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A General Synthetic Approach for the *Laurencia* Family of Natural Products Empowered by a Potentially Biomimetic Ring Expansion

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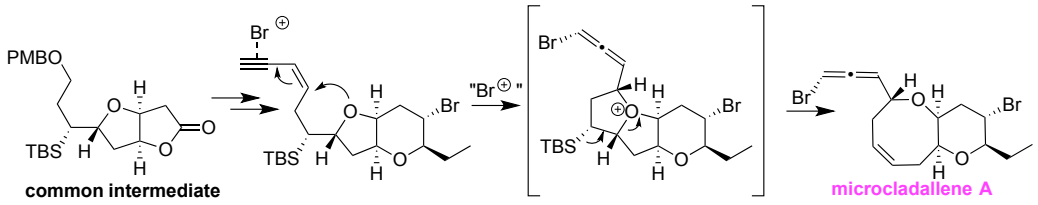
ABSTRACT: The *Laurencia* family of C_{15}-acetogenins is Nature's largest collection of halogenated natural products, with many of its members possessing a brominated 8-membered cyclic ether among other distinct structural elements. Herein, we demonstrate that a bromonium-induced ring expansion, starting from a common tetrahydrofuran-containing bicyclic intermediate and using the highly reactive bromenium source BDSB ($Et_2SBr•SbCl_5Br$), can lead to concise asymmetric total syntheses of microcladallenes A and B, desepilaurallene, laurallene, and prelaureatin. Key advances in this work include: 1) the first demonstration that the core bromonium-induced cyclization/ring-expansion can be initiated using an enyne with an internal ether oxygen nucleophile, 2) that reasonable levels of stereocontrol in such processes can be achieved both with and without appended ring systems and stereogenic centers, 3) that several other unique chemoselective transformations essential to building their polyfunctional cores can be achieved, and 4) that a single, common intermediate can lead to five different members of the class encompassing two distinct 8-membered cyclic ether ring collections. Considering this work along with past efforts leading to two other natural products in the collection, we believe the breadth of structures prepared to date affords strong evidence for Nature's potential use of similar processes in fashioning these unique molecules.



INTRODUCTION

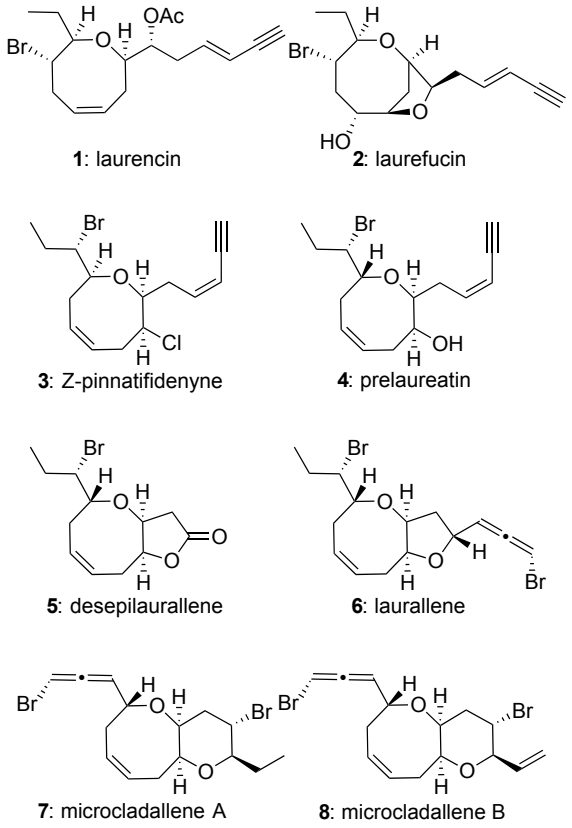
Ever since the initial isolation of laurencin (**1**, Figure 1) in 1965, its unique 15-carbon framework featuring an 8-membered brominated cyclic ether ring has captivated the attention of synthetic chemists around the world.[1] Indeed, nearly 20 total syntheses of this natural product have been achieved to date, demonstrating the range of creative solutions that can be brought to bear to fashion such a strained, medium-size ring.[2] Those operations include oxidative ring expansions,[2a] oxonium additions,[2bc] ring-closing metathesis,[2d-g] and alkylation-based ring closures,[2hi] among several others.[2j-q] As additional members of the collection have been isolated,[3] many also containing 8-membered bromoether rings albeit with distinct alkene patterning (as in **3**–**8**), *endo*- versus *exo*-cyclic bromine atoms (as in **3**–**8**), dibromination (as in **6**–**8**), as well as additional appended ring systems (as in **2** and **5**–**8**), questions regarding their biogenesis have garnered increasing significance.

The first critical insight along these lines came from Murai, whose group postulated that the linear natural product laurediol (**9**, Scheme 1), obtained from the same producing species as deacyllaurencin (**12**, sometimes also called deacetyllaurencin), could serve as a potential precursor through some type of bromonium-induced cyclization.[4] Using the crude bromoperoxidase obtained by the producing species, his team observed the formation of the desired target (**12**) in 0.015% yield (0.085% based on recovered starting material). How such a process was effected mechanistically, however, was not described, with no demonstration, to the best of our knowledge, that simple chemical brominating sources could achieve a similar transformation from **9** in any yield since this original disclosure. Key, though, was that it established the likelihood that such a bromine atom was incorporated biosynthetically as an electrophile,[4c] not as a nucleophile as has been typical of the vast majority of the laboratory syntheses of family members; indeed, nearly every laboratory synthesis has installed such bromines via alcohol substitution chemistry.[5,6]

Given this state of affairs, and the global challenges in effecting what is likely to be both an entropically and enthalpically unfavorable direct, bromonium-induced 8-*endo*-trig cyclization, several teams have proposed biosynthetic alternatives patterned around this core transformation. Most involve the initial formation of a smaller, cyclic ether which can serve as the nucleophilic partner capable of attacking a bromonium-activated alkene. Those efforts have focused principally on either epoxides[7] or oxetanes.[8] In several elegant demonstra-

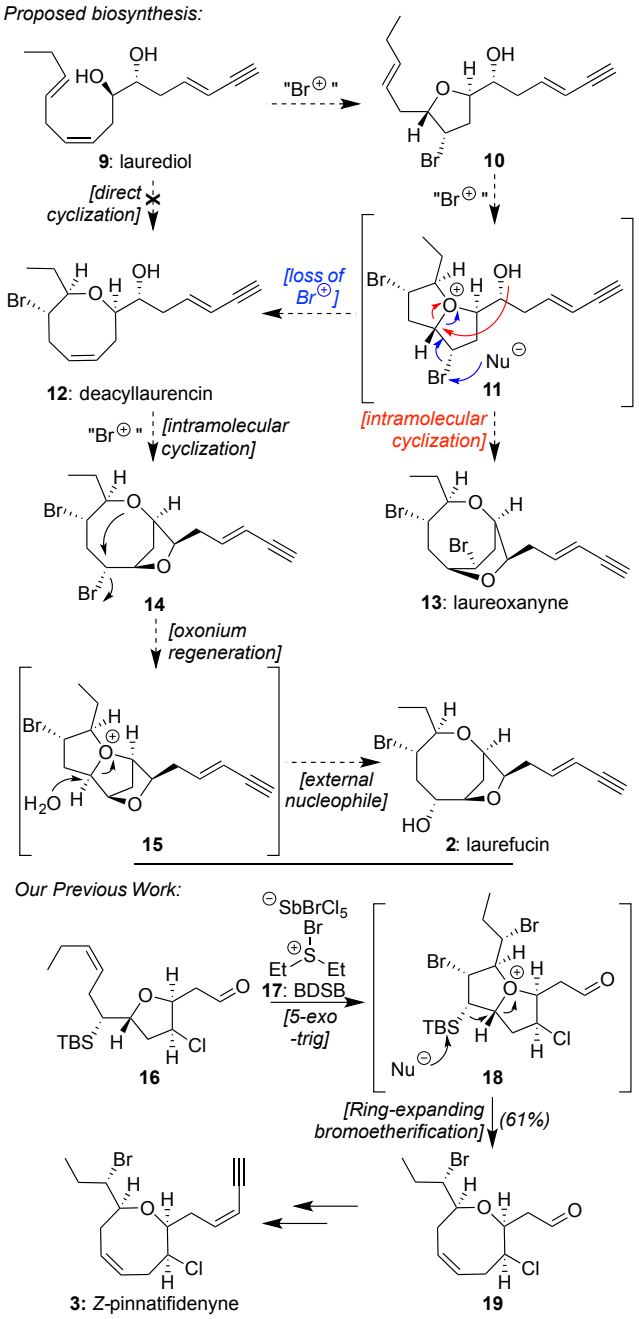
tions, such intermediates can afford an array of ring systems pertinent to the class broadly upon exposure to several different bromenium sources. Of note, these processes tend to produce mixtures which might be of biosynthetic relevance if Nature, as well, seeks non-selective reactions to generate this array of molecules. Such an outcome is not unreasonable, and could be of evolutionary advantage given that similar diversity-generation has been observed for several other natural product collections, such as phytoalexin-based polyphenols.[9,10]

Figure 1. Structures of selected lauroxocane natural products.



Our strategy, by contrast, has sought biomimetic relevance but also the capability to generate single natural products rather than mixtures. In that regard, our efforts have focused on the use of tetrahydrofuran-containing intermediates as synthetic precursors. As shown in the upper half of Scheme 1, such a key starting material could arise from laurediol (**9**) via a bromonium-induced 5-*endo*-trig cyclization. Then, if the oxygen atom of the tetrahydrofuran ring of **10** were to engage a second bromenium-activated alkene to generate oxonium intermediate **11**, arrow-pushing analysis suggests that subsequent loss of the endocyclic bromine atom, potentially facilitated by an external nucleophile, could then afford deacyllaurencin (**12**). Significantly, different mechanistic pathways using that same intermediate (i.e. **11**) could afford viable pathways to laureoxanyne (**13**) and laurefucin (**2**) as well.

Scheme 1. Proposed biosynthesis of several members of the lauroxocane class based on a series of 5-*endo*-trig cyclizations and a successful synthesis of laurefucin (**2**) based on that analysis as empowered by BDSB (**17**) as the bromenium source.



Armed with these ideas and encouraged by precedent from Braddock showing that ring expansions through oxonium formation using different systems could lead to 12-membered rings,[11,12] as well as several publications using the opposite perspective on this idea (i.e. a ring contraction of oxocane via a similar oxonium intermediate to deliver tetrahydrofuran containing natural products),[13-15] we have explored a variety of model systems as well as several fully functionalized compounds. Pleasingly, we found that the concept had broad success with high levels of stereoselectivity when the right bromenium source was utilized.[16] The bottom portion of Scheme 1 shows one example leading to a total synthesis of *Z*-pinnatifidenyne (**3**),[16] wherein treatment of **16** with our reac-

tive bromenium source BDSB[17] ($Et_2SBr•SbCl_5Br$) activated the exocyclic alkene in the presence of several functional groups to effect a subsequent cyclization and ring-opening to afford the alkene-containing product **19** in 61% yield; other bromenium sources, at least in model studies, have not demonstrated the ability to effect this functionalizing ring-expansion chemistry in commensurate yields.

Herein, we report our efforts to extend and further develop this general approach to a number of additional targets. The principal goal of our study was to illustrate that tetrahydrofuran-based ring expansions can generate the 8-membered rings of the lauroxocane collection in a number of diverse settings in terms of allied ring systems. Two questions were of particular interest. First, for targets containing an additional ring attached onto the 8-membered core, such as **5**–**8**, does the presence and/or absence of that ring impact the viability of a tetrahydrofuran-induced ring expansion? Second, could a new variant of the ring-expansion process be developed to forge concurrently an 8-membered ring and a bromoallene motif as found in **7** and **8**, and, if so, could such an event proceed with reasonable stereocontrol since the enyne is more remote from the 8-membered ring? As documented below, we have been able to individually synthesize five additional members of the collection, prelaureatin (**4**),[2b,18-20] desepilaurallene (**5**),[21] laurallene (**6**)[20ac,22-24] and microcladallenes A and B (**7** and **8**),[25,26] starting from a single, common intermediate and using new variants of our previously established ring-expansion process. These efforts demonstrate, we believe for the first time, that tetrahydrofuran ether oxygens can successfully add into bromonium-activated enyne electrophiles to induce such ring expansions. Those findings, coupled with some critical model studies, highlight that reasonable levels of stereocontrol in that ring-expansion process can be achieved independent from the presence of additional appended ring systems and chiral centers. Finally, we demonstrate that these syntheses can be conducted in both racemic and asymmetric formats. In the majority of cases, the developed routes are of comparable, if not superior, efficiency to past efforts.

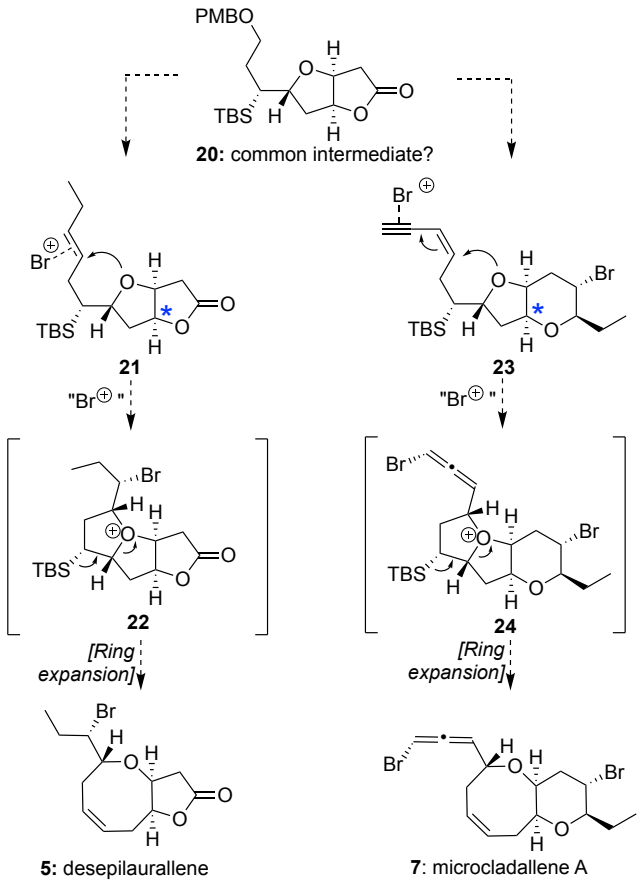
RESULTS AND DISCUSSION

1. Retrosynthetic Analysis Based on Common Intermediate Approach

Although lauroxocanes **5**–**8** possess disparate appended ring systems, the homology of their 8-membered core in terms of the site of additional ring fusion and the positioning of their internal alkene made us question whether all could arise from a common precursor; such strategies have served our group, and others, on several occasions for accessing diverse collections of natural products.[10,27,28] Keeping this idea in our minds and coupling it with the notion of using a tetrahydrofuran-based ring expansion as the key step to forge their 8-membered rings, we posited that bicyclic lactone **20** (Scheme 2) might be an ideal starting point for this subset.

As indicated from a forward synthesis perspective, we anticipated that its PMB-protected alcohol could be converted, over a series of steps, into the *trans*-disubstituted alkene of **21**. Then, using BDSB, we hoped to effect our ring-expansion strategy in a format generally similar to that deployed before as part of our *E*- and *Z*-pinnatifidenyne (**3**, cf. Figure 1) syntheses;[16] the critical difference, however, would be the presence of the appended five-membered lactone ring along with an additional stereogenic center relative to our past studies (denoted here with a star). This added motif might restrict the overall conformational flexibility of the system, reducing the reaction's overall diastereoselectivity and/or efficiency by destabilizing the transition state necessary for stereocontrol. Such transition state control could be critical since the reacting alkene is remote from the stereocontrolling elements within the core and bromenium addition to alkenes is reversible at reaction rates similar to diffusion control.[29] However, if success could be achieved in this critical operation leading to desepilaurallene (**5**), the goal would then be to utilize the appended lactone to fashion the requisite patterning of both prelaureatin (**4**) and laurallene (**6**). Success in these operations would require chemoselective engagement of that lactone in the presence of the exocyclic secondary bromide and the absence of any potentially destructive transannular reactions involving newly installed functionality with that bromine group.

Scheme 2. Proposed expansions of the developed ring-expansion approach to substrates containing additional fused ring systems as well as enynes to fashion desepilaurallene (**5**) and microcladallene A (**7**), starting from a common intermediate.



In the case of the microcladallenes (**7** and **8**), our goal was to convert the lactone ring of **20** and its PMB-protected alcohol into the 6-membered endocyclic bromoether and enyne domains of **23**, respectively. Of particular note for this design, we anticipated that the 6-membered bromoether ring system could not likely be constructed through a direct, bromonium-induced 6-*endo*-trig cyclization of an alcohol onto a 1,2-disubstituted alkene given that 5-*exo*-trig cyclizations dominate as documented both in several total syntheses as well as

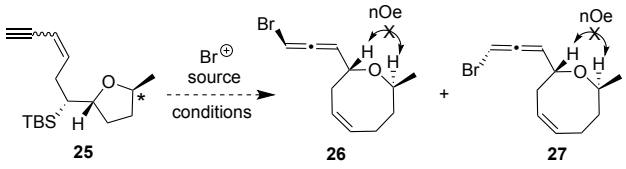
our own endeavors;[30a-i] only with an aromatic group present as part of the chain does this chemistry succeed smoothly.[30j-l] Although we would still attempt such a construction here, to see if the pre-installed THF ring of the precursor could effect some control in this case, alternate approaches would also be sought. But, of note, for the key cyclization we would be able to test the ability of an ether oxygen to engage a bromonium-activated enyne. To the best of our knowledge, despite extensive efforts exploring racemic and asymmetric variants of the process using both alcohol and carboxylic acid nucleophiles,[31] particularly by the Tang group,[32] use of an internal ether oxygen for such purposes has yet to be described. If successful, then microcladallene A (**7**) would hopefully result, with the use of precursors of different oxidation state leading to microcladallene B (**8**).

2. Model Studies for Ring-Openings with Enynes

Given the plans outlined above, its critical element, and one of equal significance from a biosynthetic perspective, was the ability and relative ease in effecting the ring expansion process leading to 8-membered rings with appended ring systems. And, for the case of the microcladallenes, that process rested on the ability to do so with the ether oxygen of the tetrahydrofuran ring by engaging a remote, bromonium-activated enyne. Thus, to set an initial framework of outcomes from both a viability and stereoselectivity perspective, particularly for the latter concern, we elected to pursue model studies using tetrahydrofurans of type **25** (with both *E*- and *Z*-disposed alkenes as part of their enyne units) but lacking the extra, appended ring system of the final molecular targets.

As shown in Table 1, using the *E*-version of **25** for most of our initial studies, addition of NBS, either with or without DABCO in $MeNO_2$,[32a] afforded no observable formation of either ring-expanded products **26** or **27** (entries 1 and 2). By contrast, upon switching the bromenium source to $Br(coll)_2PF_6$[33] and cooling the reaction temperature to –25 °C, both adducts were formed in modest yield at partial conver sion, but in a non-selective (1:1) manner (entry 3); such results suggested the importance of using a more cationic (i.e. reactive) bromenium source. To our delight, when we deployed our bromenium source (BDSB) under similar conditions, some product control was observed, albeit in similar yields but with additional decomposition products also detected (entry 4). Pleasingly, if the same reaction with BDSB was performed in $EtNO_2$ instead, enabling the temperature to be lowered to –78 °C given the freezing point of $MeNO_2$, the yield improved to ~60%, with **26** and **27** being formed in an alkene-specific *dr* of 1.9:1 (entries 5 and 6).[34] The stereochemical assignments of these two product molecules in terms of their oxocane core are based largely on nOe analysis, as we were unable to obtain crystals suitable for X-ray diffraction analysis; the bromoallene configuration was initially assigned based on transition state analysis (and later confirmed by our total synthesis of the microcladallenes, *vide infra*).

Table 1. Screening of conditions to achieve bromoallene-containing 8-membered rings.



25 **26** **27**

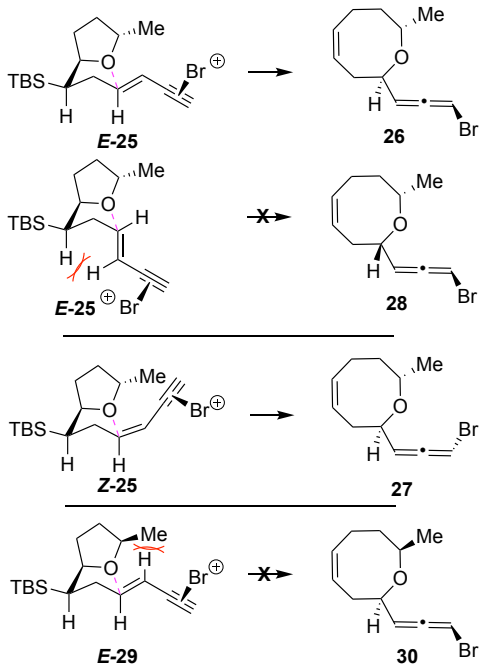
Entry	Substrate and Br^+ source	Solvent	Temp. (°C)	Yield (%)	**26**:**27**
1	*E*-**25**, NBS (1.0 equiv)	$MeNO_2$	23	0	-
2	*E*-**25**, NBS (1.0 equiv), DABCO	$MeNO_2$	23	0	-
3	*E*-**25**, $Br(Coll)_2PF_6$ (1.2 equiv)	$MeNO_2$	-25	32[a]	1.0 : 1.0
4	*E*-**25**, BDSB (0.8 equiv)	$MeNO_2$	-25	30[b]	2.7 : 1.0
5	*E*-**25**, BDSB (0.8 equiv)	$EtNO_2$	-78	61	1.9 : 1.0
6	*Z*-**25**, BDSB (0.8 equiv)	$EtNO_2$	-78	60	1.0 : 1.9

[a] Conversion was ~40% with a yield b.r.s.m. being 80%, [b] large amount of side-products observed

Indeed, as shown in Scheme 3, transition state analysis, considering the alkene geometry of the enyne coupled with the configuration of the substituents on the THF ring, may provide the means to understand the observed outcomes for the key ring-expansion process. In our proposed model, the C–Si bond and the C–O bond is likely to adopt an anti-periplanar arrangement typical of the β-silicon effect so the electrons in the C–Si bond can hyperconjugate with the C–O anti-bonding orbital;[2b,35] such an arrangement would increase the nucleophilicity of the oxygen atom and facilitate a *trans*-arrangement to deliver the observed *cis*-alkene from the ring expansion process. Further, the exocyclic side-chain alkene within *E*-**25** could exist in two different possible orientations, with the initial drawing likely being preferred on steric grounds based on the indicated interaction in the second. These features would account for the formation of the *trans*-based stereocenters in the oxocane ring of **26** instead of the *cis*-substituted ring of **28**. Similar analysis of *Z*-**25**, showing here just the productive transition state, can rationalize the observed formation of **27** as the major product. In both cases, the bromenium addition should be favored to occur from the indicated side, away from the tetrahydrofuran-containing ring; our relative assignments of the allene units within **26** and **27** are based on such suppositions. If bromenium addition occurred on the other side of the alkyne within these transition states, then that could account for the observation of **27** as the minor product with *E*-**25** and **26** as the minor product with *Z*-**25**.

More generally, we surmise that the more rapid reaction at lower temperature afforded by BDSB, also considering the reagent's relatively large size, might afford better control in such additions given that the alkyne is relatively remote to the rest of the structure of the starting material; that difference might explain how better allene stereoselectivity was observed as compared to the reaction with $Br(coll)_2PF_6$. Finally, the configuration of the substituents on the core tetrahydrofuran ring are also critical to the outcome of the process. For instance, an effort using **29** with an *E*-alkene within the enyne and a *cis*-disposition of that sidechain with the neighboring THF methyl group failed to afford *cis*-oxocane **30**; we postulate that no productive transition state could be obtained due to the indicated steric clash, thereby leading to decomposition pathways instead. If the developed ring expansion process was of biological relevance, this result could potentially explain why the *cis*-oxocane isomers of microcladallenes A and B have not yet been observed in Nature.

Scheme 3. Proposed transition state analysis to account for observed ring expansion results with model enyne substrates.

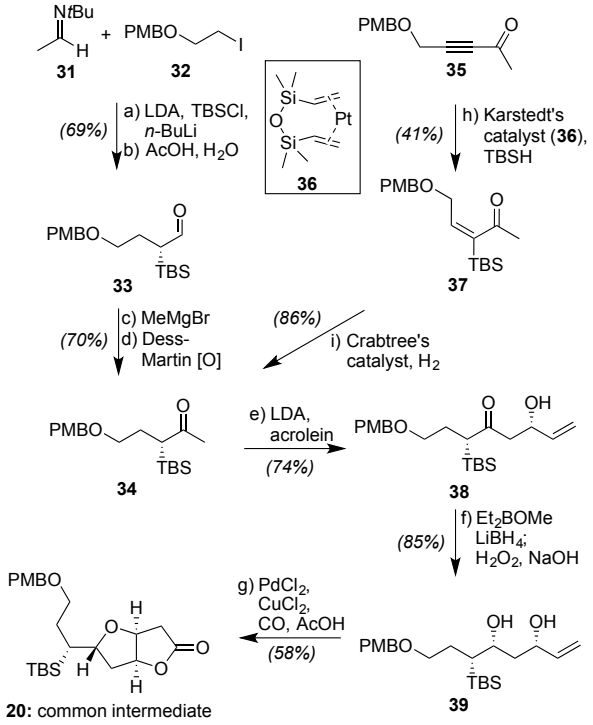


Critically, though, these initial studies highlighted that with the right bromenium source under appropriate conditions, enyne systems can be activated and engaged with a tetrahydrofuran oxygen atom. Such operations can then be terminated by a TBS-mediated alkene formation to generate the *trans*-fused 8-membered oxocane ring systems pertinent to many members of the class. In addition, despite not having any appended ring systems and the enyne motif being remote to the core tetrahydrofuran, the use of BDSB did allow for some selectivity in bromoallene formation in a manner dependent upon the initial configuration of the alkene in the enyne unit. Thus, with these studies completed, the stage was set to explore the facility and stereoselectivity of similar operations with appended ring systems to see if there would be any impact on the outcome. Such results, we hoped, could shed light on the potential biosynthetic order of ring construction within the class as well as the potential of such a ring-expansion being part of that process.

3. Racemic Total Syntheses of Microcladallenes A and B

Our target-based efforts began with the microcladallenes (**7** and **8**), starting with the preparation of common intermediate **20** (Scheme 4). The first critical operation was the synthesis of ketone **34**. a material we hoped could be elaborated readily to the final intermediate in a few further steps. In total, we developed two different racemic routes to this material. The first deployed a nucleophilic addition/oxidation approach with aldehyde **33**, formed by silylating and alkylating imine **31** with TBSCl and alkyl iodide **32**.[36] The second used Karstedt's catalyst (**36**)[37] to effect the addition of a silane across the alkyne of **35**,[38] followed by alkene reduction as modulated by Crabtree's catalyst. While the latter approach was half as long in terms of step count, the first route proved far more suitable to scale-up and, as a result, was used to generate all material supplies in our initial studies.

Scheme 4. Racemic synthesis of common intermediate **20**.[a]



[a] Reagents and conditions: (a) LDA (1.05 equiv), THF, 0 °C, 30 min; TBSCl (0.99 equiv), *n*-Bu_4I (0.02 equiv), 25 °C, 4 h; *n*-BuLi (1.05 equiv), 0 °C, 30 min; **32** (1.5 equiv), 25 °C, 12 h; (b) 1 M AcOH, CH_2Cl_2, 25 °C, 1 h, 69% over 2 steps; (c) MeMgBr (2.2 equiv), THF, -78 °C, 30 min, 85%; (d) Dess-Martin periodinane (1.05 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 25 °C, 2 h, 82%; (e) LDA (1.5 equiv), THF, -78 °C, 30 min; acrolein (1.6 equiv), -78 °C, 30 min, 74%, d.r. ~5:1; (f) Et_2BOMe (1.2 equiv), THF, -78 °C, 30 min; $LiBH_4$ (15.0 equiv), -78 to 25 °C, 4 h; NaOH (2.5 equiv), H_2O_2 (26 equiv), 0 °C, 1 h, 85%; (g) $PdCl_2$ (0.4 equiv), $CuCl_2$ (3.0 equiv), NaOAc (5.0 equiv), CO (balloon), AcOH, 25 °C, 12 h, 58%; (h) Karstedt's catalyst **36** (0.05 equiv), TBSH (1.5 equiv), CH_2Cl_2, 25 °C, 12 h, 41%; (i) Crabtree's catalyst (0.05 equiv), H_2 (balloon), CH_2Cl_2, 25 C, 12 h, 86%.

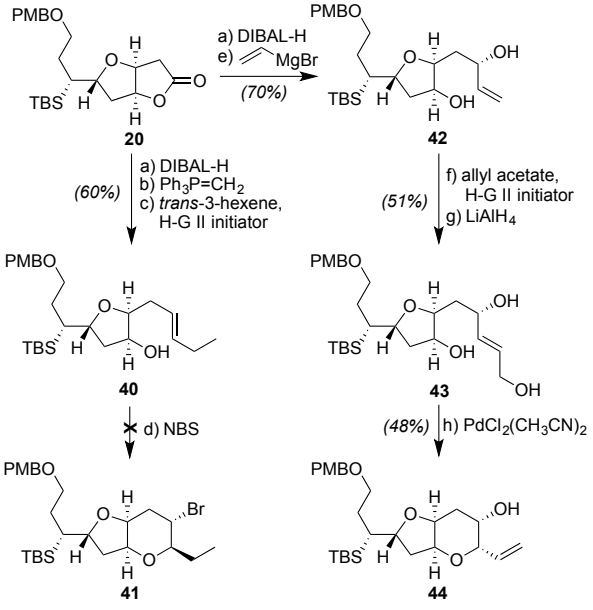
Thus, pressing forward, treatment of ketone **34** with LDA set the stage for an aldol reaction with acrolein, an operation which afforded the β-hydroxy ketone domain of **38** as a 5:1 mixture of inseparable diastereomers favoring the drawn, desired adduct. Next, a Narasaka–Prasad reduction (Et_2BOMe, $LiBH_4$) effected its smooth conversion into the desired 1,3-*cis*-diol product **39** in 85% yield.[39] That final material was contaminated by a few additional and inseparable isomers which could be removed in the subsequent step. Of note, several other non-chelating hydride sources were also examined for their ability to effect this reduction [such as $LiAl(O\textit{t}\text{-}Bu)_3H$ and L-Selectride] in hopes of their executing similar control under a Felkin–Ahn model of stereoselection; none delivered a higher yield of product. Finally, with all stereocenters and critical functionality in place, the final goal was to effect a metal-mediated cyclocarbonylation reaction to sew up the two ring systems in the form of bicyclic lactone **20**. Following some modest condition screening,[31d,40] we observed that the combination of $PdCl_2$ and $CuCl_2$ in the presence of a CO atmosphere in AcOH could convert diol **39** smoothly into common intermediate **20** in 58% yield.

The task now was to construct the 6-membered bromoether ring system of the microcladallenes from the lactone ring of **20**. The first effort was a high-risk attempt, as noted earlier, to achieve a potentially biomimetic 6-*endo*-trig bromoetherifica-

tion from a ring-opened alcohol/alkene-containing substrate. We felt such a test was worthwhile since its success would afford a highly concise solution and the test substrate was expected to be easily accessed. As shown in Scheme 5, that ring-closure precursor (i.e. **40**) could be prepared in just three steps: DIBAL-H reduction to the lactol, Wittig olefination with the ring-opened aldehyde, and a cross metathesis with *trans*-3-hexene using the Hoveyda–Grubbs second generation initiator.[41] As originally feared, subsequent efforts to induce that 6-*endo*-trig bromoetherification with a variety of bromenium sources, shown here with NBS, failed to deliver **41**. Instead, complex mixtures were observed without any of the critical signals characteristic of the desired framework as we had observed in other, successful contexts. As such, an alternate construction was pursued next by forging the tetrahydropyran ring through a Tsuji–Trost-type reaction. Indeed, the requisite substrate was also readily prepared by a three-step opening sequence followed by a final acetate cleavage using $LiAlH_4$.[42] Upon exposure of the resultant product (i.e. **43**) to $PdCl_2(CH_3CN)_2$,[43] the desired tetrahydropyran ring was indeed formed in 48% yield, but unfortunately the configuration of the vinyl side-chain was opposite that desired (based on nOe).

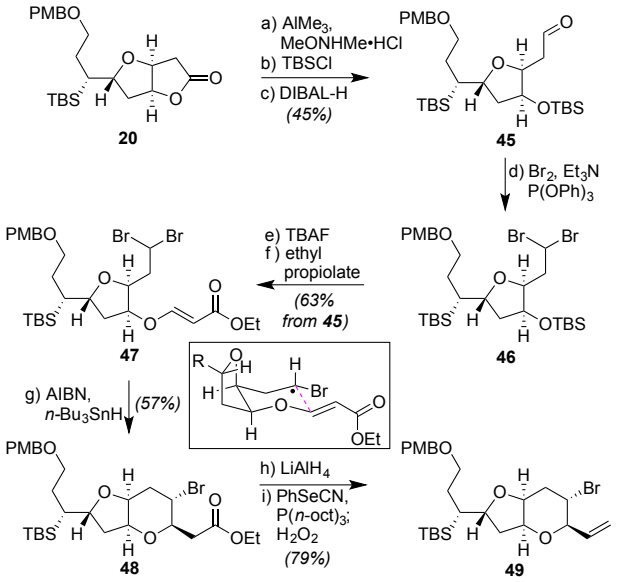
Thus, as shown in Scheme 6, a more efficacious solution was ultimately identified where the bromine atom of the final ring system could be installed directly via a radical-based ring closure. Here, following an initial 3-step manipulation of functional groups to arrive at protected aldehyde **45**,[44] subsequent treatment with Br_2 in the presence of Et_3N and $P(OPh)_3$, a procedure developed by Prati,[45] afforded the gem-dibromide of **46**. Subsequent silyl ether cleavage and oxygen addition onto ethyl propiolate then afforded the vinylogous ester of **47**, poised for a radical-based ring closure as inspired by Lee.[46] Pleasingly, upon its exposure to AIBN in the presence of *n*-Bu_3SnH in benzene at 80 °C, the desired closure to

Scheme 5. Initial failures to generate the brominated tetrahydropyran ring of the microcladallenes.[a]



[a] Reagents and conditions: (a) DIBAL-H (1.1 equiv), CH_2Cl_2, -78 °C, 15 min, 79%; (b) *t*-BuOK (3.1 equiv), Ph_3PCH_3Br (3.0 equiv), THF, 0 °C, 6 h, 85%; (c) H-G II initiator (0.05 equiv), *trans*-3-hexene (8.0 equiv), CH_2Cl_2, 25 °C, 3 h, 90%; (d) NBS (1.2 equiv), CH_2Cl_2, 0 °C, 2 h; (e) vinylmagnesium bromide (10 equiv), toluene, 25 °C, 2 h, 88%; (f) H-G II initiator (0.1 equiv), allyl acetate, 25 °C, 4 h, 54%; (g) $LiAlH_4$ (1.0 equiv), THF, 25 °C, 94%; (h) $PdCl_2(CH_3CN)_2$ (0.05 equiv), THF, 0 °C, 3 h, 48%.

Scheme 6. Synthesis of the core brominated tetrahydropyran from common intermediate **20**.[a]



[a] Reagents and conditions: (a) $AlMe_3$ (2.5 equiv), MeONHMe•HCl (5.0 equiv), THF, 0 to 25 °C, 3 h; (b) TBSCl (2.0 equiv), imidazole (6.0 equiv), DMF, 25 °C, 12 h, 57% over 2 steps; (c) DIBAL-H (1.1 equiv), CH_2Cl_2, -78 °C, 15 min, 79%; (d) Br_2 (1.7 equiv), $P(OPh)_3$ (2.0 equiv), Et_3N (3.0 equiv), CH_2Cl_2, -78 to 25 °C, 12 h; (e) TBAF (6.2 equiv), THF, 0 to 25 °C, 2 h; (f) NMM (5.0 equiv), ethyl propiolate (5.0 equiv), CH_2Cl_2, 25 °C, 4 h, 63% over 3 steps; (g) *n*-Bu_3SnH (1.2 equiv), AIBN (0.5 equiv), benzene, 90 °C, 1 h, 57%; (h) $LiAlH_4$ (1.1 equiv), THF, -78 °C, 30 min, 82%; (i) P(*n*-Oct)$_3$ (10 equiv), PhSeCN (5.0 equiv), H_2O_2 (21 equiv), THF, 0 to 25 °C, 12 h, 96%.

48 occurred in 57% yield, affording only a single stereoisomer. We presume that the preference in adopting a chair-like transition state for this event, as shown by the inset boxed structure within Scheme 6, accounts for the observed stereoselectivity; Lee and co-workers had previously observed similar stereoselection in their related systems.[46] From here, a two-step process involving reduction and dehydration converted the exocyclic ester into the vinyl group of microcladallane B in 79% overall yield.

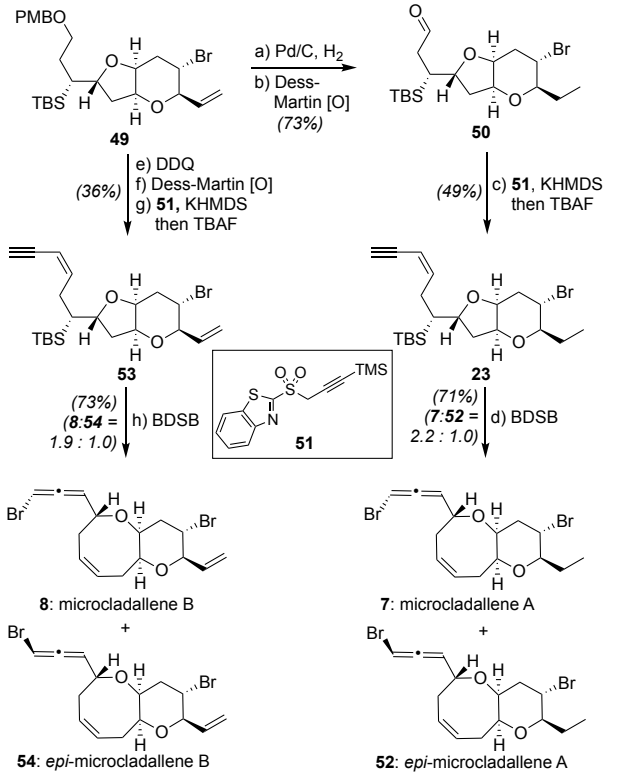
With both rings in place, the stage was now set to commence the final set of operations leading to the key bromenium-induced ring expansion. As indicated in Scheme 7, those operations began by converting the PMB-protected alcohol into the *Z*-enyne of **53** through a three-step procedure. Those transformations, a DDQ-mediated deprotection, Dess–Martin periodinane-mediated oxidation, and Julia–Kocienski olefination using the anion derived from **51**,[47] proceeded smoothly in 36% overall yield. With the requisite atoms in place, enyne **53** was then treated with 1.0 equivalent of BDSB in $EtNO_2$ at –78 °C. After 30 min of reaction time, we observed the formation of both microcladallene B (**8**) as well as its epimer, compound **54**, in a 1.9:1 ratio and a combined 73% yield. Significantly, the enyne could be chemoselectively activated in this event in preference to the vinyl group to forge the expected *trans*-oxocane ring, with the ultimate stereoselectivity of the allene observed matching that observed from our initial model systems. Similar operations converting **49** into enyne **23** set the stage for a similar ring expansion with a compound now lacking a vinyl group, leading here to a 2.2:1 mixture of microcladellene A (**7**) as well as its epimer which contained some inseparable grease-based impurity. Again, that outcome nearly matched that observed in our earlier model studies. As such, these two key ring expansions suggest that the additional

6-*endo*-bromoether ring system and its additional stereogenic center as expressed in **53** and **23** played little or no role in determining the stereochemical outcome of the core cyclization step. Thus, if Nature were to use a similar ring-expansion as part of her synthesis sequence (noting of course that she would not use a TBS-group to terminate the sequence), these findings would suggest that the 6-membered bromoether ring need not be fashioned initially if high stereocontrol is the aim of her synthetic approach; of course, enzymatic control in such a process might be higher than that achieved simply through inherent substrate preference.[6a,48] Overall, these operations completed 20-step total syntheses of these two targets, respectively. Such lengths are comparable to those developed by the Kim group in the only other synthesis of these targets,[26] although executed here through an entirely distinct strategy.

4. Racemic Total Synthesis of Desepilaurallene, Laurallene and Prelaureatin

With racemic routes to the microcladallenes completed, we next turned our attention to efforts to convert key intermediate **20** into despilaurallene (**5**), laurallene (**6**), and prelaureatin (**4**). Here, it would be the initial lactone, not a 6-membered bromoether, which would be attached to the core tetrahydrofuran system used in the ring expansion leading to the 8-membered rings of the targets. In addition, an alkene, not an enyne, would have to be activated by the bromenium source.

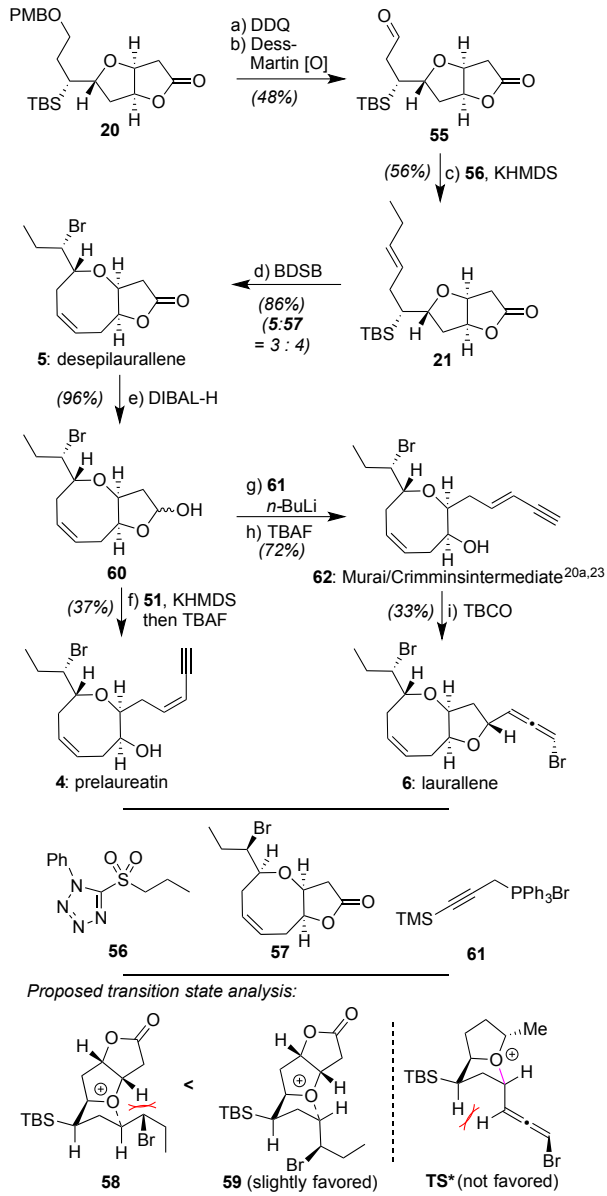
Scheme 7. Total syntheses of microcladallenes A and B (**7** and **8**).[a]



[a] Reagents and conditions: (a) Pd/C (3.0 equiv), H_2 (balloon), EtOAc, 25 °C, 6 h; (b) Dess-Martin periodinane (1.1 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 25 °C, 1 h, 73% over 2 steps; (c) **51** (3.0 equiv), KHMDS (2.5 equiv), THF, -20 to 0 °C, 1 h; TBAF (3.0 equiv), 0 °C, 10 min, 49%; (d) BDSB (1.0 equiv), $EtNO_2$, -78 °C, 30 min, 49% **7**, 22% **52**; (e) DDQ (1.5 equiv), CH_2Cl_2/H_2O (10/1 v/v), 25 °C, 1 h; (f) Dess-Martin periodinane (1.1 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 25 °C, 1 h, 83% over 2 steps; (g) **51** (3.0 equiv), KHMDS (2.5 equiv), THF, -20 to 0 °C, 1 h; TBAF (3.0 equiv), 0 °C, 10 min, 43%; (h) BDSB (1.0 equiv), $EtNO_2$, -78 °C, 30 min, 48% **8**, 25% **54**.

As shown in Scheme 8, it proved quite easy to advance compound **20** into the key BDSB-based precursor (i.e. **21**) designed to fashion desepilaurallene (**5**). Those operations included a similar PMB-based deprotection and oxidation sequence as above, followed now with a Julia–Kocienski olefination using the anion derived from sulfone **56**.[49] These steps proceeded in 27% overall yield from **20**. Then, following exposure of this material to 0.8 equivalents of BDSB in toluene at –20 °C for 30 min, we observed a 3:4 mixture of desepilaurallene (**5**) and what we have assigned as its exocyclic bromine diastereomer **57**. They were obtained collectively in 86% yield, noting that this numerical outcome includes

Scheme 8. Total syntheses of desepilaurallene (**5**), prelaureatin (**4**), and laurallene (**6**).[a]



[a] Reagents and conditions: (a) DDQ (1.5 equiv), CH_2Cl_2/H_2O (10:1 v/v), 25 °C, 1 h; (b) Dess-Martin periodinane (1.1 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 25 °C, 1 h, 48% over 2 steps; (c) **56** (3.0 equiv), KHMDS (2.7 equiv), DME, -78 °C, 30 min, 56%; (d) BDSB (0.8 equiv), toluene, -20 °C, 1 h, 86% **5**:**57** = 3:4; (e) DIBAL-H (1.05 equiv), CH_2Cl_2, -78 °C, 15 min, 96%; (f) **51** (5.0 equiv), KHMDS (4.5 equiv), THF, -20 to 0 °C, 6 h; TBAF (5.0 equiv), THF, 0 °C, 10 min, 37%; (g) **58** (3.0 equiv), *n*-BuLi (2.7 equiv), THF, 0 °C, 2 h, 84%; (h) TBAF (1.1 equiv), THF, 0 °C, 10 min, 86%; (i) TBCO (1.3 equiv), CH_2Cl_2, 25 °C, 12 h, 33%.

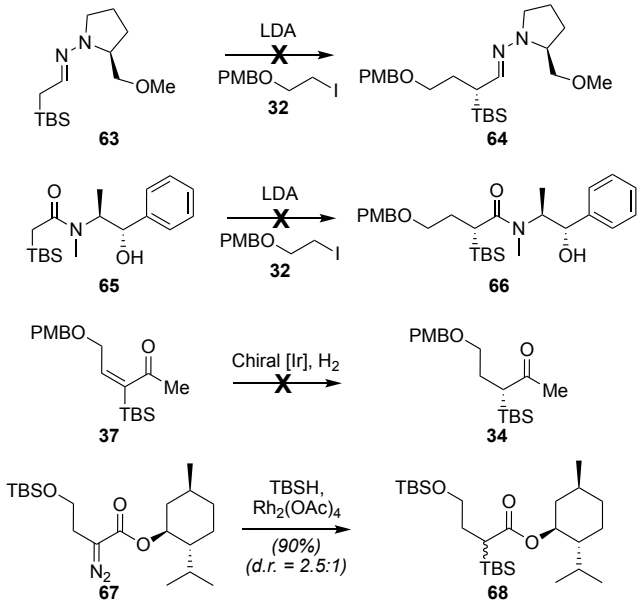
some additional trace impurities that could not be removed; their isolation and characterization required a reduction/reoxidation sequence (see SI for details) as they could not be separated directly. Of note for this cyclization, increasing the amount of BDSB led to inferior results. More interestingly, solvent effects played a key role in the outcome. Although the reaction proceeded in hexane, $MeNO_2$, $EtNO_2$, and CH_2Cl_2, toluene gave the best yield and selectivity for the desired product while CH_2Cl_2 gave the undesired isomer exclusively. To date, this particular tetrahydrofuran-induced ring expansion process reflects one of the least selective cyclizations observed, though it is in line with some of our previously published studies using silanes to terminate the process; it would thus seem that the presence of the lactone ring system had no effect on the cyclization.[16] As shown by the two proposed transition states, **58** and **59**, structures meant to capture bromonium opening (i.e. greater sp^3 character as opposed to the initial alkene of the starting material), there is potentially a minor destabilizing steric interaction as noted within **58** relative to **59** to forge **5** in enhanced amounts; the overall impact, though, is modest since a near equal (3:4) mixture of products was formed. We believe that greater sp^3 character of their brominated carbons might explain the erosion of stereoselectivity versus our earlier explored enyne-containing molecules, reflected here with a drawing of transition state **TS*** (also see *E*-**25** in Scheme 3) which would contain a strong 1,4-interaction that would impede effective formation of the oxonium intermediate due to the sp^2-hybridization of the bromoallene carbon.

In any event, we viewed the overall throughput as acceptable, and effectively non-alterable, with three bonds cleaved and three bonds forged in the process. From **5**, prelaureatin (**4**) could be obtained in two further steps involving partial reduction of the lactone to the lactol as mediated by DIBAL-H, followed by a Julia-Kocienski olefination with **51** and silyl cleavage to unveil the enyne of the target.[47] These two steps proceeded in 37% overall yield. Similarly, **60** could be converted into **62**, using Wittig reagent **61** instead of **51** to effect *E*-selectivity in its enyne formation.[50] A final TBCO-induced cyclization, as developed originally by Murai[23] and Crimmins,[20a] completed the target molecule (**6**) in 66% yield. This natural product was formed as a 1:1 mixture with another, unassigned diastereomer (undrawn). Of note, we tested BDSB in this terminal cyclization, but it was not successful. Overall, these efforts in the context of Scheme 8 completed 3 additional targets from our common intermediate (lactone **20**) in 11, 13, and 15 steps in their longest linear sequences, respectively. Given that these materials have a core distinct from that of the microcladallenes, these endeavors show the value of common building block analysis[10,27,28] in reaching complex, structural diversity. They also further highlight the power of the tetrahydrofuran-based ring expansion process, one that succeeds in the presence of an array of functional groups and appended ring systems.

5. Asymmetric Synthesis of Key Common Lactone

Finally, with racemic syntheses achieved, we next sought to develop an enantioselective synthesis of our key intermediate **20** to afford a formal, asymmetric solution to all 5 of the targets prepared. However, as indicated in Scheme 9, such a process proved far from trivial to execute. Our initial endeavors sought to identify the means to prepare the lone silicon-based stereogenic center of **34** with enantiocontrol. Unfortunately, all attempts to do so were unsuccessful. For example, use of the Enders' hydrazone derivative **63** failed to add alkyl iodide **32** successfully, despite other published examples with different electrophiles affording enantioselective alkylations.[51] Similar efforts using the Myers' pseudoephedrine amide auxiliary or Evans' oxazolidone auxiliary (not shown) with an attached TBS group (as in **65**) failed as well.[52] These results might be due to low nucleophilicity of the substrates and/or the observed instability of the α-TBS group to basic conditions. Similarly, efforts at either asymmetric hydrogenation under a variety of homogenous conditions[53] as well as efforts to effect a Rh-catalyzed Si–H insertion[54] from diazo ketone precursor **67** also were unsatisfactory. Indeed, in the former case only decomposition or no reaction was observed, while in the latter the desired adduct was formed as an inseparable mixture of two diastereomers with 2.5:1 dr. Of note, the PMB-protected variant of the **67** could not undergo the desired silylation due to the much faster intramolecular carbene-mediated C–H insertion occurred at the benzylic position. For these reasons, this approach was ultimately abandoned since enantiomerically pure **68** could not be obtained.

Scheme 9. Failed efforts to effect a direct, asymmetric synthesis of **34**.[a]

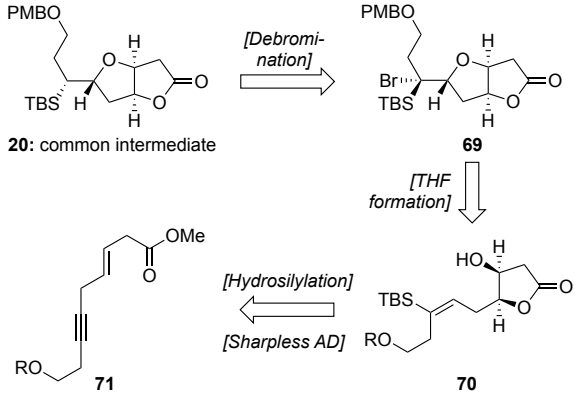


As a result, we pursued a fully distinct synthetic approach for **20** as shown retrosynthetically in Scheme 10 in which the stereogenic centers would be established in a different order. This new design was predicated, in part, on our previous efforts to generate stereogenic C–Si groups during our efforts to accomplish racemic total syntheses of *E*- and *Z*-pinnatifidenyne (**3**, cf. Scheme 1).[16] Here, the overall sequence would hinge on the ability to initially forge key diol configuration from **71**, potentially via a Sharpless asymmetric dihydroxylation, followed by a regioselective hydrosilylation. That process would then be followed by a bromenium-induced ring closure to generate the tetrahydrofuran ring followed by a radical-based process to excise the quaternary bromide atom; the latter event would need to proceed with retention of con-

figuration upon H• recapture to deliver the requisite piece as a single enantiomer.

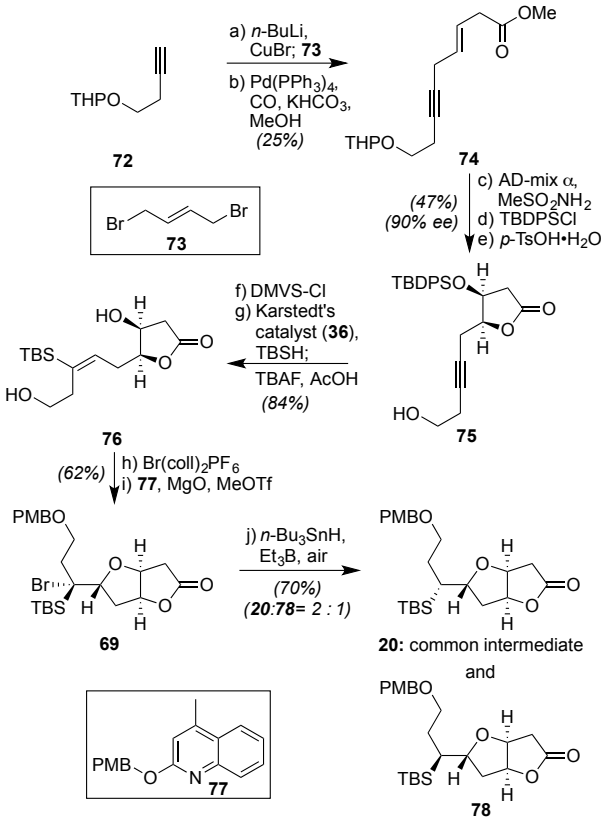
Pleasingly, that overall plan could be reduced to practice. Starting from THP-protected propargyl alcohol (**72**, Scheme 11), this material was readily converted into **74** via an initial alkylation[55] followed by a Pd-catalyzed carboxymethylation.[56] These events collectively proceeded in 25% overall yield with the initial alkylation being the throughput limiting step of the sequence at 33% yield. Next, building on well-established precedent in achieving asymmetric Sharpless dihydroxylations of alkenes within α,β-unsaturated esters,[57] **74** was converted into **75** in 47% overall yield and in 90% *ee*.[58] These operations involved initial dihydroxylation and concomitant lactonization, followed by protection of the lone secondary alcohol as a TBDPS ether and acidic-cleavage of the THP group. At this stage, the newly unveiled alcohol could be deployed, through its combination with dimethylvinylsilyl chloride (DMVS-Cl) and Et_3N, to facilitate a subsequent directed hydrosilylation as developed by Tomooka.[59] This step afforded the desired regiocontrol upon exposure to Karstedt's catalyst (**36**), with an *in situ* TBAF-mediated deprotection of the TBDPS-silyl ether unveiling the free alcohol of **76**. Critical to this final operation was TBAF buffering with AcOH, as otherwise the β-hydroxyl group on the lactone ring had a tendency to eliminate to form an α,β-unsaturated variant.

Scheme 10. Proposed retrosynthetic analysis to achieve an asymmetric synthesis of common intermediate **20**.



With these operations complete, the remaining tasks were to forge the tetrahydrofuran ring system of **20** along with its attendant silicon group as a single stereoisomer. The first operation along these lines, a bromonium-induced cyclization to generate **69**, proceeded smoothly in 62% overall yield using $Br(coll)_2PF_6$ as the halenium source followed by a subsequent PMB protection of the remaining primary alcohol with **77**.[60] Of note, the use of other halogen sources afforded less optimal results both in terms of yield as well as overall stereoselection, with the use of reagent **77** and acidic conditions being critical in the second step as the intermediate bromide was not stable to base. Finally, exposure to *n*-Bu_3SnH under radical conditions as initiated by Et_3B in air afforded a 2:1 separable mixture of **20** and its epimer **78** in 70% overall yield, presumably due to some equilibration of the radical intermediate to its thermodynamically most stable form. Several other attempts with both radical and non-radical conditions failed (*n*-Bu_3SnH/AIBN, TTMS/AIBN, and Raney Nickel). Overall, this operation completed an effective, 10-step asymmetric synthesis of key lactone **20**, thereby establishing formal asymmetric syntheses of all 5 targets presented in this work.

Scheme 11. Asymmetric synthesis of common intermediate **20**.[a]



[a] Reagents and conditions: (a) *n*-BuLi (1.05 equiv), THF, -78 °C, 10 min; CuBr (1.1 equiv), 0 °C, 1 h; **73** (2.5 equiv), 25 °C, 4 h, 33%; (b) $Pd(PPh_3)_4$ (0.05 equiv), $KHCO_3$ (1.1 equiv), CO (75 atm), MeOH, 25 °C, 24 h, 76%; (c) AD-mix-α, $MeSO_2NH_2$ (1.1 equiv), *t*-BuOH/H_2O (1:1 v/v), 0 °C, 36 h; (d) TBDPSCl (2.0 equiv), imidazole (4.0 equiv), CH_2Cl_2, 25 °C, 6 h; (e) TsOH•H_2O (0.1 equiv), MeOH, 25 °C, 3 h, 47% over 3 steps; (f) DMVSCl (1.2 equiv), Et_3N (1.5 equiv), CH_2Cl_2, 0 °C, 30 min, 88%; (g) Karstedt's catalyst (0.02 equiv), TBSH (1.5 equiv), THF, 40 °C, 2 h; AcOH (2.2 equiv), TBAF (2.2 equiv), 25 °C, 3 h, 95%; (h) $Br(coll)_2PF_6$ (1.2 equiv), $MeNO_2$, 0 °C, 30 min; (i) **77** (2.5 equiv), MgO (3.0 equiv), MeOTf (1.1 equiv), $PhCF_3$, 0 °C, 4 h, 62%; (j) *n*-Bu_3SnH (1.5 equiv), Et_3B (0.1 equiv), air, toluene, -78 °C, 30 min, 47% **20**, 23% **78**.

CONCLUSION

Over the past several decades, the unique structures of the *Laurencia* family of natural products has provided a tremendous source of inspiration for the development of novel synthetic strategies and approaches. This article details the culmination of a significant body of studies using tetrahydrofurans to effect ring-expansions leading to 8-membered oxocane rings. Of critical importance here, we show that such tetrahydrofurans can add effectively onto bromonium-activated enynes, that good levels of inherent stereocontrol in such additions can be achieved in the absence of additional rings and stereocenters for a number of targets, and that, at present, 7 natural products (which includes our previously published work)[16] and an array of model systems can result with good to excellent selectivity through the general process. In total as shown here, 5 of those natural products can arise from a single intermediate, with those materials encompassing two distinct 8-membered ring collections. As such, we believe that the

core ring-expansion process delineated here for 8-membered ring synthesis has biosynthetic relevance, with Nature using tetrahydrofuran rings as a prelude to her preparation of 8-membered, polycyclic materials. Outside of this core reaction, we have also demonstrated a number of chemoselective processes on advanced frameworks, and hope, in further work, to utilize the synthesized materials for more thorough biochemical evaluations of the class.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, copies of all spectral data and full characterization. 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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