22. An Enantioselective Synthesis and the Absolute Configuration of Natural Pumiliotoxin-C[1])

Preliminary Communication

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Dedicated to Professor *R. B. Woodward* on his 60th anniversary

(22. XII. 76)

Summary

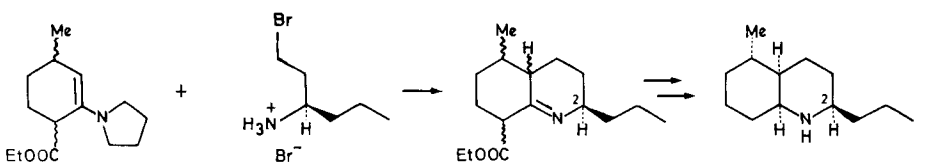
(–)-Pumiliotoxin-C-hydrochloride, as well as its unnatural enantiomer, have been synthesized in an enantioselective manner starting from (*S*)- or (*R*)-norvaline, respectively. In the crucial cycloaddition step **11** → **12** (*cf. scheme 2*) the chiral center of **11** controls to a major extent the three developing centers of chirality. This synthesis shows unambigously the (2*S*)-configuration of natural pumiliotoxin-C.

Pumiliotoxin-C a constituent of the venom of the frogs *Dendrobates pumilio* [1] and *D. auratus* [2] has been assigned structure **4** (*Scheme 1*). X-ray analysis of the hydrochloride [1] and several syntheses of the racemic alkaloid [3–7] leave no doubt about the relative configuration of the four chiral centers.

The absolute (2*R*)-configuration of the natural product was first claimed [3a] [5b] to follow from an X-ray analysis; this assignment appeared to be supported recently by the conversion of (–)-(*R*)-**2** to (–)-pumiliotoxin-C [5b] (*Scheme 1*). As will be shown below, this point needed further clarification.

We now wish to present an enantioselective synthesis of natural pumiliotoxin-C which unequivocally determines its absolute configuration. This approach (*Scheme 2*)

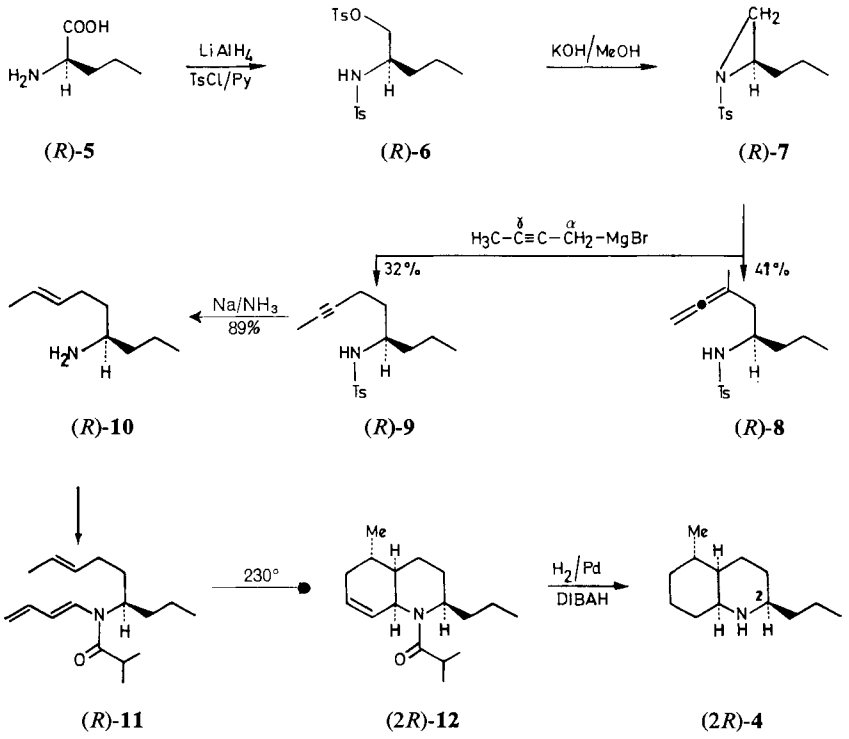
Scheme 1



(*RS*)-**1** (*R*)-**2** (2*R*)-**3** (2*R*)-**4**

[1]) Presented by one of us (*W.O.*) at the Eidgenössische Technische Hochschule Zürich, November 5, 1976.

Scheme 2



relies on the stereocontrolled induction of three chiral centers during the intramolecular cycloaddition (*RS*)-**11** → (*RS*)-**12** used as the key step for the preparation of racemic **4** [3]. Accordingly the same reaction sequence should lead selectively to the (2*R*)-pumiliotoxin-C starting from the (*R*)-amine **10**. The latter compound was obtained from (*R*)-norvaline **5**[2]) in the following way (*Scheme 2*): Reduction of (*R*)-**5** with $LiAlH_4$ followed by treatment of the crude amino alcohol with toluenesulfonyl chloride/pyridine furnished the bistoluenesulfonyl derivative (*R*)-**6**[3]), which with KOH in methanol was converted to the *N*-toluenesulfonyl aziridine (*R*)-**7**[3]) (68% yield from (*R*)-**5**). Electrophilic attack of (*R*)-**7** upon the *Grignard* reagent, prepared from 1-bromo-2-butyne ocurred both in the γ- as well as in the α-position affording a mixture of the allene (*R*)-**8**[3]) and the desired acetylene (*R*)-**9**[3])[4]) m.p. 78–80°. The latter, separated from the allene by simple crystallization, was transformed into the *trans*-(*R*)-amine **10**[3])[4]) (10 · HCl: m.p. 179–186°, 89%) with Na/NH_3, this reaction achieving concomitant reduction of the acetylene- and cleavage of the *N*-tosyl bond. The absolute configuration of (*R*)-**10** is in agreement with an indepen-

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[2]) Both, (*R*)- and (*S*)-norvaline are commercially available (*Fluka AG*); their absolute configuration has been assigned by correlation with aspartic acid [8].

[3]) The IR.- and ^{1}H-NMR. spectra of this compound are in agreement with the assigned structure.

[4]) For the specific rotation of this compound see Table 1.

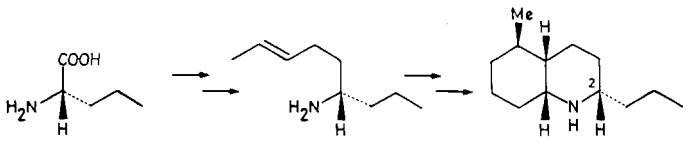
Table. *Enantiomers of* **4**, **9** *and* **10**: *Specific Rotations* ($\pm 0.3°$, $c = 1$ g/100 ml)

Compound	Origin	Solvent	$[\alpha]_D^{20}$	$[\alpha]_{436\,nm}^{20}$
Pumiliotoxin-C (**4**) HCl	Natural (*D. auratus*)	MeOH	−13.1°	−25.5°
(*R*)-**4**	from (*R*)-**10**	MeOH	+16.4°	+28.1°
(*S*)-**4**	from (*S*)-**10**	MeOH	−14.5°	−27.6°
(*R*)-**9**	from (*R*)-**5**	$CHCl_3$	−12.7°	−25.3°
(*S*)-**9**	from (*S*)-**5**	$CHCl_3$	+12.2°	+25.3°
(*R*)-**10** · HCl	from (*R*)-**9**	$CHCl_3$	−10.5°	−20.5°
(*R*)-**10** · HCl	from (*R*)-**2**	$CHCl_3$	−10.6°	−21.0°
(*S*)-**10** · HCl	from (*S*)-**9**	$CHCl_3$	+ 9.9°	+20.5°

dent elegant correlation, carried out by *Helmchen* using ^{1}H-NMR. spectroscopy [9] and high pressure liquid chromatography (HPLC.) [10] of the amide prepared from (+)-(*S*)-2-phenylpropionic acid. The HPLC. method showed the (*R*)-**4** to be 97% enantiomerically pure. Condensation of (*R*)-**10** with crotonaldehyde, treatment of the resulting crude imine with NaH (2 equ.) in dimethoxyethane at −30°, followed by addition of isobutyryl chloride and aqueous work-up afforded the dienamide (*R*)-**11** (57–87%)[3]) [3]. Thermolysis of (*R*)-**11** at 230° for 16h in toluene in the presence of 2% of bis(trimethylsilyl)-acetamide[5]) using a sealed Pyrex tube furnished (2*R*)-**12** together with minor amounts of diastereoisomeric adducts (60%). Successive catalytic hydrogenation (H_2/Pd, methanol) of the mixture, reductive cleavage of the amide bond with diisobutylaluminium hydride [11] and addition of methanolic HCl-solution furnished the crystalline (2-propanol/hexane) (+)-(2*R*)-pumiliotoxin-C (**4**) hydrochloride[3])[4]). Its m.p. (sealed capillary): 286–288° was depressed by about 40° on admixture of (+)-(2*R*)-**4**·HCl with the hydrochloride of natural **4**. The two samples exhibit the same spectral and chromatographic properties but an *opposite optical rotation*[4]), thus indicating (2*R*)-**4** to be the antipode of the natural alkaloid. In fact, the analogous reaction sequence[6]) starting from (*S*)-**5** (*Scheme 3*) furnished pure (2*S*)-**4**·HCl, m.p. 288–290°, identical with the natural **4**·HCl as shown by chiroptic[4]), spectral, chromatographic, and mixed m.p. evidence. It thus follows that natural pumiliotoxin-C exhibits the (2*S*)-configuration.

Since this result is inconsistent with the published conversion of (–)-(*R*)-**2** to natural **4** (*Scheme 1*) [5], it was decided to verify the previous stereochemical assign-

Scheme 3



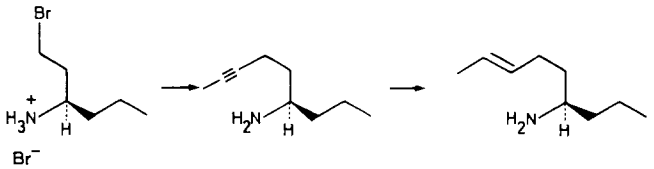
(*S*)-**5** (*S*)-**10** (2*S*)-**4**

[5]) Under similar conditions but in absence of the silylating agent variable amounts of *N*-(non-7-en-4-yl) isobutyramide were obtained; see [3].

[6]) The chirality and optical purity (97%) of (*S*)-**10** was examined in the same way as mentioned for (*R*)-**10**.

ment of (–)-**2**[7]). Accordingly, this bromoamine was treated with propynyl sodium in NH_3 to give the acetylene (*R*)-**13**[3]) (b.p. 86–87°/12 Torr, 79%) which on reduction with Na/NH_3 furnished the pure (*R*)-amine **10**[3])[4]) (89%), (*Scheme 4*).

Scheme 4



(*R*)-**2** (*R*)-**13** (*R*)-**10**

The correlation (–)-**2** → (*R*)-**10** which also provides an alternative enantioselective approach to the amine **10** thus proves the *R*-configuration of (–)-**2** as assigned earlier [5]. After completion, presentation[1]) and communication of this work to *G. Habermehl* and *B. Witkop* we were pleased to learn that in fact it was *not* the (–)-(*R*)-amine **2** hydrobromide but its antipode which gave the natural alkaloid **4** by way of (2*S*)-**3**[8]). With regard to the previously cited X-ray analysis [3a] [5b] we even more recently received notice that this analysis carried out by *I. L. Karle* also has independently proven the (2*S*)-configuration of pumiliotoxin-C, isolated from *D. pumilio*[9])[10]).

We are indebted to Prof. *G. Habermehl* and to Dr. *B. Witkop* for kindly providing us samples of natural pumiliotoxin-C hydrochloride and for valuable information prior to publication. We also thank Dr. *G. Helmchen* for determining the absolute configuration and the enantiomeric purity of (*R*)-**10** and (*S*)-**10**. Generous financial support of this work by the *Fonds National Suisse de la Recherche Scientifique*, by *Sandoz Ltd.*, Basel, and by *Givaudan SA*, Vernier, is gratefully acknowledged.

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[7]) We wish to thank Dr. *H. Andres* for communicating to us the experimental details concerning the preparation of (–)-(*R*)-**2**, $[\alpha]_D^{20} = -3.4°$, m.p. 206° prior to publication.
[8]) Prof. *G. Habermehl*, TH Darmstadt, private communication.
[9]) Dr. *B. Witkop*, National Institutes of Health, Bethesda, private communication.
[10]) In view of this new information, footnote 3 in reference [3] has to be corrected; it appears that during the earlier correspondance with the *National Institutes of Health* an interchange of two published antipodal formulas [1] had occurred by accident.