Asymmetric Syntheses of the Macrocyclic Spermine Alkaloids (−)-(*S*)-Protoverbine, (−)-(*S*)-Buchnerine, and Their Naturally Occurring Congenial Alkaloids

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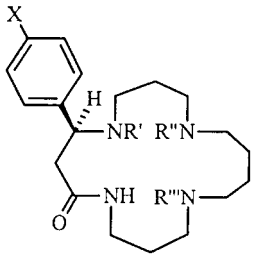
Dedicated to Prof. *Hans-Jürgen Hansen* on the occasion of his 65th birthday

Asymmetric syntheses of the following 17-membered macrocyclic spermine alkaloids are presented: (−)-(*S*)-protoverbine (=(8*S*)-8-phenyl-1,5,9,13-tetraazacycloheptadecane-6-one; **1**), (+)-(*S*)-protomethine (=(2*S*)-2-phenyl-1,5,9,14-tetraazabicyclo[12.3.1]octadecan-4-one; **2**), (−)-(*S*)-buchnerine (=(8*S*)-8-(4-methoxyphenyl)-1,5,9,13-tetraazacycloheptadecane-6-one; **8**), (+)-(*S*)-verbamethine (=(+)-(2*S*)-9-[(*E*)-phenylprop-2-enoyl]-2-phenyl-1,5,9,14-tetraazabicyclo[12.3.1]octadecan-4-one; **4**), (−)-(*S*)-verbacine (=(−)-(8*S*)-1-[(*E*)-phenylprop-2-enoyl]-8-phenyl-1,5,9,13-tetraazacycloheptadecan-6-one; **3**), (−)-(*S*)-verbasikrine (=(−)-(8*S*)-1-[(*E*)-3-(4-methoxyphenyl)prop-2-enoyl]-8-phenyl-1,5,9,13-tetraazacycloheptadecan-6-one; **26**), (−)-(*S*)-isoverbasikrine (=(−)-(8*S*)-1-[(*Z*)-3-(4-methoxyphenyl)prop-2-enoyl]-8-phenyl-1,5,9,13-tetraazacycloheptadecan-6-one; **25**), (+)-(*S*)-verbamekrine (=(+)-(2*S*)-9-[(*E*)-3-(4-methoxyphenyl)prop-2-enoyl]-2-phenyl-1,5,9,14-tetraazabicyclo[12.3.1]octadecan-4-one; **23**), and (+)-(*S*)-isoverbamekrine (=(+)-(2*S*)-9-[(*Z*)-3-(4-methoxyphenyl)prop-2-enoyl]-2-phenyl-1,5,9,14-tetraazabicyclo[12.3.1]octadecan-4-one; **24**). Effective methods for ^{1}H-NMR determination of the enantiomeric purity in which (*S*)-2-hydroxy-2-phenylacetic acid and (*S*)-2-acetoxy-2-phenylacetic acid are used as shift reagents for **1**, **8**, and related macrocyclic alkaloids are described.

Introduction. – The 17-membered tetraazamacrolactam alkaloids (−)-(*S*)-protoverbine (**1**) and (+)-(*S*)-protomethine (**2**) are the precursors in the biogenesis of a large group of alkaloids isolated from *Verbascum pseudonobile* STOJ. *et* STEF. (Scrophulariaceae) [1–5], *V. phoeniceum* L. [6][7], and *Incarvillea sinensis* LAM. (Bignoniaceae) [8] (compounds **3**–**7** and their derivatives; *Table*). To the same type of alkaloids belong the closely related (−)-(*S*)-buchnerine (**8**) and its (*S*)-*N*(1)-[(*Z*)-4-methoxycinnamoyl] derivative (**9**), both isolated from *Clerodendrum buchneri* GÜRKE (Verbenaceae) [9] (*Table*), (*S*)-prelandrine (hydroxylated derivative of **1**, detected in the roots of *Aphelandra squarrosa* NEES (Acanthaceae) [10]), and (*S*)-dihydroxyverbacine. (*S*)-Prelandrine and (*S*)-dihydroxyverbacine were recently shown to act as biogenetic precursors in the biogenesis of the bicyclic spermine alkaloids aphelandrine and orantine [11].

The (*S*)-configuration of all these alkaloids (*Table*) have been determined by chemical and chiroptic ($[\alpha]_D$, CD) correlations with (−)-(*S*)-verbascenine (**6**) [6] and a number of similar synthetic compounds [1–5][7][12]. Recently, (+)-isoverbamethine ((*Z*)-isomer of verbamethine (**4**)) was mentioned in the literature under the trivial name incasine C and was erroneously assigned the (*R*)-configuration [8]. On the other hand, the absolute configuration of (−)-buchnerine (**8**) and its *N*(1)-[(*Z*)-4-methoxycinnamoyl] derivative **9** have been proposed to be (*S*), but this contention has not been corroborated by any chemical or chiroptic evidence [9].

Table. *Selected Members of the Protoverbine Class of Macrocyclic Spermine Alkaloids*



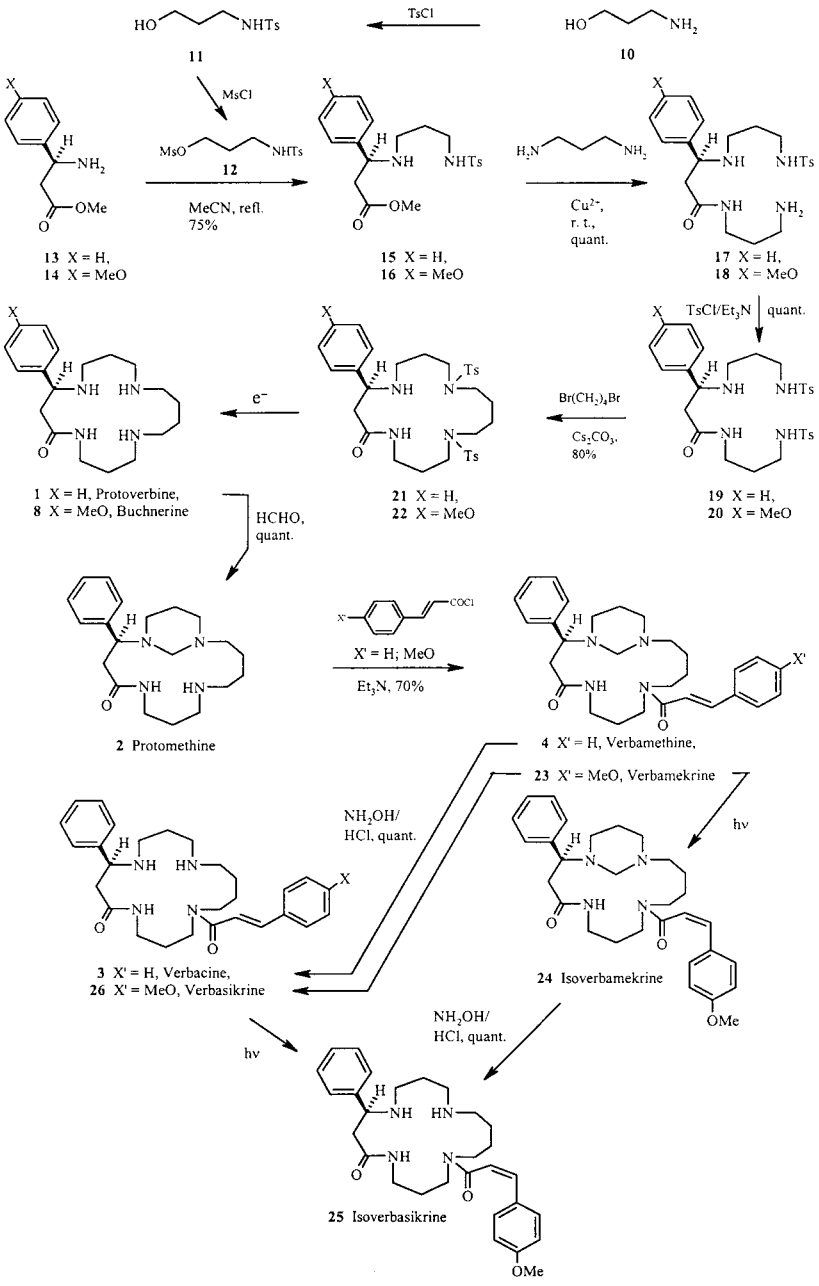
Compound	X	R′	R″	R‴
Protoverbine (**1**)	H	H	H	H
Protomethine (**2**)	H	$-CH_2-$		H
Verbacine (**3**)	H	H	H	(*E*)-$C_6H_5-CH=CH-CO$
Verbamethine (**4**)	H	$-CH_2-$		(*E*)-$C_6H_5-CH=CH-CO$
Verdoline (incasine B′) (**5**)	H	$\overset{+}{CH}$		(*E*)-$C_6H_5-CH=CH-CO$
Verbascenine (**6**)	H	H	MeCO	(*E*)-$C_6H_5-CH=CH-CO$
Verbamedine (**7**)	H	H	CHO	(*E*)-$C_6H_5-CH=CH-CO$
Buchnerine (**8**)	MeO	H	H	H
9	MeO	H	H	(*Z*)-4-MeO$-C_6H_5-CH=CH-CO$

The open question about the absolute configuration of (−)-buchnerine (**8**) and the literature discrepancies concerning the absolute configuration of (+)-isoverbamethine (incasine C) motivated us to develop an asymmetric synthesis of this type of alkaloids, starting from known chiral precursors of established absolute configuration.

Results and Discussion. – (±)-Protoverbine (**1**) and (±)-buchnerine (**8**) were synthesized earlier by antimony-template macrolactamization of the corresponding spermine-derived tetraazaamino esters (ethyl (±)-3-{[3-({4-[(3-aminopropyl)amino]-butyl}amino)propyl]amino}-3-phenylpropanoate and ethyl (±)-3-{[3-({4-[(3-amino-propyl)amino]butyl}amino)propyl]amino}-3-(4-methoxyphenyl)propanoate) [13]. An alternative synthesis of (±)-protoverbine (**1**), involving stepwise formation of the macrocycle was developed recently [1].

The method published in [1] allowed (*S*)-protoverbine (**1**) to be prepared starting from methyl (−)-(*S*)-3-amino-3-phenylpropanoate (**13**), which is easily obtained in enantiomerically pure form by a published procedure [14] (*Scheme 1*). By consecutive *N*-tosylation (to compound **11**, [15]) and *O*-mesylation of 3-aminopropan-1-ol (**10**), the reagent **12** was prepared and used for the *N*-alkylation of (−)-(*S*)-**13** to its *N*-(3-tosylamino)propane derivative (−)-(*S*)-**15**. The Cu^{2+}-catalyzed aminolysis of the methyl ester (−)-(*S*)-**15** with propane-1,3-diamine yielded the tetramine (−)-(*S*)-**17** almost quantitatively. An additional tosylation of compound **17** gave the ditosylated compound (−)-(*S*)-**19**, which was macrocyclized with 1,4-dibromobutane in DMF in the presence of Cs_2CO_3, by an established procedure [1] to give the *N*(1),*N*(13)-ditosylated derivative of (*S*)-protoverbine (**21**) in very good yield. The detosylation of compound (−)-(*S*)-**21** was achieved by the mild electrolytic method published in [1][16] to give (−)-(*S*)-protoverbine (**1**) in excellent yield.

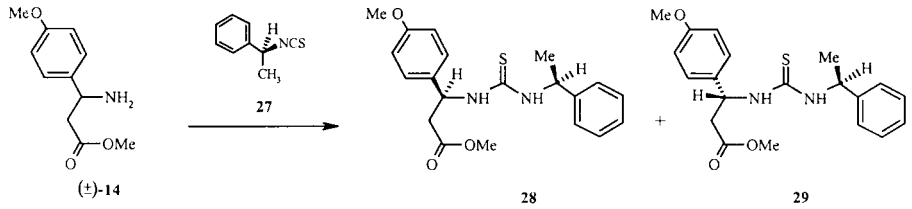
Scheme 1


TsCl
MsCl
MeCN, refl.
75%
Cu2+,
r. t.,
quant.
TsCl/Et3N
quant.
Br(CH2)4Br
Cs2CO3,
80%
e−
HCHO,
quant.
X' = H; MeO
Et3N, 70%
NH2OH/
HCl, quant.
hv
NH2OH/
HCl, quant.
hv
11
10
12
13 X = H,
14 X = MeO
15 X = H,
16 X = MeO
17 X = H,
18 X = MeO
19 X = H,
20 X = MeO
21 X = H,
22 X = MeO
1 X = H, Protoverbine,
8 X = MeO, Buchnerine
2 Protomethine
4 X' = H, Verbamethine,
23 X' = MeO, Verbamekrine
3 X' = H, Verbacine,
26 X' = MeO, Verbasikrine
24 Isoverbamekrine
25 Isoverbasikrine

Naturally, the synthetic pathway described above, starting with methyl (*S*)-3-amino-3-(4-methoxyphenyl)propanoate (**14**) instead of compound **13**, also allows the (*S*)-buchnerine (4′-MeO-protoverbine; **8**) to be prepared. Earlier, methyl (*R*)-3-amino-3-(4-methoxyphenyl)propanoate ((−)-(*R*)-**14**) was prepared asymmetrically in six steps (20% overall yield) in the course of the synthesis of (+)-jasplakinolide [17]. Here, we report a convenient procedure for large-scale preparation of both (+)-(*S*)-**14** and (−)-(*R*)-**14**. To this end, (±)-3-amino-3-(4-methoxyphenyl)propanoic acid, obtained by the method of *Johnson* and *Livak* [18], was transformed into its methyl ester (±)-**14**, which was resolved by consecutive recrystallizations of its (−)-D- and (+)-L-tartrate salts from 96% aq. EtOH[1]) to give both (+)-(*S*)-**14** and (−)-(*R*)-**14** in 90% ee.

The absolute configuration of (−)-(*R*)-3-amino-3-(4-methoxyphenyl)propanoic acid and its methyl ester (−)-(*R*)-**14** have been determined earlier [17][19]. Unfortunately, we could not reproduce the published specific rotation value ($[\alpha]_D = -91.5$) [17a] for the hydrochloride of (−)-(*R*)-**14**. Instead of the reported value of + 91.5, for the hydrochloride of (+)-(*S*)-**14**, we measured $[\alpha]_D = +9$. Using a recently published procedure for ^{1}H-NMR determination of the optical purity of chiral amines and aminoesters [20] after derivatization with (*S*)-α-phenylethyl isothiocyanate (**27**) to the corresponding thiourea derivatives **28** and **29** (*Scheme 2*), we established the enantiomeric purity (90% ee) of (+)-(*S*)-**14**, prepared by the procedure described herein. Thus, the reported $[\alpha]_D$ value (− 91.5) [17a] for the hydrochloride of (−)-(*R*)-**14** is obviously in error and should be changed to − 9.15.

Scheme 2

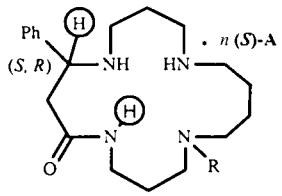


From (+)-(*S*)-**14**, by the synthetic pathway described above for (−)-(*S*)-protoverbine (**1**), *via* the intermediates **16**, **18**, **20**, and **22** (*Scheme 1*), (−)-(*S*)-buchnerine (**8**) was obtained in 60% overall yield. The synthetic (−)-(*S*)-buchnerine (**8**) is in all aspects identical to the natural one. Its $[\alpha]_D = -25.5$ value confirms the (*S*)-configuration of the natural alkaloid ($[\alpha]_D = -26$) postulated earlier [9].

(*S*)-2-Hydroxy-2-phenylacetic acid (mandelic acid) and (*S*)-2-acetoxy-2-phenylacetic acid (*O*-Ac-mandelic acid), both commercially available, have been used as shift reagents for the ^{1}H-NMR determination of the optical purity of different chiral amines [21]. With 1 equiv. of (*S*)-2-hydroxy-2-phenylacetic acid in $CDCl_3$, the ^{1}H-NMR signals of the lactam NH of the diastereoisomeric salts of (*S*)- and (*R*)-enantiomers of protoverbine (**1**) and buchnerine (**8**) are nonequivalent and appear as broad *triplets* at

[1]) The presence of 4% H_2O in the solvent is crucial for the resolution. From abs. EtOH or MeOH, the diastereoisomeric tartrates of both enantiomers crystallize together.

ca. 8.1 ppm of ((*S*)-isomer) and 7.9 ppm ((*R*)-isomer), separated well enough for a determination of the optical purity (*Fig. 1,a*). However, mandelic acid is not an effective shift reagent for the *N*(1)-acylated naturally occurring derivatives of protoverbine (**1**) and buchnerine (**8**), namely the verbacine (**3**) type alkaloids.



a: R = H, **A** = (*S*)-2-hydroxy-2-phenylacetic acid, *n* = 1.

b: R = H, **A** = (*S*)-2-acetoxy-2-phenylacetic acid, *n* = 4.

c: R = COCH=CHPh, **A** = (*S*)-2-acetoxy-2-phenylacetic acid, *n* = 3.

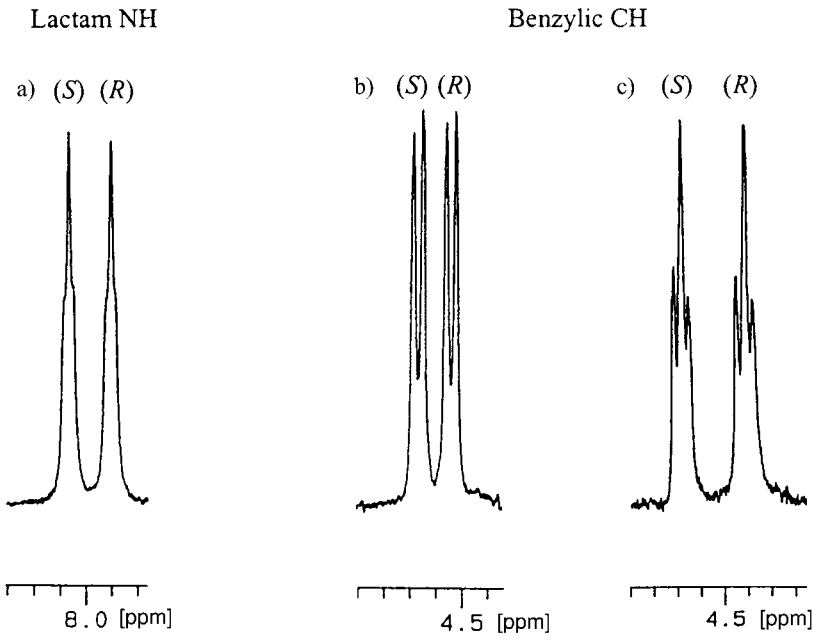


Fig. 1. *The* ^{1}*H-NMR* (300 MHz, $CDCl_3$ *nonequivalence of the lactam protons* (*a*) *and the benzylic protons* (*b*) *of the diastereoisomeric salts of protoverbine* (**1**) *with 1 equiv. of* (S)*-2-hydroxy-2-phenylacetic acid* (*a*) *and 4 equiv. of* (S)*-2-acetoxy-2-phenylacetic acid* (*b*), *and the benzylic proton of verbacine* (**3**) *with 3 equiv. of* (S)*-2-acetoxy-2-phenylacetic acid* (*c*)

With 4 equiv. of (*S*)-2-acetoxy-2-phenylacetic acid in $CDCl_3$ as a shift reagent, the signals of the benzylic H-atoms of the fully protonated (*S*)- and (*R*)-enantiomers of protoverbine (**1**) and buchnerine (**8**), appear as sharp *doublets* at *ca.* 4.65 ppm ((*S*)-isomer) and 4.55 ppm ((*R*)-isomer), and are, thus, well-separated for determination of the optical purity (*Fig. 1,b*). Moreover, when used in a molar excess (3 equiv.) for full protonation, (*S*)-2-acetoxy-2-phenylacetic acid is an effective shift reagent also for alkaloids of the verbacine (**3**) type (*Fig. 1,c*). Thus, mandelic acid and its *O*-acetyl

derivative appear to be very convenient shift reagents for the ^{1}H-NMR determination of the enantiomeric purity of macrocyclic polyamine alkaloids[2])[3]). As analyzed by these methods, the synthetically prepared (*S*)-protoverbine (**1**) and (*S*)-buchnerine (**8**) show retention of the optical purity of the starting chiral aminoesters **13** and **14** (90% ee), which is evidence for lack of racemization during synthesis. The natural (*S*)-protoverbine (**1**) and (*S*)-verbacine (**3**) exhibit 100% ee.

The CD spectra of (−)-(*S*)-protoverbine (**1**) and (−)-(*S*)-buchnerine (**8**) are shown in *Fig. 2*. Of note is that the ^1L_b *Cotton* effects of (−)-(*S*)-protoverbine (**1**) (between 250 and 275 nm) and (−)-(*S*)-buchnerine (**8**) (between 245 and 290 nm) have opposite sign, although the compounds have the same configuration. Such a reversal of chiroptical behavior of chiral phenylalkylamines with *ortho*- and/or *para*-substituted benzene chromophores directly attached to the chiral center has been studied [23]. When the substituent is an atom or group having a positive spectroscopic moment, such as Me, Cl, Br, OH, or MeO, as in the case of (−)-(*S*)-buchnerine (**8**), the chiral compound shows ^1L_b *Cotton* effects of sign opposite to that of its unsubstituted parent (−)-(*S*)-protoverbine (**1**) [23].

The strong plane curves below 245 nm (*Fig. 2*) are result of overlap of the elipticities originating from the aromatic chromophore (^1L_a $\pi \rightarrow \pi^*$ absorption transition with λ_{max} of *ca.* 200 nm) and the lactam (amide) chromophore ($n \rightarrow \pi^*$ transition with λ_{max} of *ca.* 220 nm), of which the second predominates. The registered CD spectra of (−)-(*S*)-protoverbine (**1**) and (−)-(*S*)-buchnerine (**8**) in this region have negative sign due to the similar chiral environments around the lactam chromophore in both constitutional analogs.

With 1 equiv. of HCHO, (−)-(*S*)-protoverbine (**1**) was transformed quantitatively to (+)-(*S*)-protomethine (**2**). Acylation of **2** at N(1) with (*E*)-phenylpropenoyl chloride led to the formation of (+)-(*S*)-verbamethine (**4**), which, by mild acid hydrolysis in the presence of NH_2OH, gave (−)-(*S*)-verbacine (**3**) quantitatively.

Similarly, starting from (+)-(*S*)-protomethine (**2**) with (*E*)-3-(4-methoxyphenyl)-propenoyl chloride as the acylating agent, the recently isolated (*S*)-verbamekrine (**23**) and (*S*)-verbasikrine (**26**) were prepared. Photoisomerization of (+)-(*S*)-verbamekrine (**23**) and (+)-(*S*)-verbasikrine (**26**) by irradiation of a MeOH soln. at 365 nm led to almost quantitative formation of (+)-(*S*)-isoverbamekrine (**24**) and (−)-(*S*)-isoverbasikrine (**25**).

Photoisomerization of (+)-(*S*)-verbamethine (**4**) by irradiation in MeOH soln. at 365 nm leads to (+)-(*S*)-isoverbamethine (incasine C) [2][12]. On the other hand, catalytic hydrogenation of either (+)-(*S*)-isoverbamethine (incasine C) or (+)-(*S*)-verbamethine (**4**) gives the same dihydro derivative (+)-(*S*)-dihydroverbamethine (dihydroincasine C, [12]). Thus, the (*S*)-configuration of (+)-(*S*)-isoverbamethine (incasine C) is unambiguously confirmed as the correct one.

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[2]) (*S*)-2-Hydroxy-2-phenylacetic acid was successfully used also for the determination of the optical purity of the naturally occurring *C*(8)-alkyl substituted analogues of protoverbine (**1**) and buchnerine (**8**), members of the budmunchiamine group of macrocyclic spermine alkaloids [22].

[3]) (*S*)-2-Hydroxy-2-phenylacetic acid and (*S*)-2-acetoxy-2-phenylacetic acid are not effective shift reagents for the ^{1}H-NMR determination of the enantiomeric purity of the aminoesters **13** and **14**.

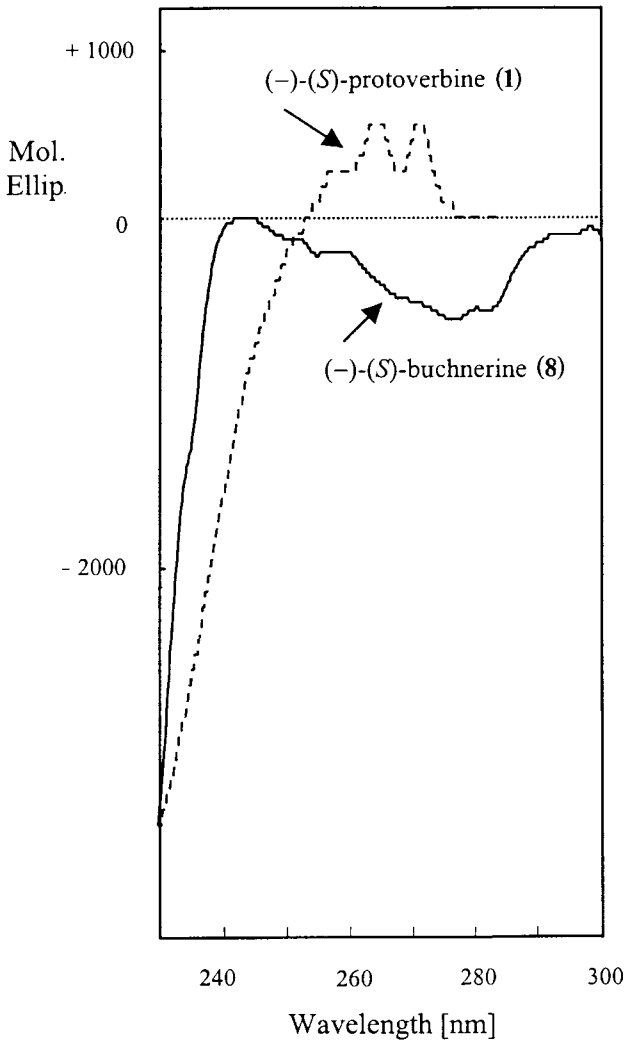

Fig. 2. *CD Spectra of (–)-(*S*)-protoverbine* (**1**) *and (–)-(*S*)-buchnerine* (**8**)

From (–)-(*S*)-buchnerine, prepared by the method described herein, were recently synthesized (–)-(*S*)-prelandrine [10] and (–)-(*S*)-dihydroxyverbacine [11a], both of which are biogenetic precursors of the macrobicyclic spermine alkaloids aphelandrine and orantine [11]. A recent biomimetic chemical study indicates that (–)-(*S*)-dihydroxyverbacine is a potential precursor also in the biogenesis of the macrobicyclic spermine alkaloid chaenorpine [24].

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Experimental Part

General. TLC: *Merck* precoated plates *Kieselgel 60 F_{254}*; detection by *Schlittler*'s (potassium iodoplatinate) [25] and *Dragendorff*'s (No. *D 156a* in [26]) reagents. CC: *Kieselgel 60* (70–230 mesh) from *Merck*. Optical rotation: *Perkin-Elmer 241* polarimeter. ^{1}H-NMR: *Bruker ARX-300*. ^{13}C-NMR: *Bruker ARX-300* (75 MHz); chemical shifts in ppm (δ scale) rel. and $CDCl_3$ as solvent, TMS as internal standard, r.t. CI-MS (NH_3 as reactant gas): *Finnigan MAT 90*. ESI-MS: *Finnigan TSQ-700* mass spectrometer.

Methyl (±)-3-Amino-3-(4-methoxyphenyl)propanoate (*rac*-**14**). A soln. of 7.2 g (±)-3-amino-3-(4-methoxyphenyl)propanoic acid, prepared by a published method [18], in 100 ml sat. methanolic HCl soln. was refluxed 1 h, then the solvent was evaporated. The glasslike residue was dissolved in H_2O, the soln. was washed with $CHCl_3$, saturated with solid K_2CO_3, and extracted with $CHCl_3$. The extract was washed with the minimal amount of H_2O, dried (Na_2SO_4), and evaporated to yield 7 g (87%) of **14** as an oil, which was used without further purification. TLC ($CHCl_3$/MeOH 9:1): R_f 0.7. ^{1}H-NMR ($CDCl_3$): 7.27 (*d*, *J* = 8.5, 2 arom. H); 6.86 (*d*, *J* = 8.7, 2 arom. H); 4.37 (*t*, *J* = 6.8, PhC*H*N); 3.78 (*s*, MeO); 3.67 (*s*, COOMe); 2.63 (*d*, *J* = 6.8, CH_2COOMe); 1.9 (*s*, NH_2). ^{13}C-NMR: 172.36 (C=O); 158.76, 136.63 (arom. quat. C); 127.11, 113.86 (arom. CH); 55.13 (MeO); 51.87 (COO*Me*); 51.46 (Ph*C*N); 43.89 (CN*C*H_2COOMe). CI-MS: 210 (32, $[M+H]^+$); 193 (100, $[M+H-NH_3]^+$).

*Methyl (+)-(3*S*)-3-Amino-3-(4-methoxyphenyl)propanoate* (**14**). Hot solns of 4.6 g (0.03 mol) (+)-L-tartaric acid in 60 ml 96% EtOH and 6.34 g (0.03 mol) (±)-**14** in 40 ml 96% EtOH were mixed, and the soln. was kept at r.t. overnight. The crystals were removed by filtration, washed with abs. EtOH, and dried to yield 4.77 g of the L-tartrate of the partly enriched (−)-(*R*)-**14** (60% ee)[4]. The mother liquor was evaporated. The residual foam (6.5 g) was dissolved in H_2O, alkalinized (saturated) with K_2CO_3, and extracted with $CHCl_3$. The org. layer was washed once with H_2O, dried (Na_2SO_4), and evaporated to yield 3.78 g (89%) of the free base of the partly enriched (*S*)-**14**, which was dissolved in 50 ml 96% EtOH. To this soln. was added 2.46 g (−)-D-tartaric acid, and the mixture was boiled until the acid was completely dissolved. Then the soln. was kept at r.t. overnight. The crystals were removed by filtration, washed with 96% EtOH, and dried to yield 3.92 g D-tartrate of (*S*)-**14**. For the preparation of the free base, the tartrate of (+)-(*S*)-**14** was dissolved in H_2O, the soln. was alkalinized (K_2CO_3), extracted ($CHCl_3$), washed (H_2O), dried (Na_2SO_4), and evaporated. **4**: Yield 65%. $[\alpha]_D = +3$ (*c* = 1.5, MeOH). The free base of (+)-(*S*)-**14** was transformed to its hydrochloride in MeOH with methanolic soln. of HCl and further evaporation of the solvent. Amorphous glasslike solid. $[\alpha]_D = +9$ (*c* = 1.43, MeOH)[5]).

*Methyl (*S*)- and (*R*)-3-(4-Methoxyphenyl)-3-{*N*′-[(*S*)-1-methylethyl]ureido}propanoate* (**28**) and **29** resp.). To a soln. of 74 mg (0.35 mmol) (*S*)-**14** (or (*R*)-**14**) in 0.5 ml EtOH was added a soln. of 57 mg (0.34 mmol) *(S)-α-phenylethyl isotiocyanate* (**27**), prepared by a published method [20] in 0.5 ml EtOH. The mixture was heated at 60° for 1 h, then the solvent was evaporated. The residue was purified by CC (CH_2Cl_2/MeCN 10:0.25) to give 120 mg (94%) of colorless glass-like solid.

Data of **28**: TLC (CH_2Cl_2/MeCN 10:0.25): R_f 0.37. ^{1}H-NMR: 7.45–6.5 (*m*, 9 arom. H, 2 NH); 5.7 (br. *s*, PhC*H*N); 4.92 (br. *s*, PhC*H*N); 3.73 (*s*, MeO); 3.58 (*s*, COOMe); 2.85 (*d*, *J* = 5, CH_2); 1.5 (*d*, *J* = 7, PhCH*Me*). ^{13}C-NMR: 179.9 (C=S); 171.8 (C=O); 158.7, 142.16, 131.59 (arom. quat. C); 128.95, 127.67, 126.87, 125.85, 113.87 (arom. CH); 55.08 (MeO); 54.13 (COO*Me*); 53.81, 51.74 (Ph*C*HN); 39.79 (PhCN*C*H_2COOMe); 23.38 (PhCH*Me*). CI-MS: 373 ($[M+H]^+$).

Data of **29**: TLC (CH_2Cl_2/MeCN 10:0.25): R_f 0.34. ^{1}H-NMR: 7.45–6.5 (*m*, 9 arom. H, 2 NH); 5.6 (br. *s*, PhC*H*N); 5.0 (br. *s*, PhC*H*N); 3.76 (*s*, MeO); 3.49 (*s*, COOMe); 2.9, 2.88 (2*d*, *J* = 16, 1 H, CH_2); 2.59, 2.57 (2*d*, *J* = 16, 1 H, CH_2); 1.44 (*d*, *J* = 7, PhCH*Me*). ^{13}C-NMR: 180.3 (C=S); 171.42 (C=O); 158.99, 142.06, 131.83 (arom. quat. C); 128.79, 127.62, 127.36, 125.85, 114.07 (arom. CH); 55.14 (MeO); 54.19 (COO*Me*); 53.75, 51.65 (Ph*C*HN); 39.51 (CH_2); 23.06 (PhCHMe). CI-MS: 373 ($[M+H]^+$).

4-Methyl-N-*{3-[(methylsulfonyl)oxy]propyl}benzenesulfonamide* (**12**). To a soln. of 1.5 g (6.5 mmol) of compound N-*(3-hydroxypropyl)-4-methylbenzenesulfonamide* (**11**; prepared by a published method [15]), according to a general procedure [27], in a mixture of 10 ml of $CHCl_3$ and 1.5 ml of Et_3N at 0°, a soln. of 0.6 ml (0.82 g, 7.15 mmol) of MsCl in 2 ml of $CHCl_3$ was added dropwise, and stirring at this temp. continued 30 min. The solvent was evaporated, and the residue was purified by CC (AcOEt) to yield 2 g (100%) of **12**. Colorless oil. TLC (AcOEt): R_f (**12**) 0.75 (R_f (**11**) 0.6). ^{1}H-NMR: 7.73 (*d*, *J* = 8, 2 arom. H); 7.31 (*d*, *J* = 8, 2 arom. H); 4.3 (*t*, 2 H); 3.06 (*t*, 2 H); 3.02 (*s*, ArMe); 2.42 (*s*, $MeSO_2$); 1.93 (*t*, 2 H). ^{13}C-NMR: 143.55, 136.54 (arom. quat. C);

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[4]) One more recrystallization of this salt from 96% EtOH led to a material of 90% ee.

[5]) Obviously, the published specific rotation value for the hydrochloride of (−)-(*R*)-**14** ($[\alpha]_D = -91.5$ (*c* = 1.42, MeOH) [17a] is a misprint and should be changed to −9.15.

129.73, 126.91 (arom. CH); 66.98 (NHCH_2); 39.09 (CH_2O); 37.15 (Ph*Me*); 29.21 ($CH_2CH_2CH_2$); 21.37 ($MeSO_2$). CI-MS: 325 ($[M+NH_3+H]^+$).

*Methyl (−)-(*S*)-3-({3-[(4-Methylphenylsulfonyl)amino]propyl}amino)-3-phenylpropanoate* (**15**) *and Methyl (−)-(*S*)-3-(4-Methoxyphenyl)-3-({3-[(4-methylphenylsulfonyl)amino]propyl}amino)propanoate* (**16**). The mixture of 5.6 mmol of *(−)-(*S*)-3-amino-3-phenylpropanoate* (**13**) (or *methyl (+)-(*S*)-3-amino-3-(4-methoxyphenyl)propanoate* **14**), 11 mmol (1.9 equiv.) of **12**, 1 ml of Et_3N, and 5 ml of MeCN was refluxed for 4 h. The solvent was evaporated, the residue was dissolved in $CHCl_3$, and washed with H_2O. The org. layer was concentrated, and the residue was purified by CC ($CHCl_3$/AcOEt 1:1).

Data of **15**: Yield 79%. Colorless, glasslike solid. TLC (AcOEt): R_f 0.52. $[\alpha]_D = -15.7$ ($c = 1.53$, $CHCl_3$). ^{1}H-NMR: 7.74 (d, $J = 8$, 2 arom. H); 7.1–7.5 (m, 7 arom. H); 3.98, 3.97 (2d, $J = 8.8$, PhC*H*N); 3.67 (s, COOMe); 3.1–2.4 (m, 9 H, incl. *Me*Ph at 2.42); 1.7–1.4 (m, $CH_2CH_2CH_2$). ^{13}C-NMR: 172.05 (C=O); 142.91, 141.79, 137.15 (arom. quat. C); 129.50, 128.62, 128.46, 127.55, 127.41, 127.01, 126.72 (arom. CH); 59.62 (Ph*C*N); 51.70 (COO*Me*); 46.13, 42.99, 42.21, 28.24 (CH_2); 21.37 (*Me*Ph). CI-MS: 391 ($[M+H]^+$).

Data of **16**: Yield 82%. Colorless, glasslike solid. TLC (AcOEt): R_f 0.52. $[\alpha]_D = -15.7$ ($c = 1.44$, $CHCl_3$). ^{1}H-NMR: 7.74 (d, $J = 8$, 2 arom. H); 7.3 (d, $J = 8$, 2 arom. H); 7.13 (d, $J = 8.7$, 2 arom. H); 6.83 (d, $J = 8.7$, 2 arom. H); 3.93, 3.90 (2d, $J = 8.8$, PhC*H*N); 3.78 (s, MeO); 3.67 (s, COOMe); 3.3–2.3 (m, 9 H, incl. *Me*Ph at 2.43); 1.7–1.4 (m, $CH_2CH_2CH_2$). ^{13}C-NMR: 172.14 (C=O); 158.91, 142.90, 137.17, 133.83 (arom. quat. C); 129.50, 127.78, 127.00, 113.97 (arom. CH); 58.97 (Ph*C*N); 55.12 (MeO); 51.67 (COO*Me*); 46.15, 43.13, 42.31, 28.20 (CH_2); 21.37 (*Me*Ph). CI-MS: 421 ($[M+H]^+$).

*(−)-(*S*)-*N*-(3-Aminopropyl)-3-({3-[(4-methylphenylsulfonyl)amino]propyl}amino)phenylpropanamide* (**17**) *and (−)-(*S*)-*N*-(3-Aminopropyl)-3-({3-[(4-methylphenylsulfonyl)amino]propyl}amino)-(4-methoxyphenyl)propanamide* (**18**). A mixture of 1 g of compound **15** (or **16**), 4 ml of propane-1,3-diamine, and 0.05 g $Cu(Ac)_2$ was stirred at r.t. 24 h. The excess propane-1,3-diamine was removed under reduced pressure at temp. not more than 50°. To the residue was added sat. aq. NaCl and the product was extracted three times with $CHCl_3$/i-PrOH 8:2. The org. extract was washed once with sat. aq. NaCl and evaporated. The residue was purified by CC ($CHCl_3$/MeOH/25% aq. soln. NH_3 7:3:1).

Data of **17**: Yield 87%. Colorless oil. TLC ($CHCl_3$/MeOH/25% aq. soln. NH_3 7:3:1): R_f 0.54. $[\alpha]_D = -19.6$ ($c = 1.53$, $CHCl_3$). ^{1}H-NMR: 7.72 (d, $J = 8$, 2 arom. H); 7.4–7.1 (m, 7 arom. H, CONH); 3.95, 3.94 (2d, $J = 9$, PhC*H*N); 3.6–2.3 (m, 16 H, incl. Me at 2.41); 1.7–1.3 (m, 4 H). ^{13}C-NMR: 171.19 (C=O); 142.95, 142.49, 137.08 (arom. quat. C); 129.53, 128.54, 127.30, 126.93, 126.71 (arom. CH); 60.12 (PhCN); 45.58, 44.43, 42.44, 39.52, 37.26, 31.78, 28.60 (CH_2); 21.36 (Me). CI-MS: 433 ($[M+H]^+$).

Data of **18**: Yield 90%. Colorless oil. TLC ($CHCl_3$/MeOH/25% aq. NH_3 7:3:1): R_f 0.54. $[\alpha]_D = -20$ ($c = 1.15$, $CHCl_3$). ^{1}H-NMR: 7.72 (d, $J = 8$, 2 arom. H); 7.39 (br. t, CONH); 7.27 (d, $J = 8$, 2 arom. H); 7.13 (d, $J = 8.6$, 2 arom. H); 6.8 (d, $J = 8.6$, 2 arom. H); 4.2–3.6 (m, 8 H, incl. MeO at 3.77); 3.4–3.1 (m, 2 H); 3.0–2.6 (m, 4 H); 2.6–2.2 (m, 6 H, incl. MePh at 2.4); 1.8–1.4 (m, 4 H). ^{13}C-NMR: 171.44 (C=O); 158.74, 142.92, 137.09, 134.44 (arom. quat. C); 129.53, 127.78, 126.94, 113.90 (arom. C); 59.37 (PhCN); 55.13 (MeO); 45.42, 44.45, 42.43, 39.13, 37.12, 31.03, 28.54 (CH_2); 21.35 (MePh). CI-MS: 463 ($[M+H]^+$).

*(−)-(*S*)-*N*-{3-[(4-Methylphenylsulfonyl)amino]propyl}-3-({3-[(4-methylphenylsulfonyl)amino]propy}amino)-3-phenylpropanamide* (**19**) and *(−)-(*S*)-3-(4-Methoxyphenyl)-*N*-{3-[(4-methylphenylsulfonyl)amino]propyl}-3-({3-[(4-methylphenylsulfonyl)amino]propyl}amino)propanamide* (**20**). To a soln. of 1 mmol of **17** (or **18**) in a mixture of 5 ml of $CHCl_3$ and 0.2 ml of Et_3N was added dropwise at 0° a soln. of 1 mmol of TsCl in 5 ml of $CHCl_3$. The mixture was stirred for 30 min, washed with H_2O, and evaporated. The residue was purified by CC (consecutively AcOEt, AcOEt/MeOH 9:1).

Data of **19**: Yield 92%. Colorless, glasslike solid. TLC ($CHCl_3$/MeOH 10:1): R_f 0.4. $[\alpha]_D = -14.3$ ($c = 1.8$, $CHCl_3$). ^{1}H- and ^{13}C-NMR spectra are superimposable with those of the racemate [1]. ESI-MS: 587 ($[M+H]^+$).

Data of **20**: Yield 90%. Colorless, glasslike solid. TLC ($CHCl_3$/MeOH 10:1): R_f 0.4. $[\alpha]_D = -14.8$ ($c = 1.85$, $CHCl_3$). ^{1}H-NMR: 7.73 (d, $J = 8$, 4 arom. H); 7.4–7.2 (m, 4 arom. H); 7.12 (d, $J = 8.7$, 2 arom. H); 6.95 (br. t, CONH); 6.79 (d, $J = 8.7$, 2 arom. H); 3.9, 3.89 (2d, $J = 9$, PhC*H*N); 3.75 (s, MeO); 3.4–3.15 (m, 2 H); 3.1–2.7 (m, 4 H); 2.65–2.3 (m, 10 H, incl. 2 MePh at 2.41 and 2.40); 1.7–1.4 (m, 4 H). ^{13}C-NMR: 171.80 (C=O); 158.83, 143.11, 137.07, 136.82, 133.92 (arom. quat. C); 129.59, 127.80, 127.00, 126.92, 113.96 (arom. C); 59.28 (PhCN); 55.13 (MeO); 45.51, 44.09, 42.71, 40.11, 36.04, 29.20, 28.29 (CH_2); 21.37 (MePh). ESI-MS: 617 ($[M+H]^+$).

*(−)-(*S*)-1,13-Bis[(4-methylphenyl)sulfonyl]-8-phenyl-1,5,9,13-tetraazacycloheptadecan-6-one* (**21**) *and (−)-(*S*)-8-(4-Methoxyphenyl)-1,13-bis[(4-methylphenyl]sulfonyl)-1,5,9,13-tetraazacycloheptadecan-6-one* (**22**). The macrocyclization was performed according to the method described in [1].

Data of **21**. Yield 75%. Colorless, glasslike solid. $[\alpha]_D = -19$ ($c = 0.71$, $CHCl_3$). ^{1}H- and ^{13}C-NMR spectra are superimposable with those of the racemate [1]. ESI-MS: 641 ($[M+H]^+$).

Data of **22**: Yield 83%. Colorless, glasslike solid. $[\alpha]_D = -26$ ($c = 0.49$, $CHCl_3$). ^{1}H-NMR: 8.21 (br. *t*, CONH); 7.67, 7.62 (2*d*, $J = 8.3$, 4 arom. H); 7.30 (*t*, $J = 8.9$, 4 arom. H); 7.15 (*d*, $J = 8.6$, 2 arom. H); 6.86 (*d*, $J = 8.6$, 2 arom. H); 3.90, 3.88 (2*d*, $J = 10$, PhC*H*N); 3.79 (*s*, MeO); 3.6–3.3 (*m*, 1 H); 3.3–2.9 (*m*, 9 H); 2.8–2.3 (*m*, 10 H, incl. 2 MePh at 2.43 and 2.41); 2.1–1.55 (*m*, 8 H). ^{13}C-NMR: 171.87 (C=O); 158.76, 143.36, 143.27, 135.68, 134.52 (arom. quat. C); 129.68, 129.61, 127.35, 127.06, 114.01 (arom. C); 58.94 (PhCN); 55.16 (MeO); 49.95, 49.51, 48.02, 47.53, 44.17, 43.64, 36.72, 30.03, 29.62, 26.06, 26.35 (CH_2); 21.36 (MePh). ESI-MS: 671 ($[M+H]^+$).

*(−)-(*S*)-8-Phenyl-1,5,9,13-tetraazacycloheptadecan-6-one* (*=(−)-(*S*)-Protoverbine*; **1**) *and (−)-(*S*)-8-(4-Methoxyphenyl)-1,5,9,13-tetraazacycloheptadecan-6-one* (*=(−)-(*S*)-Buchnerine*, **8**). The electrochemical detosylations of both (−)-(*S*)-**21** and (−)-(*S*)-**22** was performed according to the procedures described in [1][16]. After evaporation of the catholyte, the residue was dissolved in H_2O, saturated with solid K_2CO_3, and extracted 5 times with a mixture $CHCl_3$/i-PrOH 4:1. The extract was evaporated, the residue was dissolved in $CHCl_3$ and purified by CC ($CHCl_3$/MeOH/25% aq. NH_3 soln. 7:3:1).

Data of **1**: Yield 93%. Colorless, glasslike solid. TLC ($CHCl_3$/MeOH/25% aq. NH_3 soln. 7:3:1): R_f 0.43. $[\alpha]_D = -27$ ($c = 1.3$, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra of (*S*)-**1** are identical with those of the natural (−)-(*S*)-protoverbine (**1**). ESI-MS: 333 ($[M+H]^+$).

Data of **8**: Yield 95%. Colorless, glasslike solid. TLC ($CHCl_3$/MeOH/25% aq. NH_3 soln. 7:3:1): R_f 0.43. $[\alpha]_D = -32$ ($c = 2.2$, $CHCl_3$); $[\alpha]_D = -25.5$ ($c = 0.6$, MeOH) ([9]: $[\alpha]_D = -26$ ($c = 0.5$, MeOH). ^{1}H-NMR: 8.41 (br. *t*, CONH); 7.2 (*d*, $J = 9$, 2 arom. H); 6.86 (*d*, $J = 9$, 2 arom. H); 3.95, 3.94 (2*d*, $J = 9.7$, PhC*H*N); 3.79 (*s*, MeO); 3.57–3.42 (*m*, 1 H); 3.39–3.22 (*m*, 1 H); 2.9–2.3 (*m*, 12 H); 2.2–1.25 (*m*, 12 H). ^{13}C-NMR: 171.26 (C=O); 158.58, 135.37 (arom. quat. C); 127.61, 113.83 (arom. C); 59.57 (PhCN); 55.10 (MeO); 49.19, 48.82, 48.29, 48.20, 46.96, 45.70, 38.97, 28.53, 28.14, 27.22, 27.07 (CH_2). CI-MS: 363 ($[M+H]^+$).

*(+)-(*S*)-2-Phenyl-1,5,9,14-tetraazabicyclo[12.3.1]octadecan-4-one* (*=(+)-(*S*)-Protomethine*; **2**). Compound **2** was prepared from **1** and 37% aq. soln. of HCHO by the method described in [1]. The synthetic **2** is indistinguishable from the natural compound. $[\alpha]_D = +4.5$ ($c = 1.9$, $CHCl_3$); ESI-MS: 345 ($[M+H]^+$).

*(+)-(*S*)-2-Phenyl-9-[(*E*)-phenylprop-2-enoyl]-1,5,9,14-tetraazabicyclo[12.3.1]octadecan-4-one* (*=(+)-(*S*)-Verbametine*, **4**) *and (+)-(*S*)-9-[(*E*)-3-(4-Methoxyphenyl)prop-2-enoyl]-2-phenyl-1,5,9,14-tetraazabicyclo[12.3.1]octadecan-4-one* (*=(+)-(*S*)-Verbamekrine*; **23**). To a soln. of 136 mg (0.4 mmol) of (+)-(*S*)-**2** in a mixture of 3 ml of CH_2Cl_2 and 0.1 ml of Et_3N was added dropwise at 0° a soln. of 0.4 mmol of the corresponding acyl chloride ((*E*)-3-propenoyl chloride for compound **4** and (*E*)-3-(4-methoxyphenyl)propenoyl chloride [28] for compound **23**) in 2 ml of CH_2Cl_2. The mixture was stirred 2 h under cooling and overnight at r.t., and then introduced directly in a silica-gel column and eluted consecutively with CH_2Cl_2 and THF.

Data of **4**: Yield 66%. $[\alpha]_D = +13$ ($c = 2.0$, $CHCl_3$). ESI-MS: 475 ($[M+H]^+$).

Data of **23**: Yield 70%. $[\alpha]_D = +8$ ($c = 1.6$, $CHCl_3$). ESI-MS: 505 ($[M+H]^+$).

*(−)-(*S*)-8-Phenyl-1-[(*E*)-phenylprop-2-enoyl]-1,5,9,13-tetraazacycloheptadecan-6-one (=(−)-(*S*)-Verbacine;* **3**) *and (−)-(*S*)-1-[(*E*)-3-(4-Methoxyphenyl)prop-2-enoyl]-8-phenyl-1,5,9,13-tetraazacycloheptadecan-6-one* (*=(−)-(*S*)-Verbasikrine;* **26**).

Compounds **3** and **26** were prepared quantitatively by published methods [2][4] from **4** and **23**, resp., and $NH_2OH \cdot HCl$ in 1% aq. HCl.

Data of **3**: $[\alpha]_D = -14$ ($c = 23$, $CHCl_3$). ESI-MS: 463 ($[M+H]^+$).

Data of **26**: $[\alpha]_D = -17$ ($c = 1.0$, $CHCl_3$). ESI-MS: 493 ($[M+H]^+$).

*(+)-(*S*)-9-[(*Z*)-3-(4-Methoxyphenyl)prop-2-enoyl]-2-phenyl-1,5,9,14-tetraazabicyclo[12.3.1]octadecan-4-one* (*=(*S*)-Isoverbamekrine*; **24**) *and (−)-(*S*)-1-[(*Z*)-3-(4-Methoxyphenyl)prop-2-enoyl]-8-phenyl-1,5,9,13-tetraazacycloheptadecan-6-one* (*=(−)-(*S*)-Isoverbasikrine*; **25**). Compounds **24** and **25** were prepared by published method [4] by photoisomerization of **23** and **26**, resp.

Data of **24**: $[\alpha]_D = +4$ ($c = 0.6$, $CHCl_3$). ESI-MS: 505 ($[M+H]^+$).

Data of **25**: $[\alpha]_D = -13$ ($c = 0.5$, $CHCl_3$). ESI-MS: 493 ($[M+H]^+$).

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