Syntheses of the Macrocyclic Spermine Alkaloids (±)-Budmunchiamine A – C

by **Kasim Popaj**[1]) and **Manfred Hesse***

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

The syntheses of four macrocyclic spermine alkaloids, (±)-budmunchiamine A – C (**1a** – **c**) and (±)-budmunchiamine L4 (**1**), were accomplished by *Michael* addition of spermine to the α,β-unsaturated esters **3a** – **d**, followed by cyclization of the resulting α,ω-tetraamino esters **4a** – **d** with triethoxyantimony; *N*-methylation of the amino lactams **6a** – **c** yielded the budmunchiamines A – C (**1a** – **c**).

Introduction. – From the seeds of *Albizia amara* BOLV. (Leguminosae), a plant endemic to India, was isolated a mixture of three homologs macrocyclic spermine alkaloids, the budmunchiamines A – C (**1a** – **c**) [1]. The structures of these compounds were elucidated by spectroscopic methods. These compounds belong to the class of pithecolobine alkaloids reported by *Wiesner et al.* [2]. In the last years, the class of pithecolobine alkaloids has grown to *ca*. twenty members [3]. These alkaloids consist of a 17-membered macrocyclic lactam ring as the basic skeleton, which contains the spermine part and an aliphatic chain at C(4). The budmunchiamines differ from each other only in the length and the substitution pattern of the aliphatic chain.

The biological activity of the budmunchiamine alkaloids has been of interest to both research groups that were involved in the budmunchiamines chemistry. *Mar et al.* [4] found that budmunchiamines A – C and other new members of this class of alkaloids inhibit the catalytic activity of DNA polymerase, RNA polymerase, and HIV-1 reverse transcriptase, and showed cyclooxygenase activity. *Rukunga* and *Waterman* found that all nine budmunchiamine alkaloids isolated from *Albizia schimperana* [3c] and *A. gummifera* [3d], seven of them being new analogues, are active against two *Gram*-positive and two *Gram*-negative bacteria, and showed toxicity to brine shrimp larvae. Our interest was first focused on the synthesis of (±)-budmunchiamine A (**1a**).

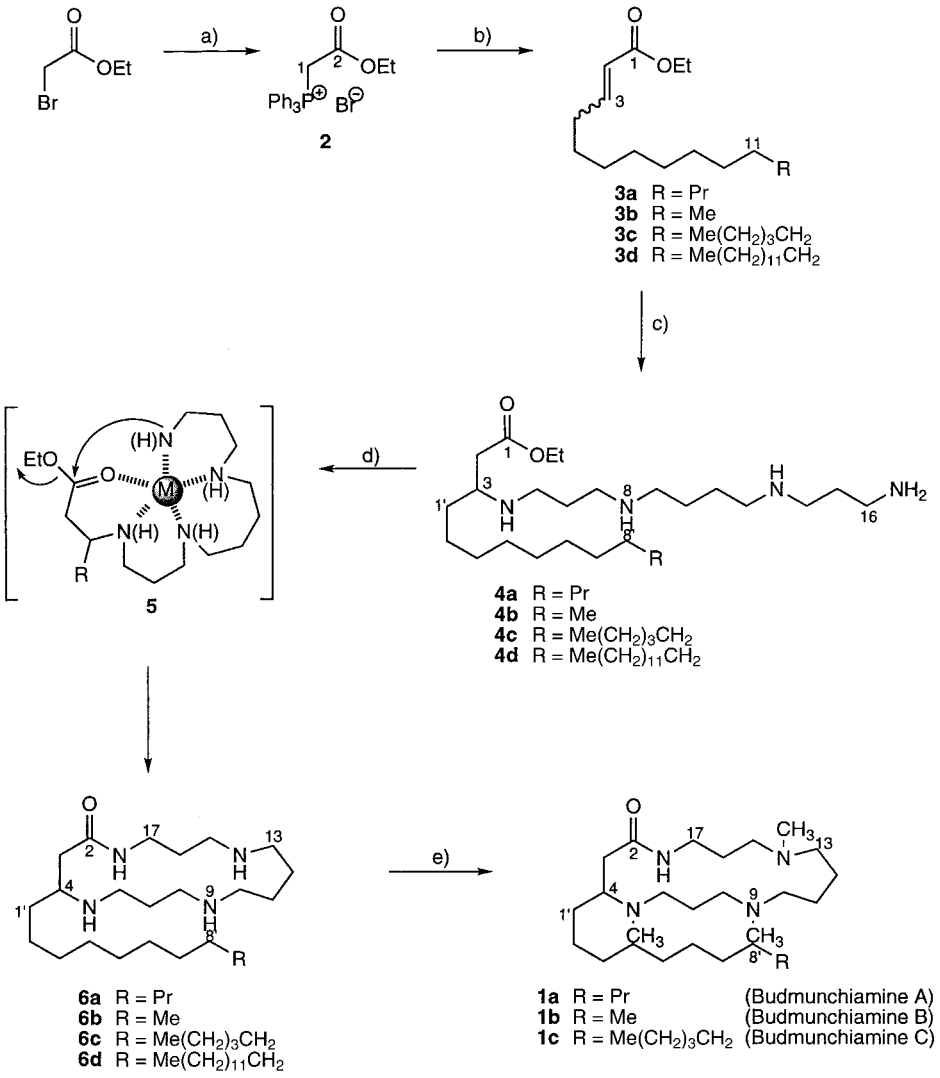
Syntheses. – The commercially available ethyl bromoacetate was reacted with Ph_3P to yield the corresponding phosphonium bromide **2** (*Scheme*). Treatment of **2** with EtONa/EtOH and lauric aldehyde (= dodecanal) gave, by a *Wittig* reaction, a (*Z*)/(*E*)-mixture of the α,β-unsaturated ester **3a** in a ratio of 1:2. For spectroscopic characterization, the two isomers were separated by column chromatography. The subsequent *Michael* addition of spermine to the (*E*)/(*Z*)-mixture of **3a** in EtOH at room temperature furnished the ester **4a** in 43% yield. The yields of the monoalkylated product **4a** could not be improved. The dialkylated spermine was a side product.

[1]) Part of the Ph.D. thesis of *K. P.*, Universität Zürich, 1999.

Nevertheless, since this reaction pathway is quite short, we applied this procedure to prepare also the homologues **4b**, **4c**, and **4d** (*Scheme*).

Preparation of the lactam **6** was achieved by a very effective method for cyclization of the α,ω-tetraamino esters developed by *Yamamoto* and co-workers [5]. Among several organometallic reagents used for the syntheses of the macrocyclic lactams, triethoxyantimony ($(EtO)_3Sb$) proved to be the best activating reagent for the ester

Scheme



a) Ph_3P, toluene, 80°; 94%. b) 1. EtONa/EtOH, r.t.; 2. dodecanal (for **3a**), decanal (**3b**), tetradecanal (**3c**), docosanal (**3d**) 10° → r.t.; 88–96%. c) Spermine, EtOH, 40°, 4–6 d; 41–71%. d) 1.3 equiv. $(EtO)_3Sb$ benzene, reflux; 74–78%. e) 1.37% Formalin soln., AcOH, 0°; 2. $NaCNBH_3$, 0° → r.t.; 80–83%.

group of the amino esters. Cyclization of the amino ester **4** to the 17-membered lactam **6** can be described as a metal template effect of the $(EtO)_3Sb$, which proceeds *via* the intermediate **5**. Thus, treatment of **4a** with $(EtO)_3Sb$ in dry benzene for 16 h under reflux gave, after chromatography, the lactam **6a** in 78% yield. Finally, methylation of **6** was achieved by a modified *Eschweiler-Clark* reaction. After several attempts according to the classical procedure, we obtained the highest yields when the reaction was carried out at low temperatures in acidic medium. Therefore, **6a** was treated with 37% aqueous H_2CO solution in AcOH at 0°, followed by $NaCNBH_3$ reduction, to give after workup (±)-budmunchiamine A (**1a**) in 83% yield. With respect to the lauric aldehyde, the total yield of **1a** was 25%. In an analogous manner, the syntheses of the natural (±)-budmunchiamine B (**1b**) and (±)-budmunchiamine C (**1c**), starting from the corresponding aldehydes, were carried out. The same procedure was applied to prepare the unnatural alkaloid (±)-budmunchiamine L4 (**1d**) with a C_{20} side chain. In this case, the overall yield starting from docosanal was 53%.

Comparison of the data of synthetic (±)-budmunchiamines A–C with the data published for the natural alkaloids [1][3a] shows that they are identical apart from their chiroptical properties. It should be mentioned that, besides mass spectroscopy, other spectroscopic methods are not sufficient to differentiate unambiguously between these homologous compounds.

We thank the analytical departments of our institute for measurements and the *Swiss National Science Foundation* for financial support.

Experimental Part

General. All commercially available reagents were used without further purification. All reactions were followed by TLC (*Merck* silica gel *60 F_{254}*). The detection was performed either with UV light or the following reagents: *Cer(IV) sulfate* and *Schlittler* reagent. Column chromatography (CC) was carried out with *Merck* silica gel *60* (40–60 m). M.p.: *Mettler FP5*. Hydrogenation: *Parr Instruments Company Inc.* IR [cm^{-1}]: *Perkin-Elmer 781*; measured as 2–3% soln. in $CHCl_3$ (*Fluka*, for spectroscopy). ^{1}H-NMR: *Bruker ARX-300* (300 MHz) or *Bruker AMX-600* (600 MHz), chemical shifts δ in ppm, Me_4Si (=0 ppm) as internal standard, coupling constants in Hz; solvent $CDCl_3$. ^{13}C-NMR: *Bruker ARX 300* (75 MHz) or *Bruker AMX-600* (150 MHz); MS: *Finnigan SSQ 700*, chemical ionization (CI) with NH_3; *Finnigan MAT 90*, electron impact (EI; 70 eV); and *Finnigan TSQ 700*, electrospray ionization (ESI).

[(Ethoxycarbonyl)methyl]phosphonium Bromide (**2**). To a suspension of Ph_3P (22 g, 84 mmol) in toluene (200 ml) was added ethyl bromoacetate (14 g, 84 mmol). The mixture was heated 6 h at 80° and stirred overnight at r.t. The mixture was filtered off, washed with toluene, and the precipitated phosphonium bromide was dried 15 h at 10^{-3} bar to give 34 g (94%) of **2**. Colorless crystals. M.p.: 153–155° ($CHCl_3$/hexane). IR: 3360*w*, 2915*s*, 2705*w*, 2400*w*, 1725*s*, 1585*w*, 1335*m*, 1370*w*, 1305*m*, 1210*m*, 1110*s*, 1020*w*, 995*w*, 845*w*, 660*m*, 620*w*. ^{1}H-NMR: 7.93–7.33 (*m*, 15 arom. H); 5.47 (*d*, J = 13.8, CH_2(1)); 4.02 (*q*, J = 7.1, MeCH_2); 1.05 (*t*, J = 7.2, Me). ^{13}C-NMR: 164.2 (*s*, C(2)); 135.1, 133.9, 133.7, 130.2, 130.1 (5*d*, 15 arom. C); 118.4, 117.2 (2*s*, 3 arom. C); 62.7 (*t*, MeCH_2); 33.4, 32.7 (2*t*, C(1)); 13.6 (*q*, *Me*CH_2). ESI-MS: 349 ($[M-Br]^+$).

Ethyl Tetradec-2-enoate (**3a**). To a soln. of EtONa (prepared from Na (575 mg, 25 mmol) and EtOH (100 ml)), **2** (10.7 g, 25 mmol) was added in portions at 10°, and the mixture was stirred 1 h at r.t. After the addition of 4.37 g (23.75 mmol) of dodecanal in CH_2Cl_2 (20 ml) and stirring overnight at r.t., the mixture was evaporated, and the crude product was filtered through 50 g of SiO_2 (Et_2O/hexane 1:2) to afford 5.1 g (88%) of **3a** as an (*E*)/(*Z*)-mixture (*ca.* 2:1). For anal. purposes, 450 mg of **3a** were purified by CC (SiO_2; Et_2O/hexane 2:98) to give 140 g (33%) of the (*Z*)-isomer and 285 mg (67%) of the (*E*)-isomer as colorless oils. IR: 2920*vs*, 2850*s*, 1720*s*, 1640*m*, 1455*m*, 1415*m*, 1360*m*, 1295*w*, 1235*m*, 1175*s*, 1115*s*, 1030*m*, 925*w*, 820*m*, 660*m*, 620*w*. (*Z*)-Isomer: ^{1}H-NMR: 6.21 (*dt*, J = 11.5, 7.5, H–C(3)); 5.75 (*d*, J = 11.5, H–C(2)); 4.16 (*q*, J = 7.2, MeCH_2O); 2.63 (*q*, J = 7.3, CH_2(4)); 1.41 (*t*, J = 6.3, CH_2(5)); 1.30–1.25 (*m*, 8 CH_2, *Me*CH_2O); 0.88 (*t*, 6.9, Me(14)). ^{13}C-NMR:

166.6 (*s*, C(1)); 150.5 (*d*, C(3)); 119.5 (*d*, C(2)); 59.6 (*t*, Me*C*H$_2$O); 34.3, 31.8, 29.6, 29.5, 29.4, 29.3, 29.1, 28.0, 22.7 (9*t*, 9 C); 14.1 (*q*, C(14)); 13.9 (*q*, *Me*CH$_2$O). (*E*)-Isomer: ^{1}H-NMR: 6.94 (*dt*, *J* = 15.6, 7.0, H–C(3)); 5.80 (*d*, *J* = 15.6, H–C(2)); 4.17 (*q*, *J* = 7.1, Me*C*H$_2$O); 2.19 (*q*, *J* = 7.0, CH$_2$(4)); 1.44 (*t*, *J* = 7.2, CH$_2$(5)); 1.32–1.26 (*m*, 8 CH$_2$, *Me*CH$_2$O); 0.87 (*t*, 6.9, Me(14)). ^{13}C-NMR: 166.8 (*s*, C(1)); 149.9 (*d*, C(3)); 121.2 (*d*, C(2)); 60.1 (*t*, Me*C*H$_2$O); 32.2, 31.9, 29.6, 29.5, 29.4, 29.3, 29.1, 28.0, 22.7 (9*t*, 9 C); 14.3, 14.1 (*q*, *Me*CH$_2$O). EI-MS: 254 (5, $M^{+\bullet}$), 209 (9, $[M - OEt]^+$), 157 (18), 127 (46), 113 (27), 99 (47), 81 (37), 67 (24), 55 (58), 43 (100).

Ethyl 16-Amino-3-undecyl-4,8,13-triazahexadecanoate (**4a**). A soln. of **3a** (3.49 g, 13.7 mmol) in EtOH (20 ml) was added, during 30 min, to soln. of spermine (2.77 g, 13.7 mmol) in EtOH (150 ml) under stirring, and the mixture was heated for 4 d at 40°. Evaporation of the solvent and purification of the residue by CC (SiO$_2$; CH$_2$Cl$_2$/EtOH/25° aq. NH$_4$OH soln. 6 : 3 : 1) gave 2.5 g (43%) of **4a**. Colorless oil. IR: 2920v*s*, 2850v*s*, 1720v*s*, 1580*w*, 1460*s*, 1370*s*, 1300*m*, 1180*m*, 1115*s*, 1025*m*, 920*m*, 885*m*, 845*m*, 655*s*, 620*w*. ^{1}H-NMR: 4.12 (*q*, *J* = 7.1, Me*CH*$_2$O); 2.92 (*quint.*, *J* = 6.4, H–C(3)); 2.78 (*t*, *J* = 6.8, CH$_2$(16)); 2.69 (*t*, *J* = 7.0, CH$_2$(9), CH$_2$(12)); 2.45 (*t*, *J* = 6.8, CH$_2$(5), CH$_2$(7), CH$_2$(14)); 2.38 (*d*, *J* = 6.3, CH$_2$(2)); 2.19 (br., NH, NH$_2$); 1.66 (*quint.*, *J* = 6.9, CH$_2$(6), CH$_2$(15)); 1.54 (*quint.*, *J* = 7.1, CH$_2$(10), CH$_2$(11)); 1.28–1.23 (*m*, 10 CH$_2$, *Me*CH$_2$O); 0.88 (*t*, 7.9, Me(11′)). ^{13}C-NMR: 172.5 (*s*, C(1)); 60.0 (*t*, Me*C*H$_2$O); 54.7 (*d*, C(3)); 49.7, 48.2, 47.6, 45.2, 40.3, 39.1 (6*t*, 6 C–N); 34.3, 33.5, 31.7, 30.3, 29.5, 29.4, 29.1, 27.7, 25.6, 22.4 (10*t*, 15 C); 14.0 (*q*, *Me*CH$_2$O); 13.9 (*q*, C(11′)). ESI-MS: 457 (28, $[M+1]^+$), 229 (100, $[M+2]^{2+}$).

4-Undecyl-1,5,9,14-tetraazacycloheptadecan-2-one (**6a**). A soln. of **4a** (1.3 g, 2.85 mmol) in dry benzene (180 ml) was treated with molecular sieves 2 h under reflux. After cooling to r.t. (EtO)$_3$Sb (950 mg, 3.7 mmol) in benzene (10 ml) was added under Ar, and the mixture was stirred for 16 h under reflux. The mixture was cooled to 10°, quenched with EtOH, and evaporated. Purification of the residue by CC (SiO$_2$; CH$_2$Cl$_2$/EtOH/25% aq. NH$_4$OH soln. 15 : 4 : 1) yielded 915 mg (78%) of **6a**. Colorless oil. IR: 3240*w*, 2920v*s*, 2850v*s*, 1640*s*, 1520*m*, 1460*m*, 1370*m*, 1220*m*, 1120*m*, 1045*w*, 925*w*, 805*m*, 660*m*, 620*w*. ^{1}H-NMR: 8.44 (br., NHCO); 3.37 (*t*, *J* = 7.7, CH$_2$(17)); 2.83 (*quint.*, *J* = 7.0, H–C(4)); 2.76–2.72 (*m*, CH$_2$(6), CH$_2$(8)); 2.68 (*t*, *J* = 5.4, CH$_2$(10), CH$_2$(13), CH$_2$(15)); 2.37 (*dd*, *J* = 15.2, 3.3, H$_a$–C(3)); 2.25 (br., NH); 2.14 (*dd*, *J* = 15.3, 7.2, H$_b$–C(3)); 1.67 (*quint.*, *J* = 6.1, CH$_2$(7), CH$_2$(16)); 1.59 (*quint.*, *J* = 8.0, CH$_2$(11), CH$_2$(12)); 1.41–1.25 (*m*, 10 CH$_2$); 0.88 (*t*, *J* = 7.0, CH$_3$(11′)). ^{13}C-NMR: 172.2 (*s*, C(2)); 55.4 (*d*, C(4)); 48.4, 48.2, 48.0, 47.3, 45.7 (5*t*, 5 C–N); 40.3, 37.6, 34.0, 31.7, 29.6, 29.4, 29.2, 28.8, 26.7, 26.6, 25.7, 22.5 (12*t*, 16 C); 13.9 (*q*, C(11′)). ESI-MS: 411 (44, $[M+1]^+$), 206 (100, $[M+2]^{2+}$).

5,9,14-Trimethyl-4-undecyl-1,5,9,14-tetraazacycloheptadecan-2-one (*=(±)-Budmunchiamine A*; **1a**). A soln. of **6a** (90 mg, 0.21 mmol) and 37% formalin (3 ml) in AcOH (10 ml) was stirred at 0°. After 7 min, NaCNBH$_3$ (250 mg, 4 mmol) in MeOH (1 ml) was added, and the mixture was stirred overnight at r.t. After cooling to 5°, the mixture was quenched with 2N aq. HCl soln., and the solvent was evaporated. The residue was dissolved in 5 ml of sat. aq. K$_2$CO$_3$ soln., extracted with CH$_2$Cl$_2$, and dried (Na$_2$SO$_4$). Evaporation of the solvent and purification of the residue by CC (SiO$_2$; CHCl$_3$/MeOH/25% aq. NH$_4$OH soln. 90 : 10 : 0.7) gave 78 mg (83%) **1a**. Colorless oil. IR: 3420*m*, 2920v*s*, 2850v*s*, 2800*s*, 1640v*s*, 1520*s*, 1460*s*, 1370*m*, 1230*m*, 1135*m*, 1050*m*, 920*w*, 845*w*, 680*w*, 655*m*. ^{1}H-NMR: 8.55 (br., NHCO); 3.32 (*dt*, *J* = 12.6, 6.8, CH$_2$(17)); 2.84 (*quint.*, *J* = 4.7, H–C(4)); 2.62 (*dt*, *J* = 12.3, 7.0, H$_a$–C(6)); 2.49–2.34 (*m*, 10 H); 2.24 (*dd*, *J* = 6.2, 1.6, 1 H–C(3)); 2.27 (*s*, MeN(9)); 2.19 (*s*, MeN(14), MeN(5)); 1.67 (*quint.*, *J* = 6.5, CH$_2$(16)); 1.64 (*quint.*, *J* = 6.4, CH$_2$(7)); 1.52 (*quint.*, *J* = 6.7, CH$_2$(11), CH$_2$(12)); 1.30–1.17 (*m*, 10 CH$_2$); 0.88 (*t*, *J* = 6.9, Me(11′)). ^{13}C-NMR: 172.5 (*s*, C(2)); 61.1 (*d*, C(4)); 56.3, 56.2, 55.8, 54.5, 51.5 (5*t*, 5 C–N); 42.8, 42.3 (2*q*, 2 MeN); 37.6, 37.0 (2*t*, 2 C); 35.1 (*q*, MeN); 31.8, 29.7, 29.6, 29.5, 29.4, 29.2, 27.5, 27.3, 27.1, 26.0, 24.4, 23.3, 22.5 (13*t*, 14 C); 13.9 (*q*, C(11′)). ESI-MS: 453 (100, $[M+1]^+$), 227 (80, $[M+2]^{2+}$). EI-MS: 452 (40, $M^{+\bullet}$), 437 (28, $[M - Me]^+$), 380 (16), 366 (31), 295 (25), 273 (19), 243 (31), 238 (20), 226 (20), 212 (19), 200 (28), 186 (16), 169 (15), 149 (33), 127 (18), 112 (21), 100 (29), 98 (35), 86 (75), 84 (100), 70 (39), 58 (57), 49 (95), 43 (69).

Ethyl Dodec-2-enoate (**3b**). As described for **3a**, from Na (1.7 g, 74 mmol), **2** (32 g, 74 mmol), and decanal (10.82 g, 69.37 mmol) in EtOH (200 ml), 14.1 g (90%) of **3b** as an (*E*)/(*Z*)-mixture (*ca.* 2 : 1) were obtained after workup. Colorless oil. For anal. purposes, 320 mg of **3b** were purified by CC (SiO$_2$; Et$_2$O/hexane 2 : 98) to give 104 mg (34%) of the (*Z*)-isomer and 205 mg (66%) of the (*E*)-isomer as colorless oils. IR: 2920v*s*, 2850v*s*, 1710v*s*, 1650*s*, 1460*m*, 1370*s*, 1310*s*, 1275*s*, 1170*m*, 1130*m*, 1035*m*, 980*m*, 825*w*, 660*w*, 620*w*. (*Z*)-Isomer: ^{1}H-NMR: 6.22 (*dt*, *J* = 11.5, 7.5, H–C(3)); 5.74 (*dt*, *J* = 11.5, 1.7, H–C(2)); 4.16 (*q*, *J* = 7.1, Me*CH*$_2$O); 2.63 (*q*, *J* = 7.3, CH$_2$(4)); 1.43 (*t*, *J* = 6.3, CH$_2$(5)); 1.30–1.25 (*m*, 6 CH$_2$, *Me*CH$_2$O); 0.87 (*t*, *J* = 7.0, Me(12)). ^{13}C-NMR: 166.4 (*s*, C(1)); 150.4 (*d*, C(3)); 119.5 (*d*, C(2)); 59.6 (*t*, Me*C*H$_2$O); 31.7, 29.4, 29.3, 29.1, 29.0, 28.9, 22.5 (7*t*, 8 C); 14.1 (*q*, C(12)); 13.9 (*q*, *Me*CH$_2$O). (*E*)-Isomer: ^{1}H-NMR: 6.95 (*dt*, *J* = 15.6, 7.0, H–C(3)); 5.80 (*dt*, *J* = 15.6, 1.6, H–C(2)); 4.16 (*q*, *J* = 7.2, Me*CH*$_2$O); 2.18 (*q*, *J* = 7.1, CH$_2$(4)); 1.45 (*t*, *J* = 7.2, CH$_2$(5)); 1.32–1.26 (*m*, 6 CH$_2$, *Me*CH$_2$O); 0.88 (*t*, *J* = 6.9, Me(12)). ^{13}C-NMR: 166.6 (*s*, C(1)); 149.3 (*d*, C(3)); 121.1 (*d*, C(2));

59.9 (*t*, Me*C*H$_2$O); 32.0, 31.7, 29.3, 29.2, 29.1, 29.0, 27.9, 22.5 (8*t*, 8 C); 14.1 (*q*, C(12)); 13.9 (*q*, *Me*CH$_2$O). CI-MS: 227 (76, $[M+1]^+$), 226 (52, $[M+NH_4-H_2O]^+$), 181 (52, $[M-OEt]^+$), 138 (16), 127 (100), 144 (22), 99 (80), 88 (28), 81 (30),55 (39), 43 (41).

Ethyl 16-Amino-3-nonyl-4,8,13-triazahexadecanoate (**4b**). As described for **4a**, from spermine (6.46 g, 32 mmol) and **3b** (7.23 g, 32 mmol) in EtOH (500 ml), 5.2 g (40%) of **4b** were obtained after workup. Colorless oil. IR: 2920v*s*, 2850*s*, 1720*m*, 1600*w*, 1510*m*, 1370*w*, 1300*w*, 1220*w*, 1115*m*, 1025*w*, 925*w*, 840*w*, 660*m*, 620*w*. ^{1}H-NMR: 4.15 (*q*, *J* = 7.2, MeC*H*$_2$); 2.92 (*quint.*, *J* = 6.2, H–C(3)); 2.77 (*t*, *J* = 6.8, CH$_2$(16)); 2.75–2.70 (*m*, CH$_2$(9), CH$_2$(12)); 2.69–2.67 (*m*, CH$_2$(5)); 2.62 (*m*, CH$_2$(7), CH$_2$(14)); 2.38 (*d*, *J* = 6.2, CH$_2$(2)); 1.98 (br., NH, NH$_2$); 1.64 (*quint.*, *J* = 6.9, CH$_2$(6), CH$_2$(15)); 1.52 (*quint.*, *J* = 6.4, CH$_2$(10), CH$_2$(11)); 1.28–1.23 (*m*, 8 CH$_2$, *Me*CH$_2$O); 0.88 (*t*, *J* = 6.5, Me(9′)). ^{13}C-NMR: 172.5 (*s*, C(1)); 60.0 (*t*, Me*C*H$_2$O); 54.7 (*d*, C(3)); 49.6, 48.2, 47.6, 45.2, 40.3, 39.1 (6*t*, 6 C); 34.2, 33.5, 31.7, 30.2, 29.6, 29.5, 29.4, 29.1, 27.6, 25.6, 22.5 (11*t*, 13 C); 14.1 (*q*, *Me*CH$_2$O); 13.9 (*q*, C(9′)). ESI-MS: 429 (43, $[M+1]^+$), 215 (100, $[M+2]^{2+}$).

4-Nonyl-1,5,9,14-tetraazacycloheptadecan-2-one (**6b**). As described for **6a**, from **4b** (4.2 g, 9.8 mmol) and (EtO)$_3$Sb (3 g, 11.7 mmol) in dry benzene (180 ml), 2.85 g (76%) of **6b** were obtained after workup. Colorless oil. IR: 2920v*s*, 2850v*s*, 1640v*s*, 1520*m*, 1460*m*, 1570*w*, 1220*m*, 1120*m*, 1050*w*, 925*w*, 805*m*, 660*m*, 620*w*. ^{1}H-NMR: 8.47 (br., NH); 3.36 (*dt*, *J* = 7.1, 6.1, CH$_2$(17)); 2.83 (*quint.*, *J* = 6.6, H–C(4)); 2.78–2.76 (*m*, CH$_2$(8), CH$_2$(10)); 2.74–2.72 (*m*, CH$_2$(6)); 2.69–2.66 (*m*, CH$_2$(13), CH$_2$(15)); 2.37 (*dd*, *J* = 15.2, 3.4, H$_a$–C(3)); 2.14 (*dd*, *J* = 15.2, 7.8, H$_b$–C(3)); 2.06 (br., NH); 1.67 (*quint.*, *J* = 6.2, CH$_2$(7), CH$_2$(16)); 1.59 (*quint.*, *J* = 5.6, CH$_2$(11), CH$_2$(12)); 1.48–1.25 (*m*, 9 CH$_2$); 0.88 (*t*, *J* = 6.4, Me(11′)). ^{13}C-NMR: 172.3 (*s*, C(2)); 55.7 (*d*, C(4)); 48.6, 48.4, 48.2, 47.6, 45.9 (5*t*, 5 C–N); 40.4, 37.8, 34.1, 31.8, 29.8, 29.7, 29.6, 29.3, 29.3, 29.0, 26.8, 25.9, 22.6 (13*t*, 14 C); 14.1 (*q*, C(11′)). ESI-MS: 383 ($[M+1]^+$).

5,9,14-Trimethyl-4-nonyl-1,5,9,14-tetraazacycloheptadecan-2-one (*=(±)-Budmunchiamine B*; **1b**). As described for **1a**, from **6b** (70 mg, 0.18 mmol), 37% formalin soln. (3 ml), and NaCNBH$_3$ (200 mg, 3.2 mmol) in AcOH (8 ml), 62 mg (80%) of **1b** were obtained after workup. Colorless oil. IR: 2920v*s*, 2850*s*, 2800*m*, 1640*s*, 1520*m*, 1455*m*, 1370*w*, 1235*m*, 1130*w*, 1050*w*, 1005*w*, 925*w*, 800*w*, 660*w*, 620*w*. ^{1}H-NMR: 8.52 (br., NH); 3.31 (*dt*, *J* = 6.9, 6.4, CH$_2$(17)); 2.84 (*quint.*, *J* = 4.6, H–C(4)); 2.62 (*dt*, *J* = 12.4, 7.0, H$_a$–C(6)); 2.50–2.33 (*m*, 10 H); 2.24 (*d*, *J* = 4.8, 1 H–C(3)); 2.27 (*s*, MeN); 2.20 (*s*, 2 MeN); 1.65 (*quint.*, *J* = 6.9, CH$_2$(7), CH$_2$(16)); 1.54 (*quint.*, *J* = 6.8, CH$_2$(11), CH$_2$(12)); 1.30–1.17 (*m*, 8 CH$_2$); 0.88 (*t*, *J* = 7.0, Me(9′)). ^{13}C-NMR: 172.5 (*s*, C(2)); 61.1 (*d*, C(4)); 56.3, 56.1, 55.6, 54.4, 51.3 (5*t*, 5 C–N); 42.5, 42.2 (2*q*, 2 MeN); 37.5, 37.1 (2*t*, 2 C); 35.3 (*q*, MeN); 31.7, 29.6, 29.5, 29, 29.1, 27.4, 27.3, 27.1, 25.5, 24.2, 23.2, 22.5 (12*t*, 12 C); 13.9 (*q*, C(9′)). ESI-MS: 425 (52, $[M+1]^+$), 213 (100, $[M+2]^{2+}$). EI-MS: 424 (51, $M^{+\cdot}$), 409 (28, $[M-Me]^+$), 352 (19), 338 (51), 297 (41), 281 (15), 224 (14), 212 (25), 210 (38), 198 (23), 184 (36), 169 (27), 155 (17), 112 (25), 100 (32), 98 (59), 86 (62), 84 (100), 72 (36), 70 (43), 58 (75), 57 (29), 43 (29).

Ethyl Hexadec-2-enoate (**3c**). As described for **3a**, from Na (1.17 g, 51 mmol), **2** (21.9 g, 51 mmol), and tetradecanal (10 g, 47.1 mmol) in EtOH (200 ml) 11.6 g (88%) of **3c** were obtained after workup as an (*E*)/(*Z*)-mixture (*ca.* 2:1). Colorless oil. For anal. purposes, 350 mg of **3c** were purified by CC (SiO_2; Et$_2$O/hexane 2:98) to give 109 mg (32%) of (*Z*)-isomer and 230 mg (68%) of (*E*)-isomer as colorless oils. IR: 2920v*s*, 2850v*s*, 1710v*s*, 1650*s*, 1460*s*, 1365*m*, 1275*s*, 1180*s*, 1125*m*, 1095*w*, 1035*m*, 980*m*, 925*w*, 810*w*, 660*w*, 620*w*. (*Z*)-Isomer: ^{1}H-NMR: 6.22 (*dt*, *J* = 11.4, 7.5, H–C(3)); 5.73 (*dt*, *J* = 11.5, 1.6, H–C(2)); 4.18 (*q*, *J* = 7.1, MeC*H*$_2$O); 2.62 (*q*, *J* = 7.3, CH$_2$(4)); 1.43 (*quint.*, *J* = 6.5, CH$_2$(5)); 1.32–1.25 (*m*, 10 CH$_2$, *Me*CH$_2$O); 0.88 (*t*, *J* = 7.0, Me(16)). ^{13}C-NMR: 169.3 (*s*, C(1)); 150.4 (*d*, C(3)); 119.5 (*d*, C(2)); 59.6 (*t*, Me*C*H$_2$O); 32.0, 31.8, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 28.9, 27.9, 22.5 (11*t*, 12 C); 14.1 (*q*, C(16)); 13.9 (*q*, *Me*CH$_2$O). (*E*)-Isomer: ^{1}H-NMR: 6.95 (*dt*, *J* = 15.6, 7.0, H–C(3)); 5.80 (*dt*, *J* = 15.6, 1.6, H–C(2)); 4.18 (*q*, *J* = 7.1, MeC*H*$_2$O); 2.18 (*q*, *J* = 7.5, CH$_2$(4)); 1.43 (*quint.*, *J* = 6.5, CH$_2$(5)); 1.32–1.25 (*m*, 10 CH$_2$, *Me*CH$_2$O); 0.88 (*t*, *J* = 7.0, Me(16)). ^{13}C-NMR: 166.6 (*s*, C(1)); 149.3 (*d*, C(3)); 121.1 (*d*, C(2)); 59.9 (*t*, Me*C*H$_2$O); 32.0, 31.8, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 28.9, 27.9, 22.5 (11*t*, 12 C); 14.1 (*q*, C(16)); 13.9 (*q*, *Me*CH$_2$O). CI-MS: 283 (<5, $[M+1]^+$), 282 (16, $[M+NH_4-H_2O]^+$), 237 (37, $[M-OEt]^+$), 194 (16), 127 (61), 114 (21), 101 (59), 99 (51), 88 (43), 81 (33), 69 (35), 57 (49), 43 (89), 41 (100).

Ethyl 16-Amino-3-tridecyl-4,8,13-triazahexadecanoate (**4c**). As described for **4a**, from spermine (4.3 g, 21.28 mmol) and **3c** (6 g, 21.28 mmol) in EtOH (900 ml), 4.25 g (41%) of **4c** were obtained after workup. Colorless oil. IR: 2920v*s*, 2850*s*, 1720*s*, 1600*w*, 1460*m*, 1370*m*, 1220*m*, 1180*m*, 1115*m*, 1025*w*, 925*w*, 805*m*, 660*m*, 620*w*. ^{1}H-NMR: 4.13 (*q*, *J* = 7.2, MeC*H*$_2$O); 2.92 (*quint.*, *J* = 6.2, H–C(3)); 2.76 (*t*, *J* = 6.8, CH$_2$(16)); 2.69–2.68 (*m*, CH$_2$(9), CH$_2$(12)); 2.64 (*m*, CH$_2$(5)); 2.62–2.60 (*m*, CH$_2$(7), CH$_2$(14)); 2.38 (*d*, *J* = 6.3, CH$_2$(2)); 1.63 (*quint.*, *J* = 7.0, CH$_2$(6), CH$_2$(15)); 1.51–1.45 (*m*, CH$_2$(10), CH$_2$(11), NH, NH$_2$)); 1.32–1.25 (*m*, 12 CH$_2$, *Me*CH$_2$O); 0.88 (*t*, *J* = 7.0, Me(13′)). ^{13}C-NMR: 172.7 (*s*, C(1)); 60.2 (*t*, Me*C*H$_2$O); 54.9 (*d*, C(3)); 49.9, 48.5, 47.8, 45.4, 40.6, 39.3 (6*t*, 6 C–N); 34.2, 33.5, 31.9, 30.6, 29.8, 29.7, 29.6, 29.3, 27.9, 25.8, 22.6 (11*t*, 15 C); 14.2 (*q*, *Me*CH$_2$O); 14.1 (*q*, C(13′)). ESI-MS: 485 (20, $[M+1]^+$), 243 (100, $[M+2]^{2+}$).

4-Tridecyl-1,5,9,14-tetraazacycloheptadecan-2-one (**6c**). As described for **6a**, from **4c** (1.7 g, 3.5 mmol) and $(EtO)_3Sb$ (1.16 g, 4.55 mmol) in dry benzene (180 ml), 1.2 g (78%) of **6c** were obtained after workup. Colorless oil. IR: 3300*m*, 2920*vs*, 2850*vs*, 1640*s*, 1520*m*, 1460*s*, 1370*m*, 1220*m*, 1115*m*, 1045*w*, 925*w*, 805*w*, 660*m*, 620*w*. ^{1}H-NMR: 8.43 (br., NHCO); 3.37 (*t*, *J* = 5.6, CH_2(17)); 2.86–2.83 (*m*, H–C(4)); 2.77–2.74 (*m*, CH_2(8), CH_2(10)); 2.72–2.78 (*m*, CH_2(6)); 2.68–2.66 (*m*, CH_2(13), CH_2(15)); 2.37 (*dd*, *J* = 15.2, 2.4, H_a–C(3)); 2.32 (br., NH)); 2.14 (*dd*, *J* = 15.3, 7.8, H_b–C(3)); 1.67 (*quint.*, *J* = 6.0, CH_2(7), CH_2(16)); 1.59–1.25 (*m*, 14 CH_2); 0.88 (*t*, *J* = 6.6, Me(13′)). ^{13}C-NMR: 172.2 (*s*, C(2)); 55.4 (*d*, C(4)); 48.4, 48.2, 48.0, 47.4, 45.8 (5*t*, 5 C–N); 40.3, 37.7, 34.0, 31.7, 29.6, 29.5, 29.4, 29.2, 28.8, 26.7, 26.6, 25.7, 22.5 (13*t*, 18 C); 13.9 (*q*, C(13′)). ESI-MS: 439 (42, $[M+1]^+$), 220 (100, $[M+2]^{2+}$).

5,9,14-Trimethyl-4-tridecyl-1,5,9,14-tetraazacycloheptadecan-2-one (= *Budmunchiamine C*; **1c**). As described for **1a**, from **6c** (100 mg, 0.228 mmol), 37% formalin soln. (5 ml), and $NaCNBH_3$ (282 mg, 4.56 mmol) in AcOH (10 ml), 91 mg (83%) of **1c** were obtained after workup. Colorless oil. IR: 2920*vs*, 2850*s*, 2800*m*, 1640*s*, 1520*m*, 1460*m*, 1370*w*, 1220*m*, 1135*w*, 1050*w*, 805*w*, 800*w*, 680*w*, 660*w*, 620*w*. ^{1}H-NMR: 8.52 (br., NH); 3.32 (*dt*, *J* = 12.6, 6.3, CH_2(17)); 2.84 (*quint.*, *J* = 4.7, H–C(4)); 2.63 (*dt*, *J* = 12.4, 6.8, H_a–C(6)); 2.46–2.24 (*m*, 10 H); 2.28 (*s*, MeN); 2.20 (*s*, 2 MeN(14)); 1.66 (*quint.*, *J* = 6.6, CH_2(7), CH_2(16)); 1.52 (*quint.*, *J* = 6.0, CH_2(11), CH_2(12)); 1.25–1.17 (*m*, 12 CH_2); 0.88 (*t*, *J* = 7.0, Me(13′)). ^{13}C-NMR: 172.5 (*s*, C(2)); 61.1 (*d*, C(4)); 56.3, 56.2, 55.7, 54.5, 51.5 (5*t*, 5 C); 42.7, 42.3 (2*q*, 2 MeN); 37.6, 37.0 (2*t*, 2 C); 35.1 (*q*, MeN); 31.7, 29.7, 29.6, 29.5, 29.4, 29.2, 27.5, 27.3, 27.1, 25.9, 24.3, 23.2, 22.5 (13*t*, 16 C); 13.9 (*q*, C(13′)). ESI-MS: 503 (< 5, $[M+Na]^+$), 481 (100, $[M+1]^+$). EI-MS: 481 (18, $[M+1]^+$), 480 (68, $M^{+\bullet}$), 465 (37, $[M-CH_3]^+$), 408 (21), 394 (56), 339 (16), 297 (58), 266 (42), 254 (38), 240 (50), 238 (30), 226 (36), 169 (32), 155 (22), 112 (27), 100 (35), 98 (69), 86 (69), 84 (100), 72 (32), 70 (41), 58 (62), 43 (25).

Docosanal. To a stirred soln. of docosan-1-ol (15 g, 46 mmol) in CH_2Cl_2 (120 ml) was added pyridinium chlorochromate (PCC; 1.5 g, 69 mmol) in portions, and the stirring was continued for 6 h at r.t. [6]. The solvent was evaporated, and the residue was purified by CC (*Florisil*®; Et_2O/hexane 2:1) to give 12.4 g (83%) of docosanal as colorless crystals. M.p. 56.5–56.8° (Et_2O/hexane) [7]. IR: 3404*w*, 2915*vs*, 2848*vs*, 1704*s*, 1471*s*, 1411*w*, 894*w*, 717*m*. ^{1}H-NMR ($CDCl_3$): 9.76 (*s*, H–C(1)); 2.41 (*t*, *J* = 7.3, CH_2(2)); 1.64 (*quint.*, *J* = 6.4, CH_2(3)); 1.28–1.25 (*m*, CH_2(4–21)); 0.87 (*t*, *J* = 6.9, Me(22)). ^{13}C-NMR ($CDCl_3$): 202.8 (*s*, C(1)); 43.9 (*t*, C(2)); 31.9 (*t*, C(3)); 29.7 (*t*, C(4), C(5), C(6), C(7), C(8)); 29.6 (*t*, C(9), C(10), C(11)); 29.4 (*t*, C(12), C(13), C(14)); 29.3 (*t*, C(15), C(16)); 29.2 (*t*, C(17), C(18), C(19)); 22.7 (*t*, C(21)); 22.1 (*t*, C(20)); 14.1 (*q*, C(22)). CI-MS: 343 (22, $[M+NH_4+1]^+$), 342 (100, $[M+NH_4]^+$), 324 (8, $M^{+\bullet}$), 306 (5).

Ethyl Tetracos-2-enoate (**3d**). As described for **3a**, from Na (823 mg, 36 mmol), **2** (15.44 g, 36 mmol), and docosanal (11.35 g, 35 mmol) in EtOH (200 ml), 13.5 g (96%) **3d** were obtained after workup as an (*E*)/(*Z*)-mixture (*ca.* 2:1). Colorless oil. For anal. purposes, 400 mg of **3d** were purified by CC (SiO_2; Et_2O/hexane 2:98) to give 135 mg (34%) of the (*Z*)-isomer and 260 mg (66%) of the (*E*)-isomer as colorless oils. IR: 2920*vs*, 2850*vs*, 1710*vs*, 1650*m*, 1460*s*, 1365*m*, 1275*s*, 1180*s*, 1125*w*, 1095*w*, 1035*m*, 980*w*, 925*w*, 810*w*, 660*w*, 620*w*. (*Z*)-Isomer: ^{1}H-NMR: 6.23 (*dt*, *J* = 11.5, 7.5, H–C(3)); 5.75 (*dt*, *J* = 11.5, 1.7, H–C(2)); 4.18 (*q*, *J* = 7.2, Me*CH*$_2$O); 2.64 (*q*, *J* = 7.1, CH_2(4)); 1.42 (*quint.*, *J* = 6.3, CH_2(5)); 1.32–1.25 (*m*, 18 CH_2, *Me*CH_2O); 0.87 (*t*, *J* = 6.8, Me(24)). ^{13}C-NMR: 166.5 (*s*, C(1)); 150.6 (*d*, C(3)); 119.6 (*d*, C(2)); 60.1 (*t*, MeCH_2O); 32.4, 31.9, 29.7, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 28.0, 22.7 (11*t*, 20 C); 14.2 (*q*, C(24)); 14.1 (*q*, *Me*CH_2O). (*E*)-Isomer: ^{1}H-NMR: 6.96 (*dt*, *J* = 15.4, 7.0, H–C(3)); 5.80 (*dt*, *J* = 15.3, 1.6, H–C(2)); 4.18 (*q*, *J* = 7.2, Me*CH*$_2$O); 2.17 (*q*, *J* = 7.2, CH_2(4)); 1.42 (*quint.*, *J* = 6.3, CH_2(5)); 1.32–1.25 (*m*, 18 CH_2, *Me*CH_2O); 0.87 (*t*, *J* = 6.8, Me(24)). ^{13}C-NMR: 166.5 (*s*, C(1)); 149.4 (*d*, C(3)); 121.2 (*d*, C(2)); 60.1 (*t*, MeCH_2O); 32.4, 31.9, 29.7, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 28.0, 22.7 (11*t*, 20 C); 14.2 (*q*, C(24)); 14.1 (*q*, *Me*CH_2O). CI-MS: 413 (26, $[M+1]^+$), 412 (16, $[M+NH_4-H_2O]^+$), 395 (21).

Ethyl 16-Amino-3-henicosyl-4,8,13-triazahexadecanoate (**4d**). As described for **4a**, from spermine (5.05 g, 25 mmol, 2.5 equiv.) and **3d** (3.94 g, 10 mmol) in EtOH (800 ml), 4.24 g (71%) of **4d** were obtained after workup. Colorless oil. IR: 2920*vs*, 2850*vs*, 1720*m*, 1600*w*, 1460*m*, 1370*w*, 1230*m*, 1180*m*, 1115*m*, 1025*w*, 925*w*, 805*w*, 660*m*, 620*w*. ^{1}H-NMR: 4.13 (*q*, *J* = 7.2, Me*CH*$_2$O); 2.91 (*quint.*, *J* = 6.3, H–C(3)); 2.76 (*t*, *J* = 6.8, CH_2(16)); 2.69–2.68 (*m*, CH_2(9), CH_2(12)); 2.67–2.66 (*m*, CH_2(5)); 2.64–2.60 (*m*, CH_2(7), CH_2(14)); 2.37 (*d*, *J* = 6.3, CH_2(2)); 1.63 (*quint.*, *J* = 6.9, CH_2(6), CH_2(15)); 1.54–1.50 (*m*, CH_2(10), CH_2(11)); 1.45 (br., NH, NH_2); 1.32–1.25 (*m*, 20 CH_2, *Me*CH_2O); 0.87 (*t*, *J* = 6.9, Me(21′)). ^{13}C-NMR: 172.6 (*s*, C(1)); 60.2 (*t*, Me*CH*$_2$O); 54.9 (*d*, C(3)); 50.0, 48.5, 47.9, 45.4, 40.6, 39.3 (6*t*, 6 C–N); 34.5, 33.8, 31.9, 30.6, 29.7, 29.3, 27.9, 25.8, 22.7 (9*t*, 20 C); 14.2 (*q*, C(21′)); 14.1 (*q*, *Me*CH_2O). ESI-MS: 619 (< 5, $[M+Na]^+$), 597 (100, $[M+1]^+$).

4-Henicosyl-1,5,9,14-tetraazacycloheptadecan-2-one (= *Budmunchiamine L4*; **6d**). As described for **6a**, from **4d** (1.8 g, 3.0 mmol) and $(EtO)_3Sb$ (1.13 g, 4.42 mmol) in dry benzene (180 ml), 1.3 g (78%) of **6d** were obtained after workup. Colorless oil. IR: 3400*s*, 2920*vs*, 2850*vs*, 1640*vs*, 1520*m*, 1460*s*, 1370*m*, 1220*m*, 1115*m*,

1045*w*, 925*w*, 805*m*, 660*m*, 620*w*. ^{1}H-NMR ($CDCl_3$): 8.48 (br., NHCO); 3.36 (*t*, *J* = 5.4, CH_2(17)); 2.84–2.82 (*m*, H–C(4)); 2.76–2.74 (*m*, CH_2(8), CH_2(10)); 2.72–2.69 (*m*, CH_2(6)); 2.67–2.66 (*m*, CH_2(13), CH_2(15)); 2.36 (*dd*, *J* = 15.2, 2.5, H_a–C(3)); 2.14 (*dd*, *J* = 15.2, 7.8, H_b–C(3)); 1.93 (br., NH); 1.66 (*quint.*, *J* = 6.0, CH_2(7), CH_2(16)); 1.58–1.56 (*m*, CH_2(11), CH_2(12)); 1.25–1.22 (*m*, 20 CH_2); 0.87 (*t*, *J* = 7.0, Me(21′)). ^{13}C-NMR: 172.1 (*s*, C(2)); 55.5 (*d*, C(4)); 48.5, 48.3, 48.1, 47.4, 45.8, (5*t*, 5 C–N); 40.2, 37.7, 34.0, 31.7, 29.5, 29.4, 29.2, 28.9, 26.7, 25.7, 22.5 (11*t*, 25 C); 13.9 (*q*, C(21′)). ESI-MS: 551 (100, $[M+1]^+$), 276 (78, $[M+2]^{2+}$).

REFERENCES

[1] J. M. Pezzuto, W. Mar, L.-Z. Lin, G. A. Cordell, A. Neszmélyi, H. Wagner, *Heterocycles* **1991**, *32*, 1961.
[2] a) K. Wiesner, D. M. MacDonald, Z. Valenta, R. Armstrong, *Can. J. Chem.* **1952**, *30*, 761; b) K. Wiesner, D. M. MacDonald, C. Bankiewicz, D. E. Orr, *Can. J. Chem*. **1968**, *46*, 1881; c) K. Wiesner, Z. Valenta, D. E. Orr, V. Liede, G. Kohan, *Can. J. Chem.* **1968**, *46*, 3617.
[3] a) J. M. Pezzuto, W. Mar, L.-Z. Lin, G. A. Cordell, A. Neszmélyi, H. Wagner, *Phytochemistry* **1992**, *32*, 1795; b) L. N. Misra, A. K. Dixit, H. Wagner, *Phytochemistry* **1995**, *39*, 247; c) G. M. Rukunga, P. G. Waterman, *Phytochemistry* **1996**, *42*, 1211; d) G. M. Rukunga, P. G. Waterman, *J. Nat. Prod*. **1996**, *59*, 850.
[4] W. Mar, G. T. Tan, G. A. Cordell, J. M. Pezzuto, K. Jurcic, F. Offermann, K. Redl, B. Steinke, H. Wagner, *J. Nat. Prod.* **1991**, *54*, 1531.
[5] a) K. Ishihara, Y. Kuroki, N. Hanaki, S. Ohara, H. Yamamoto, *J. Am. Chem. Soc*. **1996**, *118*, 1569; b) Y. Kuroki, K. Ishihara, N. Hanaki, S. Ohara, H. Yamamoto, *Bull. Chem. Soc. Jpn*. **1998**, *71*, 1221.
[6] a) E. J. Corey, J. W. Suggs, *Tetrahedron Lett*. **1975**, *31*, 2647; b) E. J. Corey, H. E. Ensley, J. W. Suggs, *J. Org. Chem*. **1976**, *41*, 380.
[7] M. Dimitrijevic, B. Grujic-Injac, S. Lajsic, *Hoppe-Seyler's Z. Physiol. Chem.* **1979**, *360*, 477.

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