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A STEREOSELECTIVE SYNTHESIS OF THE AZASPIROUNDECANE RING SYSTEM OF (-)-HISTRIONICOTOXIN FROM (+)-GLUTAMIC ACID

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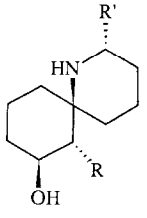
Abstract: We describe herein the first stereoselective synthesis of the natural (-)-histrionicotoxin ring system, where the chirality is derived from L-glutamic acid. The key transformation involves intramolecular dioxolenone photocycloaddition of a substrate derived from the amino acid, which establishes three of the four chiral centers in (-)-histrionicotoxin.

The structurally unique alkaloid, (-)-histrionicotoxin, 1, isolated from the skin secretions of the Columbian poison frog Dendrobates histrionicus, has challenged the imaginations of synthetic chemists for more than ten years.[4] The attention given to the synthesis of 1 (Scheme I) stems from its unique properties as a neurotoxin in conjunction with its scarcity (ca. 200 μg per frog).[5] It has been shown that both histrionicotoxin, 1, and perhydrohistrionicotoxin, 2, selectively bind to the acetylcholine receptor and interrupt transsynaptic transmission of neuromuscular impulses.[6] Both compounds are therefore of considerable importance in studying cholinergic receptor mechanisms in the neuromuscular system.[7] An efficient approach to the syntheses of 1 and 2 must successfully address issues of both relative and absolute asymmetric induction: 1) communication of stereochemical information from

SCHEME I



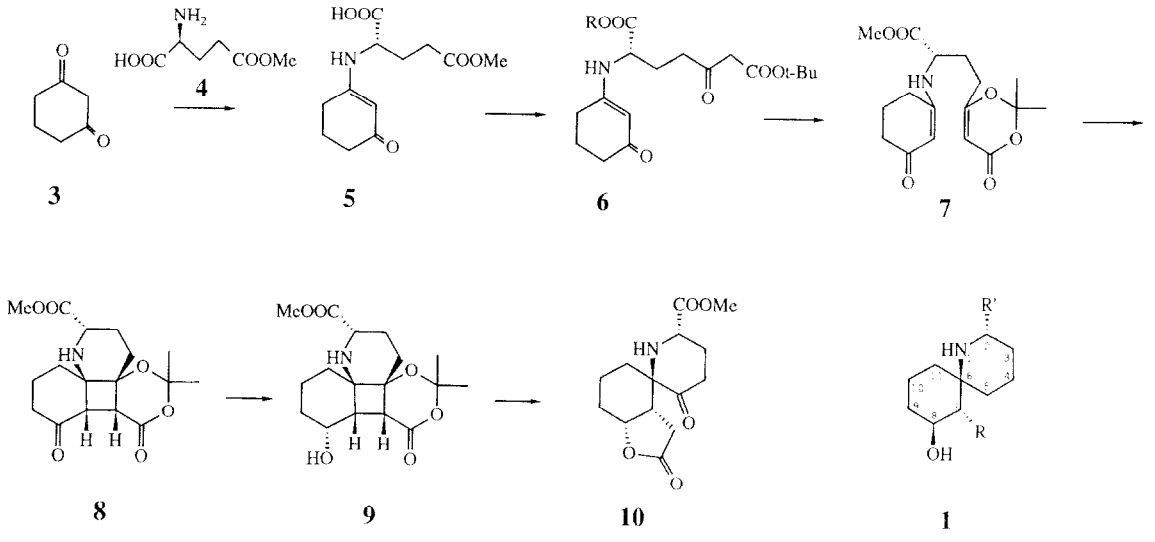
1 R = CH=CH-C≡CH
R' = CH_2-CH=CH-C≡CH

2 R = n-C_4H_9
R'= n-C_5H_{11}

one ring to the other through the connecting spiro atom, and 2) the preparation of the natural (-)-antipodes of 1 and 2. We describe herein the first stereoselective synthesis of the natural (-)-histrionicotoxin ring system, in which asymmetric induction is achieved using the intramolecular photocycloaddition reaction of dioxolenones that we have recently described.[8a,b]

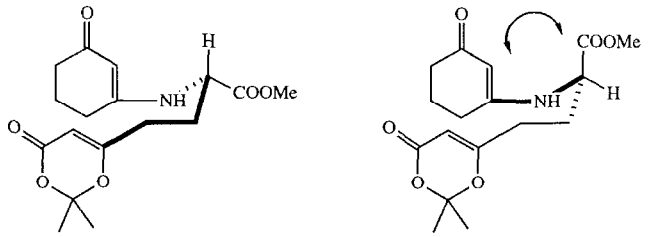
The synthesis of the photosubstrate is outlined in Scheme II. Condensation of cyclohexane-1,3-dione with L-methyl glutamate afforded the vinylogous amide 5 (benzene reflux, 3 h, $[\alpha]^{22}_D$ -94.2 [c 0.034 MeOH]). Without purification, this product was treated with the lithium enolate of tert-butylacetate[9] (4 equiv, THF, -78°C→25°C, 48 h), to provide the β-ketoester, 6 (R=H), which was purified (SiO_2) as the corresponding methyl ester, 6 (R=Me; diazomethane, tetrahydrofuran, 0°C, 62% yield over three steps, $[\alpha]^{22}_D$ -4.6 [c 0.016 CH_2Cl_2]. Conversion of 6 into the photosubstrate 7 was accomplished by dioxolenone formation using a modification of our previously described conditions[10] (4 equiv trifluoroacetic anhydride, 4 equiv acetone, trifluoroacetic acid, 25 °C, 24 h, 85% yield, $[\alpha]^{22}_D$ +57.5 [c 0.016 CH_2Cl_2]). Irradiation of 7[11] (0.01 M in degassed acetonitrile, 0°C, 75 min., 450 W Hg lamp, pyrex filter) produced a single photoadduct 8 ($[\alpha]^{22}_D$ +48.1 [c 0.007 CH_2Cl_2], m.p. 102-104° [benzene]) in quantitative yield, the stereochemistry of which was determined by X-ray crystallographic analysis.[12]

SCHEME II



The exclusive formation of 8 can be explained by examination of the diastereomeric transition states shown in Scheme III. Transition state A, in which the carboxymethyl group of the glutamic acid is oriented in a pseudo-equatorial position on the six-membered ring

SCHEME III



being formed, leads to the observed product. In this photochemical cycloaddition, the chiral center of the amino acid has induced two of the three other centers of asymmetry in the natural product, 2. While asymmetric induction in the intramolecular [2+2] photocycloaddition has been previously observed,[13] this is the first successful case of high asymmetric induction in the formation of a [4.2.0] bicyclooctane in which the chiral center is not directly attached to one of the alkenes which participate in the photocycloaddition.

We have converted 8 into the azaspiroundecane ring system in the following manner (Scheme II): Reduction of 8 (1.4 equiv $NaBH_4$, 9/1 tetrahydrofuran/ethanol, -78°C, 15 min., 66% yield) furnished the alcohol 9 ($[\alpha]^{22}_D$ 0 [c 0.037 CH_2Cl_2]) as a single product (confirmed by ^{13}C-NMR), as expected by addition of hydride from the convex face of the cis-fused 6-4 ring system. Deprotonation of 9 (1 equiv NaH, tetrahydrofuran, 25°C, 30 min.) provided the lactone 10 ($[\alpha]^{22}_D$ -131.5 [c 0.010 CH_2Cl_2], m.p. 164-165° [acetonitrile]) in 69% yield, the structure of which was confirmed by single crystal X-ray diffraction analysis.[12]

To complete an enantioselective synthesis of perhydrohistrionicotoxin, 2 (R=n-C_4H_9; R'=n-C_5H_{11}), it remains to remove the extraneous carbonyl function at C-5 (histrionicotoxin numbering), to convert the amino acid carboxyl group to the pentyl chain, to invert the stereochemistry of the oxygen substituent at C-8 and to homologate the butyl chain at C-7. These efforts are currently underway in our laboratory.

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REFERENCES

1. Recipient of a Merck Grant for Faculty Development, 1985-1986.

2. National Institutes of Health Predoctoral Trainee (GM07151).

3. Address correspondence to this author regarding the X-ray structures of 8 and 10.

4. For a good review with citations to work before 1982, see Y. Inubushi, T. Ibuka, Heterocycles 1982, 17, 507. For syntheses reported since then, see A. B. Holmes, K. Russell, E. S. Stern, M. E. Stubbs, N. K. Welland, Tetrahedron Letters 1984, 4163; D. Evans, E. Thomas, R. Cherpeck, J. Am. Chem. Soc. 1982, 104, 3695; S. Carey, M. Aratani, Y. Kishi, Tetrahedron Letters 1985, 5887; T. Ibuka, H. Minakata, M. Hashimoto, L. Overman, R. Freerks, Heterocycles 1984, 22, 485; D. Tanner, P. Somfai, Tet. Lett. 1985, 3883.

5. For an excellent general review, see C. Myers, J. Daly, Scientific American 1983, 248, 120.

6. J. Elliott, M. Raftery, Biochemistry 1979, 18, 1968 and references cited therein.

7. K. Takahashi, B. Witkop, A. Brossi, M. Maleque, E. Albuquerque, Helvetica Chimica Acta 1982, 65, 252.

8. a) J. Winkler, J. Hey, F. Hannon, Heterocycles, in press; J. Winkler, J. Hey, J. Am. Chem. Soc., in press; b) For another photochemical approach to the synthesis of histrionicotoxin, see E. Koft, A. Smith, III, J. Org. Chem. 1984, 49, 832.

9. M. Rathke, A. Lindert, J. Am. Chem. Soc. 1971, 93, 2318.

10. M. Sato, H. Ogasawara, K. Oi, T. Kato, Chem. Pharm. Bull. 1983, 31, 1896.

11. For another example of the intramolecular photocycloaddition of a vinylogous amide, see F. Schell, P. Cook, J. Org. Chem. 1984, 49, 4067.

12. Full details of the X-ray structure data will be published in the full paper.

13. For excellent recent reviews, see W. Oppolzer, Acc. Chem. Res. 1982, 15, 132; S. Baldwin, in "Organic Photochemistry.", Vol 5. A. Padwa, Ed.; M. Dekker: New York, 1981, 123.

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