JOC The Journal of Organic Chemistry

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Toward a Formal Synthesis of Laureatin: Unexpected Rearrangements Involving Cyclic Ether Nucleophiles

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Supporting Information

ABSTRACT: Laureatin, a metabolite of the red algae *Laurencia nipponica*, has shown potent activity as a mosquito larvicide. The two previously published syntheses of laureatin involved an initial preparation of the 8-membered cyclic ether, followed by formation of the oxetane ring. Our strategy was the reverse, i.e., to utilize an oxetane as the framework to construct the larger ring. During this work, attempted *N*-bromosuccinimide (NBS)-mediated cyclization of oxetane alcohol **17**, prepared from readily accessible 2-methyleneoxetane **12**, yielded epoxytetrahydrofuran **19** rather than the expected laureatin core. Further derivatization of **19** yielded *trans* fused bis-tetrahydrofuran **32**. The synthesis of **19** and **32**, as well as structural and stereochemical elucidation studies, are described.

INTRODUCTION

Strained heterocycles possessing unique structural features display interesting reactivity and have been shown to be valuable in organic synthesis.[1] We have pioneered research on one member of this important class of heterocycles, 2-methyleneoxetanes, and are exploiting them as synthetic intermediates and in the synthesis of oxetane-containing bioactive natural products.[2] Recent preparations of *psico*-nucleoside analogues further demonstrated the utility of 2-methyleneoxetanes in the syntheses of natural product analogues.[3] With a desire to extend this work toward more complex molecules, laureatin, a potent mosquito larvicide isolated as a major metabolite of the red algae *Laurencia nipponica*, was targeted.[4]

Laureatin has an oxetane embedded in an 8-membered cyclic ether as well as two bromine atoms and a *cis*-alkene for a total of eight stereogenic centers (Figure 1).[5] Previous studies suggested laureatin was most likely derived from (3*Z*,6*S*,7*S*)-laurediol (Figure 1) via prelaureatin.[6] Both compounds have been isolated from *L. nipponica*. Laurediol has been converted to prelaureatin, and prelaureatin has been converted to laureatin (with less than 0.05% yield for both) by a partially purified bromoperoxidase (BPO) from *L. nipponica* and by lactoperoxidase (LPO). An alternative pathway for the biosynthesis of laureatin via oxetane **1** was proposed by Kikuchi et al.,[7] although no evidence was presented. However, results from several groups and those presented herein suggest that neither of these pathways may be predominant (vide infra).

The two previously reported syntheses of laureatin took inspiration from the biosynthetic pathway proposed by Murai and built the 8-membered cyclic ether, followed by the oxetane ring (Figure 2).[8] Both routes encountered problems when attempting bromoetherification to incorporate the oxetane (vide infra). Our plan was to utilize a 2-methyleneoxetane as a scaffold to facilitate formation of the larger ring, a strategy that would provide laureatin in fewer steps than the previously published routes. We elected to complete a formal synthesis, targeting advanced intermediate **2** from the Kim synthesis.[8a]

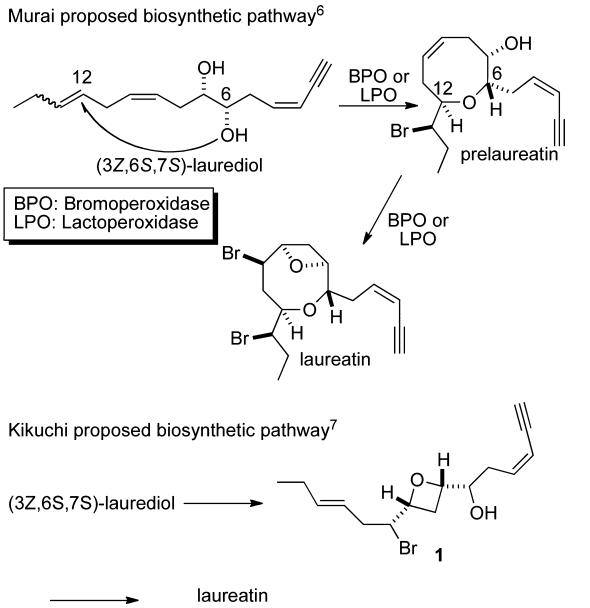


Figure 1. Proposed biosynthetic pathways for laureatin.

A key step in our approach to **2** was bromoetherification of oxetane alcohol **3**. This precursor for the 8-membered ring would be prepared from readily accessible 2-methyleneoxetane **6** (Figure 3). The synthesis of **5** from the corresponding β-lactone **7** and its conversion to the direct precursor (see **14** in

Received: May 24, 2012
Published: August 22, 2012

   dx.doi.org/10.1021/jo301048z | J. Org. Chem. 2012, 77, 7883−7890

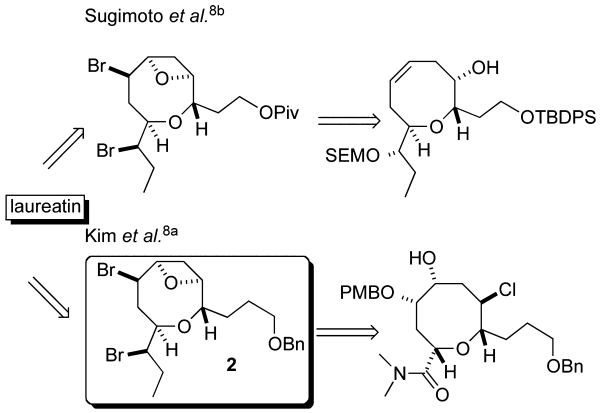


Figure 2. Key intermediates in previous syntheses of laureatin.

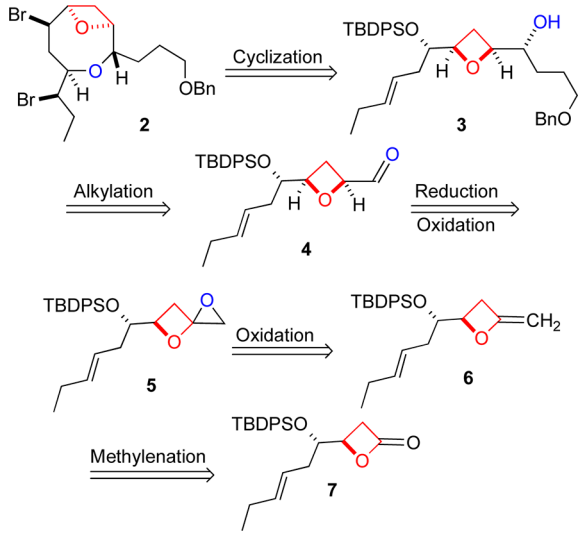


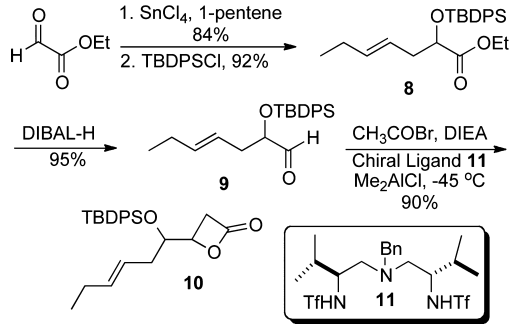
Figure 3. Approach to the formal synthesis of laureatin.

Scheme 3) to oxetane aldehyde **4** would rely on methodology we had previously developed.

RESULTS AND DISCUSSION

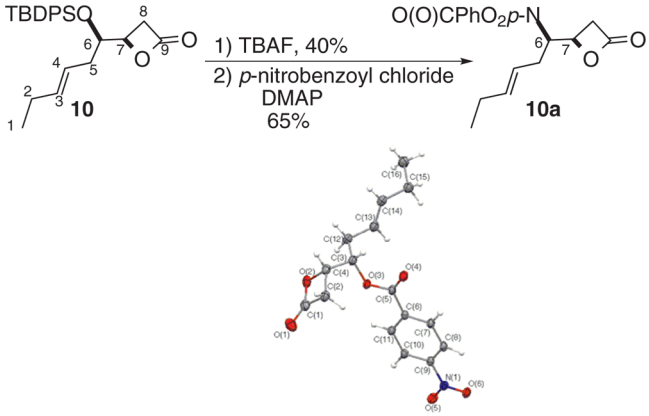
The formal synthesis of laureatin began with the preparation of *β*-lactone **10**, obtained in four steps from ethyl glyoxylate. Heteroene reaction between this and 1-pentene gave the required *trans* *α*-hydroxy ester in excellent yield using a stoichiometric amount of $SnCl_4$.[9] Conversely, a catalytic amount of $SnCl_4$ provided a mixture of *cis* and *trans* isomers in poor yield. Protection of the alcohol with *tert*-butyldiphenylsilyl chloride provided **8** in 92% yield, and DIBAL-H reduction of the ester gave aldehyde **9**. Nelson's asymmetric acyl halide−aldehyde cyclocondensation (AAC) chemistry was employed for the preparation of lactone (±)-**10**. This is an efficient strategy to access *β*-lactones in high enantioselectivities from achiral starting materials via a ketene−aldehyde cycloaddition.[10] The reaction at −45 °C of acetyl bromide with aldehyde **9** in the presence of chiral ligand **11**[11] and the Lewis acid, dimethylaluminum chloride, provided lactone (±)-**10** as a single enantiomeric pair. At higher temperatures, varying amounts of the alternate enantiomeric pair were also formed. To our knowledge, the AAC reaction had not been previously applied to aldehydes with *α*-oxygenation, and these results further illustrate the power of this transformation.

Scheme 1. Synthesis of Lactone 10



Attempts to establish the relative stereochemistry of the two asymmetric centers using a combination of molecular mechanics calculations and NOE studies on both diastereomeric sets did not provide a conclusive stereochemical assignment. Cleavage of the silyl group and conversion of the alcohol to the corresponding *p*-nitrobenzoyl ester **10a** provided a crystalline solid, which was used to establish the relative stereochemistry of the ring carbon and the adjacent exocyclic center (Scheme 2). Although this was not the relative

Scheme 2. Lactone Synthesis for X-ray Studies

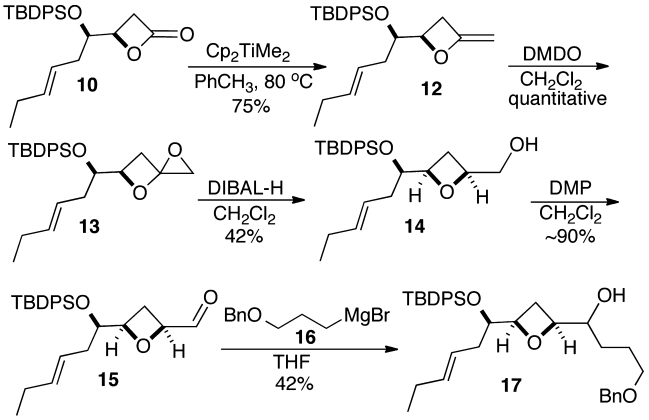


stereochemistry needed for our planned formal synthesis, we decided to move forward with **10** to evaluate the feasibility of the critical steps.

The next key intermediate was oxetane aldehyde **15** (having connectivity correspondence to **4** in Figure 3). On the basis of our synthesis of *epi*-oxetin,[2b] the two steps where potential problems were anticipated were the reductive cleavage of dioxaspirohexane **13** and subsequent oxidation of the resultant alcohol. Methylenation[12] of **10** using dimethyltitanocene proceeded smoothly in good yield (Scheme 3). The next step was the chemoselective oxidation of 2-methyleneoxetane **12** with anhydrous, acetone-free DMDO.[13] We had previously shown that the oxidation of the enol ether moiety could be accomplished in the presence of unactivated alkenes, and here dioxaspirohexane **13** was obtained in quantitative yield with good diastereoselectivity (8:1). It should be noted that the diastereomeric ratio at the dioxaspirohexane stage does not determine the relative stereochemistry at the next step. Our previous studies involving ring-opening reactions that leave the oxetane intact have supported a mechanism involving the formation of an oxetane oxocarbenium ion.[14]

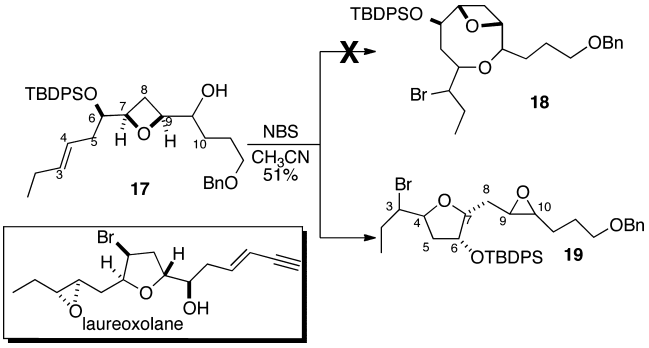
dx.doi.org/10.1021/jo301048z | J. Org. Chem. 2012, 77, 7883−7890

Scheme 3. Synthesis of Oxetane Alcohol 17



The reductive ring-opening of **13** with DIBAL-H in CH_2Cl_2 proceeded in a moderate yield of 56% (42% of the desired diastereomer) with modest diastereoselectivity (3:1). DIBAL-H in hexane or toluene provided <20% of the diastereomeric mixture. This lower diastereoselectivity in comparison to our previously reported DIBAL-H reductions of dioxaspirohexanes[2b,14] may be due to the fact that the ring substituent was more remote (on opposite carbons, rather than neighboring ones). The *syn*-relationship of the C-7 and C-9 oxetane hydrogens (see Scheme 4 for numbering) of the major product

Scheme 4. NBS-Mediated Skeletal Rearrangement of Oxetane Alcohol 17



was confirmed by NOESY experiments. Other reducing agents were also explored. Diisobutylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide has been used for diastereoselective reductions, providing cleaner reactions than DIBAL-H in some cases.[15] However, this reducing agent did not provide the desired product. Neither did $Mg(OTf)_2$ in combination with Et_3SiH. When BH_3·THF was used, the internal alkene in **13** was also reduced.

After successful synthesis of hydroxymethyloxetane **14**, the next step was oxidation of the alcohol moiety to the corresponding aldehyde. Initial attempts using pyridinium dichromate (PDC), tetra-*n*-propylammonium perruthenate (TPAP), or the SO_3·pyridine complex failed to provide desired aldehyde **15**. Gratifyingly, the Dess–Martin periodinane oxidation did so in good yield. However, **15** proved to have limited stability. A nonaqueous workup was employed, and no column purification was done. Moreover, it was critical that bath temperatures in the concentration of the reaction mixture not exceed ca. 40 °C and that the aldehyde was always used immediately after its preparation.

Access to aldehyde **15** allowed us to test the feasibility of another key step: bromoetherification. Compound **15** was reacted with Grignard reagent **16** to yield key oxetane intermediate **17**. A single diastereomer was isolated in 42% yield; no other significant product was seen. The relative stereochemistry of the newly formed asymmetric carbon was not deduced at this point. Alkenol **17** was then exposed to NBS.[8b] No reaction was observed when CH_2Cl_2 or CCl_4 was used as the solvent; reaction did occur in acetonitrile. However, instead of the desired bicyclic system **18**, epoxytetrahydrofuran **19** was isolated as a single diastereomer in 51% yield (Scheme 4). No other significant product could be isolated. The use of 1,2,5,6-tetrabromooctane for the bromoetherification resulted in a messier product distribution. The skeletal framework of **19** was confirmed by 2D-NMR studies. However, the relative stereochemistries at C-3/C-4 and C-9/C-10 could not be determined in $CDCl_3$ because of overlapping signals (vide infra).

The unexpected formation of epoxytetrahydrofuran **19** can be explained by reaction of the oxetane moiety, rather than the alcohol, with the initially formed bromonium ion **20** (Figure 4). Subsequent reaction of the alcohol group with oxonium ion **21** would provide **19**.

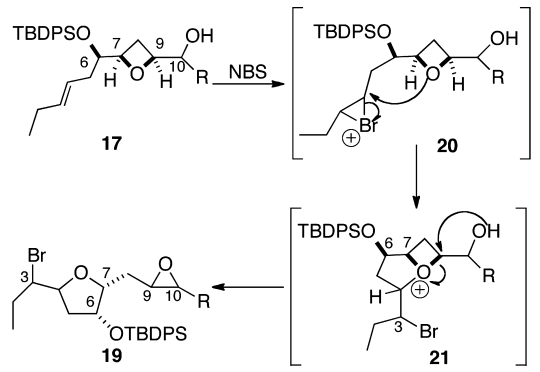


Figure 4. Proposed mechanism of NBS-mediated skeletal rearrangement.

This outcome of a cyclic ether, rather than a free OH, reacting with a bromonium ion, while unexpected, is not without precedent. Indeed, this was observed in both previous syntheses of laureatin. In a preliminary route of the synthesis by Sugimoto et al.,[8b] an attempt to incorporate the oxetane moiety via a bromoetherification of **22** failed. Tetrahydrofuranyl ketone **24**, presumably formed through a transannular attack by the furan oxygen, followed by a pinacol-type rearrangement of **23** (Figure 5a), was isolated instead. In the Kim synthesis it was mentioned in passing that a direct bromoetherification route was abandoned because of participation of the oxocene oxygen. While this manuscript was in preparation, a clever exploitation of bicyclic oxonium ions (e.g., **27**) to make eight-membered rings was reported by Snyder et al.[16] Similar to the outcome shown in Figure 5a, they observed an intramolecular nucleophilic attack by a cyclic ether followed by a pinacol-type rearrangement to give tetrahydrofuranyl ketone **25** (Figure 5b). Snyder and co-workers were also able to use bicyclic oxonium ions to make eight membered rings, as shown in Figure 5c. They developed a general strategy to access *Laurencia*-type bromo ethers **28** by strategically placing a nucleophile at C-3 of tetrahydrofuran **26**, leading to 8- and 9-membered cyclic ethers. Snyder also hypothesized that it is

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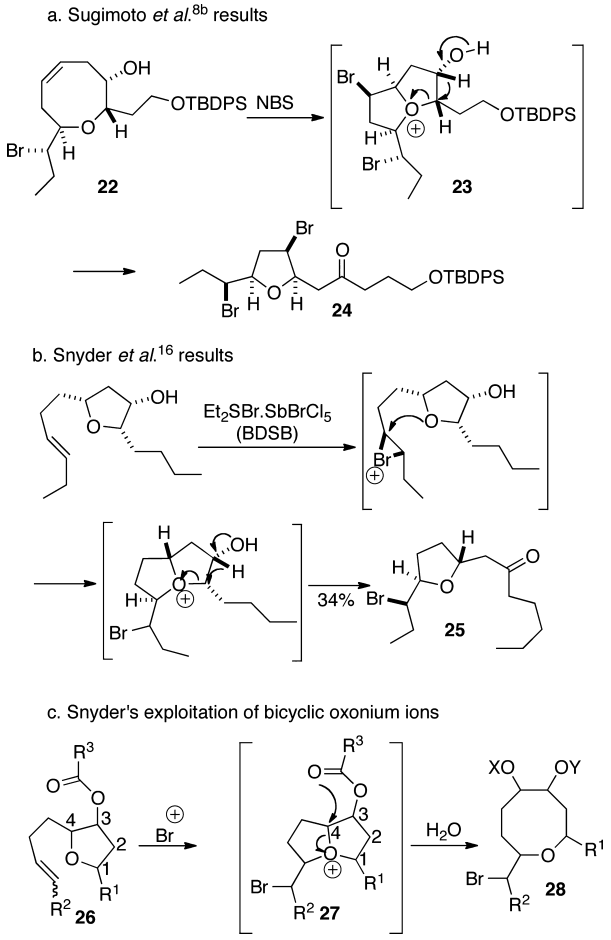
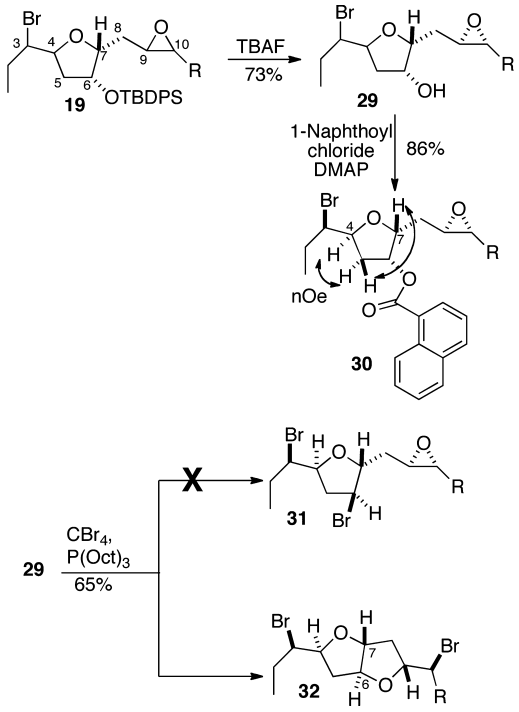


Figure 5. Cyclic ethers as nucleophiles in reactions with bromonium ions.

likely that the biosynthesis of laurenan-type terpenes may involve ethers as nucleophiles after initial bromoetherifications, rather than multiple, simple haloetherifications. Our result with oxetane **17** supports this. Interestingly, an epoxyfuranyl terpene, laureoxolane (see Scheme 4), with the cyclic ethers separated by a methylene spacer (as seen in **19**) has been isolated from *Laurencia nipponica*.[17] An additional illustration of the potential importance of ether nucleophiles in biosynthesis came with our attempts to fully establish the relative stereochemistry at all of the asymmetric carbons.

Assignment of the remaining stereochemical relationships in epoxytetrahydrofuran **19** required further derivatization. As noted above, single-crystal X-ray analysis of β-lactone **10a** allowed the assignment of the relative stereochemistry of the hydrogen atoms on C-6 and C-7 (Scheme 2), and according to our proposed mechanism, this relationship would remain unchanged in the conversion of **10** to **19**. However, further NMR experiments on **19** did not reveal the relative stereochemistries of the C-4 and C-7 tetrahydrofuran hydrogens (see Scheme 5) or of the C-9 and C-10 hydrogens, partly because of issues with overlapping signals. Consequently, we decided to cleave the TBDPS group so that the corresponding alcohol **29** could be analyzed or derivatized, if needed. Upon treatment with TBAF, epoxytetrahydrofuran **19** yielded the corresponding deprotected alcohol **29** in 73% yield. The relative stereochemistry of C-4 and C-7 in **29** could not be unequivocally established using NOESY, and **29** did not give

Scheme 5. Derivatization of Epoxytetrahydrofuran 29



crystals for X-ray analysis. Trans stereochemistry of the epoxide in **29** was tentatively deduced from the coupling constant between the epoxide hydrogens (J = 1.9 Hz).[18] Neither a *p*-nitrobenzoyl ester nor naphthoyl ester **30** provided diffractable crystals. However, the relative stereochemistries of the C-4 and C-7 hydrogens in epoxytetrahydrofuran **30** were determined by a combination of COSY and NOESY experiments (Scheme 5), and the trans-stereochemistry of the epoxide protons was confirmed (J = 2.2 Hz).

Knowing the relative stereochemistries of C-4 and C-7 and of the epoxide protons allowed the assignment of the remaining centers. If an S_N2 attack on the bromonium is assumed, the C-4 and C-7 protons could not be trans if the bromonium had formed on the opposite face (Figure 6). Also, the C-3 relative stereochemistry is determined by the facial selectivity in the formation of the bromonium. Similarly, the epoxide could not have trans substituents if the stereochemistry at C-10 were the opposite.

In another attempt to make a crystalline derivative of **29**, it was treated with Oct_3P-CBr_4[19] with an expectation that the free OH would be converted to corresponding bromide **31**. However, trans-fused bis-tetrahydrofuran **32** was isolated in 65% yield (Scheme 5). To the best of our knowledge, the transformation of epoxytetrahydrofurans to bis-tetrahydrofurans has not been previously reported. There were no NOE effects seen between C-6 and C-7,[20] but this is not conclusive proof of the trans-fusion. The assignment of a trans stereochemistry is mainly based on what we believe the pathway to be. We think that the first step in the process is the reaction of the OH group in **29** with phosphonium intermediate **33**, followed by an intramolecular epoxide attack leading to oxonium ion **34**, which reacts with bromide to give trans-fused bis-tetrahydrofuran **32** (Figure 7).

Our argument that it is the OH (rather than the epoxide) that reacts with phosphonium **33** is based on two literature reports. First, under similar (PPh_3/CCl_4) conditions, Prinzbach

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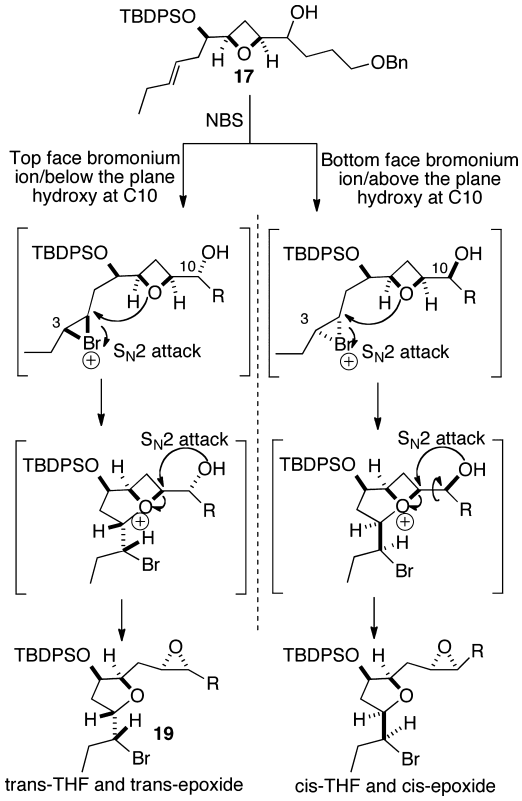

Figure 6. Deduction of remaining relative stereochemistries for **19**.

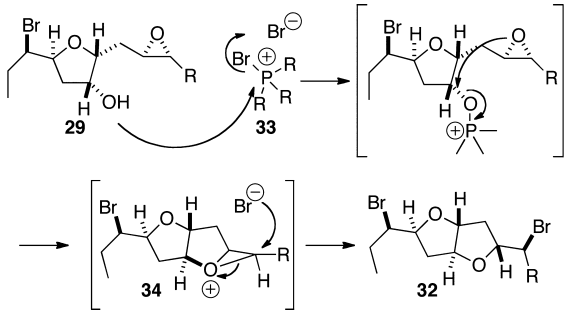

Figure 7. Postulated mechanism for the formation of trans-fused bis-tetrahydrofuran **32**.

and co-workers successfully converted an alcohol to a chloride in the presence of an epoxide (Figure 8).[21] Although the second example does not involve an epoxide, when Fujiwara et al.[22] attempted bromination, using $Oct_3P\text{-}CBr_4$, of hydroxyoxepane **35**, all of the products isolated implied an initial reaction between the free OH and the activated phosphine. Interestingly, ring contraction product **36** (15%) and retention product **37** (23%) were presumed to have arisen from oxonium ion **38** (Figure 8). The formation of bis-fused tetrahydrofuran **32** is a further illustration of the utility of cyclic ether nucleophiles in building complexity and in accessing different ring sizes. Moreover, such fused ring systems are seen in nature. For example, kumausallene and compound **39** (Figure 9) have both been isolated from red algae of the genus *Laurencia*.[23] Although these bis-tetrahydrofuran systems have cis-fusions, we believe the stereochemical outcome in **32** is a result of the relative stereochemistry of the tetrahydrofuranyl substituents in our system.

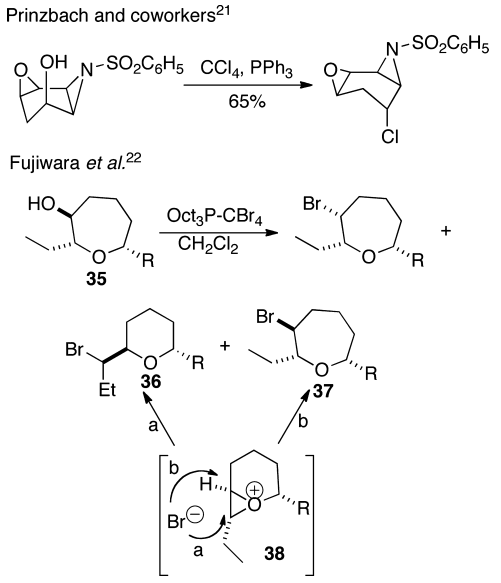

Figure 8. Literature support for initial reaction of an OH with phophonium salt in the presence of nucleophilic cyclic ethers.

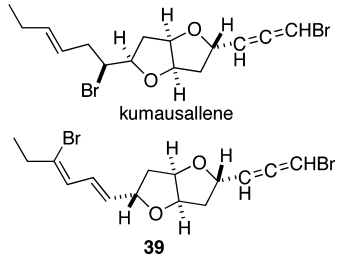

Figure 9. Natural, fused bis-tetrahydrofurans.

In conclusion, our attempts to access the natural product laureatin led to the discovery of novel rearrangements involving an oxetane alcohol and an epoxytetrahydrofuran. We believe that these transformations are further illustrations of the potential of cyclic ether nucleophiles for building molecular complexity in a stereocontrolled fashion. The core structures of the rearranged epoxytetrahydrofuran and trans-fused bis-tetrahydrofuran are found in natural products. These results also provide further support of the recent contention by Snyder[16] that some of the laurenan natural products may arise from the oxonium ions formed from intramolecular reactions by cyclic ether oxygens.

EXPERIMENTAL SECTION

(4*E*)-2-Hydroxyhept-4-enoic Acid Ethyl Ester. 1-Pentene (4.80 mL, 44.1 mmol) was added to a stirred solution of ethyl glyoxylate (5.90 mL, 29.4 mmol) in dry CH_2Cl_2 (225 mL) at −78 °C, followed by the dropwise addition of tin(IV) chloride ($SnCl_4$) (5.08 mL, 44.1 mmol) under N_2. The reaction mixture was allowed to warm to rt and stirred for 48 h. The resulting homogeneous solution was diluted with CH_2Cl_2 (200 mL) and then washed with saturated aqueous $NaHCO_3$ (200 mL) at 0 °C carefully, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with H_2O (100 mL), dried ($MgSO_4$), and concentrated to provide (4*E*)-2-hydroxyhept-4-enoic acid ethyl ester as a pale yellow oil (4.05 g, 84%) which was used without purification in the next reaction: IR (neat) 3461, 2963, 1731, 1199 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.60 (m, 1H), 5.39 (ddd, J = 14.2, 7.1, 7.1 Hz, 1H), 4.23 (m, 3H), 3.03 (br s, 1H), 2.71 (d, J = 6.2 Hz, 1H), 2.50 (m, 1H), 2.38 (ddd, J = 15.0, 7.1, 7.1 Hz, 1H), 2.02 (m,

dx.doi.org/10.1021/jo301048z | J. Org. Chem. 2012, 77, 7883−7890

2H), 1.30 (t, J = 6.1 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 136.8, 122.4, 70.3, 61.5, 37.6, 25.6, 14.2, 13.7; HRMS (ESI) calcd for $C_9H_{17}O_3$ (M^+ + H) m/z 173.1178, found 173.1164.

(4*E*)-2-(*tert*-Butyldiphenylsilanyloxy)hept-4-enoic Acid Ethyl Ester (8). (4*E*)-2-Hydroxyhept-4-enoic acid ethyl ester (7.70 g, 44.8 mmol), 4-dimethylaminopyridine (DMAP) (1.40 g, 11.2 mmol), and imidazole (6.10 g, 89.6 mmol) were dissolved in dry DMF (45 mL) under N_2, followed by the addition of *tert*-butyldiphenylsilyl chloride (TBDPSCl) (14.2 mL, 51.6 mmol). The reaction mixture was stirred at rt overnight. The viscous solution was diluted with CH_2Cl_2 (400 mL) and poured into H_2O (450 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 150 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 99:1) provided ester **8** as a clear oil (16.9 g, 92%): IR (neat) 2961, 1753, 1473, 1428, 1112 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 4H), 7.38 (m, 6H), 5.49 (m, 1H), 5.37 (m, 1H), 4.21 (dd, J = 5.8, 5.8 Hz, 1H), 3.93 (m, 2H), 2.40 (app t, J = 6.0 Hz, 2H), 1.98 (m, 2H), 1.09 (m, 12H), 0.93 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 135.9, 135.8, 135.7, 133.5, 133.3, 129.6, 127.5, 127.5, 127.4, 123.3, 72.9, 60.2, 38.6, 26.8, 25.5, 19.3, 14.0, 13.5; HRMS (FAB) calcd for $C_{25}H_{33}O_3Si$ (M^+ − H) m/z 409.2199, found 409.2186.

(4*E*)-2-(*tert*-Butyldiphenylsilanyloxy)hept-4-enal (9). Diisobutylaluminum hydride (DIBAL-H) (1.0 M in CH_2Cl_2, 11.6 mL, 11.6 mmol) was added dropwise to a solution of (4*E*)-2-(*tert*-butyldiphenylsilanyloxy)hept-4-enoic acid ethyl ester (**8**) (2.40 g, 5.81 mmol) in dry CH_2Cl_2 (120 mL) under N_2 at −78 °C. The mixture was stirred for 3 h at −78 °C, followed by the dropwise addition of MeOH (50 mL). The resulting mixture was warmed to rt. The solution was poured into aqueous NaOH (0.5 M, 50 mL) and diluted with CH_2Cl_2 (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with H_2O (40 mL) and brine (40 mL), dried ($MgSO_4$), and concentrated. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 99:1) provided aldehyde **9** as a colorless oil (2.02 g, 95%): IR (neat) 3072, 2963, 2863, 1738, 1428, 1112 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (d, J = 1.5 Hz, 1H), 7.67 (m, 4H), 7.42 (m, 6H), 5.51 (ddd, J = 15.5, 6.5, 6.5 Hz, 1H), 5.34 (ddd, J = 15.3, 7.0, 7.0 Hz, 1H), 4.07 (ddd, J = 5.9, 5.9, 1.5 Hz, 1H), 2.35 (dd, J = 6.4, 6.4 Hz, 2H), 1.99 (app qd, J = 7.2, 6.6 Hz, 2H), 1.14 (s, 9H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8, 136.5, 136.1, 133.4, 133.3, 130.3, 130.2, 128.1, 128.0, 122.8, 78.3, 36.7, 27.2, 25.9, 19.6, 13.8; HRMS (FAB) calcd for $C_{23}H_{31}O_2Si$ (M^+ + H) m/z 367.2093, found 367.2076.

(3*R)-4-[(3*E*),(1*R**)-1-(*tert*-Butyldiphenylsilanyloxy)hex-3-enyl]oxetan-2-one (10).** Dimethylaluminum chloride (1.0 M in hexanes, 1.09 mL, 1.09 mmol) was added to a solution of (2*S*,6*S*)-4-benzyl-1,7-ditriflic-2,6-diisopropyl-1,4,7-triazaheptane[11] (**11**) (0.59 g, 1.09 mmol) in dry CH_2Cl_2 (40 mL) under N_2 at rt. After the solution was stirred for 1 h, diisopropylethylamine (3.23 mL, 18.5 mmol) was added slowly via syringe. The reaction mixture was cooled to −45 °C, followed by the addition of freshly distilled acetyl bromide (1.53 mL, 20.7 mmol) and (4*E*)-2-(*tert*-butyldiphenylsilanyloxy)hept-4-enal (**9**) (4.01 g, 10.9 mmol), and the solution was stirred for 72 h at −45 °C. The reaction was warmed to rt and filtered through a pad of silica with CH_2Cl_2, and the filtrate was concentrated in vacuo. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 99:1) provided β-lactone **10** as a clear oil (5.31 g, 90%): IR (neat) 3072, 2962, 2858, 1832, 1589, 1428, 1111 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (app d, J = 7.1 Hz, 4H), 7.42 (m, 6H), 5.35 (m, 1H), 5.16 (ddd, J = 15.3, 7.6, 7.6 Hz, 1H), 4.49 (ddd, J = 4.6, 4.6, 4.6 Hz, 1H), 3.83 (ddd, J = 8.4, 4.4, 4.4 Hz, 1H), 3.28 (app d, J = 5.0 Hz, 2H), 2.27 (ddd, J = 13.8, 7.9, 7.9 Hz, 1H), 2.18 (m, 1H), 1.91 (m, 2H), 1.09 (s, 9H), 0.88 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 136.4, 136.0, 135.9, 133.7, 133.0, 130.0, 129.9, 127.8, 127.7, 122.9, 73.1, 71.9, 39.2, 36.6, 27.0, 25.6, 19.5, 13.5; HRMS (FAB) calcd for $C_{25}H_{33}O_3Si$ (M^+ + H) m/z 409.2199, found 409.2214.

(3*R)-4-[(3*E*),(1*R**)-1-(*p*-Nitrobenzoyloxy)hex-3-enyl]oxetan-2-one (10a).** TBAF (9.8 mL, 9.8 mmol) was added dropwise to a stirred solution of (3*R**)-4-[(3*E*),(1*R**)-1-(*tert*-butyldiphenylsilanyloxy)-hex-3-enyl]oxetan-2-one (**10**) (2.0 g, 4.9 mmol) in THF (15 mL) at 0 °C. After 2 h, the reaction mixture was concentrated in vacuo. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 70:30) provided the deprotected lactone as a clear oil (0.33 g). 4-Nitrobenzoyl chloride (0.77 g, 3.88 mmol), DMAP (0.24 g, 1.94 mmol), and NEt_3 (0.54 mL, 3.88 mmol) were added to a stirred solution of the lactone (0.33 g, 1.94 mmol) in CH_2Cl_2 (4 mL). After 1 h, the reaction mixture was concentrated in vacuo. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 80:20) provided lactone **10a** as a white solid (0.34 g, 26% over two steps): mp 65−67 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, J = 8.8 Hz, 2H), 8.24 (d, J = 8.5 Hz, 2H), 5.68 (m, 1H), 5.41 (m, 2H), 4.79 (m, 1H), 3.59 (dd, J = 16.5, 6.1 Hz, 1H), 3.27 (dd, J = 16.4, 4.0 Hz, 1H), 2.59 (dd, J = 6.6, 6.6 Hz, 2H), 2.02 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H).

(4*R)-4-[(3*E*,1*R**)-1-(*tert*-Butyldiphenylsilanyloxy)hex-3-enyl]-2-methyleneoxetane (12).** A solution of dimethyltitanocene (4.43 mL, 0.5 M in toluene) and (3*R**)-4-[(3*E*),(1*R**)-1-(*tert*-butyldiphenylsilanyloxy)hex-3-enyl]oxetan-2-one (**10**) (0.60 g, 1.48 mmol) was stirred in the dark at 80 °C under N_2 until the starting material was consumed on the basis of TLC. The reaction was cooled slowly to rt followed by the addition of petroleum ether (300 mL) and stirred for 24 h. The resulting mixture was filtered through a pad of Celite, which was then washed with petroleum ether until the filtrate was colorless. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography on silica gel (petroleum ether/Et_3N 96:4) to afford **12** as a clear yellow oil (0.45 g, 75%): IR (neat) 3072, 2963, 2861, 1694, 1473, 1428, 1389, 1362, 1112, 911 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (m, 4H), 7.34 (m, 6H), 5.33 (m, 1H), 5.20 (m, 1H), 4.68 (ddd, J = 6.4, 6.4, 6.4 Hz, 1H), 4.10 (m, 1H), 3.85 (ddd, J = 6.3, 6.3, 6.3 Hz, 1H), 3.70 (m, 1H), 3.04 (m, 1H), 2.95 (m, 1H), 2.22 (ddd, J = 14.0, 7.1, 7.1 Hz, 1H), 2.10 (ddd, J = 13.7, 6.9, 6.9 Hz, 1H), 1.90 (m, 2H), 1.07 (s, 9H), 0.88 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 136.0, 135.3, 134.2, 133.7, 129.6, 129.5, 127.5, 127.4, 123.7, 79.8, 79.4, 74.4, 35.5, 30.3, 26.9, 26.9, 25.4, 19.5, 13.5; HRMS (FAB) calcd for $C_{26}H_{35}O_2Si$ (M^+ + H) m/z 407.2406, found 407.2397.

(4*R)-4-[(3*E*),(1*R**)-1-(*tert*-Butyldiphenylsilanyloxy)]hex-3-enyl-1,5-dioxaspiro[3.2]hexane (13).** A solution of (4*R**)-4-[(3*E*,1*R**)-1-(*tert*-butyldiphenylsilanyloxy)hex-3-enyl]-2-methyleneoxetane (**12**) (0.39 g, 0.97 mmol) in dry CH_2Cl_2 (4 mL) under N_2 was cooled to 0 °C. A solution of DMDO (2.5 mL, 0.58 M in CH_2Cl_2) was added dropwise, and the solution was stirred at 0 °C for 1 h. The solution was then concentrated in vacuo and afforded **13** as a mixture of diastereoisomers (88:12) in quantitative yield: Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (m, 4H), 7.40 (m, 6H), 5.32 (m, 1H), 5.18 (m, 1H), 4.62 (ddd, J = 10.1, 4.8, 4.8 Hz, 1H), 3.87 (ddd, J = 9.4, 4.7, 4.7 Hz, 1H), 2.98 (dd, J = 12.4, 5.6 Hz, 1H), 2.93 (dd, J = 12.5, 7.7 Hz, 1H), 2.86 (d, J = 3.4 Hz, 1H), 2.65 (d, J = 3.4 Hz, 1H), 2.29 (ddd, J = 10.6, 7.9, 7.9 Hz, 1H), 2.14 (m, 1H), 1.90 (m, 2H), 1.07 (s, 9H), 0.88 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 136.1, 135.7, 134.4, 133.8, 129.9, 129.8, 127.8, 127.7, 127.7, 123.9, 88.7, 75.5, 74.9, 51.5, 36.1, 30.7, 27.2, 25.7, 19.7, 13.7; HRMS (FAB) calcd for $C_{26}H_{35}O_3Si$ (M^+ + H) m/z 423.2355, found 423.2330.

(2*R,4*S**)-2-[(3*E*,1*R**)1-(*tert*-Butyldiphenylsilanyloxy)]hex-3-enyl-4-hydroxymethyloxetane (14).** DIBAL-H (1.0 M in CH_2Cl_2, 0.25 mL, 0.25 mmol) was added dropwise to a stirred solution of (4*R**)-4-[(3*E*),(1*R**)-2-(*tert*-butyldiphenylsilanyloxy)]hex-3-enyl-1,5-dioxaspiro[3.2]hexane (**13**) (80 mg, 0.19 mmol) in dry CH_2Cl_2 (2 mL) under N_2 at −78 °C. After 2 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and allowed to warm to 0 °C. The reaction was quenched with 15% NaOH (5 mL) and diluted with H_2O (10 mL). The resulting solution was extracted with CH_2Cl_2 (2 × 10 mL). The organic extracts were combined, washed with H_2O (10 mL), dried ($MgSO_4$), and concentrated. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 80:20) provided **14** as a mixture of diastereomers (75:25). The required major diastereomer was isolated as a colorless oil (34 mg, 42%): IR ($CDCl_3$) 3539, 2925, 2854, 1109,

704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (m, 4H), 7.42 (m, 6H), 5.28 (m, 2H), 4.65 (m, 2H), 3.75 (ddd, J = 6.6, 6.6, 5.1 Hz, 1H), 3.53 (ddd, J = 12.7, 2.7, 2.7 Hz, 1H), 3.28 (ddd, J = 12.3, 9.3, 2.9 Hz, 1H), 2.41 (ddd, J = 11.0, 7.7, 7.7 Hz, 1H), 2.32 (ddd, J = 11.0, 7.5, 7.5 Hz, 1H), 2.17 (ddd, J = 14.1, 6.7, 6.7 Hz, 1H), 2.01 (m, 1H), 1.92 (m, 2H), 1.57 (dd, J = 9.1, 3.9 Hz, 1H), 1.07 (s, 9H), 0.90 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 136.3, 135.2, 134.6, 134.0, 129.9, 129.9, 127.7, 127.6, 124.1, 79.6, 77.6, 76.5, 64.9, 35.3, 27.3, 25.7, 23.9, 19.7, 13.8; HRMS (FAB) calcd for $C_{26}H_{35}O_3Si$ ($M^+ - H$) m/z 423.2355, found 423.2336.

(2*R,4*S**)-2-[(3*E*,1*R**)1-(*tert*-Butyldiphenylsilanyloxy)]hex-3-enyl-4-formyloxetane (15).** Dess–Martin periodinane (0.21 g, 0.49 mmol) was added to a stirred solution of (2*R**,4*S**)-2-[(3*E*,1*R**)1-(*tert*-butyldiphenylsilanyloxy)]hex-3-enyl-4-hydroxymethyloxetane (**14**) (0.14 g, 0.33 mmol) in dry CH_2Cl_2 (4 mL) under N_2 at 0 °C. The reaction mixture was slowly warmed to rt. After 16 h, the reaction mixture was concentrated in vacuo at 30 °C, and the residue was washed with petroleum ether (3 × 10 mL). The combined organic layers were concentrated in vacuo to afford **15** as a clear oil (0.12 g, 90%). The crude product was used directly in the next reaction without further purification: IR (neat) 3070, 2931, 2857, 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.65 (d, J = 1.7 Hz, 1H), 7.71–7.69 (m, 4H), 7.42–7.35 (m, 6H), 5.25 (m, 1H), 5.13 (m, 1H), 4.79 (m, 2H), 3.71 (ddd, J = 7.5, 5.2, 5.2 Hz, 1H), 2.73 (ddd, J = 11.6, 8.0, 8.0 Hz, 1H), 2.49 (ddd, J = 11.6, 7.1, 7.1 Hz, 1H), 2.21 (ddd, J = 13.4, 6.4, 6.4, 1H), 1.99 (ddd, J = 12.2, 5.3, 5.3 Hz, 1H), 1.91–1.84 (m, 2H), 1.04 (s, 9H), 0.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.3, 136.2, 136.2, 135.6, 134.4, 133.7, 129.9, 129.8, 127.8, 127.7, 123.8, 81.8, 79.4, 76.0, 35.3, 29.9, 27.3, 27.2, 25.7, 25.6, 19.7, 13.8; HRMS (ESI) calcd for $C_{26}H_{35}O_3Si$ (M^+ + H) m/z 423.2350, found 423.2335.

Benzyloxy-3-propylmagnesium Bromide (16). Magnesium chips (0.12 g, 5.1 mmol) were placed in a flame-dried flask fitted with a reflux condenser under N_2. Dry THF (0.5 mL), followed by benzyl-3-bromopropyl ether (0.30 mL, 1.7 mmol), was added at rt. After 15 min, the reaction mixture turned yellow. The concentration of magnesium bromide **16** (0.24 M in THF) was determined by titration using salicylaldehyde phenyl hydrazone as the indicator.[24]

(2*R,4*S**)-2-[(3*E*,1*R**)1-(*tert*-Butyldiphenylsilanyloxy)]hex-3-enyl-4-(1-hydroxy-4-benzyloxybutyl)oxetane (17).** (2*R**,4*S**)-2-[(3*E*,1*R**)1-(*tert*-Butyldiphenylsilanyloxy)]hex-3-enyl-4-(formyl)-oxetane (**15**) (0.040 g, 0.094 mmol) dissolved in dry THF (2 mL) under N_2 was added dropwise to the freshly prepared solution of magnesium bromide (**16**) (0.24 M, 1.2 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 8 h. The reaction was quenched with aqueous HCl (1.0 M, 1 mL) and diluted with H_2O (5 mL). The resulting solution was extracted with EtOAc (2 × 10 mL). The organic extracts were combined, washed with H_2O (10 mL), dried ($MgSO_4$), and concentrated. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 80:20) provided **17** as a colorless oil (0.020 g, 42%): IR (neat) 3500, 2931, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73–7.68 (m, 4H), 7.41–7.30 (m, 11H), 5.27–5.22 (m, 2H), 4.62 (ddd, J = 7.4, 7.4, 7.4 Hz, 1H), 4.49 (m, 1H), 4.46 (s, 2H), 3.72 (ddd, J = 6.2, 6.2, 6.2 Hz, 1H), 3.50 (m, 1H), 3.46–3.40 (m, 2H), 2.35 (m, 1H), 2.21–2.06 (m, 3H), 2.00–1.85 (m, 3H), 1.68 (m, 1H), 1.59 (m, 1H), 1.24 (m, 2H), 1.05 (s, 9H), 0.87 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 136.4, 136.3, 135.1, 134.7, 134.1, 129.9, 129.8, 128.6, 127.8, 127.8, 127.7, 127.6, 124.1, 80.0, 79.8, 76.5, 73.1, 71.5, 70.4, 35.3, 29.9, 27.4, 27.3, 26.0, 25.8, 19.7, 13.8; HRMS (ESI) calcd for $C_{36}H_{49}O_4Si$ (M^+ + H) m/z 573.3390, found 573.3395.

(2*R,3*R**,5*S**)-2-[(2*R**,3*R**)3-(3-Benzyloxypropyl)oxiran-2-yl)methyl]-3-[*tert*-butyldiphenylsilanyloxy]-5-((1*R**)-1-bromopropyl)tetrahydrofuran (19).** *N*-Bromosuccinimide (0.019 g, 0.11 mmol) was added to a solution of (2*R**,4*S**)-2-[(3*E*,1*R**)1-(*tert*-butyldiphenylsilanyloxy)]hex-3-enyl-4-(1-hydroxy-4-benzyloxybutyl)oxetane (**17**) (0.020 g, 0.036 mmol) in dry CH_3CN (2 mL) under N_2. After 16 h, the reaction mixture was concentrated in vacuo. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 90:10) to provide **19** as a colorless oil (0.012 g, 51%): ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (m, 4H), 7.44–7.25 (m, 11H), 4.48 (s, 2H), 4.28 (m, 2H), 3.97 (ddd, J = 5.9, 2.9, 2.9 Hz, 1H), 3.83 (m, 1H), 3.54–3.42 (m, 2H), 2.78 (m, 1H), 2.66 (m, 1H), 2.10–1.89 (m, 2H), 1.84 (m, 1H), 1.78–1.68 (m, 3H), 1.68–1.47 (m, 4H), 1.06 (s, 9H), 1.00 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 136.0, 136.0, 134.0, 133.2, 130.1, 130.0, 128.6, 128.0, 127.9, 127.8, 127.7, 81.1, 80.0, 75.2, 73.1, 70.0, 62.9, 59.2, 56.8, 40.2, 33.4, 29.0, 28.7, 27.2, 26.4, 19.6, 12.2; HRMS (ESI) calcd for $C_{36}H_{48}BrO_4Si$ (M^+ + H) m/z 651.2500, found 651.2477.

(2*R,3*R**,5*S**)-2-[(2*R**,3*R**)3-(3-Benzyloxypropyl)oxiran-2-yl)methyl]-3-hydroxy-5-((1*R**)-1-bromopropyl)-tetrahydrofuran (29).** TBAF (1.0 M, 0.15 mL, 0.15 mmol) was added to a solution of (2*R**,3*R**,5*S**)-2-[(2*R**,3*R**)3-(3-benzyloxypropyl)oxiran-2-yl)methyl]-3-[*tert*-butyldiphenylsilanyloxy]-5-((1*R**)-1-bromopropyl)tetrahydrofuran (**19**) (0.050 g, 0.076 mmol) in THF (2 mL) at 0 °C, and stirring was continued at rt. After 3 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography on silica gel (petroleum ether/EtOAc 70:30) to afford **29** as a colorless oil (0.023 g, 73%): ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.23 (m, 5H), 4.49 (m, 2H), 4.39 (m, 1H), 4.27 (ddd, J = 9.6, 6.0, 6.0 Hz, 1H), 4.12 (ddd, J = 8.6, 5.4, 2.9 Hz, 1H), 4.02 (ddd, J = 9.4, 6.0, 3.6 Hz, 1H), 3.49 (m, 2H), 2.86 (m, 1H), 2.77 (br s, 1H), 2.71 (m, 1H), 2.28 (dd, J = 13.9, 5.3 Hz, 1H), 2.17 (dd, J = 13.5, 6.0 Hz, 1H), 2.06 (m, 1H), 1.95 (m, 1H), 1.79–1.65 (m, 4H), 1.64–1.54 (m, 1H), 1.43 (ddd, J = 14.1, 10.1, 10.1 Hz, 1H), 1.05 (t, J = 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 128.6, 127.9, 127.8, 82.1, 80.2, 73.2, 73.2, 69.7, 63.4, 59.8, 56.1, 38.6, 32.7, 28.8, 28.7, 26.3, 12.4; HRMS (ESI) calcd for $C_{20}H_{30}BrO_4$ (M^+ + H) m/z 413.1322, found 413.1313.

(2*R,3*R**,5*S**)-2-[(2*R**,3*R**)3-(3-Benzyloxypropyl)oxiran-2-yl)methyl]-5-((1*R**)-1-bromopropyl)tetrahydrofuran-3-yl-1-naphthoate (30).** (2*R**,3*R**,5*S**)-2-[(2*R**,3*R**)3-(3-Benzyloxypropyl)oxiran-2-yl)methyl]-3-hydroxy-5-((1*R**)-1-bromopropyl)tetrahydrofuran (**29**) (0.010 g, 0.024 mmol) was dissolved in dry CH_2Cl_2 (2.0 mL) under N_2 and cooled to 0 °C. Triethylamine (0.0040 mL, 0.030 mmol) and DMAP (0.0029 g, 0.024 mmol) were added, followed by the addition of 1-naphthoylchloride (0.0046 g, 0.024 mmol). After 6 h, the reaction mixture was concentrated in vacuo and purified by flash chromatography on silica gel (petroleum ether/EtOAc 80:20) to afford **30** as a clear oil (0.012 g, 86%): IR (neat) 2925, 2854, 1714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, J = 8.3 Hz, 1H), 8.16 (dd, J = 7.3, 1.2 Hz, 1H), 8.04 (d, J = 8.2 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.61 (m, 1H), 7.55–7.46 (m, 2H), 7.30–7.25 (m, 5H), 5.65 (dd, J = 3.9, 3.9 Hz, 1H), 4.48 (d, J = 12.9 Hz, 1H), 4.45 (d, J = 12.9 Hz, 1H), 4.36 (m, 2H), 3.98 (ddd, J = 10.5, 7.4, 3.3 Hz, 1H), 3.52–3.43 (m, 2H), 2.85 (ddd, J = 6.9, 4.4, 2.2 Hz, 1H), 2.70 (ddd, J = 5.7, 5.7, 2.2 Hz, 1H), 2.48 (dd, J = 14.7, 7.0 Hz, 1H), 2.32 (ddd, J = 14.0, 9.0, 4.8 Hz, 1H), 2.11–2.02 (m, 1H), 1.98 (ddd, J = 14.0, 9.4, 4.5 Hz, 1H), 1.82–1.65 (m, 4H), 1.64–1.54 (m, 2H), 1.07 (t, J = 7.2 Hz, 3H); ^1H NMR (500 MHz, C_6D_6) δ 9.43 (d, J = 8.7 Hz, 1H), 8.23 (dd, J = 8.4, 1.3 Hz, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.41 (ddd, J = 8.3, 6.8, 1.2 Hz, 1H), 7.27–7.10 (m, 5H), 5.52 (dd, J = 3.8, 3.8 Hz, 1H), 4.32–4.29 (m, 1H), 4.27 (s, 2H), 4.15 (m, 1H), 3.66 (ddd, J = 10.9, 9.3, 3.1 Hz, 1H), 3.28–3.18 (m, 2H), 2.79 (ddd, J = 7.4, 4.0, 2.0 Hz, 1H), 2.48 (ddd, J = 6.0, 6.0, 2.0 Hz, 1H), 2.28 (dd, J = 14.4, 6.5 Hz, 1H), 2.03 (ddd, J = 13.7, 9.3, 4.1 Hz, 1H), 1.95 (ddd, J = 14.1, 9.0, 4.9 Hz, 1H), 1.90–1.82 (m, 1H), 1.69–1.54 (m, 5H), 1.54–1.43 (m, 3H), 0.94 (t, 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 138.7, 134.1, 134.1, 131.7, 130.6, 128.9, 128.6, 128.2, 127.8, 127.8, 126.7, 126.6, 125.9, 124.7, 80.4, 79.6, 76.4, 73.1, 69.9, 62.5, 59.2, 56.3, 38.6, 33.2, 29.0, 28.8, 26.4, 12.2; ^{13}C NMR (125 MHz, C_6D_6) δ 166.6, 139.6, 134.6, 134.2, 132.5, 130.8, 129.1, 127.7, 127.4, 126.8, 126.6, 124.9, 80.6, 80.1, 76.7, 73.1, 70.0, 62.7, 58.9, 56.0, 39.1, 33.7, 29.4, 30.4, 29.1, 26.9, 12.2; HRMS (ESI) calcd for $C_{31}H_{39}BrNO_5$ (M^+ + NH_4) m/z 584.2012, found 584.2001.

(2*R,3a*R**,5*S**,6a*S**)-2-[(1*S**)-(4-(Benzyloxy)-1-bromobutyl)]-5-[(1*R**)-(1-bromopropyl)hexahydrofuro[3,2-*b*]furan (32).** CBr_4 (0.020 g, 0.061 mmol) and (trioctylphosphine) $P(Oct)_3$ (0.0054 mL, 0.12 mmol), followed by pyridine (0.0060 mL), were added to a solution of (2*R**,3*R**,5*S**)-2-[(2*R**,3*R**)3-(3-benzyloxypropyl)oxiran-

dx.doi.org/10.1021/jo301048z | J. Org. Chem. 2012, 77, 7883–7890

2-yl)methyl]-3-hydroxy-5-((1*R**)-1-bromopropyl)tetrahydrofuran (**29**) (0.0050 g, 0.012 mmol) in dry toluene (2.0 mL) under N_2 at rt. The resulting mixture was stirred at 80 °C. After 6 h, the reaction mixture was concentrated in vacuo and purified by flash chromatography on silica gel (petroleum ether/EtOAc 90:10) to afford **32** as a colorless oil (0.0038 g, 65%): IR (neat) 2925, 2854 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.25 (m, 5H), 4.75 (m, 2H), 4.49 (d, J = 12.0 Hz, 1H), 4.46 (d, J = 11.9 Hz, 1H), 4.19 (m, 1H), 4.15 (m, 1H), 3.96−3.91 (m, 2H), 3.52−3.45 (m, 2H), 2.33 (dd, J = 13.6, 5.6 Hz, 1H), 2.20 (dd, J = 13.5, 5.8 Hz, 1H), 1.97−1.88 (m, 6H), 1.75−1.66 (m, 2H), 1.05 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 128.6, 127.9, 127.8, 84.9, 84.8, 82.6, 82.4, 73.2, 69.5, 62.2, 59.6, 39.1, 39.0, 32.5, 28.7, 28.2, 12.4; HRMS (ESI) calcd for $C_{20}H_{28}Br_2NaO_3$ (M^+ + Na) m/z 499.0278, found 499.0267.

■ ASSOCIATED CONTENT

Supporting Information

High-resolution ^1H and ^{13}C NMR spectra for new compounds.X-ray data for compound **10a** CIF). 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.

■ ACKNOWLEDGMENTS

This manuscript is based upon work supported by the National Science Foundation (NSF) under Grant No. CHE-0809753. We thank Yanke Liang, Prof. Scott Nelson (University of Pittsburgh), and Prof. Marc Zimmer (Connecticut College) for helpful discussions and Dr. Christopher Incarvito (Yale University) for solving the crystal structure.

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