JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

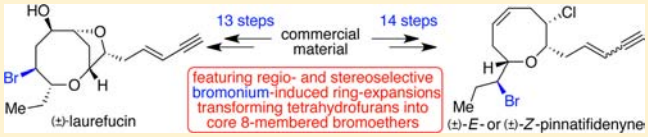
Concise Synthetic Approaches for the *Laurencia* Family: Formal Total Syntheses of (±)-Laurefucin and (±)-*E*- and (±)-*Z*-Pinnatifidenyne

Scott A. Snyder,* Alexandria P. Brucks, Daniel S. Treitler, and Ioana Moga

Department of Chemistry, Columbia University, Havemeyer Hall, 3000 Broadway, New York, New York 10027, United States

Supporting Information

ABSTRACT: Herein is presented a cohesive strategy to rapidly fashion diverse members of the lauroxocane family of natural products, leading to the shortest syntheses of any member to date. These efforts include racemic formal total syntheses of laurefucin and *E*- and *Z*-pinnatifidenyne as well as a facile preparation of the oxocene core of 3*E*-dehydrobromolaurefucin. The key elements of the design are novel diastereoselective ring-expanding bromoetherifications of tetrahydrofurans triggered by a unique bromonium source (BDSB, $Et_2SBr{\cdot}SbBrCl_5$) and strategically positioned nucleophilic traps, where altering the identity and position of these traps affords diverse functionality on the eight-membered ring backbone. Its biogenetic relevance is also discussed in light of the range of substrates that successfully undergo this key rearrangement.



INTRODUCTION

The lauroxocane natural products (including **1**−**5**, Figure 1), a significant subset of the *Laurencia* class of haloethers, have been

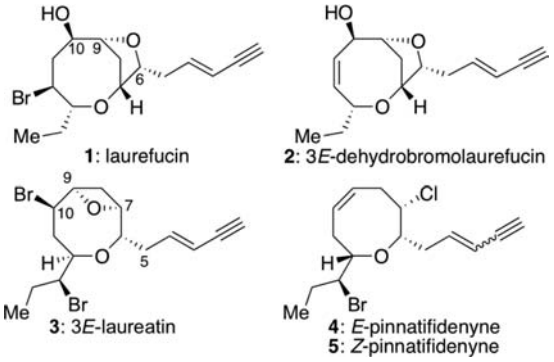


Figure 1. Structures of selected lauroxocane natural products.

the subject of much experimental interest in recent years. Whether as a testing ground to evaluate strategies for the preparation of stereochemically rich medium-sized rings[1] or as an arena to explore biogenetic hypotheses,[2] numerous discoveries continue to be made in connection with these molecules. For example, we recently developed a stereocontrolled ring-expanding bromoetherification,[3] empowered by a unique bromonium source (BDSB, $Et_2SBr{\cdot}SbBrCl_5$),[4] which proved capable of forging a diverse array of products reflective of the class.

As shown in Scheme 1, tetrahydrofuran substrates[5] possessing a strategically positioned exocyclic alkene along with an internal nucleophilic trap (such as **6**) smoothly formed eight-membered haloethers (such as **8**) upon their exposure to 1.2 equiv of BDSB in $MeNO_2$.[6] Not only was this process high yielding, but surprisingly it was also diastereoselective. This outcome was not initially expected because the remote nature of the chiral centers within **6** was unlikely to favor bromonium addition to only a single face of its double bond. However, despite the fact that both intermediates **9** and **10** could be formed, because bromonium transfer between alkenes is facile[7] and oxonium formation is likely reversible, only the less sterically hindered oxonium intermediate (**11** over **12**) would appear capable of leading to product. Pleasingly, similar facility and stereoselectivity was observed for the other substrates explored, ultimately affording an array of 8-*endo* and 8-*exo* bromoethers (such as **8** and **15**, respectively). Moreover, the design could be applied to tetrahydropyran rings as well, such as **16**, to generate nine-membered bromoethers such as **18**.

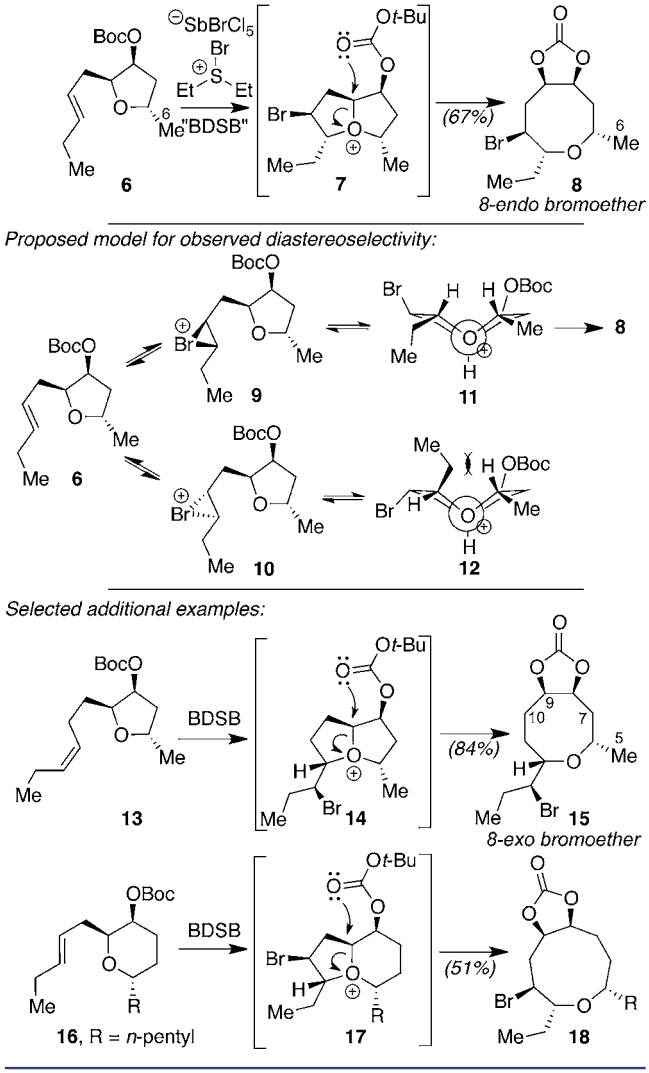
However, while this work was unique in terms of the overall breadth of frameworks accessed within the broadly defined *Laurencia* class, a comparison of these materials to their natural counterparts reveals that several major synthetic challenges remain if the approach is to afford a unified solution to the family. From model oxocanes such as **8**, these include adding a functionalized enyne side chain at C-6, stereoselectively forging the tetrahydrofuran ring system of **1** and **2** (Figure 1), and generating the *cis*-alkene of **2**. From compounds such as **15**, these encompass similar addition of an enyne side chain at C-5 along with fully altering the functional group pattern at C-7, C-9, and C-10 to that of **3**, **4**, and/or **5**. While simply stated, the timing of such events and their general compatibility with other functional groups likely to be present was not anticipated to be trivial, especially on eight-membered frameworks that have a proclivity to rearrange and/or fragment by transannular events.[8]

In this Article, we detail how these gaps can be addressed while still utilizing our key bromonium-induced ring-expansion

Received: August 3, 2012
Published: October 11, 2012

   dx.doi.org/10.1021/ja3076988 | *J. Am. Chem. Soc.* 2012, 134, 17714−17721

Scheme 1. Previous Work Delineating Diastereoselective Ring Expansions of Tetrahydrofurans and Tetrahydropyrans into Eight- and Nine-Membered Bromoethers Using BDSB[3]



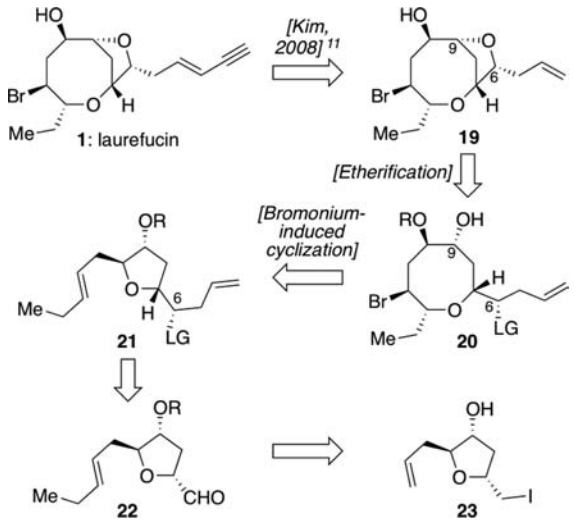
event in ways that are both extensions as well as new directions from previously published studies.[3] These efforts have enabled a 13-step synthesis of (±)-laurefucin (**1**), access to the full core of 3*E*-dehydrobromolaurefucin (**2**) in nine steps, and 14-step syntheses of (±)-*E*- and (±)-*Z*-pinnatifidenyne (**4** and **5**). These total syntheses constitute the shortest routes to any eight-membered haloether in the family to date (out of over two dozen).[1] In addition, the overall stereocontrol and facility of the key processes, coupled with the relative ease of starting material synthesis, suggests that they may have biogenetic relevance.

RESULTS AND DISCUSSION

1. Explorations of Ring Expansions Leading to 8-*endo* Bromoethers: Racemic Formal Total Synthesis of Laurefucin. We began our studies with attempts to extend the utility of our ring-expanding haloetherification process by fashioning fully functionalized 8-*endo* bromoethers, using the natural product laurefucin (**1**, Figure 1), a material first isolated in 1972 by Irie and co-workers,[9] as our proving ground. Our goals were to evaluate (1) what additional functionality could be incorporated at the C-6 position within tetrahydrofurans of general structure **6** (cf., Scheme 1) while still enabling the stereoselective ring-expanding bromoetherification step and (2) how readily the bridging tetrahydrofuran ring of the target could be assembled post ring expansion.

Retrosynthetically, the key target was alkene **19** (Scheme 2), a bromoether devoid of the enyne portion of the side chain[10]

Scheme 2. Retrosynthetic Analysis for Laurefucin (1)



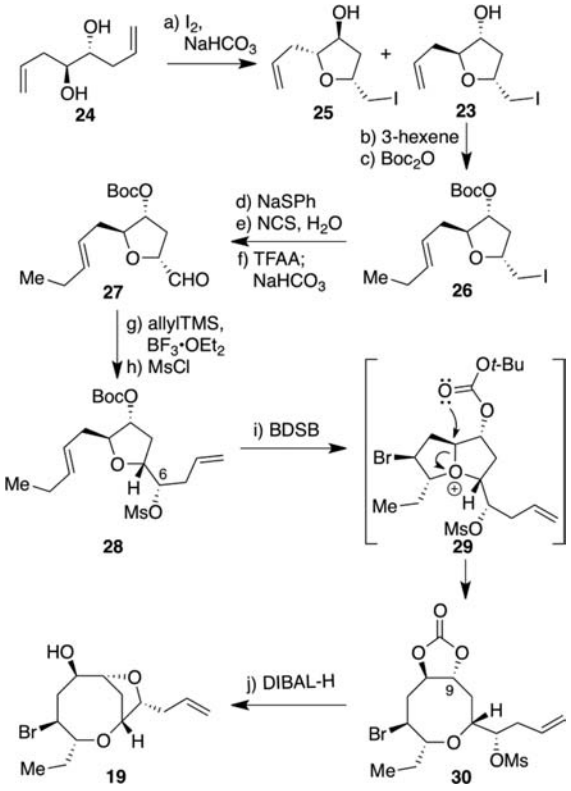
and a material that the Kim group had already shown could be advanced to laurefucin (**1**) in two additional steps.[11] Our hope was that the tetrahydrofuran ring within **19** could arise via S_N2 displacement of an appropriate leaving group at C-6 by a free C-9 hydroxyl group in an intermediate of type **20**. This analysis assumed not only that the C-6 leaving group could be installed stereoselectively, but also that the neighboring ether oxygen within the eight-membered ring would not provide any anchimeric assistance in effecting its displacement. From here, tetrahydrofuran **21** was viewed as the key precursor for the BDSB-induced ring-expanding bromoetherification, where bromonium chemoselectivity for the disubstituted alkene over the monosubstituted terminal olefin would be required. The C-6 chiral center within intermediate **21** could then, in turn, be derived from the allylation of a precursor aldehyde (i.e., **22**), assuming that the use of a Lewis acid could control the stereoselectivity of the addition. Given strong literature precedent for such stereocontrol,[12] coupled with the fact that we envisioned complex tetrahydrofuran **22** could readily be accessed in just a few steps from iodoether **23**, we set out to test our overall approach.

As shown in Scheme 3, the forward synthesis commenced with *meso*-diol **24**, prepared via either a single step Sn-mediated diallylation of glyoxal[13] or an alternate three-step process defined in the Supporting Information. An initial iodocyclization using I_2 afforded a separable 1:1.2 mixture of iodoethers **25** and **23** in 76% combined yield.[14] Although the diastereoselectivity of this operation was low, the overall ease of synthesis rendered it attractive as a means to access our key starting material.

From here, subsequent cross-metathesis of **23** with *trans*-3-hexene using the second generation Hoveyda–Grubbs initiator[15] afforded the desired *trans*-alkene. Installation of the *tert*-butylcarbonate (Boc) group then generated **26** in 68% overall yield for these two steps. With these events complete,

dx.doi.org/10.1021/ja3076988 | J. Am. Chem. Soc. 2012, 134, 17714–17721

Scheme 3. Racemic Formal Total Synthesis of Laurefucin (1) Using the BDSB Ring-Expansion Method to Access Bromoether 19[a]



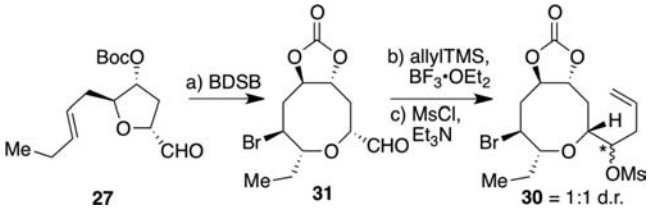
[a]Reagents and conditions: (a) I_2 (2.0 equiv), $NaHCO_3$ (2.0 equiv), MeCN, 25 °C, 3 h, 34% **25**, 42% **23**; (b) *trans*-3-hexene (6.0 equiv), Hoveyda–Grubbs second generation (0.008 equiv), CH_2Cl_2, 25 °C, 3 h, 78%; (c) Boc_2O (4.0 equiv), Et_3N (1.5 equiv), 4-DMAP (0.2 equiv), CH_2Cl_2, 25 °C, 5 h, then KOH (5.0 equiv), DMSO, 25 °C, 3 h, 87%; (d) NaH (2.0 equiv), PhSH (2.0 equiv), DMF, 25 °C, 1 h, then **26**, 25 °C, 4 h, 85%; (e) NCS (1.1 equiv), H_2O, THF, 25 °C, 12 h; (f) TFAA (3.5 equiv), 2,6-lutidine (3.5 equiv), CH_2Cl_2, 0 °C, 10 min, then $NaHCO_3$ (excess), H_2O, 25 °C, 24 h, 71% over two steps; (g) BF_3·OEt_2 (5.0 equiv), CH_2Cl_2, −78 °C, 10 min, then allylTMS (5.0 equiv), −78→−20 °C, 3 h; (h) MsCl (3.0 equiv), Et_3N (6.0 equiv), CH_2Cl_2, 0→25 °C, 2 h, 81% over two steps; (i) BDSB (1.5 equiv), $MeNO_2$, −25→25 °C, 20 min, 72%; (j) DIBAL-H (5.0 equiv), PhMe, −78→25 °C, 6 h, 46%.

the iodide now needed to be converted into the aldehyde function of **27**. While initial screens revealed that several oxygen-based nucleophiles could displace the halogen successfully, yields were generally poor due to concomitant Boc participation, an event leading to several rearranged products of undetermined structure. Fortunately, use of a three-step protocol involving NaSPh displacement of the iodide, chemoselective sulfide oxidation, and a Pummerer rearrangement avoided this issue and provided the desired aldehyde (**27**) in 60% overall yield.[16] The key cyclization precursor (i.e., **28**) was then accessed in two additional steps in 81% overall yield. The first of these was a stereoselective allylation promoted by BF_3·OEt_2, where the observed diastereoselectivity followed the Felkin–Anh model with the allyl group added into the least hindered face of the carbonyl.[17] The second step was mesylation of the resultant alcohol. Our purpose in installing the leaving group at this point was to avoid the need for additional protection/deprotection steps, hoping that the labile mesylate would be retained in the ring-expansion step, but soon thereafter could serve as a leaving group to complete the final ring of the target. Of note, however, attempts to incorporate alternate substituents at the C-6 position for the same purpose, such as I, Br, OTMS, OTIPS, OTBS, and OAc, were met with failure (usually giving recovered starting material or decomposition), indicating a very small window for effective functionalization of that alcohol motif.

With the stage now set for the key operation, **28** was treated with 1.5 equiv of BDSB in $MeNO_2$ at −25 °C for 15 min followed by 5 min of stirring at 25 °C. Upon completion, oxocane **30** was obtained in 72% yield as a single stereoisomer. Pleasingly, the process was also chemoselective in terms of the two alkenes that could be activated by BDSB (despite the presence of an excess of reagent),[18] and the potentially labile mesylate group remained intact. Next, in a final step, exposure of **30** to DIBAL-H in toluene cleaved the carbonate group[19] and enabled the resultant C-9 alkoxide to displace the mesylate directly to forge the bridging tetrahydrofuran ring of the target. In total, this racemic synthesis of intermediate **19** is 11 steps in its longest linear sequence, yielding a formal 13-step total synthesis of (±)-laurefucin (**1**) based on the Kim precedent.[11b]

As a final comment for this synthesis, it is worth noting that it also proved possible to access intermediate **30** by inverting the order of the allylation/leaving group formation and BDSB-initiated ring-expansion steps as shown in Scheme 4. However,

Scheme 4. Alternate Sequence to Generate Key Intermediate 30[a]



[a]Reagents and conditions: (a) BDSB (1.2 equiv), $MeNO_2$, −25→25 °C, 2 min, 56%; (b) BF_3·OEt_2 (5.0 equiv), CH_2Cl_2, −78 °C, 10 min, then allylTMS (5.0 equiv), −78→−20 °C, 3 h, 59%, 1:1 dr; (c) MsCl (3.0 equiv), Et_3N (6.0 equiv), CH_2Cl_2, 25 °C, 2 h, 59%.

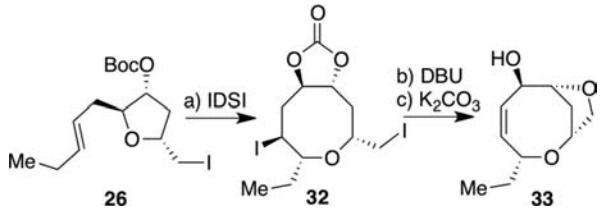
while the BDSB-cyclization of aldehyde **27** provided only a single diastereomer of **31**, allylation of this material under the same conditions as before produced the intermediate alcohol with 1:1 dr and in diminished yield. As such, this result appears to illustrate the greater utility of tetrahydrofurans over oxocanes in achieving critical stereocontrol. Thus, by being able to utilize the key ring-expansion process successfully in the late stages of the synthesis on highly functionalized intermediates, the tetrahydrofuran ring can be used as a template throughout the route, enabling more effective stereocontrol in the installation of chiral centers.

2. Explorations of Ring Expansions Leading to 8-*endo* Bromoethers: Chemoselective Synthesis of the Core of 3*E*-Dehydrobromolaurefucin. Having addressed the critical functionalization pattern of laurefucin (**1**, Figure 1), we next turned our attention to determining if we could fashion the endocyclic alkene of **2**.[20] This olefin is shared by nearly one-fourth of the several dozen members of the lauroxocane family, and its relative ubiquity made us wonder whether simple elimination of a bromide could afford this structural component. In our hands, however, attempts to eliminate the

dx.doi.org/10.1021/ja3076988 | J. Am. Chem. Soc. 2012, 134, 17714–17721

bromide within **8** (Scheme 1) and related materials afforded only recovered starting material and/or decomposition. Yet, as shown in Scheme 5, we found that if cyclization precursor **26**

Scheme 5. IDSI-Promoted Ring Expansion and Elimination[a]



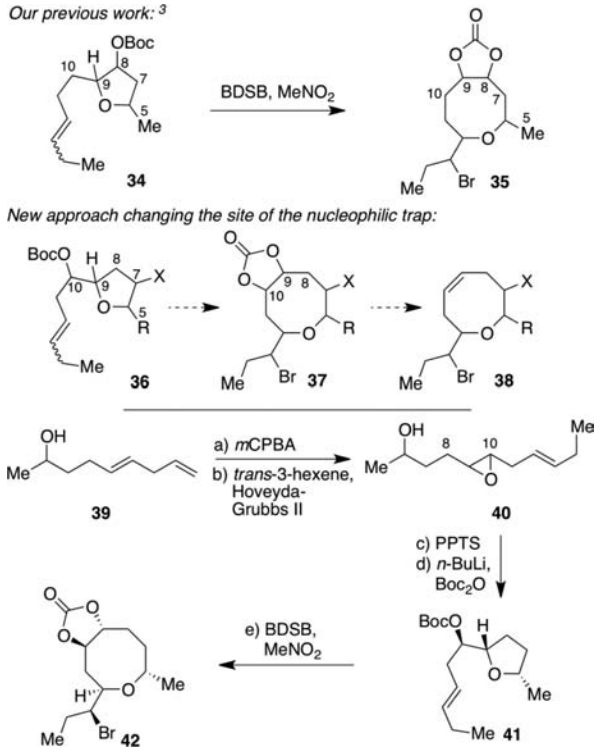
[a]Reagents and conditions: (a) IDSI (1.2 equiv), $MeNO_2$, −25→25 °C, 25 min, 54%; (b) DBU (5 equiv), PhMe, 25 °C, 24 h, 92%; (c) K_2CO_3 (10 equiv), MeOH, 25 °C, 12 h, 99%.

was subjected to IDSI (the iodine analogue of BDSB),[4b] an iodinated eight-membered haloether (i.e., **32**) could be formed. In this case, subsequent treatment with DBU in toluene at 25 °C for 12 h affected chemoselective elimination of the secondary iodide to generate the desired alkene in 92% yield. This event then set the stage for methanolysis of the carbonate group and subsequent displacement of the remaining primary iodide to complete the 3*E*-dehydrobromolaurefucin core (**33**) in quantitative yield.

3. Efforts to Form 8-*exo* Bromoether *Laurencia* Cores: Changing the Site and Identity of the Nucleophilic Trap. With approaches to form highly functionalized 8-*endo* bromoethers in hand, we turned to the challenges of fashioning their 8-*exo* counterparts, such as lauroxocanes **3**−**5** (cf., Figure 1). As noted earlier, this task would require us to build on previous achievements in 8-*exo* bromoether synthesis (shown in generalized format by the conversion of **34** into **35**, Scheme 6)[3] by finding ways to (1) incorporate the enyne unit at C-5 and (2) alter the functionalization at C-7, C-9, and C-10. We believed that some of these issues could potentially be solved by adding the desired groups onto the tetrahydrofuran prior to the bromonium-induced ring expansion; for instance, the C-7 position could likely carry a halogen directly in the cyclization step, and if suitable functionality could be attached at C-5 as noted within generalized intermediate **36**, then the enyne unit could be forged at the end of the synthesis. The bigger challenge, however, was how to place appropriate groups at the C-9 and C-10 positions. In this case, the most efficient solution appeared to be direct functionalization during the cyclization step, an outcome that could potentially be achieved if the position of the nucleophilic trap was changed from inside the ring at C-8 to outside at C-10. As such, a generalized intermediate such as **36** would afford products of structure **37**, with groups that could hopefully be converted into the C-9/C-10 functionalization patterns of **3**, **4**, and/or **5** (shown here as a carbonate within **37** or an alkene within **38**).

To test this switch in trapping group placement, we prepared model compound **41** over several standard steps from alcohol **39** as shown in the bottom portion of Scheme 6. Pleasingly, we found that 8-*exo* bromoether **42** could be generated in 76% yield as a single stereoisomer following the treatment of **41** with BDSB. However, while this reaction readily afforded groups pertinent to the synthesis of natural materials such as **3** (cf., Scheme 1), despite much effort we were unable to convert this carbonate, its diol derivative, or several related congeners into the necessary C-9/C-10 alkene possessed by natural

Scheme 6. Changing the Site of the Nucleophilic Trap to Access Alternate Functionalization Patterns for the *Laurencia* Class[a]



[a]Reagents and conditions: (a) *m*CPBA (1.0 equiv), CH_2Cl_2, 25 °C, 2 h; (b) *trans*-3-hexene (5.0 equiv), Hoveyda−Grubbs second generation (0.1 equiv), CH_2Cl_2, 25 °C, 2 h, 41% over two steps; (c) PPTS (1.4 equiv), CH_2Cl_2, 25 °C, 1 h, 42% (+44% separable diastereomer); (d) *n*-BuLi (1.05 equiv), Boc_2O (1.0 equiv), THF, 0→25 °C, 2 h, 76%; (e) BDSB (1.2 equiv), $MeNO_2$, −25→25 °C, 10 min, 76%.

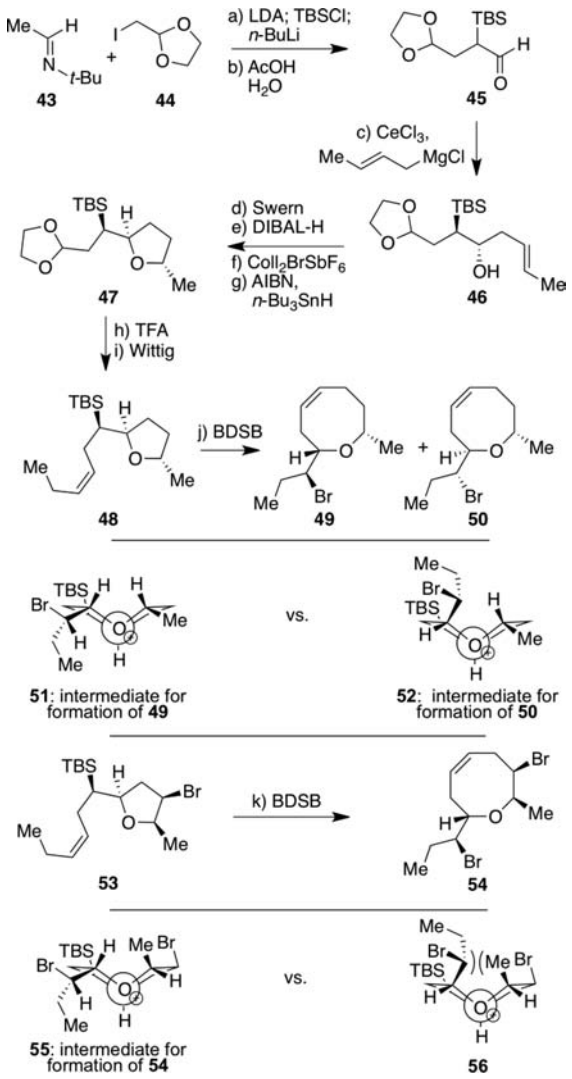
products such as **4** and **5** (i.e., **37**→**38** of Scheme 6). Thus, our goal became finding an alternate trapping group that could afford the needed olefin directly rather than providing a cyclic carbonate.

Our first efforts sought to utilize an alkylsilane, as such groups are known to have the ability to eliminate and produce alkenes directly under proper activation.[1i] As shown in Scheme 7, we thus targeted tetrahydrofuran **48** as our key model substrate. Its synthesis began with alkylation and hydrolysis of imine **43**, generating silylated aldehyde **45** in 63% yield.[21] Next, treatment of this intermediate with 2-butenylmagnesium chloride in the presence of activated $CeCl_3$ selectively generated the *trans*-linear crotylated product **46**.[22] Unfortunately, this compound possessed incorrect stereochemistry about its alcohol position, so a two-step oxidation/reduction sequence proved necessary to generate the desired *syn*-homoallylic alcohol. Finally, bromonium-induced cyclization with $coll_2BrSbF_6$[23] followed by radical-based excision of the resultant bromide atom yielded the tetrahydrofuran ring **47**. Cyclization precursor **48** was then generated via acid-induced acetal cleavage and Wittig olefination.

Pleasingly, treatment of **48** with 1.0 equiv of BDSB in $MeNO_2$ at −25 °C for 10 min afforded 8-*exo* bromoether products possessing an internal alkene in 86% yield. Thus, alkylsilane **48** must have proper stereochemistry such that upon bicyclic oxonium formation the C−Si bond is antiperiplanar to

dx.doi.org/10.1021/ja3076988 | J. Am. Chem. Soc. 2012, 134, 17714−17721

Scheme 7. Changing the Identity of the Nucleophilic Trap to an Alkylsilane[a]

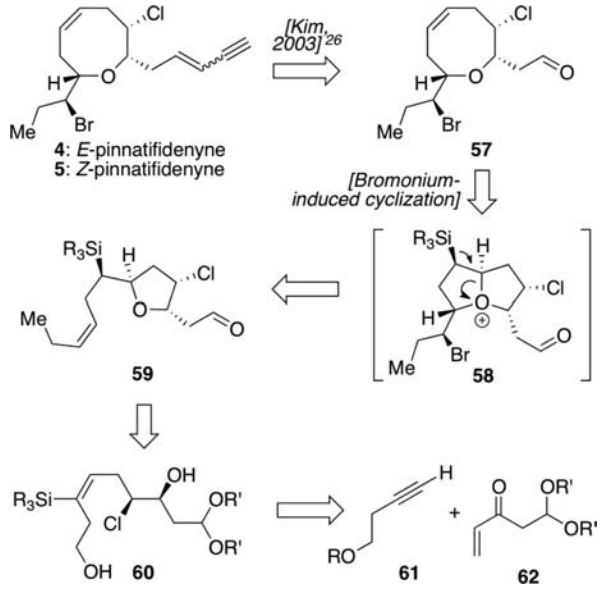


[a]Reagents and conditions: (a) LDA (1.0 equiv), THF, 0 °C, 30 min; TBSCl (0.99 equiv), *n*-Bu_4NI (0.02 equiv), 25 °C, 3 h, *n*-BuLi (1.0 equiv), 0 °C, 30 min; **44** (1.5 equiv), −50→25 °C, 12 h; (b) 1 M AcOH, CH_2Cl_2, 25 °C, 1 h, 63% over two steps; (c) $CeCl_3$ (1.5 equiv), 2-butenylmagnesium chloride (1.2 equiv), THF, 0 °C, 1 h, then **45**, −78 °C, 30 min, 63%; (d) $(COCl)_2$ (1.5 equiv), DMSO (3.0 equiv), CH_2Cl_2, −78 °C, 5 min, then **46**, 5 min, then Et_3N (6.0 equiv), −78→−30 °C, 2 h; (e) DIBAL-H (1.5 equiv), THF, −78→−20 °C, 6 h; (f) $coll_2BrSbF_6$ (1.3 equiv), $MeNO_2$, −25 °C, 20 min, 38% over three steps; (g) AIBN (0.1 equiv), *n*-Bu_3SnH (3.0 equiv), PhMe, 90 °C, 1 h, 99%; (h) TFA (13.0 equiv), THF/H_2O, 50 °C, 2 h; (i) KO*t*-Bu (4.0 equiv), $CH_3CH_2CH_2PPh_3Br$ (5.0 equiv), THF, 25 °C, 20 min, then substrate, 0 °C, 1 h, 63% over two steps; (j) BDSB (1.0 equiv), $MeNO_2/CH_2Cl_2$, −25 °C, 10 min, 38% **49**, 48% **50**; (k) BDSB (1.0 equiv), $MeNO_2/CH_2Cl_2$, −25 °C, 10 min, 74%.

the adjacent C−O bond.[24] To our surprise, however, this ring-expanding bromoetherification was not diastereoselective, generating both **49** and **50** in a 1:1.2 ratio. One explanation for this outcome is that perhaps the enhanced electron-donating capability of the silyl group may render the bicyclic oxonium formation/fragmentation pathway fast enough to preclude equilibration between oxonium intermediates **51** and **52**. However, it may also comprise a steric component, as the methyl group sits on the convex face of both oxonium intermediates **51** and **52**, thereby potentially weakening the preference for a single, product-determining intermediate. Further proof that this factor could be relevant derives from cyclization studies with a brominated diastereomer of **48** (i.e., **53**, synthesized from **45** in a similar sequence outlined in the Supporting Information). In this case, exposure of **53** to BDSB afforded compound **54** (structure verified by X-ray crystallographic analysis) in 74% yield with complete stereocontrol. Indeed, a comparison of transition state structures **55** and **56** reveals the benefit that substitution on the concave face may have in biasing oxonium formation (here in favor of **55**) to afford increased product diastereocontrol. Thus, with the expectation that a silyl neighboring/leaving group could assist in alkene incorporation, and an initial sense of some of the factors that might be behind the observed diastereoselectivity for these events, we decided as a final study to synthesize both *E*- and *Z*-pinnatifidenyne (**4** and **5**)[25] to probe this critical process further.

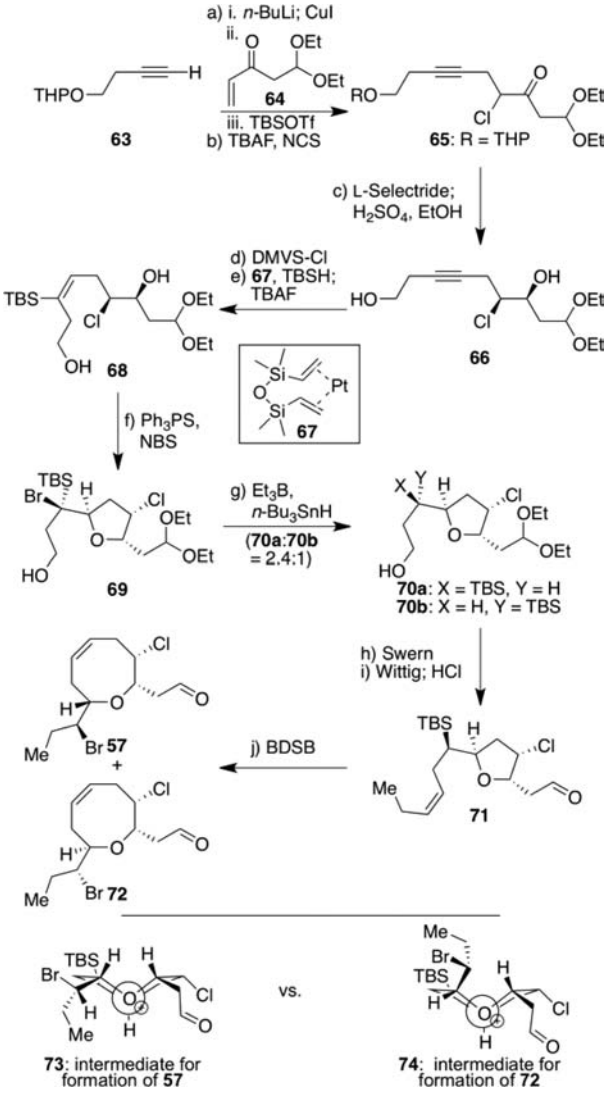
4. Efforts to Form 8-*exo* Bromoether *Laurencia* Cores: Racemic Formal Total Syntheses of *E*- and *Z*-Pinnatifidenyne. As shown in Scheme 8, our target was aldehyde **57**, a material that the Kim group had previously shown could be advanced to either **4** or **5** in three additional steps.[26] This choice rendered tetrahydrofuran **59** as our cyclization precursor target. The challenge, however, was setting all of the stereochemistry correctly and with ease, goals that our work in the context of Scheme 7 had illustrated were not necessarily straightforward. Our thought was that the tetrahydrofuran ring could be forged through a 5-*exo* cyclization initiated by an appropriate electrophile from a precursor hydroxy alkene such as **60**. This material, in turn, could arise from the 1,4-addition of the anion generated from alkyne **61** into α,β-unsaturated ketone **62**, followed by a *cis*-selective reduction of the alkyne to create a template for the formation of chlorohydrin domain within **60**. Unclear in this analysis was how readily the correct stereochemistry of the trialkylsilane within **59** could be formed, a concern that would have to await experimental analysis.

Scheme 8. Retrosynthetic Analysis for the Pinnatifidenynes (4 and 5)



dx.doi.org/10.1021/ja3076988 | J. Am. Chem. Soc. 2012, 134, 17714−17721

Scheme 9. Racemic Formal Total Synthesis of the Pinnatifidenynes Using a BDSB Initiated Ring Expansion of an Alkylsilane[a]



[a]Reagents and conditions: (a) *n*-BuLi (1.0 equiv), THF, 0 °C, 15 min; CuI (1.1 equiv), 0 °C, 1 h; **64** (1.2 equiv), TBSOTf (0.95 equiv), −70→5 °C, 12 h; (b) NCS (1.5 equiv), TBAF (1.2 equiv), THF, 3 h, −78 °C, 50% over two steps; (c) L-Selectride (1.2 equiv), THF, −78 °C, 15 min; H_2SO_4 (10 equiv), EtOH, 25 °C, 2 h, 89%; (d) DMVS-Cl (1.2 equiv), pyridine (5.0 equiv), Et_2O, −78 °C, 30 min; (e) TBSH (1.3 equiv), Karstedt's catalyst (**67**, 0.02 equiv), THF, 40 °C, 3 h; TBAF (1.5 equiv), 0 °C, 10 min; (f) NBS (1.5 equiv), AcOH (4.0 equiv), Ph_3PS (0.2 equiv), CH_2Cl_2, −55 °C, 12 h, 59% over three steps; (g) Et_3B (0.3 equiv), Bu_3SnH (1.5 equiv), PhMe, 25 °C, 3 min, 83%, 2.4:1 dr; (h) $(COCl)_2$ (1.5 equiv), DMSO (2.5 equiv), CH_2Cl_2, −78 °C, 5 min, then **70**, 5 min, then Et_3N (5.0 equiv), −78→−30 °C, 1 h; (i) KO*t*-Bu (2.0 equiv), $CH_3CH_2CH_2PPh_3Br$ (2.2 equiv), THF, 25 °C, 20 min, then substrate, 0 °C, 1 h; 1 M HCl (10 equiv), THF, 50 °C, 2 h, 57% over two steps; (j) BDSB (1.0 equiv), $MeNO_2$/CH_2Cl_2, −25 °C, 10 min, 61% **57**, 25% **72**.

Our efforts began with alkyne **63** (Scheme 9), which, after deprotonation and transmetalation to copper, added effectively into enone **64** in a Michael-type fashion in the presence of TBSOTf.[27] Without purification, the resultant silyl enol ether was exposed to TBAF in the presence of NCS, generating α-chloroketone **65**.[28] Its reduction to the desired *syn*-chlorohydrin could then be accomplished with moderate selectivity (3:1 and 6:1 dr, respectively) using $NaBH_4$ or $LiAlH_4$. Fortunately, L-Selectride provided the needed isomer with greater than 20:1 dr; acidic workup in the same pot using anhydrous ethanolic sulfuric acid cleaved the THP group, but left the diethyl acetal intact, to afford **66** in 89% yield.

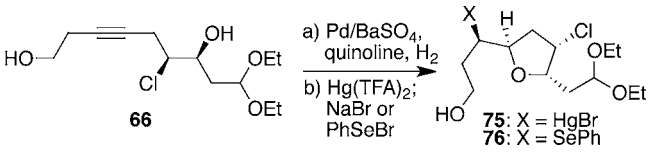
With these initial operations achieved, the challenge now was to stereoselectively incorporate the silyl group essential to the ring expansion/elimination. This requirement was accomplished by recourse to recent work from Tomooka's group, which showed that protection of propargylic or homopropargylic alcohols as dimethylvinylsilyl (DMVS) groups could facilitate directed hydrosilylation reactions with high regiocontrol.[29] Thus, treatment of **66** with DMVS-Cl and pyridine at low temperature selectively silylated the primary alcohol, which then underwent hydrosilylation using *tert*-butyldimethylsilane (TBSH)[30] in the presence of Karstedt's catalyst (**67**). In situ deprotection of the DMVS group with TBAF then yielded the desired hydrosilylated regioisomer in the form of **68**.

With these atoms in place, tetrahydrofuran ring synthesis was then attempted. Unfortunately, acid-induced cyclizations of **68** were unlikely to succeed given the proclivity of α-silylated tetrahydrofuran rings to rearrange to tetrahydropyrans at low pH.[31] Thus, we effected ring formation instead with a bromonium-induced cyclization using NBS in the presence of Ph_3PS to generate **69**,[32] followed by radical reduction to afford mostly the desired diastereomer (**70a**:**70b** = 2.4:1), presumably due to thermodynamic equilibration to the most stable radical.[33] Next, Swern oxidation and a one-pot Wittig olefination/acetal cleavage process afforded cyclization precursor **71** in 57% yield over two steps.[34] Pleasingly, upon treatment of **71** with BDSB under the standard conditions used earlier, desired oxocene **57** was generated in 61% yield alongside an additional eight-membered minor diastereomer (**72**, formed in 25% yield). Because the substituents on oxonium intermediates **73** and **74** are on the convex face, similar to our initial model system (**51** and **52** in Scheme 7), both diastereomers could be expected products. We propose that a greater amount of oxonium intermediate **73** (over **74**) may be formed due to the increased steric bulk of the aldehyde and chloride in **71** (as compared to the lone methyl of **48**), thus providing a higher degree of stereocontrol. Overall, this route could generate racemic *E*- or *Z*-pinnatifidenyne in 14 linear steps, as complex intermediate **57** was synthesized in only 11 steps.[26,35]

As a final comment, although the synthesis of **70** was concise, four steps were required to install the silicon group, form the tetrahydrofuran ring, and remove the resultant bromine atom needed for ring-closure, leading us to explore more expedient solutions. Specifically, we wondered whether tetrahydrofuran ring formation and terminating group incorporation for the key ring-expanding bromoetherification could be achieved simultaneously. Although silicon-induced cycloetherifications are not known (to the best of our knowledge), both Hg(II)[36] and Se(II)[37] are well documented for these transformations, and, given the polarization of C−Hg and C−Se bonds in the resultant products, they could likely undergo β-elimination analogous to the C−Si bond used previously. Unfortunately, although we could form both **75** and **76** (Scheme 10), these intermediates could not be advanced to the desired cyclization precursors using the Swern/Wittig sequence described previously for the related silane (**70**→**71**).

dx.doi.org/10.1021/ja3076988 | J. Am. Chem. Soc. 2012, 134, 17714−17721

Scheme 10. Alternate Cyclization Attempts toward the Pinnatifidenynes Using Different Electrophiles to Fashion the Core Starting with Tetrahydrofuran[a]



[a]Reagents and conditions: (a) 5% Pd on $BaSO_4$ (0.02 equiv), quinoline (0.2 equiv), H_2, EtOAc, 25 °C, 2 h; (b) $Hg(TFA)_2$ (1.1 equiv), CH_3CN, −40 °C, 30 min, 62% or PhSeBr (1.0 equiv), pyridine (2.0 equiv), CH_2Cl_2, −20→25 °C, 1 h, 49%.

CONCLUSION

We have developed sequences capable of rapidly delivering three natural products within the *Laurencia* family alongside several other congeners that reflect the core functionalization patterns of the class. These syntheses are the most expedient to date in terms of step count, a feature we believe derives from: (1) the relative ease of fashioning complex, stereochemically dense tetrahydrofurans, (2) the diverse range of highly stereoselective ring-expanding bromoetherifications that have been developed, with alterations in the nature and position of the terminating nucleophilic trap providing distinct functional arrays, and (3) examples of modifying eight-membered ring backbone functionality without initiating rearrangements. Overall, we expect that the approach delineated in this Article should afford expedient syntheses of other lauroxocanes as well. As a final note, given the overall range of substrates for which our key ring-expanding bromoetherification process succeeds, both as reported here and in our previous work,[3] it would seem reasonable to presume that such a rearrangement process may have biogenetic relevance[6b] given its overall facility and generally high levels of diastereocontrol.

ASSOCIATED CONTENT

Supporting Information

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

AUTHOR INFORMATION

Corresponding Author

sas2197@columbia.edu

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the NSF (CHE-0619638) for an X-ray diffractometer and Prof. Gerard Parkin and Mr. Serge Ruccolo for performing the crystallographic analysis of compound **54**. We thank Drs. J. Decatur and Y. Itagaki for NMR spectroscopic and mass spectrometric assistance, respectively. Financial support was provided by the NSF (CAREER Award CHE-0844593 and Predoctoral Fellowships to A.P.B. and D.S.T.), Columbia University (John Jay Fellowship to I.M.), the ACS Petroleum Research Fund (47481-G), the Camille and Henry Dreyfus Foundation (New Faculty Award to S.A.S.), Eli Lilly (Grantee Award to S.A.S.), and Bristol-Myers Squibb (unrestricted grant to S.A.S. and predoctoral fellowship to D.S.T.).

REFERENCES

(1) For a review, see: (a) Fujiwara, K. Total Synthesis of Medium-Ring Ethers from *Laurencia* Red Algae. In *Topics in Heterocyclic Chemistry*; Kiyota, H., Ed.; Springer-Verlag: Berlin, 2006; Vol. *5*, pp 97−148 and references therein. Additional syntheses: (b) Kim, B.; Cheon, G.; Park, J.; Lee, H.; Kim, H.; Kim, S.; Kim, D. *Heterocycles* **2007**, *74*, 171. (c) Suzuki, T.; Yoshino, N.; Uemura, T.; Hagiwara, H.; Hoshi, T. *Chem. Lett.* **2007**, *36*, 278. (d) Park, J.; Kim, B.; Kim, H.; Kim, S.; Kim, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 4726. (e) Adsool, V. A.; Pansare, S. V. *Org. Biomol. Chem.* **2008**, *6*, 2011. (f) Sasaki, M.; Hashimoto, A.; Tanaka, K.; Kawahata, M.; Yamaguchi, K.; Takeda, K. *Org. Lett.* **2008**, *10*, 1803. (g) Ortega, N.; Martín, V. S.; Martín, T. *J. Org. Chem.* **2010**, *75*, 6660. (h) Sasaki, M.; Oyamada, K.; Takeda, K. *J. Org. Chem.* **2010**, *75*, 3941. (i) Li, J.; Suh, J. M.; Chin, E. *Org. Lett.* **2010**, *12*, 4712. (j) Kim, B.; Sohn, T.-I.; Kim, S.; Kim, D.; Lee, J. *Heterocycles* **2011**, *82*, 1113.

(2) (a) Fukuzawa, A.; Masamune, T. *Tetrahedron Lett.* **1981**, *22*, 4081. (b) Fukuzawa, A.; Aye, M.; Nakamura, M.; Tamura, M.; Murai, A. *Chem. Lett.* **1990**, 1287. (c) Kikuchi, H.; Suzuki, T.; Kurosawa, E.; Suzuki, M. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1763. (d) Fukuzawa, A.; Aye, M.; Takasugi, Y.; Nakamura, M.; Tamura, M.; Murai, A. *Chem. Lett.* **1994**, 2307. (e) Murai, A. Biosynthesis of Cyclic Bromoethers from Red Algae. In *Comprehensive Natural Product Chemistry*; Sankawa, U., Ed.; Elsevier: New York, 1999; Vol. *1*, pp 303−324. (f) Braddock, D. C. *Org. Lett.* **2006**, *8*, 6055. (g) Kim, B.; Lee, M.; Kim, M. J.; Lee, H.; Kim, S.; Kim, D.; Koh, M.; Park, S. B.; Shin, K. J. *J. Am. Chem. Soc.* **2008**, *130*, 16807. (h) Braddock, D. C.; Millan, D. S.; Pérez-Fuertes, Y.; Pouwer, R. H.; Sheppard, R. N.; Solanki, S.; White, A. J. P. *J. Org. Chem.* **2009**, *74*, 1835. (i) Gutiérrez-Cepeda, A.; Fernádez, J. J.; Norte, M.; Souto, M. L. *Org. Lett.* **2011**, *13*, 2690. (j) Dyson, B. S.; Burton, J. W.; Sohn, T.-I.; Kim, B.; Bae, H.; Kim, D. *J. Am. Chem. Soc.* **2012**, *134*, 11781.

(3) Snyder, S. A.; Treitler, D. S.; Brucks, A. P.; Sattler, W. *J. Am. Chem. Soc.* **2011**, *133*, 15898.

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

(5) (a) Kang, B.; Mowat, J.; Pinter, T.; Britton, R. *Org. Lett.* **2009**, *11*, 1717. (b) Kang, B.; Chang, S.; Decker, S.; Britton, R. *Org. Lett.* **2010**, *12*, 1716.

(6) For other examples of intramolecular ring expansions with neighboring group participation, see refs 2f, 2h, and: (a) Clark, J. S.; Wong, Y.-S. *Chem. Commun.* **2000**, 1079. (b) Keshipeddy, S.; Martínez, I.; Castillo, B. F.; Morton, M. D.; Howell, A. R. *J. Org. Chem.* **2012**, *77*, 7883.

(7) (a) Bennet, A. J.; Brown, R. S.; McClung, R. E. D.; Klobukowski, M.; Aarts, G. H. M.; Santarsiero, B. D.; Bellucci, G.; Bianchini, R. *J. Am. Chem. Soc.* **1991**, *113*, 8532. (b) Rodebaugh, R.; Fraser-Reid, B. *Tetrahedron* **1996**, *52*, 7663. (c) Denmark, S. E.; Burk, M. T.; Hoover, A. J. *J. Am. Chem. Soc.* **2010**, *132*, 1232.

(8) (a) Sugimoto, M.; Suzuki, T.; Hagiwara, H.; Hoshi, T. *Tetrahedron Lett.* **2007**, *48*, 1109. (b) See refs 2f, 2g, 2h, and 2j.

(9) (a) Fukuzawa, A.; Kurosawa, E.; Irie, T. *Tetrahedron Lett.* **1972**, *13*, 3. (b) Furusaki, A.; Kurosawa, E.; Fukuzawa, A.; Irie, T. *Tetrahedron Lett.* **1973**, *14*, 4579.

(10) We hypothesized the enyne side chain would be incompatible with the BDSB-initiated ring-expansion step.

(11) (a) Baek, S.; Jo, H.; Kim, H.; Kim, H.; Kim, S.; Kim, D. *Org. Lett.* **2005**, *7*, 75. (b) See ref 2g. Here, (−)-laurefucin (**1**) was synthesized in 19 linear steps.

(12) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.

(13) Furlani, D.; Marton, D.; Tagliavini, G.; Zordan, M. *J. Organomet. Chem.* **1988**, *341*, 345.

(14) While this synthesis is racemic, it could be rendered enantioselective through the asymmetric desymmetrization of diol **24**: (a) Fujioka, H.; Nagatomi, Y.; Kotoku, N.; Kitagawa, H.; Kita, Y. *Tetrahedron Lett.* **1998**, *39*, 7309. (b) Fujioka, H.; Nagatomi, Y.; Kotoku, N.; Kitagawa, H.; Kita, Y. *Tetrahedron* **2000**, *56*, 10141.

Interestingly, if NIS was used in the cyclization, **25** was the major product (**25**:**23** = 3:1).
(15) Cossy, J.; BouzBouz, S.; Hoveyda, A. H. *J. Organomet. Chem.* **2001**, *634*, 216.
(16) Fujioka, H.; Maehata, R.; Wakamatsu, S.; Nakahara, K.; Hayashi, T.; Oki, T. *Org. Lett.* **2012**, *14*, 1054.
(17) When $TiCl_4$ is used as the Lewis acid, the product is epimeric at C-6: Danishefsky, S.; DeNinno, M. *Tetrahedron Lett.* **1985**, *26*, 823. See Supporting Information for a drawn Felkin−Anh model to account for this transformation.
(18) The amount of BDSB utilized in each particular case represents several test reactions looking to balance reaction rate and final product yield. Here, excess reagent, even in the presence of an extra alkene that could also undergo bromination, proved optimal.
(19) Marcos, I. S.; Castañeda, L.; Basabe, P.; Díez, D.; Urones, J. G. *Tetrahedron* **2008**, *64*, 10860.
(20) (a) Wratten, S. J.; Faulkner, D. J. *J. Org. Chem.* **1977**, *42*, 3343. (b) König, G. M.; Wright, A. D. *J. Nat. Prod.* **1994**, *57*, 477.
(21) (a) Campbell, K. N.; Sommers, A. H.; Campbell, B. K. *J. Am. Chem. Soc.* **1944**, *66*, 82. (b) Tietze, L. F.; Neumann, T.; Kajino, M.; Pretor, M. *Synthesis* **1995**, 1003.
(22) Snyder, S. A.; ElSohly, A. M.; Kontes, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 9693.
(23) Homsi, F.; Robin, S.; Rousseau, G. *Org. Synth.* **2000**, *77*, 206.
(24) Hudrlik, P. F.; Peterson, D. *J. Am. Chem. Soc.* **1975**, *97*, 1464.
(25) (a) González, A. G.; Martín, J. D.; Martín, V. S.; Norte, M.; Pérez, R.; Ruano, J. Z.; Drexler, S. A.; Clardy, J. *Tetrahedron* **1982**, *38*, 1009. (b) Norte, M.; González, A. G.; Cataldo, F.; Rodríguez, M. L.; Brito, I. *Tetrahedron* **1991**, *47*, 9411.
(26) Kim, H.; Choi, W. J.; Jung, J.; Kim, S.; Kim, D. *J. Am. Chem. Soc.* **2003**, *125*, 10238. Here, (+)-*E*- and (+)-*Z*-pinnatifidenyne were synthesized in 24 linear steps.
(27) (a) Matsuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* **1989**, *45*, 349. (b) Kim, S.; Lee, J. M. *Tetrahedron Lett.* **1990**, *31*, 7627. (c) Takeishi, K.; Sugishima, K.; Sasaki, K.; Tanaka, K. *Chem.-Eur. J.* **2004**, *10*, 5681.
(28) This synthesis could potentially be rendered enantioselective through a chiral α-chlorination of a silyl enol ether, although this problem constitutes a fairly open area in need of further reaction development: (a) Zhang, Y.; Shibatomi, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 15038. (b) Hajra, S.; Bhowmick, M.; Maji, B.; Sinha, D. *J. Org. Chem.* **2007**, *72*, 4872.
(29) Kawasaki, Y.; Ishikawa, Y.; Igawa, K.; Tomooka, K. *J. Am. Chem. Soc.* **2011**, *133*, 20712.
(30) We were also able to append TIPS and TES groups during this hydrosilylation step; however, subsequent chemistry revealed the TBS group to be superior.
(31) (a) Miura, K.; Hondo, T.; Saito, H.; Ito, H.; Hosomi, A. *J. Org. Chem.* **1997**, *62*, 8292. (b) Miura, K.; Hondo, T.; Takahashi, T.; Hosomi, A. *Tetrahedron Lett.* **2000**, *41*, 2129. (c) Miura, K.; Hondo, T.; Okajima, S.; Nakagawa, T.; Takahashi, T.; Hosomi, A. *J. Org. Chem.* **2002**, *67*, 6082.
(32) Denmark, S. E.; Burk, M. T. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20655.
(33) Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 5046.
(34) The minor epimer could be separated at this point by chromatography.
(35) Although our step count is less than other published routes, the Kim precedents in both cases discussed in this Article achieved enantioselective syntheses. Our step count begins with the one step synthesis of **64** from commercial materials.
(36) (a) Reitz, A. B.; Nortey, S. O.; Maryanoff, B. E.; Liotta, D.; Monahan, R. *J. Org. Chem.* **1987**, *52*, 4191. (b) Kang, S. H.; Kim, M.; Kang, S. Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 6177. (c) Takao, H.; Wakabayashi, A.; Takahashi, K.; Imagawa, H.; Sugihara, T.; Nishizawa, M. *Tetrahedron Lett.* **2004**, *45*, 1079.
(37) For a review, see: (a) Nicolaou, K. C. *Tetrahedron* **1981**, *37*, 4097. (b) Nicolaou, K. C.; Petasis, N. A. *Selenium in Natural Products Synthesis*; CSI, Inc.: Philadelphia, PA, 1984; p. 300.

NOTE ADDED AFTER ASAP PUBLICATION

Schemes 1 and 10 contained errors in the version published ASAP October 11, 2012; the correct version reposted October 12, 2012.