Tetrahedron Letters, Vol.22, No.42, pp 4197 - 4198, 1981
Printed in Great Britain

0040-4039/81/424197-02$02.00/0

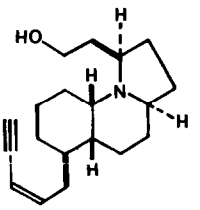
ON THE ABSOLUTE CONFIGURATION OF GEPHYROTOXIN

Roger Fujimoto and Yoshito Kishi*

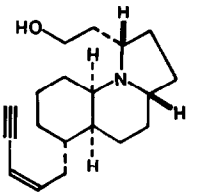
Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138, USA

Summary. It appears that the absolute configuration assigned to gephyrotoxin should be revised based on the chemical synthesis of optically active gephyrotoxin from L-pyroglutamic acid.

The novel and diverse biologically active alkaloids isolated from Dendrobatid frogs has attracted the attention of synthetic organic chemists; both gephyrotoxin[1] and perhydrogephyrotoxin[2] have been synthesized in racemic form. In this communication, we would like to report that the absolute configuration 2 previously assigned to natural gephyrotoxin by X-ray analysis[3] should be revised as 1.



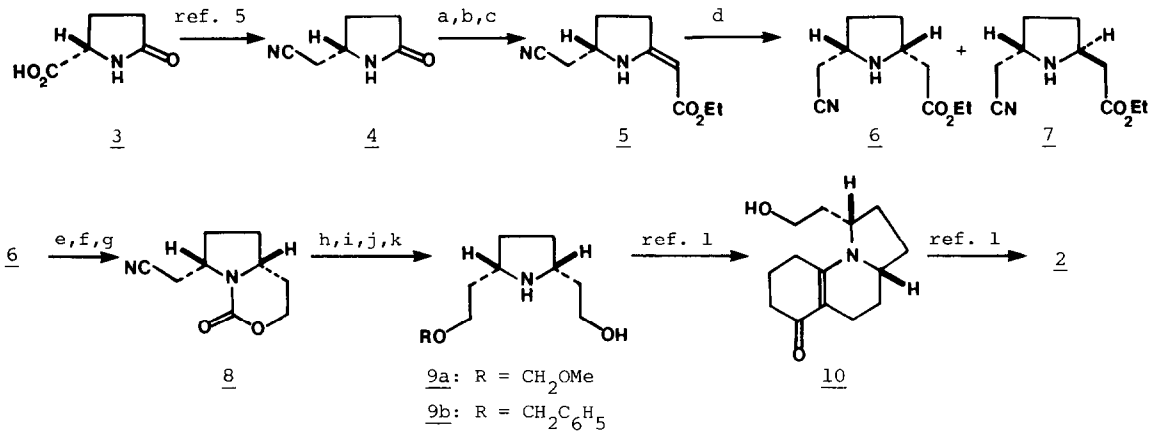
1 : gephyrotoxin



2

After some consideration, we felt that our previous synthesis[1] of racemic gephyrotoxin could be readily adapted to utilize an optically active starting material with known absolute configuration. This would serve not only to confirm the assigned absolute configuration, but would also allow us to assign the absolute configuration of the optically active pyrrolidine 9b, which had been prepared by resolution.[4]

Commercially available L-pyroglutamic acid (3) appeared to be a good starting point since it could be converted to the nitrile 4[5] [α_D -21.5°, c = 1.7 (EtOH); lit.[5] α_D -20°, c = 5 (EtOH)] without racemization. Treatment of the nitrile 4 with P_2S_5 gave a thiolactam which was subjected to the Eschenmoser sulfide contraction[6] and deacylation[7] reactions to give the vinylogous urethane 5 [α_D -150.8°, c = 0.40 (EtOH); NMR ($CDCl_3$): δ 4.57 ppm (1H, s), 4.09 (2H, q, J = 7 Hz), 2.54 (2H, d, J = 5), 1.24 (3H, t, J = 7)]. Hydrogenation of 5 afforded a 2.3 : 1 mixture of *cis*- and *trans*-pyrrolidines 6 [α_D -24.4°, c = 2.7 (EtOH); NMR ($CDCl_3$): δ 4.12 ppm (2H, q, J = 7 Hz), 2.39 (2H, d, J = 6), 1.26 (3H, t, J = 7)] and 7. The *cis*-pyrrolidine 6 was converted to the urethane 8 [α_D -38.0°, c = 0.76 (EtOH); NMR ($CDCl_3$): δ 3.07 ppm (1H, dd, J = 17, 7 Hz), 2.74 (1H, dd, J = 17, 4)]. DIBAL reduction of 8, followed by acid hydrolysis, gave an aldehyde, which was reduced and protected as a methoxymethyl ether. Base hydrolysis of this product gave the pyrrolidine 9a [α_D -0.8°, c = 2.3 (EtOH); NMR ($CDCl_3$): δ 4.60 ppm (2H, s), 3.58 (2H, t, J =



Reagents: (a) P_2S_5/Py/80°C, (b) MeCOCH(Br)CO_2Et/$NaHCO_3$/RT→reflux, (c) 0.1 N KOH/EtOH/60°C, (d) H_2 (1 atm)/5% Pt-C/$HClO_4$/MeOH/RT, (e) C_6H_5OCOCl/Py/CH_2Cl_2/RT, (f) $LiBH_4$/THF/RT, (g) KH/THF/RT, (h) DIBAL/THF-toluene/-105°C, followed by 3 N HCl workup (-105°C→RT), (i) $NaBH_4$/DME/RT, (j) $MeOCH_2Br$/(*i*-Pr)$_2$(Et)N/CH_2Cl_2/RT, (k) Ba(OH)$_2$/H_2O/reflux.

7 Hz), 3.34 (3H, s)], which must have the indicated absolute configuration. The pyrrolidine 9a was converted to the vinylogous amide 10 [α_D +538°, c = 1.4 (EtOH): mp 176-79°C], identical (NMR, IR) to the racemic material previously prepared.[1]

Following the procedures of our previous synthesis, the vinylogous amide 10 was converted to gephyrotoxin, which proved to be dextrorotatory [α_D +50.0°, c = 1.0 (EtOH)], while the natural gephyrotoxin proved to be levorotatory [α_D -51.5°, c = 1.0 (EtOH)].[8] These experiments lead us to believe that the absolute configuration of natural gephyrotoxin should be revised as depicted by structure 1.[9,10]

References and Footnotes

1. R. Fujimoto and Y. Kishi, J. Am. Chem. Soc., 102, 7154 (1980).
2. L. E. Overman and C. Fukaya, J. Am. Chem. Soc., 102, 1454 (1980).
3. J. W. Daly, B. Witkop, T. Tokuyama, T. Nishikawa, and I. L. Karle, Helv. Chim. Acta, 60, 1128 (1977).
4. Racemic pyrrolidine 9b was optically resolved in 3 steps, i.e. (1) (R)-$C_{10}H_7CH(Me)N=C=O$/CH_2Cl_2/RT, (2) separation by silica gel column chromatography, and (3) NH_3/MeOH/150°C. It was important to establish the absolute configuration of the optically resolved pyrrolidine 9b, since both enantiomers could be utilized for the synthesis of gephyrotoxin with the natural absolute configuration (note the potential symmetry element existing in 9b). The details of these experiments will be published in a full paper.
5. R. B. Silberman and M. A. Levy, J. Org. Chem., 45, 815 (1980).
6. M. Roth, P. Dubs, E. Götschi, and A. Eschenmoser, Helv. Chim. Acta, 54, 710 (1971).
7. H. Tanino, T. Nakata, T. Kaneko, and Y. Kishi, J. Am. Chem. Soc., 99, 2818 (1977).
8. The specific rotation of natural gephyrotoxin was recorded on a Perkin-Elmer 241 polarimeter by R. F. We would like to thank Dr. Daly, National Institutes of Health, for providing a sample of natural gephyrotoxin.
9. Prior to submitting this paper, we had communications regarding this result with Dr. Daly.[3] Dr. Karle re-examined the data of the previous X-ray analysis and found no mis-assignment. We may add that the gephyrotoxin used for the α_D measurement was isolated from frogs collected in the same area as the toxin used for the X-ray analysis, but in a different year.

10. Support from the National Institutes of Health, NS 12108, is gratefully acknowledged.

(Received in USA 15 July 1981)