Chiroptical Properties of the Protoverbine Class of Macrocyclic Spermine Alkaloids

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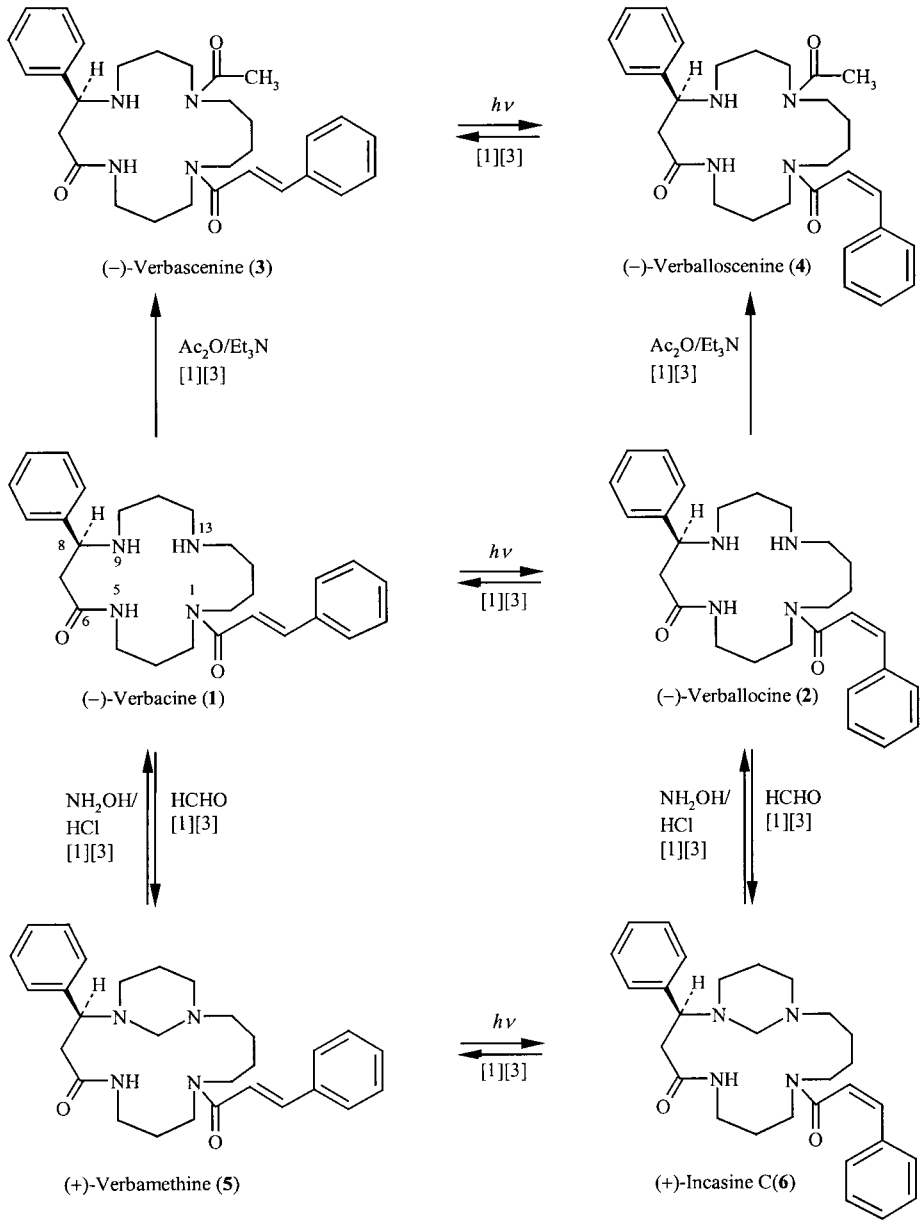
The chiroptical properties (circular dichroism, CD) of the 17-membered macrocyclic spermine lactam alkaloids (−)-protoverbine (**16**), its *N,N′*-methylene-bridged natural analogue (+)-protomethine (**17**), their natural derivatives (−)-verbacine (**1**), (−)-verballocine (**2**), (−)-verbascenine (**3**), (−)-verballoscenine (**4**), (+)-verbamethine (**5**), (+)-incasine C (**6**), (+)-verdoline (incasine B′, **30**), (+)-incasine B (**31**), and some of their isosteric analogues were studied. By chemical and chiroptical correlation, it was confirmed that an amidically bonded (*S*)-*β*-phenyl-*β*-alanine fragment forms the chiral moiety in all of these natural compounds. The signs of the registered *Cotton* effects (CEs) are interpreted in terms of the *Smith*'s quadrant rule for the ^1L_b CEs of chiral *α*-substituted benzylamines and the *Ogura*'s sign rule for n → *π** CEs of lactams. Some of the conclusions regarding configuration are supported for the rigid bicyclic compound (−)-(9*S*)-9-phenyl-1,6-diazabicyclo[4.3.1]decan-7-one (**15**) by the X-ray crystal structure of the racemate.

Introduction. – The macrocyclic spermine alkaloids (−)-verbacine (**1**) and (−)-verballocine (**2**) have been isolated from *Verbascum pseudonobile* STOJ. *et* STEF. (Scrophulariaceae) [1] (see *Scheme 1*). The *N*-acetylated analogues (−)-verbascenine (**3**) and (−)-verballoscenine (**4**) have been isolated from *V. phoeniceum* L. [2][3]. In this plant, (−)-verbacine (**1**) and (−)-verballocine (**2**) have also been detected. They are probable biogenetic precursors of (−)-verbascenine (**3**) and (−)-verballoscenine (**4**) [3]. Compounds **1**–**4** are 17-membered macrocyclic lactam alkaloids, which contain, as structural units, spermine, 3-phenylpropionyl, cinnamoyl ((*E*) for **1** and **3**, and (*Z*) for **2** and **4**), and the Ac group (in the case of **3** and **4**).

Comparison of the ORD (optical rotatory dispersion) spectra of (−)-(*S*)-*N*-ethyl-*α*-phenylethylamine and (−)-(*S*)-*α*-phenylethylamine led to the conclusion that an amidically bonded (*S*)-*β*-phenyl-*β*-alanine fragment forms the chiral part of the 17-membered macrocycle in (−)-dihydroverbascenine (**8**, *cf. Scheme 2*) and its natural unsaturated analogue, (−)-verbascenine (**3**) [2]. The absolute configuration of the related alkaloids (−)-verbacine (**1**), (−)-verballocine (**2**), and (−)-verballoscenine (**4**) was deduced by chemical and chiroptical ($[\alpha]_D$) correlation with (−)-verbascenine (**3**) [1][3].

Together with (−)-verbacine (**1**) and (−)-verballocine (**2**), the *N,N′*-methylene-bridged derivatives, namely the cyclic aminals (+)-verbamethine (**5**) and (+)-isoverbamethine (= incasine C; **6**), have been isolated from *V. pseudonobile*. Compounds **5** and **6** arise quantitatively by *N,N′*-cyclization of **1** and **2** with HCHO. It is possible that they are formed by reaction with HCHO produced from the solvents used as extractants. Because of the lack of evidence for their natural origin, **5** and **6** were considered as artifacts of **1** and **2** [1]. Compounds **5** and **6** (*Scheme 1*), and their dihydro derivative **11** (*cf. Scheme 2*) have opposite signs for their optical rotation

Scheme 1



($[\alpha]_D$) as compared to the unbridged compounds **1**, **2**, and **7**. The difference between these closely related compounds was interpreted in terms of conformational changes in the neighborhood of the center of chirality [1]. By mild acid hydrolysis in the presence of NH_2OH, which acts as an interceptor HCHO, the aminals (+)-verbamethine (**5**), (+)-isoverbamethine (**6**), and (+)-dihydroverbamethine (**11**) were converted quanti-

tatively to (−)-verbacine (**1**), (−)-verballocine (**2**), and (−)-dihydroverbacine (**7**), respectively (*Schemes 1* and *2*). Thus, it was confirmed that these six compounds have the same absolute configuration, namely (*S*) [1][3].

The biogenetic precursor of the alkaloids **1**–**4** is (−)-protoverbine (**16**, *cf. Scheme 4*) and the precursor of the *N,N′*-methylene-bridged bases **5** and **6** is (+)-protomethine (**17**). Compounds **16** and **17** were isolated from the alkaloid extract of *V. pseudonobile* and will be published elsewhere [4].

(+)-Verballocine (**2**) and its *N,N′*-methylene-bridged derivative **6** were isolated recently from *Incarvillea sinensis* LAM. (Bignoniaceae); compound **6** was named incasine C [5]. However, from the chiroptical properties of its dihydro derivative **11** (comparison of the CD spectrum with that of (+)-(*R*)-(1-phenylethyl)amine), the absolute configurations of **11** and **6** were determined to be (*R*). It will be shown in this paper that this conclusion has to be corrected.

Because of the confusion concerning the absolute configuration of **6** and **11** and the open question about the nature of the chiroptical changes of **5**, **6**, and **11** in comparison with the *N,N′*-unsubstituted analogues **1**, **2**, and **7**, a more detailed investigation of the chiroptical properties (CD) of this group of similar compounds is needed. Due to the presence of the strongly absorbing (*E*)- or (*Z*)-cinnamoyl groups in most of these alkaloids, the CD curves of their dihydro derivatives were compared. The resulting conclusions regarding the configuration are applicable to the corresponding unsaturated natural alkaloids.

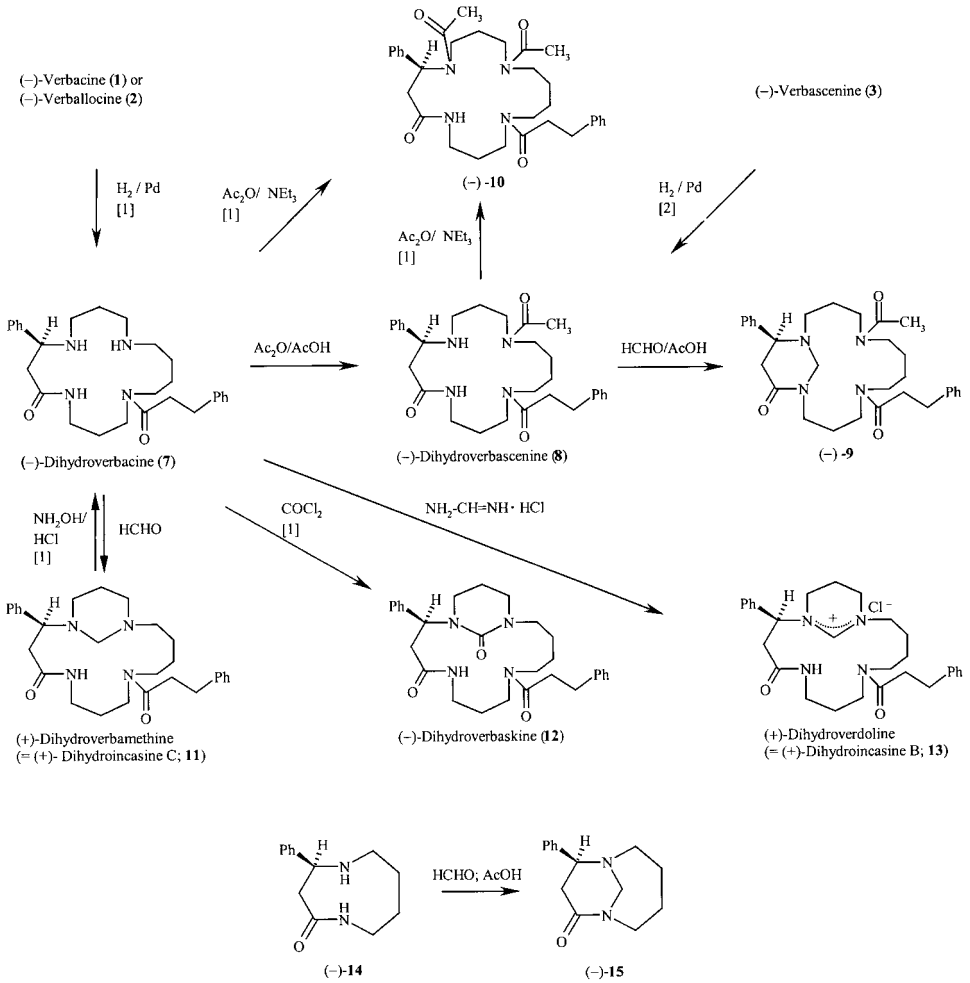
Results and Discussion. – *Synthesis.* We first examined the absolute configuration of (−)-dihydroverbacine (**7**), its *N,N′*-methylene-bridged derivative (+)-dihydroverbamethine (**11**), (−)-dihydroverbascenine (**8**), and their side-chain-unsaturated natural analogues (−)-verbacine (**1**), (−)-verballocine (**2**), (−)-verbascenine (**3**), (−)-verballoscenine (**4**), (+)-verbamethine (**5**), and (+)-incasine C (**6**) by their chemical transformation to derivatives which are unambiguously chiroptically comparable with suitable model compounds of known absolute configuration. The rings of the macrocyclic spermine alkaloids are usually very flexible and, therefore, not suitable for an unambiguous establishment of their absolute configuration. Thus, we tried to obtain derivatives which possess an additional ring that would provide rigidity of the spermine macrocycle.

(−)-Dihydroverbacine ((−)-(8*S*)-1-(3-phenylpropanoyl)-8-phenyl-1,5,9,13-tetraazacycloheptadecan-6-one; **7**) was prepared by a published method by catalytic hydrogenation of (−)-verbacine (**1**) [1]. Regioselective acetylation of **7** by Ac_2O in AcOH yielded (−)-dihydroverbascenine (**8**) almost quantitatively (*Scheme 2*). Both **7** and **8** were transformed to the diacetyl derivative (−)-**10** on treatment with Ac_2O/Et_3N. Compound **8** was then cyclized with HCHO in the presence of AcOH to give the corresponding hexahydropyrimidinone derivative (−)-**9**.

Similarly, the bicyclic derivative (−)-**15** was prepared from the nine-membered model compound (−)-**14** and HCHO. Compound (−)-**14** has been used as an intermediate in the asymmetric total synthesis of the spermidine alkaloid mayfoline [6].

To eliminate any possible sterical influences of the macrocyclic ring on the CD spectral properties of the aromatic and lactam chromophores in the bicyclic compound (−)-**9**, a selective chemical degradation of **11** was performed (*Scheme 3*). As was done

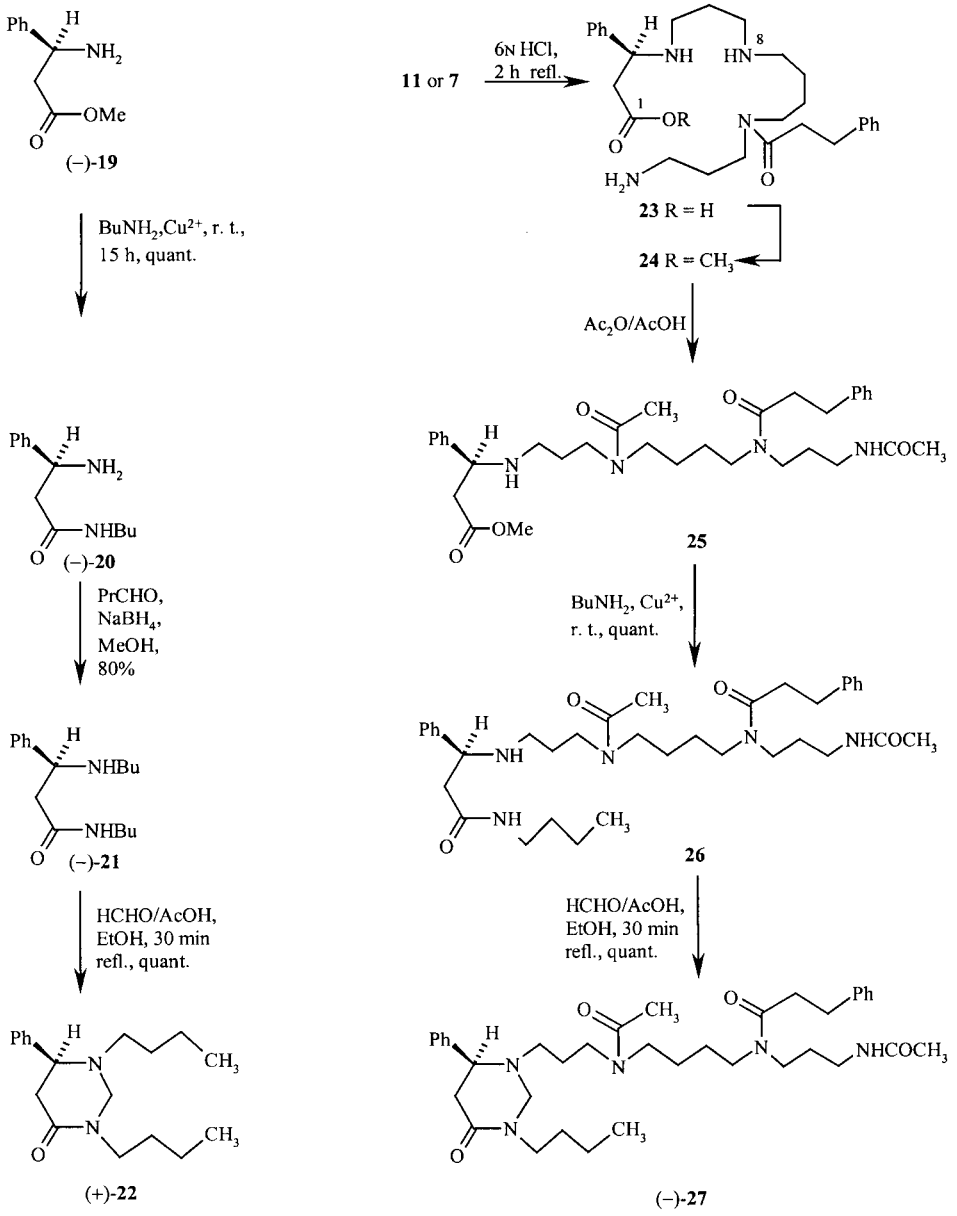
Scheme 2



with the macrocyclic spermidine alkaloid celacinnine [7], the macrocycle was opened by hydrolysis to give the corresponding amino acid **23**. The same amino acid **23** could be obtained by hydrolysis of (–)-dihydroverbacine (**7**) under the same conditions. Compound **23** was esterified to **24**. By regioselective acetylation of **24**, the partially acetylated ester **25** was formed. Compound **25** was transformed, in quantitative yield, to the amide **26** by Cu^{2+}-catalyzed aminolysis with $BuNH_2$. Cyclization of **26** with HCHO yielded the target hexahydropyrimidinone derivative (–)-**27**.

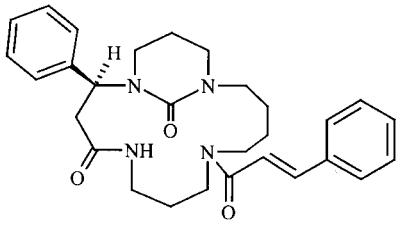
On the other hand, by starting with an authentic sample of methyl (–)-(3*S*)-3-amino-3-phenylpropanoate ((–)-**19**; *Scheme 3*) [6], the above-mentioned mild, Cu^{2+}-catalyzed aminolysis with $BuNH_2$ led to the amide (–)-**20** in quantitative yield. The corresponding *N,N′*-dibutyl derivative (–)-**21** was prepared by reductive alkylation of the primary amine (–)-**20** with PrCHO and $NaBH_4$. Addition of HCHO to (–)-**21**

Scheme 3

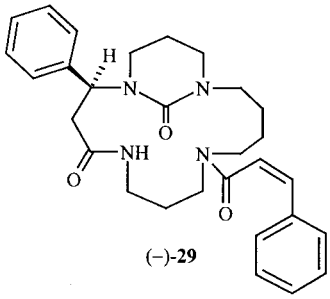


yielded the target hexahydropyrimidinone (+)-**22**. This compound was used as a model compound for the natural-product derivatives (−)-**9** and (−)-**27**. We preferred to introduce the Bu moiety at the benzylic amino group in the model compounds (−)-**21** and (+)-**22**, as this is the *N*-substituent which is similar to the long-chain residue at the benzylic N-atom in the degradation product (−)-**27** (*Scheme 3*).

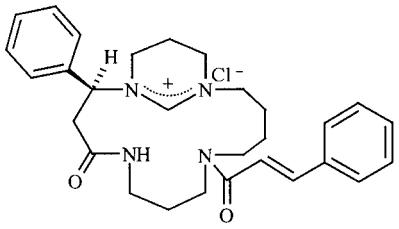
By reacting (−)-dihydroverbacine (**7**) with HCHO, the corresponding (+)-*N,N′*-methylene-bridged derivative **11** was obtained (*Scheme 2*). To compare its CD spectral properties, we prepared two other *N,N′*-bridged derivatives, *i.e.*, **12** and **13** (*Scheme 2*). (−)-Dihydroverbacine (**7**) was treated in $CHCl_3$ with phosgene to form the cyclic urea **12** [1] (*Scheme 2*). Compound **12** has been prepared earlier by catalytic hydrogenation of verbaskine **28** [8] and its (*Z*)-isomer **29** [1]. (−)-Verbaskine (**28**) was earlier thought to be a natural secondary metabolite, but later it was found to be an artifact [1].



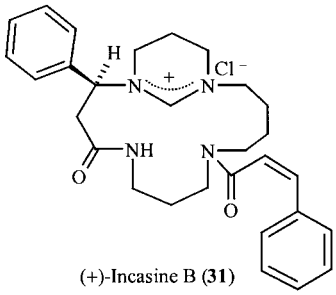
(−)-Verbaskine (**28**)



(−)-**29**



(+) -Verdoline (= (+)-Incasine B', **30**)



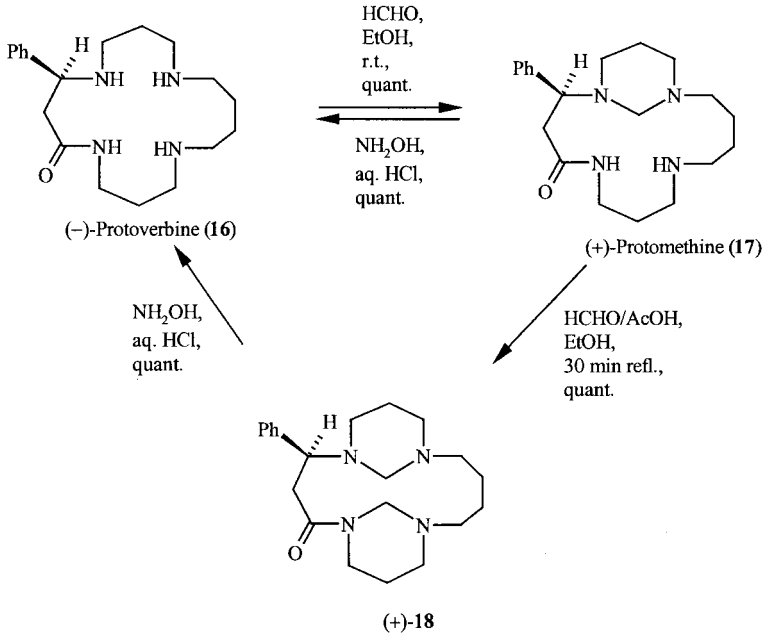
(+)-Incasine B (**31**)

The second *N,N′*-bridged derivative, the amidinium chloride **13**, was obtained in excellent yield by direct cyclization of **7** with formamidine hydrochloride (*Scheme 2*). Together with the (*E*)- and (*Z*)-isomeric side-chain unsaturated analogues **30** and **31**, compound **13** has also been the subject of published work [5].

Finally, treatment of (−)-protoverbine (**16**) or (+)-protomethine (**17**) with an excess of HCHO in the presence of AcOH in boiling EtOH gave the tricyclic compound (+)-**18** (*Scheme 4*) which was not detected in the plant [4]. At room temperature and with 1 equiv. of HCHO, but without AcOH, **16** yielded **17**.

CD Spectral Analyses. General. The results of the CD measurements are presented in *Table 1*. The compounds in which the chiral center is part of a rigid hexahydropyrimidinone ring show ellipticities of equal sign. By this comparison, the absolute (*S*)-configuration was unambiguously confirmed for (−)-verbacine (**1**), (−)-verballocine (**2**), (−)-dihydroverbacine (**7**), (−)-verbascenine (**3**), (−)-verballoscenine (**4**), (−)-dihydroverbascenine (**8**), (+)-verbamethine (**5**), (+)-incasine C (**6**), and (+)-dihydroverbamethine (**11**).

Scheme 4



The compounds under investigation can be described as chiral monoalkyl-substituted benzene derivatives which have an amine function directly bonded to the benzylic chiral center. All compounds have a secondary (or tertiary) amide group in β-position with respect to the benzene ring, namely the open-chain species (−)-**19**–(−)-**21**); the cyclic six-membered ((+)-**22** and (−)-**27**), nine-membered ((−)-**14**), and 17-membered ring compounds (**7**, **8**, (−)-**10**, and **16**), the bicyclic compounds ((−)-**9**, **11**, **12**, **13**, (−)-**15**, and **17**), and the tricyclic compound **18**.

These alkaloids show two absorption bands in the UV region, a weak one above, and a strong below 240 nm. Since the corresponding ellipticities arise by different mechanisms, the established signs of the *Cotton* effects (CEs) in these absorption regions will be discussed separately below.

Circular Dichroism above 240 nm. In the UV region between 240 and 270 nm, the compounds reported in *Table 1* show a weak absorption band with fine structure, which is typical for a monosubstituted benzene chromophore (^1L_b band) [9]. The recorded CD spectra contain a number of CEs corresponding to the ^1L_b absorption transitions.

As shown quite recently, the sign of the ^1L_b CEs for benzene derivatives with a chiral center bonded to the benzene ring depends only on the rotatory contribution of the groups directly attached to the chiral center [10–12]. On the basis of the established sequences of the strength of the rotatory contributions for several different functional groups, a quadrant rule has been formulated for the prediction of the sign of the ^1L_b CEs (*i.e.*, for the absolute configuration) for chiral (1-phenylalkyl)amines and related compounds in which one substituent at the contiguous chiral center is a H-atom [10–12]. For such compounds, the preferred conformation has been confirmed to be

Table 1. *CD Data* (96% EtOH) *and* $[\alpha]_D$ *Values of the Compounds Studied*

Compound (conc. in %)	CD (λ ($[\Theta]$))[a]			$[\alpha]_D$
	$\lambda < 240$ nm	$\lambda > 240$ nm		
		max $[\Theta]$	min and 0 $[\Theta]$	
7[b]) ((−)-Dihydroverbacine; 0.03)	230 (− 3961)	256 (+ 229) 262 (+ 468) 268 (+ 477)	252 (± 0) 258 (+ 255) 265 (+ 252) 273 (± 0)	− 22 ($c = 3.7$, $CHCl_3$) [1]
(−)-**7**[c]) (0.03)	230 (− 723) 233 (− 777)	249 (+ 136)[d]) 255 (+ 268) 257 (+ 261) 261 (+ 383) 268 (+ 333)	245 (± 0) 256 (+ 255) 258 (+ 253) 265 (+ 210) 272 (± 0)	
8[b]) ((−)-Dihydroverbascenine; 0.032)	230 (− 6818) 252 (− 99)[d])	256 (+ 168) 262 (+ 429) 268 (+ 452)	254 (± 0) 259 (+ 165) 266 (+ 200) 276 (± 0)	− 7 ($c = 0.41$, MeOH) [2]
(−)-**8**[c]) (0.032)	230 (− 2222)	244 (− 218)[d]) 249 (+ 82) 255 (+ 200) 261 (+ 314) 267 (+ 254)	248 (± 0) 252 (+ 113) 258 (+ 132) 265 (+ 94) 272 (± 0)	
(−)-**9** (0.09)	230 (− 2414) 232 (− 2663)	250 (− 212)[d]) 256 (− 32) 261 (+ 78) 268 (+ 139)	254 (− 32) 258 (± 0)[d]) 264 (+ 56) 271 (+ 92)	− 8.5 ($c = 2.0$, $CHCl_3$)
(−)-**10** (0.02)	230 (+ 10179)	255 (− 300) 262 (− 360) 269 (− 327)	251 (± 0) 258 (− 259) 265 (− 192) 273 (± 0)	− 51 ($c = 0.44$, MeOH) [2]
11 ((+)-Dihydroverbamethine = Dihydroincasine C; 0.02)	230 (− 3549)	249 (− 54) 256 (− 194) 258.5 (− 217)[d]) 262 (− 435) 268 (− 407)	248 (± 0) 252 (± 0) 258 (− 160) 266 (− 166) 274 (± 0)	+ 8.6 ($c = 1.38$, $CHCl_3$) [1]
(−)-**12** (0.02)	230 (+ 10617)	245 (+ 445)[d]) 250 (− 128)[d]) 255 (− 404) 262 (− 647) 269 (− 594)	248 (± 0) 251 (− 146) 258 (− 353) 266 (− 317) 273 (± 0)	− 45.2 ($c = 1.92$, $CHCl_3$) [1]
13 ((+)-Dihydroverdoline = Dihydroincasine B; 0.0064)	230 (+ 18577)	251 (+ 1977)[d]) 254 (+ 1090)[d]) 256 (+ 989) 263 (+ 690) 269 (+ 327)	260 (+ 287) 266 (+ 139) 272 (± 0)	+ 60 ($c = 0.85$, $CHCl_3$)
(−)-**14**[b]) (0.036)	230 (− 26865) 232 (− 30134)	256 (− 1797)[d]) 262 (− 1433) 269 (− 1006)	260 (− 1279) 267 (− 766) 278 (± 0)	− 151 ($c = 0.936$, $CHCl_3$) [6]

Table 1 (cont.)

Compound (conc. in %)	CD (λ ([Θ])[a])			$[\alpha]_D$
	$\lambda < 240$ nm	$\lambda > 240$ nm		
		max [Θ]	min and 0 [Θ]	
(−)-**14**[c]) (0.036)	230 (− 20978)	258 (− 289)[d])	256 (− 361)	
		262 (+ 82)	260 (± 0)	
		268 (+ 188)	265 (± 0)	
			271 (± 0)	
(−)-**15**[b]) (0.038)	230 (− 10714)	254 (− 2755)[d])	258 (− 2132)	− 122.8 ($c = 0.56$, $CHCl_3$)
	235 (− 24905)	261 (− 2132)[d])	264 (− 1729)	
		268 (− 1784)[d])	280 (± 0)	
(−)-**15**[c]) (0.038)	230 (− 18619)	259 (− 337)[d])	257 (− 447)	
		262 (+ 103)	261 (± 0)	
		268 (+ 139)	265 (± 0)	
			272 (± 0)	
16 ((−)-Protoverbine; 0.027)	230 (− 1750)	256 (+ 130)	252 (± 0)[d])	− 28.6 ($c = 1.47$, $CHCl_3$)
	247 (− 210)[d])	262 (+ 283)	258 (+ 135)	
		268 (+ 275)	266 (+ 131)	
			274 (± 0)	
17 ((+)-Protomethine; 0.027)	230 (− 1117)	243 (− 81)[d])	248 (− 16)	+ 4.9 ($c = 1.39$, $CHCl_3$)
	234 (− 652)[d])	246 (− 10)[d])	251 (± 0)	
	239 (− 216)[d])	249 (− 38)	258 (− 110)	
		256 (− 135)	265 (− 134)	
		262 (− 290)	273 (± 0)	
		268 (− 277)		
(+)-**18** (0.04)	230 (+ 6091)	254 (+ 319)[d])	257 (± 0)	+ 24 ($c = 1.4$, $CHCl_3$)
		259 (+ 7)[d])	266 (− 162)	
		262 (− 242)	271 (− 322)	
		269 (− 362)		
(−)-**19**[b]) (0.105)	230 (+ 840)	250 (+ 111)[d])	247 (+ 101)	− 20.3 ($c = 1.5$, $CHCl_3$) [6]
		256 (+ 171)	252 (+ 121)	
		262 (+ 233)	259 (+ 157)	
		268 (+ 197)	265 (+ 110)	
			274 (± 0)	
(−)-**19**[c]) (0.105)	230 (+ 338)	247 (+ 44)	245 (+ 43)	
		252 (+ 49)[d])	249 (+ 42)	
		254 (+ 58)[d])	259 (+ 60)	
		257 (+ 68)	265 (+ 34)	
		261 (+ 68)	271 (± 0)	
		262.5 (+ 60)[d])		
		267 (+ 51)		
(−)-**20**[b]) (0.07)	230 (+ 546)	249 (+ 92)[d])	245 (+ 76)	− 31 ($c = 1.05$, $CHCl_3$)
		251 (+ 107)[d])	258 (+ 154)	
		256 (+ 162)	265 (+ 111)	
		262 (+ 226)	273 (± 0)	
		268 (+ 193)		
(−)-**20**[c]) (0.07)	230 (+ 649)	242 (+ 100)[d])	245 (+ 59)	
		248 (+ 73)[d])	251 (+ 74)	
		254 (+ 117)	257 (+ 116)	
		261 (+ 170)	265 (+ 85)	
		267 (+ 144)	272 (± 0)	

Table 1 (cont.)

Compound (conc. in %)	CD (λ ([Θ])[a])			$[\alpha]_D$
	$\lambda < 240$ nm	$\lambda > 240$ nm		
		max [Θ]	min and 0 [Θ]	
(−)-**21**[b]) (0.21)	230 (− 365)	256 (+ 190)	248 (± 0)	− 41 ($c = 2.24$, $CHCl_3$)
	233 (− 538)	262 (+ 336)	251 (+ 45)[d])	
		268 (+ 324)	258 (+ 174)	
			265 (+ 152)	
			276 (± 0)	
(−)-**21**[c]) (0.21)	230 (+ 712)	242 (+ 101)[d])	244 (+ 89)	
		249 (+ 122)	251 (+ 121)	
		255 (+ 211)	258 (+ 176)	
		261 (+ 308)	265 (+ 134)	
		267 (+ 264)	275 (± 0)	
(+)-**22** (0.03)	230 (− 3620)	262 (+ 97)	258 (± 0)	+ 4 ($c = 2.25$, $CHCl_3$)
		268 (+ 133)	265 (+ 47)	
			272 (± 0)	
(−)-**27** (0.029)	230 (− 6026)	257 (+ 63)	256 (± 0)	− 3 ($c = 2.4$, $CHCl_3$)
		263 (+ 184)	259 (+ 96)	
		269 (+ 247)	265 (+ 179)	
			272 (+ 191)	

[a]) λ in nm, in parentheses molar ellipticity [Θ]. [b]) Free base. [c]) After acidification of the solution (EtOH solution of HCl). [d]) Shoulder.

that one in which the benzene-ring plane eclipses or almost eclipses the H-atom at the benzylic chiral center ([10] and ref. cit. therein). The quadrant projection of (*S*)-(1-phenylethyl)amine is given in *Fig. 1*. The CD curve of (*S*)-(1-phenylethyl)amine in the ^1L_b region (between *ca.* 240 and 300 nm) is in the positive part of the scale. In the established sequences, the Me (respectively CH_2) group makes a larger contribution to the ^1L_b CEs than does an amino, ammonium, or *N*-alkylamino group attached to the chiral center [10–12]. Thus, for (1-phenylalkyl)amines the right upper quadrant is positive (*Fig. 1*)

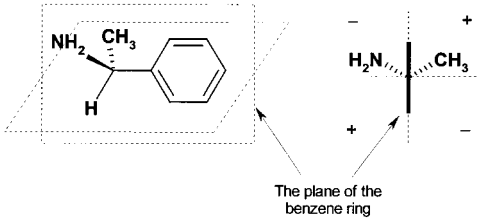


Fig. 1. *The quadrant projection of* (S)*-(1-phenylethyl)amine* (according to *Smith* and co-workers [10–12]). 'The sequences for the summation of contributions to the ^1L_b CEs (given by *Smith* and *Fontana* [10]) are SH, COO^-, Me_3C > Me, $CH_2 > NH_2$, $^+NH_3$, Me_3N^+, OH, MeO, Cl; and Me > COOH > $^+NH_3$, OH, MeO. These sequences may be used in connection with the sector signs in quadrant projection and will have a general usefulness for the establishment of the absolute configuration of related chiral benzene compounds in which one substituent at the contiguous chiral center is a hydrogen atom'.

The compounds reported in *Table 1* have the same arrangement around the chiral center, and for them the quadrant rule, depicted above, is primarily applicable. In accordance with *Smith*'s rule [10–12], the open-chained compounds (−)-**19**–(−)-**21**, the six-membered ring species (+)-**22** and (−)-**27**, the bicyclic compounds (−)-**9** and **13**, and the 17-membered cycles **7**, **8**, and **16** all show a positive sign for the ^1L_b CEs. It seems that, for these compounds, the orientation of the benzene ring and the benzylic substituents is (in EtOH solution) predominantly as given in *Fig. 1*, with the CH_2 group in the positive quadrant. In the crystalline state, such an orientation for the benzene ring has been established by an X-ray crystal-structure analysis of the 13-membered macrocyclic spermidine alkaloid (*S*)-mayfoline [6].

According to the quadrant rule, a negative sign for the ^1L_b CEs should by the result of an alternative orientation of the benzene ring, in which the C–N bond at the chiral center is eclipsed or almost eclipsed. Such an orientation of the benzene ring was established for the crystalline state of compound (±)-**15** by X-ray crystallography (*Fig. 2,a*). The quadrant projection of the (*S*)-isomer from the crystal structure of (±)-**15** shows that the CH_2 group attached to the chiral center is placed in the lower right, negative quadrant (C(8)–C(9)–C(11)–C(12) torsion angle is + 96.2 (3)°) (*Fig. 2,b*). We can conclude that such a conformation is also highly populated in an EtOH solution of (−)-(*S*)-**15**, since a negative sign was observed for the ^1L_b CEs in this solvent.

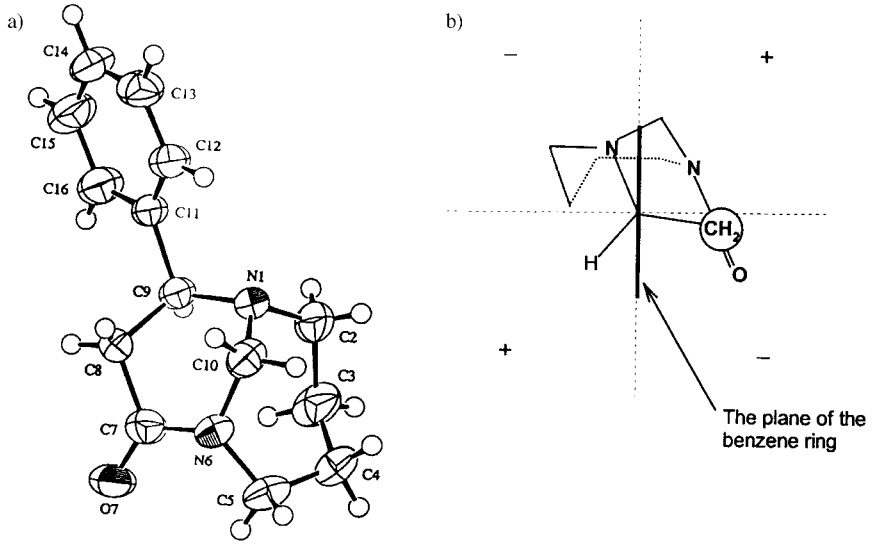


Fig. 2. a) *ORTEP Plot* [13] *of one of the symmetry-independent molecules in the structure of* (±)-**15** *and* b) *quadrant projection of its crystal structure*

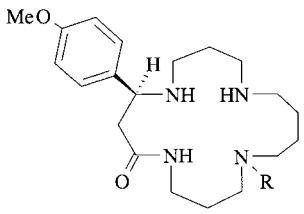
By assuming the presence of a similar, preferred orientation of the benzene ring, it is possible to explain the established negative sign of the ^1L_b CEs for the compounds diacetyldihydroverbacine ((−)-**10**), (+)-dihydroverbamethine (**11**), (−)-dihydroverbaskine (**12**), (+)-protomethine (**17**), the tricyclic compound (+)-**18**, and the model compound (−)-**14**.

The recorded negative ^1L_b CEs of the free base (−)-**14** becomes positive after acidification of its EtOH solution. In agreement with the established sequences for the strengths of the rotatory contribution [10–12] (see *Fig. 1*), the formed ammonium ion is still a weaker contributor than the CH_2 group attached to the chiral center. It is expected that an increase in the effective volume of the solvated, charged (protonated) secondary amino group in (−)-**14** causes a clockwise repulsion of the benzene ring to a predominant position in which the CH_2 group is in the upper right (positive) quadrant.

Acidification of the EtOH solution of the bicyclic compounds (+)-**11**, (−)-**15**, (+)-**17**, and of the tricyclic compound (+)-**18** also converts the sign of their ^1L_b CEs from negative to positive. These changes can be explained in the same way. The acidification of the solutions of the other compounds, *i.e.*, **7**, **8**, (−)-**19**–(−)-**21**, did not cause changes in the sign of the ^1L_b CEs.

The non-substituted 17-membered lactam alkaloid (−)-protoverbine (**16**; *Scheme 4*) was isolated from the total alkaloid-containing extract of *V. pseudonobile*. This is the biogenetic precursor of the present class of spermine alkaloids (*Scheme 1* and **28**–**31**) [4]. Similar to (−)-dihydroverbacine (**7**) and (−)-dihydroverbascenine (**8**), the ^1L_b spectral region for (−)-protoverbine (**16**) shows positive CEs. Thus, establishing the (*S*)-chirality of **16** [4]. The *N,N′*-methylene-bridged alkaloid (+)-protomethine (**17**, *Scheme 4*) exhibits, like the corresponding aminal, (+)-dihydroverbamethine (**11**), a negative ^1L_b CEs.

It has been reported earlier that the hydroxylation or methoxylation of the benzene ring bonded to the chiral center changes the sign of the ^1L_b CEs of the (1-phenylalkyl)amines [12][14]. Thus, for the related (*S*)-spermine alkaloid (−)-buchnerine (**32**) and its 1-[(*Z*)-4-methoxycinnamoyl] derivative **33** (in form of its dihydro derivative), we can expect negative ^1L_b CEs, opposite to those of (−)-(*S*)-protoverbine (**16**) and (−)-(*S*)-dihydroverbacine (**7**). The absolute configuration of (−)-buchnerine (**32**) and its derivative **33** has been postulated to be (*S*) without any chiroptical (CD or ORD) arguments [15].



32 R = H, (−)-Buchnerine [15];
33 R = (*Z*)-4-MeOC$_6$H$_4$CH=CHCO [15]

Circular Dichroism below 240 nm. All compounds reported in this paper exhibit intense UV-light absorption below 240 nm owing the presence of aromatic (^1L_a $\pi \rightarrow \pi^*$ absorption transition with λ_{max} *ca.* 200 nm) and lactam (amide) chromophores (n $\rightarrow \pi^*$ transition with λ_{max} *ca.* 220 nm). The registered CD spectra in this region show strong ellipticities, mainly corresponding to the lactam n $\rightarrow \pi^*$ absorption band.

All compounds with the (*S*)-configured chiral center incorporated into a six-membered lactam ring (**9**, (−)-**15**, (+)-**22**, and (−)-**27**) show a negative-signed plain CD curve or negative CE between 230 and 240 nm.

It has been shown for chiral four-, five-, six-, and seven-membered lactams that the sign of the n $\rightarrow\pi^*$ CE (*ca.* 220 nm) depends only on the ring conformation [16–19]. On this bases, *Takayanagi* and *Ogura* have postulated a sign rule for the prediction of the ring conformation of chiral six-membered lactams [19]. The possible conformations of such compounds have been classified into two types, type A (positive CE) and type B (negative CE), by the enantiomeric nature of the ring system (*Fig. 3*).

Type A (a positive *Cotton* effect) Type B (a negative *Cotton* effect)

Fig. 3. *Projection of the two enantiomeric types of six-membered lactams which cause a positive and negative lactam n* $\rightarrow\pi^*$ Cotton *effect, respectively* (according to *Takayanagi* and *Ogura* [19])

If we assume that the six-membered lactams (+)-**22** and (−)-**27** and the bicyclo[12.3.1] lactam (−)-**9** have a preferred quasi-chair conformation of the hexahydropyrimidinone part with an equatorially oriented benzene ring and a pseudoequatorial *N,N′*-alkyl residue, the ring will have the type-B chirality according to *Takayanagi* and *Ogura* (*Fig. 3*) [19], which is in agreement with the obtained negative-signed n $\rightarrow\pi^*$ ellipticities for these compounds. However, the X-ray structure analysis of the bicyclo[4.3.1] compound **15** showed that the rigid six-membered hexahydropyrimidinone ring has the boat conformation (*Fig. 2*). Nevertheless, a negative sign of n $\rightarrow\pi^*$ ellipticity was also recorded for (−)-**15**.

A negative sign for the ellipticities in the spectral region below 240 nm was also established for the macrocyclic compounds (−)-dihydroverbacine (**7**), (−)-dihydroverbascenine (**8**), (+)-dihydroverbamethine (**11**), (+)-protoverbine (**16**), (+)-protomethine (**17**), and the model compound (−)-**14**. It is of interest to note that the orientation of the lactam C=O group should be almost the same in the rigid six-membered azalactams **9**, (−)-**15**, (+)-**22**, and (−)-**27**, and in the flexible macrocyclic compounds **7**, **8**, **11**, (−)-**14**, **16**, and **17**. All of these compounds display a negative sign for the corresponding n $\rightarrow\pi^*$ ellipticities.

A positive sign for the CEs below 240 nm was established for the macrocycles (−)-**10**, **12**, **13**, and (+)-**18**. The additional chromophores at the N-atoms in compounds (−)-**10**, **12**, and **13** (an Ac group in **10**, a carbamoyl in **12**, and formamidinium in **13**) makes an interpretation of the observed CD spectra uncertain in terms of the above-mentioned lactam sign rule. For these compounds, an exciton coupling can be expected between the benzene chromophore at the chiral center and the additional chromophores at the benzylic N-atom. This is not the case with the tricyclic compound (+)-**18**. There is no additional chromophore directly attached to the chiral center, nevertheless, it shows a strong positive shorter wavelength ellipticity. This fact clearly indicates that the ellipticity below 240 nm in the compounds under investigation has a complex origin. It is assumed that there is a coupling between the ^1L_a $\pi\rightarrow\pi^*$ absorption transition of

the benzene chromophore at the chiral center and the electric (or magnetic) dipoles of the lactam chromophore in the β-position to the chiral center [20]. It seems that, for some of the compounds under study, such a mechanism dominates the origin of the ellipticities below 240 nm. Such a possibility should be supported by additional investigation.

For the open-chain compounds (−)-**19** and (−)-**20**, a positive sign was observed for the ellipticities in this region. No change of the sign was observed upon acidification. This is in contrast with the *N,N′*-dibutyl derivative (−)-**21**, which shows a negative sign as the free base, but a positive sign after acidification. Acidification of the solutions of **7**, **8**, and (−)-**14** only decreases the magnitudes of their negative-signed ellipticities.

Conclusion. – For the compounds of the present study, the recorded CD curves between 230 and 280 nm are complex due to the superposition of the ellipticities from two different chromophores. The CEs above 240 nm are clearly derived from the ^1L_b $\pi \rightarrow \pi^*$ absorption transitions of the benzene chromophore, which is directly attached to the chiral center. According to *Smith*'s quadrant rule, the sign of these CEs depends on the orientation of the plane of the benzene ring towards the CH_2 group bonded to the chiral center. In different members of the studied series of isosteric (*S*)-compounds, the preferred orientation of the benzene ring in EtOH solution change the localization of the neighboring CH_2 group in the upper or lower right quadrants and causes a positive- or negative-signed ^1L_b CEs, respectively.

The ellipticities below 240 nm were associated with the n $\rightarrow \pi^*$ absorption transitions of the lactam chromophore in the β-position to the chiral center. For compounds containing a (6*S*)-6-phenylhexahydropyrimidin-4-one ring, the observed negative sign of the n $\rightarrow \pi^*$ ellipticities is in agreement with the earlier proposed *Ogura*'s sign rule for six-membered lactams with a quasi-chair conformation. However, a rigid bicyclic analogue with a sterically fixed boat conformation of the six-membered azalactam ring and an equatorial Ph substituent of the (*S*)-chiral center also showed a negative sign of ellipticity.

For six-, nine-, 13- [6][21], and 17-membered azalactams in which (*S*)-β-phenyl-β-alanine is the chiral part of the cycle, the sign of the n $\rightarrow \pi^*$ ellipticities is negative. The introduction of an additional chromophore at the chiral center can convert the sign.

The independent origin of the observed CEs above and below 240 nm, and their high sensitivity to conformational and substitutional changes seriously limits the predictability of the CD-spectral method for the present type of macrocyclic lactam alkaloids. Compounds with one and the same chromophore and chirality but different substitution in the neighborhood of the chiral center can exhibit different, even enantiomorphic CD curves (*Fig. 4*). It was found that different members of the tested group of isosteric (*S*)-compounds displayed all possible combinations of signs of ^1L_b CEs for the benzene and n $\rightarrow \pi^*$ ellipticities of the lactam chromophores (above and below 240 nm) as shown in *Fig. 4*. Direct comparison of the obtained chiroptical properties with those of simpler compounds that have a similar arrangement of the chiral center ((*S*)- or (*R*)-(1-phenylethyl)amine in the case of (−)-dihydroverbascenine (**8**) and (+)-dihydroverbamethine (dihydroincasine C; **11**)) can be a source of incorrect conclusions regarding the configuration, as in the case of (+)-incasine C (**6**). Thus, the CD-spectral method for these types of natural products is limited almost only

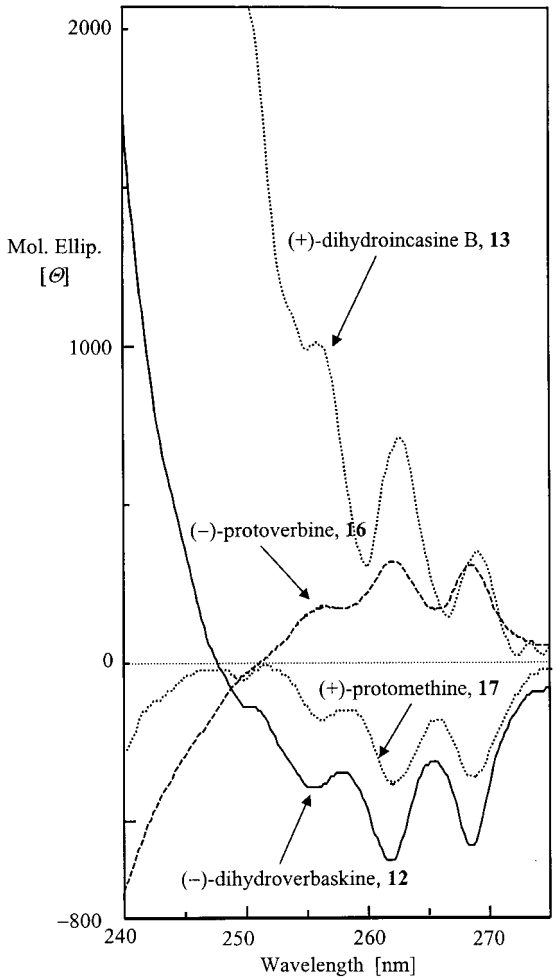


Fig. 4. *CD Curves in EtOH of (−)-(*S*)-dihydroverbaskine* (**12**), *(+)-(*S*)-dihydroincasine B* (**13**), *(−)-(*S*)-protoverbine* (**16**), *and (+)-(*S*)-protomethine* (**17**)

to comparison of the CD-spectral properties of compounds with an almost identical environment around the chiral center. The corresponding conclusions regarding configuration should be additionally supported by alternative methods.

We thank the *Swiss National Science Foundation* for generous support. *K.D.* thanks the *Prof. Dr. Hans E. Schmid Foundation* for the financial support.

Experimental Part

General. TLC: *Merck* precoated silica-gel *60* F_{254} plates and *Polygram®-Alox N/UV*$_{254}$, *Macherey-Nagel* (Germany); detection by *Dragendorff*'s and ninhydrine reagents (No. D 156a and D 127a in [22]); for more details about the TLC retention of the (*E*/*Z*)-isomeric pairs of macrocyclic spermine alkaloids, their dihydro derivatives and simpler cinnamamides, see [23]. CC: silica gel *60* (70–230 mesh) *Merck*, and *Alumina N*, act. 1,

ICN Biomedicals. CD Spectra: at r.t. in EtOH in a 1-cm quartz cell between 230 and 280 nm; *JASCO J-715* spectropolarimeter. Optical rotation: *Perkin-Elmer 241* polarimeter; for $[\alpha]_D$ values, see *Table 1*. UV: *Perkin-Elmer 555: Perkin-Elmer 297* film; in cm^{-1}. ^{1}H-NMR: *Bruker AC-300*, *ARX-300*, or *AMX-600*. ^{13}C-NMR: *Bruker AMX-600* (150 MHz); chemical shifts in ppm (δ scale) and $CDCl_3$ as solvent, TMS as internal standard, r.t. EI-MS (at 70 eV), CI-MS (NH_3 as reactant gas): *Finnigan-MAT 90*. ESI-MS: *Finnigan TSQ 700* mass spectrometer.

(+)-(2S)-2-Phenyl-9-(3-phenylpropanoyl)-1,5,9,14-tetraazabicyclo[12.3.1]octadecan-4-one (**11**). To an EtOH soln. of a sample of **7** [1], a molar excess of 40% aq. HCHO soln. was added. After several min, the mixture was evaporated to give **11** which was purified by CC (neutral alumina; AcOEt/MeOH 9:1). TLC (silica gel; AcOEt/MeOH 4:1): R_f 0.7. ^{1}H-NMR: 7.37–7.05 (*m*, 10 arom. H); 3.98 (*t*, PhCHN); 3.90–2.50 (*m*, 12 CH_2N); 2.50–1.35 (*m*, 16 aliph. CH_2). ^{13}C-NMR: 171.47, 171.40 (C=O); 141.51, 141.39 (arom. quat. C); 128.41, 128.39, 128.21, 128.18, 127.97, 127.91, 127.87, 127.84, 126.07, 126.02 (arom. CH); 64.10 (PhCHN); 50.84, 47.02, 45.12, 44.10, 36.43, 34.84, 31.71, 31.60, 27.14, 26.13, 25.59, 25.09, 21.53, 21.17 (aliph. C). ESI-MS: 499 ($[M+Na]^+$), 477 ($[M+H]^+$).

(−)-(2S)-2-Phenyl-9-(3-phenylpropanoyl)-1,5,9,14-tetraazabicyclo[12.3.1]octadecane-4,18-dione (**12**). From **7** and $COCl_2$ in $CHCl_3$ according to [1]. Compound **12** was purified by CC (neutral alumina; AcOEt/MeOH 9:1). TLC (silica gel; AcOEt/MeOH 4:1): R_f 0.8. ^{1}H-NMR: 7.37–7.20 (*m*, 10 arom. H); 6.13 (*t*, 1 H, CONH); 4.46–4.30 (*m*, H–C(2)); 3.8–2.5 (*m*, 8 CH_2); 2.0–1.25 (*m*, 5 CH_2). ^{13}C-NMR (2 conformers): 171.80/171.79, 170.57/170.39, 157.42/157.30 (3 C=O); 141.75/141.59, 139.33/139.15 (2 arom. quat. C); 128.88, 128.65, 128.61, 128.60, 128.06, 127.98, 127.65, 126.28, 126.27 (arom. CH); 47.52, 45.51, 44.76/44.45, 44.35/44.24, 44.14/43.82, 37.61/37.36, 36.73, 35.29/35.09, 31.84/31.81, 28.19, 27.13, 24.19, 23.07/22.82, 22.36/22.08 (aliph. C). EI-MS: 490 (38, $M^{+\bullet}$), 357 (100, $[M-PhCH_2CH_2C{=}O]^+$).

(−)-(8S)-13-Acetyl-8-phenyl-1-(3-phenylpropanoyl)-1,5,9,13-tetraazacycloheptadecan-6-one (**8**) [2]. A mixture of **7** (17 mg, 0.037 mmol) Ac_2O (40 µl, 40 mg, 0.41 mmol), and AcOH (2 ml) was heated at 60° for 1 h. After dilution with H_2O and extraction with $CHCl_3$, the extract was washed with H_2O, dried (Na_2SO_4), and evaporated: 13 mg (72%) of **8** as a colorless amorphous solid. Compound **8** was purified by CC (neutral alumina; acetone and acetone/MeOH 10:1). TLC (silica gel; AcOEt/MeOH 4:1): R_f 0.24. IR: 1635*s* (C=O, amide I), 1550*m* (CONH, amide II). ^{1}H-NMR: identical with the earlier published one [2]. EI-MS: 506 (53, $M^{+\bullet}$), 463 (16, $[M-COMe]^+$), 451 (100), 373 (15, $[M-PhCH_2CH_2C{=}O]^+$), 361 (18), 318 (27), 146 (56), 105 (49), 91 (79).

(−)-(8S)-9,13-Diacetyl-8-phenyl-1-(3-phenylpropanoyl)-1,5,9,13-tetraazacycloheptadecan-6-one (**10**). According to [1][2], (−)-**10** was prepared from **8** (or **7**) in $CHCl_3$ with a molar excess of Ac_2O in the presence of Et_3N at r.t. overnight. Compound (−)-**10** was purified by CC (silica gel; acetone). TLC (silica gel; AcOEt/MeOH 4:1): R_f 0.36. IR: 1635*s* (C=O, amide I), 1545*m* (CONH, amide II). ^{1}H-NMR: identical with the earlier published one [2]. ESI-MS: 571 ($[M+Na]^+$).

(+)-(2S)-2-Phenyl-9-(3-phenylpropanoyl)-1,5,9-triaza-14-azoniabicyclo[12.3.1]octadec-14(18)-en-4-one Chloride (**13**). Compound **7** (13 mg, 0.028 mmol) was treated with 30 mg (0.37 mmol) of formamidine hydrochloride in 0.5 ml of EtOH 20 h at r.t. After evaporation, conc. aq. HCl was added, the mixture extracted with $CHCl_3$, the org. extract washed with H_2O and evaporated. The remaining crude product was purified by CC (silica gel; $CHCl_3$/MeOH 4:1): 12 mg (84%) of pure **13**. Colorless amorphous solid. TLC (silica gel; $CHCl_3$/MeOH 4:1): R_f 0.52. IR: 1680*s* ($C{=}N^+$), 1640*s* (amide I), 1550*m* (amide II, CONH). ^{1}H-NMR (2 conformers): 10.10/9.96 (2*s*, $N^+{=}CHN$); 8.75/8.45 (br. 2*d*, CONH); 7.40–7.31 (*m*, 4 arom. CH); 7.30–7.24 (*m*, 3 arom. CH); 7.21–7.15 (*m*, 3 arom. CH); 5.17 (br. *t*, H–C(2)); 4.82/4.18 (br. 2*t*, H–C(17)); 4.29 (br. *t*, H–C(3)); 3.70–2.90 (*m*, 14 H); 2.67–2.45 (*m*, 3 H); 2.07–1.40 (*m*, 9 H). ^{13}C-NMR: 171.85/171.71, 168.69/168.42 (2 C=O); 151.94 ($N^+{=}CHN$); 141.48/141.32, 136.55/136.45 (arom. quat. C); 129.53, 129.29, 129.26, 128.43, 128.41, 128.36, 126.85, 126.82, 126.06 (arom. CH); 65.98/65.87 (PhCHN); 53.47/52.76; 47.17/46.54; 45.74/45.61; 43.72/43.55; 42.07; 39.24/39.02; 36.79/36.25; 35.07/34.83; 31.53/31.51; 29.66/29.10; 27.39; 24.21; 22.93/22.60/22.30; 18.95 (14 aliph. C). ESI-MS: 475 (M^+).

(−)-(17S)-5-Acetyl-17-phenyl-10-(3-phenylpropanoyl)-1,5,10,14-tetraazabicyclo[12.3.1]octadecan-15-one (**9**). A mixture of 50 mg (0.1 mmol) of **8**, 0.5 ml of 40% aq. HCHO, 0.5 ml of AcOH, and 2 ml of EtOH was refluxed for 1 h. After evaporation to dryness, H_2O was added to the residue, the mixture alkalized with 25% aq. ammonia and extracted with $CHCl_3$. The org. extract was washed with H_2O, dried (Na_2SO_4), and evaporated: **9** (almost quant.). Colorless, glass-like solid, after CC (neutral alumina; AcOEt/MeOH 9:1). TLC (silica gel; AcOEt/MeOH 8:2): R_f 0.31. IR: 1638*s* (C=O, amide I), no amide-II band (CONH). ^{1}H-NMR: 7.42–7.15 (*m*, 10 arom. H); 4.1–4.0 (*m*, H–C(17)); 4.0–2.25 (*m*, 8 CH_2); 2.05, 2.03, 1.99 (3*s*, COMe, mixture of conformers); 1.95–1.5 (*m*, 5 CH_2). ESI-MS: 541 ($[M+Na]^+$).

(−)-(9S)- and (±)-9-Phenyl-1,6-diazabicyclo[4.3.1]decan-7-one ((−)- and (±)-**15**, resp.). As described for **9**, from (−)-**14** [6]: (−)-**15**, as colorless solid. Compound (±)-**15** was prepared from 65 mg (0.3 mmol) of (±)-**14** [6] and recrystallized from hexane. M.p. 96–98°. TLC (silica gel; AcOEt/MeOH 9:1): R_f 0.71 (R_f (**14**) in the same mobile phase 0.56). ^{1}H-NMR: 7.38–7.33 (*m*, 4 arom. H); 7.27–7.24 (*m*, 1 arom. H); 4.55 (*d*, *J* = 14.3, 1 H, NCH_2N); 4.34–4.28 (*m*, 1 H–C(5)); 4.01 (*d*, *J* = 14.3, 1 H, NCH_2N); 3.71, 3.72 (2*d*, *J* = 12.8, 1 H–C(9)); 2.97, 2.96 (2*d*, *J* = 13.5, 1 H–C(5)); 2.89–2.82 (*m*, 2 H–C(2)); 2.80, 2.79 (2*d*, *J* = 14.8, 1 H–C(8)); 2.57, 2.55 (2*d*, *J* = 14.8, 1 H–C(8)); 2.17–2.12 (*m*, 1 H–C(4)); 1.85–1.77 (*m*, 1 H–C(4)); 1.60–1.51 (*m*, 2 H–C(3)). ^{13}C-NMR: 173.99 (C=O); 143.95 (arom. C(1′)); 128.63, 127.14, 126.04 (arom. C(2′)–C(6′)); 63.61 (C(10)); 61.42 (C(9)); 58.25 (C(2)); 42.35 (C(5)); 41.70 (C(8)); 27.68 (C(4)); 24.34 (C(3)). EI-MS: 230 (100, $M^{+\cdot}$), 215(12), 202(9), 187(15), 171(17), 159(43), 131(20), 118(50), 104(62), 91(43), 84(23).

(−)-(3S)-3-Amino-N-*butyl-3-phenylpropanamide* ((−)-**20**). Compound (−)-**19** [6] (540 mg, 3 mmol) was treated with 0.5 ml of $BuNH_2$ in the presence of 1 mg of $Cu(AcO)_2$ for 15 h at r.t. The mixture was concentrated, a minimal amount of 50% aq. MeOH added to the residue, the mixture alkalinized with K_2CO_3, heated at 60° for 30 min (for saponification of the traces of unchanged starting ester), and extracted with CH_2Cl_2. The extract was washed with H_2O, dried (Na_2SO_4), and evaporated: (−)-**20** (almost quant.). In the absence of Cu^{2+} ions, for 15 h, this reaction gave only *ca*. 30% yield. Colorless crystals. M.p. 64–67%. TLC (silica gel; $CHCl_3$/MeOH 10:1): R_f 0.23. ^{1}H-NMR: 7.4–7.2 (*m*, 5 arom. H); 6.82 (br. *s*, CONH); 4.37 (br. *s*, 1 H–C(3)); 3.22 (*q*, $CONHCH_2$); 2.5 (br. *s*, CH_2CO); 1.87 (br. *s*, NH_2); 1.5–1.25 (*m*, $MeCH_2CH_2$); 0.9 (*t*, Me). EI-MS: 220 (10, $M^{+\cdot}$), 119(51), 106 (100, $[PhCH{=}NH_2]^+$).

(−)-(3S)-N-*Butyl-3-(butylamino)-3-phenylpropanamide* ((−)-**21**). To a soln. of 300 mg (1.4 mmol) of **20** in 3 ml of MeOH, 140 µl (113 mg, 1.6 mmol) of PrCHO and 2 drops of AcOH were added. While cooling to 2–5°, 100 mg (2.6 mmol) of $NaBH_4$ were added portionwise. After 30 min stirring at r.t., the solvent was evaporated, H_2O added to the residue, and the mixture extracted with $CHCl_3$. The extract was washed with H_2O and evaporated. The crude material was purified by CC (neutral alumina; hexane/acetone 5:1): 265 mg (70%) of (−)-**21**. Colorless oil. TLC (silica gel; $CHCl_3$/MeOH 10:1): R_f 0.50. TLC (Al_2O_3, hexane/acetone 5:1): R_f 0.30. IR: 1640*s* (C=O, amide I), 1550*s* (CONH, amide II). ^{1}H-NMR: 7.50 (br. *s*, CONH); 7.38–7.20 (*m*, 5 arom. H); 3.95, 3.93 (2*d*, 1 H–C(3)); 3.23 (*q*, $CONHCH_2$); 2.60–2.40 (*m*, 2 H–C(2), $NHCH_2$); 1.70 (br. *s*, NH–C(3)); 1.50–1.25 (*m*, $MeCH_2CH_2$); 0.94–0.85 (*m*, 2 Me). CI-MS (NH_3); 277 ($[M+H]^+$).

(+)-(6S)-1,3-Dibutylhexahydro-3-phenylpyrimidin-4-one ((+)-**22**). A mixture of 265 mg (0.1 mmol) of (−)-**21**, 0.5 ml of 40% aq. HCHO, 0.5 ml of AcOH, and 2 ml of EtOH was refluxed for 1 h. After evaporation to dryness, H_2O was added to the residue, the mixture alkalinized with 25% aq. soln. of NH_3 and extracted with $CHCl_3$. The org. extract was washed with H_2O, dried (Na_2SO_4), and evaporated: (+)-**22** (almost quant.). Colorless oil which was purified through a short column (neutral alumina; hexane/acetone 5:1). TLC (Al_2O_3, hexane/acetone 5:1): R_f 0.44. IR: 1650*s* (C=O, amide I), no amide-II band (CONH). ^{1}H-NMR: 7.39–7.22 (*m*, 5 arom. H); 4.13 (*d*, *J* = 11.5, 1 H, NCH_2N); 4.04–3.98 (*m*, therein 4.00 (*d*, *J* = 11, 6, 1 H, NCH_2N) and 4.02 (*t*, 1 H–C(6))); 3.45–3.35 (*m*, $CONHCH_2$); 2.8–2.3 (*m*, CH_2CO, $CH_2N(1)$); 1.6–1.2 (*m*, $MeCH_2CH_2$); 0.93, 0.84 (2*t*, 2 Me). CI-MS (NH_3): 289 ($[M+H]^+$).

Methyl (3S)-8-Acetyl-18-oxo-3-phenyl-13-(3-phenylpropanoyl)-4,8,13-triazanonadecanoate (**25**). A mixture of 203 mg (0.43 mmol) of **11** and 5 ml of 6N aq. soln. of HCl was refluxed for 2 h. Compound **11** was completely transformed to **23** (TLC (silica gel; $CHCl_3$/MeOH/25% aq. soln. of NH_3 4:3:1, ninhydrine): R_f 0.3). After evaporation, the residue was dissolved in MeOH, saturated with gas. HCl, and refluxed for 1 h. TLC (silica gel; $CHCl_3$/MeOH/25% aq. soln. of NH_3 4:3:1, ninhydrine) showed **24** as the main compound (R_f 0.5). After evaporation, the residue was dissolved in MeOH, and the pH of the soln. was adjusted to 8 with an aq. soln. of $NaHCO_3$. After addition of 1 ml of AcOH, the mixture was evaporated. The residue was dissolved in 2 ml of AcOH, 0.4 ml (4 mmol) Ac_2O was added and the mixture heated at 60° for 3 h. After dilution with H_2O and extraction with $CHCl_3$, TLC of the H_2O-washed $CHCl_3$ extract (silica gel; AcOEt/MeOH 8:3) showed the presence of the partially acetylated ester **25** (R_f 0.2) and some fully (additionally at N(4)) acetylated by-product (R_f 0.32). Compound **25** was isolated by CC (silica gel; $CHCl_3$, AcOEt, then AcOEt/MeOH 8:2): 69 mg (26% overall yield) of **25**. TLC (silica gel; $CHCl_3$/MeOH/25% aq. soln. of NH_3 9:1:0.1): R_f 0.72. TLC (Al_2O_3; $CHCl_3$/acetone 1:1): R_f 0.25. IR: 1735*s* (C=O, ester), 1630*s* (C=O, amide I), 1545*m* (CONH, amide II). ^{1}H-NMR: 7.42–7.15 (*m*, 10 arom. H); 4.05 (*m*, H–C(3)); 3.7–3.6 (*m*, COOMe, mixture of conformers); 2.10–1.98 (*m*, 2 NCOMe). ^{13}C-NMR: 172.77, 172.24, 170.42, 170.21 (4 C=O); 142.38, 141.05 (2 arom. quat. C); 128.64/128.54, 128.47/128.46, 128.43/128.41, 128.40/128.39, 128.38/128.37, 128.34/128.32, 127.59, 126.96, 126.81, 126.20 (10 arom. CH); 59.59/59.57/59.48 (PhCN); 51.65/51.59 (ester C); 48.23/48.18; 47.34; 46.56; 44.71/44.41; 42.62/42.58; 42.35 (6 C–N); 35.66, 34.79, 31.64, 29.35, 27.23, 26.02, 24.98, 23.45, 21.45 (*Me*CO, acyl. CH_2, aliph. CH_2). CI-MS: 581 (42, $[M+1]^+$), 419 (33, $[M+H-PhCH{=}CH{-}COOMe]^+$), 362(9), 277(21), 180 (100, $[PhCH{=}CHCOOMe+NH_4]^+$), 163 (73, $[PhCH{=}CHCOOMe+H]^+$).

(3S)-8-Acetyl-N-*butyl-18-oxo-3-phenyl-13-(3-phenylpropanoyl)-4,8,13,17-tetraazanonadecanamide* (**26**). As described for (−)-**21**, with 25 mg (0.04 mmol) of **25**, 0.5 ml of $BuNH_2$, and 1 mg of $Cu(AcO)_2$ for 72 h: **26** (almost quant.). Colorless, glass-like solid. TLC (silica gel; $CHCl_3$/MeOH/25% aq. soln. of NH_3 9:1:0.1): R_f 0.55. TLC (Al_2O_3; $CHCl_3$/acetone 1:1): R_f 0.18. ESI-MS: 622 ($[M+H]^+$).

(−)-(6S)-1-[4-Acetyl-12-acetamido-9-(phenylpropanoyl)-4,9-diazadodecyl]-3-butylhexahydro-6-phenylpyrimidin-4-one (= N-*[3-(Acetylamino)propyl]*-N-*(4-[acetyl[3-(3-butylhexahydro-4-oxo-6-phenylpyrimidin-1-yl)propyl]amino}butyl)-3-phenylpropanamide*; (−)-**27**). From 20 mg (0.03 mmol) of **26**, 0.5 ml of 40% aq. soln. of HCHO, 0.5 ml of AcOH, and 2 ml of EtOH, (−)-**27** was obtained quantitatively after 1 h reflux. Colorless solid after purification by CC (neutral alumina; $CHCl_3$/acetone 10:3). TLC (silica gel; $CHCl_3$/MeOH/25% aq. soln. of NH_3 9:1:0.1): R_f 0.75. TLC (Al_2O_3, $CHCl_3$/acetone 1:1): R_f 0.37. IR: 1640*s* (C=O, amide I), 1550*m* (amide II, CONH; terminal acetamide). ^{1}H-NMR: 7.4–7.12 (*m*, 10 arom. H); 6.92, 6.76 (2 br. *t*, CN*H*COMe); 4.2, 4.19 (2*d*, *J* = 11.7, 1 H, NCH_2N); 4.1–3.95 (*m*, 2 H, PhCHN, 1 H, NCH_2N); 3.5–2.9 (*m*, 7 CH_2N); 2.75–1.85 (*m*, 12 H, therein 8 sharp signals (6 H) for conformers of NCOMe at 2.02, 2.00, 1.99, 1.98, 1.97, 1.95, 1.94, 1.91); 1.75–1.2 (*m*, 6 C−CH_2−C); 0.93 (*t*, *Me*CH_2). ESI-MS: 634 ($[M+H^+]$), 656 ($[M+Na]^+$), 673 ($[M+K]^+$).

*Crystal-Structure Determination of Compound (±)-***15**[1]). All measurements were conducted on a *Rigaku AFC5R* diffractometer using graphite-monochromated MoK_α radiation ($\lambda = 0.71069$ Å) and a 12-kW rotating anode generator. The intensities were collected using $\omega/2\theta$ scans and three standard reflections, which were measured after every 150 reflections, remained stable throughout the data collection. The intensities were corrected for *Lorentz* and polarization effects, but not for absorption. The structure was solved by direct methods using SHELXS86 [24] which revealed the positions of all non-H-atoms. There are two independent molecules in the asymmetric unit. There are no significant differences in their conformations, but no additional symmetry could be found. The non-H-atoms were refined anisotropically. All of the H-atoms were fixed in geometrically calculated positions (d(C−H) = 0.95 Å), and they were assigned fixed isotropic displacement parameters with a value equal to $1.2U_{eq}$ of the parent C-atom. A correction for secondary extinction was applied. Refinement was carried out on F using full-matrix least-squares procedures which minimized the function $\sum w(|F_o|-|F_c|)^2$, where $w = [\sigma^2(F_o) + (0.005F_o)^2]^{-1}$. The data collection and refinement parameters are listed in *Table 2*. A view of one of the independent molecules is shown in *Fig. 2*. Neutral atom scattering factors for non-H-atoms were taken from [25a] and the scattering factors for H-atoms from [26]. Anomalous dispersion effects were included in F_c [27]; the values for f' and f'' were taken from [25b]. All calculations were performed using the TEXSAN crystallographic software package [28].

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[1]) Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication No. CCDC-102010. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033; email: deposit@ccdc.cam.ac.uk).

Table 2. *Crystallographic Data for (±)-***15**

Crystallized from	hexane
Empirical formula	$C_{14}H_{18}N_2O$
Formula weight	230.31
Crystal color, habit	colorless, prism
Crystal dimensions [mm]	$0.18 \times 0.23 \times 0.50$
Temperature [K]	273(1)
Crystal system	triclinic
Space group	$P\bar{1}$ (#2)
Z	4
Reflections for cell determination	25
2θ Range for cell determination [°]	34 – 40
Unit cell parameters a [Å]	10.898(1)
b [Å]	19.505(3)
c [Å]	6.1565(8)
α [°]	92.25(2)
β [°]	98.90(1)
γ [°]	76.70(1)
V [Å^3]	1258.3(3)
D_x [g cm^{-3}]	1.216
$\mu(\mathrm{Mo}K_\alpha)$ [mm^{-1}]	0.0775
$2\theta_{(\max)}$ [°]	55
Total reflections measured	6042
Symmetry-independent reflections	5743
Reflections used [$I > 2\sigma(I)$]	2972
Parameters refined	308
R	0.0572
wR	0.0494
Goodness of fit	1.860
Secondary extinction coefficient	$7(1) \times 10^{-7}$
Final $\Delta_{\max}/\sigma$	0.0003
$\Delta\rho$ (max; min) [e Å^{-3}]	0.20; −0.23
Range of $\sigma(d(\mathrm{C-C}))$ [Å]	0.003 – 0.005

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