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# Simple Reagents for Direct Halonium-Induced Polyene Cyclizations

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***Abstract:*** Although there are many reagent combinations that can initiate polyene cyclizations, simple electrophilic halogen sources have not yet proven broadly effective as promoters of such processes. Herein is described a readily prepared and stable class of reagents capable of effecting such transformations for a wide range of electron-rich and -deficient terpenes derived from geraniol, farnesol, and nerol, thereby enabling the effective synthesis of a diverse array of complex chlorine-, bromine-, and iodine-containing polycyclic frameworks. Efforts to date have led to the first racemic laboratory total synthesis and structural revision of the anti-HIV natural product peyssonol A as well as an efficient and concise inaugural total synthesis of peyssonoic acid A. They have also permitted formal racemic total syntheses of aplysin-20, loliolide, K-76, and stemodin to be achieved through routes that are typically shorter, higher-yielding, and more environmentally conscious than previous efforts. Preliminary attempts to use chiral forms of the reagent class for enantioselective alkene halogenation are also described.

## Introduction

With little question, the ability to convert polyene starting materials into far more complex frameworks via stereoselective cation-$\pi$ cyclizations constitutes one of the most important strategies currently available for C−C bond construction.[1] Indeed, in the half century since Stork and Eschenmoser first advanced their hypothesis[2] for the existence of such processes, chemists have devised numerous sets of unique substrates, reaction conditions, and reagent combinations that enable such reactions to be conducted with very high levels of stereoselectivity. Specifically, numerous versions of nonmetal-[3] and metal-induced[4] [especially Hg(II),[4a−i] Pd(II),[4j−l] Pt(II),[4l−o] and Au(I)[4o−q]] cyclizations have been developed and honed to the point where the efficient synthesis of dozens of molecules of natural and designed origin can readily be achieved.[5]

What remains to be accomplished, however, is broadly initiating such processes with halogen electrophiles. Nature takes advantage of such reactivity with some frequency, as vanadium- and heme-based haloperoxidases[6] have been shown (or hypothesized) to convert simple polyene precursors into the highlighted rings of the natural products drawn in Figure 1;[7] these molecules represent a select subset of the nearly 200 chlorine- and bromine-containing compounds which possess such ring systems that have been isolated to date from both marine and terrestrial sources.[8] Yet, mirroring such reactivity in the laboratory flask has proven elusive unless haloperoxidases themselves have been utilized.[9] Indeed, the use of simple halogen electrophiles to achieve such cyclizations, even in racemic form, typically has led to modest product yields and then only for a narrow range of substrates with certain halogens.[10−13]

To the best of our knowledge, there have been no examples of any chemical reagents effecting a chloronium-induced polyene cyclization in any yield.[10] Explorations with bromine-based systems, by contrast, have been much more extensive. Nevertheless, no reagent possesses the scope of reactivity needed to handle the diverse range of C═C double bond nucleophilicity possible in functionalized terpene precursors.[11] Most reagents convert electron-rich systems into multiple, and often challenging to separate, products due to issues of olefin chemoselectivity, with electron-poor substrates typically leading to products where the cyclizations stall after forming a single ring (i.e., **6**→**7**)[11e] or an exogenous species behaves as nucleophile or base prior to cation-$\pi$ cyclization (**8**→**9**).[11g] In fact, yields of cyclized

(1) For reviews, see: (a) Sutherland, J. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, pp 341−377. (b) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730–4756.

(2) (a) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068–5077. (b) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890–1904. For a recent perspective on this work 50 years after its original publication, see: (c) Eschenmoser, A.; Arigoni, D. *Helv. Chim. Acta* **2005**, *88*, 3011–3050.

(3) For selected examples, see: (a) Yang, D.; Gu, S.; Yan, Y.-L.; Zhao, H.-W.; Zhu, N.-Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 3014–3017. (b) Ishibashi, H.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 11122–11123. (c) Zhao, Y.-J.; Chng, S.-S.; Loh, T.-P. *J. Am. Chem. Soc.* **2007**, *129*, 492–493. (d) Zhao, Y.-J.; Loh, T.-P. *J. Am. Chem. Soc.* **2008**, *130*, 10024–10029. (e) Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2009**, *131*, 13928–13929. (f) Topczewski, J. J.; Callahan, M. P.; Neighbors, J. D.; Wiemer, D. F. *J. Am. Chem. Soc.* **2009**, *131*, 14630–14631. (g) Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027–5029. (h) Knowles, R. N.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 5030–5032. (i) Corey, E. J.; Lin, S. A. *J. Am. Chem. Soc.* **1996**, *118*, 8765–8776. (j) Corey, E. J.; Lee, J.; Liu, D. S. *Tetrahedron Lett.* **1994**, *35*, 9149–9152. (k) Mi, Y.; Schreiber, J. V.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 11290–11291. (l) Zhang, J.; Corey, E. J. *Org. Lett.* **2001**, *3*, 3215–3216. (m) Shenvi, R. A.; Corey, E. J. *Org. Lett.* **2010**, *12*, 3548–3551. For selected examples of classic papers in the field, see: (n) Johnson, W. S.; Gravestock, M. B.; McCarry, B. E. *J. Am. Chem. Soc.* **1971**, *93*, 4332–4334. (o) van Tamelen, E. E.; Willet, J.; Schwartz, M.; Nadeau, R. *J. Am. Chem. Soc.* **1966**, *88*, 5937–5938. (p) van Tamelen, E. E.; Hwu, J. R. *J. Am. Chem. Soc.* **1983**, *105*, 2490–2491.

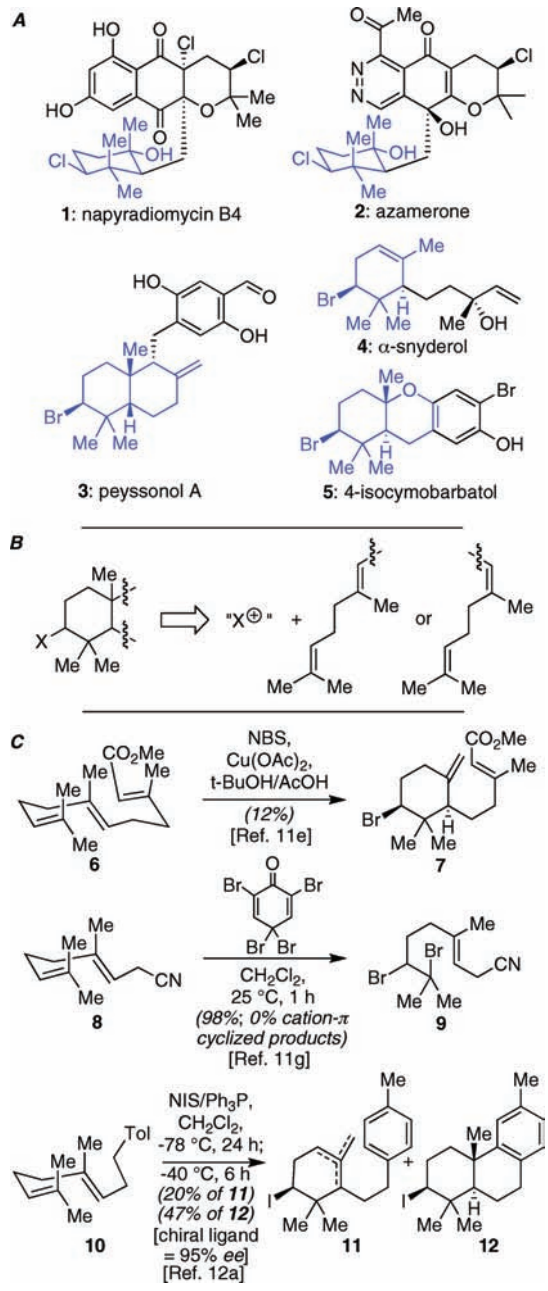


***Figure 1.*** (A) Selected natural products with rings that arise in Nature via halonium-induced cation-$\pi$ cyclizations of appropriate terpene precursors (cf. ref 7), (B) generalized retrosynthesis for their formation, and (C) selected examples of attempting such reactions with simple reagents, thereby revealing challenges in executing such reactions in the absence of enzymes.

material from electron-deficient systems using electrophilic bromine initiators have been less than 30%.

Iodonium-induced reactions[12] are the best developed, largely due to two recent advances. The first is Ishihara's use of a phosphorus-complexed form of *N*-iodosuccinimide (NIS) to cyclize three aryl-containing polyenes derived from geraniol (including **10**); when certain chiral phosphoramidites were used in stoichiometric amounts, the cyclization could be achieved with high enantioselection (95% e.e.).[12a] Key was the use of 30 h of controlled cryogenic conditions in the initial halonium-induced reaction followed by the addition of $ClSO_3H$ in a separate step to convert partially cyclized materials (such as **11**) into the final tricycle (i.e., **12**). Efforts to deploy such reactivity for enantioselective bromonium-induced cyclizations, however, were not as successful.[14] The second advance is the recent disclosure of Barluenga's hypervalent iodonium-reagent


(4) (a) Hoye, T. R.; Kurth, M. J. *J. Org. Chem.* **1979**, *44*, 3461–3467. (b) Hoye, T. R.; Caruso, A. J.; Kurth, M. J. *J. Org. Chem.* **1981**, *46*, 3550–3552. (c) Nishizawa, M.; Takenaka, H.; Nishide, H.; Hayashi, Y. *Tetrahedron Lett.* **1983**, *24*, 2581–2584. (d) Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Org. Chem.* **1986**, *51*, 806–813. (e) Corey, E. J.; Reid, J. G.; Myers, A. G.; Hahl, R. W. *J. Am. Chem. Soc.* **1987**, *109*, 918–919. (f) Gopalan, A. S.; Prieto, R.; Mueller, B.; Peters, D. *Tetrahedron Lett.* **1992**, *33*, 1679–1682. (g) Nishizawa, M.; Morikuni, E.; Asoh, K.; Kan, Y.; Uenoyama, K.; Imagawa, H. *Synlett* **1995**, 169–170. (h) Nishizawa, M.; Yadav, A.; Iwamoto, Y.; Imagawa, H. *Tetrahedron* **2004**, *60*, 9223–9234. (i) Takao, H.; Wakabayashi, A.; Takahashi, K.; Imagawa, H.; Sugihara, T.; Nishizawa, M. *Tetrahedron Lett.* **2004**, *45*, 1079–1082. (j) Kucera, D. J.; O'Connor, S. J.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 5304–5306. (k) Overman, L. E.; Abelman, M. M.; Kucera, D. J.; Tran, V. D.; Ricca, D. J. *Pure App. Chem.* **1992**, *64*, 1813–1819. (l) Koh, J. H.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 3459–3461. (m) Mullen, C. A.; Campbell, A. N.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6011–6014. (n) Feducia, J. A.; Gagné, M. R. *J. Am. Chem. Soc.* **2008**, *130*, 592–599. (o) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410–3449. (p) Fürstner, A.; Morency, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 5030–5033. (q) Sethofer, S. G.; Mayer, T.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 8276–8277.

(5) Other approaches to such frameworks have been developed as well. For a recent example featuring a carbonyl-ene reaction, see: Zhao, Y.-J.; Li, B.; Tan, L.-J. S.; Shen, Z.-L.; Loh, T.-P. *J. Am. Chem. Soc.* **2010**, *132*, 10242–10244.

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(8) For a review on halogenated natural products, see: Gribble, G. N. *Acc. Chem. Res.* **1998**, *31*, 141–152.

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(11) For representative examples, see: (a) van Tamelen, E. E.; Hessler, J. *Chem. Commun.* **1966**, 411–413. (b) Kato, T.; Ichinose, I.; Kumazawa, S.; Kitahara, Y. *Bioorg. Chem.* **1975**, *4*, 188–193. (c) Kato, T.; Ichinose, I.; Kamoshida, A.; Kitahara, Y. *J. Chem. Soc., Chem. Commun.* **1976**, 518–519. (d) Wolinsky, L. E.; Faulkner, D. J. *J. Org. Chem.* **1976**, *41*, 597–600. (e) González, A. G.; Martín, J. D.; Pérez, C.; Ramírez, M. A. *Tetrahedron Lett.* **1976**, *17*, 137–138. (f) Hoye, T. R.; Kurth, M. J. *J. Org. Chem.* **1978**, *43*, 3693–3697. (g) Kato, T.; Ichinose, I. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1051–1056. (h) Shieh, H.-M.; Prestwich, G. D. *Tetrahedron Lett.* **1982**, *23*, 4643–4646. (i) Kato, T.; Mochizuki, M.; Hirano, T.; Fujiwara, S.; Uyehara, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1077–1078. (j) Yamaguchi, Y.; Uyehara, T.; Kato, T. *Tetrahedron Lett.* **1985**, *26*, 343–346. (k) Fujiwara, S.; Takeda, K.; Uyehara, T.; Kato, T. *Chem. Lett.* **1986**, 1763–1766. (l) Tanaka, A.; Sato, M.; Yamashita, K. *Agric. Biol. Chem.* **1990**, *54*, 121–123. (m) Tanaka, A.; Oritani, T. *Biosci. Biotech. Biochem.* **1995**, *59*, 516–517.

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$Ipy_2BF_4$. When coupled with an additional equivalent of $HBF_4$, this reagent was able to convert several terpenes into cyclized products.[12b] However, neither of these two reagent combinations has been reported to successfully cyclize an electron-deficient polyene substrate; a complete listing of these, as well as other previous examples of terpene-based halonium-induced cyclizations, can be found in the Supporting Information section.

Thus, given this global range of present capabilities for all direct halonium-based cyclizations, especially that for bromine and chlorine, most natural product structures of the types represented by **1**−**5** (cf. Figure 1) have been targeted through strategies that feature indirect, multistep alternatives. These variants have included the formation and cyclization of halohydrin intermediates,[15] stoichiometric Hg(II)-induced cyclizations followed by stereoselective replacement with chlorine, bromine, or iodine[16,4a] (a reaction sequence we recently rendered enantioselective),[17] or two-step inversion and replacement sequences from oxygen-cyclized materials.[18]

Herein, we describe the development of the first class of reagents that can render possible the direct synthesis of a diverse range of chlorine-, bromine-, and iodine-containing polycycles via cation-$\pi$ cyclizations. Each reagent is a readily prepared crystalline solid that reacts with olefins highly chemoselectively and rapidly, with reactions normally complete within 5 min at low temperature. Moreover, added acids are not typically required to drive cyclizations to completion. To date, these reagents have allowed us to accomplish racemic total and formal syntheses of 7 different natural products, 6 of which are disclosed for the first time in this article (including a substantial structural revision), as well as to cyclize nearly 20 additional substrates in yields that are often multifold improvements over previously available alternatives.

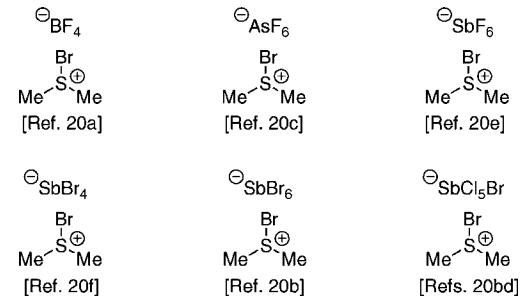



***Figure 2.*** Structures of previously synthesized materials derived from molecular $Br_2$, a sulfide, and a Lewis acid; in all cases, their chemical reactivity with double bonds was unexplored.

## Results and Discussion

**1. Development of BDSB.** Having carefully studied the precedents cited above, we chose to begin our investigations into the problem of achieving direct halonium-induced reactions by attempting to solve the bromonium-based challenge. Our goal was to identify a novel reagent with higher alkene chemoselectivity and less proclivity for side-product formation. We also added as a requirement for that search that such a reagent would need to be a stable and easily handled material rather than one that would have to be prepared *in situ*. In addition, we hoped that its molecular structure could ultimately prove applicable to generating the corresponding iodine- and chlorine-based variants and, eventually, chiral versions for asymmetric applications.

Our initial idea to achieve the desired reactivity was predicated on enhancing the electrophilicity of a typical bromine source (like $Br_2$ or NBS) while concurrently removing the potential for any other species (such as a counterion) to serve as either nucleophile or base.[19] An extensive search of the literature revealed the existence of several reagents that formally met this criteria; 6 of these compounds are presented in Figure 2, all of which are complexes of $Br_2$ with $Me_2S$ and a Lewis acid.[20]

Interestingly, although these materials have been known for some time (one was reported over 60 years ago), no report describes their chemical reactivity. As such, we sought to fill this gap, and began by preparing several members of the class. Preliminary screens quickly revealed that the use of $SbCl_5$ as the Lewis acid component most consistently afforded solid materials relative to boron or aluminum alternatives.[21a] Additionally, of the various simple dialkyl sulfides that could be

(13) For selected examples of other halonium-induced cyclization reactions not using terpene-based materials, as well as approaches that form related structures through nucleophilic attack of halogen onto carbon electrophiles, see: (a) Inoue, T.; Kitagawa, O.; Ochiai, O.; Shiro, M.; Taguchi, T. *Tetrahedron Lett.* **1995**, *36*, 9333–9336. (b) Cui, X.-L.; Brown, R. S. *J. Org. Chem.* **2000**, *65*, 5653–5658. (c) Appelbe, R.; Casey, M.; Dunne, A.; Pascarella, E. *Tetrahedron Lett.* **2003**, *44*, 7641–7644. (d) Hajra, S.; Maji, B.; Karmakar, A. *Tetrahedron Lett.* **2005**, *46*, 8599–8603. (e) Hanessian, S.; Tremblay, M.; Marzi, M.; Del Valle, J. R. *J. Org. Chem.* **2005**, *70*, 5070–5085. (f) Barluenga, J.; Trincado, M.; Rubio, E.; González, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 2406–2409. (g) Barluenga, J.; Vázquez-Villa, H.; Ballesteros, A.; González, J. M. *J. Am. Chem. Soc.* **2003**, *125*, 9028–9029. (h) Barluenga, J.; González, J. M.; Campos, P. C.; Asensio, G. *Angew. Chem., Int. Ed.* **1988**, *27*, 1546–1547. (i) Kang, S. H.; Lee, S. B.; Park, C. M. *J. Am. Chem. Soc.* **2003**, *125*, 15748–15749. (j) Haas, J.; Piguel, S.; Wirth, T. *Org. Lett.* **2002**, *4*, 297–300. (k) Grossman, R. B.; Trupp, R. J. *Can. J. Chem.* **1998**, *76*, 1233–1237. (l) Zhang, W.; Zheng, S.; Liu, N.; Werness, J. B.; Guzei, I. A.; Tang, W. *J. Am. Chem. Soc.* **2010**, *132*, 3664–3665.

(14) Part of the challenge may lie in the rapid transfer of bromonium to unreacted alkene, thereby eroding enatioselectivity: (a) Brown, R. S. *Acc. Chem. Res.* **1997**, *30*, 131–137. For similar challenges in achieving the enantioselective addition of chalcogens such as sulfur onto alkenes, see: (b) Denmark, S. E.; Collins, W. R.; Cullen, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 3490–3492. The same problem may not exist for iodine, and has recently been indicated not to be as profound an issue for chlorine: (c) Denmark, S. E.; Burk, M. T.; Hoover, A. J. *J. Am. Chem. Soc.* **2010**, *132*, 1232–1233.

(15) (a) Couladouros, E. A.; Vidali, V. P. *Chem.—Eur. J.* **2004**, *10*, 3822–3835. (b) Murai, A.; Abiko, A.; Masamune, T. *Tetrahedron Lett.* **1984**, *25*, 4955–4958.

(16) Replacement with iodine is often not completely stereoselective due to competing electrophilic and radical substitution pathways. (a) Jensen, F. R.; Gale, L. H. *J. Am. Chem. Soc.* **1960**, *82*, 148–151. (b) DePuy, C. H.; McGirk, R. H. *J. Am. Chem. Soc.* **1974**, *96*, 1121–1132.

(17) Snyder, S. A.; Treitler, D. S.; Schall, A. *Tetrahedron* **2010**, *66*, 4796–4804.

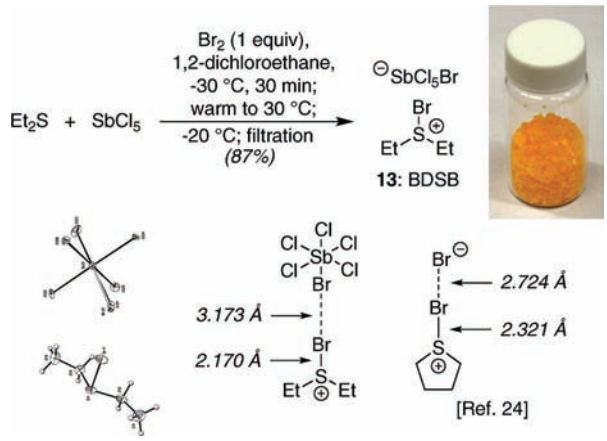
(18) (a) Su, W.-C.; Fang, J.-M.; Cheng, Y.-S. *Tetrahedron Lett.* **1995**, *36*, 5367–5370. (b) Pulicani, J.-P.; Bouchard, H.; Bourzat, J.-V.; Commerçon, A. *Tetrahedron Lett.* **1994**, *35*, 9709–9712.

(19) Conceptually, BDSB is an example where a Lewis base has activated a Lewis acid. For a review on this important mode of promoting reactivity, see: Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560–1638.

(20) (a) Bohme, H.; Boll, E. *Z. Anorg. Alleg. Chem.* **1957**, *290*, 17–23. (b) Goetz-Grandmont, G. J.; Leroy, M. J. F. *J. Chem. Res.* **1982**, 160–161. (c) Minkwitz, R.; Gerhard, V.; Werner, A. *Z. Anorg. Alleg. Chem.* **1989**, *575*, 137–144. (d) Askew, H. F.; Gates, P. N.; Muir, A. S. *J. Raman Spectrosc.* **1991**, *22*, 265–274. (e) Minkwitz, R.; Baeck, B. *Z. Naturforschung B: Chem. Sci.* **1993**, *48*, 694–696. (f) Regelmann, B.; Klinkhammer, K. W.; Schmidt, A. *Z. Anorg. Alleg. Chem.* **1997**, *623*, 1633–1638.

(21) (a) Arsenate anions were not investigated due to their toxicity. (b) The di-*t*-butyl variant decomposed rapidly, likely due to the weakness of the tertiary carbon-sulfur bond, while both the methyl and isopropyl variants were solid, crystalline materials. In terms of stability, solubility, and cost, however, **13** was superior.

***Scheme 1.*** Synthesis and Properties of BDSB (**13**)

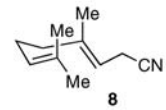
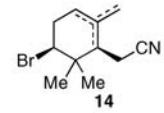
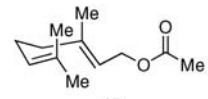
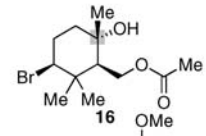
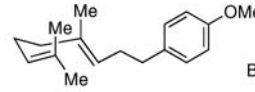
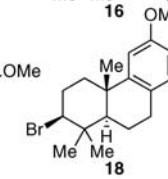
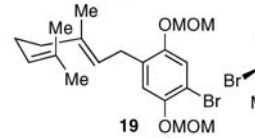
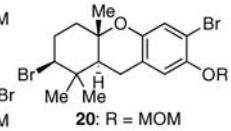
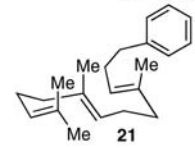
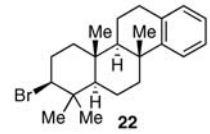
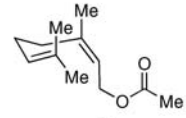
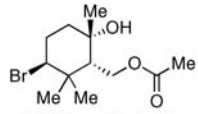



used (such as methyl, ethyl, isopropyl, or *t*-butyl), the ethyl variant was the most easily prepared.[21b] As indicated in Scheme 1, addition of a slight excess of $Et_2S$ and $SbCl_5$ to $Br_2$ in 1,2-dichloroethane at −30 °C immediately produced a yellow solid that could be recrystallized from the reaction solution to give the material shown in the inset photo in 87% yield. This odorless crystalline solid, which we have named BDSB (for bromodiethylsulfonium bromopentachloroantimonate, **13**), can be prepared smoothly on hundred-gram scale,[22] is stable at ambient temperature in an enclosed vial for at least 1 week (and for a year or more at −20 °C), and possesses good solubility in several organic solvents.[23]

Our optimism that BDSB would possess the desired reactivity for cation-$\pi$ cyclizations was enhanced upon obtaining its X-ray crystal structure. As indicated, the relatively short bromine−sulfur bond and effective sequestration of bromide to the antimonate counterion constitutes a significant departure from typical bromosulfonium complexes, an example of which is given in Scheme 1 (and which is ineffective for bromonium-induced cation-$\pi$ cyclizations).[24] Indeed, as we recently reported in a preliminary communication,[25] BDSB is very effective at inducing cation-$\pi$ cyclizations for a variety of substrates, including those that possess electron-deficient alkenes, as well as polyenes containing *Z*-alkenes.[25]

Table 1 provides a subset of the examples that were previously disclosed. It is worth noting that some of these reactions have been conducted on scales as large as 5.0 mmol in equivalent yields and that the nitromethane utilized can be recovered and reused in these large scale processes. Additionally, reactions are generally very fast (usually complete in less than 5 min), and in all cases product yields are superior to those obtained by other available methods reported in the literature. As with most cation-$\pi$ cyclizations, reaction concentrations need to be kept dilute (0.05 M on small scale; 0.01 M on larger scale) for optimal yields. In terms of chemoselectivity, BDSB will typically react cleanly with olefins prior to aromatic systems, even those that are electron-rich (such as those in **17** and **19**, Entries 3 and 4), though it can perform electrophilic aromatic bromination if no C═C bonds are present.

***Table 1.*** Exploration of the Generality of Direct, Bromonium-Induced Cation-$\pi$ Cyclizations using BDSB (1.1 equiv) and 0.1 mmol of Substrate in Nitromethane

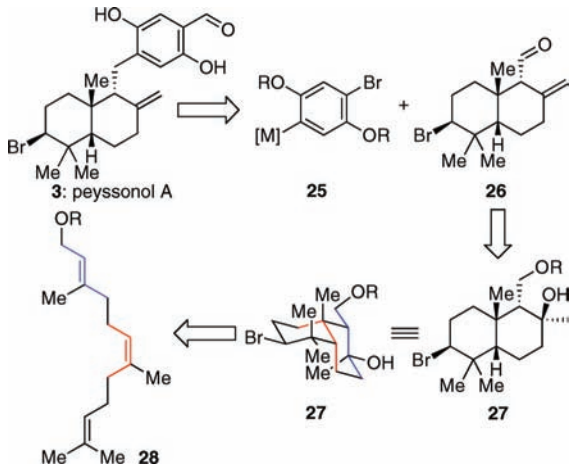
| Entry | Starting Material | Product | Temp. (°C) | Time (min) | Yield (%) |
|---|---|---|---|---|---|
| 1 |  **8** |  **14** | 25 | 5 | 73[a] |
| 2 |  **15** |  **16** | 0 | 1 | 80[b] |
| 3 |  **17** |  **18** | -25 | 5 | 76 |
| 4 |  **19** OMOM |  **20**: R = MOM | -25 | 5 | 74 |
| 5 |  **21** |  **22** | -25 | 5 | 58[c,d] |
| 6 |  **23** |  **24** [X-ray obtained] | 0 | 1 | 71 |

[a] Produced as a 6.5:2.5:1.0 mixture of tri:tetra:disubstituted alkene isomers. [b] Produced as a 3.8:1.0 mixture of separable diastereomers at the highlighted carbon favoring the drawn product. [c] Generated alongside some very minor diastereomers. [d] $MeSO_3H$ (15 equiv) added with 1 h of additional stirring to promote the final cyclization.

In its reactions with olefins, BDSB possesses typical electrophilic reactivity patterns: more substituted and more electronically activated double bonds will react faster, and usually selectively, over their less-substituted and/or electron-deficient counterparts.[26] Fortunately, steric considerations appear to be more important than electronic considerations given that in polyenes such as **19**, the more accessible, yet less electron-rich distal double bond consistently reacts preferentially to the hindered, more electron-rich central double bond. A minor side-product formed in many reactions is the proton-cyclized homologue; an acidic byproduct, likely protonated $Et_2S$, is formed as the reaction progresses and is responsible for the observed yield (usually <5%) of this undesired compound.[27] This acid cannot be neutralized *in situ* with added base, but is of value in that it may help to drive many cyclizations to

(22) Snyder, S. A. Treitler, D. S. *Org. Synth.* **2010**, submitted.
(23) **13** is fully soluble at ambient temperature in $MeNO_2$, $EtNO_2$, MeCN, DMSO, DMF, and EtOAc, moderately to slightly soluble in $CH_2Cl_2$, 1,2-dichloroethane, chloroform, and toluene, and insoluble in benzene, hexanes, and pentane. We have observed that **13** is soluble in acetone, methanol, ethanol, and THF, but reacts with these solvents.
(24) Allegra, G.; Wilson, G. E.; Benedetti, E.; Pedone, C.; Albert, R. *J. Am. Chem. Soc.* **1970**, *92*, 4002–4007.
(25) Snyder, S. A.; Treitler, D. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7899–7903.
(26) These assessments were made with various terpene-like polyenes possessing different substitution patterns in the terminal alkene position (the typical site of initiation for a cation-$\pi$ cyclization).
(27) Generally formed in higher amounts on large scale, this side-product could be suppressed by using dilute reaction concentrations (0.01 M) and adding a nitromethane solution of BDSB rapidly to the substrate.

***Scheme 2.*** Retrosynthetic Analysis of Peyssonol A (**3**)

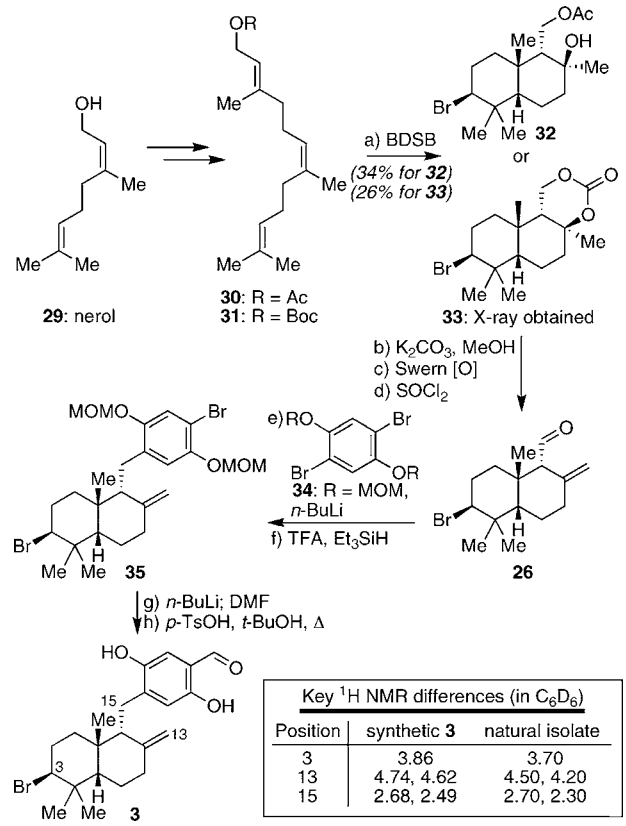



completion by promoting formation of multiple rings, especially when synthesizing tricyclic or tetracyclic materials. We note as well that while catalytic versions of this reagent design are conceivable (in terms of the sulfide), we have not pursued such explorations since we anticipate that they would not be ideal in many cases. For instance, the conversion of **8** into **14** (Entry 1, Table 1) provides products with reactive olefins, which we believe we are able to obtain in good yield only because there is rapid consumption of the starting material prior to the formation of significant amounts of product (which would likely react with BDSB if it were formed via a slower, catalytic process).

**2. Further Explorations into the Power of BDSB: Total and Formal Syntheses of Peyssonol A, Peyssonoic Acid A, and Aplysin-20.** Recent investigations with BDSB have centered on exploring its reactivity with progressively longer polyenes, especially trienes possessing unique (i.e., *Z*) stereochemistry in hopes of accessing the frameworks of several complex and structurally intriguing natural products. In particular, our attention was drawn to the structure of the secondary metabolite peyssonol A (**3**, Scheme 2), a material that was obtained from the Red Sea marine alga *Peyssonnelia sp*., that has been shown to act as an allosteric inhibitor of the reverse transcriptases of the Human Immunodeficiency Virus.[7c,d] To the best of our knowledge, this compound is the only known natural product possessing a *cis*-decalin framework likely arising from a halonium-induced cation-$\pi$ cyclization. As such, we felt it would be an ideal proving ground to evaluate the power of BDSB to effect a direct and highly challenging cation-$\pi$ cyclization to access a framework distinct from those we had previously prepared.[28]

As indicated in Scheme 2, our retrosynthetic analysis suggested that a late-stage disconnection of the pendant aryl ring,

***Scheme 3.*** Racemic Total Synthesis of the Proposed Structure of Peyssonol A (**3**) from Acyclic Terpene Precursors **30** and **31**[a]




Key $^1$H NMR differences (in $C_6D_6$)

| Position | synthetic **3** | natural isolate |
|---|---|---|
| 3 | 3.86 | 3.70 |
| 13 | 4.74, 4.62 | 4.50, 4.20 |
| 15 | 2.68, 2.49 | 2.70, 2.30 |

[a] Reagents and conditions: (a) BDSB (1.1 equiv), $MeNO_2$, 0 °C, 30 s, 34% for substrate **30**; BDSB (1.1 equiv), $MeNO_2$, −25→25 °C, 15 min, 26% for substrate **31;** (b) $K_2CO_3$ (5.0 equiv), MeOH, 40 °C, 30 min; (c) $(COCl)_2$ (2.0 equiv), DMSO (5.0 equiv), $CH_2Cl_2$, −78 °C, then substrate, then $Et_3N$ (10 equiv), −78→−50 °C, 1 h; (d) $SOCl_2$ (2.0 equiv), $Et_3N$ (6.0 equiv), $CH_2Cl_2$, −97 °C, 1 h, 91% over three steps; (e) **34** (1.2 equiv), *n*-BuLi (1.4 M in hexanes, 1.1 equiv), THF, −78 °C, 20 min, then **26,** −78 °C, 20 min, 63%; (f) TFA (5.0 equiv), $Et_3SiH$ (10 equiv), $CH_2Cl_2$, 0 °C, 30−90 min, 64%; (g) *n*-BuLi (1.4 M in hexanes, 1.2 equiv), THF, −78 °C, 20 min, then DMF (5.0 equiv), −78 °C, 20 min, 62%, (h) *p*-TsOH·$H_2O$ (0.2 M in *t*-BuOH), 65 °C, 2 h, 91%.

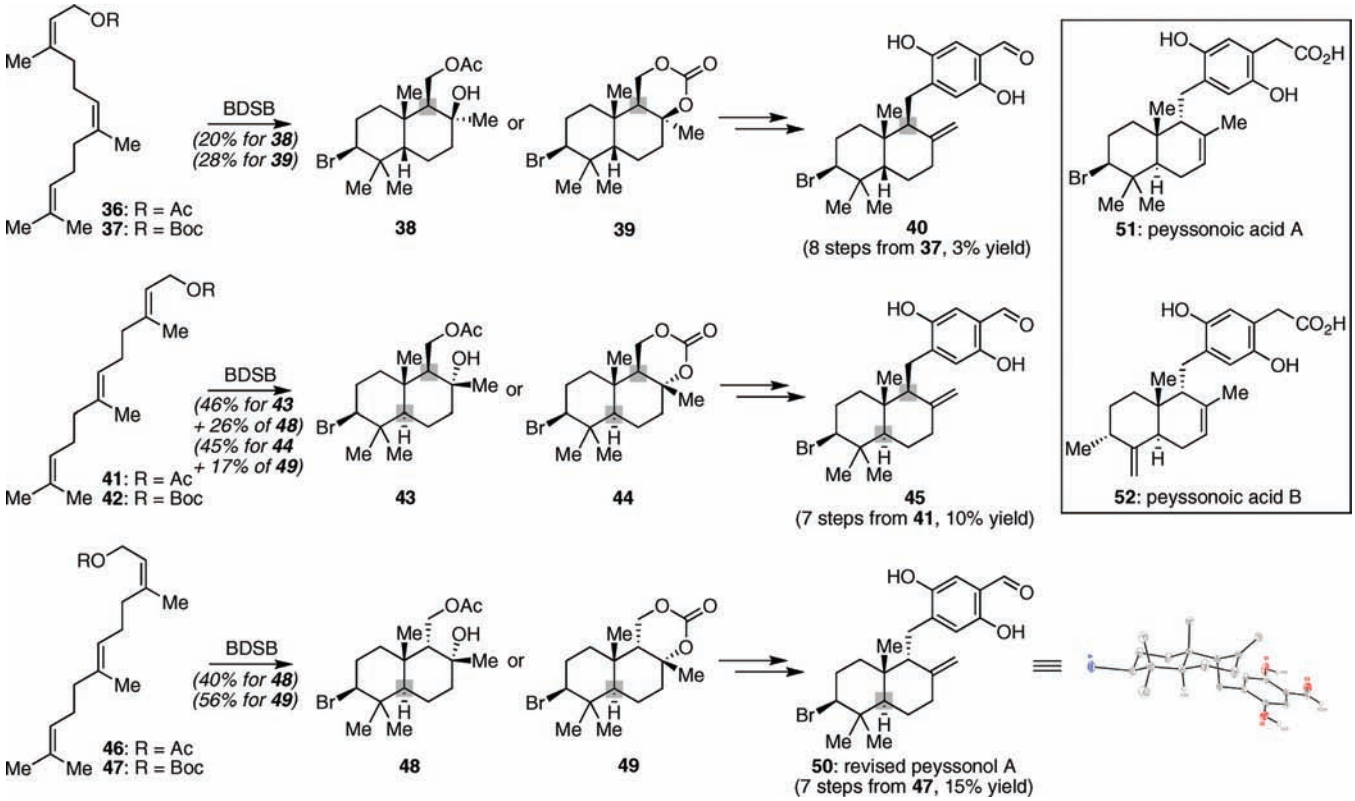
projecting a nucleophilic addition onto the aldehyde within compound **26** to effect its incorporation, might afford the most efficient means to reach a suitable polyene cyclization precursor. Compound **26** could potentially arise from *cis*-decalin **27**, which could in turn directly result from a bromonium-induced cation-$\pi$ cyclization of the (2*E*,6*Z*)-farnesol derivative **28**. Either an acetate or carbonate as group R within **28** would hopefully give rise to the desired functionality within **27**, assuming that the cation-$\pi$ cyclization could indeed be induced to proceed despite the higher degree of strain anticipated in the transition state to reach the requisite *cis*-fused ring system.

The translation of this general plan into a synthesis of the proposed structure for peyssonol A (**3**) proceeded largely without incident as shown in Scheme 3. Thus, commercially available nerol (**29**) was advanced into polyene cyclization precursors **30** and **31** in six steps each through a series of previously disclosed transformations,[29] details of which can be found in the Supporting Information section. Subsequent exposure of these materials separately to 1.1 equiv of BDSB in nitromethane

(28) Examples of polyene cyclizations involving *Z*-alkene geometries to prepare *cis*-fused decalin systems are in fact quite rare. For the seminal example, see: (a) Smit, W. A.; Semenovzky, A. V.; Kucherov, V. P. *Tetrahedron Lett.* **1964**, *5*, 2299–2306. For a more recent example, see: (b) Snowden, R. L.; Eichenberger, J.-C.; Linder, S. M.; Sonnay, C. V.; Schulte-Elte, K. H. *J. Org. Chem.* **1992**, *57*, 955–960. In general, such systems are prepared by other methods, including the cyclization of partially cyclized materials, formation of the ring junction using a Friedel-Crafts approach, or post-cyclization modification of a *trans*-fused system. (c) Saito, A.; Matsushita, H.; Kaneko, H. *Chem. Lett.* **1984**, 591–594. (d) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2002**, *124*, 3647–3655. (e) Bhar, S. S.; Ramana, M. M. V. *Tetrahedron Lett.* **2006**, *47*, 7805–7807. (f) Von Schlatter, H.-R.; Lüthy, C.; Graf, W. *Helv. Chim. Acta* **1974**, *57*, 1044–1055. (g) Raeppel, F.; Heissler, D. *Tetrahedron Lett.* **2003**, *44*, 3487–3488.

(29) (a) Kato, T.; Suzuki, M.; Toyohiko, K.; Moore, B. P. *J. Org. Chem.* **1980**, *45*, 1126–1130. (b) Yu, J. S.; Kleckley, T. S.; Wiemer, D. F. *Org. Lett.* **2005**, *7*, 4803–4806.

***Scheme 4.*** Racemic Total Syntheses of Various Diastereomers of Peyssonol A (**40**, **45**, and **50**), Ultimately Revealing that **50** is the Correct Structure




afforded access to *cis*-decalin **32** in 34% yield from **30** and its homologue **33** in 26% yield from **31**. Although the efficiency of these transformations is not as high as it was for many of the substrates we explored previously, the strain within the *cis*-fused transition states leading to **32** and **33** is significantly higher than that for the corresponding *trans*-fused system.[30] In fact, to the best of our knowledge, these cyclizations constitute the first examples of halonium-induced cation-$\pi$ cyclizations leading to *cis*-decalin frameworks, with an X-ray crystal structure of **33** (see Supporting Information section) confirming the stereochemical assignment.

In any event, both **32** and **33** could be funneled into **26** through ester or carbonate hydrolysis as achieved with $K_2CO_3$ in MeOH, oxidation of the resultant primary alcohol, and regioselective elimination of the remaining tertiary alcohol as achieved with $SOCl_2$ and $Et_3N$ in $CH_2Cl_2$ at $-97$ °C. Use of warmer temperatures or a less hindered base (such as pyridine) in this final step led to the formation of significant amounts of the regioisomeric trisubstituted alkene.[31] The remainder of the sequence proceeded smoothly as designed, with only 4 additional steps needed to complete a total synthesis of structure **3**. To our surprise, however, comparison of the spectral properties of synthetic **3** to those reported for natural peyssonol A revealed stark differences; the inset table within Scheme 3 highlights several key, and readily identifiable, peaks from their respective $^1$H NMR spectra. As such, assuming that our stereochemical assignment for synthetic **3** was accurate, the reported structure for peyssonol A (**3**) would have to be incorrect.

To confirm this hypothesis, especially given the potential for epimerization during the formation or subsequent arylation of aldehyde **26**, we synthesized *cis*-decalin **40** (see Scheme 4) with altered stereochemistry at C-9 (the highlighted center). This compound was readily prepared utilizing the same 8 step sequence, with reduced cation-$\pi$ cyclization efficiencies noted for conversion of (*Z*,*Z*)-isomers **36** and **37** into polycycles **38** and **39** (20 and 28% yield, respectively). More important, however, was that the homologue of aldehyde **26** (cf. Scheme 3) obtained through this sequence had a unique $^1$H NMR spectrum, thus suggesting that neither material had been epimerized; all other intermediates were distinct as well. As a result, we concluded that the stereochemical integrity of our assignments had not been compromised. Unfortunately, the spectral data of **40** also did not match those reported for natural peyssonol A.

Thus, based on these results, coupled with the fact that no other *cis*-decalin natural products of this type are known, we hypothesized that the correct orientation for these rings must include a *trans*-decalin framework, despite the arguments counter to this analysis presented in the original isolation paper.[7c] Consequently, we prepared the two C-9 diastereomers of such a *trans*-ring fusion (i.e., **45** and **50**), and found that compound **50** had nearly identical $^1$H and $^{13}$C spectral data to those published for the natural isolate;[32] a crystal structure of this final product was obtained as well, thereby removing any

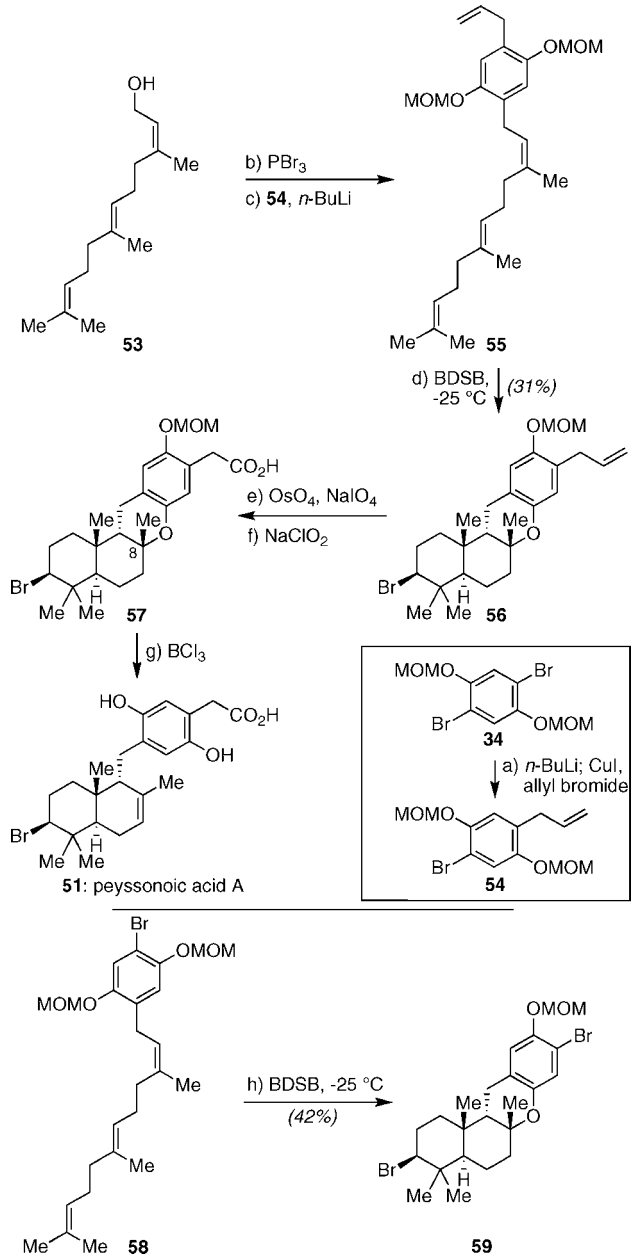
(30) The rate determining transition state for the formation of products **32** and **44** is associated with the first C−C bond formation. The activation barrier leading to **32** was estimated to be approximately 4.3 kcal/mol higher in energy than that leading to **44**. Geometries and energetics were obtained from semi-emperical (PM3) calculations using the GAMESS suite of programs. Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S. J.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347–1363.

(31) We note that the use of a bulkier base such as *i*-$Pr_2NEt$ afforded inferior regioselectivity in this dehydration step.

potential ambiguity concerning the stereochemical integrity of our sequence.[33] As such, we believe that **50** reflects the true configuration of peyssonol A, a reassignment strengthened by the fact that it matches the carbon framework of peyssonoic acid A (**51**), a compound which was recently obtained from a related marine alga along with the rearranged framework peyssonoic acid B (**52**).[34] These materials all possess an uncommon stereochemical configuration at C-9, one which places the large substituent axial; to the best of our knowledge, this synthesis of **50** constitutes a rare example of forming any such framework through an electrophilic-induced polyene cyclization.[35] It is also worth noting that the BDSB-induced cation-$\pi$ cyclization leading to this final structure was the highest yielding of all four diastereomers of *t*-butyl farnesyl carbonate, with an optimized yield of 56% obtained for tricycle **49**. Intriguingly, the (*E*,*E*)-farnesol-derived substrates **41** and **42** also provided a fair amount (26 and 17% yield, respectively) of the cation-$\pi$ cyclization products possessing the axial C-9 orientation of revised peyssonol A (i.e., **48** and **49**) in addition to the expected materials (i.e., **43** and **44**), thus reflecting a shift in reaction trajectory away from an all-chair conformation.[36] A similar switch in selectivity was recently observed by Shenvi and Corey using a differentially protected oxygen-linked termination group in the same position along the carbon framework as **41** and **42**.[3m]

Our next efforts sought to achieve additional refinement in the route to **50** to determine whether a sequence could be developed in which the aromatic ring was incorporated prior to cation-$\pi$ cyclization, since much of the overall step count derived from the postcyclization incorporation of this unit. We hoped that such an approach would also enable a total synthesis of peyssonoic acid A (**51**) to be achieved, assuming that its alternate double bond location relative to peyssonol A could be formed readily and selectively. Scheme 5 presents those endeavors, efforts which were able ultimately to achieve the total synthesis of peyssonoic acid A (**51**), but not an enhanced preparation of peyssonol A (**50**).

***Scheme 5.*** Racemic Total Synthesis of Peyssonoic Acid A (**51**) via a BDSB-Induced Cation-$\pi$ Cyclization and a Terminating Regioselective Ring-Opening/Elimination Reaction[a]




[a] Reagents and conditions: (a) **34** (1.0 equiv), *n*-BuLi (2.5 M in hexanes, 1.0 equiv), THF, −78 °C, 20 min, then CuI (0.5 equiv), 0 °C, 10 min, then allyl bromide (3.0 equiv), 0 °C, 20 min, 75%; (b) $PBr_3$ (0.5 equiv), $Et_2O$, −20→0 °C, 1 h; (c) **54** (1.7 equiv), *n*-BuLi (2.5 M in hexanes, 1.7 equiv), THF, −78 °C, 20 min, then s.m., −40→5 °C, 2 h, 74% over two steps; (d) BDSB (1.1 equiv), $MeNO_2$, −25 °C, 5 min, 31%; (e) $OsO_4$ (0.2 equiv), $NaIO_4$ (5.0 equiv), pyridine (3.0 equiv), THF/*t*-BuOH/$H_2O$ (4/1/3), 0→25 °C, 2 h, 89%; (f) $NaClO_2$ (5.0 equiv), $NaH_2PO_4$ (10 equiv), 2-methyl-2-butene (10 equiv), THF/*t*-BuOH/$H_2O$ (5/2/3), 0 °C, 20 min, 81%; (g) $BCl_3$ (1.0 M in $CH_2Cl_2$, 6.0 equiv), $CH_2Cl_2$, −78 °C, 1 h, 72%; (h) BDSB (1.1 equiv), $MeNO_2$, −25 °C, 5 min, 42%.

Our sequence began by adding an allylated form of building block **34** (i.e., **54**) onto a (2*Z*,6*E*)-farnesyl backbone to forge cation-$\pi$ cyclization precursor **55**. The allyl group was incorporated onto the aromatic ring to enable the eventual generation of the aryl acetic acid moiety of peyssonoic acid A (**51**) through oxidative cleavage. In addition, however, this monosubstituted double bond would provide a critical test for olefin chemose-

(32) The Supporting Information section contains a complete comparison table. Compound **50** possesses $^1$H NMR data that are in excellent agreement with the natural isolate; their $^{13}$C spectra possess small discrepancies, most of which are 0.5 ppm or less. Efforts based on altering water content as well as adding base or acid never afforded spectra that were perfectly identical in terms of reported values, though such factors can affect the $^{13}$C NMR spectra of compounds of this type. None of the other isomers synthesized (**3**, **40**, and **45**) had $^1$H or $^{13}$C NMR data that even remotely resembled those of the natural product. Prof. Kashman (Tel Aviv University) was contacted in hopes of obtaining either a natural sample or copies of the original physical spectra of peyssonol A, but unfortunately neither could be located, making direct comparison impossible.

(33) The Supporting Information section contains the complete synthetic route employed to access the revised structure of peyssonol A (**50**), for which further route improvement allowed for the shortening of the sequence described in Scheme 3 by one step to ultimately achieve an overall yield of 14% from (2*Z*,6*E*)-farnesol.

(34) (a) Lane, A. L.; Mular, L.; Drenkard, E. J.; Shearer, T. L.; Engel, S.; Fredericq, S.; Fairchild, C. R.; Prudhomme, J.; Le Roch, K.; Hay, M. E.; Aalbersberg, W.; Kubanek, J. *Tetrahedron* **2010**, *66*, 455–461. For a review on misassigned natural product structures, see: (b) Nicolaou, K. C.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1012–1044. For recent examples of reassignment involving a major architectural change within two fused 6-membered carbon rings, see: (c) Maugel, N.; Mann, F. M.; Hillwig, M. L.; Peters, R. J.; Snider, B. B. *Org. Lett.* **2010**, *12*, 2626–2629. (d) Spangler, J. E.; Carson, C. A.; Sorensen, E. J. *Chem. Sci.* **2010**, *1*, 202–205.

(35) For an example of an epoxide-induced cyclization leading to such a framework, see: van Tamelen, E. E.; Coates, R. M. *Bioorg. Chem.* **1982**, *11*, 171–196.

(36) Specifically, these products should arise if the second ring forms as a boat.

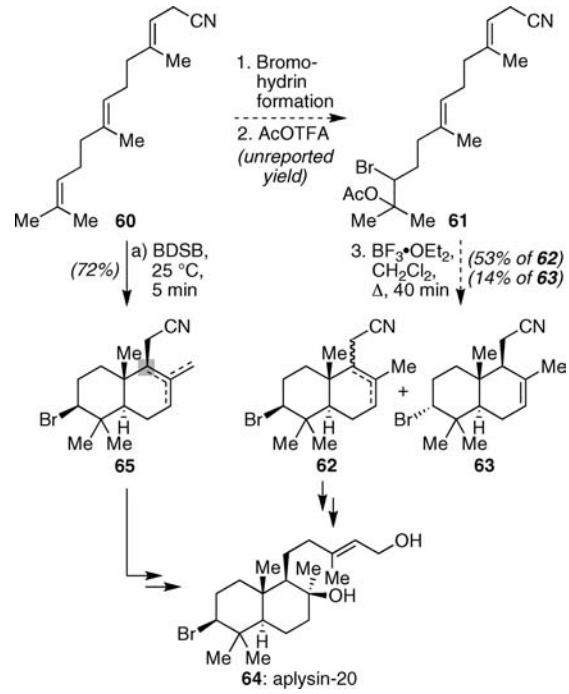
lectivity in the key BDSB-induced cyclization. Pleasingly, exposure of **55** to BDSB in nitromethane for 5 min at −25 °C afforded materials in which the allyl group remained intact; the isolated yield of **56** was 31%, thereby reflecting a cyclization efficiency of 68% per ring. From **56**, the remainder of the sequence occurred smoothly, with the key operation being a terminating exposure to excess $BCl_3$ in $CH_2Cl_2$ at −78 °C for 1 h which served to remove the protecting group and cleave the C−O bond at C-8, regioselectively affording the trisubstituted alkene of the target molecule (**51**).[37,38] Peyssonoic acid A (**51**) could also be accessed from polycycle **59** (prepared from **58** in 42% yield with BDSB) through a sequence involving initial lithiation and addition of $CO_2$ to afford a carboxylic acid that was then homologated via an Ardnt−Eistert sequence; this route, unfortunately, proceeded in significantly reduced yield relative to that of Scheme 5. In no case, however, were we ever able to convert tetracyclic materials like **56** or **59** into exocyclic alkenes, despite numerous attempts. As such, the route described earlier for peyssonol A (cf. Scheme 4) proved to be the only one capable of delivering the desired functionality chemoselectively.

As a final investigation into the power of BDSB to cyclize trienes, we then targeted a formal total synthesis of the natural product aplysin-20 (**64**, Scheme 6).[39] This unique bicycle was synthesized by Murai and co-workers in 1984[15b] through a route which employed a Lewis acid-catalyzed polyene cyclization of protected bromohydrin derivative **61**, a compound formed in 2 steps from the known nitrile **60**.[40] When the key cyclization reaction was conducted with $BF_3{\bullet}OEt_2$ in $CH_2Cl_2$ at reflux for 40 min, polycycles **62** and **63** were obtained in 53 and 14% yield, respectively, from **61**. Of these 4 cyclized diastereo- and regio-isomers, only 2 (39% combined yield) had the proper configuration (both -Br and -$CH_2CN$ in equatorial, i.e. $\beta$-positions) to be advanced to the natural product.

In an effort to render this sequence far more direct, we found that BDSB could convert **60** directly into **65** (as a 5.3/1.3/1.0 mixture of all alkene regioisomers) in 72% isolated yield. When using BDSB, in contrast to Murai's bromoacetate cyclization, stereochemical control was observed at the highlighted center for the di- and trisubstituted alkene forms of **65**, indicative of the strong preference for a chair−chair transition state as well as the synchronous nature of this cyclization.[2] Thus, all of the cyclized products (**65**) could formally be advanced to the natural product.

As a concluding comment on the uniqueness of BDSB as a reagent to effect polyene cyclizations, we note that many variants are not as effective overall, either due to challenges in their preparation or their global reactivity. For instance, attempts to prepare aryl variant **66** (Figure 3) have failed, due entirely to the reagent brominating itself; this problem can be avoided by prehalogenating the rings to form reagents such as **67**, but these materials are not readily solidified or handled. By contrast, carbonyl variants such as **68** and **69** are easily prepared and crystallized but, interestingly, afford reduced stereocontrol in cation-$\pi$ cyclizations, suggesting that they may react through a different mechanism.

***Scheme 6.*** Racemic Formal Total Synthesis of Aplysin-20 (**64**) Patterned from the Work of Murai (ref 15b) in which a BDSB-Based Cyclization Was Utilized to Access **65** Directly from **60**[a]




[a] Reagents and conditions: (a) BDSB (1.1 equiv), nitromethane, 25 °C, 5 min, 72%, 5.3:1.3:1.0 tri:di:tetrasubstituted alkenes.

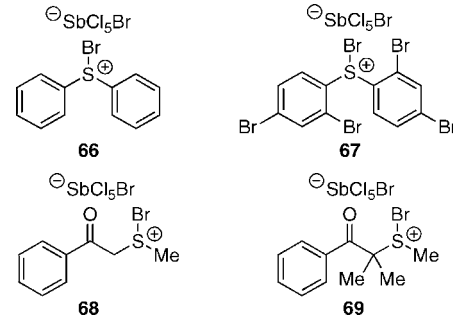



***Figure 3.*** Structures of selected BDSB derivatives (**66**−**69**) that have been investigated; of these, **67**−**69** have all been prepared successfully.

**3. Synthesis and Reactivity of IDSI: Application to the Formal Total Syntheses of Loliolide, K-76, and Stemodin.** We next sought to determine whether or not a related iodine variant of BDSB could be prepared. After several failed attempts, we were able to synthesize a crystalline form of such a material by combining molecular $I_2$, $Et_2S$, and $SbCl_5$ in 1,2-dichloroethane followed by the addition of hexanes to a saturated solution of the reagent prior to cooling.[41] We have termed this material (**70**, Scheme 7) IDSI on the basis of what we hoped would be

(37) The reaction temperature was essential to preventing lactone formation between the pendant carboxylic acid and the adjacent phenol.

(38) The synthetic sequence produced the fully protonated version of peyssonoic acid A. Initial NMR spectroscopic analysis of synthetic **51**, however, did not match that reported for the natural isolate (ref 34), primarily around the carboxylic acid residue, aromatic ring, and adjoining methylene group. Subsequent exposure of our material to $NaHCO_3$ provided the sodium salt of the carboxylate form; spectra obtained from this material fully matched the reported data. See Supporting Information for all relevant spectra and NMR data tables.

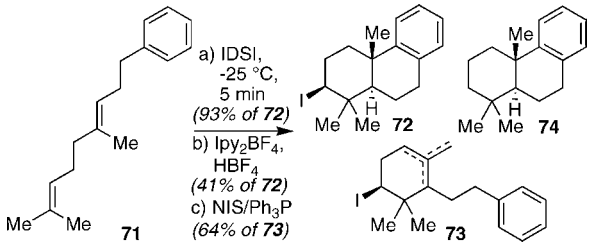
(39) (a) Matsuda, H.; Tomiie, Y.; Yamamura, S.; Hirata, Y. *J. Chem. Soc., Chem. Commun.* **1967**, 898–899. (b) Yamamura, S.; Hirata, Y. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2560–2562.

(40) Kato, T.; Kumazawa, S.; Kabuto, C.; Honda, T.; Kitahara, Y. *Tetrahedron Lett.* **1975**, *16*, 2319–2322. A total synthesis of aplysin-20 was also achieved via a TBCO-mediated cation-$\pi$ cyclization of a related starting material, albeit in low yield (cf. ref 11i).

(41) IDSI (**70**) is fully soluble at 25 °C in $MeNO_2$, $EtNO_2$, MeCN, $CH_2Cl_2$, DMSO, DMF, acetone, and EtOAc. It is moderately to slightly soluble in dioxane and $CHCl_3$, and insoluble in benzene, toluene, and hexanes.

***Scheme 7.*** Synthesis of IDSI (**70**)


***Scheme 8.*** Evaluation of Different Electrophilic Iodine Sources in Achieving Iodonium-Based Cyclizations of Substrate **71**[a]




[a] Reagents and conditions: (a) IDSI (1.2 equiv), $MeNO_2$, −25 °C, 5 min, 93%; (b) $Ipy_2BF_4$ (1.0 equiv), $HBF_4$ (1.0 equiv), $CH_2Cl_2$, −40 °C, 3 h, 41%; (c) NIS (1.0 equiv), $Ph_3P$ (0.3 equiv), $CH_2Cl_2$, −78 °C, 24 h; −40 °C, 6 h, 1.8:1.0 of **73**:**71** (<5% **72**).

reactivity equivalent to BDSB in polyene cyclizations, given that the reagent itself does not possess a structure or level of stability commensurate to BDSB. Indeed, X-ray diffraction revealed that IDSI is actually a chlorine-linked dimer, one whose crystalline form requires a maximum of −20 °C for effective storage; in addition, though the reagent can be weighed normally in air, it will decompose relatively quickly (within 30 min at 25 °C) if not properly attended, losing ICl in the process.[42] The inset picture of some needles within Scheme 7 shows this process through the discoloration of the paper on which the solid has been placed. Despite these differences, however, IDSI is quite effective and just as chemoselective as BDSB for initiating polyene cyclizations.

For instance, as shown in Scheme 8, exposure of polyene **71** to 1.2 equiv of IDSI in nitromethane at −25 °C for 5 min at a reaction concentration of 0.05 M afforded polycycle **72** as a single diastereomer in 93% yield. By contrast, neither Ishihara's[12a] nor Barluenga's reagent combinations[12b] were nearly as effective. For instance, in the case of the latter species, we obtained (after multiple attempts using various solvents and differential amounts of added $HBF_4$) an optimized 41% yield of **72**, with other major products being the partially cyclized **73**, unidentified diastereomers of **72**, and proton cyclized **74**. Similar results were obtained with NIS/$Ph_3P$.[43] Of course, materials like **73** can be converted into **72** in a subsequent step through the addition of acid; however, IDSI (like BDSB), typically avoids the need for this additional step as an acidic byproduct is produced during the course of the cyclization which can complete the sequence effectively in most cases, thereby enabling a more direct and efficient synthetic protocol.[44]

Table 2 provides our preliminary survey of IDSI reactivity with various electron-rich and electron-poor substrates derived from geraniol, farnesol, and nerol, each of which was performed with 0.1 mmol of substrate at a reaction concentration of 0.05 M. In the electron-rich cases (Entries 1−4), cyclization yields were commensurate with those observed previously with BDSB with equally fast reaction times, and only in the case of the conversion of **21** into **78** was an added acid needed at the end of the sequence to achieve complete cyclization. For electron-deficient systems (Entries 5−8; the final entry includes a nerol derivative), IDSI also worked well, though the use of various oxygen species to terminate those processes were not as efficient as BSDB. The main side-product in all of these cases was an uncyclized vicinal chloroiodide such as acetate **86** (formed from attempted IDSI cyclization of **15**, Entry 6), revealing that IDSI may have potential as an effective ICl source outside of polyene cyclizations. In any event, it is important to note that Entries 5−8 represent, to the best of our knowledge, the first examples of successful iodonium-based cyclizations of electron-deficient polyenes. All product stereochemistries were established based on comparison to previously synthesized materials and/or literature data.

On a global level, however, the true value in a direct and high yielding iodine-based cyclization lies not in forming an iodinated material (as there are no natural products isolated to date resulting from iodonium-induced cation-$\pi$ cyclizations) but rather in the ability to couple, displace, or easily eliminate the alkyl iodide within the product. For instance, we were able to readily form an alkene (i.e., **87**) in 86% yield from **72** with DBU in refluxing pyridine; the corresponding bromide is far more robust and does not participate in such chemistry.[45] As such, it seemed reasonable, given the established cyclization scope and capability for further iodine functionalization, to attempt to utilize IDSI to render more efficient and/or expeditious several previous total syntheses of various nonhalogenated natural product polycycles, particularly those cases where stoichiometric amounts of metals were required for success.

For instance, in 1983, Rouessac and co-workers[46] synthesized the natural product loliolide (**92**, Scheme 9)[47] through a Hg(II)-based polyene cyclization of **88**, which, following replacement of the organomercurial with iodine under radical conditions[16] and subsequent elimination, afforded key alkene **91** in 25% overall yield. In our hands, exposure of **88** to 1.2 equivalents of IDSI afforded cation-$\pi$ cyclization product **93** in 79% yield

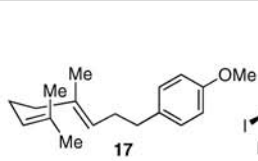
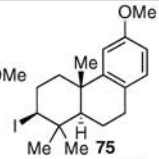
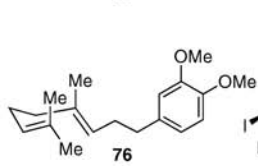
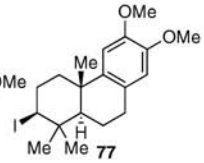
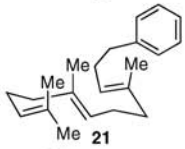
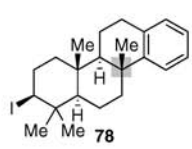
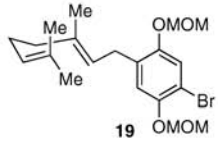
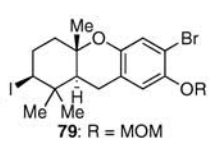
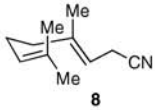
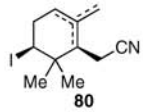
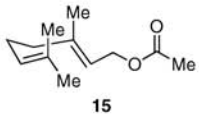
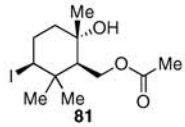
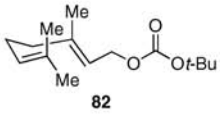
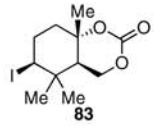
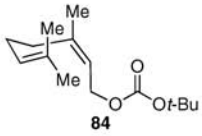
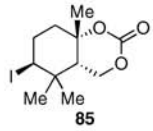
(42) The lengths of the I−Cl bonds within this material are 2.814 and 2.714 Å. These values compare favorably to related compounds such as a chlorine-linked NIS-dimer which has very similar bond lengths (2.845 and 2.910 Å) and is a source of ICl as well: Ghassenzadeh, M.; Dehnicke, K.; Goesmann, H.; Fenske, D. *Zeit. Naturforschung B: Chem. Sci.* **1994**, *49*, 602–608. We note that the average I-Cl bond length is 2.553 Å according to the Cambridge Structural Database, version 5.31, 2009. The dimethysulfonium variant of IDSI was reported as a monomeric species: Minkwitz, R.; Prenzel, H. *Z. Anorg. Alleg. Chem.* **1987**, *548*, 97–102.

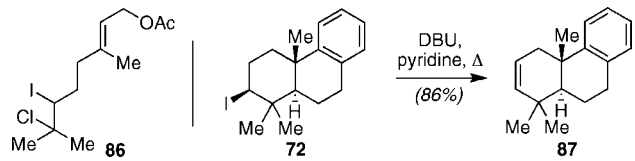
(43) See Supporting Information section for complete details.

(44) We note, however, that IDSI should be viewed as having complementary reactivity to Barluenga's reagent. For instance, electron-rich aromatic rings undergo electrophilic aromatic substitution when pendant monosubstituted double bonds are activated with $Ipy_2BF_4$; IDSI will not cleanly perform such reactions.

(45) For selected examples of the elimination of alkyl iodides to form alkenes, see: (a) Furber, M.; Kraft-Klaunzer, P.; Mander, L. N.; Pour, M.; Yamauchi, T.; Murofushi, N.; Yamane, H.; Schraudolf, H. *Aust. J. Chem.* **1995**, *48*, 427–444. (b) Jin, L.; Nemoto, T.; Nakamura, H.; Hamada, Y. *Tetrahedron: Asymmetry* **2008**, *19*, 1106–1113. (c) Eidman, K. F.; MacDougall, B. S. *J. Org. Chem.* **2006**, *71*, 9513–9516. (d) Soorukram, D.; Qu, T.; Barrett, A. G. M. *Org. Lett.* **2008**, *10*, 3833–3835.

***Table 2.*** Exploration of the Generality of Direct, Iodonium-Induced Cation-$\pi$ Cyclizations using IDSI (1.2 equiv) and 0.1 mmol of Substrate in Nitromethane

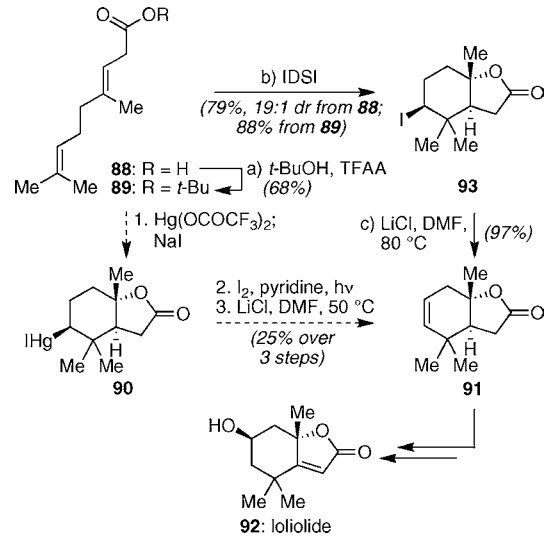
| Entry | Starting Material | Product | Temp. (°C) | Time (min) | Yield (%) |
|---|---|---|---|---|---|
| 1 |  **17** |  **75** | -25 | 5 | 90 |
| 2 |  **76** |  **77** | -25 | 5 | 73 |
| 3 |  **21** |  **78** | -25 | 30 | 60[a,b] |
| 4 |  **19** |  **79**: R = MOM | -25 | 5 | 85 |
| 5 |  **8** |  **80** | 25 | 5 | 85[c] |
| 6 |  **15** |  **81** | 0 | 1 | 45 |
| 7 |  **82** |  **83** | 0→25 | 30 | 57 |
| 8 |  **84** |  **85** | 0→25 | 30 | 48 |




[a] Isolated as a 2:1 mixture of inseparable stereoisomers about the highlighted carbon atom favoring the drawn diastereomer. [b] $MeSO_3H$ (15 equiv) added with 1 h of additional stirring to promote the final cyclization. [c] Produced as a 8.5:1.4:1.0 mixture of tri:tetra:disubstituted alkene isomers.

with 19:1 diastereoselectivity at the bridgehead methyl position, while the use of the *t*-butyl ester-protected variant (**89**, formed in 68% yield from **88**) enabled an IDSI-based synthesis of **93** as a single diastereomer in 88% yield. Subsequent LiCl-induced elimination afforded **91** in 97% yield, thereby accounting for an overall yield of 73% of alkene **91** (an ~3 fold improvement

***Scheme 9.*** Racemic Formal Total Synthesis of Loliolide (**92**) Patterned from the Work of Rouessac (ref 46) in which an IDSI-Based Cyclization and Subsequent LiCl-Induced Elimination Was Utilized to Access **91**[a]



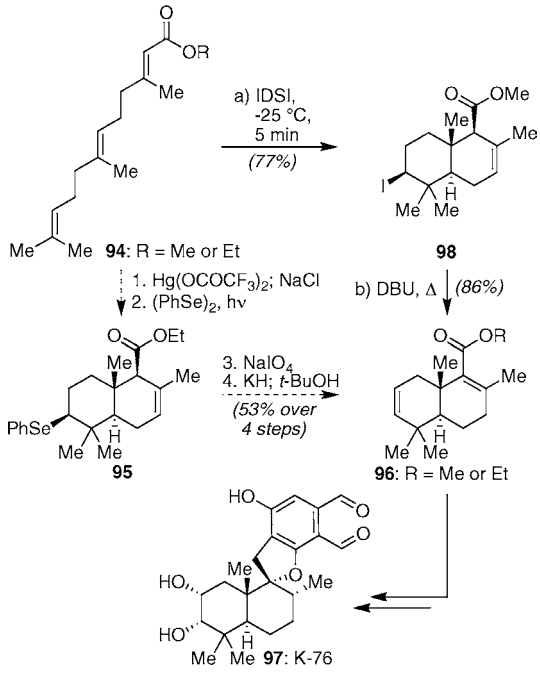

[a] Reagents and conditions: (a) TFAA (5.0 equiv), *t*-BuOH, 0 to 25 °C, 20 min, 68%; (b) IDSI (1.2 equiv), $MeNO_2$, 5 min, 79% and 19:1 d.r. from **88** at −25 °C, 88% from **89** at 0 °C; (c) LiCl (50 equiv), DMF, 80 °C, 12 h, 97%.

in fewer steps) from **88**, without the use of stoichiometric Hg(II). Similarly, IDSI proved quite effective in our efforts to prepare **96** (Scheme 10), a key intermediate in the McMurry and Erion total synthesis[48] of K-76 (**97**)[49] reported in 1985. In this case, bicycle **98** was prepared in 77% yield using IDSI, illustrating its utility as a powerful cation-$\pi$ initiator as even the very electron-deficient olefin within **94** participated in this cyclization reaction. Typically, such non-nucleophilic olefins (in this case an $\alpha,\beta$-unsaturated ester) do not participate in cation-$\pi$ cyclizations unless Hg(II) is utilized.[1,4] A subsequent elimination using DBU at elevated temperatures provided the requisite alkene **96** in 66% overall yield for the two-step sequence. This outcome compares favorably to the 53% overall yield obtained over the 4 steps of the McMurry and Erion route in which stoichiometric Hg(II) and Se were employed.[50] It should be noted that in our hands neither NIS/$Ph_3P$ nor $Ipy_2BF_4$/$HBF_4$ was able to fully cyclize the same substrate of Scheme 10 (i.e., **94**) in any yield.[43]

It must be mentioned, however, that Hg(II)-based cyclizations certainly do have merit. For instance, in the Corey total synthesis[51] of stemodin (**101**, Scheme 11),[52] polyene **99** was

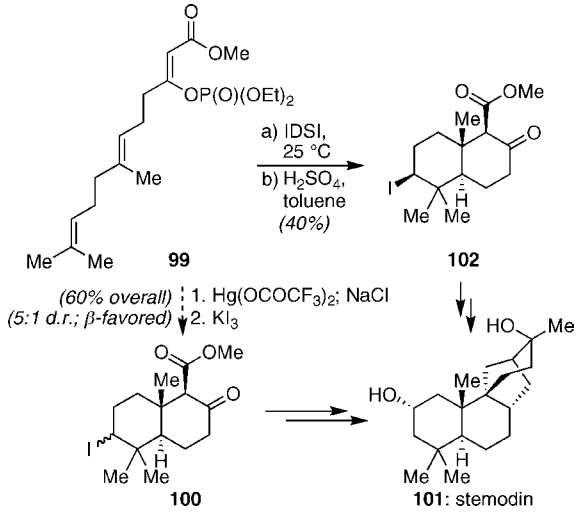
(46) (a) Rouessac, F.; Zamarlik, H.; Gnonlonfoun, N. *Tetrahedron Lett.* **1983**, *24*, 2247–2250. For other papers in the series, see: (b) Rouessac, A.; Rouessac, F.; Zamarlik, H. *Bull. Chim. Soc. Fr.* **1981**, 199–203. (c) Zamarlik, H.; Gnonlonfoun, N.; Rouessac, F. *Can. J. Chem.* **1984**, *62*, 2326–2329.
(47) (a) White, E. P. *New Zealand J. Agric. Res.* **1958**, *1*, 859–865. (b) Hodges, R.; Porte, A. L. *Tetrahedron* **1964**, *20*, 1463–1467.
(48) (a) McMurry, J. E.; Erion, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 2712–2720. (b) Erion, M. D.; McMurry, J. E. *Tetrahedron Lett.* **1985**, *26*, 559–562.
(49) Kaise, H.; Shinohara, M.; Miyazaki, W.; Izawa, T.; Nakano, Y.; Sugawara, M.; Sugawara, K. *J. Chem. Soc., Chem. Commun.* **1979**, 726–727.
(50) For an alternate total synthesis of K-76, see: Mori, K.; Komatsu, M. *Liebigs Ann. Chem.* **1988**, 107–119. This route did not utilize a cation-$\pi$ cyclization, but used the same key intermediate, compound **96**, to achieve their synthesis. Compound **96** was accessed in 9 steps and 2.5% overall yield from commercial materials.
(51) Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc.* **1980**, *102*, 7612–7613.

***Scheme 10.*** Racemic Formal Total Synthesis of K-76 (**97**) Patterned from the Work of McMurry (ref 48) in which an IDSI-Based Cyclization and Subsequent DBU-Induced Elimination Was Utilized to Access **96**[a]




[a] Reagents and conditions: (a) IDSI (1.2 equiv), $MeNO_2$, −25 °C, 5 min, 77%; (b) DBU (20 equiv), pyridine, 120 °C, 12 h, 86%.

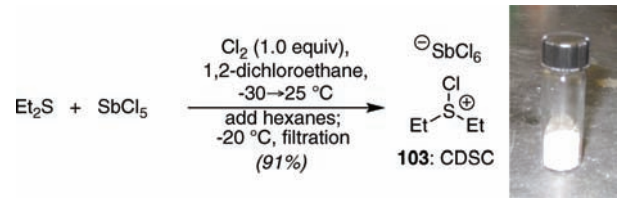
***Scheme 11.*** Racemic Formal Total Synthesis of Stemodin (**101**) Patterned from the Work of Corey (ref 51) in which an IDSI-Based Cyclization Was Utilized to Access **102**[a]




[a] Reagents and conditions: (a) IDSI (1.2 equiv), $MeNO_2$, 25 °C, 5 min; (b) conc. $H_2SO_4$ (15 equiv), toluene, 0 °C, 30 min, 40% over two steps.

smoothly converted into **100** in 60% yield via treatment with $Hg(OCOCF_3)_2$ to effect the cyclization followed by replacement of the intermediate organomercurial with iodine.[53] IDSI was able to form similar materials from **99**, but in reduced yield as the predominant products obtained were partially cyclized. In our hands, only a portion of these could only be successfully converted into **102** through the use of an acid-promoted cyclization (concentrated $H_2SO_4$ in toluene) in a separate step; extensive efforts to differentially functionalize the enol ether in **99** (including groups such as a methyl-, methoxymethyl-, and various silyl-enol ethers) afforded no improvement above the 40% yield indicated within Scheme 11. Thus, in this case, the overall yield of the polycycle was not superior through the use of IDSI, though the toxic metal species used for the polyene cyclization could still be avoided.

***Scheme 12.*** Synthesis of CDSC (**103**)




**4. Synthesis and Reactivity of CDSC.** We next sought to determine if direct, chloronium-induced cyclizations could be achieved with a reagent of the general design of BDSB and IDSI. The synthesis of our test reagent, a derivative of a previously reported $Me_2S$ variant[54] which we name CDSC (chloro diethylsulfonium hexachloroantimonate, **103**), is shown in Scheme 12.

Similar to BDSB and IDSI, this compound is a crystalline solid that is stable at −20 °C for at least several months and can be handled and weighed in air. As indicated in Table 3, polyene cyclizations of various materials possessing differential electron wealth were undertaken with CDSC, all at a reaction concentration of 0.05 M. Though the resultant product yields are not nearly as high as those observed with BDSB and IDSI for the same substrates, these entries represent, to the best of our knowledge, the first examples of effecting chloronium-induced polyene cyclizations in any yield via an ionic pathway.[10] Of note, these cyclizations do not, for the most part, possess diastereocontrol, perhaps reflecting a global challenge in reactivity due to greater tertiary carbocation rather than bridged chloronium-character in the initial reactive intermediate (as indicated by the structures at the bottom of Table 3).[55]

**5. Efforts toward Asymmetric Induction.** Finally, we desired to prepare chiral versions of CDSC, BDSB, and IDSI in a preliminary investigation of their potential to achieve asymmetric versions of the reactions described above. Although

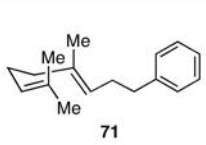
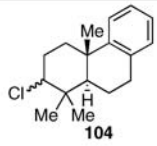
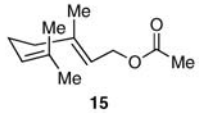
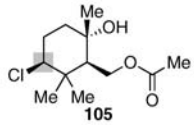
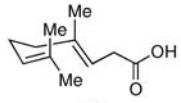
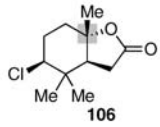
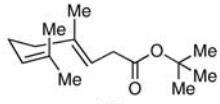
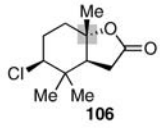
(52) Manchand, P. S.; White, J. D.; Wright, H.; Clardy, J. *J. Am. Chem. Soc.* **1973**, *95*, 2705–2706.

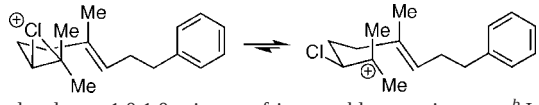
(53) The Corey group also used a similar route to prepare the natural product K-76: Corey, E. J.; Das, J. *J. Am. Chem. Soc.* **1982**, *104*, 5551–5553.

(54) Meerwein, H.; Zenner, K.-F.; Gipp, R. *Justus Liebigs Ann. Chem.* **1965**, 67–77.

(55) Several experimental studies (pioneered by the Olah group) have postulated that some halonium ions, especially chloronium ions, exist not as traditional 3-membered rings but as "open" carbocations, or perhaps as an equilibrium between the two species. This appears especially true when one or more of the carbons of the potential chloronium ion is tertiary: (a) Olah, G. A.; Westerman, P. W.; Melby, E. G.; Mo, Y. K. *J. Am. Chem. Soc.* **1974**, *96*, 3565–3573. (b) Olah, G. A.; Bollinger, J. M.; Mo, Y. K.; Brinich, J. M. *J. Am. Chem. Soc.* **1972**, *94*, 1164–1168. (c) Olah, G. A.; Bollinger, J. M. *J. Am. Chem. Soc.* **1968**, *90*, 947–953. (d) Berman, D. W.; Anicich, V.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1979**, *101*, 1239–1248. A more recent NMR analysis of tetrasubstituted chloronium ions indicates that open structures predominate. (e) Ohta, B. K.; Hough, R. E.; Schubert, J. W. *Org. Lett.* **2007**, *9*, 2317–2320. Theoretical studies also corroborate that the open carbocation is favored in the specific case of the trisubstituted chloronium ion. (f) Yamabe, S.; Tsuji, T.; Hirao, K. *Chem. Phys. Lett.* **1988**, *146*, 236–242. As noted by a referee, a plausible alternative explanation for the lack of stereocontrol in chloronium ion cyclizations is reaction through both chair/chair and boat/chair conformations, perhaps owing to the higher reactivity and electrophilicity of the chloronium ion electrophile compared to the bromonium and iodonium counterparts.

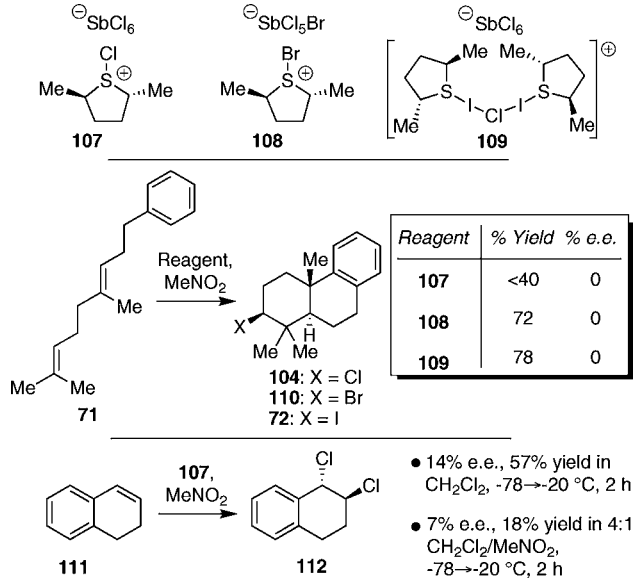
***Table 3.*** Exploration of the Generality of Direct, Chloronium-Induced Cation-$\pi$ Cyclizations using CDSC (1.1 equiv) and 0.1 mmol of Substrate in Nitromethane

| Entry | Starting Material | Product | Temp. (°C) | Time (min) | Yield (%) |
|---|---|---|---|---|---|
| 1 |  **71** |  **104** | -25 | 5 | 46[a] |
| 2 |  **15** |  **105** | 0 | 1 | 18[b] |
| 3 |  **88** |  **106** | -25 | 5 | 38[c] |
| 4 |  **89** |  **106** | 0 | 5 | 20[c] |



[a] Isolated as a 1.0:1.0 mixture of inseparable stereoisomers. [b] Isolated as a 2.2:1.0 mixture of separable diastereoisomers at the highlighted carbon favoring the drawn product. [c] Produced as a 4.0:1.0 mixture of separable diastereomers at the highlighted carbon favoring the drawn product.

***Scheme 13.*** Initial Explorations into Asymmetric Versions of the Developed Reagent Class




several chiral sulfides are known, we focused our attention on materials with $C_2$-symmetry,[56] using a sequence involving an enzymatically controlled step to synthesize (2*R*,5*R*)-(+)-2,5-dimethylthiolane[57] for reagents **107**, **108**, and **109** (Scheme 13, all putative structures). Unfortunately, all endeavors with these, and related compounds, afforded no asymmetry in the cation-$\pi$ cyclization of substrate **71**, though they all led to the formation of the expected racemic products. Interestingly, however, with reagent **107** we were able to add $Cl_2$ across the double bond of **111** with some enantioselection (up to 14% e.e.);[58] initial screens have shown that solvent is a critical factor in the efficiency of this process, suggesting that further refinement may enable improvement on this preliminary finding. It is important to note that the reagent formed with the omission of $SbCl_5$ did not afford any **112**, indicative of the importance of the normally inert $SbCl_6$ counterion. Explorations seeking to build upon these initial results are the subject of current endeavors.

## Conclusion

Although direct halonium-induced polyene cyclizations have long been achievable only through the use of enzymes *in vivo*, this article describes the first class of simple reagents that can effect such reactions in a reaction flask for a broad range of substrates. Consequently, the direct total and formal syntheses of 6 different natural products were achieved, one of which required a substantive structural revision following the synthesis and cyclization of 4 stereochemically distinct polyene systems. In addition, chiral forms of the reagent class have shown some promise in enantioselective halogenations, indicating that they have potential for a number of significant applications outside of cation-$\pi$ cyclizations.

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**Supporting Information Available:** Experimental procedures, compound characterization, copies of spectral data, and X-ray crystallographic structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(56) $C_2$-symmetric ligands were chosen due to our previous success in utilizing them for asymmetric Hg(II)-induced cyclizations (cf. ref 17).
(57) (a) Julienne, K.; Metzner, P. *J. Org. Chem.* **1998**, *63*, 4532–4534. (b) Braun, W.; Calmuschi, B.; Haberland, J.; Hummel, W.; Liese, A.; Nickel, T.; Steizer, O.; Salzer, A. *Eur. J. Inorg. Chem.* **2004**, *11*, 2235–2243.
(58) For a recent total synthesis featuring an enantioselective chlorination of an isolated alkene, see: Snyder, S. A.; Tang, Z.-Y.; Gupta, R. *J. Am. Chem. Soc.* **2009**, *131*, 5744–5745.