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# A General Strategy for the Stereocontrolled Preparation of Diverse 8- and 9-Membered *Laurencia*-Type Bromoethers

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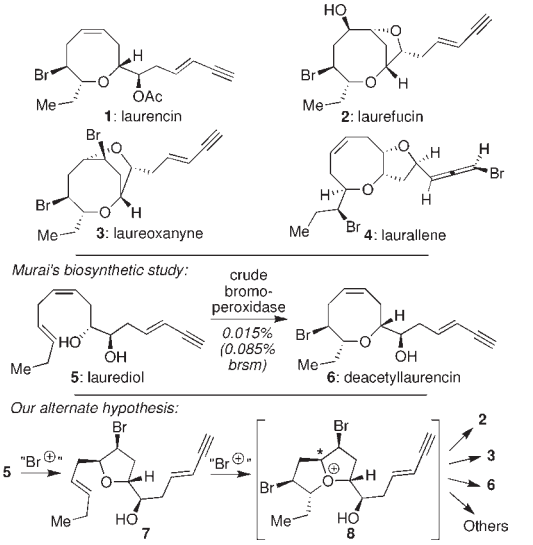
Supporting Information

**ABSTRACT:** A unique procedure to effect a ring-expanding bromoetherification process is described, wherein tetrahydrofurans and tetrahydropyrans are smoothly transformed into 8- and 9-membered bromoethers in a regio- and stereocontrolled manner through the use of BDSB (bromodiethylsulfonium bromopentachloroantimonate). These products resemble the cores of the *Laurencia* C15 acetogenins. In light of the generality and effectiveness of the approach, this work provides a unique strategy for their laboratory preparation and may implicate a possible biosynthesis pathway.

Some of the most fascinating halogenated natural products[1] are the *Laurencia* C15 acetogenins, of which the inaugural member, laurencin (**1**, Scheme 1), was first reported by Irie and co-workers in 1965.[2,3] Since then, more than 140 members have been isolated, most containing a cyclic bromoether core ranging in size from 4- to 12-membered.[4] The lauroxocanes (including **1**−**4**) possess an 8-membered ring system and represent the largest subset of the family. These medium-ring bromoethers, encompassing more than 50 natural products, have elicited much attention not only for the synthetic challenges they provide but also for the general question of their biogenesis.

The Murai group first showed that these rings could arise via bromoperoxidase-catalyzed bromoetherifications of linear precursors (as in **5**→**6**).[5] The incredibly low yield of product observed, however, may imply that direct 8-*endo* cyclization of precursor **5** is an unfavorable event,[6] even within the confines of an enzyme pocket. As such, we wondered if these challenging domains could also arise via a series of two potentially more favorable 5-membered ring-forming steps. Specifically, if **5** underwent an initial 5-*endo* bromoetherification to form **7**,[7] a second bromoetherification might then lead to a bicyclic oxonium intermediate (i.e., **8**). Such a material could then lead to lauroxocane natural products (**2**, **3**, **6**, and others) via reactions at the starred carbon, such as intramolecular cyclization, external nucleophile attack, and/or elimination.[8,9] Although this exact hypothesis has not, to the best of our knowledge, been published before, ring expansions through oxonium formation have been demonstrated by Braddock for the formation of the 12-membered ring obtusallenes and related marilzabicycloallenes in moderate yield.[10,11] Additionally, Kim and co-workers[12] have published the opposite perspective on this idea: the tricyclic oxonium ion derived from a ring contraction of the oxocane prelaurefucin could lead to two tetrahydrofuran-containing natural products.[13] The key challenge, however, is translating these ideas into practical laboratory syntheses of single members. Perhaps for this reason, none of the 30 published total syntheses of lauroxocanes[3,14] have forged their medium-sized cores through a direct bromonium-induced reaction.[15] In this communication, we show that with the proper brominating reagent and appropriate substrates, ring expansion of oxonium species akin to **8** can lead to selective and stereocontrolled laboratory syntheses of diverse 8- and 9-membered bromoethers resembling the *Laurencia* C15 acetogenins.

**Scheme 1. Structures of Selected Lauroxocane Natural Products, Murai's Biomimetic Study, and an Alternative**




Our first insight that a ring-expansion process could afford 8-membered rings derived from the discovery that hydroxytetrahydrofuran **9** (Scheme 2) was converted into ketone **11** rather than bromoether **10** (a model compound resembling **2**) upon exposure to BDSB.[16] Although not an 8-membered ring, its presumed formation through a bicyclic oxonium formation−hydride shift process[17] suggested the materials needed for a controlled ring-expanding bromoetherification. Specifically, if the alcohol of **9** was moved to the 4-position of the tetrahydrofuran ring and protected as an ester or carbonate (as in **12**), then a similar rearrangement terminated by ring opening of the bicyclic oxonium ion (i.e., **13**)[18] could yield an 8-*exo* (laurenan-like)[19] bromoether with differentiated oxygen functionalities (i.e., **14** or **15**).[20] Similarily, substrates with one less methylene unit between

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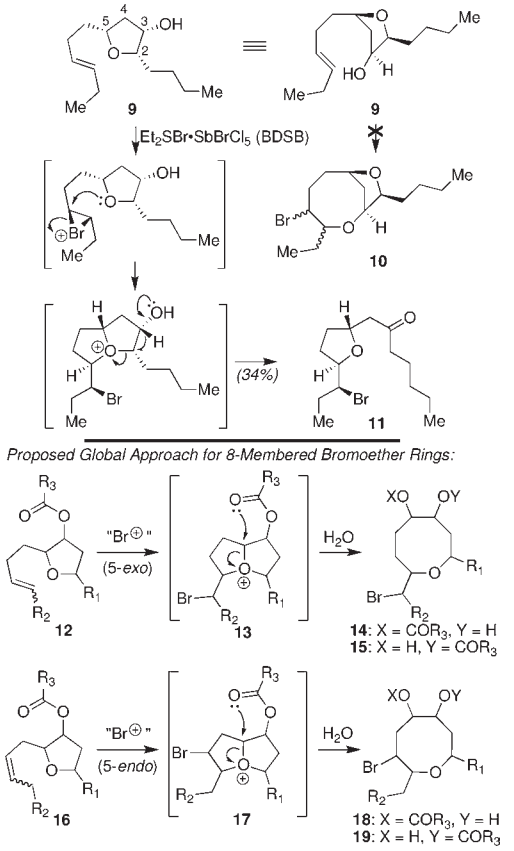
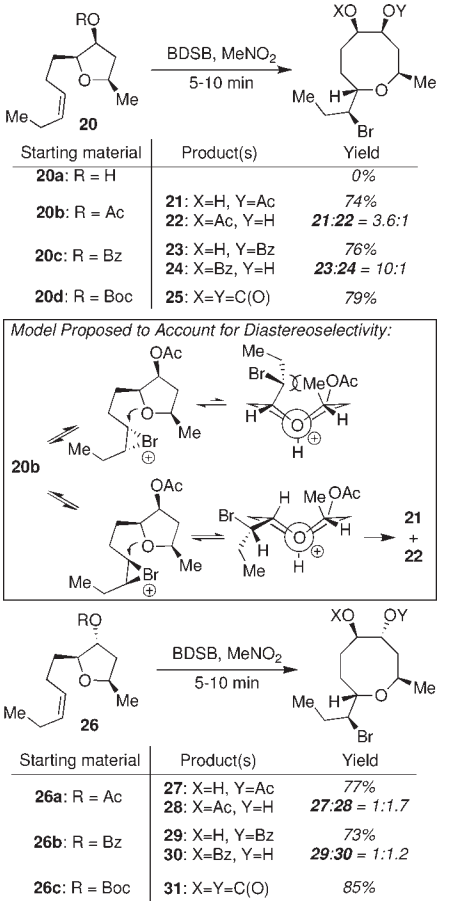
**Scheme 2. Inspiration of a General Approach for Controlled 8-Membered Cyclic Bromoether Synthesis**




**Scheme 3. Initial Explorations of 8-Membered Bromoether Formation Using Substrates 20 and 26**




| Starting material | Product(s) | Yield |
|---|---|---|
| **20a**: R = H | | *0%* |
| **20b**: R = Ac | **21**: X=H, Y=Ac<br>**22**: X=Ac, Y=H | *74%*<br>***21:22*** *= 3.6:1* |
| **20c**: R = Bz | **23**: X=H, Y=Bz<br>**24**: X=Bz, Y=H | *76%*<br>***23:24*** *= 10:1* |
| **20d**: R = Boc | **25**: X=Y=C(O) | *79%* |

| Starting material | Product(s) | Yield |
|---|---|---|
| **26a**: R = Ac | **27**: X=H, Y=Ac<br>**28**: X=Ac, Y=H | *77%*<br>***27:28*** *= 1:1.7* |
| **26b**: R = Bz | **29**: X=H, Y=Bz<br>**30**: X=Bz, Y=H | *73%*<br>***29:30*** *= 1:1.2* |
| **26c**: R = Boc | **31**: X=Y=C(O) | *85%* |

the tetrahydrofuran ring and the alkene (i.e., **16**) could afford the corresponding 8-*endo* (lauthisan-like)[19] materials (i.e., **18** and **19**). Critically, if the process was fully stereocontrolled, then all lauroxocane cores could be predictably accessed, one at a time.

Our studies began with variants of model compound **20** (Scheme 3), prepared readily through the approach of Britton and co-workers (see Supporting Information (SI)).[21] Although attempted cyclization of the free alcohol variant (**20a**) failed to produce any ring-expanded ketone, exposure of the acetylated version (**20b**) to 1.2 equiv of BDSB for 5 min at −25 °C yielded the desired 8-*exo* bromoether as a 3.6:1 mixture of acetate regioisomers (i.e., **21** and **22**) in 74% yield. Significantly, this reaction process was both stereo- and regioselective, indicating that it proceeded through only one of two facially distinct bromonium ions and only with 5-*exo* attack by the tetrahydrofuran oxygen (not the 6-*endo* alternative). Since the alkene is significantly removed from the chirality of the tetrahydrofuran, a likely possibility is that both faces are accessible, but ultimately the more reactive bromonium ion is accessed by bromonium transfer processes to funnel to the observed single diastereomer.[22] Molecular models are drawn in the center of Scheme 3; for steric reasons, the brominated side chain of the oxonium species likely prefers an *exo* orientation with respect to the concave oxonium.

From a practical standpoint, however, the acetylated products proved difficult to handle due to facile migration of their acetate groups (i.e., **21**⇌**22**). Pleasingly, the benzoate congener (**20c**) solved this problem[23] and led to higher regiochemical differentiation, affording a 10:1 mixture of separable **23** and **24** in 76% yield. Hydrolysis of these materials to the diol followed by rebenzoylation afforded a 6.6:1 ratio of **24**:**23** in 90% yield, allowing access to either monobenzoylated regioisomer in good yield. In the interest of affording only a single product, the *tert*-butoxycarbonyl (Boc) variant **20d** smoothly underwent ring expansion to carbonate **25** in 79% yield. In addition to varying the identity of the ring-opening group, we also altered its stereochemistry. We were delighted to find that all variants of **26** afforded diastereomeric 8-*exo* bromoethers with similarly good yields. The relative stereochemistries of **21**−**25** and **27**−**31** were confirmed by X-ray diffraction of their crystalline diol derivatives (see SI). Worth noting is that the efficiency of the cyclizations was dependent upon the bromonium source used. While BDSB provided the optimal yield for the synthesis of **25**, TBCO (2,4,4,6-tetrabromo-2,5-cyclohexadienone) and $(coll)_2BrOTf$ afforded a 62% and 52% yield of **25**, respectively, while NBS gave less than 10% of the desired product, even after 48 h (the use of *N*,*N*-dimethylacetamide as a nucleophilic promoter failed to enhance this yield).[24]

To evaluate the diastereocontrol needed to access the entire range of lauroxocane natural products selectively, we next examined 7 analogues of **20d** that systematically varied the relative stereochemistry of their C2- and C5-alkyl groups and the position and *E*/*Z*-stereochemistry of the alkene. All substrates possessed Boc groups to afford a single product and were cyclized using BDSB. Although all bromoethers in this study were prepared without regard for absolute stereochemistry, each synthesis could be rendered asymmetric.[21]


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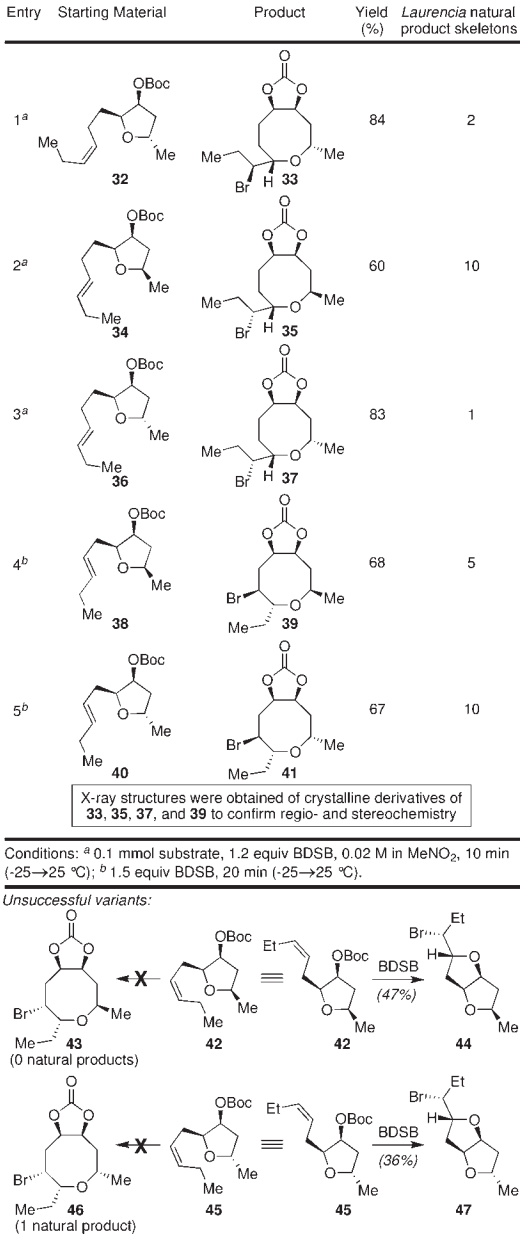
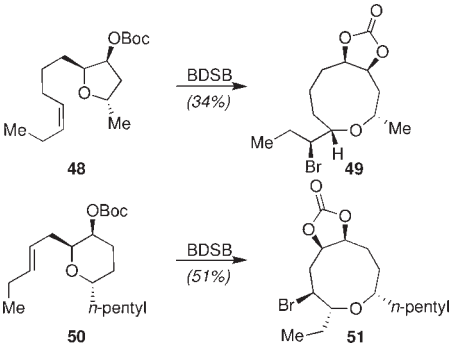
**Table 1. Exploration of the Generality of Ring-Expansion**




As shown in Table 1, stereoisomers of **20d** (**32**, **34**, and **36**) stereoselectively afforded the expected 8-*exo* bromoether products after only 10 min. Of the analogous substrates shortened by one methylene (**38**, **40**, **42**, and **45**), only *E*-alkenes **38** and **40** underwent ring expansion to 8-*endo* bromoether products.[25] The two *cis*-disposed materials (**42** and **45**) instead gave bicycles **44** and **47** as the predominant products. 5-*Endo* haloetherifications are often significantly slower with *Z*-alkene substrates;[26] here, that suggests substrates **42** and **45** failed due to side reactions achieving competitive reaction rates. For example, the Boc group may have been deprotected under the acidic conditions (BDSB is a Lewis acid at both sulfur and bromine and could react with trace water to form HBr and $Et_2SOH^+$), thereby enabling the resulting alcohol to attack the bromonium intermediate preferentially. This hypothesis is supported by the observation that BDSB cyclization of the

**Scheme 4. Formation of 9-*Exo* and 9-*Endo* Ring Systems[a]**




[a] The diol derived from **49** was confirmed by X-ray.

unprotected alcohol precursors to **42** and **45** produced **44** and **47** in near quantitative yield. Despite the failure of these substrates, the desired products (i.e., **43** and **46**) have the same stereochemical relationship as only one known *Laurencia* natural product. By contrast, the other 6 frameworks produced model at least 28 different isolates and one core (i.e., **25**) that has not been observed in nature.[27] As such, these collated results illustrate the potential of the approach for controlled lauroxocane synthesis through a direct bromonium-induced process.

As a final exploration of reaction scope for this study, we evaluated its feasibility for 9-membered ring formation, as at least 10 naturally occurring lauroxonanes (9-membered bromoethers) have been isolated to date. Pleasingly, both substrates investigated (i.e., tetrahydrofuran **48** and tetrahydropyran **50**, Scheme 4) led to the expected products upon reaction with BDSB, yielding one 9-*exo* and one 9-*endo* product (i.e., **49** and **51**).[28] We expect that diastereomeric 9-membered products, and potentially larger rings, could arise from similar processes.

In conclusion, a novel procedure for bromonium-induced ring expansion effected by BDSB has afforded access to medium-sized cyclic bromothers resembling those of the *Laurencia* acetogenins. This process is fast, regio- and stereoselective, and has been demonstrated to produce seven stereochemically distinct 8-membered bromoethers as well as two 9-membered derivatives. Additionally, its overall generality may shed new light on potential biosynthetic pathways that should be considered for the family. Current work is directed toward applying this approach to natural product syntheses exploring the range of ring sizes and stereochemistries accessible.

## ■ ASSOCIATED CONTENT

**Supporting Information.** Detailed experimental procedures, copies of spectral data, and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) There are at least two dozen more lauroxocane structures that are not fully characterized stereochemically or that are missing one or more of the stereocenters due to elimination of the bromide.

(28) The ring expansion of **48** using BDSB also produced the byproduct shown below in 26% yield (as verified by COSY NMR). The remainder of the mass balance for ring expansions of **48** and **50** consisted of multiple uncharacterized products.