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71. The Total Synthesis of (±)-Pumiliotoxin-C[1])

Preliminary Communication

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(24. 1. 75)

Zusammenfassung. Die erste Totalsynthese des racemischen Alkaloids Pumiliotoxin-C (**9**) ausgehend von *trans*-1-Brom-3-penten (**1**) wird beschrieben. Die Schlüsselstufe **6** → **7** verläuft über eine intramolekulare *Diels-Alder*-Reaktion unter weitgehender sterischer Kontrolle von vier Chiralitätszentren. Die Struktur des synthetischen Produkte **9** wurde durch eine Röntgenstrukturanalyse des kristallinen Hydrogenmalcinates bestätigt.

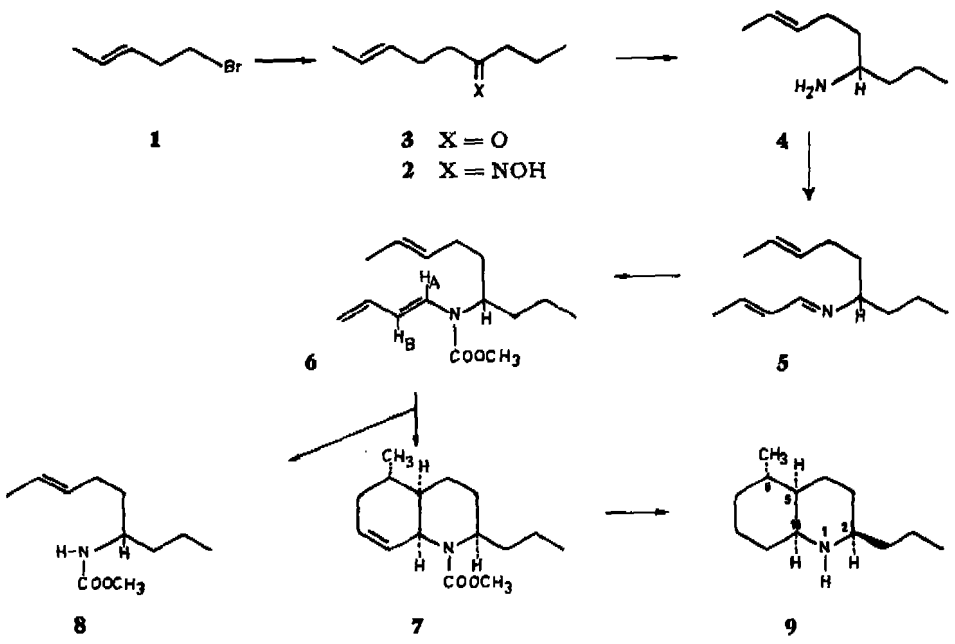
Pumiliotoxin-C, isolated from the skin of *Dendrobates pumilio* [1] and of *Dendrobates auratus*[2]) has been shown by X-ray analysis of its hydrochloride to have structure **9** [1][3]).

We wish to report the first total synthesis of racemic pumiliotoxin-C (*Scheme 1*), which exploits a stereoselective approach to *cis*- fused octahydroquinolines, described in the preceding communication [2].

The *Grignard* reagent, prepared from *trans*-1-bromo-3-pentene (**1**) [3] was reacted with 1.1 mol of butyronitrile in refluxing ether [4] to give after acidic aqueous work up

[1]) Presented in a lecture, given at the University of Giessen, December 5, 1974.
[2]) *W. Kissing*, TH Darmstadt, private communication.
[3]) The absolute configuration of pumiliotoxin-C, as depicted in formula **9**, has been established by X-ray analysis: *I. L. Karle*, private communication.

Scheme 1



the ketone **2**[4]) (b.p. 82°/10 Torr, IR. (film): 1728, 970 cm^{-1}, 62% yield), which was converted [5] to its oxime **3**[4]) (b.p. 118–119°/10 Torr; IR. (film): 1650, 967 cm^{-1}; 52% yield). Reduction of the oxime **3** with $LiAlH_4$ in ether [6] furnished the amine **4**[4]) (b.p. 75–77°/10 Torr; IR. (film): 3360, 970 cm^{-1}; 70% yield), which was purified by four crystallisations of its hydrochloride (m.p. 156–157°) from CH_2Cl_2/hexane. Condensation [7] of the free amine **4** with crotonaldehyde afforded the conjugated azomethine **5**[4]) (dist. 80° (bath)/0.6 Torr; IR. (film): 1652, 970 cm^{-1}; UV. (cyclohexane): λ_{max} = 222.5 nm, log ε = 4.29; 80% yield), which by subsequent treatment with 1.5 mol of sodium hexamethyldisilazane and 2 mol of methyl chloroformate in toluene at −40°[5]) gave the *trans*-dienamide **6**[4]) (dist. 110° (bath)/0.01 Torr; ^{1}H-NMR. ($CDCl_3$): δ_{HA} = 6.78 ppm, J_{AB} = 13 Hz; IR. (film): 1720, 1645 cm^{-1}; UV. (CH_3OH): λ_{max} = 260 nm/log ε = 4.34; 49% yield). Thermolysis of the dienamide **6** in toluene (5% solution in a sealed ampoule) at 215° after 20 h afforded a mixture of the desired octahydroquinoline **7**[4]) (dist. 115° (bath)/0.05 Torr; IR. (film): 1700, 770 cm^{-1}, 25% yield) and the elimination product **8**[4]) (dist. 110° (bath)/0.05 Torr; IR. (film): 3335, 1702 cm^{-1}, 37% yield), which was separated by chromatography on silica gel. The quinoline **7** on hydrogenation with Pd/C in methanol (25°/5 h), followed by acid hydrolysis (refluxing conc. HCl/HOAc/H_2O 1:1:1, 30 h) was converted to the racemic pumiliotoxin-C hydrochloride (**9**)[4]) (m.p. (sealed capillary) 245°, after crystallisation from 2-propanol), which exhibited the same ^{1}H-NMR. ($CDCl_3$)-spectrum and chromatographic properties[6]) as the natural alkaloid.

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[4]) The IR.- and ^{1}H-NMR.($CDCl_3$)-spectra are in full agreement with the assigned structure.

[5]) See [8], procedure b.

[6]) Silica gel, C_6H_6/CH_3OH/sat. aqu. NH_4OH (95:5:0.5)

Further investigation of the crude mixture obtained from **7** by hydrogenation and hydrolysis revealed the presence of a minor[7]) product (**7** · HCl, m.p. 218–220°), which appears to be an isomer of **9** as it has similiar ^{1}H-NMR.- and mass-spectra.

Hence it appears, that the chiral center of the dienamide **6** controls to a major extent the relative configuration of the three chiral centers which are formed simultaneously in the cycloaddition-process.

In order to obtain an unambigous structural proof the synthetic pumiliotoxin-C was submitted to X-ray analysis. A crystal of the corresponding hydrogen maleate (m.p. 176–178°) was used to measure the intensities on a diffractometer. The structure was solved by direct methods [9] and refined to R = 0.0389 with 1029 significant reflexions for 316 structural parameters. The result is shown in the Figure. Further details of the X-ray analysis will be given elsewhere.

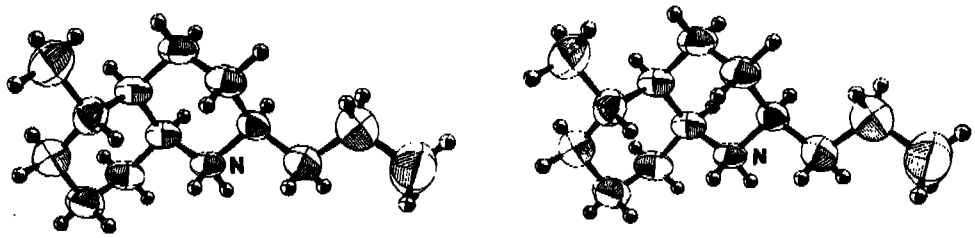

Fig. *Stereoscopic view of (±)-pumiliotoxin-C as found in the crystal of its hydrogen maleate*

Separation of the racemic amine **4** into its enantiomers and conversion of the (*R*)-amine **4** into the natural, optically active pumiliotoxin-C is under study.

Note added in proof: Since this work has been submitted for publication a different, independent synthesis of (±)-pumiliotoxin-C hydrochloride, m.p. 232°, was reported [10].

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[7]) The products **9** and its more polar isomer were obtained in a ratio of *ca.* 3:1.