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A Simple Synthesis of Cyclotribromoveratrylene (CTBV) An Extractive of the Red Alga *Halopytis pinastroides*.

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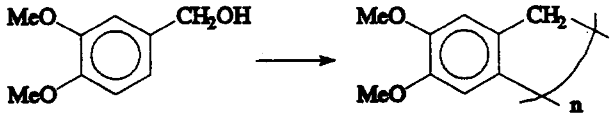
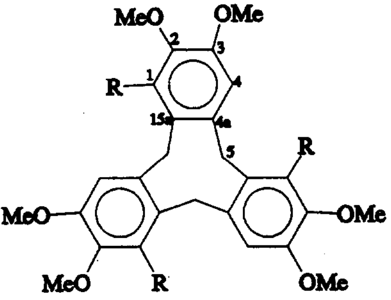
Abstract: Treatment of 5-bromoveratryl alcohol with trifluoroacetic acid yields 1,6,11-tribromo-10,15-dihydro-2,3,7,8,12,13-hexamethoxy-5H-tribenzo[a,d,g]cyclononene(CTBV), previously isolated from the red alga, *Halopytis pinastroides.*

Well over 200 phenolic substances have been described from marine organisms of which red and brown algae have been particularly rich sources.[1] Constituents of the red alga *Halopytis pinastroides* (syn. *H. incurvus*) have been reported[2,3] and associated antibiotic activity of several bromo-phenolic products from that source noted.[3] Subsequent re-examination of the same alga, by extract isolation involving hydrochloric acid and diazomethane, yielded a cyclic trimer, cyclotribromoveratrylene (CTBV) 1 whose structure was established by reductive debromination to the the known trimer 2.[4,5] Treatment of 2 with bromine-acetic acid resulted in a mixture of *seco* products.[6] Consequently, the short method herein reported provides the first synthesis of CTBV (1).



3 R=H
7 R=Br

4 n=4
5 n=5
6 n=6



1 R=Br
2 R=H

We have recently shown that treatment of veratryl alcohol 3 with a dilute solution of trifluoroacetic acid (TFA) in $CHCl_3$ yielded cyclo-oligomers 2, 4, 5 and 6.[7] When the readily available[8] 5-bromoveratryl alcohol 7 (650 mg) was treated with TFA under the same conditions (10% in $CHCl_3$, 100 ml, 24 h, room temp.) followed by evaporation under reduced pressure, ^1H NMR analysis indicated a mixture in which 7 had totally reacted, but in which the expected CTBV was correspondingly absent. When this mixture [or 7(650 mg)] was allowed to stand in neat TFA over 3 days at ambient temperature and worked up as before, the ^1H NMR spectrum of the residual mixture revealed CTBV as a major mixture component[9] which was readily isolated without resort to chromatographic separation. Crystallization from chloroform-ethanol gave six crops of crystalline material, the first three of which proved to be mixtures(^1H NMR) and the last three consisted of CTBV 1 (needles 163 mg; 27%), mp 221 °C (lit[4,5] mp 222 °C). ^1H NMR($CDCl_3$) at 300 MHz: δ 3.83 (OMe), 3.84 (OMe), 4.13 (-CH_2-), and 6.92 (Ar$\underline{H}$). ^{13}C NMR($CDCl_3$) at 75 MHz, $CDCl_3$=77.00 PPM: δ 38.25 (C-5), 56.00 (O$\underline{Me}$ C-3), 60.41 (O$\underline{Me}$ C-2), 115.00 (C-4), 121.56 (C-1), 129.87 (C-4a), 135.25 (C-15a), 145.32 (C-2), and 151.41 (C-3).

Although CTBV 1 is usually included in review compilations of marine natural products,[10] a strong presumption must prevail that it is in fact an extraction artifact. This method of synthesis does not dispel this premise.

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8. Gerecke, M.; Brossi, A.; *Helv. Chim. Acta* 1979, *62*, 1549. We prepared 7 by reduction of commercially available aldehyde precursor with $NaBH_4$ in methanol; ^1H NMR ($CDCl_3$): δ 3.84 (OMe), 3.87 (OMe), 4.60 (CH_2), 6.88 (d, J 1.7, ArH) and 7.10 (d, J 1.7, ArH).
9. The ^1H NMR spectrum also indicated the presence of higher oligomers.
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