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

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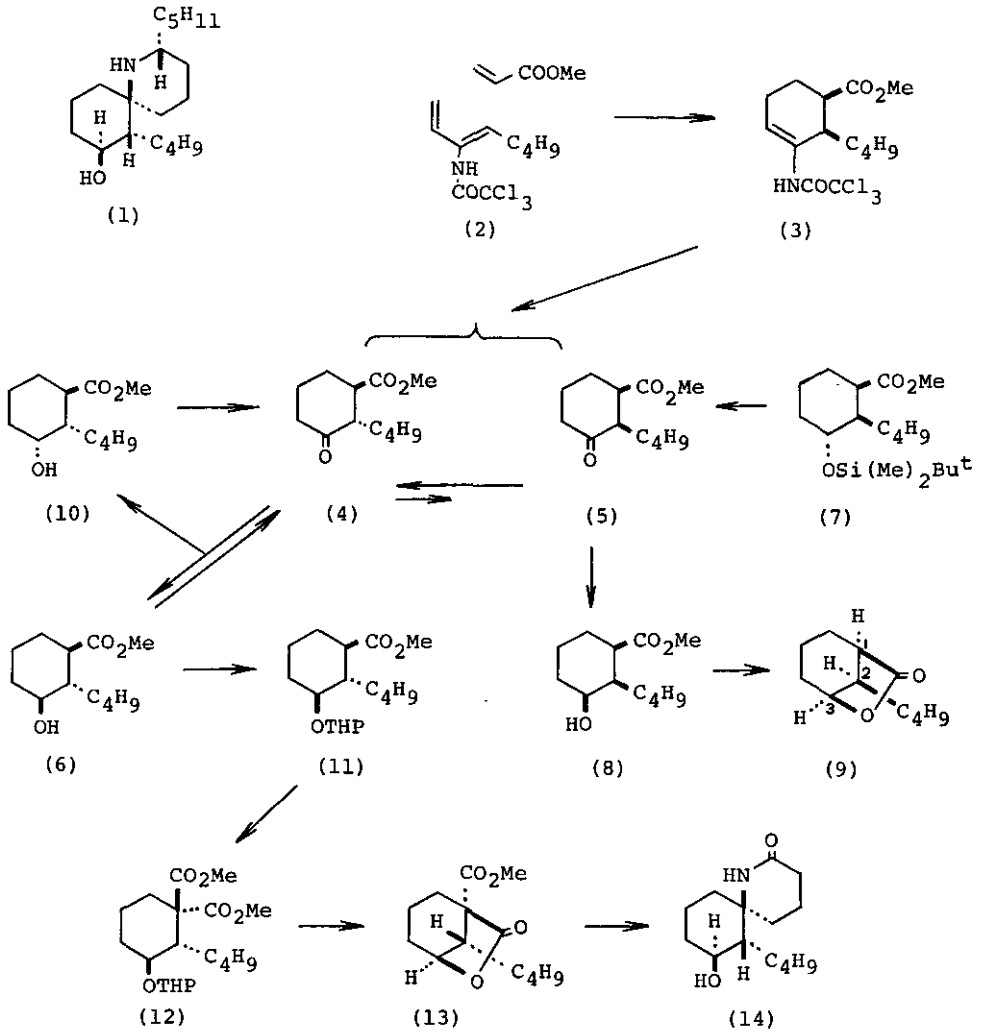
Abstract — A formal synthesis of perhydrohistrionicotoxin via the Diels-Alder cycloadduct obtained by reaction of (3Z)-4-butyl-3-trichloroacetamido-1,3-butadiene with methyl acrylate is presented.

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 $^1$H-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 % $HClO_4$-$Et_2O$ 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 % $HClO_4$-$Et_2O$ 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) MeOH-5 % HCl; 6) Jones oxid.]. Furthermore, the stereochemical assignment for keto-ester (5) was consistent with the $^1$H-NMR splitting pattern due to the C-3 proton ($\delta$ 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 MeOH-AcOH-$H_2O$ (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

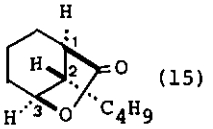
REFERENCES AND NOTES

*1 Except for the hydroxy-ester (8), which cyclized upon strage to yield the lactone (9), all compounds described in this report gave satisfactory IR, $^1$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); $^1$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 $C_{14}H_{20}O_3NCl_3$ 355.0508, found 355.0509.

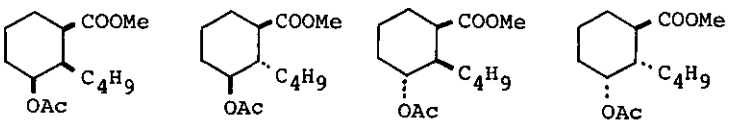
*3 Although the major isolated product was recovered starting material (3), exposure of (3) at 25°C to 20 % $HClO_4$-$Et_2O$ for a short time period gave the keto-ester (5) in a high yield based on consumed starting material.

*4 The $^1$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.



(15)

*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).



(16) (17) (18) (19)

*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); $^1$H-NMR ($CDCl_3$)(δ): 0.86 (3H, tripletoid m, $-CH_3$), 2.5-2.7 (1H, m, H-C-$CO_2Me$), 3.72 (3H, s, $OCH_3$).

(5), IR ($CHCl_3$)($cm^{-1}$): 1731 and 1716 (CO); $^1$H-NMR ($CDCl_3$)(δ): 0.85 (3H, tripletoid m, $-CH_3$),

2.9-3.2 (1H, m, H-C-$CO_2$Me), 3.67 (3H, s, $OCH_3$).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