Synthesis of Several Naturally Occurring Polyhalogenated Monoterpenes of the Halomon Class

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In 1992, Boyd and coworkers reported the isolation of an acyclic polyhalogenated monoterpene, 1, named halomon, as the major component of the organic extracts of the red alga Porphyra hornemannii. 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. 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 Chondrocompet hornemannii then but renamed P. hornemannii later) by Moore and his co-workers many years earlier, 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.

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 (Sn1, Sn2, 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.

This route to 4 began with the formation of the iodide 10a from the known bromocyclopropane 9a 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 acetate with the iodide 10a. The tertiary chloride was prepared by treatment of the anion of the resulting β-keto ester with CuCl2 to give 11a in 62% yield. Formation of the trimethylsilyl end 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 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,
formed in 76% yield from the known iodide 10b 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 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 alkene using iodosobenzene dichloride, followed by dehydrobromination, gave the diene 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).