Antimony-Templated Macrolactamization of Tetraamino Esters. Facile Synthesis of Macrocyclic Spermine Alkaloids, (±)-Buchnerine, (±)-Verbacine, (±)-Verbaskine, and (±)-Verbascenine

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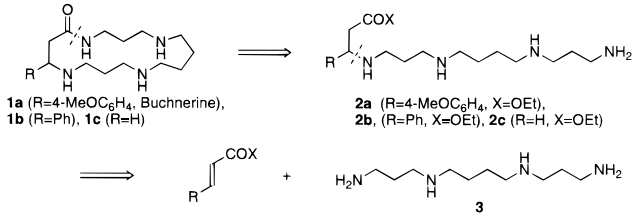
The macrocyclic lactams containing the biogenetic base spermine are of particular interest as synthetic targets for the organic chemist in view of the broad activity which has been established for spermine-containing compounds in biological systems and because of the structural complexity of the molecules themselves.[1] We have been interested in the possibility of metal-templated cyclization of spermine derivatives 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.[2] It was previously reported by Kimura *et al*. that the one-pot macrocyclization of tetramines with α,β-unsaturated esters slowly proceeds under reflux conditions in methanol, usually, for 2 or 3 weeks to afford the corresponding macrolactam in a moderate yield.[3] Unfortunately, they failed in an attempt to synthesize macrocyclic spermine alkaloids using a similar manner and almost no cyclization reaction occurred.[3g] Reported herein is a new synthetic strategy in which the key reaction of synthetic planning is a macrocyclization of long open chains with α- and ω-functional groups, taking advantage of an antimony-template effect.

(±)-Buchnerine (**1a**) is an attractive target for our present synthesis. This was isolated in 1993 by Lumbu and Hootelé from *Clerodendrum buchneri* (Verbenaceae)[4] and is characterized by the presence of a 17-membered ring reflecting spermine and 4-methoxycinnamoyl precursory units. The synthetic design was based on a strategy which can be summarized as follows (Scheme 1): (1) A linear tetraamino ester such as **2a** was envisaged as an ideal progenitor of macrocyclic spermine skeleton **1a**. (2) Spermine (**3**), which is commercially available, could be provided as a basic unit in **1a**. (3) A 17-membered ring of **1a** could be elaborated *via* the metal-templated cyclization of **2a**.

Scheme 1



Selected results in macrocyclization of tetraamino esters are listed 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 6),[2] no lactams were obtained in the cyclization of **2c** (entry 2).[5] Among several other organometallic reagents for the cyclization of tetraamino esters **2a**−**c** to 17-membered lactams **1a**−**c** screened, we found antimony(III) ethoxide to be quite effective (entries 3−5). A solution of the ester **2a** in dry, freshly distilled benzene was treated with antimony(III) ethoxide (1.2 equiv) 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 **1a** in 76% yield (entry 5); this was homogeneous by TLC, with IR, ^{1}H NMR, and mass spectra in accord with the assigned structure.[4] Since none of the polymerization or regioisomeric product was formed, the isolation of the lactam was simple. Although titanium(IV) ethoxide and zirconium(IV) isopropoxide were somewhat effective reagents (19% and 23% from **2c**, respectively), most of the tetraamino esters were decomposed to spermine and α,β-unsaturated ester by β-elimination.

The novel regioselective macrolactamization of tetraamino esters **2a**−**c** derived from spermine **3** with antimony(III) ethoxide can be ascribed to the metal template effect. Interestingly, antimony(III) ethoxide did not provide satisfactory results in the cyclization of triamino ester **5** derived from spermidine (entries 7 and 8). These results suggest that antimony(III) ion is a rather suitable size as a metal template of a 17-membered spermine macrolactam. Thus, the possible intermediates **4a**−**c** generated by transamination of antimony(III) ethoxide could reasonably be expected to undergo a facile, sterically driven cyclization to **1a**−**c**.[6,7] Nevertheless, we cannot exclude the possibility of a simple intramolecular hydrophilic interaction of tetraamino esters in a nonpolar solvent such as benzene.

The starting tetraamino ester **2a** was prepared in 61% overall yield by Michael addition of spermine **3** to ethyl 3-(4-methoxyphenyl)propiolate[8] and hydrogenation of the enamino group over platinum oxide in the presence of $CHCl_3$.[9] **2b** was also prepared in the same manner. On the other hand, **2c** could be directly prepared in 70% yield by Michael addition of spermine **3** to ethyl acrylate.

The present cyclization process provided crucial information leading to an unusually concise synthesis of other macrocyclic spermine alkaloids, (±)-verbacine (**7**),[10] (±)-verbaskine (**8**),[10,11] and (±)-verbascenine (**9**),[10,12] from a common intermediate **1b** (Scheme 2).

(1) Reviews: (a) Bachrach, U. *Function of Naturally Occurring Polyamines*; Academic Press: New York, 1973. (b) Hesse, M.; Schmid, H. Macrocyclic Spermidine and Spermine Alkaloids. In *International Review of Science*, Series II, Vol. 9; Hey, H. D., Wiesner, K., Eds.; Butterworth: London, 1976; p 265. (c) Badawi, M. M.; Bernauer, K.; Van den Broek, P.; Groger, D.; Guggisberg, A.; Johne, S.; Kompis, I.; Schneider, F.; Veith, H.-J.; Hesse, M.; Schmid, H. *Pure Appl. Chem.* **1973**, *33*, 81.

(2) We previously described that the use of boron-templated cyclization of triamino esters with tris(dimethylamino)borane is highly efficient as a key step in the total synthesis of macrocyclic spermidine alkaloids containing 13 members. (a) Yamamoto, H.; Maruoka, K. *J. Am. Chem. Soc.* **1981**, *103*, 6133. (b) Ishihara, K.; Kuroki, Y.; Yamamoto, H. *Synlett* **1995**, 41.

(3) (a) Machida, R.; Kimura, E.; Kodama, M. *Inorg. Chem.* **1983**, *22*, 2055. (b) Kimura, E.; Machida, R.; Kodama, M. *J. Am. Chem. Soc.* **1984**, *106*, 5497. (c) Kimura, E.; Koike, T.; Takahashi, M. *J. Chem. Soc., Chem. Commun.* **1985**, 385. (d) Kimura, E.; Koike, T.; Nada, H.; Iitaka, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 1322. (e) Kimura, E.; Yamaoka, M.; Morioka, M.; Koike, T. *Inorg. Chem.* **1986**, *25*, 3883. (f) Kimura, E.; Shionoya, M.; Mita, T.; Iitaka, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 1712. (g) Kimura, E.; Koike, T.; Uenishi, K.; Hediger, M.; Kuramoto, M.; Joko, S.; Arai, Y.; Kodama, M.; Iitaka, Y. *Inorg. Chem.* **1987**, *26*, 2975. (h) Kimura, E.; Joko, S.; Koike, T.; Kodama, M. *J. Am. Chem. Soc.* **1987**, *109*, 5528. (i) Kodama, M.; Anan, H.; Koike, T.; Kimura, E. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 4044. (j) Kimura, E.; Kotake, T.; Koike, M.; Shionoya, M.; Shiro, M. *Inorg. Chem.* **1990**, *29*, 4991. (k) Kimura, E.; Koike, T.; Shiota, T.; Iitaka, Y. *Inorg. Chem.* **1990**, *29*, 4621. (l) Kimura, E.; Shionoya, M.; Shiro, M. *Inorg. Chem.* **1991**, *30*, 4524.

(4) Lumbu, S.; Hootelé, C. *J. Nat. Prod.* **1993**, *56*, 1418.

(5) Tris(dimethylamino)borane, which has a tendency to form a tridentate complex, was not appropriate for a macrolactamization of tetraamino esters.

(6) It has been known that triorganoantimony(III) compounds have a strong tendency to form multidentate complexes. Thayer, J. S. *Organometallic Chemistry*; VCH Publishers, Inc.: New York, 1988; p 56.

(7) It has been known that treatment of $Sb(NMe_2)_3$ with CH_3CO_2Et at room temperature leads in a smooth reaction to $Sb(OEt)_3$ and CH_3CONMe_2. Krommes, P.; Lorberth, J. *J. Organomet. Chem.* **1975**, *97*, 59.

(8) Sakamoto, T.; Shiga, F.; Yasuhara, A.; Uchiyama, D.; Kondo, Y.; Yamanaka, H. *Synthesis* **1992**, 746.

(9) Secrist, J. A., III; Louge, M. W. *J. Org. Chem.* **1972**, *37*, 335. Palladium on charcoal is not effective for hydrogenation of the enamino group under comparable reaction conditions.[2a]

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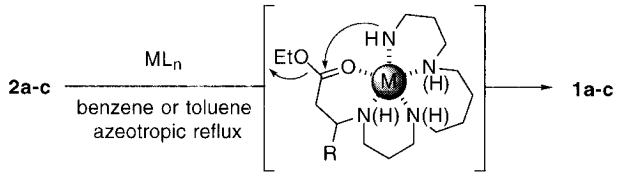
Table 1. Antimony-Templated Macrolactamization of Spermine Derivatives

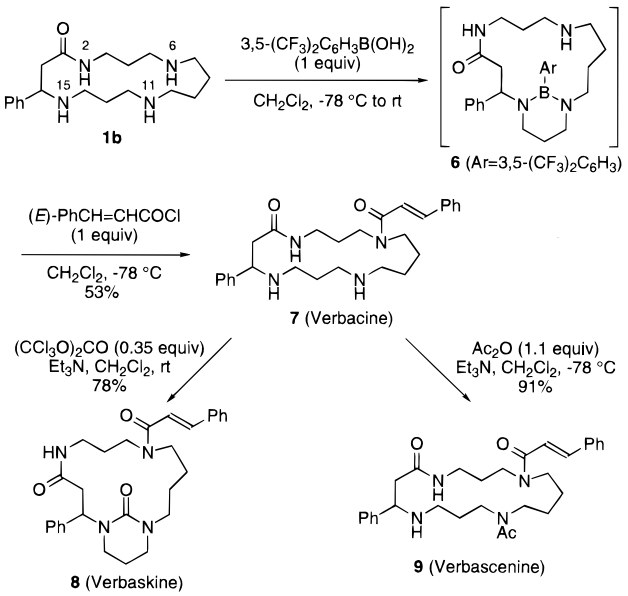


4a (R=4-MeOC$_6$H$_4$), **4b** (R=Ph), **4c** (R=H)

entry	amino ester	ML_n	conditions	yield (%)
1	**2c**	*a*	80 °C, 10 h	0[b]
2		$B(NMe_2)_3$[c]	60 °C, 48 h	0[d]
3		$Sb(OEt)_3$[e]	80 °C, 15 h	65
4	**2b**	$Sb(OEt)_3$[e]	80 °C, 9 h	90
5	**2a**	$Sb(OEt)_3$[e]	80 °C, 14 h	76
6	**5**[f]	$B(NMe_2)_3$[c]	145 °C, 8 h[g]	74[g]
7		$Sb(OEt)_3$[c]	80 °C, 19.5 h	0[b]
8		$Sb(OEt)_3$[c]	110 °C, 51 h	38[h]

[a] No addition of reagents. [b] No reaction. [c] 2 equiv of reagent was used. [d] Starting material decomposed. [e] 1.2 equiv of reagent was used. [f] Methyl 3-phenyl-4,8,13-triazatridecanoate (**5**). [g] Xylene was used as solvent. See ref 2b. [h] Some unknown byproducts were included.

Scheme 2



Synthesis of verbacine **7** from **1b** required the selective acylation at N-6 of **1b** (Scheme 2). This was accomplished by addition of cinnamoyl chloride to a 1:1 mixed solution of **1b** and (3,5-bis(trifluoromethyl)phenyl)boronic acid in dichloromethane to give **7** as the major product in 53% yield, together with recovered **1b**, the monocinnamoyl amide acylated at N-11 of **1b**, and the dicinnamoyl amide acylated at both N-6 and N-11 of **1b**.[13] Analytical data of the synthetic verbacine were identical, in all respects, with those reported in the literature.[10] The acylation of **1b** with acyl chloride or acid anhydride in the absence of boronic acid gave only the dicinnamoyl amide. 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-ring intermediate **6** generated by complexation of **1b** with the boronic acid at N-11 and N-15 could reasonably be expected to undergo acylation with free amino group at N-6.[14]

Verbacine (**7**) was readily transformed to verbaskine (**8**), which contained a cyclic urea unit, in good yield by treatment with triphosgene in dichloromethane. This result clearly indicated that **1b** was not acylated at N-11 but at N-6. Also, **7** was transformed to verbascenine (**9**) in almost quantitative yield by selective acetylation at N-11 of **1b**. This was readily accomplished with 1 equiv of acetic anhydride in the presence of triethylamine at −78 °C. Analytical data of **8** and **9** were completely identical with those reported in the literature, respectively.[10,11b,12a]

The efficiency of the antimony(III) ethoxide as an intermolecular amidation catalyst was also studied, and the results are summarized below.[7,15] The reaction was carried out with various structurally diverse methyl esters or carboxylic acids and amines in the presence of 5−10 mol % of antimony(III) ethoxide under reflux conditions in toluene ($C_{11}H_{23}CONHC_7H_{15}$, 91%; $C_{11}H_{23}CONHBn$, 90%; $PhCONHC_7H_{15}$, 84%; c-C_6H_{11}-$CONHC_7H_{15}$, 86%; $C_{11}H_{23}CONH$-c-C_6H_{11}, 64%; c-C_6H_{11}-CONH-c-C_6H_{11}, 47%; 1-(4-phenylbutyryl)-3,5-piperidine, 44%). In the reaction 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 (86% yield amides, the ratio of 95:5). This characteristic of antimony(III) ethoxide is reflected in the exclusive regioselectivity in the above macrolactamization. Methyl cinnamate did not give Michael adduct, but the corresponding amide in high yield ((*E*)-$PhCH{=}CHCONHC_7H_{15}$, 86%).

In conclusion, 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 tetraamino ester is covalently or coordinately attached to the antimony before the final cyclization step. *As far as we know, this is the first example of the use of antimony(III) alkoxide as a promoter of amidation.*[7,15,16]

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Supporting Information Available: Experimental details for antimony(III)-templated macrolactamization of **2a**−**c**, regioselective monoacylation of **1b** to **7**, and characterization data for **1a**−**c** (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(10) **7** was isolated in 1995 by Drandarov from *Verbascum pseudonobile* Stoj. et Stef. (*Scrophulariaceae*). Unfortunately, it was found that **8** is not a natural substance, but an artifact produced from **7** by reaction with the phosgene in the chloroform used as extractant. Drandarov, K. *Tetrahedron Lett.* **1995**, *36*, 617.

(11) (a) Ninova, P.; Abdusamatov, A.; Yunusov, S. Yu. *Khim. Prir. Soedin.* **1971**, 540. (b) Koblicová, Z.; Turecek, F.; Ninova, P.; Trojánek, J.; Bláha, K. *Tetrahedron Lett.* **1983**, *24*, 4381.

(12) **9** was isolated in 1982 by Hesse and his colleagues from *Verbascum phoeniceum L.* and *Verbascum nigrum L.* (a) Seifert, K.; Johne, S.; Hesse, M. *Helv. Chim. Acta* **1982**, *65*, 2540. For total synthesis of (±)-**9**, see: (b) Wasserman, H. H.; Robinson, R. P. *Tetrahedron Lett.* **1983**, *24*, 3669.

(13) Although similar results were given in the use of methylboronic acid and phenylboronic acid, regioselectivity and chemical yield were best when (3,5-bis(trifluoromethyl)phenyl)boronic acid was used.

(14) We failed in an attempt to construct a cyclic urea unit bridged at N-11 and N-15 regioselectively by treatment of **1b** with triphosgene.

(15) For references on amidation reactions using triphenylantimony dicarboxylate or triphenylstibine oxide, see: (a) Nomura, R.; Wada, T.; Yamada, Y.; Matsuda, H. *Chem. Lett.* **1986**, 1901. (b) Nomura, R.; Nakano, T.; Yamada, Y.; Matsuda, H. *J. Org. Chem.* **1991**, *56*, 4076.

(16) For a review on synthetic applications of organoantimony compounds, see: Huang, Y.-Z. *Acc. Chem. Res.* **1992**, *25*, 182.