Asymmetric Synthesis. 21.[1] The First Enantioselective Synthesis of Natural (+)-Tetraponerine-8: A New Extention of the CN(*R*,*S*) Method to an Uncommon Skeleton

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Received October 31, 1989

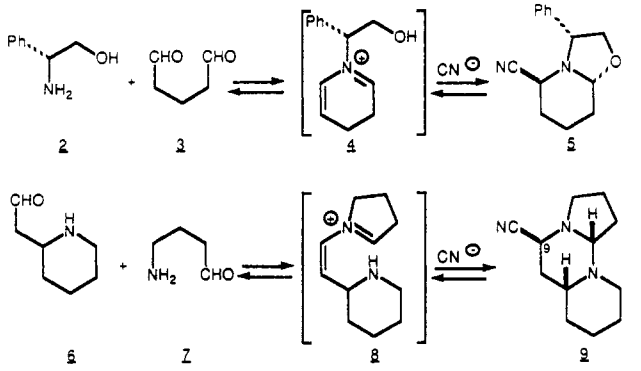
Summary: The first synthesis of natural (+)-tetraponerine-8 (1) has been accomplished in six steps and 34% overall yield from 2-cyano-6-oxazolopiperidine synthon **5** and has allowed assignment of the absolute configuration.

Tetraponerine-8 (1) (Scheme II) was isolated recently from the venom of Neoguinean ant Tetraponera sp.[2] This compound is the major constituent of the ant defense secretion which contains other alkaloids of related structure (T-1 to T-8), differing in the alkyl side chain and the relative stereochemistry, and has been found to exhibit interesting insecticidal properties.[2a] Tetraponerine-8 (1) appeared to be an attractive target molecule because of the biological properties of this compound, its uncommon structure,[3] and the scarcity of the natural source. Indeed, a total synthesis of racemic **1** was published[2c] very soon after its isolation. In the present paper we report the first asymmetric synthesis of natural (+)-tetraponerine-8 (1) according to a route using a new extension of the CN(*R*,*S*) method.[4] Moreover the absolute configuration of the natural product has been established for the first time.

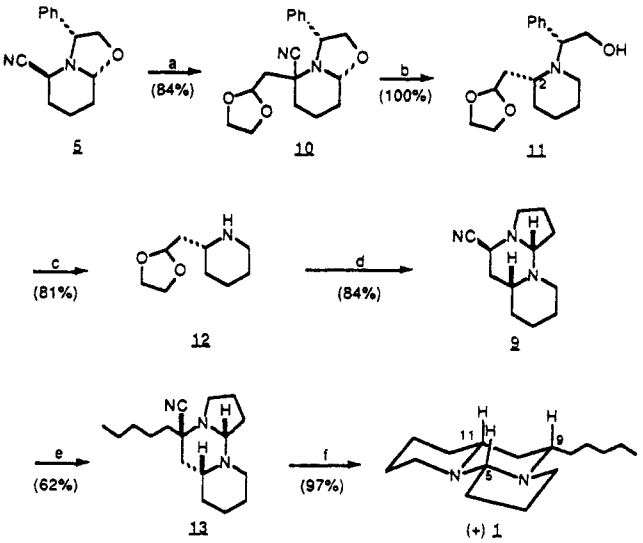
Cyano aminal **9** was the key intermediate in this synthesis; its preparation was envisaged by the cross-condensation of two different amino aldehydes, **6** and **7**, via the enamine–iminium species **8** in a scheme which parallels the previously reported[5,6] preparation of the chiral 2-cyano-6-oxazolopiperidine **5** (Scheme I). The synthesis of **9** can be considered as an extention of the CN(*R*,*S*) method because of the methodological analogy in preparation of **5** and **9** and also because of the possible transformation of **9** to the tetraponerines with the suitable stereochemistry. Indeed it has been previously shown that replacement of nitrile of **5** by an alkyl chain can be directed to produce either equatorial or axial α-alkylpiperidine derivatives as required.[5a] Furthermore, chiral amino aldehyde **6** was prepared with the desired configuration starting from **5**, thus the CN(*R*,*S*) method was used twice in the proposed scheme. Finally, the relative stereochemistry of **9** can be predicted to be the desired one since its formation was thermodynamically controlled and tetraponerine-8 represents the more stable structure.

The anion of chiral 2-cyano-6-oxazolopiperidine **5** was alkylated with 2-(bromomethyl)-1,3-dioxolane in the presence of HMPA (5 equiv) to give **10** in 84% yield (Scheme II). Treatment of **10** with $NaBH_4$ in ethanol led to reduction of both potential iminium groups to furnish **11** in a quantitative yield. This step was stereospecific:

Scheme I



Scheme II[a]



[a] Reagents: (a) LDA–HMPA, THF, −78 °C, 2-(bromomethyl)-1,3-dioxolane; (b) $NaBH_4$, EtOH, Δ, 2 h; (c) H_2, Pd/C 10%, MeOH, 40 min; (d) dilute HCl, room temperature, overnight, then, 4-aminobutyraldehyde diethyl acetal, KCN, pH 2–3, 2 h, room temperature; (e) LDA–HMPA, THF, −78 °C, $Br(CH_2)_4CH_3$; (f) Na, NH_3 liquid, −78 °C, 20 min.

only one product was found in the crude reaction mixture after NMR and chromatographic analyses. A 2*R* configuration (corresponding to C-11 for the natural product numbering) was assigned to alcohol **11** on the basis of our previous work.[5] Hydrogenolysis (H_2, Pd/C) of the N-benzylic bond of **11** gave **12** in a 81% yield after purification. Condensation of the amino aldehyde (not isolated) resulting from the acid cleavage of the acetal of **12** with commercially available 4-aminobutyraldehyde diethyl acetal in the presence of potassium cyanide led to a 84% yield of a single tricyclic cyano aminal. We were unable to isolate any other isomer of this compound, and it was assumed that the more stable product **9**[7] had been ob-

(1) Part 20: Zhu, J.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1989**, *30*, 6323.

(2) (a) Braekman, J.-C.; Daloze, D.; Pasteels, J.-M.; Van Hecke, P.; Declerc, J.-P.; Sinnwell, V.; Francke, W. *Z. Naturforsh.* **1987**, *42C*, 627. (b) Merlin, P.; Braekman, J.-C.; Daloze, D. *J. Chem. Ecol.* **1988**, *14*, 517. (c) Merlin, P.; Braekman, J.-C.; Daloze, D. *Tetrahedron Lett.* **1988**, *29*, 1691.

(3) Very few alkaloids contain an aminal function; see for e.g.: Ban, Y.; Kimura, M.; Oishi, T. *Heterocycles* **1974**, *2*, 323.

(4) Referring to the desired obtention of a *R* or *S* configuration α to the nitrogen by elimination of the CN group. For valuable examples on this strategy see ref 5.

(5) (a) Guerrier, L.; Royer, J.; Grierson, D. S.; Husson, H.-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754. (b) Royer, J.; Husson, H.-P. *J. Org. Chem.* **1985**, *50*, 670. (c) Husson, H.-P. *J. Nat. Prod.* **1985**, *48*, 894.

(6) For a related reaction, see: Kukla, M. J.; Breslin, H. J. *J. Org. Chem.* **1987**, *52*, 5046.

(7) **9**: mp 75 °C (CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.2–2.1 (m, 13 H), 2.2 (tdd, *J* = 10, 2, 2 Hz, 1 H), 2.6 (q, *J* = 8.5 Hz, 1 H), 2.78 (dd, *J* = 8, 6 Hz, 1 H), 2.9 (bd, *J* = 12 Hz, 1 H), 3.0 (ddd, *J* = 8, 2, 2 Hz, 1 H), 4.1 (dd, *J* = 5, 2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) 19.3, 23.8, 25.1, 28.7, 31.5, 34.8, 49.3, 49.8, 50.4, 57.8, 79.0, 116.2.

0022-3263/90/1955-1140$02.50/0

tained. Examination of the ^1H NMR spectrum (200 MHz) with the help of 2D $^1H/^1H$ and $^1H/^{13}C$ correlations confirmed this hypothesis: protons on C-5 and C-11 are both axial and the cyano group occupied an axial position.

After ensuring the correct relative stereochemistry at carbons 5 and 11 it was necessary to introduce the pentyl side chain in the proper equatorial configuration. According to the CN(*R*,*S*) method, this was possible by simple decyanation of alkylated amino nitrile as **13**. Indeed, cyano aminal **9** was alkylated with *n*-pentyl bromide after deprotonation by LDA-HMPA to give **13** in 62% yield. The cyano group of **13** was removed in a stereospecific manner using Na in liquid ammonia to give (+)-tetraponerine-8 (**1**) in 97% yield.[8]

Synthetic (+)-tetraponerine-8 (**1**) exhibited all analytical data (^1H and ^{13}C NMR, MS) in full agreement with those of natural material.[2a] The same optical rotation and sign were also obtained: $[\alpha]_D$ +99° (*c* 0.6, $CHCl_3$) [lit.[2a] $[\alpha]_D$ +102° (*c* 0.15, $CHCl_3$)]. The relative configuration of tetraponerine-8 being known[2] it was thus possible to assign the 5*R*,9*S*,11*R* absolute configuration to synthetic and natural (+)-tetraponerine-8.

Acknowledgment. We want to thank Drs. Braekman, Daloze, and Merlin for valuable discussions.

(8) The direct alkylation of **9** by a nucleophilic reagent (as a Grignard reagent) would lead in the opposite to the introduction of the side chain in an axial position.[5a]

Photoactivation through (π^* + σ^*) LUMO Mixing. Photochemistry and Photophysics of the 7-Chloro-2-(trimethylsiloxy)norbornenes[1]

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Received October 27, 1989

Summary: The syn and anti isomers of 7-chloro-2-(trimethylsiloxy)norbornene have been synthesized and found to be comparably and minimally photoactive, a result which contrasts with previous observations for the *exo*- and *endo*-6-chloro-2-(trimethylsiloxy)norbornenes and which confirms the role of (π^* + σ^*) LUMO mixing as the source of relatively facile C–Cl photolytic cleavage of the *exo*-6-chloro isomer.

The chemical consequences of orbital interactions between distal functionalities have been extensively investigated for molecular ground states[2] but much less so for electronic excited states. As part of our continuing interest in such interactions as a mechanism for the photoactivation of distal functionalities[3] we recently reported on the photochemistry and photophysics of the exo and endo isomers of 6-chloro-2-(trimethylsiloxy)norbornene (ExoCl and EndoCl, respectively).[4] Ab initio calculations predict, and the ultraviolet absorption and electron transmission spectra give evidence for, the admixture of an appreciable C–Cl σ^* component in the, predominantly π^*, LUMO of ExoCl but not EndoCl. Such mixing of an antibonding σ^* orbital into the LUMO should facilitate C–Cl homolysis upon photochemical excitation and such is indeed observed for ExoCl, with EndoCl almost 9-fold less reactive.[4]

However, orbital mixing is not uniquely capable of rationalizing photolytic dehalogenation of ExoCl and, for example, one can derive a plausible alternative involving electron transfer from an initially excited silyl enol ether chromophore.[4] Though arguments against this alternative have been presented,[4] ab initio calculations on the related pair of isomers, *syn*- and *anti*-7-chloro-2-(trimethylsiloxy)norbornene (SynCl and AntiCl, respectively) suggested that a study of the spectroscopic and photochemical properties of these compounds could provide a definitive test of the orbital mixing mechanism. This is so because, despite the similar relative orientation of the C–Cl bond to the trimethylsilyl enol ether functionality in ExoCl and AntiCl, the calculations (see below) predict much less orbital mixing in (and thus a lower reactivity for) the AntiCl isomer. One would also anticipate a diminution in the anti/syn reactivity ratio for the 7-chloro pair relative to that observed for the exo/endo 6-chloro pair. By contrast, were an electron-transfer mechanism operating, a consideration of the relative distances of C-7 and C-6 to C-2 of the silyl enol ether moiety (2.35 Å vs 2.43 Å by ab initio calculation) would suggest that C–Cl homolysis in AntiCl should be comparable to that observed for ExoCl. Furthermore, the particularly close approach of the chlorine atom to C-2 in SynCl (3.16 Å), relative to that in AntiCl (4.08 Å) could well be expected to produce a particularly facile homolysis in the syn isomer. As we will show below, our results are consistent with the conclusions predicted by the orbital mixing hypothesis.

Table I. π^*/σ^* LUMO Mixing in 6-Chloro- and 7-Chloro-2-(trihydrosiloxy)norbornenes

molecule	LUMO constitution[a]	
	% σ^* C–Cl	% π^* C=C
ExoCl	27.3	53.6
EndoCl	3.9	66.9
AntiCl	3.7	67.6
SynCl	4.5	66.0

[a] 3-21G*//3-21G* calculations with the percentages calculated as previously described.[4]

Ab initio calculations[5] were performed on the trihydrosiloxy analogues of the four compounds (ExoCl,

(1) Organic Photochemistry, Part 85. Part 84: Wu, Z. Z.; Morrison, H. *J. Am. Chem. Soc.* **1989**, *111*, 9267. We thank the National Science Foundation (Grant CHE 8700333) for suport of this research.

(2) For a recent theoretical discussion, see: Paddon-Row, M. N.; Jordan, K. D. In *Modern Models of Bonding and Delocalization*; Liebman, J. F., Greenberg, A., Eds.; VCH: New York, 1988; Chapter 3.

(3) Morrison, H. A. *Rev. Chem. Intermed.* **1987**, *8*, 125.

(4) Maxwell, B. D.; Nash, J. J.; Morrison, H. A.; Falcetta, M. L.; Jordan, K. D. *J. Am. Chem. Soc.* **1989**, *111*, 7914.

(5) Ab initio calculations utilized the GAUSSIAN86 package: Frisch, M. J.; Binkely, J. S.; Schlegel, H. B.; Raghavachari, K.; Melius, C. F.; Martin, R. L.; Stewart, J. J. P.; Bobrowicz, F. W.; Rohlfing, C. M.; Kahn, L. R.; Defrees, D. J.; Seeger, R.; Whiteside, R. A.; Fox, D. J.; Fleuder, E. M.; Pople, J. A. Carnegie-Mellon Quantum Chemistry Publishing Unit, Pittsburgh, PA, 1984.

0022-3263/90/1955-1141$02.50/0