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A Unified Approach for the Enantioselective Synthesis of the Brominated Chamigrene Sesquiterpenes

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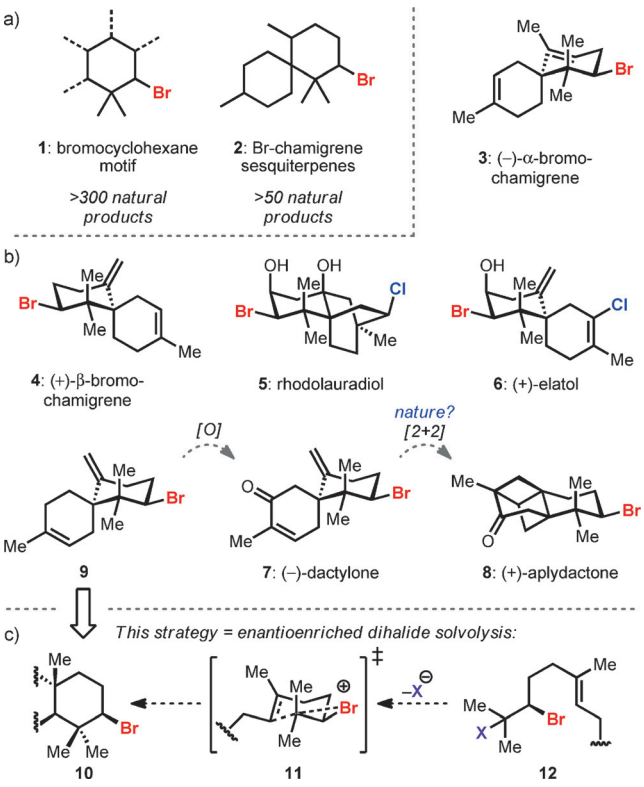
Abstract: *The brominated chamigrene sesquiterpenes constitute a large subclass of bromocyclohexane-containing natural products, yet no general enantioselective strategy for the synthesis of these small molecules exists. Herein we report a general strategy for accessing this family of secondary metabolites, including the enantioselective synthesis of (−)-α- and (−)-ent-β-bromochamigrene, (−)-dactylone, and (+)-aplydactone. Access to these molecules is enabled by a stereospecific bromopolyene cyclization initiated by the solvolysis of an enantiomerically enriched vicinal bromochloride.*

Of the roughly 300 natural products containing a bromocyclohexane motif **1** that have been isolated and structurally characterized,[1a–c] more than 50 are represented by the brominated chamigrene sesquiterpenes **2** (Scheme 1 a). Most members of this family differ in their level of saturation, halogenation, and oxygenation (see structures **3**–**8**, Scheme 1 b). The structural variety within the halogenated chamigrenes is complemented by diverse biological activities, including antibacterial,[2] antifungal,[3] antiviral,[4] anthelmintic,[5] and anticancer[6] effects. To date, the total synthesis of (+)-elatol (**6**) by Stoltz, Grubbs, and co-workers[7a] constitutes the only catalytic enantioselective synthesis of a member of the halogenated chamigrene sesquiterpenes. *A general catalytic enantioselective approach for the synthesis of this class of molecules has yet to be reported.*[7b–e] Along these lines, we set out to develop a strategy that would enable the rapid construction of the spirocyclic core and thus facilitate elaboration to structurally disparate members of this family of small molecules for further chemical and biological investigations.

We were particularly intrigued by the cancer-preventive agent dactylone (**7**)[8] and a related congener, aplydactone (**8**).[9] Dactylone has been shown to suppress phenotype expression at noncytotoxic doses in human lung, colon, and skin tumor cell lines and therefore holds promise as a molecular tool for anticancer studies.[8c] Dactylone and aplydactone were originally isolated from the sea hare *Aplysia dactylomela* in 1987; however, the structure of aplydactone was not disclosed until 2001 with the assistance of X-ray crystallography.[9] In that report, it was suggested that **8** may arise from



Scheme 1. The halogenated chamigrene sesquiterpenes. a) Ubiquitous bromocyclohexane motif and bromochamigrene skeleton; b) representative members of the natural product class; c) this approach.

an intramolecular [2+2] cycloaddition of **7**. Accordingly, we selected dactylone **7** as a synthetic target with the objective of also interrogating its conversion into aplydactone **8**. We hoped this investigation would shed light on the feasibility of this transformation both in a biosynthetic and a laboratory setting. We were confident that **7** could be obtained directly from its corresponding deoxygenated precursor **9**. This diene, although it has not yet been isolated, is representative of the simplest members of the brominated chamigrenes, specifically its isomeric natural product counterparts, α- and β-bromochamigrene[3,10,11] (**3** and **4**, Scheme 1 b). We thus devised a strategy that was capable of providing facile access to numerous brominated spirodienes in enantiomerically enriched form.

We targeted the isoprenoid-derived bromocycle **10**, which could be rapidly elaborated to the spirocyclic chamigrene core (**10**→**9**, Scheme 1 c), thus providing a general way of accessing this class of natural products. Although a bromonium-induced carbocationic cyclization would provide

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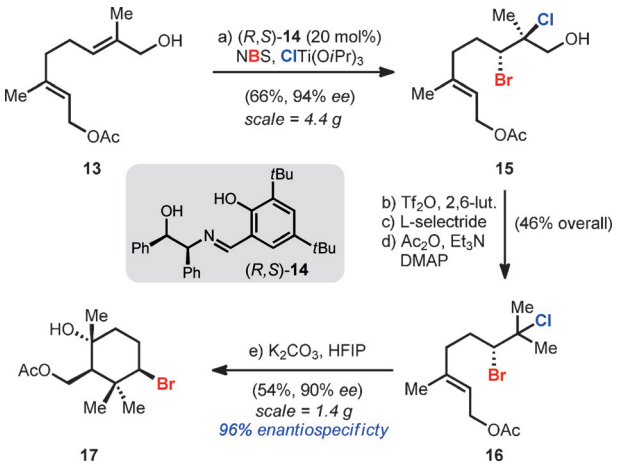
a direct means to access candidate carbocycles, no enantioselective bromopolyene cyclization protocols have been reported on natural product relevant scaffolds.[12] Cognizant of this methodological gap, we saw an opportunity to use enantiomerically enriched vicinal dihalides as progenitors of bromonium ions. Enantiomerically pure bromonium ions have been previously generated from enantiomerically enriched bromohydrin derivatives and have been captured in an intra- and intermolecular fashion.[12c,d,13b] However, to our knowledge the generation and subsequent trapping of an enantiomerically enriched bromonium ion from a vicinal dihalide has not been reported. Recently, we disclosed an enantioselective Schiff base catalyzed di- and interhalogenation reaction of allylic alcohols to give highly enantiomerically enriched bromochlorides,[14a] dibromides, and dichlorides.[14b–d] We hypothesized that subjecting these species to ionizing conditions could facilitate the generation of an enantiomerically enriched halonium ion that could be captured intramolecularly for productive cyclization (**12**→**10** via **11**, Scheme 1c).

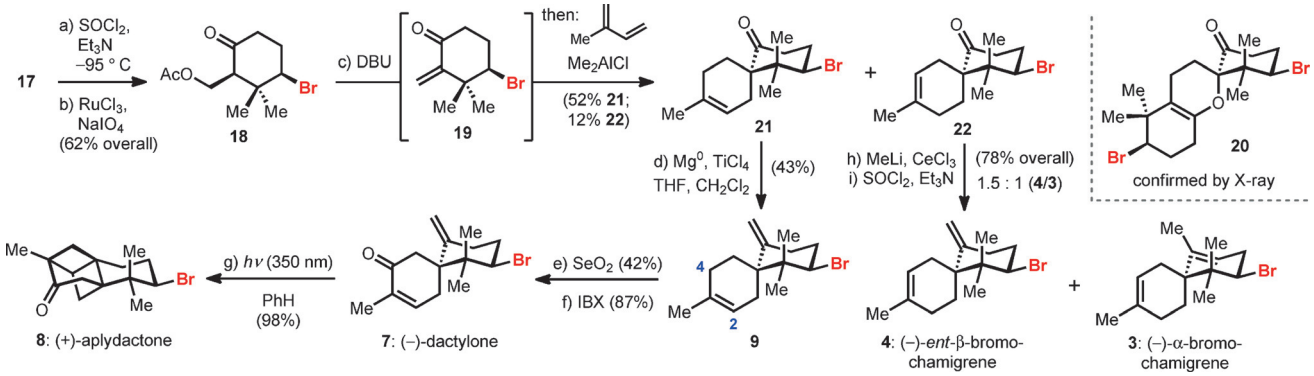
This plan called for the enantioselective dihalogenation of allylic alcohol **13** (Scheme 2), which can be prepared in one step from commercially available geranyl acetate.[15] Under conditions previously disclosed by our research group, bromochlorination catalyzed by the Schiff base (*R*,*S*)-**14** proceeded in good yield (66%) and with excellent enantioselectivity (94% *ee*) on a 4.4 g scale to deliver bromochloride **15**. Two-step deoxygenation[14d] followed by reacylation provided more than 1 g of bromochlorogeranyl acetate **16**.

With the requisite precursor in hand, we subjected **16** to ionizing conditions in basic hexafluoroisopropanol (HFIP),[13] optimistic that an enantiomerically pure nonracemizing bromonium ion could be generated and captured by the pendant allylic acetate. To our delight, the cyclization proceeded smoothly and afforded bromocarbocycle **17** in 54% yield as a single isolated diastereomer with near-perfect enantiospecificity (**17**: 90% *ee*; 96% enantiospecificity). Analogous dibromoalcohols were observed to racemize under the ionizing conditions and were unstable to the deoxygenation conditions. To our knowledge this is the first example of the solvolysis and intramolecular capture of an enantiomerically enriched dihalide.

We next sought to elaborate the enantiomerically enriched carbocycle **17** to the spirocyclic framework relevant to the brominated chamigrene sesquiterpenes (Scheme 3). We envisioned that an isoprene Diels–Alder transformation with a corresponding exocyclic enone could provide the desired scaffold. Bromocycle **17** was cleanly dehydrated to the exocyclic olefin[16] with subsequent oxidative cleavage[17] to afford ketone acetate **18** in good yield (62% over two steps). Facile elimination of the acetate to the exocyclic enone **19**



Scheme 2. Enantioselective dihalogenation and key solvolytic bromopolyene cyclization. Reagents and conditions: a) *N*-bromosuccinimide (1.05 equiv), $ClTi(OiPr)_3$ (1.1 equiv), (*R*,*S*)-**14** (20 mol%), hexanes, −20°C, 66%; b) triflic anhydride (1.2 equiv), 2,6-lutidine (2.0 equiv), CH_2Cl_2, −78°C, 85%; c) L-selectride (5.5 equiv), THF, −78°C→RT, 58%; d) acetic anhydride (1.0 equiv), 4-dimethylaminopyridine (0.05 equiv), triethylamine (1.2 equiv), CH_2Cl_2, room temperature, 94%; e) potassium carbonate (1.5 equiv), hexafluoroisopropanol (0.05 M), room temperature, 54%.



Scheme 3. Synthesis of (−)-dactylone, (+)-aplydactone, and (−)-α- and (−)-*ent*-β-bromochamigrene. Reagents and conditions: a) thionyl chloride (1.5 equiv), triethylamine (5 equiv), CH_2Cl_2, −196→−95°C; b) ruthenium(III) chloride (0.02 equiv), sodium periodate (1.5 equiv), $MeCN/CCl_4/H_2O$, room temperature, 62% from **17**; c) 1,8-diazabicycloundec-7-ene (1.1 equiv), isoprene (20 equiv), Me_2AlCl (3.5 equiv), toluene, −78→−10°C, **21**: 52%, **22**: 12%; d) magnesium (8.0 equiv), titanium tetrachloride (2.0 equiv), THF/CH_2Cl_2, 0°C→RT, 43%; e) selenium dioxide (1.5 equiv), dioxane, 80°C, 42%; f) 2-iodoxybenzoic acid (2.0 equiv), dimethyl sulfoxide, room temperature, 87%; g) *hν* (350 nm), benzene, room temperature, 98%; h) methyllithium (4.5 equiv), cerium(III) chloride (5.0 equiv), THF, −78→0°C; i) thionyl chloride (2.1 equiv), triethylamine (5.4 equiv), CH_2Cl_2, −78→0°C, 78% combined.

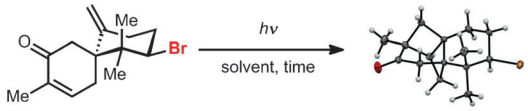
occurred in the presence of DBU with mild heating, but attempts at its isolation led to rapid formation of the unusual hetero-Diels–Alder dimer **20** upon concentration and standing. Circumventing the isolation of this unstable intermediate, we generated enone **19** in situ and treated it with dimethylaluminum chloride and excess isoprene.[18] In this way, the desired Diels–Alder adduct was readily obtained as a 4.3:1 (52% **21** + 12% **22**) mixture of separable epimers. Access to these diastereomeric spiroketones served as a convenient diversification point in our synthesis, thus providing access to the doubly unsaturated, isomeric α- and *ent*-β-bromochamigrenes **3** and **4**, respectively.

Transformation of spiroketones **21** and **22** into their corresponding exocyclic olefins was next required for the synthesis of *ent*-β-bromochamigrene (**4**) and dactylone (**7**). An initial survey of standard methylenation conditions[19] failed to convert any of the spiroketone **21** into the desired olefin **9**. We reasoned that failed olefination was due to the combination of the extremely hindered neopentyl ketone and the bulkiness of reagents. We thus turned our attention to conditions successful for the methylenation of highly hindered substrates[20] and used dichloromethane as a methylene equivalent in combination with $TiCl_4$ and Mg^0. These conditions were sufficient to convert **21** into the doubly unsaturated spirocycle **9** in 43% yield. An exhaustive investigation of known olefination conditions did not provide superior results. Surprisingly, attempts to convert the epimeric spiroketone **22** into (−)-*ent*-β-bromochamigrene (**4**) under these conditions resulted in diminished yields as compared to that observed for its isomer **21**. However, a two-step protocol involving the addition of methylcerium dichloride,[7] followed by dehydration in the presence of thionyl chloride, afforded (−)-α- and (−)-*ent*-β-bromochamigrene as a 1.5:1 mixture in 78% yield.

The conversion of spirodiene **9** into dactylone **7** called for selective allylic oxidation of the methylene group at C4 to the ketone oxidation state. Unfortunately, conditions to directly effect this transformation[21] failed to selectively oxidize the allylic methylene group at C4 over C2. Selenium dioxide[22] efficiently produced the C4 allylic alcohol, which was readily oxidized to the corresponding enone with 2-iodoxybenzoic acid (IBX), thus completing the first synthesis of (−)-dactylone (**7**). Cognizant of the reported failed attempts of the isolation team to convert dactylone (**7**) into aplydactone (**8**) under long-term UV irradiation,[9] we nevertheless subjected dactylone (**7**) to known enone [2+2] conditions under irradiation with 350 nm light. To our delight, dactylone (**7**) underwent clean conversion over a period of 36 h into aplydactone (**8**; see Table 1 for the X-ray crystal structure), which we were able to isolate in near-quantitative yield (98%) after silica-gel chromatography.[23]

Irradiation of dactylone (**7**) with 254 nm light led to the formation of small amounts of **8** as a complex mixture (Table 1, entry 1), thus indicating that judicious selection of the light source is crucial to the success of the intramolecular [2+2] cycloaddition. Standard conditions for enone–olefin cycloaddition reactions of 350 nm irradiation delivered **8**, although prolonged reaction times were necessary (Table 1, entries 2 and 3). The exposure of dactylone (**7**) to ambient sunlight over a period of 8 days (Table 1, entry 4) resulted in the formation of aplydactone (**8**), albeit in small quantities (15% conversion).[24] This observation raises an interesting question about the role of sunlight in the biosynthesis of aplydactone, in particular whether or not enzymatic machinery is necessary in its biogenesis. Photochemical transformations, specifically those utilizing sunlight, have been directly implicated in the biosynthesis of marine natural products.[25]

Table 1: Conversion of **7** into **8** under UV irradiation.



7: (–)-dactylone **8**: (+)-aplydactone [X-ray]

Entry	Solvent	*hν*	*t*	Conv. [%] (Yield [%])
1	THF	254 nm	15 min	100 (7[a])
2	benzene	350 nm	20 h	85 (ca. 85)
3	benzene	350 nm	36 h	100 (98[b])
4	$CDCl_3$	Californian sunlight	8 days	15 (ca. 15)

[a] Yield based on ^{1}H NMR spectroscopy with 1,4-dinitrobenzene as an internal standard. [b] Yield of the isolated product.

The enantioselective total synthesis of (−)-α- and (−)-*ent*-β-bromochamigrene, (−)-dactylone, and (+)-aplydactone was enabled by the gram-scale enantiospecific solvolytic cyclization of an enantiomerically enriched bromochloride. Access to this interhalogenated motif was enabled by the highly chemo-, diastereo-, and enantioselective Schiff base catalyzed bromochlorination of allylic alcohol **13**. This study highlights a highly general approach to the halogenated chamigrene sesquiterpenes, and we anticipate that it will find use in the synthesis of additional members of this class. Studies along those lines as well as a comprehensive investigation into the solvolytic cyclization of enantiomerically enriched dihalides are in progress and will be reported in due course.

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