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Letter

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Strategies for the Total Synthesis of Diverse Bromo-Chamigrenes

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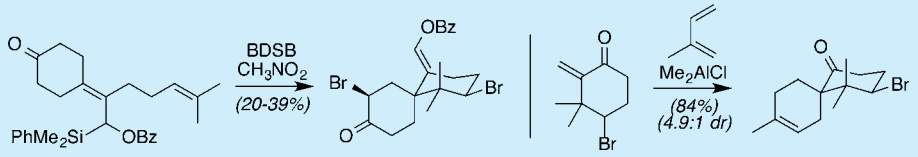
Supporting Information



ABSTRACT: Several dozen spirocyclic sesquiterpenoids known as the bromo-chamigrenes have been isolated to date. Yet, despite their unique structures, synthetic efforts toward this collection have been modest. Herein, we outline two strategies to generate their skeletons based on (1) a biomimetic bromonium-induced polyene cyclization using BDSB ($Et_2SBr{\cdot}SbCl_5Br$) and (2) a Diels–Alder reaction which ultimately delivered four members of the class. In addition, X-ray crystallography reveals that one member has a structure in need of revision.

Nature produces an array of halogenated natural products, with one particularly extensive class being the sesquiterpenes known as the bromo-chamigrenes.[1] Selected members of this family, a collection which numbers over 50, are shown in Scheme 1 in 3-D form reflecting their absolute configuration. Of note, certain subsets, such as the dactylones (**3**[2] and **4**[3]) and **5**,[2] are oxidized versions of the core bromo-chamigrene framework as represented by **1**[4,5b] and **2**,[5] while others, such as elatol (**6**),[6] incorporate additional halogens or, like aplydactone (**7**),[7] appear to be the result of further modifications. Significantly, this family has broad biological properties.[8,9]

Despite these attractive features, synthetic efforts toward this collection have been relatively limited. The inaugural synthesis of any member was achieved by Wolinsky and Faulkner through a biomimetic bromonium-induced cyclization;[10] this event afforded **9** in modest yield from ketone **8**, with three further steps rearranging the initial framework into **2**. Later, the Kato group accomplished a similar synthesis of **2** from a related starting material in better yield,[11] while Martin and co-workers achieved an asymmetric synthesis of several more highly oxidized members (i.e., **11** and **12**) using a different polyene precursor,[12] though again with a low yielding key cyclization step. More recent efforts have generally avoided biomimicry, with an effort by Stoltz, Grubbs, and co-workers achieving a catalytic asymmetric synthesis of elatol (**6**) using a palladium-catalyzed asymmetric decarboxylative allylation and metathesis to fashion key ring elements,[13] and a recent endeavor by the Trauner group generating racemic aplydactone (**7**).[14] Finally, the Burns group disclosed the first enantioselective route to aplydactone (**7**) and an array of other bromo-chamigrenes.[15] That effort employed an asymmetric bromochlorination reaction developed in their laboratory[16] to effectively generate a chiral bromine-containing intermediate for use in a Diels–Alder process reminiscent of past efforts that have generated the core chamigrene framework (shown here in the formation and conversion of **15** into **16**);[17] of particular note, they established that dactylone (**4**) could be transformed into aplydactone (**7**) through a [2 + 2]-reaction.[18]

In this letter, we disclose our efforts toward this same collection of natural products, studies which have explored the merits of both biomimetic polyene cyclizations as well as Diels–Alder reactions to generate the bromo-chamigrene framework. These efforts have culminated in an effective polyene cyclization process to generate the desired spirocyclic core, racemic syntheses of natural products **1**, **3**, and **4**, the determination that a structural revision of natural product **5** is necessary, and a formal total synthesis of aplydactone (**7**). Critically, though parts of our independently developed design mirror the Burns synthesis of several targets, we disclose here a number of complementary findings that shed information on certain steps.

Our interest in the chamigrenes has been longstanding, and grew principally out of the unique structure of aplydactone (**7**) with its two fused cyclobutane rings as well as our general interest in effecting bromonium-induced polyene cyclizations through the development of new halonium sources. In the latter regard, in 2009 we identified a reagent, BDSB ($Et_2SBr{\cdot}SbCl_5Br$),[19] which has proven to be a particularly competent source of bromonium ion that has cyclized a diverse array of polyenes and other substrates,[20] effected regioselective electrophilic aromatic substitutions,[21] and served as a design model for effective iodonium[20a,f,22] and chloronium[20a,23] sources. Given the results shown in Scheme 1, we wondered whether BDSB could afford superior results with related starting materials. Our initial screens sought to utilize materials similar to those proposed to be Nature's starting materials (i.e., **17** and **18**, Scheme 2). Although we never registered any positive results with these frameworks, we did

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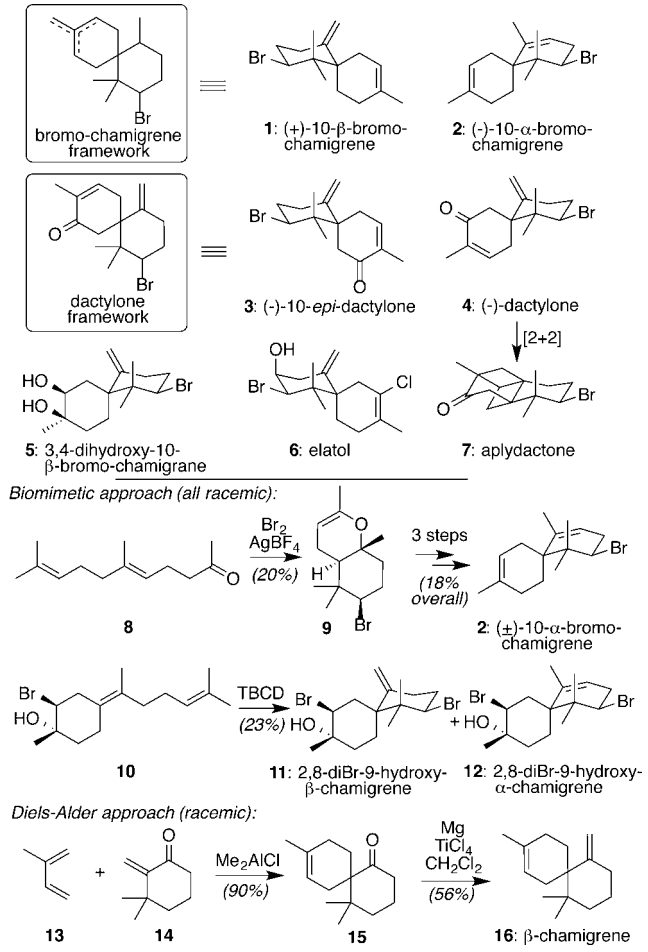
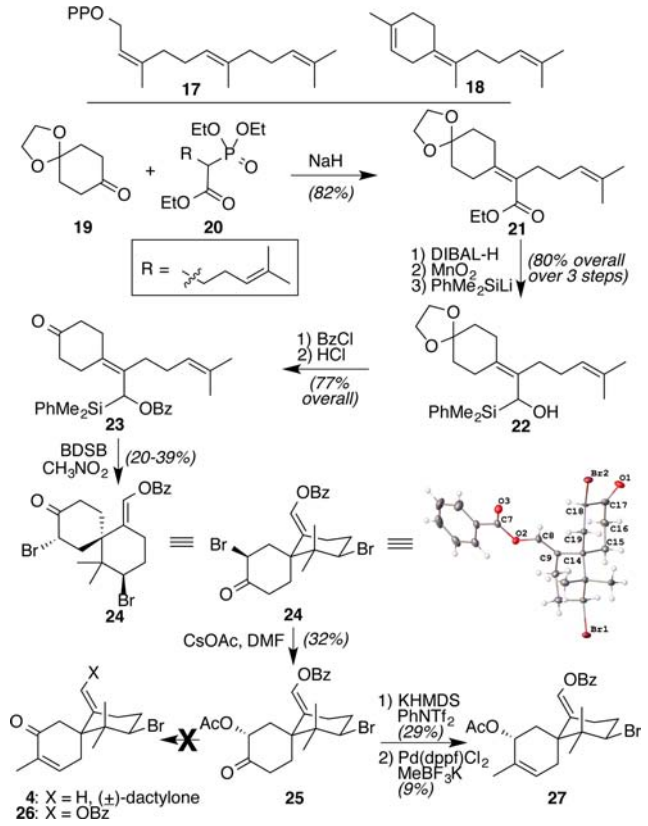
Scheme 1. Chamigrene Family of Natural Products and Selected Approaches To Generate Their Spirocyclic Frameworks



identify one potentially superior solution with an oxidized variant of **18** (i.e., **23**). This material was designed with an emphasis on two key aspects: (1) attempting to ensure initial bromonium addition at the terminal, and arguably less electron-rich olefin, by modulating the sterics and electronics around the internal tetrasubstituted alkene and (2) sufficiently stabilizing the resultant intermediate carbocation via the β-silicon effect[24] to afford the desired product ring size and only an exocyclic alkene. As shown in Scheme 2, that compound was prepared in just five transformations following Horner–Wadsworth–Emmons coupling of **19** and phosphonate **20**.[25]

In the key event, stirring of **23** with 2.0 equiv of BDSB in CH_3NO_2 for 15 min at 23 °C afforded spirocycle **24** in a reproducible range of 20–39% yield (largely scale dependent) with 6:1 dr in which not only the desired bromonium-induced cyclization occurred but also a regio- and stereoselective α-bromination of the ketone resulted; that outcome was verified by X-ray. Use of less than 2.0 equiv of BDSB in some of our initial studies (with **24** and some differentially protected analogs) generally afforded incomplete conversion, lower yields, and inseparable mixtures of cyclized mono- and dibrominated products, noting that other halogen sources were ineffective in promoting this same step in terms of specifically generating **24**.[26] Of particular significance, the reaction failed if the oxygen substituent on the same carbon as the key silicon functionality was absent (with the tetrasubstituted alkene appearing to react first

Scheme 2. Successful Execution of a Bromonium-Induced Polyene Cyclization To Generate a Functionalized Chamigrene Core



instead), with many other protecting groups on that oxygen atom affording inferior yields.[27]

From here, efforts to manipulate the framework to that of the dactylones proved challenging. Among the few successes registered, we found that treatment of **24** with 5.0 equiv of CsOAc at 40 °C in DMF effected displacement of one of the bromine atoms to deliver **25** in 32% yield.[28] Significant efforts to convert this material into either dactylone (**4**) or its OBz-containing analog **26** ultimately failed, though we were able to generate, in very low yield, compound **27**, which possesses the global patterning of the desired targets, via regioselective triflation and subsequent Pd-catalyzed methylation.[29]

Given these outcomes, our sense was that despite the successful polyene cyclization developed, one which may have pertinence to other targets, there might exist an easier way to access and finalize an array of bromo-chamigrene frameworks. Thus, we elected to explore the general Diels–Alder approach shown in Scheme 1 (i.e., **15** → **16**) already documented for creating the carbogenic framework of the chamigrenes.[17] Our goal was to utilize an appropriate brominated precursor to determine if any diastereoselectivity in the Diels–Alder process could be achieved to favor one particular spirocyclic form. As shown in Scheme 3, that idea proved relatively easy to test in a racemic sense through the synthesis of compound **29** over six steps from commercial materials (three steps from known bromoketone **28**).[30] Of note, although **29** will homodimerize through a Diels–Alder reaction if left under vacuum for prolonged periods,[15] it can be isolated and characterized. To our delight, its exposure to isoprene in CH_2Cl_2 from −78 °C to −50 °C in the presence of stoichiometric Me_2AlCl (1.2 equiv) afforded the desired Diels–Alder products

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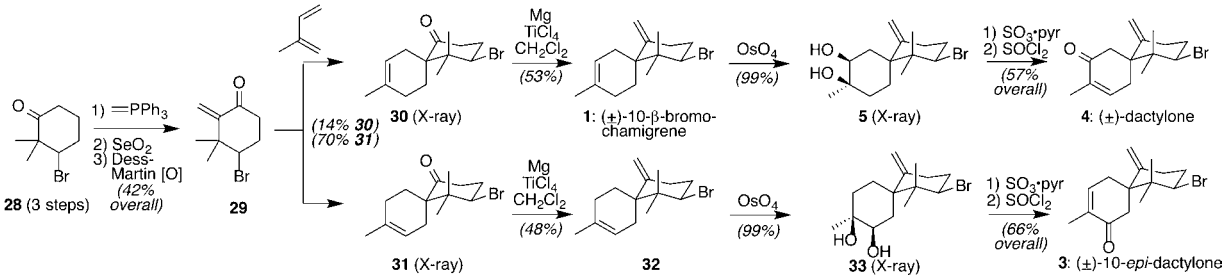
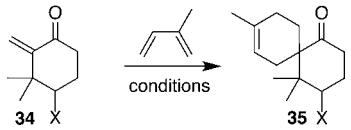
Scheme 3. Diels–Alder Approach to the Chamigrene Family of Natural Products



31 and **30** in a 4.9:1 ratio, with the relative configuration of each established by X-ray crystallographic analysis. This finding mirrors that disclosed by the Burns team.[15] As shown in Table 1, other conditions using related promoters provided variable, but

Table 1. Exploration of the Key Diels–Alder Step



entry	substituent X	Lewis acid promoter	temp (°C)[a]	dr[b]	yield (%)
1	Br	Me_2AlCl	−78 to −50	4.9:1.0	84
2	Br	Me_2AlCl	−78	3.2:1.0	n.d.
3	Br	Me_2AlCl	−30 to 0	1.0:0	60
4	Br	Et_2AlCl	−78	1.8:1.0	n.d.[d]
5	Br	$SnCl_4$	−78	5.9:1.0	n.d.[d]
6	OTBS	Me_2AlCl	−78 to −50	1.4:1.0[c]	89
7	OTBS	Me_2AlCl	−30 to 0	1.0:1.0[c]	66
8	OMe	Me_2AlCl	−78 to −50	1.2:1.0[c]	55
9	OAc	Me_2AlCl	−78 to −50	1.3:1.0[c]	75

[a]For reactions under a single temperature, quench was conducted after maintaining them at this temperature for 4 h. For reactions under a temperature range, see the Supporting Information for full details. [b]d.r. was determined by ^{1}H NMR of the crude product. [c]The specific identity of the two diastereomers was not determined. [d]Isolation was attempted but the product was obtained in impure format.

still reasonable, levels of dr (entries 2–5), with Et_2AlCl and $SnCl_4$ (entries 4 and 5) being unsuitable alternatives for material preparation due to their inferior yields and the presence of several inseparable impurities. Critically, we believe the source of the diastereoselectivity observed consistently with this substrate is related to reaction temperature (entries 1–3) and some interplay between the steric and stereoelectronic effects of the bromine atom. Indeed, exploration of related starting materials possessing oxygen substituents in lieu of the bromide of **29** (i.e., **34**) under the same conditions afforded only modest or effectively no dr; of note, resubjecting pure **30** to the same conditions from −78 to 0 °C led only to recovered s.m., indicating that the dr observed is the likely result of kinetic control without olefin isomerization in the products.

From here, separate olefination of **30** and **31** using Mg powder and $TiCl_4$ in CH_2Cl_2/THF as solvent[31] at carefully controlled temperatures (~31–33 °C) afforded racemic **2** and **32** in 53% and 48% yield, respectively.[32] These elevated temperatures were critical in effecting methylenation of both substrates. Subsequent dihydroxylation under standard OsO_4 conditions then afforded **5** and **33**, each as a single diastereomer whose configuration was determined by X-ray. To our surprise, though the structure of **5** matches that as drawn by the team who originally isolated it, its spectral properties are not in harmony in the reported NMR solvent (C_6D_6). Although we are unable to discern the source of the discrepancy,[2,33] it would appear that the structure of natural **5** needs revision; **33** also does not match the natural isolate.

In any event, two additional bromo-chamigrenes were then synthesized through a two-step procedure involving Parikh–Doering oxidation and $SOCl_2$-promoted alcohol elimination. These processes effected regiospecific constructions of both dactylone (**4**) and 10-*epi*-dactylone (**3**). Given the findings by the Burns group,[15] our racemic preparation of **4** achieves a formal racemic total synthesis of aplydactone (**7**).

In conclusion, we have developed an effective means to generate a highly functionalized bromo-chamigrene core through a halonium-induced cyclization of a polyene precursor, uniquely effected with our bromonium source BDSB. We then developed racemic total and formal syntheses of four different members of the collection through a Diels–Alder-based sequence. Key discoveries in the latter approach include the observation that a bromine atom plays a key role in dictating the diastereoselectivity of the cycloaddition, the determination that a bromo-chamigrene appears to need a structural revision, and protocols and reaction conditions distinct from the Burns approach to convert the Diels–Alder products into chamigrenes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02478.

Full experimental details, copies of spectral data, X-ray crystal structures (PDF)

Crystallographic data (CIF, CIF, CIF, CIF, CIF)

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Notes

The authors declare no competing financial interest.

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an advance copy of his accepted manuscript regarding his group's bromo-chamigrene syntheses. Financial support was provided by the NSF (CAREER Award CHE-0844593), Columbia University, The Scripps Research Institute, the University of Chicago, the Deutscher Akademischer Austauschdienst (DAAD, postdoctoral fellowship to M.K.), and the Organic Division of the American Chemical Society (fellowship to Z.G.B.).

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(26) Other bromonium sources such as TBCO or $Br(coll)_2PF_6$ under either typically reported or similar reaction conditions as optimized for BDSB did not afford **24**; instead, a complex mixture of products and unreacted **23** resulted. We cannot rule out that bromonium-induced cyclization occurred in these experiments, but there was no single major product generated suggesting that if formed, such reactions proceeded with low efficiency/chemoselectivity.

(27) The absence of the silyl substituent in any form generally resulted in decomposition, bromohydrin formation, or *5-exo* cyclization products; other silicon groups were hard to incorporate. In addition, the absence of a protecting group on the secondary alcohol generally resulted in decomposition or protodesilylation. Replacement of the Bz group simply with Ac led to a significantly diminished yield.

(28) Attempts to olefinate the ketone within **24** failed as did efforts to add methyl-based nucleophiles. The α-bromo atom of **24** could be substituted by a PhS unit (NaH, PhSH), but attempts to utilize the resulting thioether for a Pummerer rearrangement were not successful. Furthermore, it could also be exchanged directly for an OH; that process, however, occurred in low and irreproducible yields.

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(32) Common methylenation protocols, including the Tebbe reagent, $Rh(PPh_3)_3Cl/TMSCHN_2$, and the Nysted reagent/$TiCl_4$ failed with spirocyclic ketone **30**. Several protocols conducted under basic conditions rapidly transformed **30** into a des-HBr compound that appears to possess a cyclopropane. See the Suppporting Information.

(33) Efforts to obtain copies of the original spectra from the isolation team have been unsuccessful thus far.

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