Organic Syntheses

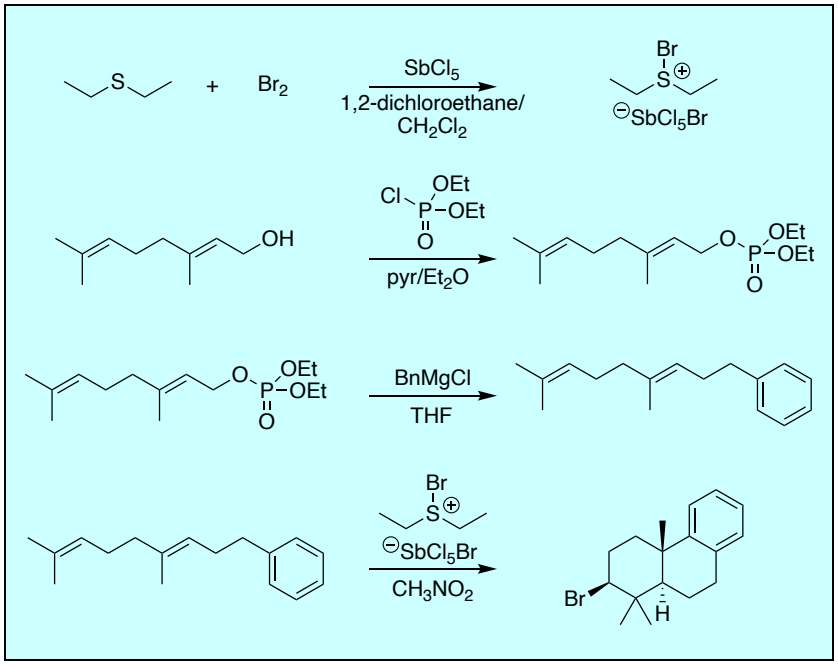
Discussion Addendum for:

Synthesis of $Et_2SBr•SbCl_5Br$ and its Use in Biomimetic Brominative Polyene Cyclizations

Cooper A. Taylor and Scott A. Snyder*[1]

Department of Chemistry, The University of Chicago, 5735 S. Ellis Avenue, Chicago, IL, 60637, USA

Original Article: Snyder, S. A.; Treitler, D. S. Org. Synth. ***2011****, 88, 54–69*

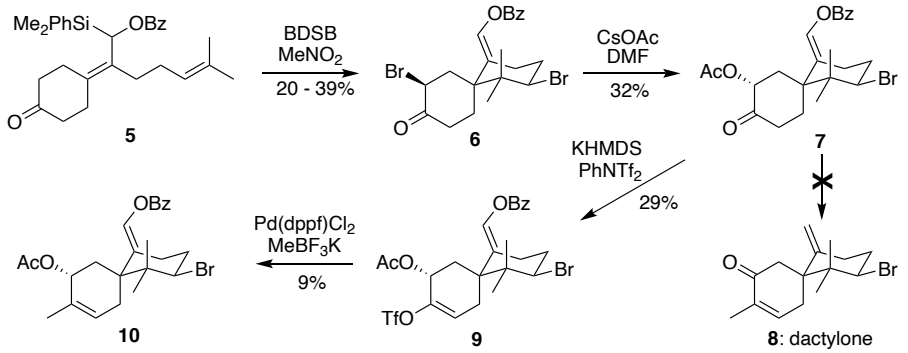


Halogenation reactions have long been viewed as one of the most useful transformations in organic synthesis, either to directly install a halogen atom or to generate a reactive intermediate that can promote further transformations (i.e. cyclization, ring-expansion, etc.). In a 2011 *Organic*

Syntheses article,[2] Snyder and Treitler outlined the development of a novel, highly electrophilic bromonium ion source, BDSB ($Et_2SBr•SbCl_5Br$), and discussed its successful application to bromonium-induced polyene cyclizations of varied substrates.[3] In 2015, an update to the general reaction scope that BDSB can facilitate was published in the *Encyclopedia of Reagents for Organic Synthesis* (EROS).[4] At that time, BDSB had been applied to several reaction processes outside of polyene cyclizations, including both ring-expanding bromoetherification[5-8] as well as electrophilic aromatic bromination,[9-11] with results in some cases that were not replicated by other bromonium sources. In this contribution, further exploration of the general scope of BDSB using examples that either were not covered in that EROS contribution or that have appeared in more recent work, is provided. The scope of these efforts is split across three major applications: (1) bromonium-induced polyene cyclizations, (2) electrophilic bromination of aromatic rings, and (3) bromoetherifications.

Bromonium-Induced Polyene Cyclizations

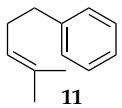
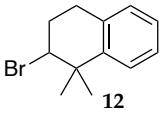
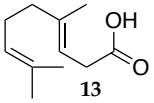
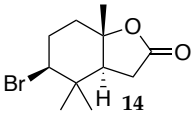
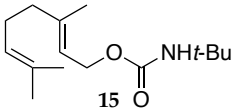
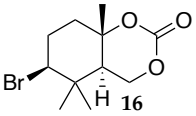
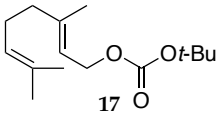
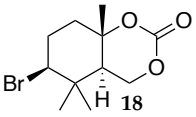
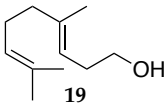
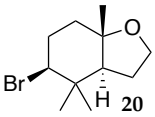
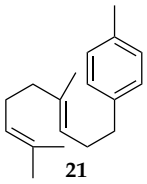
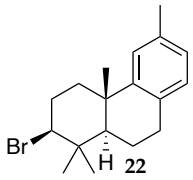
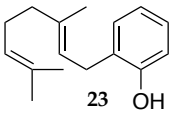
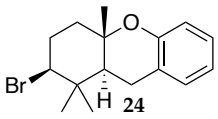
In 2016, Snyder *et al.* reported two distinct strategies toward the bromochamigrene collection of natural products, which includes (±)-dactylone (**8**, Scheme 1).[12] One of these was a putative biomimetic approach utilizing BDSB to enact a polyene cyclization. Of note, in the key transformation converting **5** into **6**, not only was the polyene cyclization accomplished in a reproducible yield of 20–39% (dependent on scale) at 25 °C in $MeNO_2$, but a second regio- and stereoselective α-bromination of the ketone occurred as well when using 2.0 equivalents of BDSB; this result was further confirmed through X-ray crystallographic analysis. Critical to its overall success, especially in terms of avoiding bromination of the central alkene prior to initiation at the less substituted terminal alkene, was protection of the alcohol with a deactivating group in the form of a benzoate ester. Although efforts to form (±)-dactylone (**8**) from this product were unsuccessful, intermediate **10**, which shares the same overall patterning of the desired targets, could be obtained, albeit in low yield.



Scheme 1. Polyene cyclization towards the bromo-chamigrene framework

In more recent efforts, several groups have sought to develop additional reagents that can serve as powerful bromonium ion sources, with BDSB being used as a typical point of comparison. For example, Gulder and co-workers discovered in 2018 that the use of NBS in HFIP with a morpholine•HFIP additive could achieve polyene cyclization yields commensurate to BDSB in most cases (Table 1). However, there were some examples which showed higher yield and/or diastereoselectivity. At present, these results suggest a strong substrate-dependence within the context of this transformation, with no particular trends being obvious other than BDSB generally does not perform well in the presence of free alcohols (as in **19**, *vide infra*).

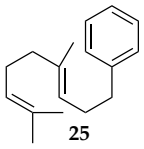
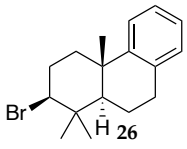
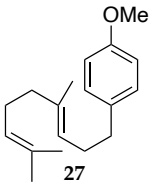
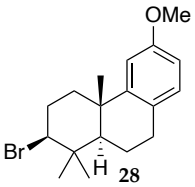
Table 1. Exploration of scope of NBS/morpholine•HFIP salt compared to BDSB[a,b]

Substrate	Product	Yield (d.r.) NBS/ morpholine•HFIP	Yield (d.r.) BDSB
 **11**	 **12**	83%	79%
 **13**	 **14**	58% (89:11)	73% (>95:5)
 **15**	 **16**	57% (>95:5)	13%[c] (>95:5)
 **17**	 **18**	38% (>95:5)	65% (83:17)
 **19**	 **20**	78% (>95:5)	22%[c]
 **21**	 **22**	72% (>95:5)	67% (>94:6)
 **23**	 **24**	77%[d] (>95:5)	72% (>95:5)

[a] NBS (1.2 equiv) was added to morpholine•HFIP salt (1.4 equiv) in HFIP at 0 °C. After stirring for 10 min at 0 °C, substrate (1.0 equiv) was added. [b] BDSB (1.0 equiv) was dissolved in $MeNO_2$ and was added to substrate (1.0 equiv) in $MeNO_2$ at –25 °C. [c] Several attempts to convert substrate using BDSB resulted mainly in decomposition of starting material. [d] 1.1 equiv NBS were used.

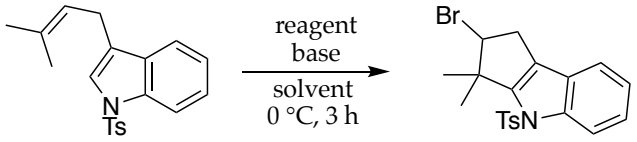
As exemplified in the X-ray crystal structure of BDSB, the antimonate counterion generates a more naked source of bromonium ion than the complex of a simple sulfide with molecular Br_2 alone by increasing the distance between the two bromine atoms of the original halogen source. Similarly, the Hennecke group sought to develop a new brominating agent based on counterion selection that could serve as an alternative to BDSB in polyene cyclizations. They ultimately found that tetrakis [3,5-bis(trifluoromethyl)phenyl] borate ($BArF^-$) served as a desirable coordinating counterion that could greatly increase the reactivity of the bromiranium ion of adamantylidene adamantane ($[Ad_2Br][BArF]$).[14] Although the yields observed for their initial polyene substrates proved to be lower than that of BDSB (Table 2), they were able to further expand their reaction scope in 2019 to the cyclization of indole terpenoid polyenes such as **29** (Table 3),[15] achieving superior yields to all other known cyclization methods/tools.[3,13] These conditions were applicable to the cyclization of farnesyl indoles, establishing a pentacyclic core in a single step.

Table 2. Comparing the efficiency of $[Ad_2Br][BArF]$/HMDS to BDSB for hydrocarbon polyene cyclizations

Substrate	Product	Yield $[Ad_2Br][BArF]$/HMDS[a]	BDSB[b]
 **25**	 **26**	64%[c] (26%)[d]	75%
 **27**	 **28**	50%[c] (30%)[d]	76%

[a] Substrate was treated with HMDS (2.0 equiv) in CH_2Cl_2 at 0 °C followed by $[Ad_2Br][BArF]$ (1.0 equiv) for 3 h. [b] BDSB (1.0 equiv) was dissolved in $MeNO_2$ and was added to substrate (1.0 equiv) in $MeNO_2$ at –25 °C and stirred for 15 min. [c] Yield after column chromatography to give products of ~90% purity. [d] Yield after crystallization from acetone.

Table 3. Condition screening for electrophilic bromocyclization of an indole core



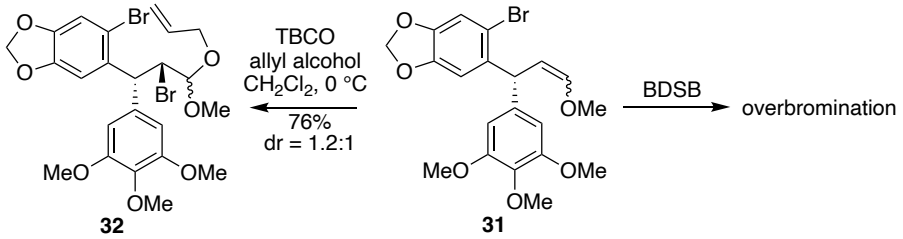
29 **30**

Entry	Reagent	Eq.	Base	Solvent	Yield (%)
1	NBS	1.2	—	CH_2Cl_2	0
2	TBCO	1.2	—	CH_2Cl_2	0
3	DBDMH	1.2	—	CH_2Cl_2	2
4	NBS	1.2	morpholine	HFIP	8
5	BDSB	1.1	—	$MeNO_2$	5
6	$[Ad_2Br][BArF]$	1.2	HMDS	CH_2Cl_2	59

Of global note, BDSB was shown to provide the desired product in all cases screened across the examples delineated in this section. While in some examples those yield values were low compared to other reagents, that broad utility for this reaction process appears to be a unique feature.

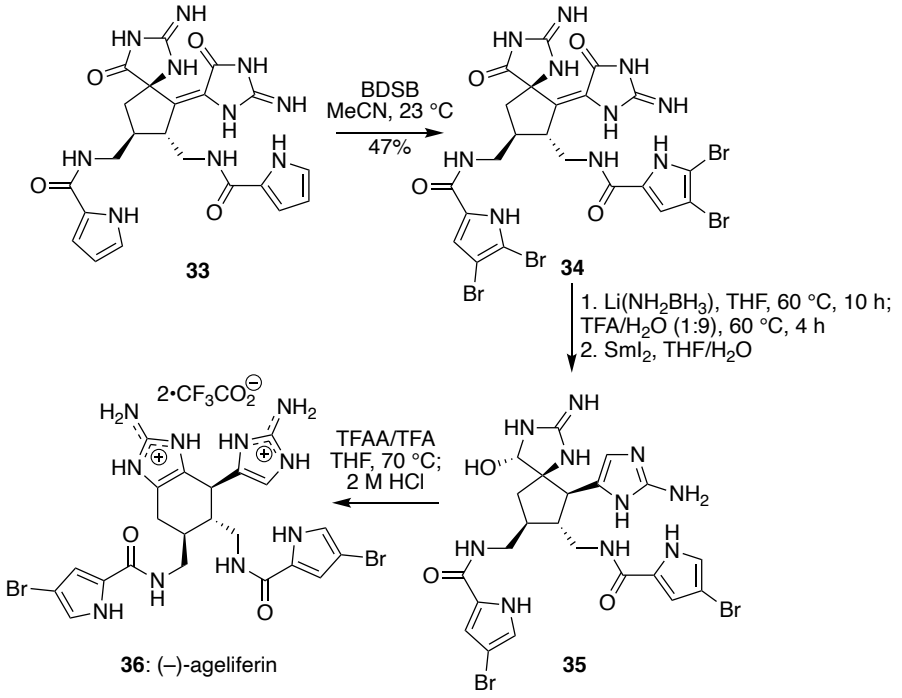
Electrophilic Bromination

Given the highly electrophilic nature of BDSB, it is typically able to achieve selective bromination of the most electron-rich olefin or aromatic system within a scaffold of interest, even when multiple variants of each are present. In some cases, though, selectivity can be challenging to achieve. For instance, in work by Peng *et al.* in 2018 during their synthetic efforts toward podophyllotoxin and related family members,[16] it was shown that when **31** (Scheme 2) was exposed to BDSB, they obtained an over-brominated product in which the most electron-rich aromatic ring was brominated as well as the electron-rich alkene of the enol ether. While sub-optimal here, with TBCO affording the desired adduct (i.e. **32**), it does highlight the power of BDSB to execute electrophilic aromatic substitutions without the need for any added Lewis acids.



Scheme 2. Electrophilic bromination on the way to (–)-podophyllotoxin

That property proved advantageous during the Harran group's synthesis of (–)-ageliferin (Scheme 3),[17] where these researchers faced the practical problem of poor substrate solubility given the highly polar nature of their advanced intermediates, thus affording challenges for further derivatization in general terms. However, they found that bromination of the pyrrole rings improved solubility, and here the only bromination source that yielded a desirable result with **33** in reasonable yield was BDSB. That event provided the tetra-brominated product **34** in 47% yield with high regioselectivity in the four brominations achieved. Other halogen sources such as Br_2 and NBS could react with **33**, but uncontrolled/non-specific polyhalogenation was observed instead. As shown in Scheme 3, this product could then be properly manipulated over 3 steps,[18] including a chemoselective SmI_2-mediated reduction event which also regioselectively cleaved two of the four bromines introduced by BDSB, to generate (–)-ageliferin (**36**).



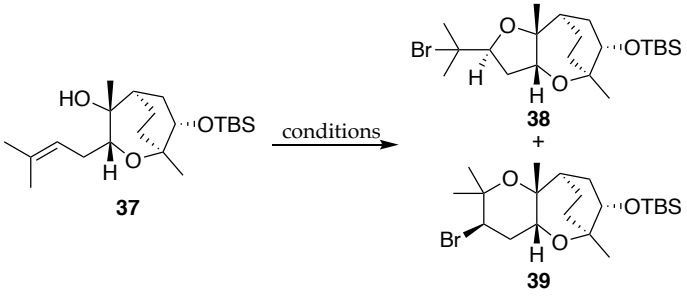
Scheme 3. Electrophilic tetrabromination on the way to (–)-ageliferin

Bromoetherification

Among functional groups involving bromine atoms, cyclic bromoethers are common structural motifs, particularly in natural products obtained from marine sources. Despite that ubiquity, however, they can be challenging to synthesize through direct cyclization reactions involving bromonium-activated alkene electrophiles and alcohol nucleophiles. For example, one of the most difficult is the direct formation of 6-*endo* cyclization products when 5-*exo* products can also result, especially in flexible systems lacking high degrees of locking sp^2-hybridization. For example, in 2014, Koshino, Takahashi, and co-workers sought to develop an efficient synthesis of aldingenin C,[19] a novel halogenated terpenoid from the *Laurencia* family of natural products.[20] During their investigations, they sought to construct a brominated tetrahydropyran (THP) fused to a 2-oxabicyclo[3.2.2]nonane system, which they envisioned could be mediated by an electrophilic bromonium source (i.e. the formation of **39** from **37**,

Table 4). Despite screening BDSB, TBCO, and DBDMH in various solvents and temperatures, they only observed the dominant formation of the respective tetrahydrofuran (THF) analogue (**38**). Only in the case of TBCO in $MeNO_2$ at 0 °C, was the desired THP product **39** obtained in 25% yield along with **38** in 20% yield (entry 3, Table 4). BDSB resulted in the formation of **38** in up to 15% yield in EtOAc and MeCN at 0 °C for both cases, with 4% and 2% yields of **39**, respectively.

Table 4. Bromonium-induced cyclization of 37

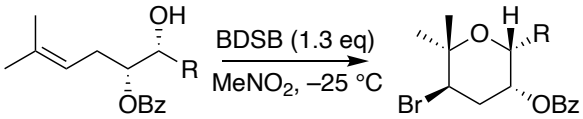


Entry	Reagent (1.2 eq)	Solvent	Temp (°C)	Time	**38** (%)	**39** (%)
1	TBCO	CH_2Cl_2	–78 - 0 °C	1 h	36	7
2	TBCO	MeCN	–23 - 0 °C	1.5 h	44	4
3	TBCO	$MeNO_2$	0 °C	1 h	20	25
4	BDSB	EtOAc	0 °C	10 min	15	4
5	BDSB	MeCN	0 °C	18 h	15	2
6	BDSB	$MeNO_2$	0 °C	1 h	1	2
7	DBDMH	CH_2Cl_2	0 - 23 °C	1 h	4	1
8	DBDMH	MeCN	0 - 23 °C	1 h	7	10
9	DBDMH	$MeNO_2$	0 - 23 °C	1 h	12	2

In 2015, Snyder *et al.* provided a potential explanation for the modest observed product formation for these events.[21] Specifically, it was found that the desired 6-*endo* BDSB-induced bromoetherifications to form THP systems provided moderate to good yields with high diastereoselectivity when the respective cyclization precursor was a secondary alcohol versus the tertiary alcohol counterpart (see Table 5). Although the subsequent

addition of methyl groups to generate what would formally have been tertiary alcohol precursors did not succeed, a variety of derivatizations were possible with the presence of a benzylic group at position R. As for the tertiary alcohol precursors that would directly map to known natural products, ~1:1 mixtures of the 6-*endo* and 5-*exo* products were observed at low temperatures (–25 °C in $MeNO_2$), but use of higher temperatures, longer reaction times, and/or subsequent exposure to acid or re-exposure to BDSB resulted in the formation of the 5-*exo* product exclusively. Calculations (MM2) also suggested the thermodynamic product is the 5-*exo* cyclization, thus indicating the 5-*exo* product is both thermodynamically and kinetically favored for most tertiary alcohol-containing substrates. Indeed, among bromoetherifications, this reaction (first explored in depth by Corey and co-workers, where 5-*exo* products also predominated)[22] remains one of the most challenging for available bromonium sources.

Table 5. Selective 6-membered bromoether formation



40 **41**

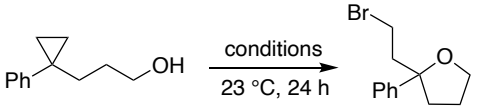
Entry	R	Yield (%)
1	-$CH_2C{=}CH_2$	66
2[a]	-$CH{=}CHCH_3$	57
3[b]	-Ph	70
4[c]	-(*p*-OBn)Ph	55

[a] starting material = ~12:1 dr
[b] starting material = 4.6:1 dr
[c] starting material = ~5.7:1 dr

By contrast, events that can resize rings, particularly those with strain, can perform quite well with appropriate bromonium sources to generate bromoether products. One example involving cyclopropane starting materials was described by Hennecke *et al.* in 2015.[23] Here, it is believed that

the highly strained nature of the cyclopropane ring within substrates such as **42** confers upon it similar reactivity as unsaturated C–C bonds when appropriate nucleophiles are nearby (Table 6).[24-25] In this case, although elemental Br_2 and less electrophilic brominating reagents such as TBCO and NBS provided the desired halocyclization product (**43**) in modest to good yields (41–60%), the highly electrophilic brominating reagent BDSB produced an impressive 79% yield (Table 4, Entry 4). This result was only matched by DBDMH (76%) when the reaction was performed in CH_2Cl_2.

Table 6. Halocyclization of cyclopropanol 42

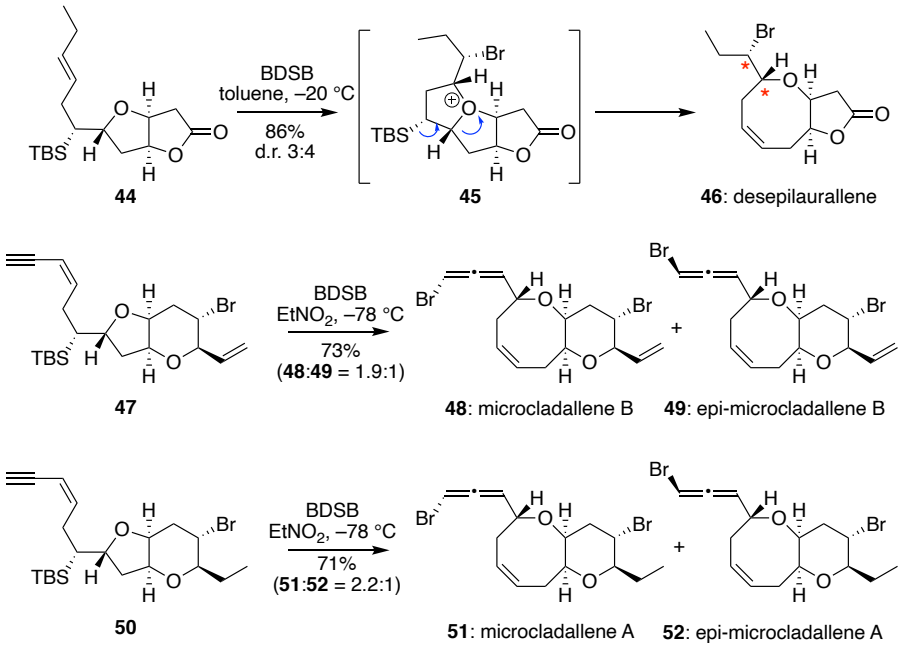


42 **43**

Entry	Reagent (1.2 eq)	Solvent	Yield (%)
1	Br_2	CH_2Cl_2	41
2	TBCO	CH_2Cl_2	47
3	NBS	CH_2Cl_2	60
4	BDSB	CH_2Cl_2	79
5	DBDMH	CH_2Cl_2	76
6	DBDMH	THF	39
7	DBDMH	CH_3CN	49
8	DBDMH	toluene	14

The Snyder group has also greatly expanded the applicability of BDSB and ring-expanding bromoetherifications to the total syntheses of numerous members of the *Laurencia* family of natural products as a means to prepare 8-membered bromoether ring systems. Nine members have been prepared to date,[5, 26-27] six since the publication of the BDSB review in EROS.[4] In recent cases, the use of BDSB allowed for the development of a general synthetic approach to the core of many *Laurencia* family members (Scheme 4), [26] and was applied for both ring-expanding bromoetherification (**44**→**46**) as well as bromoallene formation (**47**→**48**/**49** and **50**→**51**/**52**), both facilitated through silyl elimination. Impressive, in the latter two cases in particular, was the

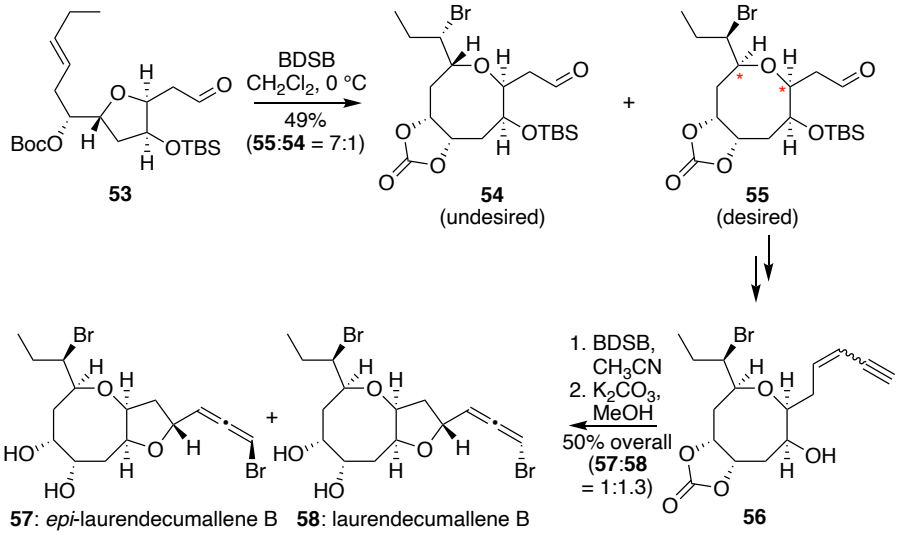
selectivity of the BDSB reagent in the presence of several potentially reactive π-systems, including a new alkene formed at the end of the sequence. However, it must be noted that in all three cases the transformations were not fully diastereoselective, with each case having its own inherent structural bias leading to one product over another. For instance, the desired diastereomer of desepilaurallene (**46**) was consistently found to be the minor diastereomer in terms of the stereochemistry produced at the positions denoted by the red stars (in a 3:4 ratio). Biosynthetically, these results potentially indicate that the additional rings and stereocenters attached to the portion of the molecule undergoing ring-resizing cannot fully control the stereoselectivity if Nature were to use a similar event as part of her construction.



Scheme 4. BDSB-induced ring-expanding bromoetherification and bromoallene formation

Nevertheless, this reaction process has significant breadth, as was demonstrated most recently when the Snyder group also applied BDSB in two distinct steps towards the total synthesis of laurendecumallene B (**58**,

Scheme 5).[27] First, a ring-expanding bromoetherification facilitated by a Boc-protected secondary alcohol was used to form the 8-membered cyclic bromoether **55** with 7:1 *d.r.*, favoring the *cis*-disposition of the hydrogen atoms at the red-starred positions. This process required thorough screening, and was only successful with moderate yield (~50%) and an optimal *d.r.* of 7:1 when using CH_2Cl_2 at 0 °C. Of note, the event was successful despite the presence of a potentially sensitive aldehyde functional group. Furthermore, the conditions developed by the Gulder group (NBS in HFIP with added morpholine•HFIP salt)[13] resulted in no reaction. Lastly, the second BDSB-induced transformation, leading here to the targeted natural product (**58**), records the first example of BDSB fashioning a bromoallene from a free alcohol/enyne precursor.[27] Although it is believed the resultant epimeric ratio from this type of transformation can be solvent dependent based on other findings in related systems,[28] a ~1:1 *d.r.* was consistently observed here across several solvents.



Scheme 5. Total synthesis of laurendecumallene B using BDSB

Conclusion

In summary, the highly electrophilic bromonium agent BDSB has proven to be a valuable tool for various aspects of chemical synthesis.

These processes include accomplishing unique polyene cyclizations in high yield and diastereoselectivity, serving as a simple to use and highly reactive electrophilic brominating reagent for aromatic systems, and allowing for the elegant and efficient construction of bromoallene and medium-sized cyclic bromoethers. Furthermore, BDSB has also acted as a strong and consistent benchmark for the development of new brominating reagents in the decade since its introduction, and it is hoped that it will inspire additional tools of high utility in the years to come as well as be used for new and useful applications.

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1. The University of Chicago, Department of Chemistry, 5735 S. Ellis Avenue, Searle Chemistry Laboratory, Chicago, IL 60615. Email: sasnyder@uchicago.edu. ORCID: 0000-0003-3594-8769. Current financial support from the University of Chicago is gratefully acknowledged, as is the initial support provided by a Camille and Henry Dreyfus New Faculty Award, an American Chemical Petroleum Research Fund Type G grant, and an NSF CAREER Award (CHE-0844593) that served to launch and facilitate our investigations into the halogenation chemistry that led to BDSB. S.A.S. also wishes to thank all members of his group, past and present, who have contributed to this body of science.
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Cooper completed his B.S. in Chemistry at the University of Richmond in 2017 where he conducted computational chemistry research in the laboratory of Professor Carol Parish, centered on molecular dynamics. Cooper is currently a fourth-year graduate student in the lab of Scott Snyder at the University of Chicago, where his work is focused on the total syntheses of complex natural products. He is also the recipient of a NIH Chemistry-Biology Interface (CBI) Predoctoral Training Grant Fellowship.

Scott completed his undergraduate studies at Williams College in 1999 and earned his doctoral degree in 2004 with K. C. Nicolaou at The Scripps Research Institute in La Jolla, CA. He was then an NIH Postdoctoral Fellow at Harvard University with E. J. Corey and began his independent career at Columbia University in 2006. Scott moved to the Jupiter, FL campus of The Scripps Research Institute in September of 2013 as an Associate Professor, and was recruited by the University of Chicago as a Professor in September of 2015. To date he has co-authored more than 100 research articles, reviews, and book chapters as well as 5 books. Recent honors include a Quantrell Excellence in Undergraduate Teaching Award and a Swiss Chemical Society Lectureship.