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A Unifying Stereochemical Analysis for the Formation of Halogenated C_{15}-Acetogenin Medium-Ring Ethers From *Laurencia* Species via Intramolecular Bromonium Ion Assisted Epoxide Ring-Opening and Experimental Corroboration with a Model Epoxide

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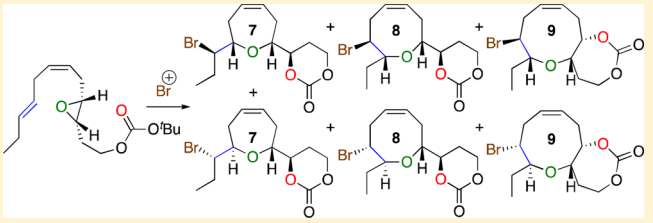
Supporting Information

ABSTRACT: A unifying stereochemical analysis for the formation of the constitutional isomeric halogenated C_{15}-acetogenin medium-ring ether natural products from *Laurencia* species is presented, where an intramolecular bromonium ion assisted epoxide ring-opening reaction of enantiomerically pure epoxides can account for ring-size, the position of the halogen substituents, and relative and absolute configurations of the known natural products. Experimentally, a model epoxide corroborates the feasibility of this process for concurrent formation of 7-, 8- and 9-ring ethers corresponding to the halogenated medium-ring ethers of known metabolites from *Laurencia* species.



INTRODUCTION

Since the isolation and structural elucidation of laurencin (**1a**) in the 1960s,[1] a dazzlingly diverse array of diastereo- and constitutional isomers of halogenated C_{15}-acetogenin medium-ring ethers have been isolated from species of the marine red algae *Laurencia* (Figures 1, 2).[2] These metabolites are either 7-, 8- or 9-membered ring ethers (often incorporating a second oxygen-containing ring as an oxetane, tetrahydrofuran or tetrahydropyran) with a characteristic C-12 or C-13 bromide substituent, oxygenated at C-6 and C-7 (Figure 1) or with a chloride substituent at one of these positions (Figure 2), along with an enyne or bromoallene side-chain.[3−5] The synthetic challenges of medium-ring ether formation, control of the *cis*- or *trans*-α,α' ether stereochemistry, stereoselective halide incorporation and selective enyne or bromoallene formation has resulted in much synthetic interest, and state-of-the-art total syntheses over the past five decades have been continually reported.[6−20]

The generally accepted biogenesis of this class of metabolites finds its origins in the isolation of C_{15}-(3*E*,6*R*,7*R*)-laurediol **18** and its oppositely configured diol (3*Z*,6*S*,7*S*)-**18** by Irie in 1972.[21] Later studies by Murai and co-workers[22] showed that the constitutional isomeric eight-membered medium-ring ethers deacetyllaurencin (**1b**) and prelaureatin (**3**) (with molecular formulas of $C_{15}H_{21}BrO_2$) were formed, albeit in very low yields, from the two diols respectively via lactoperoxidase (LPO) and (partially purified) bromoperoxidase (BPO)-catalyzed bromoetherifications with no apparent crossover between the two series (Scheme 1).[23,24] Subsequent intramolecular bromoetherification events, involving the formation of favored ring-sizes, allows for the formation of the constitutional isomeric bicyclic dibromides **4**, **6** and **7** (with molecular formulas of $C_{15}H_{20}Br_2O_2$).[22,24,25] However, the

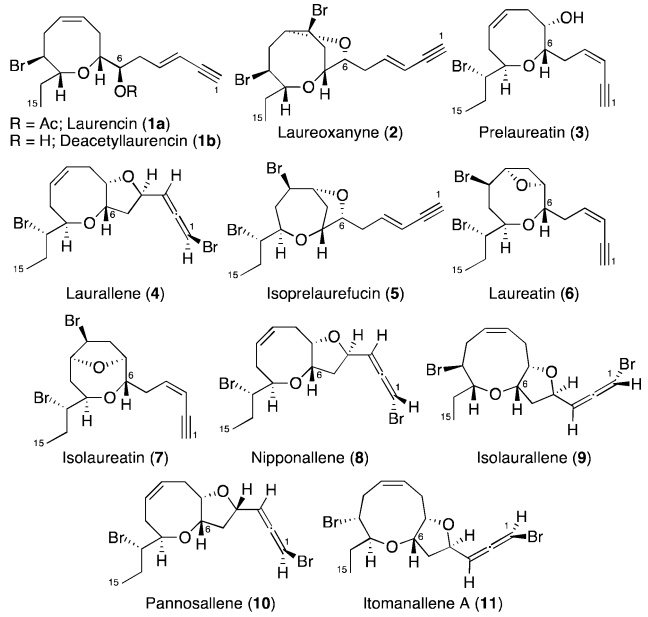


Figure 1. Diastereo- and constitutional isomers of the formula $C_{15}H_{21}BrO_2$ (**1b**, **3**) and $C_{15}H_{20}Br_2O_2$ (**2**, **4**−**11**) of halogenated medium-ring ethers from *Laurencia* species that are oxygenated at both C-6 and C-7. Laurencin (**1a**) is related as the acetate of **1b**.

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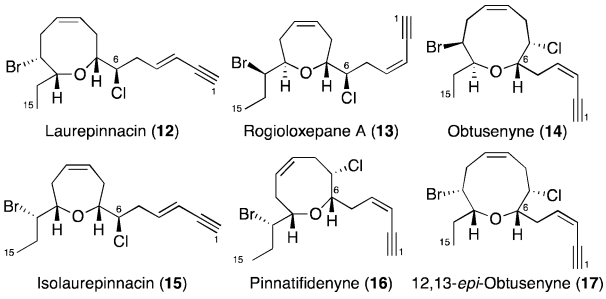
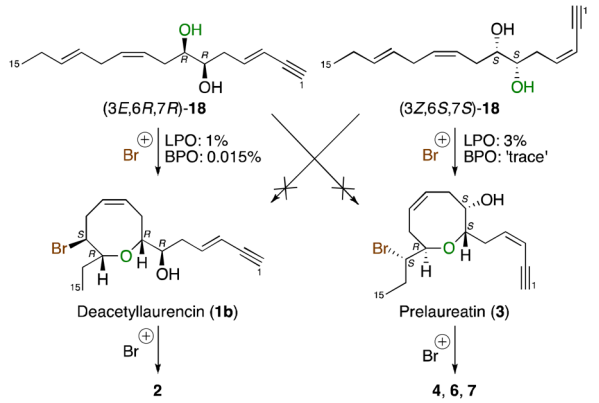


Figure 2. Diastereo- and constitutional isomers of the formula $C_{15}H_{20}BrClO$ (**12**–**17**) of halogenated medium-ring ethers from *Laurencia* species that are chlorinated at either C-6 or C-7.

Scheme 1. Irie–Murai Biogenesis



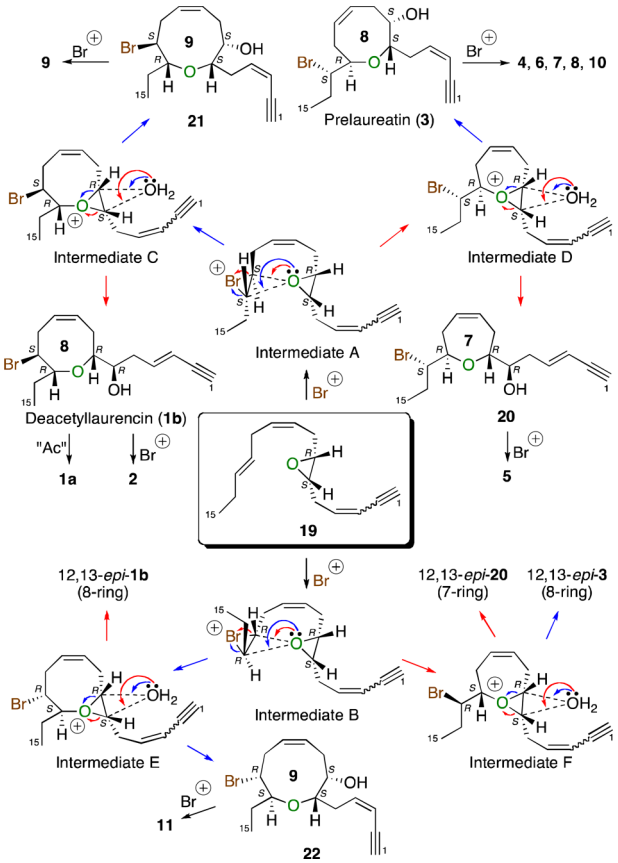
biogenesis of the equally ubiquitous 7- or 9-membered medium-ring ethers of the family has yet to be elucidated, nor has a nonenzymatic direct bromonium-induced cyclization of a linear precursor been reported for any member of the family regardless of ring size.[26] Other cyclization pathways not involving intramolecular bromoetherification reactions with alcohols as the nucleophile to access such eight-membered ring systems may also be possible. Given also their common molecular formulas, the identification of a single potential biogenetic precursor would be intellectually and scientifically satisfying. By the same token, identification of such a species could allow for a laboratory synthesis of all the isomeric members of the family from a single precursor (albeit necessarily as a mixture of isomers).

Herein, we present a stereochemical analysis that correlates these medium-ring ethers with an enantiomerically pure epoxide via intramolecular bromonium ion assisted epoxide ring-opening,[27] with water (for the medium-ring ethers shown in Figure 1) or chloride (for the medium-ring ethers shown in Figure 2) functioning as external nucleophiles.[28] Experimentally, we show with a model epoxide the feasibility of an intramolecular bromonium ion assisted epoxide ring-opening for the concurrent formation of 7-, 8- and 9-ring ethers corresponding to the halogenated medium-ring ethers of known metabolites from *Laurencia* species. This also constitutes the first time that the medium-ring of any of these natural products has been constructed by a nonenzymatic bromonium-induced cyclization process from a linear precursor.

RESULTS AND DISCUSSION

Our stereochemical analysis commences by correlating the medium-ring ethers shown in Figure 1 with enantiomerically pure (3*E* or 3*Z*,6*S*,7*R*)-epoxide **19**, and *not* the lauredials,[29] via intramolecular bromonium ion assisted epoxide ring-opening,[27] with water functioning as an external nucleophile (Scheme 2).[28]

Scheme 2. Unifying Stereochemical Analysis for the Medium-Ring Ethers of Figure 1 via Bromonium Ion Assisted Ring-Opening of Epoxide 19[a]



[a]Medium-ring ethers **20**–**22** are unknown compounds but are implicated as plausible naturally occurring compounds by the isolation of **5**,[3a] **9**,[5b] and **11**,[5d] respectively. 12,13-*epi*-**1b**, 12,13-*epi*-**3** and 12,13-*epi*-**20** are unknown compounds.

Here we invoke bromonium ion formation on *either* face of the C(12)–C(13) alkene of epoxyalkene **19** (giving intermediates A and B) and subsequent nucleophilic attack by the epoxide at *either* the C-12 or C-13 position of the bromonium ions (stereospecifically with inversion of stereochemistry at that position), where the subsequent oxonium ions (intermediates C–F) are attacked by water at *either* the C-6 or C-7 position (also stereospecifically with inversion of stereochemistry). By invoking this reaction mechanism, a single epoxide precursor can be correlated to eight diastereo- and constitutional isomers with molecular formulas of $C_{15}H_{21}BrO_2$. It leads to two 7-, four 8- and two 9-membered medium-rings (and no other ring-sizes), where the molecular diversity arises from the non-regioselectivity of the process, while the final absolute and relative stereochemistries at the C-6, C-7, C-12 and C-13 positions for each compound are controlled by the diastereospecific nature of the two ring-opening steps as defined by

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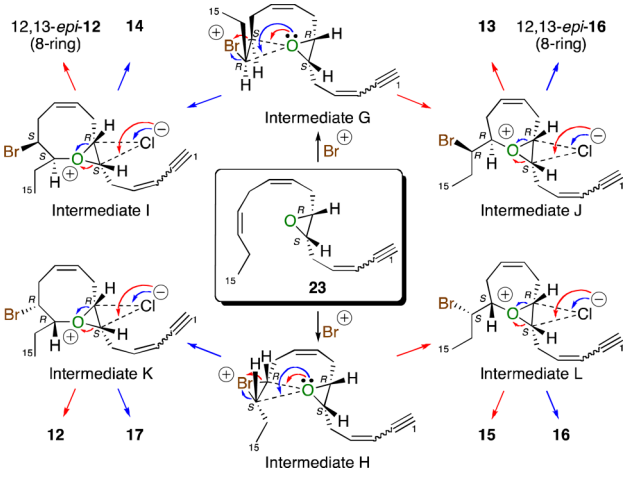
the original absolute stereochemistry of the epoxide, and the initial (*E*)-geometry of the C(12)−C(13) alkene. For the eight medium-ring ethers to arise from this analysis, two of these are the known eight-membered medium-ring ethers (**1b** and **3**), three (**20**, **21** and **22**) are plausible precursors to other known compounds (**5**, **9** and **11**, respectively) by further intramolecular bromoetherification, and three more (12,13-*epi*-**1b**, 12,13-*epi*-**3** and 12,13-*epi*-**20**) are unknown. Leaving aside for the moment the question of enzymatic control, this analysis can unify ring-size, the position of the halogen substituents, and absolute and relative configurations for the halogenated medium-ring ether metabolites.[30]

A similar analysis is applicable for the chlorine-containing medium-ring ether natural products shown in Figure 2 of formula $C_{15}H_{20}BrClO$ (**12**−**17**) isolated from *Laurencia* species, where chloride now functions as the external nucleophile (Scheme 3).[28] Analysis of the C-12 and C-13

Scheme 3. Unifying Stereochemical Analysis for the Medium-Ring Ethers of Figure 2 via Bromonium Ion Assisted Ring-Opening of Epoxide 23[a]



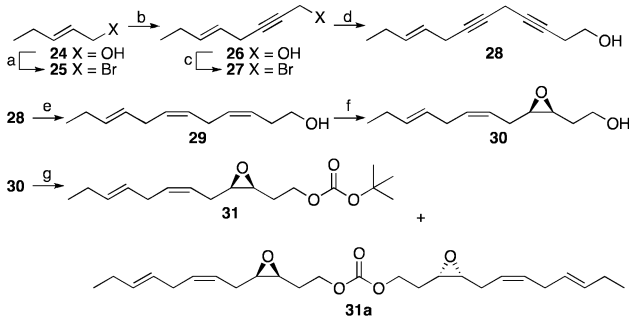
[a]Medium-ring ethers 12,13-*epi*-**12** and 12,13-*epi*-**16** are unknown compounds.

stereochemistries of these compounds reveals that they must arise from electrophilic bromination of a (*Z*)-configured alkene at C(12)−C(13), rather than (*E*): epoxide **23** emerges as the precursor.[31] As before, eight possible diastereo- and constitutional isomers arise, with two 7-, four 8- and two 9-ring systems possible. Remarkably, these map onto all six of the known natural products with formula $C_{15}H_{20}BrClO$ (**12**−**17**) with complete fidelity and where 12,13-*epi*-**12** and 12,13-*epi*-**16** are unknown compounds.

From a *reactivity* standpoint, the bromonium ion assisted epoxide ring-opening reaction[27,28] benefits enthalpically from the opening of two small rings. For the systems above, along with the conformational constraint provided by the *Z*-configured C(9)−C(10) olefin, this feature may counterbalance the unfavorable entropic restrictions associated with medium-ring ether formation.

In order to investigate the feasibility of the above cyclizations, a model compound of epoxide **19** was required, and epoxides **30** and **31** were targeted (Scheme 4). The substrates both feature the requisite (*S*,*R*)-epoxide, to be installed by directed asymmetric epoxidation of *Z* homoallylic alcohol **29**, and the two olefins matching the C(9)−C(10) *Z* and C(12)−C(13) *E*

Scheme 4. Preparation of Cyclization Precursors 30 and 31[a]



[a]Conditions: (a) PPh_3Br_2, pyridine, CH_2Cl_2, 0 °C to room temperature (rt), 1.5 h, 81%; (b) propargyl alcohol, ^{i}PrMgCl, THF, 0−70 °C, 1.5 h, then CuCl, **25**, Et_2O, 0−70 °C, 3 h, 92%; (c) CBr_4, PPh_3, CH_2Cl_2, −15 °C to rt, 2 h; (d) 3-butyn-1-ol, K_2CO_3, CuI, NaI, acetone, 0−70 °C, 22 h, 39% (2 steps); (e) 5% Pd-$BaSO_4$, quinoline, H_2, 1:1 MeOH/cyclohexene, rt, 2.5 h, 68%; (f) $Zr(O^tBu)_4$, (+)-DBTA, CHP, 4 Å MS, CH_2Cl_2, −40 °C, 44 h, 82%, 78:22 (3*S*,4*R*):(3*R*,4*S*); (g) Boc_2O, NEt_3, DMAP, PhMe, 0 °C to rt, 16 h, 56% (**31a** 32%).

double bonds of epoxide **19**. Epoxide **31** represents an "armed" version of alcohol **30**, where the *tert*-butyl carbonate is positioned as an intramolecular nucleophile[27c,d] to terminate an intramolecular bromonium ion assisted epoxide ring-opening reaction (and a cyclic carbonate should result).

Accordingly, readily available (*E*)-2-penten-1-ol (**24**) was converted through a known sequence with minor modifications to bromide **27**.[32] A second copper-mediated coupling[33] with 3-butyn-1-ol gave oxygen-sensitive enediyne **28**.[34] Enediyne **28** was chemoselectively hydrogenated to afford (*E*,*Z*,*Z*)-doubly skipped triene **29** using hydrogen gas and a quinolone-poisoned palladium on barium sulfate catalyst[35] where the use of sacrificial cyclohexene in methanol solution was critical to avoid over-reduction. Regioselective catalytic asymmetric epoxidation of the homoallylic alcohol in **29** was achieved using Onaka's conditions,[36] providing (*S*,*R*)-epoxy-diene **30**.[37] "Armed" substrate **31** was obtained by treating alcohol **30** with Boc-anhydride, triethylamine and catalytic DMAP, along with unavoidable formation of pseudo dimer **31a**.[38]

Attempts to induce an intramolecular bromonium ion assisted epoxide ring-opening of substrate **30** using our previously developed conditions,[28] with NBS and water as the nucleophile (and solvent), was unsuccessful, and instead a variety of bromohydrin regioisomers, dibromides and dibromotetrahydrofurans were obtained **30a**−**d**, (Scheme 5).[39] The use of Jamison's conditions (NBS, hexafluoroisopropanol, 4 Å MS)[27d] to induce intramolecular bromonium ion assisted epoxide ring-opening of "armed" substrate **31** was also unsuccessful. Much to our delight, the application of Snyder's highly reactive $Et_2SBr{\cdot}SbCl_5Br$ reagent (BDSB)[40] to induce intramolecular bromonium ion assisted epoxide ring-opening of "armed" substrate **31** gave carbonates **32**−**37**, which were hydrolyzed in quantitative yields to medium-ring ethers **39**−**44** (Scheme 6).[41] Thus, six[42] of the eight anticipated diastereo- and constitutional isomeric medium-ring ethers (two 7-, two 8- and two 9-ring) are formed by this intramolecular bromonium ion assisted epoxide ring-opening reaction, and these correlate to the known natural products as shown in Scheme 6.

None of the cyclic medium-ring ether compounds isolated in this study proved to be crystalline, and so the structures of diastereo- and constitutional isomeric carbonates **32**−**36** and diols **39**−**45** was achieved using 2D COSY, DEPT-135, HSQC

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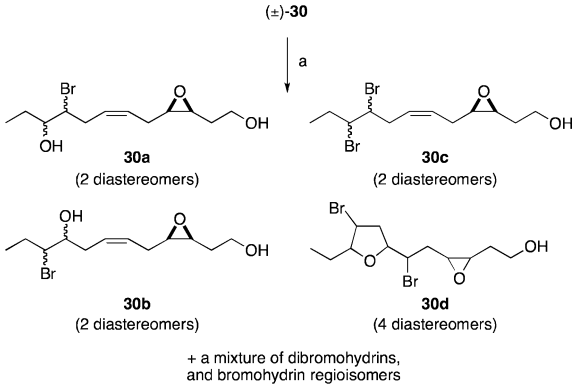
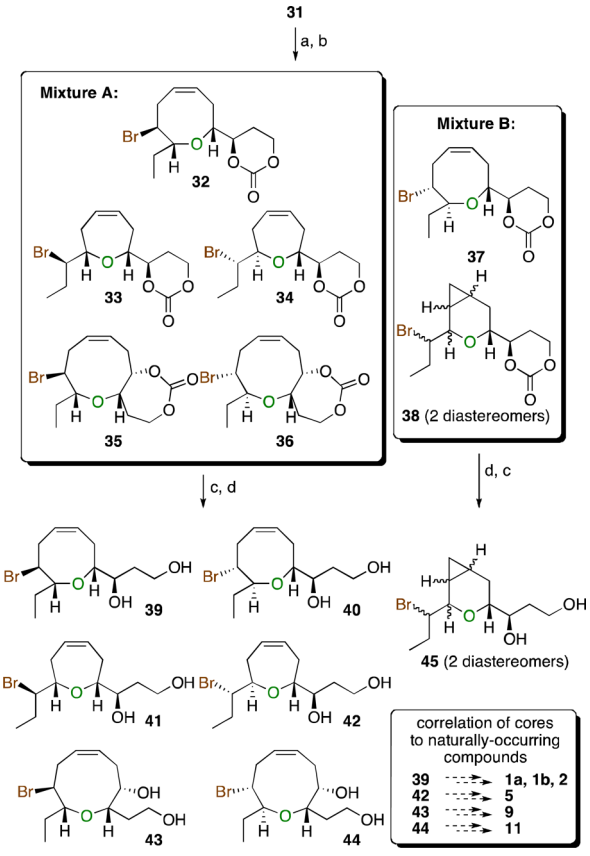
Scheme 5. Unsuccessful Attempt at Bromonium Ion Assisted Epoxide Ring-Opening of (±)-30[a]



[a]Conditions: (a) H_2O, NBS, TMG, rt, 65 h: **30a** and **30b**, 10%; **30c**, 1%; **30d**, 2%; other dibromohydrins, 10%; other bromohydrin regioisomers, 4%.

Scheme 6. Intramolecular Bromonium Ion Assisted Epoxide Ring-Opening of 31 to Form Medium-Ring Ethers and Subsequent Hydrolysis[a]



[a]Conditions: (a) $Et_2SBr{\cdot}SbCl_5Br$, NO_2Me, rt, 1 h: **32**, 4.1%; **33**, 1.4%; **34**, 1.2%; **35** and **36**, 1.8%; **37**, 3.5%; **38**, 5.8%; (b) column chromatography; (c) preparative HPLC; (d) NaOH, MeOH, rt, 2 h.

and HMBC NMR experiments (see Supporting Information for spectra). The CHBr ^{13}C NMR resonance for each compound was readily identified in this manner as at either C-12 (and hence endocyclic) or C-13 (and hence exocyclic).[43] A strong correlation between CHBr ^{13}C NMR resonances emerged where all endocyclic CHBr resonances were observed at ca. 56 ppm, whereas the exocyclic resonances were observed ca. 62 ppm (Table 1). The ^{13}C NMR C=O carbonate resonances

Table 1. ^{13}C NMR Shifts of Carbon-Bearing Bromide in Carbonates 32–36 and Diols 39–44[a]

entry	ether	δ_C CHBr[b]
1	**32**	56.0 (C-12)
2	**33**	61.9 (C-13)
3	**34**	62.8 (C-13)
4	**35** or **36**	56.8 (C-12)
5	**35** or **36**	56.8 (C-12)
6	**39**	55.7 (C-12)
7	**40**	55.2 (C-12)
8	**41**	62.5 (C-13)
9	**42**	62.8 (C-13)
10	**43** or **44**	57.7 (C-12)
11	**43** or **44**	55.2 (C-12)

[a]All spectra recorded in $CDCl_3$. [b]Chemical shift reported in ppm. The C-12 or C-13 descriptor in parentheses refers to the carbon number to which the bromide is attached.

were likewise characteristic at ca. 149 ppm for a six-membered carbonate (Table 2, entries 1–3) and ca. 154 ppm for a seven-

Table 2. ^{13}C NMR Shifts of C=O in Cyclic Carbonates 32–36[a]

entry	ether	δ_C CHBr[b]
1	**32**	148.5
2	**33**	148.9
3	**34**	148.9
4	**35** or **36**	154.2
5	**35** or **36**	154.2

[a]All spectra recorded in $CDCl_3$. [b]Chemical shift reported in ppm.

ring system (entries 4–5).[44] These observations in conjunction allow assignment of the compounds as either 7- 8- or 9-membered ring ethers. HMBC correlations were also observed between H-7 and C-13 of **39** and also H-7 and C-12 of **33**, thus inherently confirming the formation of the medium-ring itself and also supporting the assignment of 8- and 7-membered ring ethers respectively. The absolute and relative stereochemistry at the C-6 and C-7 positions in all cases was deduced by consideration of the (6*S*,7*R*)-configuration of the initial epoxide, which must undergo bromonium ion assisted epoxide ring-opening[27,28] with inversion of configuration at the center attacked by the carbonate (as inferred from the carbonate ring-size). The relative stereochemistry of the C-12 and C-13 positions was also set as either (12*R*,13*S*) or (12*S*,13*R*) due to the initial *trans*-geometry of the C(12)–C(13) alkene of substrate **31**: the bromonium ion must be formed with either the (12*R*,13*R*)- or (12*S*,13*S*)-configuration followed by stereospecific attack leading to stereochemical inversion at the C-12 or C-13 position. Therefore only the relative stereochemistry across the ether oxygen and the ring size (as deduced by the position of the bromine at C-12 or C-13 and the original ring-size of the carbonate) needs to be known in order to be able to assign the overall absolute and relative stereochemistry for these compounds.

For 7- and 8-membered medium-ring ethers, it was found that there is a correlation between the ^1H NMR chemical shifts of the flanking ether protons and the relative stereochemistry

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across the ether oxygen (Table 3). For the *cis*-α,α′ ether compounds the C(9)−C(10) alkene evidently shields these protons resulting in an upfield shift of both protons compared to the *trans*-α,α′ compounds. This is exemplified by the direct comparison of the chemical shifts of the *cis*-α,α′carbonate **33** (entry 2) and *trans*-α,α′ carbonate **34** (entry 3) for 7-membered medium-ring ethers [Δδ ca. 0.6 ppm], and by comparison of *cis*-α,α′diol **39** (entry 6) and *trans*-α,α′ diol **40** (entry 7) for 8-membered medium-ring ring ethers [Δδ ca. 0.3 ppm]. The ^{1}H NMR spectra of structurally related natural products exhibit the same *trans*-α,α′ versus *cis*-α,α′ effect, supporting the assignments made.[45] In the case of 8-membered ring ether **39**, an NOE was also observed between H-7 and H-13, confirming the *cis*-α,α′ relationship. For the 9-membered ring-ethers, both as carbonates **35** and **36**, and diols **43** and **44** (Table 3, entries 4, 5, 10 and 11), the above effect was not evident with the ^{1}H NMR spectra being markedly similar, and the two possible (6*S*,7*S*,12*R*,13*S*) and (6*S*,7*S*,12*S*,13*R*) diastereoisomers could not be distinguished.

Table 3. Comparison of ^{1}H NMR Shifts of *trans*- and *cis*-α,α′ Ether Protons of Carbonates 32−36 and Diols 39−44[a]

entry	ether	δ_H CHOCH[b]
1	**32**	3.51−3.45 (H-7 and H-13)
2	**33**	3.65 (H-12), 3.59 (H-7)
3	**34**	4.28 (H-7), 4.22 (H-12)
4	**35** or **36**	4.58 (H-6), 4.16 (H-13)
5	**35** or **36**	4.60 (H-6), 4.17 (H-13)
6	**39**	3.76 (H-13), 3.55 (H-7)
7	**40**	3.97 (H-13), 3.82 (H-7)
8	**41**	3.75 (H-12), 3.34 (H-7)
9	**42**	4.10−3.97 (H-7 and H-12)
10	**43** or **44**	4.15 (H-13), 3.76 (H-6)
11	**43** or **44**	4.18 (H-13), 3.79 (H-6)

[a]All spectra recorded in $CDCl_3$. [b]Chemical shift(s) reported in ppm. The descriptors in parentheses are the designation of the α,α′ protons according to the note on numbering of compounds reported in the Supporting Information.

A comparison of the ^{13}C NMR data for carbon atoms C-5 to C-15 of monocyclic 8-membered medium-ring ether **39** with laurencin (**1a**)[46] is shown in Table 4.[47] The root-mean-square of Δδ of 1.0 ppm is an excellent fit and provides further corroboration of the structure of **39**, and hence all the other medium-ring ethers prepared in this study by the intramolecular bromonium ion assisted ring-opening of epoxide **31**.

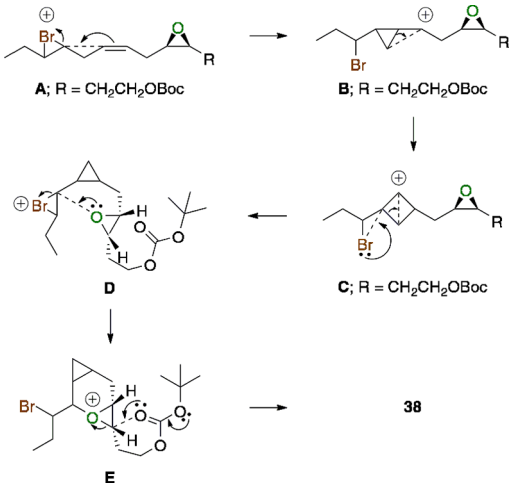
Table 4. Comparison of the ^{13}C NMR Shifts for C-5 to C-15 for Monocyclic Ether 39 and Laurencin (1a)[a]

entry	carbon no.	**39** δ_C[b]	**1a** δ_C[b,c]	Δδ
1	5	34.9	33.8	+1.1
2	6	74.2	76.7	−2.5
3	7	84.6	84.6	0.0
4	8	32.3	32.3	0.0
5	9	128.8	128.9	−0.1
6	10	129.4	129.2	+0.2
7	11	30.4	29.7	+0.7
8	12	55.7	56.0	−0.3
9	13	83.8	81.8	+2.0
10	14	25.8	25.8	0.0
11	15	9.3	9.3	0.0

[a]All spectra recorded in $CDCl_3$. [b]Chemical shift reported in ppm. [c]Data taken from ref 8j.

A 15:2 mixture of diastereomeric cyclopropanes **45** was also isolated from the bromonium ion assisted epoxide ring-opening reaction of epoxide **31** with BDSB, followed by hydrolysis (Scheme 6). They were identified using NMR methods (see Supporting Information), where C-10 diastereotopic methylene cyclopropane resonances were apparent at δ_H 0.95 and 0.39 ppm, C-13 was found to be the bromine bearing carbon (δ_C 61 ppm), a HMBC correlation between C-7 and H-12 confirmed the presence of a cyclic ether and defined the ring-size. As for the medium-ring ethers, the absolute stereochemistry at C-6 and C-7 is controlled by the original configuration of the epoxide. However, *cis*-α,α′ or *trans*- α,α′ ether stereochemistry could not be established, and the absolute stereochemistry of the other stereocenters remains unknown. A plausible mechanism (Scheme 7) to form carbonate **38** invokes an initial intramolecular attack of a bromonium ion **A** of epoxide **31** by the C(9)−C(10) olefin,[48] subsequent rearrangement of cyclopropyl cation **B** via cyclobutyl cation **C**,[49] followed by bromonium ion assisted epoxide ring-opening[26,27] on the new bromonium ion **D**, where the newly formed cyclopropane may provide a beneficial conformational constraint to favor ring-closure. The sequence is completed by intramolecular attack of oxonium ion **E** by the *tert*-butyl carbonate.

Scheme 7. Plausible Mechanism of Cyclopropane 38 Formation from Bromonium Ion A



CONCLUSIONS

In conclusion, we have shown that an "armed" epoxide **31** is a viable precursor for an intramolecular bromonium ion assisted epoxide ring-opening process using Snyder's powerful BDSB reagent, providing concurrently six medium-ring ether products, which correlate to several medium-ring natural products of formulas $C_{15}H_{21}BrO_2$ and $C_{15}H_{20}Br_2O_2$ from *Laurencia* species. This experimental corroboration using a model epoxide raises an important and interesting question. Does this represent a possible biogenetic pathway to the medium-ring ethers from *Laurencia* species from epoxides **19** and **23**? If so, since the stereochemical information contained in the epoxides is translated to the four stereocenters of the medium-ring products by the stereospecific nature of the process, the ability of an enzyme to provide an asymmetric environment may not

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be necessary.[50] Furthermore, the stereochemical analysis of such intramolecular bromonium ion assisted epoxide ring-opening processes for epoxides **19** (Scheme 2) and **23** (Scheme 3) shows that there are eight such medium-ring ethers possible from each epoxide, where 12,13-*epi*-**1b**, 12,13-*epi*-**3**, 12,13-*epi*-**12**, 12,13-*epi*-**16**, **20**, 12,13-*epi*-**20**, **21** and **22** may therefore represent the cores of as yet undiscovered naturally occurring medium-ring ethers from *Laurencia* species.[51]

EXPERIMENTAL SECTION

(*E*)-Oct-5-en-2-yn-1-ol (26). A solution of bromine (20.5 g, 128 mmol, 1.1 equiv) in dichloromethane (40 mL) was added dropwise to a solution of triphenylphosphine (33.6 g, 128 mmol, 1.1 equiv) in dichloromethane (140 mL) at 0 °C. The orange-yellow triphenylphosphine dibromide suspension was stirred at 0 °C for 30 min, and pyridine (10.1 g, 128 mmol, 1.1 equiv) was added, followed by a solution of alcohol **24** (10.0 g, 116 mmol, 1.0 equiv) in dichloromethane (60 mL). The reaction mixture was allowed to warm to room temperature and stirred for 1.5 h. The mixture was washed with 1 M hydrochloric acid (2 × 100 mL), and the layers were separated. The aqueous portion was extracted with dichloromethane (2 × 50 mL), the organics were combined and dried over sodium sulfate. The solvent and product were distilled away from the triphenylphosphine oxide under reduced pressure, and collected using a cold trap. The triphenylphosphine oxide was washed thoroughly with pentane, which was combined with the solution of the product in dichloromethane. The solvent was carefully removed by distillation, to provide the known bromide[32e] **25** (14.0 g, 81%) as a pale brown liquid, contaminated with small quantities of triphenylphosphine oxide and dichloromethane: R_f 0.62 (petroleum spirit:ethyl acetate, 4:1); IR (neat) 2964, 2932, 1660, 1459, 1436, 1203, 962 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.88−5.81 (m, 1H), 5.75−5.67 (m, 1H), 3.98 (d, J = 8.0 Hz, 2H), 2.15−2.08 (m, 2H), 1.03 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 125.4, 33.4, 25.1, 13.0; MS (EI^+) m/z 147 ($M^{+\cdot}$). The crude bromide was used in the next step without further purification. A solution of *iso*propylmagnesium chloride in THF (200 mL, 2.0 M, 397 mmol, 2.5 equiv) was added dropwise to a stirred solution of propargyl alcohol (12.0 mL, 206 mmol, 1.3 equiv) in THF (100 mL) at 0 °C, heated to 70 °C for 1.5 h and recooled to 0 °C. Copper(I) chloride (3.14 g, 32 mmol, 0.2 equiv) was added, followed by dropwise addition of a solution of bromide **25** (23.6 g, 159 mmol, 1.0 equiv) in diethyl ether (170 mL). The mixture was heated at 70 °C for 3 h, allowed to cool to room temperature, and the mixture was washed with saturated ammonium chloride solution (2 × 200 mL). The aqueous layer was separated and extracted with ethyl acetate (4 × 150 mL). The organics were combined, washed with brine (2 × 200 mL) and dried over sodium sulfate. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (petroleum spirit:ethyl acetate, 4:1) to give the known propargylic alcohol[32a] **26** (18.1 g, 92%) as a pale yellow oil: R_f 0.20 (petroleum spirit:ethyl acetate, 4:1); IR (neat) 3600−3050, 2964, 2873, 1463, 1373, 1009, 965 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.76−5.70 (m, 1H), 5.45−5.38 (m, 1H), 4.31 (t, J = 2.2 Hz, 2H) 2.98−2.96 (m, 2H), 2.10−2.03 (m, 2H), 1.01 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.1, 122.6, 84.1, 79.9, 51.4, 25.3, 22.0, 13.5; MS (CI) m/z 142 $(M + NH_4)^+$; HRMS (Magnetic Sector CI^+, NH_3) m/z calcd for $C_8H_{16}NO$ $(M + NH_4)^+$ 142.1232, found 142.1236.

(*E*)-Dodec-9-ene-3,6-diyn-1-ol (28). Carbon tetrabromide (58.3 g, 175 mmol, 1.2 equiv) was added to a solution of propargylic alcohol **26** (18.1 g, 146 mmol, 1.0 equiv) in dichloromethane (500 mL) at −15 °C. A solution of triphenylphosphine (49.8 g, 190 mmol, 1.3 equiv) in dichloromethane (200 mL) was added dropwise, and the mixture was allowed to warm to room temperature and stirred for 2 h. The mixture was concentrated to approximately 100 mL, petroleum spirit (400 mL) was added, cooled to −78 °C, filtered through a short plug of silica (to remove triphenylphosphine oxide and bromoform), and the solvent was removed under reduced pressure to give the known product bromide[32e] **27** as a pale yellow oil, contaminated with a small quantity of bromoform: R_f 0.55 (petroleum spirit:ethyl acetate, 4:1); IR (neat) 2963, 1459, 1419, 1208, 1143, 966 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.77−5.70 (m, 1H), 5.43−5.36 (m, 1H), 3.98 (t, J = 2.2 Hz, 2H), 3.00−2.98 (m, 2H), 2.10−2.03 (m, 2H), 1.01 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.3, 122.2, 85.7, 76.8, 25.3, 22.1, 15.5, 13.5; MS (EI) m/z 187 $(M + H)^+$. The crude product was used in the next step without further purification. A solution of 3-butyn-1-ol (11.0 mL, 146 mmol, 1.0 equiv) in acetone (500 mL) was added to a solution of bromide **27** (146 mmol, 1.0 equiv) in acetone (100 mL) at 0 °C. Potassium carbonate (40.3 g, 292 mmol, 2.0 equiv), sodium iodide (43.8 g, 292 mmol, 2.0 equiv) and copper(I) iodide (27.7 g, 146 mmol, 1.0 equiv) were added, and the cloudy yellow mixture was heated at 70 °C for 22 h. The reaction mixture was subsequently concentrated to approximately 100 mL, and ethyl acetate (400 mL) was added. The mixture was washed with saturated aqueous ammonium chloride solution (2 × 200 mL) and water (2 × 200 mL). The aqueous washings were combined, extracted with ethyl acetate (3 × 400 mL), and the organics were combined, dried over sodium sulfate and filtered. The solvent was removed under reduced pressure, and the product was purified by column chromatography (petroleum spirit:ethyl acetate, 4:1) to give alcohol **28** (10.0 g, 39% *over 2 steps*) as a yellow oil: R_f 0.21 (petroleum spirit:ethyl acetate, 4:1); IR (neat) 3650−3100, 2963, 1670, 1419, 1314, 1041, 966 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.75−5.66 (m, 1H), 5.42−5.35 (m, 1H), 3.70 (t, J = 6.3 Hz, 2H), 3.18−3.14 (m, 2H), 2.90−2.88 (m, 2H), 2.47−2.43 (m, 2H), 2.16 (br s, 1H), 2.07−2.00 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.8, 123.0, 78.4, 76.9, 76.7, 75.7, 61.1, 25.3, 23.1, 21.9, 13.5, 9.8; MS (CI) m/z 194 $(M + NH_4)^+$; HRMS (Magnetic Sector CI^+, NH_3) m/z calcd for $C_{12}H_{20}NO$ $(M + NH_4)^+$ 194.1545, found 194.1539.

(3*Z*,6*Z*,9*E*)-Dodeca-3,6,9-trien-1-ol (29). 5% Pd-$BaSO_4$ (0.80 g) and quinoline (2.0 mL) were added to a solution of dienyne **28** (2.0 g, 11.4 mmol) in methanol/cyclohexene (1/1, 100 mL). The mixture was stirred vigorously under hydrogen gas (1 atm). After 2.5 h the reaction mixture was filtered through a short plug of silica, and the solvent removed under reduced pressure. The crude mixture was subjected to column chromatography (petroleum spirit:acetone, 4:1) to give product **29** (1.40 g, 68%) as a pale yellow oil: R_f 0.48 (petroleum spirit:acetone, 2:1); IR (neat) 3600−3020, 3013, 2962, 2933, 1647, 1439, 1396 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.57−5.35 (m, 6H), 3.65 (t, J = 6.5 Hz, 2H), 2.86−2.82 (m, 2H), 2.79−2.75 (m, 2H), 2.39−2.33 (m, 2H), 2.05−1.90 (m, 3H), 0.99 (t, J = 3.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.5, 131.0, 128.3, 128.0, 126.9, 125.6, 62.1, 30.8, 30.4, 25.6 (x2), 13.8; MS (CI^+) m/z 198 $(M + NH_4)^+$; HRMS (Magnetic Sector CI^+, NH_3) m/z calcd for $C_{12}H_{24}NO$ $(M + NH_4)^+$ 198.1858, found 198.1838.

(3*S,4*R**,6*Z*,9*E*)-3,4-Epoxydodeca-6,9-dien-1-ol (±-30).** *tert*-Butyl hydroperoxide (0.36 mL) was added dropwise to a solution of triene **29** (129 mg, 0.72 mmol, 1.0 equiv) and vanadyl acetylacetonate (10 mg, 0.04 mmol, 5 mol %) in dichloromethane (10 mL) at 0 °C. The mixture was stirred at room temperature for 16 h, diluted with dichloromethane (10 mL) and washed with 10% w/w aqueous sodium sulfite solution (10 mL). The layers were separated, and the aqueous portion was extracted with diethyl ether (2 × 10 mL). The combined organics were washed with brine (20 mL), dried over sodium sulfate, and purified by column chromatography to give epoxide (±)-**30** (68 mg, 48%) as a colorless oil: R_f 0.19 (petroleum spirit:ethyl acetate, 2:1); IR (neat) 3600−3050, 3010, 2964, 2930, 2874, 1455, 1385 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.62−5.38 (m, 4H), 3.94−3.85 (m, 2H), 3.13 (dt, J = 7.8, 4.5 Hz, 1H), 3.00 (td, J = 6.4, 4.1 Hz, 1H), 2.77 (app t, J = 6.4 Hz, 2H), 2.48−2.39 (m, 1H), 2.29−2.20 (m, 1H), 2.07−2.00 (m, 2H), 1.97−1.73 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.9, 130.8, 126.6, 124.1, 60.8, 56.0, 55.0, 30.6, 30.5, 26.3, 25.5, 13.8; MS (CI) m/z 214 $(M + NH_4)^+$; HRMS (Magnetic Sector CI^+, NH_3) m/z calcd for $C_{12}H_{24}NO_2$ $(M + NH_4)^+$ 214.1807, found 214.1803.

(3*S*,4*R*,6*Z*,9*E*)-3,4-Epoxydodeca-6,9-dien-1-ol (30). Zirconium(IV) *t*-butoxide (1.58 mL, 10.2 mmol, 0.40 equiv) was added to (2*R*,3*R*)-*N*,*N*′-dibenzyl-2,3-dihydroxybutanediamide (2.01 g, 6.1 mmol, 0.60 equiv) and activated 4 Å molecular sieves (1.03 g) in dichloromethane (75 mL) at room temperature. The mixture was

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stirred for 2 h, cooled to −40 °C, and cumene hydroperoxide (3.77 mL) was added dropwise, followed by dropwise addition of a solution of (3*Z*,6*Z*,9*E*)-dodeca-3,6,9-trien-1-ol (**29**) (1.84 g, 10.2 mmol, 1.0 equiv) in dichloromethane (5 mL). After 20 h, further cumene hydroperoxide (1.80 mL) was added, and after a further 24 h aqueous sodium sulfite (10 mL) and diethyl ether (100 mL) were added, and the reaction mixture was allowed to warm to room temperature. Sodium sulfate (40.0 g) and silica (4.0 g) were added, and the mixture was stirred for 30 min before passing through a plug of silica, eluting with ethyl acetate (200 mL). The solvent was removed under reduced pressure, and the crude mixture was subjected to column chromatography (petroleum spirit:ethyl acetate, 2:1), providing epoxide **30** (1.64 g, 82%) as a colorless oil: $[\alpha]^{20}_{D}$ −8.9 (*c* 0.87, CH_2Cl_2) [where the trityl derivative recorded an e.r. of 78:22, (3*S*,4*R*):(3*R*,4*S*); see below]; all other data was identical with that reported above.

(3*S*,4*R*,6*Z*,9*E*)-3,4-Epoxydodeca-6,9-dien-1-yl trityl ether. Triethylamine (0.07 mL, 0.51 mmol, 2.0 equiv) and trityl chloride (78 mg, 0.28 mmol, 1.1 equiv) were added to a solution of epoxide **30** (50 mg, 0.24 mmol, 1.0 equiv) in dichloromethane (2.5 mL) at room temperature. The mixture was stirred for 18 h, diluted with dichloromethane (15 mL) and washed with water (15 mL). The aqueous phase was extracted with dichloromethane (3 × 15 mL), and the combined organics were washed with brine (20 mL). The organics were dried over sodium sulfate, filtered, and the solvent was removed under reduced pressure. The crude mixture was subjected to column chromatography (petroleum spirit:ethyl acetate, 20:1) to provide the product (82 mg, 73%) as a colorless oil: R_f 0.38 (petroleum spirit:ethyl acetate, 10:1); $[\alpha]^{20}_{D}$ −0.9 (*c* 0.98, CH_2Cl_2); IR (neat) 3063, 3026, 2963, 2926, 2875, 1490, 1447, 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53−7.48 (m, 6H), 7.38−7.32 (m, 6H), 7.31−7.26 (m, 3H), 5.62−5.37 (m, 4H), 3.33 (t, *J* = 6.5 Hz, 2H), 3.20−3.15 (m, 1H), 3.01 (td, *J* = 6.4, 4.3 Hz, 1H), 2.79 (app t, *J* = 6.3 Hz, 2H), 2.45−2.37 (m, 1H), 2.30−2.22 (m, 1H), 2.10−2.01 (m, 2H), 1.98−1.81 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 132.8, 130.6, 128.7, 127.8, 127.0, 126.7, 124.5, 86.8, 61.1, 56.4, 54.9, 30.6, 28.7, 26.3, 25.6, 13.9; MS (ESI) *m*/*z* 461 $(M + Na)^+$; HRMS (ES-ToF) *m*/*z* calcd for $C_{31}H_{34}O_2Na$ $(M + Na)^+$ 461.2457, found 461.2451; e.r. = 78:22, (3*S*,4*R*):(3*R*,4*S*); HPLC (ChiralPak AD), *n*-hexane:*i*-propanol = 99.75:0.25, wavelength = 200 nm; injection volume = 10 μL, flow rate = 0.25 mL/min, t_R = 105.7 min (3*S*,4*R*), t_R = 93.9 min (3*R*,4*S*).

Procedure for the Treatment of Epoxide (±)-30 with NBS and Water. Tetramethylguanidine (23 mg, 0.2 mmol, 5 mol %) and NBS (0.65 g, 3.7 mmol, 1.0 equiv) were added to a stirred solution of epoxide (±)-**30** (0.72 g, 3.7 mmol, 1.0 equiv) in water (370 mL). The mixture was stirred at room temperature for 3 days, and the products were extracted with ethyl acetate (3 × 100 mL). The organics were combined and washed with 10% w/w aqueous sodium sulfite solution (2 × 100 mL) and brine (100 mL). The organics were dried over sodium sulfate, and the solvent was removed under reduced pressure to give a colorless oil. Separation of products and purification was achieved by column chromatography (petroleum spirit:ethyl acetate, 2:1, to 100% ethyl acetate) and HPLC (*n*-hexane/*i*-propanol) where appropriate to give the following compounds. **(3*R**,4*S**,6*Z*,9*S**,10*R**)-9-Bromo-3,4-epoxydodec-6-ene-1,10-diol and (3*R**,4*S**,6*Z*,9*R**,10*S**)-9-Bromo-3,4-epoxydodec-6-ene-1,10-diol (30a). Diastereomer 1:** Isolated as a single diastereomer, with the overall relative stereochemistry unassigned: 32 mg, 3.0% as a colorless oil; IR (KBr) 3700−3100, 2967, 2880, 1643, 1438, 1385 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.75−5.64 (m, 2H), 4.16−4.07 (m, 1H), 3.93−3.83 (m, 2H), 3.67 (ddd, *J* = 8.8, 5.8, 3.3 Hz, 1H), 3.18 (dt, *J* = 7.6, 4.6 Hz, 1H), 3.07 (dt, *J* = 7.0, 5.0 Hz, 1H), 2.86−2.76 (m, 1H), 2.63−2.57 (m, 1H), 2.45−2.37 (m, 1H), 2.33−2.26 (m, 1H), 1.98−1.89 (m, 1H), 1.84−1.69 (m, 2H), 1.62−1.51 (m, 1H), 1.02 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.3, 126.9, 75.0, 60.6, 60.5, 56.1, 55.7, 31.3, 30.6, 26.8, 26.7, 10.1; MS (CI^+, NH_3) 310 $(M + NH_4)^+$; HRMS (Magnetic Sector CI^+, NH_3) *m*/*z* calcd for $C_{12}H_{25}NO_3{}^{79}Br$ $(M + NH_4)^+$ 310.1018, found 310.1018; HPLC (*n*-hexane:*i*-propanol, 95:5), 4.00 mL/min, 240 nm, t_R 22.5 min. **Diastereomer 2:** Isolated as a single diastereomer, with the overall relative stereochemistry unassigned: 55 mg, 5.1% as a colorless oil; IR (KBr) 3750−3100, 2978, 2818, 1641, 1421, 1265 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.69−5.60 (m, 2H), 4.16−4.10 (m, 1H), 3.93−3.81 (m, 2H), 3.70 (dt, *J* = 8.8, 3.9 Hz, 1H), 3.13 (dt, *J* = 7.7, 4.4 Hz, 1H), 3.03 (dt, *J* = 6.4, 4.4 Hz, 1H), 2.73−2.61 (m, 2H), 2.45−2.27 (m, 2H), 1.98−1.87 (m, 1H), 1.81−1.54 (m, 3H), 1.03 (t, J = 7.4, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.0, 126.7, 76.1, 62.0, 60.6, 55.9, 55.2, 31.4, 30.6, 26.7, 26.6, 10.3; MS (CI^+, NH_3) 310 $(M + NH_4)^+$; HRMS (Magnetic Sector CI^+, NH_3) *m*/*z* calcd for $C_{12}H_{25}NO_3{}^{79}Br$ $(M + NH_4)^+$ 310.1018, found 310.1021; HPLC (*n*-hexane:*i*-propanol, 95:5), 4.00 mL/min, 240 nm, t_R 24.5 min. **(3*R**,4*S**,6*Z*,9*S**,10*R**)-10-Bromo-3,4-epoxydodec-6-ene-1,9-diol and (3*R**,4*S**,6*Z*,9*R**,10*S**)-10-Bromo-3,4-epoxydodec-6-ene-1,9-diol (30b). Diastereomer 1:** Isolated as a single diastereomer, with the overall relative stereochemistry unassigned: 10 mg, 0.9% as a colorless oil; IR (KBr) 3700−3050, 2850, 2770, 1642, 1404 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.75−5.63 (m, 2H), 4.07 (ddd, *J* = 9.7, 5.0, 3.4 Hz, 1H), 3.95−3.79 (m, 3H), 3.18−3.14 (m, 1H), 3.09−3.04 (m, 1H), 2.52−2.31 (m, 4H), 2.04−1.76 (m, 4H), 1.12 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.6, 127.4, 74.0, 64.7, 60.5, 56.0, 55.6, 31.8, 30.6, 27.0, 26.5, 12.5; MS (CI^+, NH_3) 310 $(M + NH_4)^+$; HRMS (Magnetic Sector CI^+, NH_3) *m*/*z* calcd for $C_{12}H_{22}O_3{}^{79}Br$ $(M + H)^+$ 293.0752, found 293.0750; HPLC (*n*-hexane:*i*-propanol, 95:5), 4.00 mL/min, 240 nm, t_R 27.5 min. **Diastereomer 2:** Isolated as a single diastereomer, with the overall relative stereochemistry unassigned: 8 mg, 0.7% as a colorless oil; IR (KBr) 3700−3050, 2850, 2771, 1642, 1402 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.77−5.63 (m, 2H), 4.12−4.05 (m, 1H), 3.96−3.85 (m, 2H), 3.74 (dt, *J* = 8.2, 4.4 Hz, 1H), 3.20 (dt, *J* = 7.8, 4.5 Hz, 1H), 3.10−3.05 (m, 1H), 2.51−2.29 (m, 4H), 2.02−1.65 (m, 5H), 1.12 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.9, 127.6, 73.6, 65.1, 60.6, 56.0, 31.9, 30.7, 27.3, 26.2, 12.5; MS (CI^+, NH_3) 310 $(M + NH_4)^+$; HRMS (Magnetic Sector CI^+, NH_3) *m*/*z* calcd for $C_{12}H_{22}O_3{}^{79}Br$ $(M + H)^+$ 293.0752, found 293.0766; HPLC (*n*-hexane:*i*-propanol, 95:5), 4.00 mL/min, 240 nm, t_R 28.5 min. **(3*R**,4*S**,6*Z*,9*R**,10*S**)-9,10-Dibromo-3,4-epoxydodec-6-en-1-ol and (3*R**,4*S**,6*Z*,9*S**,10*R**)-9,10-Dibromo-3,4-epoxydodec-6-en-1-ol (30c).** Isolated as a mixture of two diastereomers (it was not possible to estimate the ratio from the ^1H NMR spectrum): 10 mg, 0.9% as a colorless oil; IR (KBr) 3650−3050, 1717, 1350, 1054 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.73−5.66 (m, 4H), 4.26−4.14 (m, 4H), 3.96−3.85 (m, 4H), 3.16 (dt, *J* = 7.8, 4.5 Hz, 2H), 3.08−2.97 (m, 4H), 2.92−2.84 (m, 2H), 2.51−2.21 (m, 6H), 2.07−1.90 (m, 4H), 1.83−1.55 (m, 4H), 1.12 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.7, 127.6, 127.4, 127.3, 60.7, 60.6, 60.4, 57.5, 57.3, 55.9, 55.8, 55.1, 55.0, 35.2, 35.1, 30.6, 30.5, 30.3, 29.7, 11.1; MS (CI^+, NH_3) 372 $(M + NH_4)^+$; HRMS (Magnetic Sector CI^+, NH_3) *m*/*z* calcd for $C_{12}H_{24}NO_2{}^{79}Br_2$ $(M + NH_4)^+$ 372.0174, found 372.0157; HPLC (*n*-hexane:*i*-propanol, 98.5:1.5), 3.50 mL/min, 206 nm, t_R 40.5 min. **(3*R**,4*S**,6*R**)-6-Bromo-6-[(2*R**,4*S**,5*R**)-4-bromo-5-ethyltetrahydrofuran-2-yl]-3,4-epoxy-hexan-1-ol, (3*R**,4*S**,6*R**)-6-Bromo-6-[(2*R**,4*R**,5*S**)-4-bromo-5-ethyltetrahydrofuran-2-yl]-3,4-epoxyhexan-1-ol, (3*R**,4*S**,6*S**)-6-Bromo-6-[(2*S**,4*S**,5*R**)-4-bromo-5-ethyltetrahydrofuran-2-yl]-3,4-epoxyhexan-1-ol and (3*R**,4*S**,6*S**)-6-Bromo-6-[(2*S**,4*R**,5*S**)-4-bromo-5-ethyltetrahydrofuran-2-yl]-3,4-epoxyhexan-1-ol (30d). Diastereomers 1 and 2:** Isolated as a mixture of two diastereomers in a ratio of 1.2:1.0 (found by integration of the signals at 4.36 and 4.27 ppm): 15 mg, 1.1% as a colorless oil; IR (KBr) 3600−3100, 2974, 1715, 1640, 1445, 1379, 1098, 948 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.40−4.36 (m, 1H), 4.31−4.27 (m, 1H), 4.25−4.18 (m, 2H), 4.08−4.04 (m, 4H), 3.94−3.84 (m, 4H), 3.29−3.19 (m, 3H), 3.18−3.14 (m, 1H), 2.53−2.46 (m, 2H), 2.40−2.19 (m, 4H), 2.08−2.02 (m, 2H), 1.98−1.57 (m, 8H), 1.03 (t, *J* = 7.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 88.7, 88.6, 79.9, 79.0, 60.5, 60.4, 55.6, 55.1, 54.9, 54.8, 54.6, 53.2, 48.3, 48.2, 40.4, 40.2, 34.0, 33.7, 31.0, 30.6, 26.4, 26.3, 10.0, 9.9; MS (CI^+, NH_3) 370 $(M + H)^+$; HRMS (ES-ToF) *m*/*z* calcd for $C_{12}H_{21}O_3{}^{79}Br_2$ $(M + H)^+$ 370.9857, found 370.9860. **Diastereomers 3 and 4:** Isolated as a mixture of two diastereomers (it was not possible to estimate the ratio from the ^1H NMR spectrum due to overlapping resonances): 16 mg, 1.2% as a colorless oil; IR (KBr)

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3600−3050, 2969, 2916, 1712, 1641, 1379, 1260, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.27−4.21 (m, 3H), 4.18−4.12 (m, 1H), 4.07−4.01 (m, 2H), 3.94- 3.86 (m, 6H), 3.30−3.25 (m, 2H), 3.24−3.20 (m, 1H), 3.18−3.13 (m, 1H), 2.76−2.68 (m, 2H), 2.40−2.19 (m, 4H), 2.12−2.05 (m, 2H), 1.99−1.50 (m, 8H), 1.03 (t, J = 7.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 87.4, 87.3, 79.5, 79.1, 60.6, 60.4, 55.6, 55.1, 54.9, 54.8, 54.5, 53.4, 46.7, 46.5, 40.4, 40.2, 33.4, 33.1, 31.0, 30.6, 25.3, 25.2, 9.9, 9.8; MS (CI^+, NH_3) 370 $(M + H)^+$; HRMS (ES-ToF) m/z calcd for $C_{12}H_{21}O_3{}^{79}Br_2$ $(M + H)^+$ 370.9857, found 370.9867.

***tert*-Butyl (3*S*,4*R*,6*Z*,9*E*)-3,4-epoxydodeca-6,9-dienyl carbonate (31).** Triethylamine (3.83 mL, 27.7 mmol, 2.0 equiv) and DMAP (337 mg, 2.8 mmol, 0.2 equiv) were added to a solution of epoxide **30** (2.71 g, 13.8 mmol, 1.0 equiv) in toluene (50 mL) at 0 °C. Di-*t*-butyl dicarbonate (4.28 mL, 18.7 mmol, 1.35 equiv) was added dropwise, and the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 16 h, the solvent was removed under reduced pressure, and the mixture was immediately subjected to column chromatography (petroleum spirit:ethyl acetate, 9:1), to give first **31** (2.30 g, 56%) as a colorless oil: R_f 0.59 (petroleum spirit:ethyl acetate, 2:1); $[\alpha]^{20}{}_D$ −3.8 (c 1.05, CH_2Cl_2); IR (neat) 2973, 1739, 1457, 1395, 1370, 1276, 1252, 1159, 1102, 967 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.62−5.35 (m, 4H), 4.31−4.23 (m, 2H), 3.12−3.05 (m, 1H), 3.00 (td, J = 6.4, 4.1 Hz, 1H), 2.81−2.74 (m, 2H), 2.45−2.35 (m, 1H), 2.29−2.19 (m, 1H), 2.08−1.81 (m, 4H), 1.51 (s, 9H), 0.98 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 132.9, 130.8, 126.6, 124.1, 82.2, 64.3, 56.2, 54.0, 30.6, 27.8, 27.6, 26.1, 25.6, 13.8; MS (CI) m/z 314 $(M + NH_4)^+$; HRMS (Magnetic Sector CI^+, NH_3) m/z calcd for $C_{17}H_{32}NO_4$ $(M + NH_4)^+$ 314.2331, found 314.2323. The second, **bis(3*R*,4*S*,6*Z*,9*E*)-3,4-epoxydodeca-6,9-dienyl carbonate (31a)**, was given as a pale yellow oil (0.93 g, 32%): R_f 0.49 (petroleum spirit:ethyl acetate, 2:1): $[\alpha]^{20}{}_D$ −6.4 (c 1.57, CH_2Cl_2); IR (neat) 2963, 1745, 1461, 1403, 1251, 966 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.62−5.35 (m, 8H), 4.38−4.31 (m, 4H), 3.08 (dt, J = 7.1, 4.5 Hz, 2H), 3.01 (td, J = 6.4, 4.2 Hz, 2H), 2.80−2.74 (m, 4H), 2.46−2.37 (m, 2H), 2.28−2.19 (m, 2H), 2.06−1.97 (m, 6H), 1.93−1.84 (m, 2H), 0.98 (t, J = 7.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 132.9, 130.9, 126.6, 124.0, 65.4, 56.2, 53.8, 31.4, 27.5, 26.1, 25.5, 13.8; MS (CI) m/z 436 $(M + NH_4)^+$; HRMS (Magnetic Sector CI^+, NH_3) m/z calcd for $C_{25}H_{42}NO_5$ $(M + NH_4)^+$ 436.3063, found 436.3056.

Procedure for Cyclization of Carbonate 31 and Subsequent Hydrolysis. A solution of $Et_2SBr{\cdot}SbCl_5Br$ (885 mg, 1.61 mmol, 1.0 equiv) in nitromethane (1 mL) was added rapidly to a solution of carbonate **31** (477 mg, 1.61 mmol, 1.0 equiv) in nitromethane (80 mL) at room temperature. After 1 h the reaction mixture was diluted with ethyl acetate (200 mL) and washed with a mixture of aqueous sodium sulfite solution (100 mL) and saturated aqueous sodium bicarbonate solution (100 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (4 × 100 mL). The organics were combined, washed with brine (200 mL), dried over sodium sulfate, filtered, and the solvent was removed under reduced pressure. The crude mixture was subjected to column chromatography (petroleum spirit:ethyl acetate, 3:1 to 1:2) to give two components, first **Mixture A** (105 mg) as a pale yellow oil and second **Mixture B** (91 mg) as a colorless oil. **Mixture A**: R_f 0.35 (ethyl acetate:petroleum spirit, 3:1). Analysis of the ^1H NMR spectrum provides the following calculated yields from carbonate **31**:**32** (21 mg, 4.1%), **33** (7 mg, 1.4%), **34** (6 mg, 1.2%), **35** and **36** (9 mg, 1.8%). These compounds were separated by preparative HPLC. **(4*R*)-4-[(2*R*,4*Z*,7*S*,8*R*)-7-Bromo-8-ethyl-3,6,7,8-tetrahydro-2*H*-oxocin-2-yl]-1,3-dioxan-2-one (32).** Colorless oil (containing 12% of compound **34**, found by relative integration of the resonance at 5.95 ppm with the resonance at 5.74 ppm): $[\alpha]^{26}{}_D$ +20.0 (c 1.20, CH_2Cl_2); IR (neat) 2967, 2923, 1748, 1449, 1408, 1248, 1192, 1124, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.03−5.91 (m, 2H), 4.55 (dt, J = 11.1, 3.7 Hz, 1H), 4.52−4.35 (m, 2H), 4.04 (dt, J = 9.9, 3.4 Hz, 1H), 3.51−3.45 (m, 2H), 3.17 (ddd, J = 14.1, 8.5, 3.6 Hz, 1H), 2.60−2.46 (m, 2H), 2.23−2.13 (m, 2H), 2.09−1.97 (m, 2H), 1.56−1.49 (m, 1H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 129.3, 128.9, 85.2, 81.1, 80.2, 67.0, 56.0, 32.3, 28.7, 26.0, 22.7, 9.8; MS (CI) m/z 336 $(M + NH_4)^+$; HRMS (Magnetic Sector CI^+, NH_3) m/z calcd for $C_{13}H_{23}NO_4{}^{79}Br$ $(M + NH_4)^+$ 336.0810, found 336.0807; HPLC (*n*-hexane:*i*-propanol, 94:6); 1.05 mL/min; 203 nm; t_R 148 min. **(4*R*)-4-{(2*R*,7*S*)-7-[(1*R*)-1-bromopropyl]-2,3,6,7-tetrahydrooxepin-2-yl}-1,3-dioxan-2-one (33).** Colorless oil (containing 27% by mole of an unidentified saturated compound, found by relative integration of the resonance at 3.70 ppm with the resonance at 3.65 ppm): $[\alpha]^{23}{}_D$ +22.6 (c 0.30, CH_2Cl_2); IR (neat) 2970, 2931, 1747, 1407, 1251, 1192, 1124 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.83−5.80 (m, 2H), 4.55−4.46 (m, 2H), 4.39−4.32 (m, 1H), 3.96−3.90 (m, 1H), 3.65 (ddd, J = 9.9, 4.5, 2.0 Hz, 1H), 3.59 (ddd, J = 10.7, 3.4, 1.6 Hz, 1H), 2.65−2.56 (m, 1H), 2.52−2.30 (m, 2H), 2.29−2.24 (m, 2H), 2.09−1.72 (m, 3H), 1.06 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.9, 129.1, 128.8, 83.3, 80.6, 79.6, 66.8, 61.9, 34.2, 31.9, 26.5, 23.4, 12.4; MS (CI) m/z 336 $(M + NH_4)^+$; HRMS (Magnetic Sector CI^+, NH_3) m/z calcd for $C_{13}H_{23}NO_4{}^{79}Br$ $(M + NH_4)^+$ 336.0810, found 336.0811; HPLC (*n*-hexane:*i*-propanol, 94:6); 1.50 mL/min; 203 nm; t_R 140 min. **(4*R*)-4-{(2*R*,7*R*)-7-[(1*S*)-1-Bromopropyl]-2,3,6,7-tetrahydrooxepin-2-yl}-1,3-dioxan-2-one (34).** The product was isolated as a colorless oil (containing 9% of **32** and 20% of **33**, found by relative integration of the resonance at 5.95 ppm with the resonance at 5.76 ppm and the resonance at 5.74 ppm): $[\alpha]^{26}{}_D$ −9.0 (c 0.20, CH_2Cl_2); IR (neat) 2925, 2857, 1748, 1410, 1249, 1191, 1119 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.73−5.70 (m, 2H), 4.54 (ddd, J = 10.8, 5.0, 3.4 Hz, 1H), 4.46 (ddd, J = 10.2, 4.3, 2.5 Hz, 1H), 4.35 (td, J = 11.1, 3.6 Hz, 1H), 4.28 (dt, J = 11.7, 1.8 Hz, 1H), 4.22 (ddd, J = 10.5, 4.3, 1.7 Hz, 1H), 4.03 (dt, J = 9.7, 4.0 Hz, 1H), 2.85−2.78 (m, 1H), 2.67−2.54 (m, 1H), 2.38−2.17 (m, 3H), 2.09−2.01 (m, 1H), 1.93−1.72 (m, 2H), 1.10 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 127.8, 127.7, 80.9, 77.9, 75.5, 66.8, 62.8, 30.5, 30.2, 28.3, 23.3, 12.4; MS (CI^+, NH_3) m/z 336 $(M + NH_4)^+$; HRMS (Magnetic Sector CI^+, NH_3) m/z calcd for $C_{13}H_{23}NO_4{}^{79}Br$ $(M + NH_4)^+$ 336.0810, found 336.0807; HPLC (*n*-hexane:*i*-propanol, 94:6); 1.50 mL/min; 203 nm; t_R 145 min. **(5*aS*,7*R*,8*S*,10*Z*,12*aS*)-8-Bromo-7-ethyl-4,5,5*a*,7,8,9,12,12*a*-octahydro[1,3]dioxepino[5,4-*b*]oxonin-2-one (35) and (5*aS*,7*S*,8*R*,10*Z*,12*aS*)-8-Bromo-7-ethyl-4,5,5*a*,7,8,9,12,12*a*-octahydro[1,3]dioxepino[5,4-*b*]oxonin-2-one (36). Diastereomer 1:** Colorless oil (containing 16% by mole of an unidentified compound, found by relative integration of the resonance at 4.40 ppm with the resonance at 4.50 ppm): $[\alpha]^{26}{}_D$ +15.0 (c 0.20, CH_2Cl_2); IR (neat) 2925, 1790, 1171, 1055 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.84−5.75 (m, 1H), 5.69−5.61 (m, 1H), 4.62−4.46 (m, 2H), 4.26−4.20 (m, 1H), 4.19−4.13 (m, 1H), 3.92−3.84 (m, 2H), 3.04−2.84 (m, 2H), 2.71−2.55 (m, 2H), 2.33−2.20 (m, 1H), 2.09−1.94 (m, 3H), 1.12 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2, 129.6, 124.8, 81.9, 79.3, 60.5, 58.2, 56.8, 36.1, 35.1, 31.6, 30.4, 11.0; MS (ESI) m/z 319 $(M + H)^+$; HPLC (*n*-hexane:*i*-propanol, 94:6); 1.50 mL/min; 203 nm; t_R 97 min. It was not possible to obtain high resolution mass spectrometry data for this compound using either CI or ESI modes of ionization. **Diastereomer 2:** Colorless oil (containing ca. 20% of Diastereomer 1, found by relative integration of the alkene resonances in the ^{13}C NMR spectrum): $[\alpha]^{24}{}_D$ +18.5 (c 0.20, CH_2Cl_2); IR (neat) 2968, 1793, 1385, 1174, 1054 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.85−5.77 (m, 1H), 5.69−5.61 (m, 1H), 4.64−4.57 (m, 1H), 4.53−4.47 (m, 1H), 4.27−4.21 (m, 1H), 4.20−4.14 (m, 1H), 3.93−3.84 (m, 2H), 3.05−2.84 (m, 2H), 2.70−2.50 (m, 2H), 2.31−2.24 (m, 1H), 2.06−1.94 (m, 3H), 1.12 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 130.0, 124.4, 81.1, 78.6, 60.5, 58.2, 56.8, 36.2, 35.2, 31.3, 30.4, 11.0; MS (ESI) m/z 319 $(M + H)^+$; HPLC (*n*-hexane:*i*-propanol, 94:6); 1.50 mL/min; 203 nm; t_R 102 min. It was not possible to obtain high resolution mass spectrometry data for this compound using either CI or ESI modes of ionization. **Mixture B**: R_f 0.29 (ethyl acetate:petroleum spirit, 3:1). Analysis of the ^1H NMR spectrum provides the following calculated yields from *tert*-butyl (3*R*,4*S*,6*Z*,9*E*)-epoxydodeca-6,9-dienyl carbonate **31**:**37** (18 mg, 3.5%) and **38** (30 mg, 5.8%). This mixture of carbonates was subjected to basic hydrolysis. Sodium hydroxide (171 mg, 4.28 mmol. 15.0 equiv) was added to a solution of **Mixture B** (91 mg, 0.29 mmol, 1.0 equiv) in methanol at room temperature. After 2 h saturated aqueous ammonium chloride solution (136 mg, 2.54 mmol, 9.0 equiv) was

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added, and the mixture was stirred for an additional 10 min. The crude mixture was filtered through a plug of silica, eluting with diethyl ether (100 mL), and the solvent was subsequently evaporated under reduced pressure to provide **Mixture C** (75 mg) as a colorless oil. **Mixture C**: R_f 0.31 (ethyl acetate:petroleum spirit, 3:1). These compounds were separated by preparative HPLC. **(1*R*)-1-[(2*R*,4*Z*,7*R*,8*S*)-7-Bromo-8-ethyl-3,6,7,8-tetrahydro-2*H*-oxocin-2-yl]propane-1,3-diol (40).** Colorless oil (containing 7% by mole of an unidentified compound, found by relative integration of the resonance at 4.26 ppm with the resonance at 4.20 ppm): $[\alpha]^{26}_{D}$ −25.5 (*c* 1.00, CH_2Cl_2); IR (neat) 3600−3050, 2933, 1457, 1386, 1152, 1046 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81−5.71 (m, 2H), 4.20 (ddd, *J* = 10.0, 7.5, 2.9 Hz, 1H), 3.97 (ddd, *J* = 9.8, 6.7, 3.2 Hz, 1H), 3.93−3.81 (m, 4H), 3.13−3.05 (m, 1H), 2.83 (br s, 1H), 2.74−2.65 (m, 1H), 2.57 (br s, 1H), 2.44−2.29 (m, 2H), 2.05−1.94 (m, 1H), 1.93−1.82 (m, 1H), 1.81−1.67 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.1, 127.7, 78.3, 77.7, 73.0, 61.1, 55.2, 35.3, 34.9, 29.8, 26.2, 9.0; MS (CI) *m*/*z* 310 $(M + NH_4)^+$; HRMS (ES-ToF) *m*/*z* calcd for $C_{12}H_{22}O_3{}^{79}Br$ $(M + H)^+$ 293.0752, found 293.0742; HPLC (*n*-hexane:*i*-propanol, 94:6); 4.00 mL/min; 203 nm; t_R 48 min. **1-[2-(1-Bromopropyl)-3-oxabicyclo[4.1.0]hept-4-yl]propane-1,3-diol (45).** Colorless oil (two diastereomers in a ratio of 15:2, found by relative integration of the resonance at 0.25 ppm with the resonance at 0.40 ppm; the following resonances given are for the major diastereomer): $[\alpha]^{26}_{D}$ +7.7 (*c* 1.90, CH_2Cl_2); IR (neat) 3600−3000, 2928, 1460, 1066 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.29 (td, *J* = 8.8, 3.1 Hz, 1H), 3.93 (dd, *J* = 8.8, 2.1 Hz, 1H), 3.85 (app t, *J* = 5.1 Hz, 2H), 3.53 (ddd, *J* = 12.7, 6.4, 2.1 Hz, 1H), 3.31 (ddd, *J* = 11.3, 6.5, 4.5 Hz, 1H), 2.81 (d, *J* = 2.4 Hz, 1H), 2.66 (br s, 1H), 2.19−2.05 (m, 1H), 1.98−1.83 (m, 2H), 1.75−1.64 (m, 2H), 1.38−1.27 (m, 2H), 1.16−1.08 (m, 4H), 0.90−0.81 (m, 1H), 0.39 (dd, *J* = 10.7, 5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.4, 74.6, 70.9, 61.1, 60.8, 34.0, 27.5, 24.8, 11.8, 11.3, 11.2, 7.0; MS (CI) *m*/*z* 310 $(M + NH_4)^+$; HRMS (ES-ToF) *m*/*z* calcd for $C_{12}H_{22}O_3{}^{79}Br$ $(M + H)^+$ 293.0752, found 293.0739; HPLC (*n*-hexane:*i*-propanol, 94:6); 4.00 mL/min; 203 nm; t_R 42 min.

General Procedure for the Hydrolysis of the Cyclic Carbonates Isolated from Mixture A. Sodium hydroxide (15.0 equiv) was added to a solution of carbonate **32**, **33**, **34**, **35** or **36** (1.0 equiv) in methanol (42 mM) at room temperature. After stirring for 2 h ammonium chloride (9.0 equiv) was added and stirred for a further 10 min. The mixture was filtered through a plug of silica, eluting with diethyl ether, and the solvent was subsequently removed under reduced pressure to provide the product **39**, **41**, **42**, **43** or **44**, respectively, in quantitative yield.

(1*R*)-1-[(2*R*,4*Z*,7*S*,8*R*)-7-Bromo-8-ethyl-3,6,7,8-tetrahydro-2*H*-oxocin-2-yl]propane-1,3-diol (39). Colorless oil (containing 12% of **42**, in accordance with what was found for compound **32**): $[\alpha]^{28}_{D}$ +11.0 (*c* 1.20, CH_2Cl_2); IR (neat) 3650−3050, 2922, 1649, 1447, 1055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.02−5.89 (m, 2H), 4.10 (dt, *J* = 9.9, 3.4 Hz, 1H), 3.92−3.84 (m, 2H), 3.79−3.73 (m, 1H), 3.58−3.53 (m, 1H), 3.29−3.15 (m, 2H), 2.92 (d, *J* = 2.9 Hz, 1H), 2.56−2.48 (m, 1H), 2.44−2.35 (m, 1H), 2.22−2.13 (m, 1H), 2.10−1.98 (m, 1H), 1.82−1.75 (m, 2H), 1.69−1.59 (m, 1H), 1.01 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 129.4, 128.8, 84.6, 83.9, 74.3, 61.4, 55.7, 34.9, 32.3, 30.4, 25.8, 9.3; MS (CI) *m*/*z* 310 $(M + NH_4)^+$; HRMS (Magnetic Sector CI^+, NH_3) *m*/*z* calcd for $C_{12}H_{22}O_3{}^{79}Br$ $(M + H)^+$ 293.0752, found 293.0745.

(1*R*)-1-{(2*R*,7*S*)-7-[(1*R*)-1-Bromopropyl]-2,3,6,7-tetrahydrooxepin-2-yl}propane-1,3-diol (41). Colorless oil (containing 27% by mole of an unidentified saturated compound, in accordance with what was found for compound **33**): $[\alpha]^{28}_{D}$ +43.0 (*c* 0.20, CH_2Cl_2); IR (neat) 3600−3050, 2929, 1667, 1423, 1260, 1059 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.80−5.76 (m, 2H), 4.01−3.95 (m, 1H), 3.88−3.83 (m, 2H), 3.79−3.70 (m, 2H), 3.38−3.30 (m, 1H), 2.61−2.57 (m, 1H), 2.54−2.46 (m, 1H), 2.37−2.25 (m, 2H), 2.00−1.78 (m, 2H), 1.76−1.70 (m, 2H), 1.08 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.8, 128.4, 83.9, 83.0, 74.6, 62.5, 61.2, 34.7, 34.2, 32.8, 26.4, 12.6; MS (CI) *m*/*z* 310 $(M + NH_4)^+$; HRMS (Magnetic Sector CI^+, NH_3) *m*/*z* calcd for $C_{12}H_{25}NO_3{}^{79}Br$ $(M + NH_4)^+$ 310.1018, found 310.1021.

(1*R*)-1-{(2*R*,7*R*)-7-[(1*S*)-1-Bromopropyl]-2,3,6,7-tetrahydrooxepin-2-yl}propane-1,3-diol (42). The product was isolated as a white solid (containing 9% of **39** and 20% of **41**, in accordance with what was found for compound **34**): $[\alpha]^{28}_{D}$ −10.0 (*c* 0.01, CH_2Cl_2); IR (neat) 3650−3000, 2926, 1639, 1455, 1055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.78−5.68 (m, 2H), 4.30−4.24 (m, 1H), 4.10−3.97 (m, 2H), 3.91−3.84 (m, 2H), 3.83−3.75 (m, 1H), 2.93 (d, *J* = 4.5 Hz, 1H), 2.74−2.64 (m, 1H), 2.57−2.53 (m, 1H), 2.36−2.20 (m, 2H), 1.98−1.65 (m, 4H), 1.10 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.2, 127.6, 78.0, 77.9, 74.2, 62.8, 61.2, 35.1, 31.2, 31.0, 27.4, 12.6; MS (CI) *m*/*z* 310 $(M + NH_4)^+$; HRMS (Magnetic Sector CI^+, NH_3) *m*/*z* calcd for $C_{12}H_{25}NO_3{}^{79}Br$ $(M + NH_4)^+$ 310.1018, found 310.1021. Insufficient material was available to record a melting point.

(2*S*,3*S*,5*Z*,8*S*,9*R*)-8-Bromo-9-ethyl-2-(2-hydroxyethyl)-2,3,4,7,8,9-hexahydrooxonin-3-ol (43) and (2*S*,3*S*,5*Z*,8*R*,9*S*)-8-Bromo-9-ethyl-2-(2-hydroxyethyl)-2,3,4,7,8,9-hexahydrooxonin-3-ol (44). Diastereomer 1: Off-white solid (containing 16% by mole of an unidentified compound, in accordance with what was found for Diastereomer 1 of compound **35** or **36**): $[\alpha]^{28}_{D}$ +1.0 (*c* 0.02, CH_2Cl_2); IR (neat) 3650−3000, 2923, 1642, 1457, 1262, 1057 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.72−5.65 (m, 2H), 4.22 (td, *J* = 8.8, 3.4 Hz, 1H), 4.17−4.12 (m, 1H), 3.93−3.86 (m, 2H), 3.80−3.72 (m, 1H), 3.60−3.53 (m, 1H), 3.02−2.79 (m, 2H), 2.40−1.92 (m, 4H), 1.85−1.72 (m, 2H), 1.08 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.7, 127.9, 73.9, 73.5, 61.2, 60.6, 57.7, 35.2, 35.0, 32.1, 30.3, 11.1; MS (CI) *m*/*z* 310 $(M + NH_4)^+$; HRMS (Magnetic Sector CI^+, NH_3) *m*/*z* calcd for $C_{12}H_{25}NO_3{}^{79}Br$ $(M + NH_4)^+$ 310.1018, found 310.1018. Insufficient material was available to record a melting point. **Diastereomer 2:** White solid (containing 21% of Diastereomer 1, in accordance with what was found for Diastereomer 2 of compound **35** or **36**): $[\alpha]^{28}_{D}$ −1.0 (*c* 0.01, CH_2Cl_2); IR (neat) 3600−3050, 2928, 1671, 1458, 1061 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.73−5.67 (m, 2H), 4.27−4.22 (m, 1H), 4.21−4.16 (m, 1H), 3.97−3.87 (m, 2H), 3.83−3.76 (m, 1H), 3.64−3.57 (m, 1H), 3.04−2.83 (m, 2H), 2.45−1.95 (m, 4H), 1.92−1.75 (m, 2H), 1.11 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.5, 128.1, 73.9, 73.5, 61.1, 60.6, 57.8, 35.2, 35.1, 32.1, 30.3, 11.1; MS (CI) *m*/*z* 310 $(M + NH_4)^+$; HRMS (Magnetic Sector CI^+, NH_3) *m*/*z* calcd for $C_{12}H_{25}NO_3{}^{79}Br$ $(M + NH_4)^+$ 310.1018, found 310.1021. Insufficient material was available to record a melting point.

■ ASSOCIATED CONTENT

Supporting Information

General experimental; copies of ^1H and ^{13}C NMR spectra for **26**, **28**, **29**, **30**, **31**, **31a** and trityl derivative of **30**; HPLC chromatogram of the racemic and enantioenriched trityl derivative of **30**; ^1H and ^{13}C NMR spectra of compounds **30a−d**, including Br-induced isotopic shift for compounds **30a** (Diastereomer 1) and **30b** (Diastereomers 1 and 2); ^1H NMR spectrum of Mixture A before preparative HPLC. HPLC chromatogram of Mixture A and C; note on numbering of compounds; copies of ^1H, ^{13}C, DEPT-135, COSY and HSQC NMR spectra for carbonates **32**, **33**, **34**, **35** and **36**, and HMBC NMR spectrum of **33**; copies of ^1H, ^{13}C, DEPT-135, COSY and HSQC NMR spectra for diols **39**, **40**, **41**, **42**, **43**, **44** and **45**, and HMBC and NOESY NMR spectra of **39** and **45**; comparison of ^1H NMR spectrum of **32** with **1a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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12084−12085. For the intermolecular capture of a bromonium ion by an epoxide, see: (e) Zhou, L.; Tan, C. K.; Zhou, J.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 10245−10247. For the intramolecular capture of a bromonium ion by the oxygen of a tetrahydrofuran, see: (f) Braddock, D. C.; Millan, D. S.; Perez-Fuertes, Y.; Pouwer, R.; Sheppard, R. N.; Solanki, S.; White, A. J. P. *J. Org. Chem.* **2009**, *74*, 1835−1841. (g) See also ref 26. (h) For the intramolecular capture of a bromonium ion by the oxygen of an oxetane, see: Keshipeddy, S.; Martínez, I.; Castillo, B. F., II; Morton, M. D.; Howell, A. R. *J. Org. Chem.* **2012**, *77*, 7883−7890.

(28) For an intramolecular bromonium ion assisted epoxide ring-opening reaction with capture of the oxonium ion with an added external nucleophile, see: Bonney, K. J.; Braddock, D. C.; White, A. J. P.; Yaqoob, M. *J. Org. Chem.* **2011**, *76*, 97−104.

(29) Lauredials *R,R*-**18** and *S,S*-**18** could *both* arise from stereospecific ring-opening of the 6*S*,7*R*-epoxide **19** with water at the C-6 and C-7 positions, respectively. Murai proposed an epoxide to be a plausible precursor of the laurediols; see ref 22.

(30) The natural products neoisoprelaurefucin (7-membered ring, see refs 3d and 7) and neolaurallene (9-membered ring, see refs 5c and 15) would arise from a (6*R*,7*S*)-configured epoxide instead of the (6*S*,7*R*)-epoxide of **19** by this analysis. The former epoxide has been invoked in the proposed biogenesis of the obtusallene family of natural products from *Laurencia* species: Braddock, D. C. *Org. Lett.* **2006**, *8*, 6055−6058.

(31) The (12*Z*)-geometrical laurediol isomer has been isolated from *Laurencia* species: Fukuzawa, A.; Honma, T.; Takasugi, Y.; Murai, A. *Phytochemistry* **1993**, *32*, 1435−1438.

(32) (a) Loreau, O.; Maret, A.; Poullain, D.; Chardigny, J. M.; Sébédio, J. L.; Beaufrère, B.; Noël, J. P. *Chem. Phys. Lipids* **2000**, *106*, 65−78. See also: (b) Young, W. G.; Richards, L.; Azorlosa, J. *J. Am. Chem. Soc.* **1939**, *61*, 3070−3074. (c) Cossío, F. P.; Ganboa, I.; Palomo, C. *Tetrahedron Lett.* **1985**, *26*, 3041−3044. (d) Smith, L. M.; Smith, R. G.; Loehr, T. M.; Daves, G. D., Jr.; Daterman, G. E.; Wohleb, R. H. *J. Org. Chem.* **1978**, *43*, 2361−2366. (e) Añorbe, B.; Martin, V. S.; Palazón, J. M.; Trujillo, J. M. *Tetrahedron Lett.* **1986**, *27*, 4991−4994.

(33) Villalva-Servin, N. P.; Laurent, A.; Fallis, A. G. *Can. J. Chem.* **2004**, *82*, 227−239.

(34) The moderate yield for this two-step process is a reflection of the chromatographic purification of the desired linear product away from branched isomers. The branched isomers originate from competing S_N2' processes/isomerization pathways in steps a and b of Scheme 4.

(35) For a representative example see: Miyaoka, H.; Tamura, M.; Yamada, Y. *Tetrahedron* **2000**, *56*, 8083−8094.

(36) Okachi, T.; Murai, N.; Onaka, M. *Org. Lett.* **2003**, *5*, 85−87.

(37) The e.r. of **30** was determined by chiral HPLC methods to be 78:22 (see the Supporting Information). This was achieved by tritylation of the primary alcohol and comparison with a racemic sample obtained by epoxidation of triene **29** (followed by tritylation) using 5 mol% vanadyl acetylacetonate and stoichiometric TBHP according to the method of Mihelich: Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 7690−7692. The absolute configuration of **30** was assigned by reference to Onaka's work (ref 36) using *cis*-hexen-3-ol and the published conditions (0.20 equiv of $Zr(O^tBu)_4$, 0.22 equiv of (+)-DBTA, PhCl, 4 Å MS, −40 °C, 40 h) which in our hands gave the (3*S*,4*R*)-epoxide in 47% ee (100% conversion). Our modified conditions (0.40 equiv of $Zr(O^tBu)_4$, 0.60 equiv of (+)-DBTA, CH_2Cl_2, 4 Å MS, −40 °C, 18 h) gave the same (3*S*,4*R*)-epoxide in 71% ee (100% conversion) with the same sense of asymmetric induction.

(38) Evidently, Boc-protected alcohol **31** is more reactive to a second nucleophilic attack by **30** than Boc_2O itself. Experiments using large excesses of Boc_2O increased the ratio of desired product **31** relative to **31a**, but removal of excess Boc_2O was problematic.

(39) The combination of NBS, a carboxylic acid and catalytic TMG in dichloromethane solution had also proven effective in our previous studies (ref 28), but complicated mixtures of inseparable bromoacetates were obtained when they were applied to substrate **30**.

(40) (a) Snyder, S. A.; Treitler, D. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7899−7903. (b) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *J. Am. Chem. Soc.* **2010**, *132*, 14303−14314. (c) Snyder, S. A.; Treitler, D. S. *Org. Synth.* **2011**, *88*, 54−69.

(41) The separation of these constitutional and diastereomeric medium-ring ethers with the same molecular formulas was challenging, and perfect separation was not obtained; the yields reported in Scheme 6 are based on a ^1H NMR analysis before separation (see the Supporting Information).

(42) A medium-ring ether with the prelaureatin (**3**) motif could not be detected.

(43) For a note on numbering in these systems, see the Supporting Information.

(44) The IR stretching frequency of the carbonate C═O was also found to be diagnostic for the size of the cyclic carbonate. Compounds with a 6-membered carbonate were found to have an IR absorption at 1748 cm^{-1}, whereas for a 7-membered carbonate the absorption due to C═O was at 1793 cm^{-1}.

(45) For example, 7-membered medium-ring *cis*-α,α' ether isolaurepinnacin (**15**) (ref 3b) has ^1H NMR ($CDCl_3$) resonances at 3.52 and 3.59 ppm for its H-7 and H-12 protons respectively. Epimeric *trans*-α,α' ether rogioloxepane A (**13**) (ref 3c) has its resonances ($CDCl_3$) at 4.32 and 4.24 ppm, respectively.

(46) ^{13}C NMR data for deacetyllaurencin (**1b**) has not been reported in the literature.

(47) As shown in Figure 1, all the other naturally occurring medium-ring ethers, apart from prelaureatin (**3**) (see also ref 42), that are oxygenated at C-6 and C-7 are bicyclic, and so a meaningful comparison of their shifts with those of monocyclic ethers **39**−**44** is not feasible. A meaningful comparison with the monocyclic ethers **12**−**17** is also not feasible since they are necessarily epimeric at C-12 or C-13.

(48) For cyclopropane formation by attack of a bromonium ion by an alkene, see: (a) Simsek, N.; Arici, C.; McKee, M. L.; Ulku, D.; Balci, M. *Struct. Chem.* **2001**, *12*, 305−311. (b) Katsushima, T.; Maki, K.; Yamaguchi, R.; Kawanisi, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2031−2035.

(49) The interconversion between cyclopropylalkyl, cyclobutyl and allylic carbocations has been well documented, especially for the $C_4H_7^+$ system: (a) Staral, J. S.; Yavari, I.; Roberts, J. D.; Prakash, G. K. S.; Donovan, D. J.; Olah, G. A. *J. Am. Chem. Soc.* **1978**, *100*, 8016−8018. (b) Staral, J. S.; Roberts, J. D. *J. Am. Chem. Soc.* **1978**, *100*, 8018−8020. (c) Brittain, W. J.; Squillacote, M. E.; Roberts, J. D. *J. Am. Chem. Soc.* **1984**, *106*, 7280−7282.

(50) For a review on halogenating enzymes, see: Vaillancourt, F. H.; Yeh, E.; Vosburg, D. A.; Garneau-Tsodikova, S.; Walsh, C. T. *Chem. Rev.* **2006**, *106*, 3364−3378.

(51) Studies on bromonium ion induced transannular oxonium ion formation-fragmentation in model obtusallene systems (ref 27f), resulted in the formation of a [5.5.1]bicyclotridecane, and we speculated that it may represent the core of an undiscovered natural product from *Laurencia* species. New natural products with exactly this core have since been reported: Gutierrez-Cepeda, A.; Fernandez, J. J.; Norte, M.; Souto, M. L. *Org. Lett.* **2011**, *13*, 2690−2693.