Buchnerine and Budmunchiamine C

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The syntheses of two macrocyclic spermine alkaloids, analogues **1** and **2** of budmunchiamine C and buchnerine, in which *N*,*N*′-bis(2-aminoethyl)hexane-1,6-diamine (PA 262; **4**) replaces spermine as polyamine backbone, were accomplished by two different methods. The first synthetic approach was based on a metal-template intramolecular amidation of tetraamino esters prepared from a *Michael* addition of protected PA 262 **10** to ethyl hexadec-2-ynoate (**12**) and ethyl prop-2-ynoate **17**, respectively (see *Schemes 4* and *5*, resp.). The consecutive *Michael* addition of ethane-1,2-diamine to unsaturated esters and aminolysis was employed in the second synthetic approach to prepare the precursors **23** and **24** (*Scheme 6*). The macrocyclic lactams were then constructed by macrocyclization of sulfonamido derivatives **25** and **26** in DMF with $Cs_2CO_3$ as catalyst.

**1. Introduction.** – From the leaves of *Clerodendrum buchneri* GÜRKE (Verbenaceae), the macrocyclic spermine alkaloid buchnerine was isolated [1], which is characterized by the presence of a 17-membered macrocyclic lactam ring reflecting spermine (= *N*,*N*′-bis(3-aminopropyl)butane-1,4-diamine) and 4-methoxycinnamoyl precursor units (*Fig. 1*). Another class of spermine alkaloids, the budmunchiamine A–C, was isolated as a mixture from the seeds of *Albizia amara* BOLV. (Leguminosae) [2]. These compounds belong to the class of pithecolobine alkaloids reported by *Wiesner* and co-workers [3] and feature the same 17-membered lactam ring as the basic skeleton and an aliphatic chain at C(4). The budmunchiamines differ from each other only in the length of their aliphatic chains.

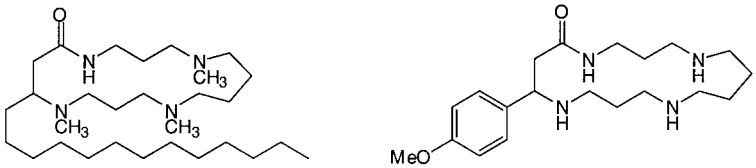


Fig. 1. *Structures of budmunchiamine C and buchnerine*

The total synthesis of (±)-buchnerine was first accomplished by *Yamamoto* and co-workers in 1996 [4]. Their synthetic design was based on a strategy in which the linear tetraamino ester was envisaged as an ideal precursor of the macrocyclic spermine skeleton. The construction of macrocyclic lactams was efficiently carried out by the metal-templated cyclization of tetraamino esters. Among several organometallic

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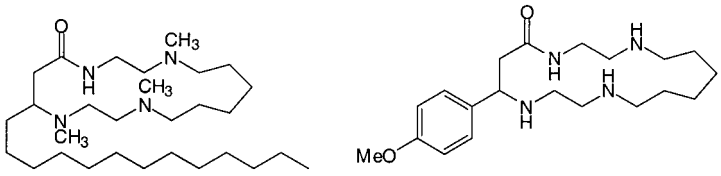
reagents used, antimony(III) ethoxide was found to be the most effective intramolecular cyclization catalyst. By the same synthetic procedure, the syntheses of budmunchiamine A – C have recently been completed in our research group [5].

The macrocyclic lactams containing the biogenic base spermine are of particular interest in view of their broad activity in biological systems. The research on the budmunchiamine alkaloids established that this class of alkaloids inhibits the catalytic activity of DNA polymerase, RNA polymerase, and HIV-1 reverse transcriptase [6]. These interesting results prompted us to make further studies in this field. We expected that the comparison of synthetic analogues with their natural counterparts will be able to reveal some more insights to the DNA/alkaloid interactions and help to conduct the study of polyamine alkaloids for pharmacological application in the future.

It was well known that the polyamine backbones of alkaloids play a key role in their binding to DNA. The binding of polycationic amines to DNA by purely electrostatic interactions and H-bonding leads to the stabilization of the double and triple helices of DNA [7], and this stability depends, to a large extent, on the number of N-atoms, the distance between the N-atoms, and the charges that these molecules can bear at physiological pH values [8][9].

Based on these findings, model compounds **1** and **2** were chosen as the analogues of budmunchiamine C and buchnerine, respectively (*Fig. 2*). Change of the basic skeleton of natural alkaloids involves the substitution of spermine with *N*,*N*′-bis(2-aminoethyl)hexane-1,6-diamine (PA 262), which has the same chain length as spermine, but the amino groups are separated by two and six instead of three and four $CH_2$ groups.




Isobudmunchiamine C
**1**

Isobuchnerine
**2**

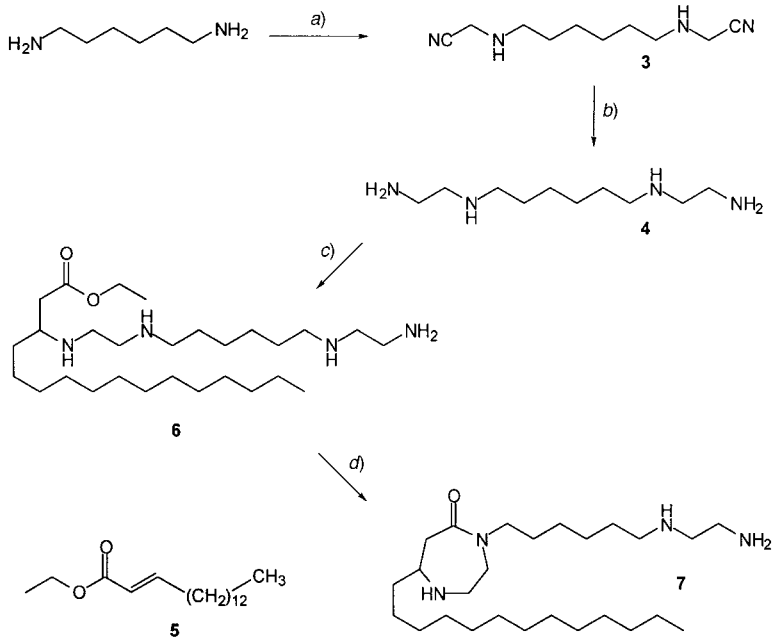
Fig. 2. *Structures of isobudmunchiamine C and isobuchnerine*

We describe in this paper the syntheses of these two spermine-alkaloid analogues by two different macrocyclization methods. The synthetic potential of the *Yamamoto* procedure in macrolactamization was studied with different tetraamino esters, and its synthetic advantage was compared with the alkylation of sulfonamide derivatives under high-dilution conditions.

**2. Results and Discussion.** – The first attempt to synthesize isobudmunchiamine C (**1**) is outlined in *Scheme 1*. The key synthetic step was to construct the tetraamino ester precursor, *i.e.*, **6**, for the employment of the *Yamamoto* protocol.

When hexane-1,6-diamine was treated with bromoacetonitrile in MeCN in the presence of KF/*Celite*, the dinitrile **3** was selectively obtained in good yield. KF/*Celite* acted as a weak-base catalyst for the nucleophilic alkylation in aprotic solvent [10]. The subsequent hydrogenation, which was carried out in the presence of *Raney*-Ni catalyst

*Scheme 1*

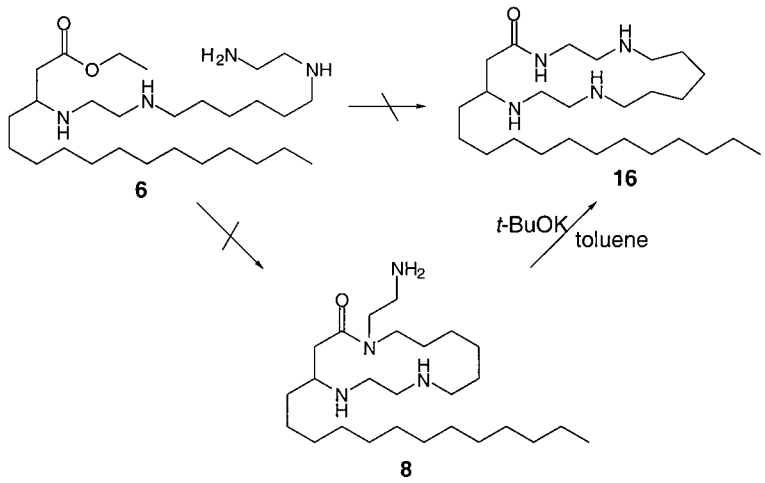



*a*) $BrCH_2CN$, KF/*Celite*, MeCN, r.t., 2 d; 71%. *b*) $H_2$, *Raney*-Ni, 25% $NH_4OH$ soln., EtOH, r.t., 20 h; 98%. *c*) **5**, EtOH, 40°, 2 d; 12%. *d*) $Sb(OEt)_3$, benzene, reflux, 20 h; 60%.

in EtOH at 50 psi, provided *N*,*N*′-bis(2-aminoethyl)hexane-1,6-diamine (**4**; PA 262). However, *Michael* addition of this polyamine to ethyl hexadec-2-enoate (**5**) in EtOH at 40° furnished the tetraamino ester **6** in a disappointing yield of only 12%. The yield could not be improved even after prolonged reaction time or at elevated temperature. Although catalysis was suggested to be desirable and necessary for an efficient reaction [11], neither base nor acid catalysts were found suitable in our case. The subsequent antimony-templated cyclization was carried out by means of the procedure developed by *Yamamoto* and co-workers [4]. Thus, amino ester **6** was refluxed for 22 h in dry benzene in the presence of antimony(III) ethoxide. The main product was isolated by chromatography in a yield of 60%. However, the absence of the amide NH signal in the $^1$H-NMR spectrum (*ca.* 8.0 ppm) and the typical double carbonyl absorption (1650 and 1515 $cm^{-1}$ in $CHCl_3$) in the IR spectrum of this product suggested the presence of an *N*-substituted lactam **7** or **8** rather than a 17-membered macrocyclic lactam. This was further confirmed by the molecular mass and the positive result of the test with the *Fluram*® reagent, which clearly showed the presence of a primary amino group in the cyclization product. Although the 7-membered-ring lactam **7** has strong preference, the possibility of forming 14-membered-ring lactam **8** could not be precluded since these two structures have quite similar $^1$H- and $^{13}$C-NMR spectra. The assignment of structure **7** to the cyclization product was based on a base-catalyzed ring-enlargement reaction, taking advantage of the different N-substituents of lactams **7** and **8**. When the

*Yamamoto*-cyclization product was treated with potassium *tert*-butoxide in boiling toluene, no reaction occurred. Since it is well established that the 'Zip' reaction proceeds reasonably well when a linear unit with two to four atoms has to be incorporated into the ring [12], the lactam **8** with a 2-aminoethyl substituent at the amide N-atom should undergo a ring enlargement smoothly to be transformed into lactam **16** (precursor of **1**) in the presence of strong base (*Scheme 2*), while this is impossible in the case of lactam **7**.

*Scheme 2*

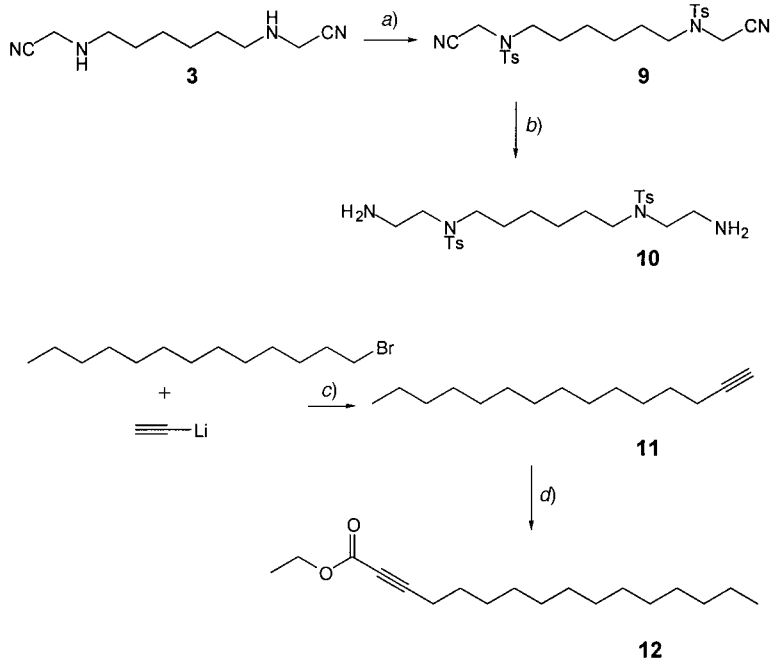



A similar procedure had been successfully employed by us [5] in the syntheses of budmunchiamine A–C; the antimony-templated cyclization proceeded smoothly to give the macrocyclic lactam rings. In those cases, the formation of the 17-membered ring is favored over the formation of the 8-membered ring. This is reasonable since the enthalpy effects, especially *Pitzer* strain and transannular interactions, come into play in the ring-closure reactions to form medium-sized rings, particularly those with eight to eleven members.

It became evident that the internal amino groups of the tetraamino ester should be protected to prevent this macrocyclization from happening. Thus, the protected polyamine **10** was prepared by catalytic hydrogenation of compound **9**, which was obtained from the reaction of dinitrile **3** with TsCl (*Scheme 3*). However the subsequent *Michael* addition of protected polyamine **10** to ethyl hexadec-2-enoate (**5**) proceeded even more sluggishly than that of its unprotected counterpart PA 262 (**4**). Thus, ethyl hexadec-2-ynoate (**12**), the more-active unsaturated ester, was prepared and used to improve the reactivity of the *Michael* addition of the protected polyamine. Coupling of the commercially available 1-bromotridecane with lithium acetylenide/ethane-1,2-diamine complex gave alkyne **11** [13] in high yield. Treatment of **11** with butyllithium and ethyl chloroformate (=ethyl carbonochloridate) furnished ethyl hexadec-2-ynoate (**12**) in 90% yield [14].

The unsaturated amino ester **13**, obtained from the *Michael* addition of **10** to **12** in 56% yield (*Scheme 4*), was subjected to catalytic hydrogenation over $PtO_2$ in MeOH/

*Scheme 3*



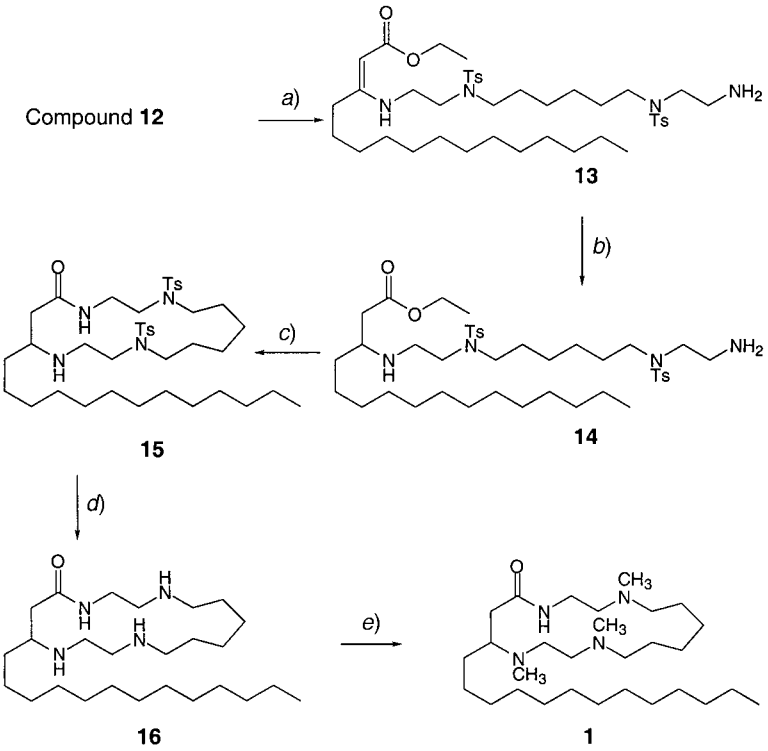

*a*) TsCl, $Et_3N$, $CH_2Cl_2$, r.t., 12 h; 90%. *b*) $H_2$, *Raney*-Ni, 25% $NH_4OH$ soln., EtOH, r.t., 20 h; 95%. *c*) DMSO, r.t., 1 h; 91%. *d*) BuLi, ethyl carbonochloridate THF, 0°, 1 h; 85%.

$CHCl_3$ at a pressure of 55 psi to give the tetraamino ester **14** in an excellent yield of 90%.

The mechanism proposed for the antimony-templated cyclization is based on a rather suitable size of the antimony(III) ion and on the formation of a metal-amino complex as the intermediate [8]. Since all the tetraamino esters used successfully in the construction of macrocyclic lactams contain three internal secondary amino groups, the two tosyl protecting groups at the chain N-atoms of tetraamino ester **14** might decrease the effectiveness of the antimony coordination and prevent the cyclization sterically. However, it was gratifying to find that refluxing of **14** in benzene in the presence of antimony(III) ethoxide resulted in the formation of 17-membered macrolactam **15** in a moderate yield of 60%. The mild electrolytic detosylation [15] of lactam **15** was carried out with 0.1M $NH_4Cl$ in 95% EtOH as catholyte and anolyte to afford lactam **16** in 80% yield. Lactam **16** was then treated with 37% aqueous $H_2CO$ solution in AcOH at 0°, and the imino derivative obtained was reduced directly by $NaCNBH_3$. Thus, isobudmunchiamine C (**1**) was finally obtained by this modified *Eschweiler–Clark* methylation reaction [5] in a yield of 88%.

Starting from the prop-2-ynoate **17**, the synthesis of buchnerine analogue **2** was carried out in an analogous approach (*Scheme 5*). Compound **17** was prepared from 4-iodoanisole by a Pd-catalyzed cross-coupling reaction according to [4b]. In contrast to ethyl hexadec-2-ynoate (**12**), the subsequent *Michael* addition of **17** with polyamine **10**

*Scheme 4*




*a*) **10**, EtOH, reflux, 2 h; 56%. *b*) $H_2$, $PtO_2$, EtOH/$CHCl_3$, r.t., 4 h; 90%. *c*) $Sb(OEt)_3$, benzene, reflux, 22 h; 60%. *d*) Electrolysis; 80%. *e*) 1. Formaline (37%), AcOH, 0°; 2. $NaCNBH_3$, r.t.; 88%.

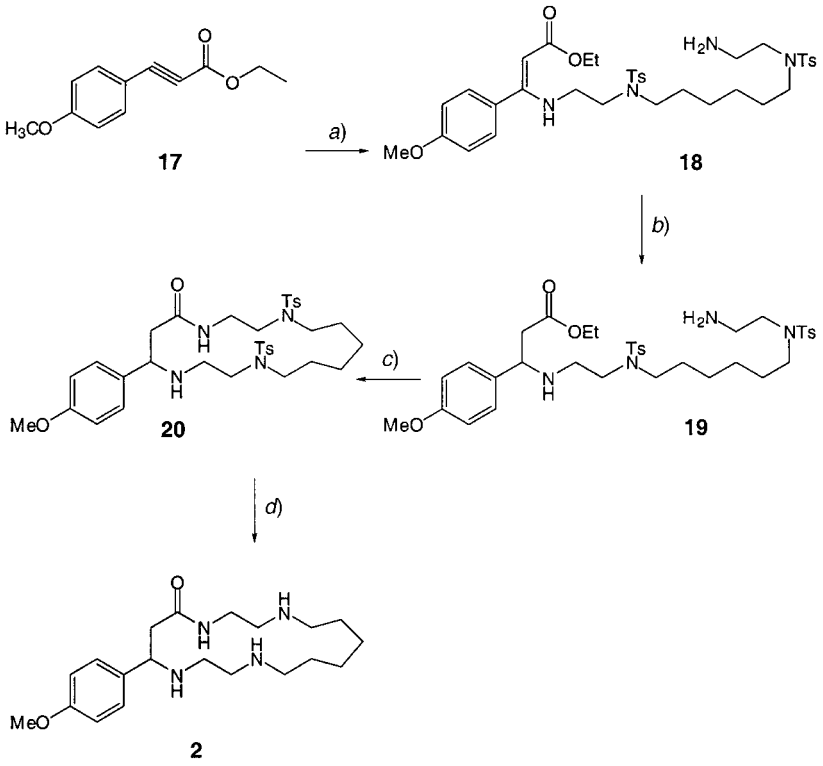
proceeded smoothly with an improved yield. The equilibrium of this reaction was driven in the direction of the product because of the increased stability of compound **18** due to the resonance of the enamino moiety with the phenyl group. Hydrogenation of the unsaturated amino ester **18**, followed by antimony-templated cyclization of tetraamino ester **19** furnished the macrocyclic lactam **20**. Finally, isobuchnerine (**2**) was obtained after removal of the tosyl protecting group by the electrolysis procedure.

Although the preparation of analogues of buchnerine and budmunchiamine C by this route was practical and convenient, the yield was limited by the multiple steps. Therefore, we decided to explore shorter synthetic routes to these two model compounds.

Ring closure by N-alkylation of the corresponding *N*-tosyl derivatives with alkali-metal carbonates under high-dilution conditions is a general method to construct the macrocyclic-lactam rings in the synthesis of polyamine alkaloids [16][17] (see *Fig. 3*). This procedure was normally carried out in aprotic polar solvent such as DMF with $Cs_2CO_3$ as base to deprotonate the *N*-tosyl derivatives.

The key step in applying this method to the synthesis of macrocyclic spermine alkaloids is the formation of the precursor for this cyclization. The problem has been

*Scheme 5*




*a*) **10**, EtOH, reflux, 2 h; 65%. *b*) $H_2$, $PtO_2$, EtOH/$CHCl_3$, r.t., 4 h; 90%. *c*) $Sb(OEt)_3$, benzene, reflux, 22 h; 67%. *d*) Electrolysis; 98%.

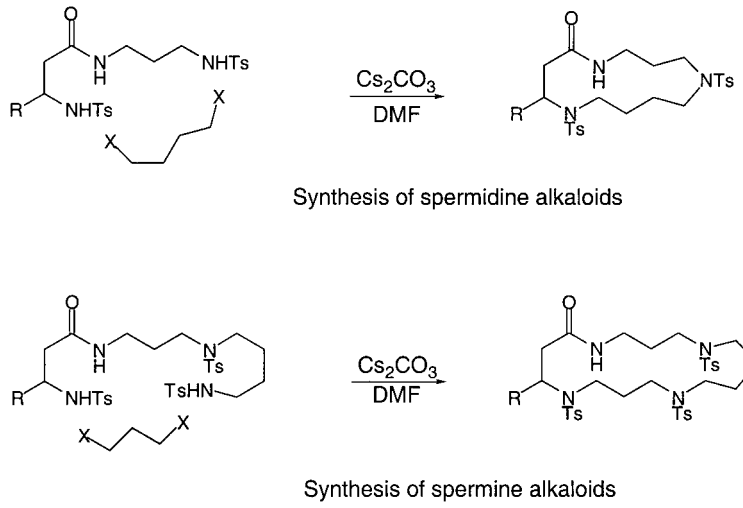
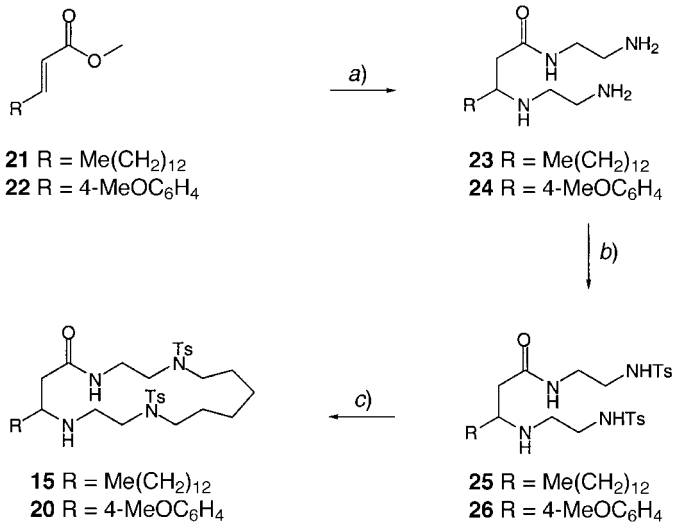



Fig. 3. *Construction of macrocyclic lactam rings by N-alkylation of* N*-tosyl derivatives under high-dilution conditions*

approached by the reaction of 3-phenylprop-2-enoic acid derivatives with primary amines. The amine would be added at the 3-position, and then a 3-(alkylamino)-3-phenylpropenamide would be formed by aminolysis. However, it was found that this potential derivatization could not be carried out experimentally [18]. Recently, a modified protocol to construct macrocyclic spermine alkaloids was reported by *Guggisberg et al.* [19] in their synthesis of protoverbine. The 3-phenylprop-2-enamide was obtained when a 3-phenylprop-2-enoate was heated with propane-1,3-diamine in refluxing xylene.

Thus, the application of this method to the syntheses of the analogues of buchnerine and budmunchiamine C was examined. The methyl esters of the unsaturated acid, prepared according to the reported procedure for their ethyl counterparts [5], were used in these studies due to their high reactivity towards amines. When the unsaturated esters **21** and **22** were heated with neat ethane-1,2-diamine at 70° for 1 d (*Scheme 6*), the polyaminoamides **23** and **24** were obtained almost quantitatively by consecutive *Michael* addition and aminolysis. After evaporation of the excess amount of ethane-1,2-diamine, these products of high purity were used directly in the next step without further purification, because of their strong polarities. The missing hydrocarbon skeleton fragments between the amino groups of **23** and **24**, which contain already all four N-atoms of the polyamine skeleton, were introduced by a modified *Richman–Atkins* procedure [20]. The protection/activation by tosylation gave the disubstituted derivatives **25** and **26**, respectively, which were cyclizated with hexane-1,6-diyl bis[mesylate] in DMF in the presence of $Cs_2CO_3$ to give the macrolactams **15** and **20**, respectively.

*Scheme 6*




*a*) Ethane-1,2-diamine, 70°, 1 d; quant. *b*) TsCl, $Et_3N$, $CH_2Cl_2$, 12 h; **25** (65%); **26** (67%). *c*) $MsO(CH_2)_6OMs$, $Cs_2CO_3$, DMF, 50°, 2 d; **15** (40%); **20** (55%).

Compared with the metal-templated macrolactamization (*Schemes 4* and *5*), the procedure of *Scheme 6* is much more versatile. The high yield and short route allow to synthesize similar spermine alkaloids on a large scale.

We thank the analytical units of our institute for spectra and analyses. Financial support of this work by the *Swiss National Science Foundation* is gratefully acknowledged.

## Experimental Part

*General*. All reactions involving air-sensitive reagents were performed under Ar. Solvents and reagents were purchased from *Fluka*. For hydrogenations, an apparatus of *Parr Instruments Company Inc.* was used. TLC: *Merck* precoated silicon-gel *60F-254* plates. Column chromatography (CC): *silica gel 60* (*Merck*; 230–400 mesh). FC = flash chromatography. M.p.: *Mettler FP-5/FP-52*; uncorrected. IR Spectra: *Perkin-Elmer 297* spectrometer; as film, unless otherwise stated. $^1$H- and $^{13}$C-NMR Spectra: *Bruker ARX-300* at 300 and 75 MHz, resp.; $\delta$ in ppm. rel. to internal $SiMe_4$, coupling constants $J$ in Hz. MS: chemical ionization (CI) with $NH_3$ as reactant gas on a *Finnigan MAT-90* and electrospray ionization (ESI) on a *Finnigan TSQ-700* mass spectrometer; in $m/z$ (rel. %).

N,N′-*(Hexane-1,6-diyl)bis[aminoacetonitrile]* (**3**). To a mixture of hexane-1,6-diamine (1.25 g, 10.7 mmol) and KF/*Celite* (13.5 g) in MeCN (250 ml) was added a soln. of bromoacetonitrile (2.70 g, 22.6 mmol) in MeCN (50 ml) within 1 h. The mixture was stirred at r.t. for 2 d and then filtered. The residue was washed with MeCN. The combined org. phase was evaporated and the residue was purified by FC ($CH_2Cl_2$/MeOH 10 : 1): **3** (1.52 g, 71%). Light yellow oil. IR: 3332*m*, 2930*s*, 2857*s*, 2233*w*, 1473*m*, 1421*w*, 1381*w*, 1330*w*, 1175*w*, 1129*s*, 870*m*, 748*w*. $^1$H-NMR: 3.60 (*s*, 4 H); 2.73 (*t*, $J$ = 6.8, 4 H); 1.59–1.45 (*m*, 4 H); 1.43–1.32 (*m*, 4 H); 1.24 (br. *s*, 2 H). $^{13}$C-NMR: 117.7 (*s*); 48.6, 37.2, 29.2, 26.7 (4 *t*). CI-MS: 165 ($[M+H]^+$).

N,N′-*Bis(2-aminoethyl)hexane-1,6-diamine* (**4**). To a soln. of **3** (1.0 g, 5.15 mmol) in EtOH (100 ml) and 25% aq. $NH_3$ soln. (28 ml) was added *Raney*-Ni (2.8 g). The hydrogenation was carried out at r.t. under 50 psi for 20 h. Then, the mixture was filtered through a pad of *Celite*, and the filtrate evaporated: **4** (1.02 g, 98%). Colorless oil. IR: 3300*s*, 2920*s*, 2860*s*, 1560*m*, 1450*s*, 1400*w*, 1375*w*, 1260*m*, 1120*s*, 1090*m*, 1050*w*, 1010*w*, 870*m*. $^1$H-NMR: 2.82 (*t*, $J$ = 6.0, 4 H); 2.72–2.57 (*m*, 8 H); 1.84 (br. *s*, 6 H); 1.58–1.43 (*m*, 4 H); 1.40–1.28 (*m*, 4 H). $^{13}$C-NMR: 52.2, 49.5, 41.4, 29.8, 27.1 (5 *t*). CI-MS: 203 (100, $[M+H]^+$), 160 (30).

*Ethyl 16-Amino-3-tridecyl-4,7,14-triazahexadecanoate* (= *Ethyl 3-{[2-{[6-[(2-Aminoethyl)amino]hexyl}-amino}ethyl]amino}hexadecanoate*; **6**). To a soln. of **4** (2.02 g, 10.0 mmol) in EtOH (100 ml) was added a soln. of ethyl hexadec-2-enoate (**5**; 2.82 g, 10.0 mmol) in EtOH (30 ml). The mixture was stirred for 2 d at 40°. Evaporation and purification of the residue by FC ($CH_2Cl_2$/MeOH/25% aq. $NH_4OH$ soln. 8 : 2 : 1) gave **6** (0.58 g, 12%). Colorless oil. IR: 3300*s*, 2925*s*, 2854*s*, 1733*s*, 1658*m*, 1559*w*, 1464*s*, 1371*w*, 1303*w*, 1179*w*, 1126*w*, 1036*w*, 721*w*. $^1$H-NMR: 4.13 (*q*, $J$ = 7.1, 2 H); 2.92 (*quint.*, $J$ = 6.2, 1 H); 2.79 (*q*, $J$ = 5.7, 2 H); 2.74–2.62 (*m*, 6 H); 2.61–2.55 (*m*, 4 H); 2.38 (*d*, $J$ = 6.3, 2 H); 1.55–1.43 (*m*, 4 H); 1.42–1.29 (*m*, 10 H); 1.28–1.20 (*m*, 26 H); 0.88 (*t*, $J$ = 6.7, 3 H). $^{13}$C-NMR: 172.6 (*s*); 60.2 (*t*); 54.7 (*d*); 52.7, 49.9, 49.8, 46.2, 41.9, 39.6, 34.6, 31.9, 30.2, 29.7, 29.6, 29.6, 29.3, 29.3, 27.4, 25.8, 22.2 (17 *t*); 14.3, 14.1 (2 *q*). CI-MS: 485 (100, $[M+H]^+$), 439 (12), 300 (8), 227 (18), 203 (62).

*4-{6-[(2-Aminoethyl)amino]hexyl}hexahydro-7-tridecyl-5*H*-1,4-diazepin-5-one* (**7**). A soln. of **6** (0.100 g, 0.207 mmol) in dry benzene (20 ml) was treated with molecular sieves for 2 h under reflux. After cooling to r.t., antimony(III) ethoxide (69 mg, 0.268 mmol) was added. The mixture was stirred for 20 h under reflux. The mixture was cooled to 10°, quenched with EtOH, and evaporated. Purification of the residue by FC ($CH_2Cl_2$/MeOH/25% aq. $NH_4OH$ soln. 100 : 15 : 3) afforded **7** (54 mg, 60%). Colorless oil. IR: 3300*m*, 2920*s*, 2850*s*, 1680*s*, 1475*m*, 1460*s*, 1430*m*, 1120*w*, 750*s*, 660*m*. $^1$H-NMR: 3.54 (*q*, 1 H); 3.49–3.40 (*m*, 2 H); 3.28–3.08 (*m*, 2 H); 2.84–2.70 (*m*, 4 H); 2.38–2.50 (*m*, 6 H); 1.58–1.20 (*m*, 36 H); 0.88 (*t*, $J$ = 6.5, 3 H). $^{13}$C-NMR: 173.6 (*s*); 53.7 (*d*); 52.5, 51.4, 49.6, 48.5, 48.2, 46.2, 41.7, 37.0, 31.7, 29.9, 29.5, 29.5, 29.3, 29.1, 27.8, 26.9, 26.6, 25.7, 22.5 (19 *t*); 13.9 (*q*). CI-MS: 439 (100, $[M+H]^+$), 396 (5).

N,N′-*(Hexane-1,6-diyl)bis[*N-*(2-cyanomethyl)-4-methylbenzenesulfonamide]* (**9**). To a soln. of **3** (0.87 g, 4.48 mmol) and $Et_3N$ (1.4 ml, 10.1 mmol) in $CH_2Cl_2$ (25 ml) was added dropwise a soln. of TsCl (1.75 g, 9.18 mmol) in $CH_2Cl_2$ (10 ml). After stirring at r.t. for 12 h, the mixture was diluted with $CH_2Cl_2$ (50 ml), washed with sat. aq. $NaHCO_3$ soln., $H_2O$, and brine, and dried ($MgSO_4$). The residue obtained after evaporation was purified by recrystallization (MeOH): **9** (2.26 g, 90%). Colorless crystals. M.p. 131–132°. IR (KBr): 2924*m*, 2875*m*, 1629*m*, 1579*m*, 1495*w*, 1452*m*, 1425*m*, 1347*s*, 1324*m*, 1310*w*, 1277*w*, 1226*w*, 1197*w*, 1160*s*, 1136*m*, 1090*m*,

1067*m*, 1049*w*, 987*w*, 936*m*, 878*s*, 850*m*, 817*m*, 754*m*, 727*s*, 664*s*, 597*w*, 572*m*, 542*m*. $^1$H-NMR: 7.72 (*d*, *J* = 8.2, 4 H); 7.36 (*d*, *J* = 8.2, 4 H); 4.24 (*s*, 4 H); 3.18 (*t*, *J* = 7.1, 4 H); 2.44 (*s*, 6 H); 1.66–1.52 (*m*, 4 H); 1.42–1.34 (*m*, 4 H). $^{13}$C-NMR: 144.6, 134.3 (2 *s*); 130.1, 127.5 (2 *d*); 113.6 (*s*); 47.2, 35.1, 26.9 (3 *t*); 21.6 (*q*). CI-MS: 520 (80, $[M+NH_4]^+$), 364 (56, $[M+NH_4-Ts]^+$), 347 (100, $[M-Ts]^+$).

N,N′-*(Hexane-1,6-diyl)bis[*N-*(2-aminoethyl)-4-methylbenzenesulfonamide]* (**10**). To a soln. of **9** (2.0 g, 3.98 mmol) in EtOH (100 ml) was added 25% aq. $NH_4OH$ soln. (28 ml). The mixture was hydrogenated at r.t. under 55 psi for 20 h in the presence of *Raney*-Ni (1.2 g). The mixture was filtered through a pad of *Celite* and evaporated. The residue was purified by CC ($CH_2Cl_2$/MeOH/25% aq. $NH_4OH$ soln. 100 : 6 : 1): **10** (1.93 g, 95%). Glasslike solid. IR ($CHCl_3$): 3300*s*, 2940*s*, 2860*m*, 1670*w*, 1600*m*, 1510*w*, 1490*w*, 1460*m*, 1335*s*, 1305*w*, 1160*s*, 1090*m*, 1020*w*, 815*m*, 650*m*. $^1$H-NMR: 7.67 (*d*, *J* = 8.2, 4 H); 7.29 (*d*, *J* = 8.2, 4 H); 3.19–3.02 (*m*, 8 H); 2.83 (*t*, *J* = 6.4, 4 H); 2.41 (*s*, 6 H); 1.58–1.45 (*m*, 4 H); 1.41 (br. *s*, 4 H); 1.32–1.29 (*m*, 4 H). $^{13}$C-NMR: 143.2, 136.5 (2 *s*); 129.7, 127.1 (2 *d*); 51.8, 49.2, 41.1, 28.7, 26.1 (5 *t*); 21.4 (*q*). ESI-MS: 511 ($[M+1]^+$).

*Pentadec-1-yne* (**11**). A mixture of lithium acetylenide/ethane-1,2-diamine (1.75 g, 19.0 mmol) in dried DMSO (7.5 ml) was cooled to 8°. Within 10 min, 1-bromotridecane (3.95 g, 14.96 mmol) was added dropwise while the temp. was maintained at 8°. Then, the mixture was allowed to warm to r.t. and held at r.t. for 1 h. Subsequently, $H_2O$ (3.5 ml) was added carefully to the vigorously stirred soln., maintaining the temp. below 35°. The hydrolyzed mixture was poured into $H_2O$ (50 ml), and the resulting mixture was extracted with hexane (3 × 100 ml). The combined extract was dried ($MgSO_4$) and evaporated and the residue distilled (80°/0.09 Torr): **11** (2.80 g, 91%). IR: 3315*m*, 2925*s*, 2854*s*, 2115*w*, 1466*m*, 1377*w*, 1273*w*, 1064*w*, 721*w*, 626*m*. $^1$H-NMR: 2.17 (*dt*, *J* = 6.9, 2.6, 2 H); 1.91 (*t*, *J* = 2.6, 1 H); 1.59–1.45 (*m*, 2 H); 1.44–1.32 (*m*, 2 H); 1.31–1.20 (*m*, 18 H); 0.88 (*t*, *J* = 6.7, 3 H). $^{13}$C-NMR: 84.5 (*s*); 67.8 (*d*); 31.8, 29.5, 29.3, 29.2, 28.9, 28.6, 28.3, 22.5, 18.2 (9 *t*); 13.9 (*q*).

*Ethyl Hexadec-2-ynoate* (**12**). To a soln. of **11** (4.16 g, 20.0 mmol) in THF (40 ml) was added a soln. of 1.6M BuLi in hexane (16.7 ml, 26.7 mmol) at −10°. After stirring for 30 min, a soln. of ethyl carbonochloridate (2.39 g, 22.0 mmol) in THF (10 ml) was added at −10°. Then, the mixture was stirred for 1 h at 0°, quenched with sat. aq. $NH_4Cl$ soln., and extracted with AcOEt. The combined org. phase was washed with $H_2O$ and brine, dried ($MgSO_4$), and evaporated. The residue was purified by CC (hexane/AcOEt 100 : 1): **12** (4.76 g, 85%). Colorless oil. IR: 2926*s*, 2855*s*, 2236*m*, 1714*s*, 1466*m*, 1366*w*, 1250*s*, 1074*m*, 864*w*, 752*m*. $^1$H-NMR: 4.20 (*q*, *J* = 7.2, 2 H); 2.31 (*t*, *J* = 7.1, 2 H); 1.64–1.52 (*m*, 2 H); 1.46–1.35 (*m*, 2 H); 1.34–1.18 (*m*, 21 H); 0.88 (*t*, *J* = 6.9, 3 H). $^{13}$C-NMR: 153.9, 89.4, 73.2 (3 *s*); 61.7, 31.9, 29.7, 29.6, 29.4, 29.3, 29.0, 28.9, 27.6, 22.7, 18.7 (11 *t*); 14.1 (*q*). CI-MS: 235 (100, $[M-EtO]^+$), 168 (90), 154 (48), 139 (25).

*Ethyl 16-Amino-7,14-bis[(4-methylphenyl)sulfonyl]-3-tridecyl-4,7,14-triazahexadec-2-enoate* (= *Ethyl 3-{[2-{[6-{(2-Aminoethyl)[(4-methylphenyl)sulfonyl]amino}hexyl][(4-methylphenyl)sulfonyl]amino}ethyl]amino}-hexadec-2-enoate*; **13**). A soln. of **10** (0.545 g, 1.07 mmol) and **12** (0.390 g, 1.07 mmol) in dry EtOH (30 ml) was heated under reflux for 2 h. After cooling, the mixture was evaporated, and the residue purified by CC ($CH_2Cl_2$/MeOH/25% aq. $NH_4OH$ soln. 97 : 3.5 : 0.3): **13** (0.47 g, 63%). Colorless oil. IR: 3382*w*, 3285*w*, 2926*s*, 2855*s*, 1651*s*, 1605*s*, 1495*m*, 1464*m*, 1338*s*, 1239*m*, 1159*m*, 1049*m*, 954*w*, 815*w*, 786*w*, 724*w*. $^1$H-NMR: 8.58 (br. *s*, 1 H); 7.70, 7.68 (2 *d*, *J* = 8.3, 4 H); 7.31 (*d*, *J* = 8.0, 4 H); 4.48 (*s*, 1 H); 4.06 (*q*, *J* = 7.1, 2 H); 3.49–3.39 (*m*, 2 H); 3.17–3.04 (*m*, 8 H); 2.84 (*t*, *J* = 6.3, 2 H); 2.41 (*s*, 6 H); 2.18 (*t*, *J* = 7.3, 2 H); 1.58–1.42 (*m*, 6 H); 1.40–1.17 (*m*, 29 H); 0.89 (*t*, *J* = 7.3, 3 H). $^{13}$C-NMR: 170.6, 165.4, 143.3, 143.0, 136.4, 135.9 (6 *s*); 129.6, 129.5, 127.0, 82.2 (4 *d*); 58.2, 51.7, 49.8, 49.1, 49.0, 42.5, 41.0, 32.0, 31.7, 29.4, 29.3, 29.2, 29.1, 28.7, 28.5, 28.0, 26.0, 25.9 (18 *t*); 21.3, 14.4, 13.9 (3 *q*). ESI-MS: 563 (47, $[M+1]^+$), 511 (100).

*Ethyl 16-Amino-7,14-bis[(4-methylphenyl)sulfonyl]-3-tridecyl-4,7,14-triazahexadecanoate* (= *Ethyl 3-{[2-{[6-{(2-Aminoethyl)[(4-methylphenyl)sulfonyl]amino}hexyl]{(4-methylsulfonyl]amino}ethyl}amino}hexadecanoate*; **14**). A mixture of **13** (0.32 g, 0.40 mmol) and $PtO_2$ (50 mg) in $CHCl_3$ (0.8 ml) and EtOH (40 ml) was stirred at r.t. under $H_2$. After 4 h, the mixture was filtered through a pad of *Celite*, the filtrate evaporated, and the residual oil purified by CC ($CH_2Cl_2$/MeOH/25% aq. $NH_4OH$ soln. 95 : 5 : 0.5): **14** (0.28 g, 90%). Colorless oil. IR: 2926*s*, 2855*s*, 1732*s*, 1653*w*, 1599*m*, 1494*w*, 1465*m*, 1339*s*, 1240*w*, 1159*s*, 1119*w*, 1091*m*, 1036*w*, 949*w*, 815*m*, 723*m*, 654*m*. $^1$H-NMR: 7.68 (*d*, *J* = 8.2, 4 H); 7.34–7.26 (*m*, 4 H); 4.13 (*q*, *J* = 7.1, 2 H); 3.20–3.04 (*m*, 8 H); 2.91 (*quint.*, *J* = 6.1, 1 H); 2.84 (*t*, *J* = 6.4, 2 H); 2.75 (*t*, *J* = 6.8, 2 H); 2.41 (*s*, 6 H); 2.37–2.34 (*m*, 2 H); 1.58–1.44 (*m*, 4 H); 1.40–1.28 (*m*, 34 H); 0.88 (*t*, *J* = 6.7, 3 H). $^{13}$C-NMR: 172.3, 143.1, 142.9, 136.6, 136.4 (5 *s*); 129.6, 129.5, 127.0 (3 *d*); 60.1, 54.7, 51.7, 49.1, 48.9, 48.7, 45.5, 41.0, 39.2, 34.4, 31.7, 29.6, 29.5, 29.2, 28.7, 28.5, 26.1, 26.0, 25.6, 22.5 (20 *t*); 21.3, 14.1, 13.9 (3 *q*). ESI-MS: 793 ($[M+1]^+$).

*1,11-Bis[(4-methylphenyl)sulfonyl]-7-tridecyl-1,4,8,11-tetraazacycloheptadecan-5-one* (**15**). a) *From* **14**: To a soln. of **14** (104 mg, 0.131 mmol) in dry benzene (10 ml) was added antimony(III) ethoxide (41 mg, 0.157 mmol). The mixture was heated under reflux for 1 d under Ar. After cooling to 10°, the reaction was

quenched with EtOH. The residue obtained after evaporation was purified by CC ($CH_2Cl_2$/MeOH 100:4): **15** (59 mg, 60%). Colorless oil.

b) *From* **25**: A mixture of **25** (0.5 g, 0.753 mmol) and $Cs_2CO_3$ (0.49 g, 1.51 mmol) in dry DMF (100 ml) was stirred at 60° for 15 min. After cooling to r.t., a soln. of hexane-1,6-diyl bis[methanesulfonate] (0.206 g, 0.753 mmol) in dry DMF (50 ml) was added dropwise. After stirring for 1 d at 40°, the mixture was evaporated. The residue was purified by CC ($CH_2Cl_2$/MeOH 40:1): **15** (0.31 g, 55%). IR: 3384*w*, 3302*w*, 2923*s*, 2854*s*, 1728*w*, 1667*s*, 1598*w*, 1535*m*, 1463*m*, 1338*s*, 1300*w*, 1159*s*, 1090*m*, 1037*w*, 982*w*, 913*w*, 875*m*, 727*m*, 653*m*. $^1$H-NMR: 7.72, 7.65 (2 *d*, *J* = 8.5, 4 H); 7.30 (*d*, *J* = 8.4, 4 H); 3.52–3.34 (*m*, 2 H); 3.28–3.17 (*m*, 2 H); 3.16–3.07 (*m*, 4 H); 3.06–2.88 (*m*, 4 H); 2.84–2.74 (*m*, 1 H); 2.48–2.14 (*m*, 2 H); 2.41 (*s*, 6 H); 1.59–1.50 (*m*, 4 H); 1.49–1.34 (*m*, 4 H); 1.33–1.18 (*m*, 26 H); 0.88 (*t*, *J* = 6.5, 3 H). $^{13}$C-NMR: 172.4, 143.4, 143.0, 136.1, 135.1 (5 *s*); 129.6, 129.5, 127.1, 54.9 (4 *d*); 50.7, 49.5, 45.8, 39.6, 38.8, 34.1, 31.7, 29.5, 29.2, 28.5, 27.8, 25.8, 25.0, 24.8, 22.5 (15 *t*); 21.3, 13.9 (2 *q*). ESI-MS: 747 ($[M+1]^+$).

*7-Tridecyl-1,4,8,11-tetraazacycloheptadecan-5-one* (**16**). According to [15]: The electrolysis was carried out at 5° under Ar with 0.1M $NH_4Cl$ in 94% EtOH as catholyte and anolyte. When the reaction was finished, the cathodic soln. was evaporated. The residue was dissolved in $H_2O$, saturated with $K_2CO_3$, and extracted with $CH_2Cl_2$. The combined org. phase was dried ($Na_2CO_3$) and evaporated, and the residue purified by CC ($CH_2Cl_2$/MeOH/25% aq. $NH_4OH$ soln. 7:3:1). From 300 mg of **15**, 144 mg (80%) of **16** was obtained. Slightly yellow oil. IR: 3285*m*, 2924*s*, 2853*s*, 1650*s*, 1551*m*, 1465*m*, 1369*w*, 1133*w*, 1028*w*, 965*w*, 809*w*, 724*w*. $^1$H-NMR: 8.32 (*m*, 1 H); 3.40 (*m*, 2 H); 3.00 (br. *s*, 3 H); 2.90–2.66 (*m*, 11 H); 2.45 (*dd*, *J* = 2.9, 15.5, 1 H); 2.23 (*dd*, *J* = 7.4, 15.5, 1 H); 1.65–1.53 (*m*, 2 H); 1.53–1.38 (*m*, 6 H); 1.37–1.15 (*m*, 24 H); 0.88 (*t*, *J* = 6.9, 3 H). $^{13}$C-NMR: 172.4 (*s*); 55.2 (*d*); 49.2, 48.9, 47.8, 45.6, 39.4, 38.4, 33.5, 31.7, 29.5, 29.4, 29.1, 27.9, 27.4, 25.9, 25.1, 24.8, 22.5 (17 *t*); 13.9 (*q*). ESI-MS: 497 (45), 439 (100, $[M+1]^+$).

*Ethyl 3-(4-Methoxyphenyl)prop-2-ynoate* (**17**). To a soln. of ethyl prop-2-ynoate (1.96 g, 20 mmol) in THF (50 ml) was added 1.6M BuLi in hexane (12.5 ml, 20 mmol) at −78°. After stirring for 30 min at −78°, a soln. of anh. zinc chloride (8.2 g, 60 mmol) in THF (60 ml) was added. The mixture was allowed to warm to r.t. and stirred for 1 h. To the ice-cooled soln. were added 4-iodoanisole (2.34 g, 10 mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.35 g, 0.5 mmol). After stirring at 50° for 3 h, the mixture was filtered through a *Celite* pad. The filtrate was extracted with $Et_2O$, the combined extract dried ($MgSO_4$) and evaporated, and the residue purified by CC (hexane/AcOEt 6:1): **17** (1.40 g, 68%). Colorless oil. IR: 2983*w*, 2841*w*, 2206*s*, 1705*s*, 1605*s*, 1567*w*, 1511*s*, 1463*w*, 1390*w*, 1367*m*, 1288*s*, 1253*s*, 1195*s*, 1165*s*, 1110*w*, 1025*m*, 947*w*, 834*m*, 748*m*. $^1$H-NMR: 7.54 (*dd*, *J* = 2.2, 6.7, 2 H); 6.87 (*dd*, *J* = 2.1, 6.8, 2 H); 4.29 (*q*, *J* = 7.1, 2 H); 3.82 (*s*, 3 H); 1.35 (*t*, *J* = 7.1, 3 H). $^{13}$C-NMR ($CDCl_3$): 161.4, 154.2 (2 *s*); 134.8, 114.2 (2 *d*); 111.3, 86.7, 80.0 (3 *s*); 61.7 (*t*); 55.1, 14.0 (2 *q*). CI-MS: 222 (100, $[M+NH_4]^+$), 205 (56, $[M+1]^+$), 176 (20), 150 (17).

*Ethyl 16-Amino-7,14-bis[(4-methylphenyl)sulfonyl]-3-(4-methoxyphenyl)-4,7,14-triazahexadec-2-enoate* (= *Ethyl 3-{[2-{[6-{(2-Aminoethyl)[(4-methylphenyl)sulfonyl]amino}hexyl][(4-methylphenyl)sulfonyl]amino}ethyl]amino}-3-(4-methoxyphenyl)prop-2-enoate*; **18**). A soln. of **17** (1.70 g, 8.33 mmol) and **10** (4.25 g, 8.33 mmol) in EtOH (50 ml) was heated under reflux for 2 h. After cooling, the soln. was evaporated, and the residue purified by CC ($CH_2Cl_2$/MeOH/25% aq. $NH_4OH$ soln. 100:3:0.3): **18** (3.87 g, 65%). IR ($CHCl_3$): 3300*w*, 2940*s*, 2860*m*, 1645*m*, 1610*s*, 1570*w*, 1510*w*, 1490*w*, 1465*w*, 1340*m*, 1305*w*, 1290*w*, 1250*m*, 1160*s*, 1090*m*, 1030*m*, 910*w*, 860*w*, 840*w*, 815*w*. $^1$H-NMR: 8.47 (br. *s*, 1 H); 7.68 (*d*, *J* = 8.2, 2 H); 7.57 (*d*, *J* = 8.3, 2 H); 7.33–7.23 (*m*, 6 H); 6.92 (*d*, *J* = 8.8, 2 H); 4.60 (*s*, 1 H); 4.13 (*q*, *J* = 7.1, 2 H); 3.83 (*s*, 3 H); 3.31–3.20 (*m*, 2 H); 3.17–2.97 (*m*, 6 H); 2.96–2.88 (*m*, 2 H); 2.85 (*t*, *J* = 6.4, 2 H); 2.42, 2.40 (2 *s*, 6 H); 1.90 (br. *s*, 2 H); 1.58–1.10 (*m*, 8 H); 1.26 (*t*, *J* = 7.1, 3 H). $^{13}$C-NMR: 170.3, 164.2, 160.5, 143.3, 136.3 (5 *s*); 129.7, 129.2 (2 *d*); 127.9 (s); 127.2, 127.1, 113.9, 86.6 (4 *d*); 58.8 (*t*); 55.4 (*q*); 51.8, 49.4, 49.2, 48.9, 43.6, 41.1, 28.9, 28.4, 26.2, 26.0 (10 *t*); 21.5, 14.6 (2 *q*). ESI-MS: 715 ($[M+H]^+$).

*Ethyl 16-Amino-7,14-bis[(4-methylphenyl)sulfonyl]-3-(4-methoxyphenyl)-4,7,14-triazahexadecanoate* (= *Ethyl 3-{[2-{[6-{(2-Aminoethyl)[(4-methylphenyl)sulfonyl]amino}hexyl][(4-methylphenyl)sulfonyl]amino}ethyl]amino}-3-(4-methoxyphenyl)propanoate*; **19**). A mixture of **18** (2.25 g, 3.15 mmol), $PtO_2$ (90 mg) in $CHCl_3$ (0.8 ml), and EtOH (40 ml) was stirred at r.t. under $H_2$. After 12 h, the mixture was filtered through a pad of *Celite*, the filtrate evaporated, and the residual oil purified by CC ($CH_2Cl_2$/MeOH/25% aq. $NH_4OH$ soln. 100:6:0.6): **19** (2.02 g, 90%). Slightly yellow oil. IR: 3379*w*, 2936*s*, 2864*m*, 1730*s*, 1599*w*, 1611*w*, 1513*m*, 1494*w*, 1463*m*, 1337*s*, 1305*w*, 1248*m*, 1158*s*, 1110*w*, 1091*m*, 1034*m*, 952*w*, 816*w*, 753*m*. $^1$H-NMR: 7.69, 7.63 (2 *d*, *J* = 8.3, 4 H); 7.33–7.16 (*m*, 6 H); 6.83 (*d*, *J* = 8.2, 2 H); 4.10 (*t*, *J* = 7.1, 2 H); 3.98 (*m*, 1 H); 3.17–2.95 (*m*, 8 H); 2.85 (*t*, *J* = 6.4, 2 H); 2.67–2.47 (*m*, 4 H); 2.41, 2.40 (2 *s*, 6 H); 1.55 (br. *s*, 3 H); 1.54–1.33 (*m*, 4 H); 1.23–1.12 (*m*, 4 H); 1.20 (*t*, *J* = 7.2, 3 H). $^{13}$C-NMR: 171.5, 158.8, 143.1, 142.9, 136.6, 136.4 (6 *s*); 129.6, 129.4, 128.0, 127.0,

113.8 (5 *d*); 60.3 (*t*); 58.7 (*d*); 55.1 (*q*); 51.6, 49.1, 48.6, 48.2, 45.7, 42.9, 41.0, 28.7, 28.4, 26.1, 26.0 (11 *t*); 21.3, 14.0 (2 *q*). ESI-MS: 717 (100, $[M+1]^+$), 515 (25).

*7-(4-Methoxyphenyl)-1,11-bis[(4-methylphenyl)sulfonyl]-1,4,8,11-tetraazacycloheptadecan-5-one* (**20**). a) *From* **19**: A mixture of **19** (0.200 g, 0.279 mmol) and antimony(III) ethoxide (80 mg, 0.307 mmol) in dry benzene (20 ml) was refluxed under Ar for 22 h. After cooling to 10°, the reaction was quenched with EtOH. The residue obtained after evaporation was purified by CC ($CH_2Cl_2$/MeOH 100:3): **20** (125 mg, 67%). Colorless oil.

b) *From* **26**: A mixture of **26** (1.0 g, 1.70 mmol) and $Cs_2CO_3$ (1.16 g, 3.57 mmol) in dry DMF (150 ml) was stirred at 60° for 15 min. After cooling to r.t., a soln. of hexane-1,6-diyl bis[methanesulfonate] (0.466 g, 1.70 mmol) in dry DMF (50 ml) was added dropwise. The mixture was stirred for 1 d at 40° and then evaporated. The residue was purified by CC ($CH_2Cl_2$/MeOH 50:1): **20** (0.69 g, 61%). IR: 3308*w*, 2933*m*, 2862*m*, 1674*s*, 1512*m*, 1461*m*, 1387*m*, 1336*s*, 1249*m*, 1160*s*, 1091*s*, 1033*w*, 984*w*, 919*w*, 817*w*, 727*w*. $^1$H-NMR: 7.67, 7.63 (2 *d*, *J* = 8.5, 4 H); 7.37–7.15 (*m*, 8 H); 6.85 (*d*, *J* = 8.6, 2 H); 4.10–4.02 (*m*, 1 H); 3.80 (*s*, 3 H); 3.63–3.48 (*m*, 2 H); 3.44–3.30 (*m*, 2 H); 3.27–2.92 (*m*, 6 H); 2.68–2.59 (*m*, 2 H); 2.57–2.48 (*m*, 2 H); 2.42, 2.40 (2 *s*, 6 H); 1.90 (br. *s*, 1 H); 1.75–1.55 (*m*, 4 H); 1.53–1.34 (*m*, 4 H). $^{13}$C-NMR: 171.7, 158.7, 143.5, 142.9, 136.0, 135.1 (6 *s*); 129.7, 129.5, 127.7, 127.2, 127.1, 58.9 (6 *d*); 55.1 (*q*); 50.9 (*t*); 49.8 (*t*); 49.7, 49.2, 46.5, 44.2, 39.0, 28.8, 28.2, 25.3 (10 *t*); 21.3 (*q*). ESI-MS: 671 ($[M+1]^+$).

*(2-Methoxy-2-oxoethyl)triphenylphosphonium Bromide*. A suspension of $Ph_3P$ (22 g, 84 mmol) and methyl bromoacetate (12.8 g, 84 mmol) in toluene (200 ml) was heated for 2 h at 80° and stirred overnight at r.t. The white precipitate was filtered, washed with toluene, and dried under h.v. to give (2-methoxy-2-oxoethyl)-triphenylphosphonium bromide (33.0 g, 95%). M.p. 160–161°. IR (KBr): 3007*w*, 2802*m*, 1723*s*, 1587*w*, 1485*w*, 1440*m*, 1423*m*, 1385*w*, 1320*s*, 1201*s*, 1161*w*, 1110*s*, 996*w*, 890*w*, 877*m*, 800*w*, 748*w*, 727*w*, 688*m*. $^1$H-NMR: 7.95–7.63 (*m*, 15 H); 5.58 (*d*, *J* = 13.6, 2 H); 3.59 (*s*, 3 H). $^{13}$C-NMR: 165.0 (*s*); 135.0, 133.9, 133.8, 130.3, 130.1 (5 *d*); 118.3, 117.2 (2 *s*); 53.3 (*q*); 33.3, 32.5 (2 *t*).

*Methyl Hexadec-2-enoate* (**21**). To a soln. of MeONa (prepared from Na (0.725 g, 31.5 mmol)) in MeOH (150 ml), (2-methoxy-2-oxoethyl)triphenylphosphonium bromide (13.07 g, 31.5 mmol) was added in small portions at 10°. After stirring for 1 h at r.t., a soln. of myristaldehyde (= tetradecanal; 6.36 g, 30.0 mmol) in $CH_2Cl_2$ (30 ml) was added dropwise. The resulting soln. was stirred overnight at r.t. and then evaporated. The residue was filtered through a short column of silica gel with $Et_2O$ to give **21** (6.5 g, 80%) as a (*E*)/(*Z*)-mixture (1.6:1). A sample of this mixture was separated by CC (hexane/$Et_2O$ 50:1) for analyses. IR: 2925*s*, 2854*s*, 1729*s*, 1659*m*, 1466*m*, 1436*m*, 1311*w*, 1269*m*, 1196*m*, 1174*m*, 1127*w*, 1043*w*, 981*w*, 819*w*, 720*w*. $^1$H-NMR: (*Z*)-isomer: 6.21 (*dt*, *J* = 11.5, 7.5, 1 H); 5.75 (*dt*, *J* = 11.5, 1.7, 1 H); 3.70 (*s*, 3 H); 2.64 (*qt*, *J* = 1.7, 7.3, 2 H); 1.50–1.37 (*m*, 2 H); 1.36–1.22 (*m*, 20 H); 0.88 (*t*, *J* = 6.5, 3 H). $^{13}$C-NMR: 166.7 (*s*); 150.8, 119.0 (2 *d*); 50.8 (*q*); 31.8, 29.5, 29.3, 29.2, 28.8, 22.5 (6 *t*); 13.9 (*q*). (*E*)-isomer: 6.99 (*dt*, *J* = 15.6, 7.0, 1 H); 6.82 (*dt*, *J* = 15.6, 1.6, 1 H); 3.72 (*s*, 3 H); 2.19 (*qt*, *J* = 1.6, 7.0, 2 H); 1.50–1.40 (*m*, 2 H); 1.38–1.22 (*m*, 20 H); 0.88 (*t*, *J* = 6.5, 3 H). $^{13}$C-NMR: 167.0 (*s*); 149.7, 120.7 (2 *d*); 51.2 (*q*); 32.1, 31.8, 29.5, 29.2, 29.0, 27.9, 22.5 (7 *t*); 13.9 (*q*). CI-MS: 286 (100, $[M+NH_4]^+$), 269 (40, $[M+1]^+$).

*Methyl 3-(4-Methoxyphenyl)prop-2-enoate* (**22**). Through a suspension of 4-methoxycinnamic acid (5.0 g, 28.1 mmol) in MeOH (150 ml) was passed gaseous HCl until it became clear. The soln. obtained was refluxed for 4 h. After removal of the solvent, the residue was recrystallized from MeOH to give **22** (4.8 g, 90%). White crystals. M.p. 86–87°. IR (KBr): 2948*m*, 2843*m*, 1716*s*, 1637*s*, 1603*s*, 1574*m*, 1513*s*, 1433*m*, 1331*m*, 1303*m*, 1288*s*, 1256*s*, 1206*s*, 1175*s*, 1111*m*, 1026*m*, 1012*m*, 984*m*, 962*w*, 933*w*, 839*s*, 823*s*, 768*m*, 633*w*. $^1$H-NMR: 7.65 (*d*, *J* = 16, 1 H); 7.48 (*d*, *J* = 8.6, 2 H); 6.90 (*d*, *J* = 8.8, 2 H); 6.29 (*d*, *J* = 16, 1 H); 3.83, 3.78 (2 *s*, 6 H). $^{13}$C-NMR: 167.7, 161.4 (2 *s*); 144.5, 129.7 (2 *d*); 127.2 (*s*); 115.3, 114.3 (2 *d*); 55.4, 51.5 (2 *q*).

N-*(2-Aminoethyl)-3-[(2-aminoethyl)amino]hexadecanamide* (**23**). A soln. of **21** (2.0 g, 7.46 mmol) in ethane-1,2-diamine (20 ml) was stirred for 1 d at 70°. After cooling, the excess amount of ethane-1,2-diamine was evaporated: **23** (2.70 g, quant.). Light yellow oil. IR: 3291*m*, 2923*s*, 2853*s*, 1652*s*, 1552*m*, 1467*m*, 1344*w*, 1108*w*, 952*w*. $^1$H-NMR: 8.21 (br. *s*, H); 3.33–3.25 (*m*, 2 H); 2.93–2.85 (*m*, 1 H); 2.84–2.79 (*m*, 4 H); 2.72–2.59 (*m*, 2 H); 2.40, 2.20 (2 *q*, 2 H); 1.40 (br. *s*, 5 H); 1.34–1.18 (*m*, 24 H); 0.88 (*t*, *J* = 6.5, 3 H). $^{13}$C-NMR: 172.3 (*s*); 54.8 (*d*); 48.7, 41.9, 41.8, 41.5, 39.5, 34.0, 31.7, 29.5, 29.2, 25.7, 22.5 (11 *t*); 13.9 (*q*). CI-MS: 357 ($[M+1]^+$).

N-*(2-Aminoethyl)-3-[(2-aminoethyl)amino]-3-(4-methoxyphenyl)propanamide* (**24**). A soln. of **22** (2.0 g, 10.4 mmol) in ethane-1,2-diamine (30 ml) was stirred for 1 d at 70°. After cooling, the excess amount of ethane-1,2-diamine was evaporated: **24** (3.0 g, quant.). Light yellow oil. IR: 3268*s*, 2934*s*, 2846*s*, 1649*s*, 1610*m*, 1552*m*, 1512*s*, 1461*m*, 1356*w*, 1303*w*, 1248*s*, 1178*m*, 1112*w*, 1032*m*, 952*w*, 833*m*, 732*w*. $^1$H-NMR: 7.60 (*m*, 1 H); 7.21, 6.86 (2 *d*, *J* = 8.7, 4 H); 3.97 (*m*, 1 H); 3.77 (*s*, 3 H); 3.38–3.17 (*m*, 2 H); 2.87–2.71 (*m*, 4 H); 2.55–2.40 (*m*, 4 H);

2.47 (*s*, 5 H). $^{13}$C-NMR: 172.1, 158.9, 134.9 (3 *s*); 127.8, 114.0, 58.9 (3 *d*); 55.1 (*q*); 48.3, 44.5, 41.4, 40.9 (4 *t*). ESI-MS: 281 ($[M+1]^+$).

N-*{2-{[(4-Methylphenyl)sulfonyl]amino}ethyl}-3-{{2-{[(4-methylphenyl)sulfonyl]amino}ethyl}amino}hexadecanamide* (**25**). To a soln. of **23** (1.91 g, 5.36 mmol) in $CH_2Cl_2$ (30 ml) containing $Et_3N$ (5.41 g, 53.6 mmol) was added slowly a soln. of TsCl (2.04 g, 10.7 mmol) in $CH_2Cl_2$ (20 ml) at 0°. After stirring at r.t. for 12 h, the mixture was diluted with $CH_2Cl_2$ (50 ml), washed with $H_2O$ and brine, and dried ($Na_2SO_4$). The residue obtained after removal of the solvent was purified by CC ($CH_2Cl_2$/MeOH/25% aq. $NH_4OH$ soln. 96 : 3.5 : 0.3): **25** (2.31 g, 65%). Light yellow oil. IR: 3284*m*, 2925*s*, 2854*s*, 1651*s*, 1596*w*, 1549*m*, 1495*w*, 1455*m*, 1327*s*, 1160*s*, 1093*s*, 949*w*, 874*m*, 661*m*. $^1$H-NMR: 8.23 (br. *s*, 1 H); 7.70, 7.66 (2 *d*, $J = 8.3$, 4 H); 7.21 (*d*, $J = 8.7$, 4 H); 3.40–3.21 (*m*, 2 H); 3.15–2.89 (*m*, 4 H); 2.82–2.68 (*m*, 2 H); 2.67–2.50 (*m*, 1 H); 1.28–1.05 (*m*, 24 H); 0.80 (*t*, $J = 6.4$, 3 H). $^{13}$C-NMR: 172.9, 143.3, 143.2, 136.9 (4 *s*); 129.6, 126.9, 126.8, 54.5 (4 *d*); 45.0, 43.0, 39.6, 38.4, 33.9, 31.8, 29.5, 29.2, 25.6, 22.5 (10 *t*); 21.3, 13.9 (2 *q*). CI-MS: 665 (100, $[M+1]^+$), 571 (20), 493 (10), 429 (30).

*3-(4-Methoxyphenyl)*-N-*{2-{[(4-methylphenyl)sulfonyl]amino}ethyl}-3-{{2-{[(4-methylphenyl)sulfonyl]amino}ethyl}amino}propanamide* (**26**). To a soln. of **24** (3.10 g, 11.06 mmol) in $CH_2Cl_2$ (50 ml) containing $Et_3N$ (11.18 g, 0.111 mol), a soln. of TsCl (4.22 g, 22.14 mmol) in $CH_2Cl_2$ (20 ml) was slowly added at 0°. After stirring at r.t. for 12 h, the mixture was diluted with $CH_2Cl_2$ (100 ml), washed with $H_2O$ and brine, dried ($Na_2SO_4$), and evaporated. The residue was purified by CC ($CH_2Cl_2$/MeOH 95 : 4): **26** (4.4 g, 67.5%). Light yellow oil. IR: 3280*s*, 3010*s*, 1650*s*, 1610*w*, 1510*s*, 1460*w*, 1440*w*, 1420*w*, 1325*m*, 1305*w*, 1250*w*, 1225*m*, 1210*m*, 1150*s*, 1090*s*, 1035*w*, 930*w*, 790*s*, 730*s*, 670*s*. $^1$H-NMR: 7.98 (*m*, 1 H); 7.80–7.70 (*m*, 4 H); 7.30–7.20 (*m*, 4 H); 7.08 (*d*, $J = 8.6$, 2 H); 6.78 (*d*, $J = 8.7$, 2 H); 6.10 (br. *s*, 2 H); 3.94–3.83 (*m*, 1 H); 3.74 (*s*, 3 H); 3.47–3.28 (*m*, 2 H); 3.16–3.03 (*m*, 2 H); 3.02–2.80 (*m*, 2 H); 2.60–2.44 (*m*, 3 H); 2.43–2.30 (*m*, 2 H); 3.38 (*s*, 6 H). $^{13}$C-NMR: 172.5, 158.8, 143.4, 143.3, 136.9, 134.4 (6 *s*); 129.8, 129.7, 127.7, 127.0, 126.9, 114.0, 58.3 (7 *d*); 55.2 (*q*); 45.5, 44.0, 42.9, 42.6, 38.9 (5 *t*); 21.5 (*q*). CI-MS: 611 (100, $[M+Na]^+$), 589 (100, $[M+1]^+$), 375 (35).

*Hexane-1,6-diyl Bis[methanesulfonate]*. To a suspension of hexane-1,6-diol (2.0 g, 16.9 mmol) in THF (30 ml), $Et_3N$ (5.9 ml, 42.4 mmol) and MsCl (2.9 ml, 37.2 mmol) were added at 0°. After stirring at r.t. for 2 h, the mixture was evaporated. The residue was extracted with $CH_2Cl_2$, the combined extract washed with $H_2O$, 5% aq. HCl soln., and brine, dried ($MgSO_4$), and evaporated. The crude product was purified by recrystallization (AcOEt/hexane): 4.3 g (92%). Colorless needle-like crystals. M.p. 58–59°. IR (KBr): 3033*w*, 3019*w*, 2953*w*, 2923*w*, 1480*w*, 1351*s*, 1228*w*, 1173*s*, 1068*w*, 1024*w*, 987*s*, 954*s*, 851*s*, 750*m*. $^1$H-NMR: 4.23 (*t*, $J = 6.4$, 4 H); 3.00 (*s*, 6 H); 1.83–1.70 (*m*, 4 H); 1.52–1.42 (*m*, 4 H). $^{13}$C-NMR: 69.6 (*t*); 37.2 (*q*); 28.8, 24.8 (2 *t*). CI-MS: 292 ($[M+NH_4]^+$).

*1,8,11-Trimethyl-7-tridecyl-1,4,8,11-tetraazacycloheptadecan-5-one* (*Isobudmunchiamine C*; **1**). To a soln. of **16** (84 mg, 0.192 mmol) in AcOH (10 ml) was added 37% formaldehyde soln. (3 ml) at 0°. After stirring at 0° for 7 min, a soln. of $NaCNBH_3$ (250 mg, 4 mmol) in MeOH (1 ml) was added. The mixture was stirred overnight at r.t. The reaction was quenched with 2N aq. HCl soln. at 5°. The residue obtained after evaporation was dissolved in sat. aq. $K_2CO_3$ soln. and extracted with $CH_2Cl_2$, the combined org. phase dried ($Na_2SO_4$) and evaporated, and the residue purified by CC ($CH_2Cl_2$/MeOH/25% aq. $NH_4OH$ soln. 90 : 10 : 1): **1** (82 mg, 88%). Slightly yellow oil. IR: 3306*m*, 2925*s*, 2853*s*, 2789*m*, 1711*w*, 1648*s*, 1538*m*, 1463*m*, 1367*w*, 1279*w*, 1127*w*, 1038*w*. $^1$H-NMR: 8.28 (br. *s*, 1 H); 3.44–3.18 (*m*, 2 H); 2.88–2.76 (*m*, 1 H); 2.75–2.62 (*m*, 1 H); 2.59–2.39 (*m*, 7 H); 2.38–2.32 (*m*, 2 H); 2.30–2.18 (*m*, 2 H); 2.29 (*s*, 6 H); 2.20 (*s*, 3 H); 1.63–1.37 (*m*, 8 H); 1.36–1.14 (*m*, 24 H); 0.88 (*t*, $J = 6.5$, 3 H). $^{13}$C-NMR: 172.7 (*s*); 61.3 (*d*); 56.7, 55.8, 55.4, 49.7 (4 *t*); 42.7, 41.9 (2 *q*); 37.2, 36.9 (2 *t*); 36.5 (*q*); 31.7, 29.6, 29.5, 29.4, 29.3, 29.1, 28.1, 27.1, 25.9, 25.5, 25.1, 25.0, 22.5 (13 *t*); 13.9 (*q*). CI-MS: 481 ($[M+1]^+$).

*7-(4-Methoxyphenyl)-1,4,8,11-tetraazacycloheptadecan-5-one* (= *Isobuchnerine*; **2**). As described for **16**, from **20** (320 mg): 170 mg (98%) of **2**. Slightly yellow oil. IR: 3290*s*, 2930*s*, 2854*m*, 1650*s*, 1611*w*, 1552*m*, 1512*s*, 1462*s*, 1364*w*, 1303*w*, 1249*s*, 1178*m*, 1130*m*, 1035*m*, 923*w*, 832*m*, 732*m*. $^1$H-NMR: 8.02 (*m*, 1 H); 7.18 (*d*, $J = 8.6$, 2 H); 6.84 (*d*, $J = 8.6$, 2 H); 3.96 (*m*, 1 H); 3.77 (*s*, 3 H); 3.45–3.25 (*m*, 2 H); 2.83–2.74 (*m*, 2 H); 2.73–2.43 (*m*, 10 H); 2.35 (br. *s*, 3 H); 1.66–1.27 (*m*, 8 H). $^{13}$C-NMR ($CDCl_3$): 171.8, 158.6, 134.7 (3 *s*); 127.5, 117.8, 58.7 (3 *d*); 55.1 (*q*); 49.2, 48.8, 48.1, 47.9, 46.3, 44.1, 38.8, 28.8, 28.0, 25.4, 25.2 (11 *t*). CI-MS: 363 ($[M+1]^+$).

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