Total Synthesis of (±)-Celacinnine, (±)-Celallocinnine, (±)-Celafurine, and (±)-Celabenzine

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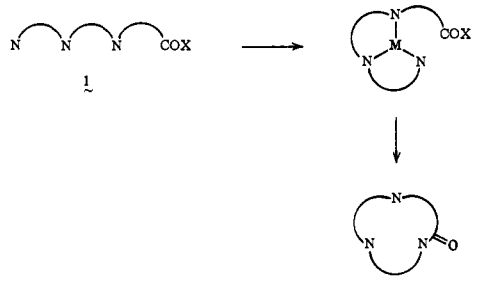
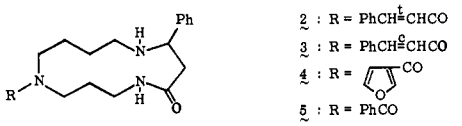
Abstract: The total synthesis of spermidine alkaloids, (±)-celacinnine (**2**), (±)-celallocinnine (**3**), (±)-celafurine (**4**), and (±)-celabenzine (**5**), is described. The use of boron-templated cyclization within the context of constructing macrolactam has been explored, and the combination of triamino ester with tris(dimethylamino)borane is found to be highly efficient. The present cyclization in addition to the refinement of each step produces macrocyclic spermidine alkaloids, **2**, **4**, and **5**, by a five-step sequence in ~41% overall yield starting from 1,4-diaminobutane. Irradiation of **2** affords **3** in 50% yield.

In order to induce long open chains with α- and ω-functional groups to condence internally into large rings, a template effect may play an extraordinally important role.[2] One impressive example has been reported by Eschenmoser in developing synthetic access to vitamine B_{12}.[3] We have been interested for some time in the possibility of metal templated cyclization of spermidine derivative **1** which, if successful, would result in the direct formation of large ring alkaloids with amino groups at the positions where they are normally formed in natural products. We report in this paper on the initial results which show the feasibility and limitations of this approach.

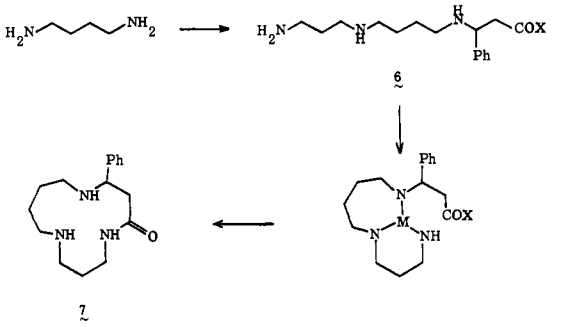


Celacinnine (**2**) is an attractive target for our present synthesis. This was isolated from *Maytenus arbutifolia* (Hochst., ex A. Rich) R. Wilczek and *Tripterygium wilfordii* Hook, together with the related alkaloids, celallocinnine (**3**), celafurine (**4**), and celabenzine (**5**).[4] These alkaloids are characterized by the presence of a 13-membered ring reflecting spermidine and cinnamoyl precursorial units,[5] and represent novel variants of the few known macrocyclic lactam alkaloids derived from spermidine.

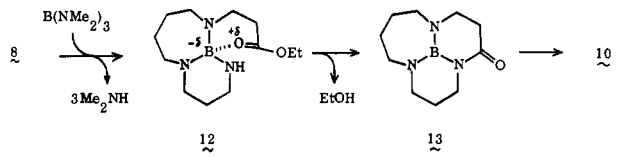


Synthetic design was based on the strategy summarized in Scheme I. 1,4-Diaminobutane provided a basic unit in spermidine and spermine alkaloids.[6] A triamino acid derivative such as **6** was envisaged as an ideal progenitor of the macrocyclic spermidine skeleton **7**, which could then be elaborated via metal-templated cyclization and selective acylation to (±)-celacinnine (**2**), (±)-celallocinnine (**3**), (±)-celafurine (**4**), and (±)-celabenzine (**5**).

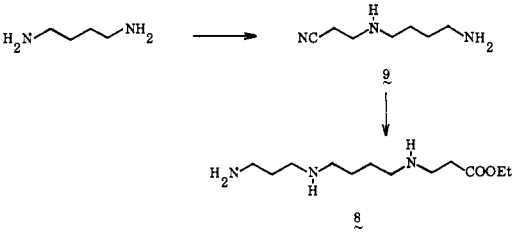
Scheme I



Scheme II



At the outset of this study, we were concerned with the development of the new macrolactam formation via metal-templated cyclization. The starting triamino ester **8** was prepared in 46%



overall yield by cyanoethylation of 1,4-diaminobutane, Michael addition of the resulting *N*-(cyanoethyl)-1,4-diaminobutane (**9**) to ethyl acrylate, and hydrogenation of the cyano group over platinum oxide in the presence of concentrated hydrochloric acid. The cyclization of triamino ester **8** giving the 13-membered lactam

(1) Department of Applied Chemistry, Faculty of Engineering, Nagoya University, Chikusa, Nagoya 464, Japan.

(2) For the metal-templated synthesis, see: (a) Busch, D. H. *Rec. Chem. Prog.* 1964, *25*, 107. (b) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* 1974, *96*, 5614. (c) Masamune, S.; Kamata, S.; Schilling, W. *Ibid.* 1975, *97*, 3515. (d) Pedersen, C. J. *Org. Synth.* 1972, *52*, 66.

(3) Eschenmoser, A. *Pure Appl. Chem.* 1969, *20*, 1.

(4) For the isolation and structural elucidation of the alkaloids **2**, **3**, **4**, and **5**, see: Kupchan, S. M.; Hintz, H. P. J.; Smith, R. M.; Karim, A.; Cass, M. W.; Court, W. A.; Yatagami, M. *J. Chem. Soc., Chem. Commun.* 1974, 329; *J. Org. Chem.* 1977, *42*, 3660.

(5) The characterization of maytenine, an alkaloid from *Maytenus chuchuasha*, as the di-*trans*-cinnamoylamide of the terminal primary amides of spermidine has been recently reported. See: Englert, G.; Klinga, K.; Raymond-Hamet; Schlittler, E.; Vetter, W. *Helv. Chim. Acta* 1973, *56*, 474.

(6) For recent reviews of macrocyclic spermidine and spermine alkaloids, see: (a) Badawi, M. M.; Bernauer, K.; Van den Broek, P.; Groger, D.; Guggisberg, A.; Johne, S.; Kompis, I.; Schneider, F.; Veith, Hh.-J.; Hesse, M.; Schmid, H. *Pure Appl. Chem.* 1973, *33*, 81. (b) Hesse, M.; Schmid H. "International Review of Science", Hey, D. H., Wiener, K., Eds.; Butterworths: London, 1976, Series II, Vol 9, pp 265–307. (c) Fujita, E. *Yuki Gosei Kagaku* 1980, *38*, 333.

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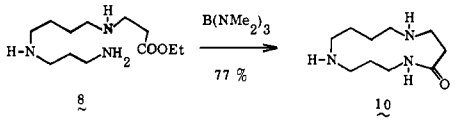
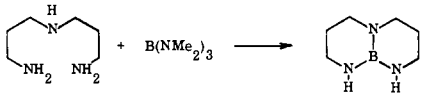
10 was accomplished by the use of tris(dimethylamino)borane[7] as a key reagent: A mixture of the ester **8** and a catalytic amount of ammonium chloride in dry, freshly distilled xylene was treated with tris(dimethylamino)borane in xylene at 25 °C. The reaction mixture was stirred for 30 min at 25 °C, and then heated at reflux for 15 h. Upon solvent removal in vacuo the crude product was



8 10

directly chromatographed on silica gel to give the pure lactam **10** (77% yield): homogeneous by TLC and having IR, ^{1}H NMR, and mass spectra in accord with the assigned structure. Since none of the polymerization or regioisomeric product was formed, the isolation of the lactam is simple.

The transamination of 3,3′-iminobis(propylamine) with tris(dimethylamino)borane was reported to give 1,8,10,9-triazaboradecalin (**11**).[8] Thus, the efficiency of this cyclization reaction



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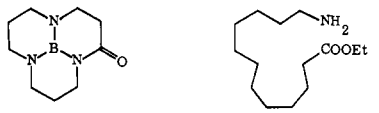
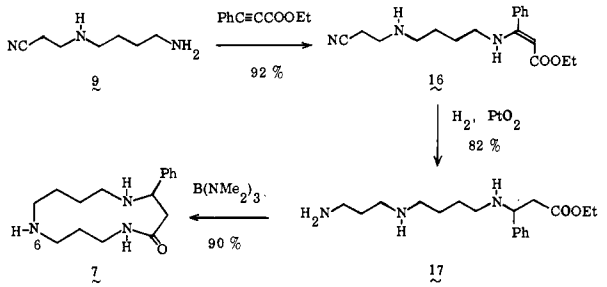
may be ascribed to the boron-mediated template effect. Convincing evidence was obtained for operation of the boronation–lactam formation–deboronation mechanism as outlined in Scheme II. When a mixture of ethyl 4,8,12-triazadodecanoate, tris(dimethylamino)borane, and a catalytic amount of ammonium chloride in xylene was heated at reflux for 3 h, a single intermediate **14** was isolated in 93% yield. Surprisingly, this compound was highly stable, and attempted hydrolysis of **14** under various acidic conditions resulted in the total recovery of the starting material without much decomposition. In contrast to the smooth cyclization of **8**, the ω-amino ester **15** afforded no lactam under conditions similar to those used for **8** or even under more forcing circumstances. Obviously, boron-templated structures such as depicted in Scheme II are not possible with **15**. Thus, the possible



14 15

intermediate **12** generated by transamination of triaminoborane could reasonably be expected to undergo a facile, sterically driven cyclization to **13**. Furthermore, attempted reaction of tris(dimethylamino)borane with ethyl 3-phenylpropionate in the presence or absence of spermidine under comparable conditions resulted in the total recovery of the starting materials.

The present cyclization process provided the crucial information leading to an unusually simple synthesis of macrocyclic spermidine alkaloids, (±)-celacinnine (**2**), (±)-celallocinnine (**3**), (±)-celafurine (**4**), and (±)-celabenzine (**5**).[9] Thus, Michael addition of *N*-(cyanoethyl)-1,4-diaminobutane (**9**) to ethyl phenylpropionate yielded ethyl 11-cyano-4,9-diaza-3-phenyl-2-undecenoate (**16**) (92%), which was converted to ethyl 3-phenyl-4,9,13-triazatridecanoate (**17**) (81%) by hydrogenation of both cyano and olefinic groups over platinum oxide.[10] Cyclization of the triamino ester **17** was effected with tris(dimethylamino)borane in xylene under reflux to furnish the desired diaminolactam **7** in 90% yield. Although the synthetic approach described herein is similar to the Ganems' method using cathecolborane,[9] it is not likely at the present stage that their cathecolborane procedure can form a triaminoborane intermediate such as **12** with the triamino ester **17** in order to promote the efficient cyclization.



9 16 7 17

Completion of the synthesis of the celacinnine family by this route required the selective acylation at N-6 of **7**. This was best accomplished with the corresponding acid chlorides in the presence of 4-(dimethylamino)pyridine[11] at low temperature to give **2**, **4**, and **5** in almost quantitative yield. The synthetic celacinnine was identical, in all respects, with an authentic sample.[12] Irradiation of **2** in benzene as solvent under argon using a Pyrex container and an external UV lamp (>300 nm) afforded after purification (±)-celallocinnine (**3**, 50%), together with recovered **2** (30%).

The present boron-templated cyclizations proved to be highly useful for the synthesis of macrocyclic spermidine alkaloids. We are continuing our studies on the mechanism and synthetic scope of these cyclizations. The rate accelerations and high selectivities observed in the present work clearly support a mechanism where the acyclic amino ester is covalently attached to the boron before the final cyclization step. It would not be surprising if ω-amino esters which have hydroxy, carbonyl, or mercaptyl groups on the chain showed similar synthetically useful template effects with boron reagent.

Experimental Section

General. The infrared spectra were recorded on a Perkin-Elmer 710A spectrometer; mass spectra on a Varian MAT high-resolution mass spectrometer; ^{1}H NMR spectra on a Varian EM-360 or HA-100 spectrometer; and fourier transfer ^{13}C NMR spectra on a Varian XL-100 spectrometer. The chemical shifts are expressed in parts per million downfield from internal tetramethylsilane (δ 0). Splittering patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Melting-point determinations were performed by using a Büchi-510 capillary melting point apparatus in open capillaries and are uncorrected. All experiments were carried out under an atmosphere of dry argon. For TLC analysis throughout this work, Merck precoated TLC plates (silica gel 60 F_{254}, 0.2 mm) were used. The products were purified by preparative TLC on silica gel plates (Merck), or by preparative column chromatography on silica gel E. Merck Art. 9385, or silanized silica gel E. Merck Art. 7719.

In experiments requiring dry solvents, benzene, and xylene were freshly distilled from sodium metal. Dichloromethane was distilled from phosphorus pentoxide and stored over 4A molecular sieves. Pyridine and triethylamine were stored over potassium hydroxide pellets. Other simple chemicals were purchased and used as such. Tris(dimethylamino)borane was prepared according to the literature procedure.[7]

***N*-(Cyanoethyl)-1,4-diaminobutane (9).** Acrylonitrile (9.94 mL) was added dropwise to a solution of 1,4-diaminobutane (13.22 g, 0.15 mol) in methanol (3.5 mL) at 25 °C over 1 h. The reaction was exothermic. The resulting mixture was allowed to stand at 25 °C overnight. Purification of the mixture by column chromatography on silica gel (*i*-$PrNH_2$–MeOH–$CHCl_3$, 1:5:15) gave pure **9** (13.38 g, 68% yield) as a colorless oil: TLC, R_f 0.37 (*i*-$PrNH_2$–MeOH–$CHCl_3$, 1:4:4); ^{1}H NMR ($CDCl_3$) δ 2.35–3.10 (8 H, m, NCH_2), 1.37 (3 H, s, NH), 1.27–1.70 (4 H, m, CCH_2C).

Ethyl 11-Cyano-4,9-diazaundecanoate. An ethanolic solution (5 mL) of ethyl acrylate (1 g, 10 mmol) was added at 25 °C over 1 h to an

(7) Niedenzu, K.; Dawson, J. W. *Inorg. Synth.* **1967**, *10*, 135.

(8) Several interesting triazaborabicyclic compounds have been reported. See: (a) Niedenzu, K.; Fritz, P.; Dawson, J. W. *Inorg. Chem.* **1964**, *3*, 1077. (b) Bielawski, J.; Niedenzu, K. *Synth. React. Inorg. Met.-Org. Chem.* 1979, *9*, 309.

(9) For other approaches to racemic celacinnine and celabenzine, see: (a) Mcmanis, J. S.; Ganem, B. *J. Org. Chem.* **1980**, *45*, 2041. (b) Wasserman, H. H.; Robinson, R. P.; Matsuyama, H. *Tetrahedron Lett.* **1980**, *21*, 3493.

(10) Secrist, J. A., III; Louge, M. W. *J. Org. Chem.* **1972**, *37*, 335. Palladium on chacoal is not effective for the reduction of **16** under comparable reaction conditions.

(11) Hofle, G.; Steglich, W.; Vorbruggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.

(12) We are grateful to Professor B. Ganem for providing synthetic (±)-celacinnine.

ethanolic solution (10 mL) of **9** (1.41 g, 10 mmol). Stirring was continued at 25 °C for 5 h. Evaporation of the solvent left the oil, which was purified by column chromatography (*i*-$PrNH_2$–$CHCl_3$, 1:25, then 1:15) to give the title compound (1.973 g, 82% yield) as a colorless oil: TLC, R_f 0.32 (*i*-$PrNH_2$–$CHCl_3$, 1:20); IR (liquid film) 3365, 2250, 1745, 1480, 1388, 1195, 1135, 1040, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.17 (2 H, q, J = 7.0 Hz, OCH_2), 2.33–3.10 (12 H, m, CH_2N, CH_2CN, $CH_2C{=}O$), 1.29 (3 H, t, J = 7.0 Hz, CH_3), 1.17–1.78 (6 H, m, CCH_2C, NH).

The title compound was converted to its diacetamide derivative with use of acetic anhydride–pyridine (1:1 ratio) at 25 °C for 1 day: TLC, R_f 0.47 (MeOH–$CHCl_3$, 1:9); IR ($CHCl_3$) 2410, 1735, 1645, 1427, 1210 cm^{-1}.

Ethyl 4,9,13-Triazatridecanoate (8). Ethyl 11-cyano-4,9-diazaundecanoate (1.205 g, 5 mmol) in ethanol (50 mL) was treated with concentrated hydrochloric acid (1.5 mL, 17.5 mmol) at 25 °C, and the resulting mixture was hydrogenated over platinum oxide (150 mg) under hydrogen at 25 °C and 1 atm for 1 h. Filtration of the mixture, washing of the residue with methanol, and concentration of the combined filtrates left the ammonium salt of **8**, which was directly chromatographed on silica gel (*i*-$PrNH_2$–MeOH–$CHCl_3$, 1:5:5, then 2:5:5) to give **8** (1.1 g, 90% yield) as a colorless oil: TLC, R_f 0.26 (*i*-$PrNH_2$–MeOH, 1:5); IR (liquid film) 3350, 1733, 1475, 1315, 1185, 1112 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.12 (2 H, q, J = 7.2 Hz, OCH_2), 2.38–2.98 (12 H, m, CH_2N, $CH_2C{=}O$), 1.38 (4 H, s, NH), 1.25 (3 H, t, J = 7.2 Hz, CH_3), 1.10–1.85 (6 H, m, CCH_2C).

The title compound was transformed into its triacetamide derivative with use of acetic anhydride–pyridine as described above: TLC, R_f 0.34 (*i*-$PrNH_2$–$CHCl_3$, 1:10); IR (liquid film) 3450, 1730, 1630, 1430, 1375 cm^{-1}.

Cyclization to 2,6,11-Triazacyclotridecanone (10). A solution of tris(dimethylamino)borane (426 mg, 3 mmol) in xylene (5 mL, freshly distilled) was added to a stirred solution of the triamino ester **8** (665 mg, 2.7 mmol) in xylene (22 mL) at 25 °C. The resulting mixture was stirred at 25 °C for 30 min and then under reflux for 15 h to furnish a yellow precipitate. Evaporation of the solvent and purification of the residue by column chromatography (*i*-$PrNH_2$–MeOH–$CHCl_3$, 2:5:5, then 3:5:5) afforded the pure lactam **10** (413 mg, 77% yield) as white crystals: TLC, R_f 0.16 (*i*-$PrNH_2$–MeOH, 1:5), 0.31 (silanized TLC, *i*-$PrNH_2$–MeOH–$CHCl_3$, 1:5:5); mp 113.5–115 °C (recrystallized from EtOAc–hexane); IR ($CHCl_3$) 3245, 1645, 1537, 1466, 1442, 1122 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.65 (1 H, br, s, NHC=O), 3.12–3.58 (2H, m, $CH_2NC{=}O$), 2.13–3.04 (10 H, m, NCH_2), 1.34–1.94 (6 H, m, CCH_2C); mass m/z (%) 199 (65), 182 (39), 84 (80), 70 (100); exact mass m/z 199.174 (calcd for $C_{10}H_{21}N_3O$, 199.168); ^{13}C NMR ($CDCl_3$, ppm from Me_4Si) 172.43, 49.85, 49.32, 46.32, 39.98, 36.81, 38.62, 27.56.

The structure of **10** was further confirmed by acylation to the corresponding diacetamide (Ac_2O–Py·): TLC, R_f 0.30 (MeOH–$CHCl_3$, 1:9); IR ($CHCl_3$) 3350, 1640, 1627, 1426, 1365, 1220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.95 (1 H, br s, HNC=O), 3.08–3.95 (10 H, m, NCH_2), 2.25–2.65 (2 H, m, $CH_2C{=}O$), 2.13 (6 H, s, $CH_3C{=}O$), 1.38–2.09 (6 H, m, CCH_2C); mass m/z (%) 283 (48), 240 (100); exact mass m/z 283.197 (calcd for $C_{14}H_{25}N_3O_3$, 283.190).

Ethyl 4,8,12-Triazadodecanoate. An ethanolic solution (1 mL) of ethyl acrylate (330 mg, 3.3 mmol) was added slowly at 25 °C to an ethanolic solution (4 mL) of 3,3′-iminobis(propylamine) (393 mg, 3 mmol) over 30 min. The resulting solution was further stirred at 25 °C overnight. After removal of solvent, the residue was purified by column chromatography (*i*-$PrNH_2$–MeOH–$CHCl_3$, 1:4:4) to give the title compound (248 mg, 36% yield) as a colorless oil: TLC, R_f 0.43 (aqueous $EtNH_2$–MeOH, 1:10); IR ($CHCl_3$) 3320, 1725, 1545, 1460, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.13 (2 H, q, J = 7.0 Hz, OCH_2), 2.30–3.10 (12 H, m, CH_2N, $CH_2C{=}O$), 1.55 (4 H, s, NH), 1.40–2.01 (4 H, m, CCH_2C), 1.25 (3 H, t, J = 7.0 Hz, CH_3); mass m/z 231, 187, 186, 157, 144, 130; exact mass m/z 231.194 (calcd for $C_{11}H_{25}N_3O_2$, 231.195).

The title compound was also obtained by the following sequence: cyanoethylation of 1,3-diaminopropane, Michael addition of the resulting *N*-(cyanoethyl)-1,3-diaminopropane to ethyl acrylate, and hydrogenation of the cyano group as described for preparation of **8**.

The triacetamide of the title compound showed the following physical and spectral properties: TLC, R_f 0.35 (MeOH–$CHCl_3$, 1:5); IR ($CHCl_3$) 3390, 1730, 1635, 1425, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.19 (2 H, q, J = 7.0 Hz, OCH_2), 3.12–3.73 (10 H, m, CH_2N), 2.59–2.95 (2 H, m, $CH_2C{=}O$), 2.01, 2.15 (9 H, two s, $CH_3C{=}O$), 1.28 (3 H, t, J = 7.0 Hz, $OCCH_3$); exact mass m/z 357.233 (calcd for $C_{17}H_{31}N_3O_5$, 357.226).

Diazaboralactam 12. The cyclization of ethyl 4,8,12-triazadodecanoate (231 mg, 1 mmol) was carried out as previously described utilizing tris(dimethylamino)borane (157 mg, 1.1 mmol) and ammonium chloride (5.4 mg, 0.1 mmol) in xylene (10 mL) under reflux for 3 h. Removal of solvent and purification by column chromatography on silanized silica gel (*i*-$PrNH_2$–MeOH–$CHCl_3$, 1:2:2) gave **12** (180 mg, 93% yield) as colorless crystals: TLC, R_f 0.18 (aqueous $EtNH_2$–MeOH, 1:5), 0.5 (silanized silica gel TLC, *i*-$PrNH_2$–MeOH–$CHCl_3$, 1:2:2); mp 92–93 °C (recrystallized from EtOAc); IR ($CHCl_3$) 1656, 1552, 1445, 1388, 1327, 1198 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.24–3.61 (2 H, m, $CH_2NC{=}O$), 2.71–3.12 (8 H, m, CH_2N), 2.24–2.71 (2 H, m, $CH_2C{=}O$), 1.58–2.10 (4 H, m, CCH_2C); mass m/z (%) 193 (74), 192 (100), 191 (63), 164 (24), 150 (47); exact mass m/z 193.143 (calcd for $C_9H_{16}N_3OB$, 193.139).

Attempted hydrolysis of **12** with use of methanolic hydrochloric acid (4.46 M) under reflux for 2 h, concentrated hydrochloric acid under reflux for 4 h, or acetic acid under reflux for 2 h was unsuccessful.

Reaction of ω-Amino Ester 15 with Triaminoborane. A mixture of ethyl 12-aminododecanoate (**15**) (243 mg, 1 mmol) with tris(dimethylamino)borane (157 mg, 1.1 mmol) in xylene (10 mL) was heated under reflux for 1 day in the presence of a catalytic amount of ammonium chloride to recover the starting material.

Reaction of Ethyl 3-Phenylpropionate with Triaminoborane. Attempted reaction of ethyl 3-phenylpropionate with tris(dimethylamino)borane (1.1 equiv) in xylene under reflux was carried out in the presence or absence of spermidine (1 equiv) to give only the recovery of the starting materials.

Ethyl Phenylpropiolate. A solution of *n*-butyllithium in *n*-hexane (1.6 M, 69 mL, 0.11 mol) was added dropwise to a solution of phenylacetylene (11 mL, 0.1 mol) in ether (150 mL) at 0 °C, and the resulting mixture was stirred at 0 °C for 30 min. This mixture was then transferred to a solution of ethyl chloroformate (28.7 mL, 0.3 mol) in ether (100 mL) at 0 °C. After further stirring for 30 min at 0 °C, the mixture was poured onto iced water and extracted with ether. Dryness over anhydrous sodium sulfate, evaporative concentration, and distillation of the crude product under reduced pressure gave the title compound (15.83 g, 91% yield) as a colorless oil: bp 103 °C (0.3 mmHg); ^1H NMR ($CDCl_3$) δ 7.16–7.72 (5 H, m, aryl CH), 4.20 (2 H, q, J = 7.0 Hz, OCH_2), 1.32 (3 H, t, J = 7.0 Hz, CH_3).

Ethyl 11-Cyano-4,9-diaza-3-phenyl-2-undecenoate (16). A mixture of **9** (7.05 g, 50 mmol) and ethyl phenylpropiolate (17.4 g, 100 mmol) in dry ethanol (50 mL) was heated under reflux for 2 h. The solvent was then evaporated and the residue was directly applied to column chromatography (MeOH–$CHCl_3$, 1:40) to give **16** (14.5 g, 92% yield) as a colorless oil: TLC, R_f 0.37 (MeOH–$CHCl_3$, 1:15); IR (liquid film) 3330, 2260, 1659, 1614, 1488, 1300, 1175, 1147, 1040, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.63 (1 H, br s, C=C—NH), 7.44 (5 H, s, aryl CH), 4.69 (1 H, s, C=CH), 4.13 (2 H, q, J = 7.2 Hz, OCH_2), 2.29–3.27 (8 H, m, NCH_2, CH_2CN), 1.23–1.66 (5 H, m, CCH_2C, NH), 1.27 (3 H, t, J = 7.2 Hz, CH_3); mass m/z 315, 270, 232, 206, 192; exact mass m/z 315.199 (calcd for $C_{18}H_{25}N_3O_2$, 315.195).

Ethyl 3-Phenyl-4,9,13-triazatridecanoate (17). The cyanodiamino ester **16** (12.8 g, 40.6 mmol) in chloroform–ethanol (1:50 ratio, 408 mL) was hydrogenated over platinum oxide (1.2 g) under hydrogen at 25 °C and 1 atm for 8 h. Filtration of the mixture, washing of the residue with methanol, and concentration of the combined filtrates left the white ammonium salt, which was purified by column chromatography on silica gel (*i*-$PrNH_2$–MeOH–$CHCl_3$, 1:5:15) to furnish the triamino ester **17** (10.51 g, 81% yield) as a light yellow oil: TLC, R_f 0.33 (*i*-$PrNH_2$–MeOH–$CHCl_3$, 1:5:15) IR ($CHCl_3$) 3340, 1733, 1462, 1375, 1178, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36 (5 H, s, aryl CH), 4.49 (5 H, br, s, NH), 4.09 (2 H, q, J = 7.2 Hz, OCH_2), 4.03 (1 H, t, J = 7.2 Hz, PhC*H*), 2.29–3.10 (10 H, m, NCH_2, $CH_2C{=}O$), 1.39–2.09 (6 H, m, CCH_2C), 1.17 (3 H, t, J = 7.2 Hz, CH_3); mass m/z 321, 277, 235, 193, 161, 136, 128; exact mass m/z 321.249 (calcd for $C_{18}H_{31}N_3O_2$, 321.242).

The title compound **17** was converted to its triacetamide derivative with use of acetic anhydride–pyridine (1:1 ratio) at 25 °C for 1 day: TLC, R_f 0.28 (MeOH–$CHCl_3$, 1:10); IR ($CHCl_3$) 3410, 1748, 1652, 1543, 1435, 1385, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37 (5 H, s, aryl CH), 5.53 (1 H, t, J = 7.2 Hz, PhC*H*), 4.18 (2 H, q, J = 7.2 Hz, OCH_2), 2.83–3.52 (10 H, m, $NCH_2CH_2C{=}O$), 1.98, 2.03, 2.37 (9 H, three s, $CH_3C{=}O$), 1.01–1.53 (9 H, m, CCH_2C, O—CCH_3); mass m/z 447, 404, 358, 270, 169; exact mass m/z 447.270 (calcd for $C_{24}H_{37}N_3O_5$, 447.273).

The title compound **17** was also obtained by the direct hydrogenation of the crude **16** with platinum oxide. Thus, the intermediate **16** prepared from **9** (282 mg, 2 mmol) and ethyl phenylpropiolate (696 mg, 4 mmol) in ethanol (2 mL) in a similar manner was, without isolation, diluted with chloroform–ethanol (1:50 ratio, 18.4 mL) and hydrogenated over PtO_2 (60 mg) according to the procedure described above to give **17** (477 mg) in 74% yield from **9** after purification.

12-Phenyl-2,6,11-triazacyclotridecanone (7). A solution of tris(dimethylamino)borane (393 mg, 2.76 mmol) in xylene (4 mL, freshly distilled) was added to a stirred solution of the triamino ester **17** (804 mg, 2.5 mmol) in xylene (21 mL) at 25 °C to give the colorless solution,

which turned to the white suspension in about 30 s. Stirring was continued at 25 °C for 30 min, then under reflux for 3 h. Removal of the solvent and purification by column chromatography on silica gel (*i*-$PrNH_2$–MeOH–$CHCl_3$, 1:5:5) gave a mixture of **7** and **17**. Repurification with *i*-$PrNH_2$–MeOH–$CHCl_3$ (1:5:10, then 2:5:5) afforded the pure **7** (619 mg, 90% yield) as white crystals: TLC, R_f 0.37 (*i*-$PrNH_2$–MeOH–$CHCl_3$, 1:5:5); mp 132–133 °C (recrystallized from EtOAc)[9]; IR ($CHCl_3$) 3224, 1640, 1525, 1103 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.70 (1 H, br s, HNC=O), 7.37 (5 H, s, aryl CH), 4.01 (1 H, t, J = 7.0 Hz, PhC*H*N), 2.40 (2 H, d, J = 7.0 Hz, CH_2C=O), 2.30–4.19 (10 H, br m, CH_2N, NH), 1.15–2.07 (7 H, br m, CCH_2C, NH); mass m/z (%) 275 (12), 259 (18), 258 (100), 208 (15); exact mass m/z 275.207 (calcd for $C_{16}H_{25}N_3O$, 275.200).

The title compound **7** was converted to its diacetamide derivative with use of acetic anhydride–pyridine (1:1 ratio) at 25 °C for 1 day: TLC, R_f 0.34 (MeOH–$CHCl_3$, 1:9); IR ($CHCl_3$) 3367, 1640, 1430, 1370, 1318, 1220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (5 H, s, aryl CH), 5.53–5.93 (1 H, m, PhC*H*), 2.54–4.23 (8 H, br m, NCH_2), 2.12, 2.48 (2:1 ratio, 9 H, two s, CH_3C=O), 1.43–1.93 (6 H, m, CCH_2C); mass m/z 359, 316, 269; exact mass m/z 359.218 (calcd for $C_{20}H_{29}N_3O_3$, 359.221).

(±)-Celacinnine (2). A solution of *trans*-cinnamoyl chloride (109 mg, 0.65 mmol) in dichloromethane (2 mL) was added dropwise at −78 °C to a stirred solution of the lactam **7** (120 mg, 0.44 mmol) and 4-(dimethylamino)pyridine (150 mg, 1.23 mmol) in dichloromethane (20 mL). Stirring was continued at −78 °C for 2.5 h, then at −20 °C for 10 h. The reaction mixture was poured onto 14% ammonium hydroxide (10 mL) and extracted with dichloromethane three times. Purification of the concentrated crude product by column chromatography (MeOH–$CHCl_3$, 1:15) gave (±)-celacinnine (**2**) (172 mg, 97% yield) as a colorless oil: TLC, R_f 0.33 (MeOH–$CHCl_3$, 1:9); mp 178–181 °C (recrystallized from EtOAc–hexane) [lit.[4] mp 203–204 °C ($CHCl_3$–hexane)]; IR ($CHCl_3$) 3357, 1659, 1603, 1415, 1113 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.76 (1 H, d, J = 15.2 Hz, PhCH=C), 7.14–7.58 (10 H, m, aryl CH), 6.58 (1 H, d, J = 15.2 Hz, PhC=CH), 4.02 (1 H, t, J = 7.0 Hz, PhC*H*N), 2.94–3.91 (6 H, m, CH_2NC=O), 2.52 (2 H, d, J = 7.0 Hz, CH_2C=O), 2.34–2.71 (2 H, m, NCH_2), 1.21–2.18 (7 H, m, CCH_2C, NH); mass m/z (%) 405 (23), 274 (100), 260 (25), 160 (19), 146 (23), 131 (62); exact mass m/z 405.239 (calcd for $C_{25}H_{31}N_3O_2$, 405.242). TLC behaviors of the synthetic (±)-celacinnine with several solvent systems (MeOH–$CHCl_3$, 1:20; MeOH–EtOAc, 1:15; *i*-$PrNH_2$–ether, 1:20) are completely identical with those of the authentic (±)-celacinnine.[11]

Mild acetylation of **2** with use of acetic anhydride–pyridine (1:4 ratio) at 25 °C for 1 day furnished *N*-acetyl-(±)-celacinnine: TLC, R_f 0.32 (MeOH–EtOAc, 1:9); IR ($CHCl_3$) 3406, 1640, 1596, 1445, 1423, 1360, 1320, 1110, 967 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.76 (1 H, d, J = 15 Hz, PhCH=C), 7.07–7.58 (10 H, m, aryl CH), 6.87 (1 H, d, J = 15 Hz, PhC=CH), 5.71 (1 H, br d, J = 12 Hz, PhC*H*N), 2.64–4.55 (10 H, m, NCH_2, CH_2C=O), 2.46 (3 H, s, CH_3C=O), 1.43–1.91 (6 H, m, CCH_2C); mass m/z (%) 447 (39), 404 (68), 316 (50), 149 (100); exact mass m/z 447.256 (calcd for $C_{27}H_{33}N_3O_3$, 447.252).

(±)-Celabenzine (5). A solution of benzoyl chloride (42 mg, 0.3 mmol) in dichloromethane (2 mL) was added dropwise to a stirred solution of the lactam **7** (55 mg, 0.2 mmol) in dichloromethane (8 mL) in the presence of 4-(dimethylamino)pyridine (73 mg, 0.6 mmol) at −20 °C. Stirring was continued at −20 °C for 7 h, then at 0 °C for 1 day. The reaction mixture was worked up and purified as described for preparation of (±)-celacinnine to give (±)-celabenzine (**5**) (74 mg, 98% yield) as a colorless oil: TLC, R_f 0.40 (MeOH–$CHCl_3$, 1:9); mp 172–173 °C (recrystallized from EtOAc) [lit.[4] mp 156–158 °C (EtOAc)]; IR ($CHCl_3$) 3370, 1665, 1630, 1438, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.19–7.53 (10 H, m, aryl CH), 3.94 (1 H, t, J = 7.0 Hz, PhC*H*N), 2.83–3.80 (6 H, m, CH_2NC=O), 2.46 (2 H, d, J = 7 Hz, CH_2C=O), 2.30–2.67 (2 H, m, NCH_2), 1.10–2.17 (7 H, m, CCH_2C, NH); mass m/z (%) 379 (24), 274 (23), 146 (24), 106 (100); exact mass m/z 379.234 (calcd for $C_{23}H_{29}N_3O_2$, 379.226).

3-Furoyl Chloride. A mixture of 3-furoic acid (920 mg, 8.2 mmol) and thionyl chloride (3 mL) was heated to reflux for 1.5 h. Then excess thionyl chloride was removed, and the residue was distilled under reduced pressure to furnish 3-furoyl chloride (910 mg, 85% yield) as a colorless oil: bp 119–123 °C (62 mmHg, bath temperature);[13] ^1H NMR ($CDCl_3$) δ 6.84 (1 H, m, C(4)—H), 7.55 (1 H, t, J = 1.8 Hz, C(5)—H), 8.27 (1 H, d, J = 1.8 Hz, C(2)—H).

(±)-Celafurine (4). The lactam **7** (110 mg, 0.4 mmol) in dichloromethane (16 mL) was treated with 3-furoyl chloride (78 mg, 0.6 mmol) in dichloromethane (4 mL) in the presence of 4-(dimethylamino)pyridine (146 mg, 1.2 mmol) at −20 °C for 3 h, at 0 °C for 5 h, then at 25 °C for 10 h. The reaction was quenched in a similar manner. Purification by column chromatography (MeOH–$CHCl_3$, 1:5) gave (±)-celafurine (**4**) (142 mg, 96% yield) as a colorless oil: TLC, R_f 0.42 (MeOH–$CHCl_3$, 1:9); mp 151–152 °C (recrystallized from EtOAc) [lit.[4] mp 154–155 °C (EtOAc)]; IR ($CHCl_3$) 3355, 1665, 1625, 1440, 1320, 1170, 1113, 865 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.73 (1 H, d, J = 1.5 Hz, furyl CH), 7.45 (1 *H*, t, J = 1.5 Hz, furyl CH), 7.33 (5 H, m, aryl CH), 6.58 (1 H, d, J = 1.5 Hz, furyl CH), 3.98 (1 H, t, J = 7.2 Hz, PhC*H*N), 2.95–3.81 (6 H, m, CH_2NC=O), 2.28–2.72 (2 H, m, NCH_2), 2.49 (2 H, d, J = 7.2 Hz, CH_2C=O), 1.15–2.18 (7 H, m, NH, CCH_2C); mass m/z (%) 369 (65), 274 (31), 224 (32), 160 (24), 146 (50), 95 (100); exact mass m/z 369.201 (calcd for $C_{21}H_{27}N_3O_3$, 369.205).

(±)-Celallocinnine (3). A solution of **2** (30 mg) in benzene (1.5 mL) was irradiated for 35 h by an external UV lamp through the filter plate 0-504 (>300 nm). Benzene was evaporated, and the residue was purified with use of an analytical TLC plate (MeOH–AcOEt, 1:9) to give (±)-celallocinnine (**3**) (15 mg, 50% yield) in addition to the recovered (±)-celacinnine (**2**) (9 mg, 30% yield): TLC, R_f 0.40 (MeOH–AcOEt, 1:9); IR ($CHCl_3$) 3350, 1656, 1617, 1440, 1110, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20–7.53 (10 H, m, Aryl CH), 6.66 (1 H, d, J = 13.0 Hz, PhCH=), 6.05 (1 H, d, J = 13.0 Hz, —CH—C=O), 3.93 (1 H, t, J = 7.0 Hz, PhC*H*N), 2.47 (2 H, d, J = 7.0 Hz, CH_2C=O); mass m/z (%) 405 (11), 334 (7), 274 (25), 210 (18), 208 (23), 149 (64), 127 (100); exact mass m/z 405.246 (calcd for $C_{25}H_{31}N_3O_2$, 405.242).

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