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# Metal-Templated Macrolactamization of Triamino and Tetramino Esters. Facile Synthesis of Macrocyclic Spermidine and Spermine Alkaloids, (*S*)-(+)-Dihydroperiphylline, (±)-Buchnerine, (±)-Verbacine, (±)-Verbaskine, and (±)-Verbascenine

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The total synthesis of spermidine and spermine alkaloids, (*S*)-(+)-dihydroperiphylline (**1**), (±)-buchnerine (**2**), (±)-verbacine (**3**), (±)-verbaskine (**4**), and (±)-verbascenine (**5**), is described. The construction of macrocyclic lactams has been efficiently accomplished by the metal-templated cyclization of triamino esters and tetraamino esters. It was also found that the antimony(III) ethoxide is useful as an intermolecular amidation catalyst.

The macrocyclic polyamine lactams containing the biogenetic base spermidine and spermine are of particular interest as synthetic targets for organic chemists in view of the broad activity which has been established for spermidine- and spermine-containing compounds in biological systems and because of the structural complexity of the molecules themselves.[1)]

(*S*)-(+)-Dihydroperiphylline (**1**) is one of six alkaloids isolated from the leaves of *Peripterygia marginata* by Husson et al.[2)] All of these alkaloids contain a 13-membered ring system derived from dicinnamoylspermidine (Chart 1). The total synthesis of (±)-**1** was first accomplished by Wasserman and Matsuyama in 1981.[3,4)] More recently, the enantioselective route of **1** from *N*-Boc-(*S*)-$\beta$-phenyl-$\beta$-alanine, prepared from diethyl L-tartrate in 15 steps, was reported by Kibayashi et al.[5)] Also, (±)-buchnerine (**2**) was isolated in 1993 by Lumbu and Hootelé from *Clerodendrum buchneri* (Verbenaceae),[6)] and was characterized by the presence of a 17-membered ring reflecting spermine and 4-methoxycinnamoyl precursory units. It was previously reported by Kimura et al. that the one-pot macrocyclization of tetramines with $\alpha,\beta$-unsaturated esters slowly proceeds under reflux condition in methanol, usually, for two or three weeks to afford the corresponding macrolactam in a moderate yield.[7)] However, an attempt to synthesize macrocyclic spermine alkaloids using a similar process has been unsuccessful.[7g)] We have been interested in the possibility of metal-templated cyclization of spermidine derivatives **6** and spermine derivatives **7** which would result in the direct formation of large ring alkaloids with amino groups at the positions where they are normally formed in natural products (Scheme 1).[8)] In this work we discuss the feasibility and limitations of this approach.[9)]

## Results and Discussion

Our strategy for the synthesis of these derivatives is based on the metal-templated cyclization of **6** and **7**. The retrosynthetic pathway of (*S*)-(+)-dihydroperiphylline **1** and (±)-buchnerine **2** is shown in Schemes 2 and 3, respectively. In Scheme 2, (*S*)-(−)-$\beta$-phenyl-$\beta$-alanine methyl ester (**9**) as a key intermediate was accessible from *N*-benzylidenebenzhydrylamine (**10**) via highly enantioselective aldol-type reaction with ketene trimethylsilyl acetal **11** derived from *t*-butylacetate using the chiral (*S*)-BLA **12**, which was developed by us.[10)] The triamino and tetraamino acid derivatives **8** and **13** were envisaged as ideal models of the macrocyclic spermidine and spermine skeletons **6** and **7**, which could then be elaborated via metal-templated cyclization to **1** and **2**.

**I. Enantioselective Total Synthesis of 1.**[9a)] Methyl (*S*)-3-(benzhydrylamino)-3-phenylpropionate (**16**) was prepared in 56% yield and 96% ee by enantioselective aldol-type reaction of *N*-benzylidenebenzhydrylamine **10** with ketene silyl acetal **11** derived from *t*-butyl acetate in the presence of the (*S*)-BLA **12**[10)] and sequent transesterification (Scheme 4). (*S*-Binaphthol was recovered in > 95% yield. The removal of *N*-benzhydryl protecting group of **16** was done selectively by catalytic hydrogenation (10% Pd/C, $H_2$, MeOH) without debenzylation of 3-phenylpropionate moiety.[10)] Optically pure (*S*)-**9** was obtained by optical resolution of **9** (1 equimolar amount of oxalic acid in methanol, one recrystallization from

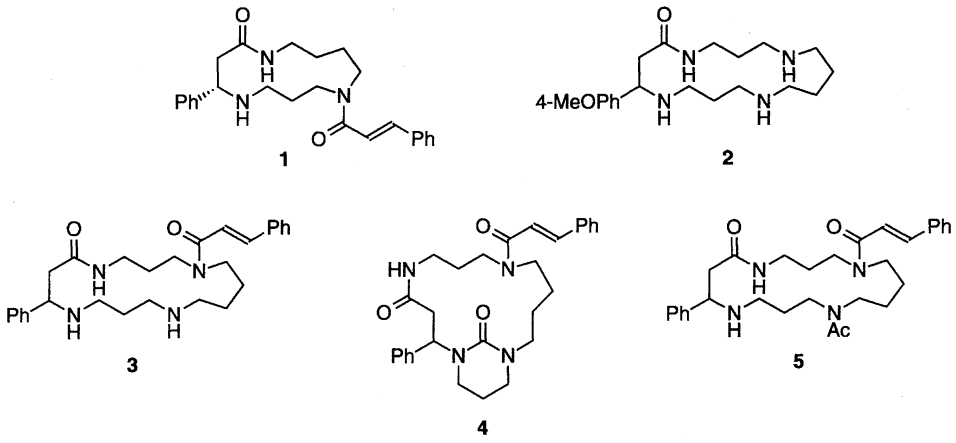
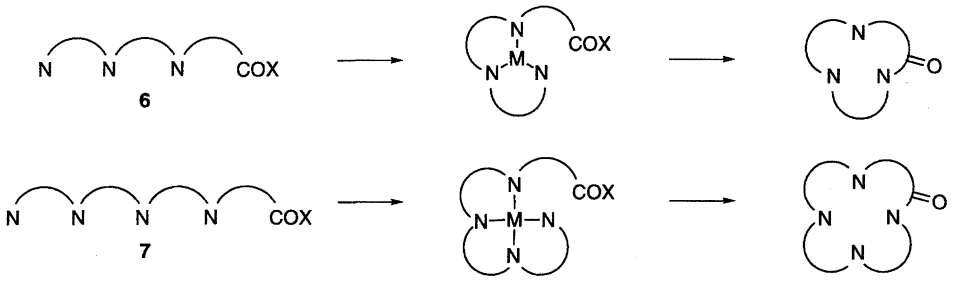
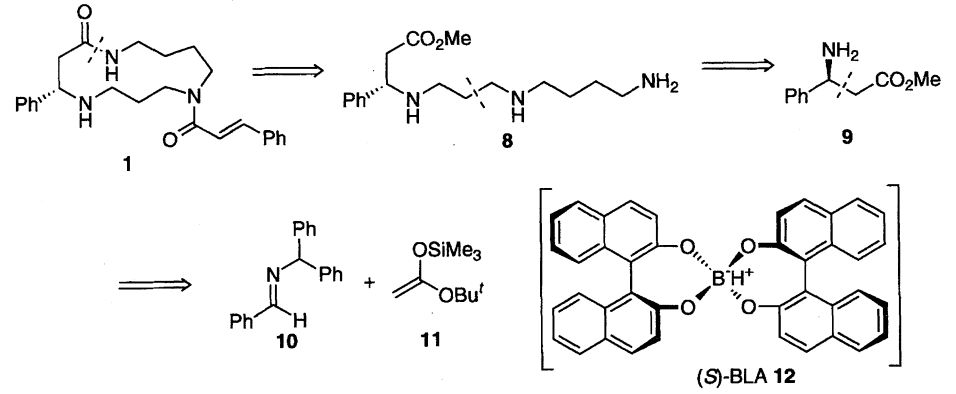


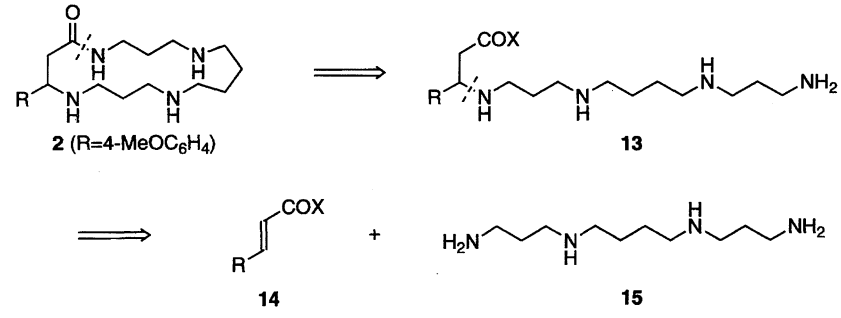
Chart 1.



Scheme 1.



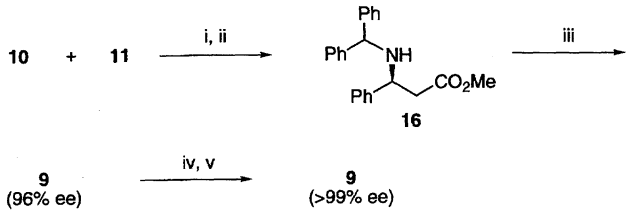
Scheme 2.



Scheme 3.

methanol alone at −20 °C and treatment of the salt with 1 mol dm$^{-3}$ NaOH) in good yield.[11]

The diamine unit **20** was next prepared from 3-amino-1-propanol (**17**) and 4-bromobutyronitrile as outlined in Scheme 5. *N*-(2-naphthyl)methylation of **17** occurred in 97% yield by sequential imine condensation with 2-naphthaldehyde and reduction with sodium borohydride (sodium tetrahydroborate), and then the cyanopropylation of **19** with



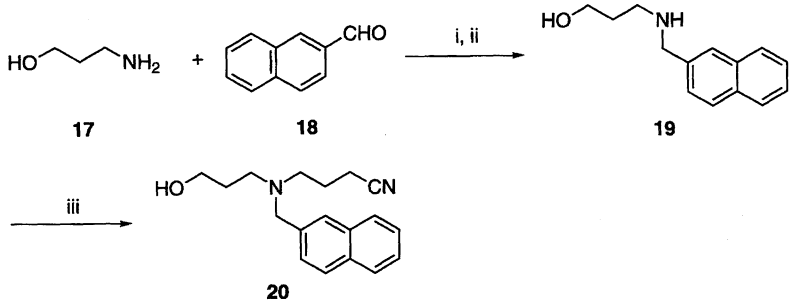

Scheme 4. i) (*S*)-BLA **12**, toluene-$CH_2Cl_2$ (1 : 1), −78 °C, 20 h. ii) *concd* $H_2SO_4$, MeOH, reflux, 2 h. iii) Pd/C, $H_2$, MeOH, 25 °C, 2.5 h. iv) $(CO_2H)_2 \cdot 2H_2O$, MeOH, recrystallization. v) 1 mol $dm^{-3}$ NaOH.

4-bromobutyronitrile gave **20** in 98% yield.

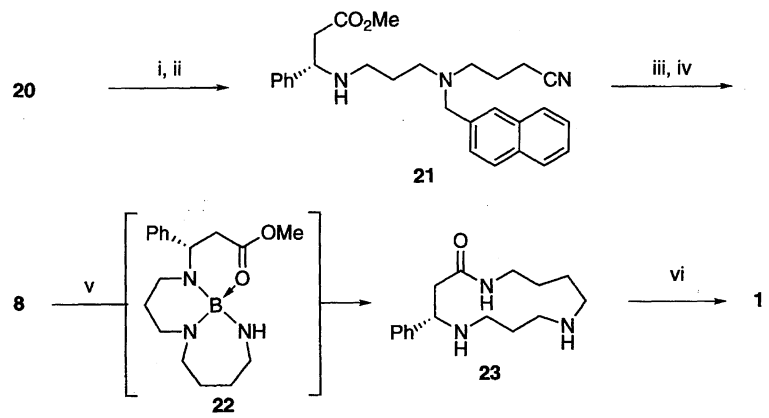
The coupling of key components **9** and **20** proceeded smoothly in the presence of triflic anhydride (trifluoromethanesulfonyl anhydride) and excess *N*,*N*-diisopropylethylamine to form the triamino unit **21** in 92% yield (Scheme 6). Hydrogenolysis of *N*-(2-naphthyl)methyl group of **21** over 10% activated palladium on carbon and subsequent hydrogenation of cyano group over platinum(IV) oxide[12] in the presence of concentrated hydrochloric acid gave triamino ester **8** in 74% yield from **21**. Cyclization of triamino ester **8** was effected with tris(dimethylamino)borane in xylene under reflux to furnish the desired lactam **23** in 74% yield. We speculated that the possible intermediate **22** generated by transamination of triaminoborane could reasonably be expected to undergo a facile, sterically driven cyclization to **23** as well as the cyclization step in the synthesis of cellacinnine.[8] It is noted that, in using the *t*-butyl ester in place of the methyl ester **8**, the present cyclization proceeded and **23** was obtained in 25% yield even at reflux over 2 d. The selective acylation at *N*-7 of **23** was accomplished with cinnamoyl chloride in the presence of 4-(dimethylamino)-pyridine at low temperature to give **1** in almost quantitative yield.[8] The optical rotation determined for **1** ($[\alpha]_D^{26} = +3.6$ (*c* 1.19, $CHCl_3$)) and the NMR spectra were in good agreement with the reported values for synthetic (+)-(*S*)-dihydroperiphylline.[3,5]

**II. Total Synthesis of 2—5.**[9b] **II-I. Metal-Templated Macrolactamization.** The starting tetramino esters **13a** and **13b** were prepared by Michael addition of spermine **15** to ethyl 3-(4-methoxyphenyl)propiolate (**24a**)[13] or ethyl 3-phenylpropiolate (**24b**) and hydrogenation of **25** over platinum(IV) oxide in the presence of $CHCl_3$[12] in 61 and 40% yields from **24**, respectively (Scheme 7). On the other hand, unsubstituted amino esters **13c** and **13d** have been directly prepared by Michael addition of spermine **15** and 1, 12-dodecanediamine to ethyl acrylate in 70 and 40% yields, respectively.

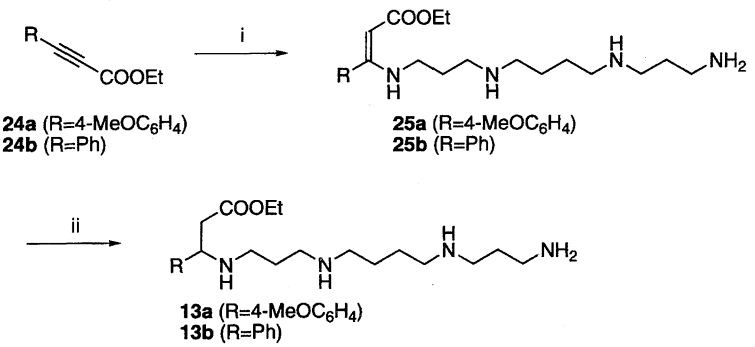
Initially, the preliminary investigations were carried out in order to optimize conditions for macrocyclization of tetramino ester **13c** (Entries 1—3) in Table 1. Although tris(dimethylamino)borane was previously found to be effective for the cyclization of triamino esters giving 13-membered lactams (e.g., Entry 7),[8,9a] no lactams were obtained in the cyclization of **13c** (Entry 2).[14] Titanium(IV) ethoxide and zirconium-



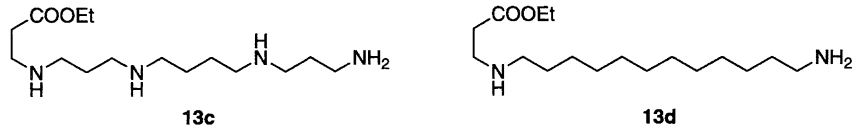

Scheme 5. i) benzene, azeotropic reflux. ii) $NaBH_4$, 25 °C, 1 h. iii) 4-bromobutyronitrile, $Et_3N$, toluene, reflux, 3.5 h.




Scheme 6. i) $Tf_2O$, $CH_2Cl_2$–*i*-$Pr_2NEt$ (10 : 1), −78 °C, 1 h. ii) **9**, −78 °C warm to 25 °C, 16 h. iii) 10 % activated Pd/C, $H_2$, MeOH, 25 °C, 0.5 h, filtration. iv) 12 mol% $PtO_2$, $H_2$, *concd* HCl–MeOH, 25 °C, 4 h. v) $B(NMe_2)_3$, xylene, reflux, 8 h. vi) cinnamoyl chloride, DMAP, $CH_2Cl_2$, −78 °C, 20 min.

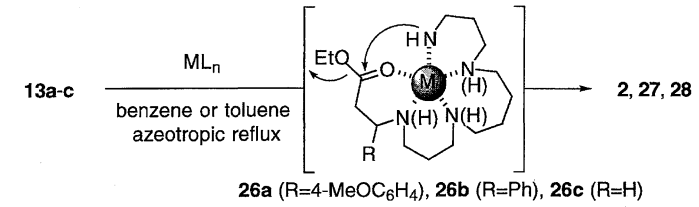


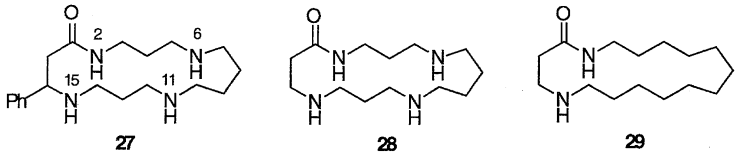

i) spermine **15**, EtOH, reflux, 2 h. ii) $PtO_2$, $H_2$, EtOH–$CHCl_3$ (50 : 1), 25 °C, 12 h.




Scheme 7.

Table 1. Antimony-Templated Macrolactamization of Spermine Derivatives




| Entry | Amino ester | $ML_n$ | Conditions | Yield (%) |
|---|---|---|---|---|
| 1 | **13c** | —[a] | 80 °C, 10 h | 0[b] |
| 2 | **13c** | $B(NMe_2)_3$[c] | 60 °C, 48 h | 0[d] |
| 3 | **13c** | $Sb(OEt)_3$[e] | 80 °C, 15 h | 65 |
| 4 | **13b** | $Sb(OEt)_3$[e] | 80 °C, 9 h | 90 |
| 5 | **13a** | $Sb(OEt)_3$[e] | 80 °C, 14 h | 76 |
| 6 | **13d** | $Sb(OEt)_3$[e] | 80 °C, 15 h | 69 |
| 7 | **8** | $B(NMe_2)_3$[c] | 145 °C, 8 h[f] | 74[f] |
| 8 | **8** | $Sb(OEt)_3$[c] | 80 °C, 19.5 h | 0[b] |
| 9 | **8** | $Sb(OEt)_3$[c] | 110 °C, 51 h | 38[g] |

a) No reagents added. b) No reaction. c) 2 mol amt. of reagent was used. d) Starting material decomposed. e) 1.2 mol amt. of reagent was used. f) Xylene was used as solvent. See Ref. 8b. g) Some unknown by-products were included.

(IV) isopropoxide were somewhat effective reagents (19 and 23% from **13c**, respectively), but most tetramino esters were decomposed to spermine and $\alpha,\beta$-unsaturated ester by $\beta$-elimination. Among several other organometallic reagents screened for the cyclization of tetramino esters **13a—c** to 17-membered lactams **2**, **27**, and **28**, we found antimony(III) ethoxide to be quite effective (Entries 3—5). A solution of the tetramino ester **13a** in dry, freshly distilled benzene was treated with antimony(III) ethoxide (1.2 mol amt.) in benzene at reflux for 14 h. Upon solvent removal in vacuo, the crude product was directly chromatographed on silica gel to give the pure lactam **2** in 76% yield (Entry 5); this was homogeneous by TLC and with IR, $^1$H NMR, and mass spectra in accord with the assigned structure.[6] Since none of the polymerization or regioisomeric product was formed, the isolation of the lactam was simple.

The novel regioselective macrolactamization of tetramino esters **13a—c** derived from spermine **15** with antimony(III) ethoxide can be ascribed to the metal template effect. Interestingly, the cyclization of diamino ester **13d** gave the

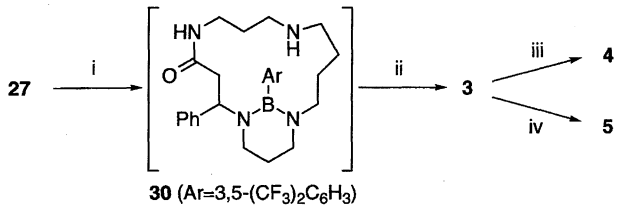
corresponding monomeric lactam **29** in 69% yield (Entry 6). However, antimony(III) ethoxide did not provide satisfactory results in the cyclization of triamino ester **8** derived from spermidine (Entries 8 and 9). These results suggest that antimony(III) ion is a suitable size as a metal-template of a 17-membered spermine macrolactam. Thus, the possible intermediate **26** generated by transamination of antimony(III) ethoxide could reasonably be expected to undergo a facile, sterically driven cyclization to **2**, **27**, **28**, and **29**.[15,16] Nevertheless, we cannot exclude the possibility of a simple intramolecular hydrophilic interaction of tetramino esters in nonpolar solvent such as benzene.

**II-II. Selective Acylation.** The present cyclization process provided crucial information leading to an unusually concise synthesis of other macrocyclic spermine alkaloids: (±)-verbacine **3**,[17] (±)-verbaskine **4**,[17,18] and (±)-verbascenine **5**[17,19] from the intermediate **27** (Scheme 8).

Synthesis of verbacine **3** from **27** required the selective acylation at *N*-6 of **27** (Scheme 8). This was accomplished by addition of cinnamoyl chloride to a 1 : 1 mixed solution of **27** and 3,5-bis(trifluoromethyl)phenylboronic acid in dichloromethane to give **30** as major product in 53% yield, together with recovered **27**, the monocinnamamide acylated at *N*-11 of **27**, and the dicinnamamide acylated both at *N*-6 and *N*-11 of **27**.[20] Analytical data of the synthetic verbacine were identical in all respects with those reported in the literature.[17] The acylation of **27** with acyl chloride or acid anhydride in the absence of boronic acid gave only the dicinnamamide. The efficiency of the present regioselective acylation can, therefore, be ascribed to the stability of a 1,3-diaza-2-boracyclohexane unit. Thus, the possible six membered-cyclic intermediate **30** generated by complexation of **27** with the boronic acid at *N*-11 and *N*-15 could reasonably be expected to undergo acylation with the free amino group at *N*-6.[21]

Verbacine **3** was readily transformed in good yield to verbaskine **4**, which contained a cyclic urea unit, by treatment with triphosgene (bis(trichloromethyl) carbonate) in dichloromethane. This result clearly indicated that **27** was not acylated at *N*-11 but at *N*-6. Also, **3** was transformed to verbascenine **5** in almost quantitative yield by selective acetylation at *N*-11 of **27**. This was readily accomplished with an equimolar amount of acetic anhydride in the presence of triethylamine at −78 °C. Analytical data of **4** and **5** were completely identical with those reported in the literature.[17,18b,19a]

**II-III. Antimony(III) Ethoxide-Catalyzed Amide Condensation Reaction.** The efficiency of the antimony(III) ethoxide as an intermolecular amidation catalyst was also studied, and the results are summarized in Table 2.[16,22] The reaction was carried out with various structurally diverse




**30** (Ar=3,5-$(CF_3)_2C_6H_3$)

Scheme 8. i) 3,5-$(CF_3)_2C_6H_3B(OH)_2$, $CH_2Cl_2$, −78 °C to r.t. ii) (*E*)-PhCH=CHCOCl, $CH_2Cl_2$, −78 °C. iii) $(CCl_3O)_2CO$, $Et_3N$, $CH_2Cl_2$, r.t. iv) $Ac_2O$, $Et_3N$, $CH_2Cl_2$, −78 °C.

Table 2. $Sb(OEt)_3$ Catalyzed Amidation Reaction[a]

$RCO_2Me$ or $RCO_2H$ + $R^1R^2NH$ —$Sb(OEt)_3$ (10 mol%), toluene, azeotropic reflux→ $RCONR^1R^2$

| Entry | $RCO_2Me$ or $RCO_2H$ | $R^1R^2NH$ | Yield % |
|---|---|---|---|
| 1 | $C_{11}H_{23}CO_2Me$ | $PhCH_2NH_2$ | 90 |
| 2 | $C_{11}H_{23}CO_2Me$ | $C_7H_{15}NH_2$ | 91 |
| 3 | $C_{11}H_{23}CO_2Me$ | *c*-$HexNH_2$ | 64 |
| 4[b] | $C_{11}H_{23}CO_2Me$ | *c*-$HexNH_2$+$C_7H_{15}NH_2$ | 86 (5 : 95)[c] |
| 5 | $Ph(CH_2)_3CO_2H$ | $C_7H_{15}NH_2$ | 87 |
| 6 | $Ph(CH_2)_3CO_2H$ | 3,5-Dimethylpiperidine | 44 |
| 7 | (*E*)-PhCH=$CHCO_2Me$ | $C_7H_{15}NH_2$ | 86 |
| 8[d] | $PhCO_2Me$ | $C_7H_{15}NH_2$ | 84 |
| 9 | *c*-$HexCO_2Me$ | $C_7H_{15}NH_2$ | 86 |
| 10 | *c*-$HexCO_2Me$ | $PhCH_2NH_2$ | 80 |
| 11 | *c*-$HexCO_2Me$ | *c*-$HexNH_2$ | 42 |
| 12 | *c*-$HexCO_2H$ | *c*-$HexNH_2$ | 47 |

a) Unless otherwise noted, a 1 : 1 mixture of esters or carboxylic acids and amines was heated in toluene at reflux for several hours or 1 d. b) A 1 : 1 : 1 mixture of the ester and two amines were used. c) The ratio of cyclohexylamide and heptylamide produced is indicated in parentheses. d) 5 mol% of $Sb(OEt)_3$ was used.

methyl esters or carboxylic acids and amines in the presence of 5—10 mol% of antimony(III) ethoxide under a reflux condition in toluene. In the reactions of esters or carboxylic acids with primary amines, the corresponding amides were formed in high yield. Better yields were obtained with less hindered substrates, and high chemoselectivity for less hindered primary amine was observed in the amidation of methyl dodecanoate with a 1 : 1 mixture of heptylamine and cyclohexylamine (Entry 4). This characteristic of antimony(III) ethoxide reflects exclusive regioselectivity in the above macrolactamization. Methyl cinnamate did not give Michael adduct but the corresponding amide in high yield (Entry 7).

In conclusion, tris(dimethylamino)borane proved to be highly beneficial for the metal-templated cyclization of not only ethyl 12-amino-3-phenyl-4,9-diazadodecanoate, the precursor of celacinine, but also methyl 12-amino-3-phenyl-4,8-diazadodecanoate **8**. On the other hand, novel antimony-templated cyclizations proved to be highly useful for the synthesis of macrocyclic spermine alkaloids. The rate accelerations and high regioselectivities observed in this work suggest a mechanism in which the acyclic triamino ester and tetramino ester are convalently or coordinately attached to the borane and the antimony before the final cyclization step, respectively. *As far as we know, this is the first example of the use of antimony(III) alkoxide as a promoter of amidation.*[3,22,23] The selective acylation of cyclic aminolactams was also achieved by using 3,5-bis(trifluoromethyl)phenylboronic acid.

## Experimental

**General.** Infrared (IR) spectra were recorded on a Shimadzu FT-IR 8100 spectrometer. $^1$H NMR spectra were measured on a Varian Gemini-200 or Gemini-300 Spectrometer. High-performance liquid chromatography (HPLC) was done with Shimadzu 6 Å or 9 Å instruments using 4.6 mm×25 cm Daicel CHIRALCEL OD-H. Optical rotations were measured on a JASCO DIP-140 digital polarimeter. Melting points were determined using a Yanaco MP-J3. All experiments were carried out under an atmosphere of dry argon. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 $GF^{254}$, 0.25 mm) were used. The products were purified by preparative column chromatography on silica gel E. Merck 9385. Microanalyses were accomplished at the School of Agriculture, Nagoya University. High-resolution mass (HRMS) analyses were carried out at Daikin Industries, Ltd.

In experiments requiring dry solvents, ether and tetrahydrofuran (THF) were purchased from Aldlich Chemical Co. as "anhydrous" and stored over 4A molecular sieves. Benzene, hexane, and toluene were dried over sodium metal. Dichloromethane was freshly distilled from calcium hydride. Trimethyl borate was distilled from sodium metal under argon. Other simple chemicals were purchased and used as such.

***N*-Benzylidenebenzhydrylamine (10):**[10] A mixture of benzhydrylamine (9.48 mL, 55 mmol), benzaldehyde (5.59 mL, 55 mmol), and $MgSO_4$ (8.8 g) was stirred at room temperature for 4 h. The reaction mixture was filtered, and the filtrate was concentrated. The residue was recrystallized from hexane to afford **10** (10.93 g, 73% yield). $^1$H NMR ($CDCl_3$) $\delta$ = 5.56 (s, 1H, $Ph_2CH$), 7.18—7.88 (m, 15H, 3Ph), 8.42 (s, 1H, N=C*H*Ph).

**1-*t*-Butoxy-1-(trimethylsilyloxy)ethylene (11):**[10] A solution of lithium diisopropylamide (LDA) (24 mmol) in THF (40 mL) was cooled to −78 °C, and *t*-butyl acetate (2.7 mL, 20 mmol) was added dropwise over a few minutes. The solution was stirred for 1 h at that temperature, and then chlorotrimethylsilane (TMSCl) (2.8 mL, 22 mmol) was added. This mixture was allowed to warm to room temperature over several hours. The white solid, which was generated from the resulting suspension, was removed by a Celite filter, and the filtrate was concentrated in vacuo. The residue was distilled under reduced pressure. $^1$H NMR ($CDCl_3$) $\delta$ = 0.23 (s, 9H, $Si(CH_3)_3$), 1.35 (s, 9H, *t*-Bu), 3.42 (d, $J$ = 1.8 Hz, 1H, C*H*H) 3.44 (d, $J$ = 1.8 Hz, 1H, CH*H*).

***t*-Butyl (*S*)-3-(Benzhydrylamino)-3-phenylpropionate:**[10] To the white precipitate of (*S*)-**12** in dichloromethane (3 mL) were added 2 mL of dichloromethane, 5 mL of toluene, and the corresponding *N*-benzhydrylimine **10** (95 mg, 0.35 mmol) at 0 °C, and the yellow suspension was stirred at 0 °C for 10 min. After the suspension was cooled to −78 °C, ketene silyl acetal **11** (132 mg, 0.7 mmol) was added dropwise. After being stirred for 20 h, the solution was washed with water and saturated $NaHCO_3$ solution and then dried over $MgSO_4$. Evaporation of the solvent and purification by column chromatography on silica gel gave the corresponding product (79 mg, 58% yield). The optical purity was shown to be 96% ee by HPLC analysis (Daicel OD-H column, hexane : *i*-PrOH = 100 : 1, flow rate = 0.5 mL min$^{-1}$, $t_R$ = 10.1 min for (*R*), $t_R$ = 12.1 min for (*S*); $^1$H NMR ($CDCl_3$) $\delta$ = 1.39 (s, 9H, *t*-Bu), 2.53 (dd, $J$ = 5.6, 14.6 Hz, 1H, C*H*H), 2.66 (dd, $J$ = 8.6, 14.6 Hz, 1H, CH*H*), 3.97 (dd, $J$ = 5.6, 8.6 Hz, 1H, PhC*H*), 4.58 (s, 1H, $Ph_2CH$), 7.10—7.40 (m, 15H, 3Ph).

**Methyl (*S*)-3-(Benzhydrylamino)-3-phenylpropionate (16):**[10] *t*-Butyl (*S*)-3-(benzhydrylamino)-3-phenylpropionate (1.2 g, 3.1 mmol, 96% ee) was refluxed with *concd* $H_2SO_4$ (1 mL) in MeOH (10 mL) for 2 h. The reaction mixture was cooled to 0 °C, neutralized with 1 mol dm$^{-3}$ NaOH, and extracted with $CHCl_3$. The organic layer was washed with brine, dried, and filtered. Evaporation of the solvent and purification by column chromatography on silica gel (hexane : ethyl acetate = 10 : 1) gave the corresponding product **16** (1.1 g, 99.5% yield, 96% ee). $^1$H NMR ($CDCl_3$) $\delta$ = 2.41 (br, 1H, N*H*), 2.64 (dd, $J$ = 5.3, 15.2 Hz, 1H, C*H*H), 2.75 (dd, $J$ = 9.1, 15.2 Hz, 1H, CH*H*), 3.67 (s, 3H, OMe), 3.97 (dd, $J$ = 5.3, 9.1, 1H, PhC*H*) 4.58 (s, 1H, $Ph_2CH$), 7.15—7.38 (m, 15H, 3Ph).

**(*S*)-β-Pheny-β-alanine Methyl Ester (9):**[11] Methyl (*S*)-3-(benzhydrylamino)-3-phenylpropionate **16** (200 mg, 0.58 mmol, 96% ee) and 10% Pd/C (50 mg) were stirred under $H_2$ (1 atm) in MeOH (8 mL). After being stirred for 2.5 h, the reaction mixture was filtered by a Celite filter. Evaporation of the solvent and purification by column chromatography on silica gel (ethyl acetate) gave the corresponding product **9** (100 mg, 95%). A solution of **9** (96% ee, 1.22 g, 6.82 mmol) in MeOH (5 mL) was added to a refluxing solution of oxalic acid dihydrate (0.86 g, 6.82 mmol) in MeOH (5 mL). After being stirred for 30 min, the reaction mixture was crystallized overnight at −20 °C and filtered off. A solution of the solid in 1 mol dm$^{-3}$ NaOH (10 mL) was extracted three times with $CHCl_3$. The organic layer was dried over $Na_2SO_4$ and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate) to give the corresponding product **9** (1.0 g, 82% yield). The optical purity was shown to be > 99%ee, as judged by comparison with the optical rotation value reported in the literature,[11b,11c] and HPLC analysis (Daicel OD-H column, hexane : *i*-PrOH = 20 : 1 flow rate = 1 mL min$^{-1}$, $t_R$ = 14.7 min for (*R*), $t_R$ = 17.7 min for (*S*). $^1$H NMR ($CDCl_3$) $\delta$ = 1.69 (br, 2H, $NH_2$), 2.68 (d, $J$ = 6.5 Hz, 2H, $CH_2$), 3.70 (s, 3H, OMe), 4.44 (t, $J$ = 6.5 Hz, 1H, PhC*H*), 7.21—7.39 (m, 5H, Ph); $[\alpha]_D^{26}$ = −18.2 (*c* 1.46,

$CHCl_3$).

**3-(2-Naphthylmethylamino)-1-propanol (19):** The mixture of 2-naphthaldehyde (3.12 g, 20 mmol) and 3-amino-1-propanol (1.53 mL, 20 mmol) in benzene (100 mL) was azeotropic-refluxed for 2.5 h. After the solvent was removed, it was added to $NaBH_4$ (757 mg, 20 mmol) in MeOH (30 mL) and stirred for 1 h at 0 °C. The reaction mixture was poured onto ice water (15 mL) and extracted with $CHCl_3$ three times. Purification of the concentrated crude product by column chromatography (EtOAc : $CH_2Cl_2$ : MeOH = 10 : 10 : 1) gave the desired amino alcohol **19** (4.17 g, 97% yield). TLC, $R_f$ = 0.25 (EtOAc : $CH_2Cl_2$ : MeOH = 10 : 10 : 1); $^1$H NMR ($CDCl_3$) $\delta$ = 1.76 (m, 2H, $CH_2$), 2.22 (br, 2H, OH, NH), 2.95 (t, $J$ = 5.5 Hz, 2H, $CH_2OH$), 3.83 (t, $J$ = 5.0 Hz, 2H, $CH_2NH$), 3.97 (s, 2H, $CH_2Ar$), 7.41—7.85 (m, Ar-*H*, 7H); IR (KBr) 3293, 2934, 1509, 1455, 1069, 818. HRMS (EI) Found: *m/z* 215.1306. Calcd for $C_{14}H_{17}NO$: $M^+$, 215.1310.

***N*-(3-Cyanopropyl)-*N*-(2-naphthylmethyl)-3-amino-1-propanol (20):** The mixture of 3-(2-naphthylmethylamino-1-propanol **19** (4.1 g, 18.6 mmol), 4-bromobutyronitrile (3.7 mL, 37.2 mmol), and triethylamine (13 mL, 93.0 mmol) in toluene (30 mL) was refluxed for 3.5 h. After the solution cooled at r.t., the solution was diluted with $CHCl_3$ (200 mL) and washed with 1 mol dm$^{-3}$ NaOH (30 mL). Purification of the concentrated crude product by column chromatography (EtOAc : Hex : MeOH = 10 : 10 : 1) gave product **20** (5.12 g, 98% yield). TLC, $R_f$ = 0.35 (EtOAc : Hex : MeOH = 5 : 5 : 1); $^1$H NMR ($CDCl_3$) $\delta$ = 1.77—1.92 (m, 4H, $CCH_2C$), 2.35 (t, $J$ = 7.1 Hz, 2H, $CH_2CN$), 2.63 (t, $J$ = 7.1 Hz, 2H, $NCH_2$), 2.73 (t, $J$ = 6.2 Hz, 2H, $NH_2$), 3.76 (m, 4H, $NCH_2Ar$, $CH_2O$), 7.45—7.86 (m, 7H, Ar-*H*); IR (neat) 3380, 2247, 1127, 1061, 817, 1061, 818. HRMS (EI) Found: *m/z* 282.1723. Calcd for $C_{18}H_{22}N_2O$: $M^+$, 282.1732.

**Methyl 11-Cyano-8-(2-naphthylmethyl)-3-phenyl-4,8-diazaundecanoate (21):** To the mixture of *N*-(3-cyanopropyl)-*N*-(2-naphthylmethyl)-3-amino-1-propanol **20** (1.58 g, 5.6 mmol) and *i*-$Pr_2NEt$ (10 mL) in $CH_2Cl_2$ (100 mL) at −78 °C, $Tf_2O$ (0.940 mL, 5.6 mmol) was added. After the solution was stirred for 1 h at −78 °C, $\beta$-amino ester **9** (500 mg, 2.8 mmol) was added and this mixture was warmed to 25 °C for 16 h. The solution was diluted with $CHCl_3$ (100 mL), washed with 1 mol dm$^{-3}$ NaOH (10 mL), and dried with $Na_2SO_4$. Purification of the concentrated crude product by column chromatography (EtOAc : $CH_2Cl_2$ : MeOH = 10 : 10 : 1) gave product **21** (1.14 g, 92% yield). TLC, $R_f$ = 0.66 (EtOAc : $CH_2Cl_2$ : MeOH = 5 : 5 : 1); $^1$H NMR ($CDCl_3$) $\delta$ = 1.60 (br, 1H, N*H*), 1.64 (tt, $J$ = 6.7, 7.1 Hz, 2H, $CCH_2C$), 1.74 (tt, $J$ = 6.8, 6.7 Hz, 2H, $CCH_2C$), 2.26 (t, $J$ = 7.1 Hz, 2H, $CH_2CN$), 2.42—2.58 (m, 6H, $3CH_2N$), 2.62 (d, $J$ = 5.5 Hz, 1H, C*H*$HCO_2Me$), 2.65 (d, $J$ = 8.2 Hz, 1H, CH*H*$CO_2Me$), 3.61 (s, 3H, $OCH_3$), 3.62 (d, $J$ = 13.8 Hz, 1H, NC*H*HNp), 3.64 (d, $J$ = 13.8 Hz, 1H, NCH*H*Np), 4.02 (dd, $J$ = 5.5, 8.2 Hz, 1H, PhC*H*), 7.20—7.83 (m, 12H, Ar-*H*); IR (neat) 2247, 1736, 1601, 1455, 1169. HRMS (EI) Found: *m/z* 443.2578, Calcd for $C_{28}H_{33}N_3O_2$: $M^+$, 443.2573.

**Methyl 12-Amino-3-phenyl-4,8-diazadodecanoate (8):** The mixture of methyl 11-cyano-8-(2-naphthylmethyl)-3-phenyl-4,8-diazaundecanoate **21** (155 mg, 0.35 mmol) and Pd/C (10% activated, 80 mg) in MeOH (2 mL) was stirred under hydrogen (1 atm) at 25 °C for 0.5 h. After filtration of the mixture and washing of the residue with methanol (20 mL), the solution was treated with concentrated hydrochloric acid (117 mg, 1.12 mmol) at 25 °C and the resulting solution was hydrogenated over platinum(IV) oxide (10.3 mg, 0.046 mmol) under hydrogen at 25 °C and 1 atm for 4 h. Filtration of the mixture, washing of the residue with methanol and concentration of the combined filtrates left the ammonium salt of methyl 12-amino-3-phenyl-4,8-diazadodecanoate **8**; this salt was directly chromatographed on silica gel (EtOAc : Hex : *i*-$PrNH_2$ = 5 : 5 : 4) to give the desired product **8** (79 mg, 74% yield). TLC, $R_f$ = 0.21 (EtOAc : Hex : *i*-$PrNH_2$ = 5 : 5 : 4); $^1$H NMR ($CDCl_3$) $\delta$ = 1.45—1.90 (m, 10H, $3CCH_2C$, 2N*H*, $NH_2$), 2.47—2.79 (m, 10H, $4CH_2N$, $CH_2CO_2Me$), 3.68 (s, 3H, $OCH_3$), 4.08 (dd, $J$ = 5.4, 8.6 Hz, 1H, PhC*H*), 7.22—7.40 (m, 5H, Ar-*H*); IR (neat) 3260, 1736, 1455, 1437, 1169. HRMS (FAB) Found: *m/z* 308.2334. Calcd for $C_{17}H_{29}N_3O_2$: $M^+$ + 1, 308.2338.

**12-Phenyl-2,7,11-triazacyclotridecan-1-one (23):**[5] A solution of tris(dimethylamino)borane (0.075 mL, 0.424 mmol) in xylene (1 mL, freshly distilled) was added to a stirred solution of the triamino ester **8** (100 mg, 0.326 mmol) in xylene (1 mL) at 25 °C to give the colorless solution, which turned to a white suspension in about 30 s. Stirring was continued at 25 °C for 0.5 h, then the mixture was refluxed for 8 h. Removal of the solvent and purification by column, chromatography on silica gel ($CHCl_3$ : MeOH : *i*-$PrNH_2$ = 30 : 1 : 1) gave the pure product (**23**) (66 mg, 74% yield) as white crystals. TLC, $R_f$ = 0.39 (EtOAc : Hex : *i*-$PrNH_2$ = 5 : 5 : 3); $^1$H NMR ($CDCl_3$) $\delta$ = 1.38—1.90 (m, 8H), 2.48—2.95 (m, 8H), 3.11—3.59 (m, 2H), 3.58 (dd, $J$ = 5.4, 8.4 Hz, 1H, PhC*H*), 7.20—7.40 (m, 5H, Ar-*H*), 8.69 (br, 1H, N*H*CO); IR (neat) 3245, 1645, 1537.

**(+)-(*S*)-Dihydroperphylline (1):**[3,5] A solution of *trans*-cinnamoyl chloride (30.3 mg, 0.182 mmol) in dichloromethane (2 mL) was added dropwise at −78 °C to a stirred solution of the lactam **23** (50 mg, 0.182 mmol) and 4-(dimethylamino)pyridine (67 mg, 0.546 mmol) in dichloromethane (2 mL). Stirring was continued at −78 °C for 20 min. The solution was diluted with $CHCl_3$ (10 mL), washed with 1 mol dm$^{-3}$ NaOH (1 mL), and dried with $Na_2SO_4$. Purification of the concentrated crude product by column chromatography ($CHCl_3$ : MeOH = 30 : 1) gave (+)-(*S*)-dihydroperphylline **1** (64 mg, 88% yield) as colorless crystals. TLC, $R_f$ = 0.25 ($CHCl_3$ : MeOH = 10 : 1); $^1$H NMR ($CDCl_3$, 50 °C) $\delta$ = 1.49—2.01 (7H, m, $3NCCH_2$, N*H*), 2.32—2.50 (m, 3H, C*H*NH, $CH_2CO$), 2.55—2.68 (m, 1H, C*H*NH), 3.06—3.89 (m, 6H, $3CH_2NCO$), 3.91 (m, 1H, C*H*Ph), 6.79 (d, $J$ = 15.4 Hz, 1H, C=C*H*CO), 7.16—7.47 (m, 11H, Ar-*H*, N*H*CO), 7.67 (d, $J$ = 15.4 Hz, 1H, C=C*H*Ph); IR (KBr) 1647, 1595, 1470, 1453, 976; $[\alpha]_D^{26}$ = +3.6 (*c* 1.19, $CHCl_3$); mp 82.5—83.5 °C.

**Ethyl 3-(4-Methoxyphenyl)propiolate (24a):**[13] To a solution of ethyl propiolate (6.1 mL, 60 mmol) in anhydrous THF (150 mL) was added a butyllithium (1.6 mol dm$^{-3}$ in hexane; 37.5 mL, 60 mmol) at −78 °C under argon atmosphere. After stirring at −78 °C for 30 min, anhydrous zinc chloride (24.5 g, 180 mmol) in anhydrous THF (180 mL) was added. The mixture was gradually heated to room temperature and stirred for 1 h. To the ice-cooled mixture were added 4-iodoanisole (7.0 g, 30 mmol) and dichlorobis(triphenylphosphine)palladium(II) (1.05 g, 1.5 mmol) and the mixture was stirred at 50 °C for 3 h. The mixture was filtered through a Celite pad. The filtrate was extracted with ether and the combined ether extracts were dried over anhydrous magnesium sulfate. The residue obtained by evaporating the solvent was purified by chromatography on silica gel (hexane : EtOAc = 5 : 1) and distilled (140 °C/5 Torr, 1 Torr = 133.322 Pa) to give **24a** (3.96 g, 65% yield) as a colorless oil. TLC, $R_f$ = 0.32 (hexane : $Et_2O$ = 4 : 1); $^1$H NMR ($CDCl_3$) $\delta$ = 1.35 (t, $J$ = 7.1 Hz, 3H, $CH_3CH_2$), 3.84 (s, 3H, $CH_3O$), 4.29 (q, $J$ = 7.1 Hz, 2H, $MeCH_2$), 6.88 (dd, $J$ = 2.2 and 6.9 Hz, 2H, Ar), 7.54 (dd, $J$ = 2.2 and 6.9 Hz, 2H, Ar).

**Ethyl 16-Amino-3-(4-methoxyphenyl)-4,8,13-triazahexadecenoate (25a):** A solution of **24a** (1.01 g, 4.94 mmol) and spermine (1.08 g, 4.94 mmol) in ethanol (30 mL) was heated at reflux for 2 h. After cooling, the solution was concentrated in vacuo,

and the residual oil was purified by chromatography on silica gel ($CHCl_3$ : MeOH : *i*-$PrNH_2$ = 10 : 1 : 1—10 : 2 : 2) to give **25a** (1.50 g, 75% yield) as a colorless oil. TLC, $R_f$ = 0.35 ($CHCl_3$ : MeOH : *i*-$PrNH_2$ = 7 : 3 : 3); IR ($CHCl_3$) 2950, 2850, 1640, 1610, 1252, 1170, 839 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ = 1.26 (dt, *J* = 7.1 and 10.1 Hz, 3H, $CH_3CH_2$), 1.40—1.73 (m, 12H), 2.50—2.80 (m, 10H), 3.08—3.20 (m, 2H, $CH_2NHC{=}C$), 3.84 (s, 3H, $CH_3O$), 4.13 (q, *J* = 7.1 Hz, 2H, $MeCH_2$), 4.58 (s, 1H, $CH{=}C$), 6.90 (d, *J* = 8.9 Hz, 2H, Ar), 7.29, (d, *J* = 8.9 Hz, 2H, Ar), 8.48—8.58 (br, 1H, $C{=}CNH$). HRMS (EI) Found: *m/z* 406.2931. Calcd for $C_{22}H_{38}N_4O_3$: $M^+$, 406.2944.

**Ethyl 16-Amino-3-phenyl-4,8,13-triaza-2-hexadecenoate (25b):** A solution of ethyl phenylpropiolate[8] (0.86 g, 4.94 mmol) and spermine (1.08 g, 4.94 mmol) in ethanol (30 mL) was heated at reflux for 2 h. After cooling, the solution was concentrated in vacuo, and the residual oil was purified by chromatography on silica gel ($CHCl_3$ : MeOH : *i*-$PrNH_2$ = 10 : 1 : 1—10 : 2 : 2) to give **25b** (1.10 g, 59% yield) as a colorless oil. TLC, $R_f$ = 0.48 $CHCl_3$ : MeOH : *i*-$PrNH_2$ = 7 : 3 : 3); IR ($CHCl_3$) 2950, 2850, 1649, 1610, 1590, 1483, 1294, 1167, 909 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ = 1.00—1.70 (m, 15H), 2.50—2.80 (m, 10H), 3.07—3.15 (m, 2H, $CH_2NHC{=}C$), 4.14 (q, *J* = 7.1 Hz, 2H, $MeCH_2$), 4.58 (s, 1H, $CH{=}C$), 7.30—7.46 (m, 5H, Ph), 8.50—8.62 (br, 1H, $C{=}CNH$). HRMS (EI) Found: *m/z* 376.2835. Calcd for $C_{21}H_{36}N_4O_2$: $M^+$, 376.2838.

**Ethyl 16-Amino-3-(4-methoxyphenyl)-4,8,13-triazahexadecanoate (13a):** A mixture of **25a** (0.736 g, 1.8 mmol) and platinum(IV) oxide (53 mg) in $CHCl_3$ (0.5 mL) and ethanol (25 mL) was stirred at room temperature under $H_2$ atmosphere. After 12 h, the mixture was filtered through a Celite pad and concentrated in vacuo. The residual oil was purified by chromatography on silica gel ($CHCl_3$ : MeOH : *i*-$PrNH_2$ = 10 : 1 : 1—10 : 2 : 2) and Alumina 90 ($CHCl_3$ : MeOH : *i*-$PrNH_2$ = 10 : 1 : 1) to give **13a** (0.595 g, 81% yield) as a colorless oil. TLC, $R_f$ = 0.31 ($CHCl_3$ : MeOH : *i*-$PrNH_2$ = 7 : 3 : 3); IR (film) 2980, 2850, 1732, 1510, 1248, 831 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ = 1.22 (dt, *J* = 7.1 and 12.4 Hz, 3H, $CH_3CH_2$), 1.35—1.70 (m, 15H), 2.40—2.80 (m, 12H), 3.80 (s, 3H, $CH_3O$), 3.97—4.03 (m, 1H, $ArCH$), 4.09 (q, *J* = 7.1 Hz, 2H, $MeCH_2$), 6.86 (d, *J* = 8.8 Hz, 2H, Ar), 7.23 (d, *J* = 8.8 Hz, 2H, Ar). HRMS (EI) Found: *m/z* 408.3086. Calcd for $C_{22}H_{40}N_4O_3$: $M^+$, 408.3100.

**Ethyl 16-Amino-3-phenyl-4,8,13-triazahexadecanoate (13b):** A mixture of **25b** (0.847 g, 2.2 mmol) and platinum(IV) oxide (66.0 mg) in $CHCl_3$ (0.5 mL) and ethanol (25 mL) was stirred at room temperature under $H_2$ atmosphere. After 12 h, the mixture was filtered through a Celite pad and concentrated in vacuo. The residual oil was purified by chromatography on silica gel ($CHCl_3$ : MeOH : *i*-$PrNH_2$ = 10 : 1 : 1—10 : 2 : 2) and Alumina 90 ($CHCl_3$ : MeOH : *i*-$PrNH_2$ = 10 : 1 : 1) to give **13b** (0.568 g, 68% yield) as a colorless oil. TLC, $R_f$ = 0.30 ($CHCl_3$ : MeOH : *i*-$PrNH_2$ = 7 : 3 : 3); IR (film) 2950, 2850, 1725, 1410, 1266, 907 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ = 1.20 (t, *J* = 7.1 Hz, 3H, $CH_3CH_2$). 1.30—1.70 (m, 15H), 2.40—2.80 (m, 12H), 4.00—4.15 (m, 1H, $phCH$), 4.09 (q, *J* = 7.1 Hz, 2H, $MeCH_2$), 7.20—7.40 (m, 5H, Ph). HRMS (EI) Found: *m/z* 378.2991. Calcd for $C_{21}H_{38}N_4O_2$: $M^+$, 378.2995.

**Ethyl 16-Amino-4,8,13-triazahexadecanoate (13c):** To a solution of spermine (1 g, 4.94 mmol) in ethanol (20 mL) was slowly added ethyl acrylate (0.536 mL, 4.94 mmol) at room temperature for 2.5 h, and the solution was stirred at room temperature for 12 h. After the solvent was evaporated, the residual oil was purified by chromatography on silica gel ($CHCl_3$ : MeOH : *i*-$PrNH_2$ = 4 : 1 : 1) to give **13c** (1.05 g, 70% yield) as a colorless oil. TLC, $R_t$ = 0.56 ($CHCl_3$ : MeOH : *i*-$PrNH_2$ = 16 : 2 : 1); IR (film) 3700—3000, 2930, 1732, 1658, 1557, 1466, 1371, 1124, 1051 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ = 1.26 (t, *J* = 6.5 Hz, 3H, $CH_3CH_2$), 1.40—1.75 (m, 4H), 2.52 (t, *J* = 6.2 Hz, 2H, $CH_2COOEt$), 2.57—2.73 (m, 10H), 2.77 (t, *J* = 6.7 Hz, 2H, $CH_2NH_2$), 2.89 (t, *J* = 6.2 Hz, 2H, $CHCH_2COOEt$), 4.23 (q, *J* = 6.5 Hz, 2H, $MeCH_2$). HRMS (EI) Found: *m/z* 302.2691. Calcd for $C_{15}H_{34}N_4O_2$: $M^+$, 302.2682.

**Ethyl 16-Amino-4-azahexadecanoate (13d):** To a solution of 1,12-dodecanediamine (1.01 g, 5 mmol) in ethanol (70 mL) was slowly added ethyl acrylate (0.542 mL, 5 mmol) at room temperature for 3 h, and the solution was stirred at room temperature for 9 h. After evaporating the solvent, the residual oil was purified by chromatography on silica gel ($CHCl_3$ : MeOH : *i*-$PrNH_2$ = 100 : 10 : 1—100 : 20 : 1) to give **13d** (0.598 g, 40% yield) as a white powder. TLC, $R_f$ = 0.82 ($CHCl_3$ : MeOH : *i*-$PrNH_2$ = 16 : 2 : 1); IR ($CHCl_3$) 3500—3000, 2930, 2856, 1725, 1461, 1375, 1184, 1115 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ = 1.26 (t, *J* = 7.1 Hz, 3H, $CH_3CH_2$), 1.20—1.35 (m, 16H), 1.37—1.57 (m, 3H), 2.52 (t, *J* = 6.5 Hz, 2H, $CH_2COOEt$), 2.61 (t, *J* = 7.2 Hz, 2H, $CH_2NHCH_2$), 2.68 (t, *J* = 7.0 Hz, 2H, $CH_2NH_2$), 2.88 (t, *J* = 6.5 Hz, 2H, $CH_2CH_2COOEt$), 4.15 (q, *J* = 7.1 Hz, 2H, $MeCH_2$). HRMS (EI) Found: *m/z* 300.2765. Calcd for $C_{17}H_{36}N_2O_2$: $M^+$, 300.2777.

**(±)-Buchnerine (2):**[6] A dry 50 mL round-bottom flask fitted with a stirbar and a 10 mL pressure-equalized addition funnel (containing a cotton plug and ca. 4 g of 4 Å molecular sieves (pellets) and functioning as a Soxhlet extractor) surmounted by a reflux condenser was charged with **13a** (0.0759 g, 0.19 mmol) and dry benzene (10 mL; dried over $CaH_2$). An argon atmosphere was secured, and the solution was brought to reflux (bath temperature 95—100 °C). After 2 h, the mixture was cooled to room temperature and to the solution was added antimony(III) ethoxide (1 mol $dm^{-3}$ in toluene; 0.22 mL, 0.22 mmol) and the reaction mixture was stirred at reflux (bath temperature 95—100 °C) for 14 h. After cooling to 0 °C, the mixture was quenched with methanol (5 mL) and purified by chromatography on silica gel ($CHCl_3$ : MeOH : *i*-$PrNH_2$ = 10 : 1 : 1) to give **2** (0.0513 g, 76% yield) as a colorless oil. TLC, $R_f$ = 0.62 ($CHCl_3$ : MeOH : *i*-$PrNH_2$ = 7 : 3 : 3); IR (film) 3283, 2930, 2836, 1650, 1512, 1250, 831 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ = 1.40—2.90 (m, 23H), 3.25—3.70 (m, 2H), 3.80 (s, 3H, $CH_3O$), 3.96 (dd, *J* = 3.5 and 9.6 Hz, 1H, $ArCH$), 6.87 (d, *J* = 8.8 Hz, 2H, Ar), 7.21 (d, *J* = 8.5 Hz, 2H, Ar), 8.35—8.48 (br, 1H, $CONH$). HRMS (EI) Found: *m/z* 362.2694. Calcd for $C_{20}H_{34}N_4O_2$: $M^+$, 362.2682.

**16-Phenyl-2,6,11,15-tetraazacycloheptadecan-1-one (27):** A dry 50 mL round-bottom flask fitted with a stirbar and a 10 mL pressure-equalized dropping funnel (containing a cotton plug and ca. 4 g of 4 Å molecular sieves (pellets) and functioning as a Soxhlet extractor) surmounted by a reflux condenser was charged with **13b** (0.178 g, 0.49 mmol) and dry benzene (15 mL). An argon atmosphere was secured, and the solution was brought to reflux (bath temperature 95—100 °C). After 2 h, the solution was cooled to room temperature and to the solution was added antimony(III) ethoxide (1 mol $dm^{-3}$ in toluene; 0.6 mL, 0.6 mmol) and the reaction mixture was stirred at reflux (bath temperature 95—100 °C) for 9 h. After cooling to 0 °C, the mixture was quenched with methanol (5 mL) and purified by chromatography on silica gel ($CHCl_3$ : MeOH : *i*-$PrNH_2$ = 10 : 1 : 1) to give **27** (0.149 g, 90% yield) as a colorless oil. TLC, $R_f$ = 0.65 ($CHCl_3$ : MeOH : *i*-$PrNH_2$ = 7 : 3 : 3); IR (film) 3283, 2928, 2850, 1650, 1552, 1127, 752 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ = 1.40—2.92 (m, 23H), 3.25—3.38 (m, 1H), 3.46—3.58 (m, 1H), 4.01 (dd, *J* = 3.6 and 9.7 Hz, 1H, $PhCH$), 7.20—7.40 (m, 5H, Ph), 8.38—8.48 (br, 1H, $CONH$). HRMS (EI) Found: *m/z* 332.2580. Calcd for $C_{19}H_{32}N_4O$: $M^+$, 332.2576.

**2,6,11,15-Tetraazacycloheptadecanone (28):** A dry 50 mL round-bottom flask fitted with a stirbar and a 10 mL pressure-

equalized dropping funnel (containing a cotton plug and ca. 4 g of 4 Å molecular sieves (pellets) and functioning as a Soxhlet extractor) surmounted by a reflux condenser was charged with **13c** (0.156 g, 0.5 mmol) and dry benzene (15.5 mL; dried over $CaH_2$). An argon atmosphere was secured, and the solution was brought to reflux (bath temperature 95—100 °C). After 2 h, the mixture was cooled to room temperature and to the solution was added antimony(III) ethoxide (1 mol $dm^{-3}$ in toluene; 0.62 mL, 0.62 mmol) and the reaction mixture was stirred at reflux (bath temperature 95—100 °C) for 15 h. After cooling to 0 °C, the mixture was quenched with methanol (5 mL) and purified by chromatography on silica gel ($CHCl_3$ : MeOH : *i*-$PrNH_2$ = 8 : 1 : 1—5 : 1 : 1) to give **28** (0.0864 g, 65% yield) as a colorless oil. TLC, $R_f$ = 0.64 ($CHCl_3$ : MeOH : *i*-$PrNH_2$ = 16 : 2 : 1); IR (film) 3300, 2932, 1651, 1559, 1470, 1364, 1125 $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ = 1.40—2.00 (m, 4H), 2.00—2.48 (m, 4H), 2.48—2.95 (m, 12H), 3.39 (dd, $J$ = 7.1 and 11.4 Hz, 2H, CONHC$H_2$), 8.16—8.28 (br, 1H, CON*H*). HRMS (EI) Found: *m/z* 256.2258. Calcd for $C_{13}H_{28}N_4O$: $M^+$, 256.2263.

**2,15-Diazacycloheptadecanone (29):** A dry 50 mL round-bottom flask fitted with a stirbar and a 10 mL pressure-equalized addition funnel (containing a cotton plug and ca. 4 g of 4 Å molecular sieves (pellets) and functioning as a Soxhlet extractor) surmounted by a reflux condenser was charged with **13d** (0.148 g, 0.5 mmol) and dry benzene (15 mL; dried over $CaH_2$). An argon atmosphere was secured, and the solution was brought to reflux (bath temperature 95—100 °C). After 2 h, the mixture was cooled to room temperature and to the solution was added antimony(III) ethoxide (1 mol $dm^{-3}$ in toluene; 0.6 mL, 0.6 mmol) and the reaction mixture was stirred at reflux (bath temperature 95—100 °C) for 15 h. After cooling to 0 °C, the mixture was quenched with methanol (5 mL) and purified by chromatography on silica gel ($CHCl_3$ : MeOH : *i*-$PrNH_2$ =100 : 5 : 1 — 100 : 10 : 1) to give **29** (0.0873 g, 69% yield) as a white powder. TLC, $R_f$ = 0.56 ($CHCl_3$ : MeOH : *i*-$PrNH_2$ = 16 : 2 : 1); IR ($CHCl_3$) 3300—3000, 2930, 2857, 1647, 1559, 1464, 1211 $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ = 1.20—1.65 (m, 20H), 1.75—2.15 (br, 1H, N*H*), 2.36 (dd, $J$ = 6.0 and 11.2 Hz, 2H, HNC$H_2$C$H_2$CO), 2.63 (dd, $J$ = 6.0 and 11.2 Hz, 2H, NHC$H_2$C$H_2$CO), 2.87 (dt, $J$ = 1.4 and 15.6 Hz, 2H, HNC$H_2$), 3.17—3.30 (m, 2H, CONHC$H_2$), 8.50—8.63 (br, 1H, CON*H*). HRMS (EI) Found: *m/z* 254.2360. Calcd for $C_{15}H_{30}N_2O$: $M^+$, 254.2358.

**(±)-Verbacine (3):**[17] To a suspension of 3,5-bis(trifluoromethyl)phenylboronic acid (0.232 g, 0.9 mmol) in $CH_2Cl_2$ (10 mL) was added **27** (0.296 g, 0.9 mmol) in $CH_2Cl_2$ (2 mL) at −78 °C, and the solution was stirred at room temperature for 1 h. After cooling to − 78 °C, to the solution was slowly added cinnamoyl chloride (0.150 g, 0.9 mmol) in $CH_2Cl_2$ (3 mL), and the resulting mixture was stirred at −78 °C for 2 h. The reaction mixture was quenched with methanol (2 mL) and purified by chromatography on silica gel ($CHCl_3$ : MeOH : *i*-$PrNH_2$ = 50 : 1 : 1 — 20 : 1 : 1) to give **3** (0.219 g, 53% yield) as a colorless solid. TLC, $R_f$ = 0.69 ($CHCl_3$ : MeOH : *i*-$PrNH_2$ = 8 : 1 : 1); IR (film) 3300, 1647, 1599, 1550, 980, 908 $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ = 1.40—2.20 (m, 10H), 2.30—2.80 (m, 8H), 3.20—3.80 (m, 6H), 3.97 (t, $J$ = 10.0 Hz, 1H, PhC*H*), 6.74 (d, $J$ = 15.4 Hz, 0.5H, PhCH=C*H*), 6.83 (d, $J$ = 15.4 Hz, 0.5H, PhCH=C*H*), 7.15—7.58 (m, 10H, 2Ph), 7.67 (d, $J$ = 15.4 Hz, 1H, PhC*H*=CH), 7.96—8.13 (br, 1H, CON*H*). HRMS (EI) Found: *m/z* 462.2997. Calcd for $C_{28}H_{38}N_4O_2$: $M^+$, 462.2995.

**11-Cinnamoyl Isomer:** $R_f$ = 0.76 ($CHCl_3$ : MeOH : *i*-$PrNH_2$ = 8 : 1 : 1); $^1$H NMR ($CDCl_3$) $\delta$ = 1.40—2.20 (m, 10H), 2.30—2.80 (m, 8H), 3.20—3.80 (m, 6H), 3.92—4.02 (m, 1H, PhC*H*), 6.85 (d, $J$ = 15.0 Hz, 1H, PhCH=C*H*), 7.08—7.62 (m, 10H, 2Ph), 7.70 (d, $J$ = 15.0 Hz, 1H, PhC*H*=CH), 8.30—8.40 (br, 1H, CON*H*).

**6,11-Dicinnamoyl Isomer:** $R_f$ = 0.82 ($CHCl_3$ : MeOH : *i*-$PrNH_2$ = 8 : 1 : 1); $^1$H NMR ($CDCl_3$) $\delta$ = 1.55—2.00 (m, 8H), 2.25—2.73 (m, 4H), 3.00—4.20 (m, 12H), 6.64—6.47 (m, 2H, PhCH=C*H*), 7.10—7.50 (m, 15H, 3Ph), 7.61 (d, $J$ = 15.1 Hz, 1H, PhC*H*=CH), 7.80—7.90 (m, 1H, PhC*H*=CH), 8.04 (s, 1H, CON*H*).

**(±)-Verbaskine (4):**[17,18] To a solution of **3** (0.0782 g, 0.17 mmol) in $CH_2Cl_2$ (2 mL) were added triethylamine (0.049 mL, 0.35 mmol) and triphosgene (0.0177 g, 0.06 mmol) in $CH_2Cl_2$ (1 mL) at 0 °C, and the reaction solution was stirred at room temperature. After 20 h, the solution was quenched with methanol (1 mL) and purified by chromatography on silica gel ($CHCl_3$ : MeOH = 20 : 1) to give **4** (0.0601 g, 78% yield) as a colorless solid. TLC, $R_f$ = 0.42 ($CHCl_3$ : MeOH = 8 : 1); IR ($CHCl_3$) 3450, 3300, 3006, 1647, 1601, 1510, 909 $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ = 1.30—2.20 (m, 9H), 2.60—4.00 (m, 12H), 4.30—4.55 (m, 1H), 6.19 (dd, $J$ = 2.0 and 12.6 Hz, 1H), 6.80 (dd, $J$ = 2.7 and 15.4 Hz, 1H, PhCH=C*H*), 7.20—7.80 (m, 10H), 7.70 (d, $J$ = 15.4 Hz, 1H, PhC*H*=CH), 7.90—8.00 (br, 1H, CON*H*); (DMSO-$d_6$) 1.30—2.10 (m, 9H), 2.60—3.70 (m, 12H), 4.19 (t, $J$ = 10.6 Hz, 1H), 6.10—6.20 (m, 1H), 7.10 (d, $J$ = 15.4 Hz, 1H, PhCH=C*H*), 7.20—7.60 (m, 8H, Ph), 7.71 (d, $J$ = 15.4 Hz, 1H, PhC*H*=CH), 7.63—7.76 (m, 2H, Ph), 8.10—8.22 (br, 1H, CON*H*); $^{13}$C NMR ($CDCl_3$) $\delta$ = 170.4, 166.3, 159.4, 142.6, 142.4, 129.7, 129.5, 128.7, 127.8, 127.7, 127.6, 117.3, 52.5, 47.5, 45.4, 45.1, 43.9, 39.9, 37.4, 37.1, 28.8, 26.8, 24.8, 21.9. HRMS (EI) Found: *m/z* 488.2794. Calcd for $C_{29}H_{36}N_4O_3$: $M^+$, 488.2787.

**(±)-Verbascenine (5):**[17,19] To a solution of **3** (0.0709 g, 0.15 mmol) and triethylamine (0.064 mL, 0.46 mmol) in $CH_2Cl_2$ (2 mL) was added acetic anhydride (0.016 mL, 0.17 mmol) at −78 °C. After stirring at that temperature for 2 h, the solution was quenched with methanol (0.5 mL), then purified by chromatography on silica gel ($CHCl_3$ : MeOH = 20 : 1) to give **5** (0.0702 g, 91% yield) as a colorless solid. TLC, $R_f$ = 0.32 ($CHCl_3$ : MeOH = 8 : 1); IR (film) 3250, 2993, 2939, 2864, 1550-1700, 1456, 1360, 1170, 1127, 976, 907 $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ = 1.10—2.20 (m, 9H), 2.02 (s, 1.5H), C$H_3$CO), 2.07 (s, 1.5H, C$H_3$CO), 2.30—2.70 (m, 5H), 3.10—3.75 (m, 10H), 3.95—4.10 (m, 1H, PhC*H*), 6.83 (d, $J$ = 15.4 Hz, 0.5H, PhCH=C*H*), 6.85 (d, $J$ = 15.4 Hz, 0.5H, PhCH=C*H*), 7.15—7.60 (m, 10H, 2Ph), 7.73 (d, $J$ = 15.4 Hz, 1H, PhC*H*=CH), 8.05—8.12 (br, 1H, CON*H*); $^{13}$C NMR ($CDCl_3$), $\delta$ = 171.5, 170.4, 166.3, 142.8, 142.5, 135.3, 129.6, 128.8, 127.8, 127.6, 126.2, 117.3, 59.3, 49.9, 48.8, 47.7, 47.3, 46.7, 46.3, 45.1, 44.6, 43.6, 37.1, 30.3, 29.0, 26.4, 25.1, 21.9. HRMS (EI) Found: *m/z* 504.3111. Calcd for $C_{30}H_{40}N_4O_3$: $M^+$, 504.3100.

**General Procedure for Antimony(III) Ethoxide-Catalyzed Amide Condensation Reaction (Table 2).** A dry 50 mL round-bottom flask fitted with a stirbar and a 10 mL pressure-equalized addition funnel (containing a cotton plug and ca. 4 g of 4 Å molecular sieves (pellets) and functioning as a Soxhlet extractor) surmounted by a reflux condenser was charged with carboxylic acids (1 mmol) or the corresponding methyl esters (1 mmol), amines (1 mmol), and dry toluene (5 mL; dried over $CaH_2$). An argon atmosphere was secured, and the solution was brought to reflux. After 1 h, the mixture was cooled to room temperature and to the solution was added antimony(III) ethoxide (1 mol $dm^{-3}$ in toluene; 0.1 mL, 0.1 mmol). Then the reaction mixture was stirred at reflux for several hours or 1 d. After cooling to 0 °C, the mixture was quenched with methanol (1 mL) and purified by chromatography on silica gel to give amides. The physical properties and analytical data of the amides thus obtained were identical with those reported.

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