

NEW SYNTHETIC ROUTE TO PERHYDROHISTRIONICOTOXIN USING
(3Z)-4-BUTYL-3-TRICHLOROACETAMIDO-1,3-BUTADIENE

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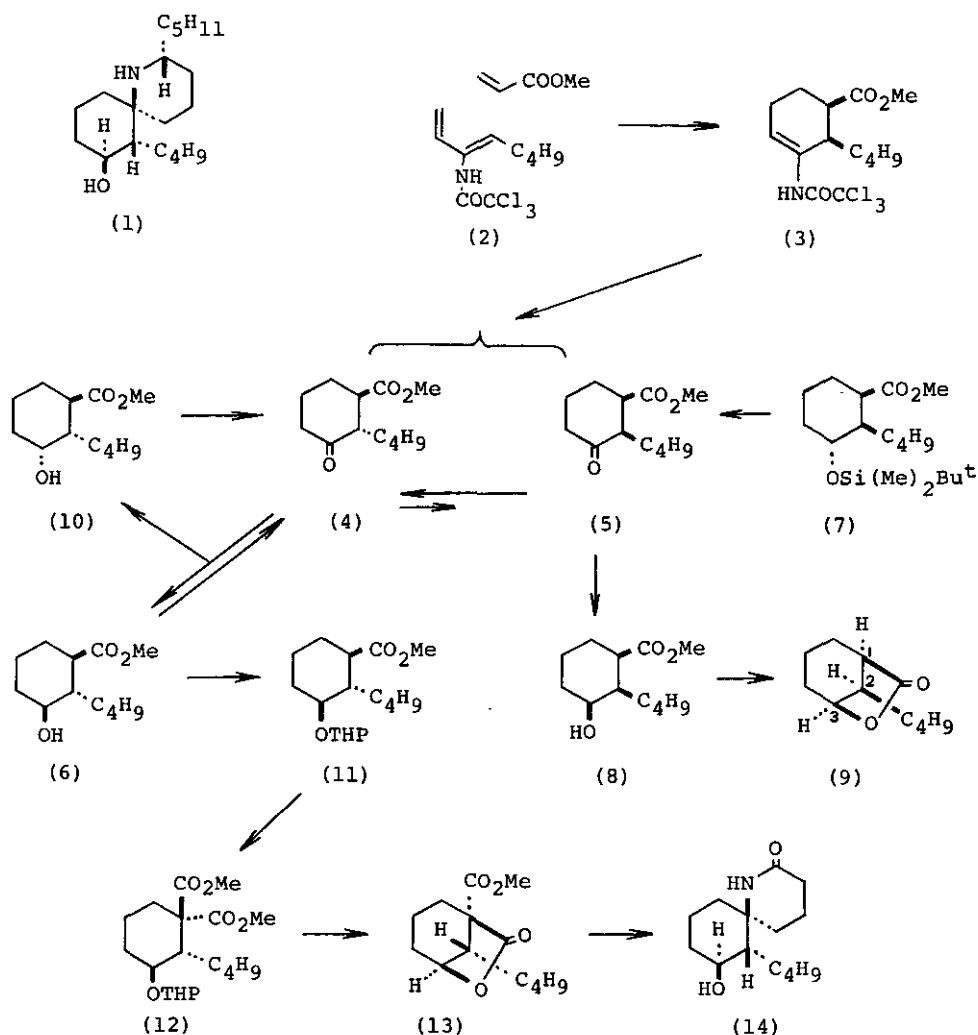
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Abstract — A formal synthesis of perhydrohistrionicotoxin via the Diels-Alder cycloadduct obtained by reaction of (3Z)-4-butyl-3-trichloroacetamido-1,3-butadiene with methyl acrylate is presented.

The pioneering work of Witkop, Daly and their co-workers on the toxic constituents of skin extracts of Neotropical poison dart frogs, Dendrobates histrionicus and other Dendrobates species, have resulted in the isolation and structure elucidation of many histrionicotoxins.¹ The scarcity of these natural toxins together with their unusual spiropiperidine structures and interesting pharmacological activities have made these alkaloids attractive targets for total synthesis.^{1,2,3} It has also been reported that biological activity in this series is not associated with the unsaturated cis-enyne side chains of histrionicotoxin, since perhydrohistrionicotoxin (1) retains significant biological activity.⁴ The utility of amino-⁵ and oxygen-⁶ substituted 1,3-dienes for the preparation of toxic alkaloids of poison dart frogs has been reported previously by the present authors. In this communication we present a formal synthesis of perhydrohistrionicotoxin (1) from (3Z)-4-butyl-3-trichloroacetamido-1,3-butadiene (2).^{5c,5d}

The Diels-Alder reaction of the diene (2) with methyl acrylate in benzene under an argon atmosphere at 85-95° C in a sealed glass tube for 65 h gave a mixture of cycloadducts. High performance liquid chromatographic separation using a μ -PORASIL column resulted in the isolation of the endo-adduct (3)^{*1} (83 %) and an isomeric adduct (4 %).^{*2} The ¹H-NMR spectrum of (3) revealed a signal assignable to the C-1 proton at δ 2.78 (1H, ddd, J=12, 5, and 3.5 Hz) suggesting the stereostructure of the endo-adduct (3). This result indicated that the regiochemistry in the cycloaddition was controlled by the butyl group and reflects the greater regiocontrol typically exerted by a terminal diene substituent^{5b} as well as electron withdrawal by the trichloroacetyl group.⁷



Upon treatment of (3) with 20 % $\text{HClO}_4\text{-Et}_2\text{O}$ at 25°C or preferably with 6 % HCl-MeOH at 60°C , a ca. 2:1 mixture of keto-esters (4) and (5) was obtained.^{*3} Pure samples of (4) and (5) were readily equilibrated to mixtures of (4) and (5) upon prolonged exposure to 20 % $\text{HClO}_4\text{-Et}_2\text{O}$ at 25°C . The keto-ester (4) was identical with an authentic sample of (4) prepared from the known compound (6)⁸ by Jones oxidation at 0°C . Similarly, the keto-ester (5) was identical with an authentic specimen prepared from ketone (7)⁹ by a standard reaction sequence [1) LDA ; 2) Me_3SiCl ; 3) O_3 ; 4) CH_2N_2 ; 5) $\text{MeOH-5 \% HCl}$; 6) Jones oxid.]. Furthermore, the stereochemical assignment for keto-ester (5) was consistent with the $^1\text{H-NMR}$ splitting pattern due to the C-3 proton (δ 4.57 (1H, d, $J=4.5$ Hz))¹⁰ of lactone (9), which was derived from the hydroxy-ester (8).^{*4}

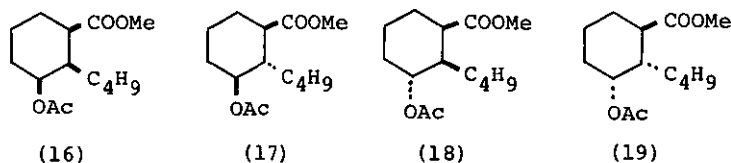
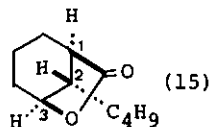
Reduction of ketone (4) with sodium borohydride in a mixture of $\text{MeOH-AcOH-H}_2\text{O}$ (100:2:3) at -20°C gave the known hydroxy-ester (6) (79 %) and its isomer (10) (21 %).^{*5} Compound (6) is the desired

intermediate for the present synthetic route to perhydrohistrionicotoxin (1), and although NaBH_4 reduction of (4) was not highly stereoselective, the reduction is in essence satisfactory, since the minor compound (10) can be recycled to the ketone (4) by Jones oxidation in 91 % yield.

Conversion of (6) to tetrahydropyranyl ether (11), followed by methoxycarbonylation gave the diester (12), which was refluxed in MeOH with 5 % HCl to provide the lactone (13) in a 69 % overall yield. Since the lactone (13) has been converted previously into the spirolactam (14),^{6b} a key intermediate for perhydrohistrionicotoxin (1), the present synthesis of (13) constitutes a formal synthesis of perhydrohistrionicotoxin starting from (3Z)-4-butyl-3-trichloroacetamido-1,3-butadiene (2).^{*6}

REFERENCES AND NOTES

- *1 Except for the hydroxy-ester (8), which cyclized upon storage to yield the lactone (9), all compounds described in this report gave satisfactory IR, $^1\text{H-NMR}$, and microanalyses and/or mass spectral data consistent with their assigned structures.
- *2 It is not clear whether this minor adduct is a stereoisomer or regioisomer of adduct (3). Spectral data for the minor adduct is as follows: IR (CHCl_3) (cm^{-1}), 3400 (OH), 1723 (CO); $^1\text{H-NMR}$ (CDCl_3) (δ), 0.89 (tripletoid m, CH_3), 3.71 (3H, s, OCH_3), 6.26 (1H, t, $J=4.1$ Hz, olefinic proton), 7.45 (1H, broad s, NH); exact MS, m/z calcd. for $\text{C}_{14}\text{H}_{20}\text{O}_3\text{NCl}_3$ 355.0508, found 355.0509.
- *3 Although the major isolated product was recovered starting material (3), exposure of (3) at 25°C to 20 % $\text{HClO}_4\text{-Et}_2\text{O}$ for a short time period gave the keto-ester (5) in a high yield based on consumed starting material.
- *4 The $^1\text{H-NMR}$ spectrum of the isomeric lactone (15) showed a triplet ($J=4.5$ Hz) signal due to the C-3 proton at δ 4.63.
- *5 For the conformation in solution of the four possible stereoisomers (16), (17), (18), and (19) and their derivatives, see: T. Ibuka, H. Minakata, and M. Hashimoto, *Synthetic Commun.*, accepted for publication (June 7, 1983).



- *6 Spectroscopic data of some selected compounds are as follows:

(3), IR (CHCl_3) (cm^{-1}): 3400 (NH) and 1723 (CO).

(4), IR (CHCl_3) (cm^{-1}): 1730 and 1712 (CO); $^1\text{H-NMR}$ (CDCl_3) (δ): 0.86 (3H, tripletoid m, $-\text{CH}_3$), 2.5-2.7 (1H, m, $\text{H}-\text{C}-\text{CO}_2\text{Me}$), 3.72 (3H, s, OCH_3).

(5), IR (CHCl_3) (cm^{-1}): 1731 and 1716 (CO); $^1\text{H-NMR}$ (CDCl_3) (δ): 0.85 (3H, tripletoid m, $-\text{CH}_3$),

2.9-3.2 (1H, m, $\text{H}-\text{C}-\text{CO}_2\text{Me}$), 3.67 (3H, s, OCH_3).

1. B. Witkop and E. Gössinger, "The Alkaloids", 1983, vol. XXI, p. 139, Academic Press, New York.
2. a) J. W. Daly, "Fortschritte der Chemie organischer Naturstoffe", 1982, vol. 41, p. 205, Springer-Verlag, New York. b) C. W. Myers and J. W. Daly, Scientific American, 1983, vol. 248, p. 120.
3. S. A. Godleski, D. J. Heacock, J. D. Meinhardt, and S. V. Wallendaal, J. Org. Chem., 1983, 48, 2101 and references cited therein.
4. E. X. Albuquerque, B. A. Barnard, T. H. Chiu, A. J. Lapa, J. O. Dolly, S.-E. Jansson, J. Daly, and B. Witkop, Proc. Nat. Acad. Sci. USA, 1973, 70, 949.
5. a) L. E. Overman, D. Lesuisse, and M. Hashimoto, J. Am. Chem. Soc., 1983, 105, 5373. b) L. E. Overman, Accounts of Chem. Res., 1980, 13, 218. c) L. E. Overman and L. A. Clizbe, J. Am. Chem. Soc., 1976, 98, 2352. d) L. E. Overman, L. A. Clizbe, R. L. Freerks, and C. K. Marlowe, J. Am. Chem. Soc., 1981, 103, 2807. e) L. E. Overman, G. F. Taylor, C. B. Petty, and P. J. Jessup, J. Org. Chem., 1978, 43, 2164. f) L. E. Overman and P. J. Jessup, J. Am. Chem. Soc., 1978, 100, 5179. g) L. E. Overman and R. L. Freerks, J. Org. Chem., 1981, 46, 2833. h) L. E. Overman and C. Fukaya, J. Am. Chem. Soc., 1980, 102, 1454.
6. a) Y. Inubushi and T. Ibuka, Heterocycles, 1977, 12, 633. b) Y. Inubushi and T. Ibuka, Heterocycles, 1982, 17, 507. c) T. Ibuka, Y. Mori, and Y. Inubushi, Tetrahedron Lett., 1976, 3169. d) T. Ibuka, Y. Mori, and Y. Inubushi, Chem. Pharm. Bull., 1978, 26, 2442. e) T. Ibuka, Y. Mori, T. Aoyama, and Y. Inubushi, Chem. Pharm. Bull., 1978, 26, 456. f) T. Ibuka, Y. Mitsui, K. Hayashi, H. Minakata, and Y. Inubushi, Tetrahedron Lett., 1981, 22, 4425.
7. L. E. Overman, G. F. Taylor, K. N. Houk, and L. S. Domelsmith, J. Am. Chem. Soc., 1978, 100, 3182.
8. T. Ibuka, H. Minakata, Y. Mitsui, E. Tabushi, T. Taga, and Y. Inubushi, Chemistry Lett., 1981, 1409.
9. T. Ibuka, H. Minakata, Y. Mitsui, K. Kinoshita, Y. Kawami, and N. Kimura, Tetrahedron Lett., 1980, 21, 4073.
10. N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry", Holden-Day, Inc., San Francisco, 1964, p. 74 and p. 82.

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