Synthesis of Several Naturally Occurring Polyhalogenated Monoterpenes of the Halomon Class[1]

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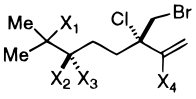
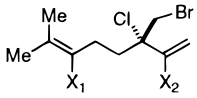
In 1992, Boyd and co-workers reported the isolation of an acyclic polyhalogenated monoterpene, **1**, named halomon, as the major component of the organic extracts of the red alga *Portieria hornemannii*.[4] This compound was found to exhibit highly differential cytotoxicity against a variety of tumor cell lines. Using the National Cancer Institute's *in vitro* human tumor cell line screening panel, it was found that brain, renal, and colon cancer cell lines were sensitive to halomon while leukemia and melanoma cell lines showed much less sensitivity. In 1994, Boyd and co-workers reported that several recollections of *P. hornemannii* from the same location and one collection from another site led to the isolation of more compounds (**2**−**7**) with great structural similarity to halomon.[5] Each of these collections resulted in the isolation of different members of this series in different proportions (and in one case, no significant quantities of halomon and several related compounds). Three of these new compounds (**2**, **4**, **5**) also exhibited differential cytotoxicity comparable to halomon **1** in the NCI cell lines. It is interesting that nearly all of these same compounds had been isolated from the same red alga (called *Chondrococcus hornemanni* then but renamed *P. hornemannii* later) by Moore and his co-workers many years earlier,[6] although the relative and absolute stereochemistry was not determined. A recent report indicates that halomon **1** is highly bioavailable and well distributed in the body, especially in fatty tissues.[7]



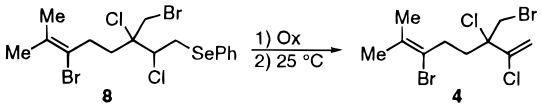
1 X_1 = Cl, X_2 = Br, X_3 = H, X_4 = Cl (halomon)
2 X_1 = Br, X_2 = H, X_3 = Cl, X_4 = Cl (isohalomon)
3 X_1 = Cl, X_2 = Br, X_3 = H, X_4 = H



4 X_1 = Br, X_2 = Cl
5 X_1 = Cl, X_2 = Cl
6 X_1 = H, X_2 = Cl
7 X_1 = H X_2 = H

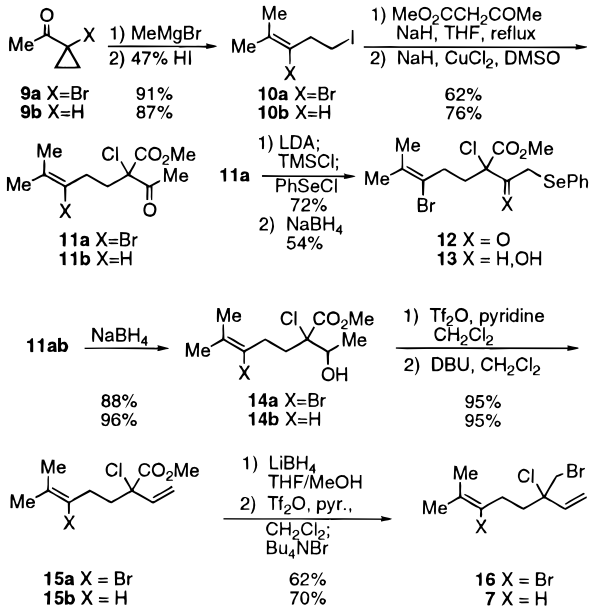
As a result of these encouraging preliminary studies, the NCI Decision Network Committee selected halomon for preclinical drug development. Since there is no consistent biological source for these natural products and since they have very promising antitumor activities, we have undertaken the task of developing a short and efficient laboratory synthesis of these compounds from readily available materials, that could be used to prepare not only the natural products themselves but also their structural analogues. We describe herein the first total synthesis of two naturally occurring polyhalogenated monoterpene dienes of the halomon class, namely the active antitumor compounds **4** and **7**.

Since the tertiary allylic chloride present in all of the halomons **1**−**7** was likely to be a very sensitive functional group and quite reactive toward both substitution and elimination (S_N1, S_N2', E1, E2), our first approach followed a strategy that would lead to formation of this reactive functionality, e.g., the terminal double bond, under mild conditions in the last step of the synthesis. One of the many possibilities would be a thermal elimination of a selenoxide in the final step, e.g., mild oxidation of the selenide **8** followed by elimination of the derived selenoxide at fairly low temperature in order to afford the necessary chloroalkene, e.g., **4**.



8 **4**

This route to **4** began with the formation of the iodide **10a** from the known bromocyclopropane **9a**[8] by addition of methylmagnesium bromide followed by dehydration and ring opening with hydriodic acid to give **10a** in 91% yield. The entire carbon skeleton could then be constructed by alkylation of the anion of methyl acetoacetate with the iodide **10a**. The tertiary chloride was prepared by treatment of the anion of the resulting β-keto ester with $CuCl_2$ to give **11a** in 62% yield. Formation of the trimethylsilyl enol ether of **11a** followed by addition of PhSeCl gave in 72% yield the α-seleno ketone **12**, which was reduced to the desired alcohol **13** with sodium borohydride. Unfortunately, all methods tested for conversion of the alcohol **13** to the chloride led to loss of the



9a X=Br 91% **10a** X=Br 62%
9b X=H 87% **10b** X=H 76%

11a X=Br
11b X=H

12 X = O
13 X = H,OH

88% **14a** X=Br 95%
96% **14b** X=H 95%

15a X = Br 62% **16** X = Br
15b X = H 70% **7** X = H

phenylselenide group (usually to give the simple alkene). Although this strategy could not be used for a synthesis of **4** because of the difficulty in introducing the chlorine at C2, it did lead to a synthesis of **7**. The ketone **11b**,

(1) Presented at the 214th National American Chemical Society meeting, Las Vegas, NV, September 1997.
(2) American Chemical Society Arthur C. Cope Scholar, 1995.
(3) Departmental Prize for Excellence during the First Year of Graduate Study, UCLA, 1993.
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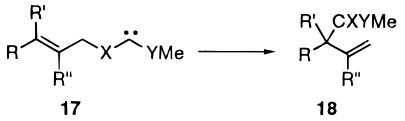
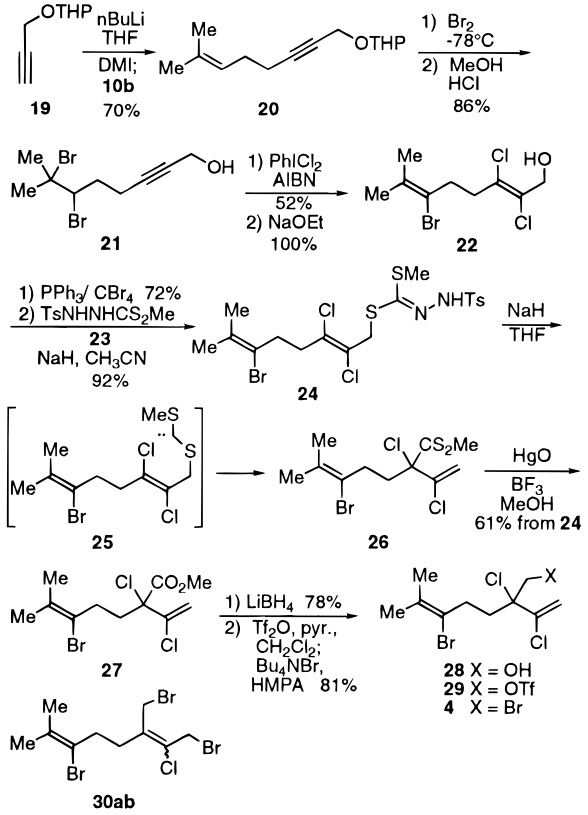
formed in 76% yield from the known iodide **10b**[9] as shown, was reduced with sodium borohydride to give the alcohol **14b** in 96% yield. Formation of the triflate, followed by elimination with DBU, gave the diene **15b** in 95% yield. The synthesis of **7** was completed by reduction of the ester to the primary alcohol with lithium borohydride, conversion of the alcohol to the triflate, and final displacement with bromide by treatment with tetrabutylammonium bromide in HMPA. Thus the naturally occurring halomon **7** is available in only seven steps from the iodide **10b**. We could also prepare the brominated analogue **16** by a simple application of this route, namely via the brominated intermediates **14a** and **15a** to give **16** in 52% overall yield from **11a**.

The successful approach to the synthesis of **4** was based on the idea of using a [2,3]-sigmatropic rearrangement of an allylic bis-heterosubstituted carbene, e.g., **18** from **17**. A suitably substituted carbene (R or R′ = R″ = Cl) would lead to the critical β,γ-unsaturated ester necessary for the synthesis of many of the halomon-related compounds. There is a reasonable amount of precedent for



17 **18**

this rearrangement, although in some cases the rearrangement is nonconcerted and no allylic shift occurs.[10−13] Thus for **17** (X = O, Y = NMe), β,β-disubstituted allylic systems rearrange poorly.[10a] We chose to utilize a dithiocarbene, e.g., **17** (X = Y = S) which would yield the dithioesters **18** (X = Y = S) since Baldwin has reported good yields in this type of process.[10b] The appropriate dichloroalkene was made beginning with the alkylation of the THP ether of propargyl alcohol **19** with the iodide **10b** to give the alkyne **20** in 70% yield. Selective bromination of the alkene in the presence of the alkyne was achieved by slow addition of bromine at −78 °C. Deprotection of the THP ether then furnished the alcohol **21** in 86% yield over two steps. Chlorination of the alkyne using iodosobenzene dichloride, followed by dehydrobromination, gave the dienol **22** in 52% yield. The alcohol **22** could then be converted to the bromide and reacted with the anion of the dithiocarbazate **23** to give the tosylhydrazone **24** in 66% yield. Formation of the anion with sodium hydride, followed by heating to 65 °C, led to loss of nitrogen and toluenesulfinate anion to generate the carbene **25**, which then underwent a [2,3]-sigmatropic rearrangement to give the dithioester **26**. Treatment of **26** with mercuric oxide and BF_3 in methanol converted the dithioester into the ester **27** in 61% yield for the two steps. Reduction of this ester with lithium borohydride afforded the alcohol **28** which was converted into the triflate **29** and displaced with bromide as before to give the desired product **4** in 63% yield from **27**. One also obtained small amounts of the chlorotribromides **30ab** as a nearly 1:1 mixture of geometric isomers. Thus the racemic antitumor agent **4** can be prepared from the iodide **10b** and the alkyne **19** in only 11 steps and 8% overall yield.



In summary, we have achieved the first total synthesis of two naturally occurring halogenated monoterpenes of the halomon class and developed an efficient route to analogues, which utilizes a novel [2,3]-sigmatropic rearrangement. Further work is in progress.

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Supporting Information Available: Experimental procedures and characterization data for compounds **4**, **7**, **10**−**16**, **20**−**30** (18 pages).

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