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A NEW STEREOSELECTIVE SYNTHETIC ROUTE TO PERHYDROHISTRIONICOTOXIN

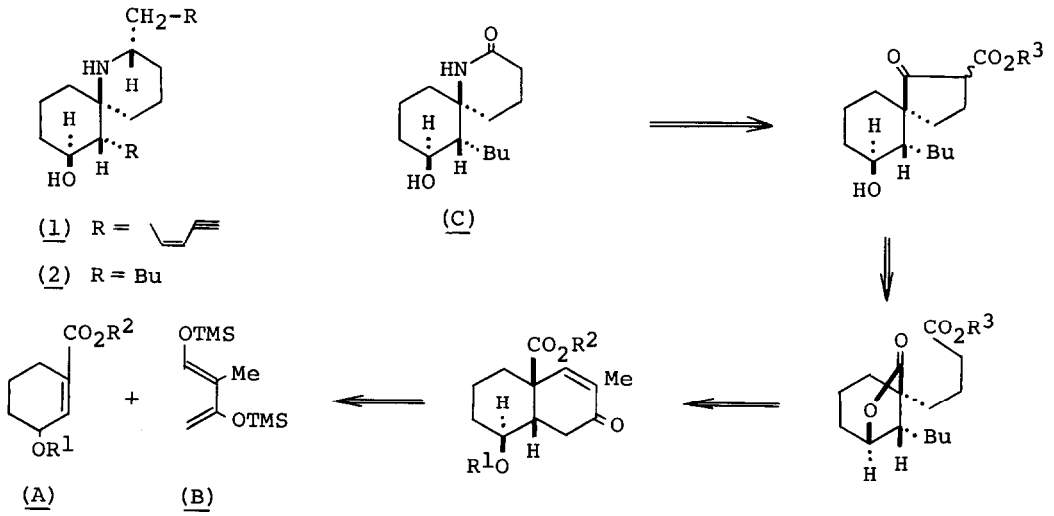
Toshiro Ibuka,* Yoshinori Mitsui, Kenji Hayashi, Hiroyuki Minakata, and Yasuo Inubushi

Faculty of Pharmaceutical Sciences, Kyoto University, Sakyo, Kyoto 606, Japan

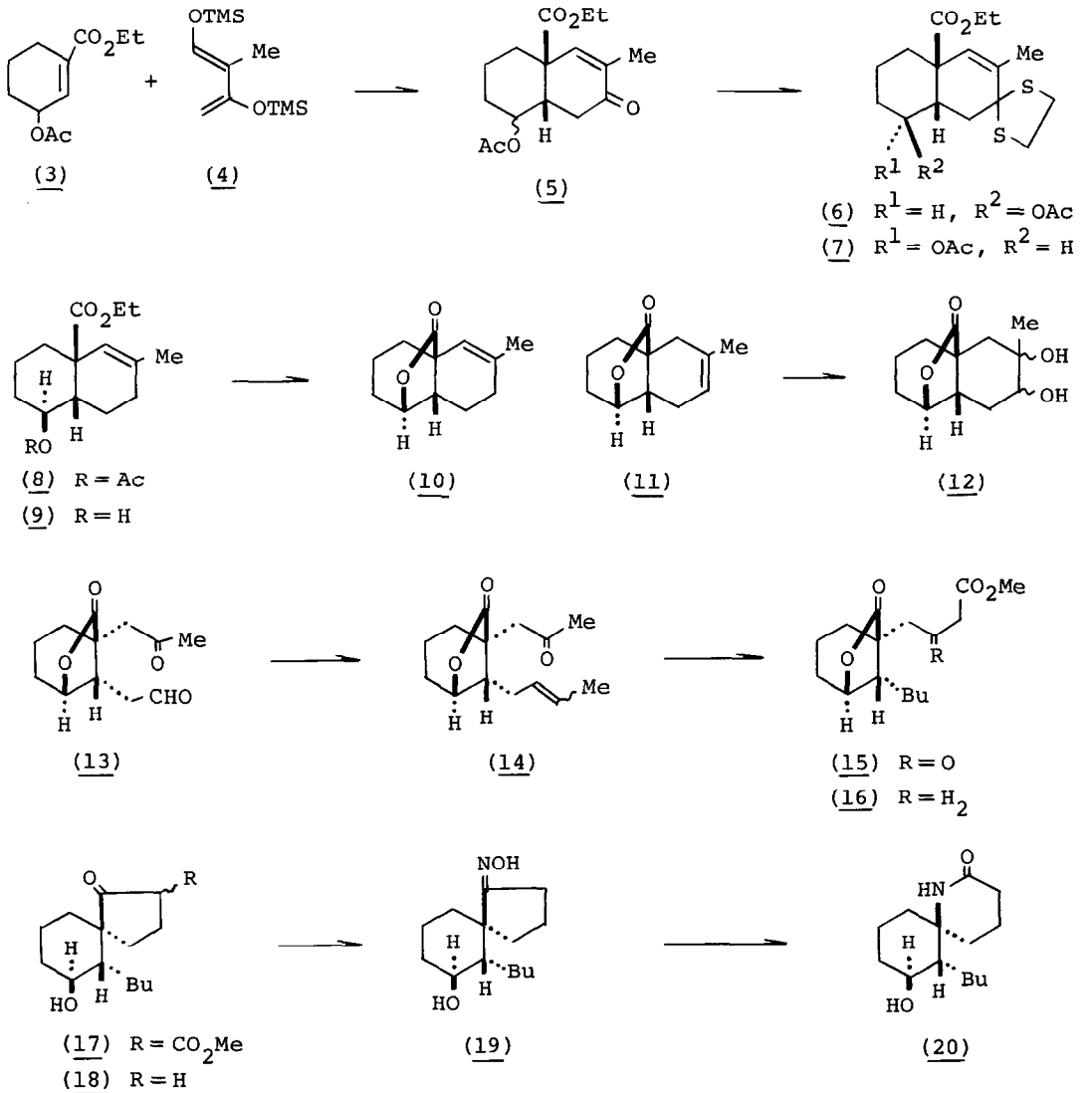
Summary: A stereoselective synthesis of rel-(6S,7S,8S)-7-butyl-8-hydroxy-1-azaspiro[5.5]undecan-2-one, a key intermediate for the synthesis of perhydrohistrionicotoxin, was described.

Histrionicotoxin (1) isolated from the skin extracts of Neotropical arrow poison frog Dendrobates histrionicus and its perhydro derivative (2) obtained by reduction of the carbon-carbon unsaturated bonds of natural histrionicotoxin possess a unique spiropiperidine structure and the alkaloids reversibly block the excitatory ionic transduction system in the synaptic and sarcolemmal membranes of mammalian skeletal muscle cells.[1] A limited amount of the natural toxins available for the pharmacological studies and an unusual spiropiperidine structure have urged chemists to establish synthetic methods of the toxins culminating in many synthetic routes to the bases.[2]

Retrosynthetic analysis of the key intermediate (C) for perhydrohistrionicotoxin (2) suggested that the three chiral centers in (C) could be stereoselectively constructed in the first step by the Diels-Alder reaction of readily available γ-oxygenated-α,β-unsaturated ester (A) with 2-methyl-1,3-bis-(trimethylsiloxy)-1,3-butadiene (B). We describe here a highly stereoselective synthetic route to perhydrohistrionicotoxin.[3]



2-Methyl-1,3-bis(trimethylsiloxy)-1,3-butadiene (4), previously synthesized by the authors,[4] was successfully employed for the present synthesis. Thus, the Diels-Alder reaction of the ester (3) with the diene (4)[4] at 170° (48 hrs) and then at 190° (72 hrs) in mesitylene in a sealed glass tube under argon followed by hydrolysis with 5% HCl gave an inseparable mixture of the enone (5) in 72% yield. Thioacetalization of (5) and subsequent silica gel column chromatographic separation afforded two crystalline thioacetals (6) (mp. 83°, 85% yield) and (7) (mp. 106°, 12% yield). Desulfurization of the major thioacetal (6) with Raney W-2 nickel in THF at room temperature afforded the acetoxy-ester (8) (37% yield) which was subsequently treated with KOH-H_2O-EtOH(1:6:30) at 50° to yield the hydroxy-ester (9) in 97% yield.



(3) (4) (5)

(6) R^1 = H, R^2 = OAc
(7) R^1 = OAc, R^2 = H

(8) R = Ac
(9) R = H

(10) (11) (12)

(13) (14)

(15) R = O
(16) R = H_2

(17) R = CO_2Me
(18) R = H

(19) (20)

Treatment of (9) in toluene with a catalytic amount of p-TsOH under reflux for 20 min. gave a mixture of lactones (10) (major) and (11) (minor), however prolonged refluxing (ca. 8 hrs.) of the mixture afforded the thermodynamically stable lactone (11) as a single product in 89% yield (mp. 54°, ν ($CHCl_3$): 1767; δ ($CDCl_3$): 5.37 (1H, m, olefinic H)). The glycol (12) (mp. 123-124°), obtained by oxidation with OsO_4/N-methylmorpholine-1-oxide[5] in 74% yield, was subjected to HIO_4 oxidation in a 2:3 mixture of THF and H_2O under argon at -50° for 25 min. to afford the labile keto-aldehyde (13) in 98% yield (ν($CHCl_3$): 1773, 1723; δ($CDCl_3$): 9.73 (1H, s, CHO), 2.13 (3H, s, $COCH_3$)).

With the keto-aldehyde (13) in hand, the next task was chemoselective carbon-carbon bond formation at the aldehyde group. The Wittig reaction of (13) with triphenylphosphine ethylidene (1.14 equiv.) in THF-DMSO (15:3.5) at -40∿-50° afforded the keto-lactone (14) in 59% yield (δ($CDCl_3$): 5.80-5.10 (2H, m, olefinic H), 2.11 (3H, s, $COCH_3$)). In this chemoselective carbon-carbon bond formation, the temperature and the solvent system seemed to be critical. Catalytic hydrogenation of (14) over PtO_2 in MeOH, followed by methoxycarbonylation according to the method of Whitlock[6] gave the β-keto-ester (15) (83% yield) (ν($CHCl_3$): 1766, 1720, 1660), which was reduced to the ester (16) in 97% overall yield by the following operations [1). $NaBH_4$ in MeOH, -30∿-40°; 2). CH_3SO_2Cl-Et_3N in benzene, 4°; 3). DBU-Et_3N, 4∿7°; 4). H_2/PtO_2 in MeOH].

The Dieckmann condensation of (16) with KH[7] in THF at 0∿2° provided the spirane (17) in 75% yield, and the product was subsequently treated with 1,4-diazabicyclo[2.2.2]octane in refluxing xylene[8] to afford the hydroxy-ketone (18) (ν($CHCl_3$): 3350, 1725) in 67% yield. Oximation of (18) gave the hydroxy-oxime (19) (mp. 129∿130°, 93% yield), whose spectral data are identical with those reported by Corey.[2a] The Beckmann rearrangement of (19) with p-TsCl in pyridine afforded the spiro-lactam (20) (25% yield)[9] which was identical with a sample kindly provided by Professor Evans.[2f,10] Since the lactam (20) has been converted into perhydrohistrionicotoxin (2) by Kishi,[2e] Corey,[2b] and Evans,[2f,10] the stereoselective synthesis of (20) constitutes a formal total synthesis of perhydrohistrionicotoxin (2).

References and Footnotes

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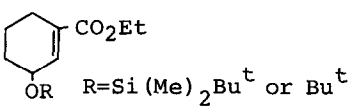
Heating of the diene (4) with the dienophile (21) under the same reaction condition did not give the Diels-Alder adduct.



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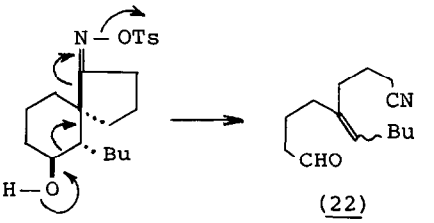
9) One of the by-products in the Beckmann rearrangement was the cyano-aldehyde (22), 23% yield. $\nu(CHCl_3)$: 2255 (CN), 2725 and 1725 (CHO); $\delta(CDCl_3)$: 9.60 (1H, triplet, J=1.5 Hz, CHO), 5.17 (1H, tripletoide multiplet, olefinic H). Mass spectrum: $C_{14}H_{23}ON$ (M^+, 221).



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10) The authors are grateful to Professor D. A. Evans, C. I. T., Calif., U. S. A., for providing us with an authentic sample and its spectral data as well as a manuscript of full detail prior to publication. The authors are indebted to Professor W. N. Speckamp, Amsterdam, The Netherlands, for authentic spectra of the keto-lactam (20).

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