

22. An Enantioselective Synthesis and the Absolute Configuration of Natural Pumiliotoxin-C¹⁾

Preliminary Communication

by Wolfgang Oppolzer and Elmar Flaskamp

Département de Chimie Organique, Université de Genève, CH-1211 Genève 4
Dedicated to Professor R. B. Woodward on his 60th anniversary

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Summary

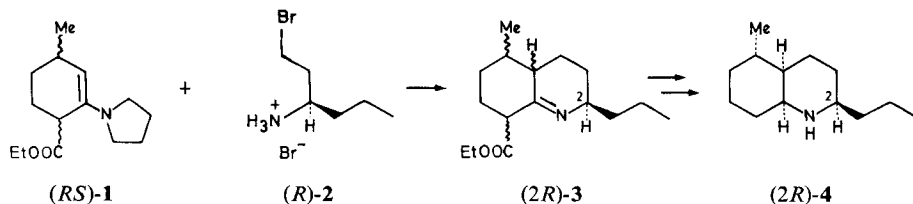
(–)-Pumiliotoxin-C-hydrochloride, as well as its unnatural enantiomer, have been synthesized in an enantioselective manner starting from (*S*)- or (*R*)-norvaline, respectively. In the crucial cycloaddition step **11** → **12** (*cf. scheme 2*) the chiral center of **11** controls to a major extent the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

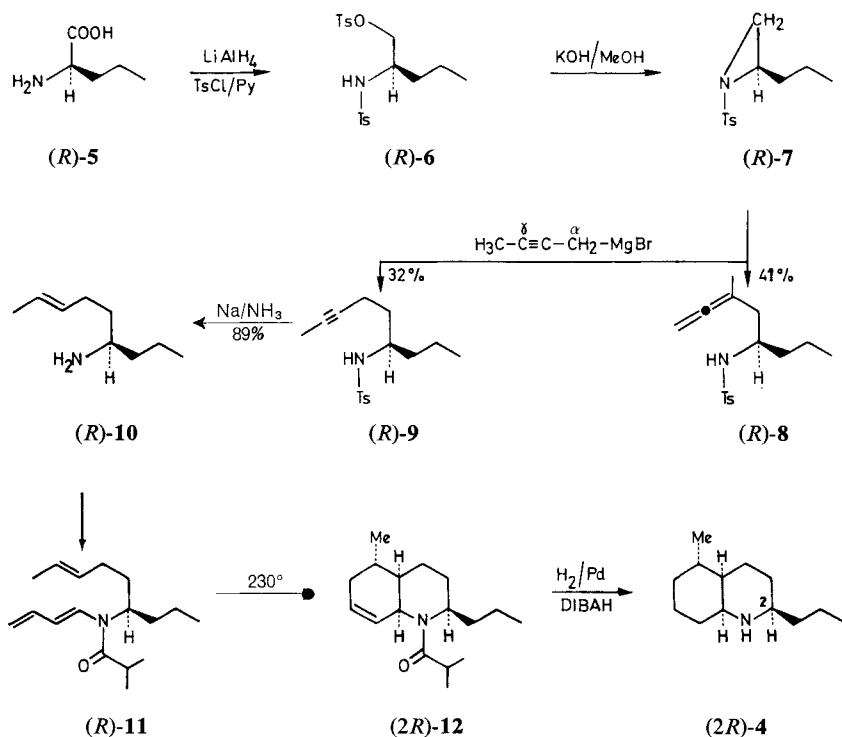
We now wish to present an enantioselective synthesis of natural pumiliotoxin-C which unequivocally determines its absolute configuration. This approach (*Scheme 2*)

Scheme 1



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 $(RS)\text{-}11 \rightarrow (RS)\text{-}12$ used as the key step for the preparation of racemic **4** [3]. Accordingly the same reaction sequence should lead selectively to the $(2R)$ -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 $(R)\text{-}5$ with LiAlH_4 followed by treatment of the crude amino alcohol with toluenesulfonyl chloride/pyridine furnished the bistoluenesulfonyl derivative $(R)\text{-}6$ ³⁾, which with KOH in methanol was converted to the N -toluenesulfonyl aziridine $(R)\text{-}7$ ³⁾ (68% yield from $(R)\text{-}5$). Electrophilic attack of $(R)\text{-}7$ upon the Grignard reagent, prepared from 1-bromo-2-butyne occurred both in the γ - as well as in the α -position affording a mixture of the allene $(R)\text{-}8$ ³⁾ and the desired acetylene $(R)\text{-}9$ ³⁾⁴⁾ m.p. $78\text{--}80^\circ$. The latter, separated from the allene by simple crystallization, was transformed into the *trans*- (R) -amine **10**³⁾⁴⁾ ($10 \cdot \text{HCl}$: m.p. $179\text{--}186^\circ$, 89%) with Na/NH_3 , this reaction achieving concomitant reduction of the acetylene- and cleavage of the N -tosyl bond. The absolute configuration of $(R)\text{-}10$ is in agreement with an indepen-

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 ^1H -NMR. spectra of this compound are in agreement with the assigned structure.

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

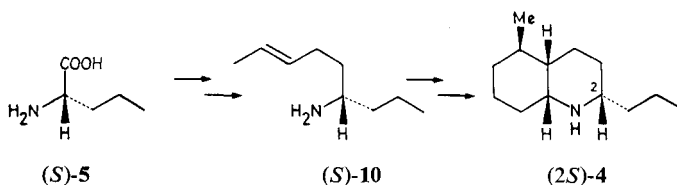
Table. Enantiomers of **4**, **9** and **10**: Specific Rotations ($\pm 0.3^\circ$, $c = 1$ g/100 ml)

Compound	Origin	Solvent	$[\alpha]_D^{20}$	$[\alpha]_{436\text{ nm}}^{20}$
Pumiliotoxin-C (4) HCl	Natural (<i>D. auratus</i>)	MeOH	-13.1°	-25.5°
(<i>R</i>)- 4	from (<i>R</i>)- 10	MeOH	$+16.4^\circ$	$+28.1^\circ$
(<i>S</i>)- 4	from (<i>S</i>)- 10	MeOH	-14.5°	-27.6°
(<i>R</i>)- 9	from (<i>R</i>)- 5	CHCl ₃	-12.7°	-25.3°
(<i>S</i>)- 9	from (<i>S</i>)- 5	CHCl ₃	$+12.2^\circ$	$+25.3^\circ$
(<i>R</i>)- 10 · HCl	from (<i>R</i>)- 9	CHCl ₃	-10.5°	-20.5°
(<i>R</i>)- 10 · HCl	from (<i>R</i>)- 2	CHCl ₃	-10.6°	-21.0°
(<i>S</i>)- 10 · HCl	from (<i>S</i>)- 9	CHCl ₃	$+9.9^\circ$	$+20.5^\circ$

dent elegant correlation, carried out by *Helmchen* using $^1\text{H-NMR}$. 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 isobutryl chloride and aqueous work-up afforded the dienamide (*R*)-**11** (57–87%)³⁾ [3]. Thermolysis of (*R*)-**11** at 230° for 16 h in toluene in the presence of 2% of bis(trimethylsilyl)-acetamide⁵⁾ 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**) hydrochloride³⁾⁴⁾. Its m.p. (sealed capillary): $286\text{--}288^\circ$ 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 sequence⁶⁾ starting from (*S*)-**5** (Scheme 3) furnished pure (2*S*)-**4**·HCl, m.p. $288\text{--}290^\circ$, identical with the natural **4**·HCl as shown by chiroptic⁴⁾, 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

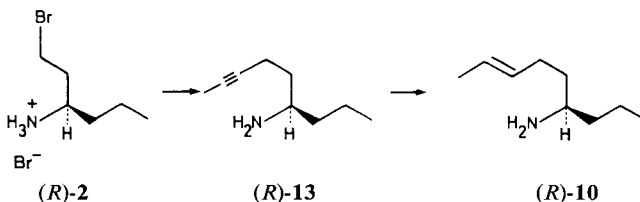


⁵⁾ Under similar conditions but in absence of the silylating agent variable amounts of *N*-(non-7-en-4-yl) isobutyramide were obtained; see [3].

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 NH₃ to give the acetylene (R)-**13**³⁾ (b.p. 86–87°/12 Torr, 79%) which on reduction with Na/NH₃ furnished the pure (R)-amine **10**³⁾⁴⁾ (89%), (*Scheme 4*).

Scheme 4



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, presentation¹⁾ 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**, $[\alpha]_D^{20} = -3.4^\circ$, 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 correspondence with the *National Institutes of Health* an interchange of two published antipodal formulas [1] had occurred by accident.