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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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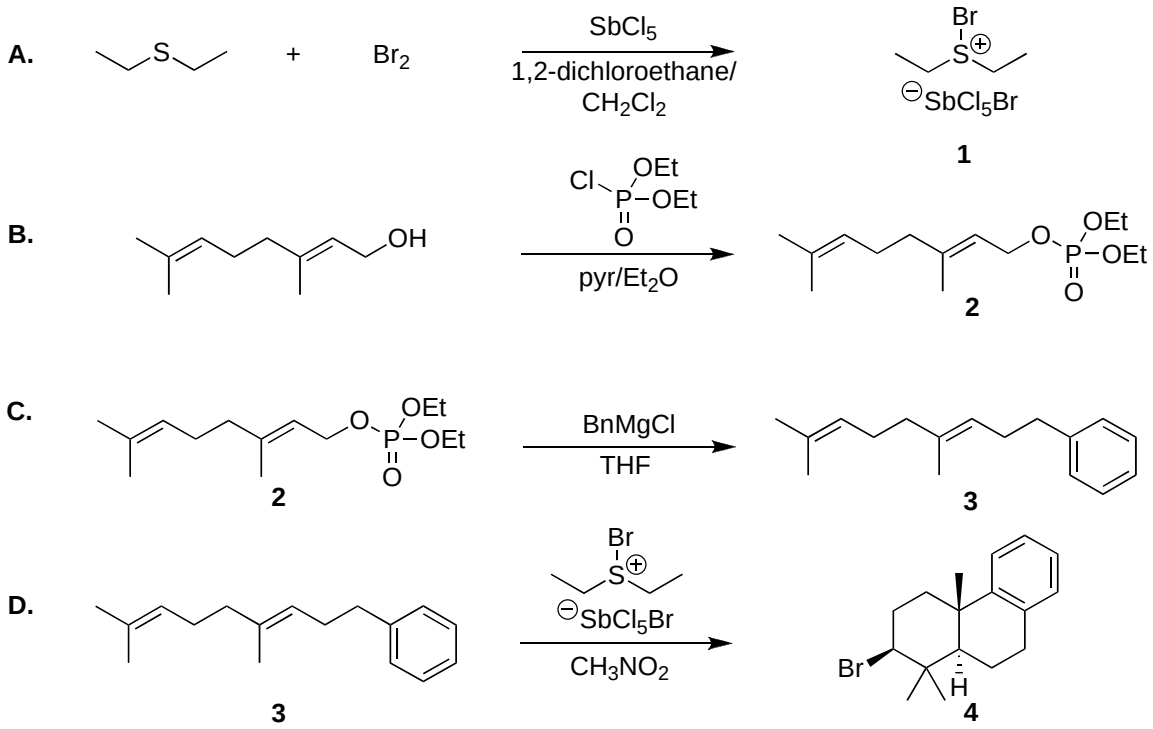
SYNTHESIS OF $Et_2SBr•SbCl_5Br$ AND ITS USE IN BIOMIMETIC BROMINATIVE POLYENE CYCLIZATIONS



Submitted by Scott A. Snyder and Daniel S. Treitler.[1] Checked by Nobuhiro Satoh and Tohru Fukuyama.
Discussion Addendum *Org. Synth.* **2020**, *97*, 339-354

1. Procedure

Caution: Bromine, diethyl chlorophosphate, and antimony pentachloride solution are highly toxic, caustic liquids that may be fatal if inhaled, swallowed, or absorbed through skin. All manipulations should be carefully carried out in a well ventilated fume hood.

A. *Bromodiethylsulfonium Bromopentachloroantimonate ("BDSB") (**1**).* An oven-dried, one-necked, 500-mL round-bottomed flask containing a magnetic stirring bar (egg-shaped, 45 mm length and 20 mm diameter) is purged with argon and sealed using a rubber septum and an argon inlet (Note 1). 1,2-Dichloroethane (200 mL) (Note 2) and bromine (4.27 mL, 13.3 g, 83.3 mmol, 1.0 equiv) (Note 3) are syringed into the flask, which is then cooled in a –30 °C dry ice-cooled acetone bath. To this vigorously stirring

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dark red solution is added diethyl sulfide (9.88 mL, 8.27 g, 91.7 mmol, 1.1 equiv) (Note 4) via syringe over the course of 1 min. The solution instantly lightens to a yellow-orange color. Maintaining the temperature of the bath between –30 and –35 °C by occasionally adding more dry ice, an antimony pentachloride solution (100 mL, 1 M in CH_2Cl_2, 100 mmol, 1.2 equiv) (Note 5) is cannulated slowly into the reaction flask over 10 min. The color of the solution first darkens to an orange-red, and as the addition proceeds, a yellow precipitate is observed. After the addition is complete, the reaction mixture is stirred at –30 °C for an additional 30 min and then the acetone bath is replaced with a cold water bath (~10 °C). The water bath is heated slowly (~2 °C per min) until all of the precipitate has dissolved (bath temperature = 26–32 °C), yielding a transparent homogeneous red solution. At this time, the rubber septum and argon inlet are quickly replaced with a tightly sealed cap and the flask is moved to a 4 °C refrigerator. After 8 h at 4 °C, the flask (now containing significant amounts of orange crystals) is moved to a –20 °C freezer, where it is kept for 14 h. The crystalline product (**1**) is isolated by decanting the majority of the solvent and then removing any residual solvent via pipette. The crystals are then washed with cold (–20 °C) CH_2Cl_2 (2 × 10 mL) (Note 6) and dried under high vacuum (23 °C, 1 mmHg, 2 h) to afford 39.2–39.8 g (86–87%) of pure BDSB (**1**) as light orange plates (Note 7).

B. *Geranyl Diethyl Phosphate (**2**).* To an argon-purged 500-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar (round, with removable pivot ring, 40 mm length and 8 mm diameter), a rubber septum, and argon inlet is added geraniol (14.0 mL, 12.3 g, 80.0 mmol, 1.0 equiv) (Note 8), pyridine (16.1 mL, 15.8 g, 200 mmol, 2.5 equiv) (Note 9) and diethyl ether (60 mL) (Note 10) via syringe. The clear solution is cooled in a –30 °C dry ice-cooled acetone bath and stirred vigorously while diethyl chlorophosphate (17.4 mL, 20.7 g, 120 mmol, 1.5 equiv) (Note 11) is added dropwise via syringe over the course of 10 min. Once the addition is complete, the reaction flask is removed from the cold bath (now –20 °C) and allowed to warm to 23 °C. Significant amounts of white precipitate appear as the reaction proceeds (Note 12). After stirring for 6.5 h at 23 °C, the reaction is quenched by the addition of ice-cold 1 M NaOH (150 mL) over ~1 min (a slight exotherm occurs). The biphasic mixture is stirred vigorously for 30 min, then transferred to a 1-L separatory funnel and extracted into EtOAc (3 × 150 mL) (Note 13). The combined organic layers are washed with 1 M HCl (2 × 150 mL), saturated aqueous $NaHCO_3$ (150 mL) and brine (150 mL), and dried over $MgSO_4$ (Note 14). The drying

agent is removed by vacuum filtration (medium-pore frit) and the filtrate is concentrated by rotary evaporation (30 °C, 150→10 mmHg) and then under high vacuum (23 °C, 1 mmHg, 1 h). The crude yellow oil is pipetted onto a plug of packed silica gel (5 × 10 cm) (Note 15) and transferred quantitatively by adding CH_2Cl_2 washes (3 × 5 mL). The product is eluted with pressurized air directly into a 2-L round-bottomed flask with ice-cold hexanes (300 mL) (Note 16) followed by hexanes:EtOAc (2:3, 1.25 L). The bulk of the solvent is removed by rotary evaporation (30 °C, 150→10 mmHg) and the resultant geranyl diethyl phosphate (Note 17) is transferred to a 500-mL, one-necked round-bottom flask and co-evaporated with dry toluene (3 × 15 mL; 30 °C, 10 mmHg) (Note 18) to remove both residual EtOAc and trace water.

C. *Homogeranylbenzene (**3**).* A magnetic stirring bar (round, with removable pivot ring, 40 mm length and 8 mm diameter) is added to the flask containing crude geranyl diethyl phosphate, which is dried under vacuum (20 min, 23 °C, 1 mmHg), back-filled with argon and sealed with a rubber septum and argon inlet. The viscous yellow oil is dissolved in dry THF (30 mL) (Note 19) and cooled in a –45 °C dry ice-cooled acetone bath. A solution of benzylmagnesium chloride in THF (0.5 M, 320 mL, 160 mmol, 2 equiv) (Note 20) is cannulated into the stirring geranyl diethyl phosphate solution over the course of 20 min (Note 21), with the continuous addition of dry ice to the cold bath to maintain its temperature between –40 °C and –45 °C. Upon completion of the addition of the Grignard reagent, the cold bath is allowed to warm slowly for 2.5 h (to 5 °C) and then is removed (Note 22). The light brown solution is stirred for an additional 2 h at 23 °C. Saturated aqueous NH_4Cl (75 mL) and water (75 mL) are added carefully to quench any remaining Grignard reagent and the biphasic mixture is stirred vigorously for 5 min (slight exotherm). This mixture is poured into a 1-L separatory funnel and extracted with hexanes:EtOAc (2:1, 3 × 150 mL). The combined organic layers are washed with saturated aqueous $NaHCO_3$ (150 mL) and brine (150 mL), dried over $MgSO_4$, filtered, then concentrated by rotary evaporation (30 °C, 150→10 mmHg) and dried under high vacuum (23 °C, 1 mmHg, 1 h). The crude yellow oil is then pipetted onto a column of packed silica gel (360 g, 80 mm diameter) (Note 23) and transferred quantitatively by adding hexanes rinses (3 × 5 mL). The column is eluted with hexanes (300 mL), then fraction collection is initiated (30 mL each) with further elution being performed with hexanes:CH_2Cl_2 (19:1, 900 mL) followed by hexanes:CH_2Cl_2 (9:1, 900 mL). The desired product is found in pure form in fractions 17–43 (fractions 44–50 are contaminated with

bibenzyl and are discarded), which are concentrated by rotary evaporation (30 °C, 300→10 mmHg) and dried under high vacuum (23 °C, 1 mmHg, 1 h) to afford 16.7 g (92% from geraniol) of homogeranylbenzene as a colorless oil (Notes 24 and 25).

D. *Cyclization of **3** to **4***. Homogeranylbenzene (1.14 g, 5.0 mmol, 1.0 equiv) is added to a 1-L, three-necked, round-bottomed flask containing a magnetic stirring bar (egg-shaped, 45 mm length and 20 mm diameter). The flask is purged with argon, and two of the necks are equipped with an argon inlet and a low-temperature thermometer, respectively. Dry nitromethane (485 mL) (Note 26) is poured through a funnel into the flask, and the third neck is capped. The colorless solution is cooled using a dry ice-cooled acetone bath (approx –30 °C) until the interior temperature reaches –25 °C. A solution of BDSB (3.02 g, 5.5 mmol, 1.1 equiv) in nitromethane (15 mL) that has been sealed and pre-cooled to –20 °C in a freezer is syringed in rapidly (Note 27) while stirring vigorously. The dark yellow solution is stirred for 5 min at –25 °C (Notes 28 and 29) at which time the flask is removed from the cold bath and the now light yellow solution is quenched by the addition of 2% aqueous Na_2SO_3 (Note 30; 300 mL) and saturated aqueous $NaHCO_3$ (100 mL). The biphasic mixture is stirred vigorously and allowed to warm to 23 °C over 60 min (Note 31). The quenched reaction mixture is then poured into a 2-L separatory funnel and extracted vigorously with hexanes (4 × 300 mL) (Note 32). The combined hexanes layers are washed with brine (300 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporation (30 °C, 100 mmHg). The crude product is dried under high vacuum (23 °C, 1 mmHg, 1 h) to afford 1.45–1.62 g of a white solid that is approximately 85–90% pure product by ^{1}H NMR (Note 33). The crude product is dissolved in 100 mL of boiling methanol (Note 34), and the light yellow solution is allowed to cool slowly to 23 °C overnight. The crystallization is allowed to proceed for an additional 12 h at 4 °C and 24 h at –20 °C. The first crop is then isolated by vacuum filtration using a medium-pore fritted funnel, washed with cold (–20 °C) methanol (5 mL) and dried under vacuum (23 °C, 1 mmHg, 1 h) to afford 0.952–0.955 g of **4** as white plates. A second crop is obtained by concentrating the combined mother liquor and methanol wash to a volume of ~20 mL by rotary evaporation (35 °C, 80 mmHg) (Note 35), heating to reflux if necessary to render the solution homogenous, and cooling to 4 °C for 24 h followed by 24 h at –20 °C. Filtration and rinsing with cold methanol (2 mL) yields an additional 0.136–0.147 g of **4** as off-white needles, for a total of 1.09–1.10 g (71–72%) of pure **4** (Note 36).

2. Notes

1. For all reactions run under positive argon pressure: a balloon securely attached to the barrel of a 5-mL plastic syringe using Teflon tape and Parafilm is inflated with argon, capped with a needle and inserted through the rubber septum.

2. 1,2-Dichloroethane is purchased from Sigma-Aldrich (anhydrous, 99.8%) and used as received. A second experiment was also performed in which the 1,2-dichloroethane was distilled from calcium hydride onto 3 Å molecular sieves. The product yields and activities were identical, indicating that rigorous drying of the solvent is not necessary.

3. Bromine is purchased from Kanto Chemical (>99.0%) (checker), or Sigma-Aldrich (ACS Reagent Grade, 99.5+%) (submitter) and used as received.

4. Diethyl sulfide is purchased from Sigma-Aldrich (98%) and used as received.

5. Antimony(V) chloride is purchased from Sigma-Aldrich (1.0 M in dichloromethane). The entire 100 mL bottle is used for the reaction, and is thus assumed to contain 100 mL [previous experiments have established that slightly more or less than 1.2 equiv of antimony(V) chloride have negligible impact on the yield of BDSB obtained].

6. Dichloromethane (J.T. Baker, ACS Grade, 99.5% min) is purchased from VWR International and used as received.

7. Appearance: The color of BDSB is generally light orange, although different batches can vary from dark yellow to orange. The color of the crystals is also slightly temperature-dependent; they are noticeably more yellow in color when cold, and become darker orange if warmed. This color change appears to be reversible. Stability: BDSB has proven to be stable in a sealed container stored at –20 °C for at least one year, with no observed depreciation in reactivity. If left out in open air at 23 °C, BDSB will slowly hydrolyze to the sulfoxide over the course of minutes to hours depending on the size of the crystals as well as the humidity of the air. The short-term stability of BDSB in air allows it to be isolated, weighed, or otherwise manipulated in air. Solubility: BDSB is soluble in nitromethane, nitroethane, acetonitrile, dimethylsulfoxide, *N*,*N*-dimethylformamide, and ethyl acetate. It is slightly soluble in dichloromethane, dichloroethane, chloroform, and toluene, and insoluble in trifluoroethanol, hexafluoroisopropanol, benzene, hexanes, and pentane. The compound is not stable to ethereal or alcoholic solvents such as water, methanol, ethanol,

diethyl ether, or tetrahydrofuran. Characterization: mp = 102 – 105 °C (with decomposition); IR (KBr) ν_{max} 2985, 2939, 1455, 1403, 1384, 1261, 932, 877 cm^{-1}; ^1H NMR (400 MHz, CD_3NO_2, solvent referenced at 4.33 ppm) δ: 1.67 (t, *J* = 7.3 Hz, 6 H), 3.92 (dq, *J* = 1.4, 7.3 Hz, 4 H); ^{13}C NMR (100 MHz, CD_3NO_2, solvent referenced at 63.8 ppm) δ: 11.3, 46.3. NMR spectra show trace amounts of diethyl sulfoxide (^1H NMR δ: 1.55 (t, *J* = 7.3 Hz, 6 H), 3.54 (q, *J* = 7.3 Hz, 4 H); ^{13}C NMR δ: 8.1, 44.3) if the sample is not prepared in a rigorously anhydrous manner.

8. Geraniol is purchased from Sigma-Aldrich (98%) and used as received.

9. Pyridine is purchased from Sigma-Aldrich (anhydrous, 99.8%), distilled from calcium hydride and stored over 3 Å molecular sieves.

10. Diethyl ether (Kanto Chemical, dehydrated, >99.5% (checker) or EMD Chemicals, OmniSolv, 99.9% min (submitter)) is dried using an anhydrous solvent delivery system equipped with activated alumina columns.

11. Diethyl chlorophosphate is purchased from Sigma-Aldrich (97%) and used as received.

12. The reaction can be followed by TLC (Merck 60 F_{254}, 0.25 mm thickness (checker) or EMD Chemicals 60 F_{254}, 0.25 mm thickness (submitter)). Solvent system: 1:1 Hex:EtOAc; stain: Cerium molybdate (prepared by dissolving 2.0 g ammonium cerium sulfate and 5.0 g ammonium heptamolybdate in 200 mL of 1 M aqueous sulfuric acid); R_f = 0.56 (S.M.), 0.31 (product).

13. Ethyl acetate (Kanto Chemical, 99.0% min (checker) or Malinckrodt Chemicals, ChromAR, 99.5% min (submitter)) is used as received.

14. Magnesium sulfate (anhydrous powder certified) is purchased from Wako Pure Chemical Industry (checker) or Fisher Chemical Company (submitter).

15. Silica gel (Kanto Chemical, spherical neutral, 40–100 μm particle size, 60 Å pore size (checker) or EMD Commercial grade, 40–63 μm particle size, 60 Å pore size (submitter)) is used as received.

16. Hexanes (Wako Pure Chemical Industry, 95.0% min (checker) or J.T. Baker, ACS Grade, 98.5% min (submitter)) is used as received. The exotherm that accompanies this first elution is enough to decompose some of the product (~3–5%) if room temperature hexanes is used.

17. The crude geranyl diethyl phosphate obtained by this procedure is ~90% pure by ^1H NMR analysis. The major impurities are ethyl acetate,

geraniol (~3%), linalool (~5%), and an unidentified diethylphosphate by-product (~2%). In order to obtain pure compound, the silica gel plug can be replaced by flash column chromatography (elution with a gradient of 20 to 70% EtOAc in hexanes provides the best results). The pure product exhibits the following spectral characteristics: IR (film) ν_{max} 2980, 2917, 1457, 1395, 1263, 1034, 820 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34 (dt, *J* = 0.9, 7.4 Hz, 6 H), 1.60 (s, 3 H), 1.68 (s, 3 H), 1.71 (s, 3 H), 2.03–2.13 (m, 4 H), 4.11 (quin, *J* = 7.3 Hz, 4 H), 4.57 (t, *J* = 7.8 Hz, 2 H), 5.08 (m, 1 H), 5.40 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.8 (d, *J* = 7 Hz, 2 C), 17.1, 18.3, 26.3, 26.9, 40.2, 64.3 (d, *J* = 6 Hz, 2 C), 64.8 (d, *J* = 6 Hz), 119.7 (d, *J* = 6 Hz), 124.3, 132.6, 143.2; HRMS (FAB) calcd. for $C_{14}H_{27}NaO_4P^+$ $[M+Na]^+$ 313.1545, found 313.1534.

18. Toluene (Wako Pure Chemical Industry, 99.0% min) is used as received (checker). Toluene (BDH, ACS Grade, 99.5% min) is dried using an anhydrous solvent delivery system equipped with activated alumina columns (submitter).

19. Tetrahydrofuran (Kanto Chemical, dehydrated super, 99.5% min (checker) or EMD Chemicals, OmniSolv, 99.9% min (submitter)) is dried using an anhydrous solvent delivery system equipped with activated alumina columns.

20. A 0.5 M BnMgCl solution can be prepared by dilution of commercially available benzylmagnesium chloride solution (use of benzylmagnesium bromide must be avoided as it is seriously detrimental to the yield). Alternatively, 320 mL of 0.5 M benzylmagnesium chloride can be synthesized as follows: magnesium turnings (7.77 g, 320 mmol, 4 equiv) (Reagent Grade, 98%, purchased from Sigma-Aldrich) are activated by sequential rinsing in a medium-pore frit with 0.2 M HCl (40 mL), water (3 × 40 mL), acetone (2 × 40 mL), and diethyl ether (2 × 40 mL). The activated magnesium turnings are added to a 500 mL one-necked round-bottomed flask with a magnetic stirring bar and dried at 100 °C (1 mmHg) for 1 h; they are then allowed to cool to 23 °C and the flask is sealed under argon with a rubber septum and an argon inlet. Meanwhile, benzyl chloride (18.4 mL, 160 mmol, 2 equiv) (ReagentPlus, 99%, purchased from Sigma-Aldrich and used as received) and dry THF (300 mL) are syringed into an oven-dried 500-mL, one-necked, round-bottomed flask sealed under argon with a rubber septum and argon inlet. Approximately 15 mL of this solution is cannulated onto the magnesium turnings, which are stirred at 23 °C until a sudden exotherm indicates that the formation of the Grignard reagent is underway (initiation time varies from 20 s to ~5 min). Once the reaction has initiated,

the magnesium-containing flask is cooled to 0 °C using an ice-water bath and stirred at 0 °C while the remainder of the benzyl chloride solution is slowly cannulated down the inner wall of the flask over 20 min. An additional 60 min of stirring at 0 °C yields a gray-brown solution of benzylmagnesium chloride in THF (~0.5 M).

21. Due to the viscosity of the benzylmagnesium chloride solution, it may be necessary to pull a slight vacuum on the receiving flask to encourage the cannula transfer to proceed at a reasonable rate. This task is performed by attaching a needle to a hose secured to a vacuum line, insertion of this needle through the septum of the receiving flask, and very briefly opening the hose to vacuum every few minutes as necessary.

22. The reaction can be followed by TLC (silica gel plates using 10% CH_2Cl_2 in hexanes as eluent and visualization with cerium molybdate solution prepared as in Note 12. R_f = 0.02 (S.M.), 0.48 (product)).

23. The column is wet-packed (hexane) with Kanto Chemical, 40-100 μm particle size, 60 Å pore size silica gel (checker). The column is dry loaded with EMD Commercial grade, 40–63 μm particle size, 60 Å pore size silica gel and packed with three column volumes of hexanes using pressurized air (submitter). The desired product is visualized by TLC using hexanes:CH_2Cl_2 (9:1) to elute and a UV lamp (254 nm) to observe the product (R_f = 0.48). The major contaminant is bibenzyl (formed via Würtz-type coupling in the Grignard formation step; R_f = 0.41).

24. The product exhibits the following physical and spectral characteristics: bp = 84 °C (1 mmHg); IR (film) ν_{max} 3085, 3062, 3027, 2966, 2923, 2855, 1496, 1454, 1376, 1108, 1030, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.55 (s, 3 H), 1.65 (s, 3 H), 1.69 (s, 3 H), 1.90–2.09 (m, 4 H), 2.31 (q, *J* = 7.4 Hz, 2 H), 2.64 (app t, *J* = 7.8 Hz, 2 H), 5.10 (m, 1 H), 5.19 (dt, *J* = 7.4, 0.9 Hz, 1 H), 7.18 (m, 3 H), 7.27 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.6, 18.4, 26.4, 27.4, 30.6, 36.8, 40.4, 124.3, 125.0, 126.3, 128.9 (2 C), 129.2 (2 C), 132.0, 136.4, 143.1; HRMS (DART) calcd for $C_{17}H_{25}^+$ $[M+H]^+$ 229.1956, found 229.1945; Anal. calcd. for $C_{17}H_{24}$: C, 89.41; H, 10.59. Found: C, 89.66; H, 10.60.

25. 84% yield was obtained on half that scale. Submitter's yield is 83%.

26. Nitromethane (Aldrich, ACS reagent, >99.0%) is stored over 3 Å molecular sieves (checker). Nitromethane (Fisher Chemical, Certified ACS, 99.9%) is purchased from Fisher Scientific and used as received (submitter). In general, the nitromethane used as solvent for cyclization must be quite anhydrous. The submitters have found that most commercial nitromethane

can be used as received, but that once opened, nitromethane should be stored over activated 3 Å molecular sieves for best results (slight yellowing of the solvent is typical and is not detrimental to the reaction). Unfortunately, reducing the amount of this relatively expensive solvent by a factor of 10 results in an ~20% decrease in yield depending on the substrate. However, an alternative, biphasic reaction using hexanes:nitromethane (4:1) and 1.2 equivalents BDSB for 30 min at –25 °C enables a decrease in the total nitromethane volume without any decrease in product yield. It is not known whether this modification works for all substrates, or only very hydrophobic ones such as homogeranylbenzene.

27. A fast rate of addition (~5 s) is important for obtaining a reproducible yield. A slower rate of addition results in more side-products including significant amounts of the proton-cyclized product.

28. A slight exotherm of 2–3 °C is common immediately following the addition of the BDSB solution.

29. Although the reaction proceeds very quickly (usually complete within 1 min), TLC can be utilized to follow its progress (silica gel plates using 10% CH_2Cl_2 in hexanes as eluent and visualization with cerium molybdate solution prepared as in Note 12. R_f = 0.48 (SM), 0.40 (product)).

30. Sodium sulfite is purchased from Wako Pure Chemical Industry (>97.0%) (checker) or Sigma-Aldrich (98+%, ACS reagent) (submitter). The sodium sulfite solution is prepared freshly by dissolving 6 g in 300 mL de-ionized water (it has been found that stock solutions of sodium sulfite slowly lose their reducing potential over time).

31. Quenching the reaction leads to the formation of a white insoluble precipitate presumed to be made up of antimony salts. The sticky nature of this precipitate renders the extractions somewhat messy, but attempts to remove these salts prior to extraction by filtration were unsuccessful due to their propensity to clog fritted funnels. At the conclusion of the work-up, any residual precipitate can be cleaned from glassware by rinsing with 1 M HCl.

32. The separatory funnel contains three layers: hexanes, water, and nitromethane (from top to bottom). Because of this occurrence, thorough extraction is necessary to partition the desired product into the hexanes layer (each extraction consists of shaking the separatory funnel vigorously, with occasional venting, for approximately 2 min). At the conclusion of the extractions, the used nitromethane can be recovered, dried over $MgSO_4$, and filtered to yield approximately 95% of the original 500 mL. By ^{1}H NMR analysis, this recovered solvent is quite pure, containing ~3% water, ~2%

hexanes, and trace amounts of sulfide, thiol, and sulfoxide by-products (<1% each). After storing for 48 h over activated 3 Å molecular sieves (10% by weight), the water content is <0.5% by ^{1}H NMR analysis and this recycled nitromethane can be reused (without distillation) as the solvent for subsequent cyclizations without any decrease in reaction yield.

33. The major impurities appear to be a diastereomer of the product with opposite stereochemistry at the bromine position (~5%) and trace amounts of monocyclic products that failed to undergo the second, Friedel–Crafts-based cyclization step.

34. Methyl alcohol (Wako, 99.5% min (checker) or Malinckrodt Chemicals, ChromAR ACS Grade, 99.9% min (submitter)) is used as received.

35. The mother liquor may darken in color to red or brown when concentrated.

36. The product exhibits the following physical and spectral characteristics: mp = 104.1–105.9 °C; R_f = 0.49 (silica gel, hexanes:CH_2Cl_2, 4:1); IR (film) ν_{max} 3059, 2969, 2947, 2838, 1488, 1475, 1448, 1392, 1377, 875, 763 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.06 (s, 3 H), 1.16 (s, 3 H), 1.24 (s, 3 H), 1.47 (dd, *J* = 12.0, 2.3 Hz, 1 H), 1.59 (dt, *J* = 13.3, 3.7 Hz, 1 H), 1.81 (m, 1 H), 1.97 (m, 1 H), 2.21–2.43 (m, 3 H), 2.82–3.00 (m, 2 H), 4.05 (dd, *J* = 12.8, 4.1 Hz, 1 H), 7.02–7.22 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.9, 21.3, 25.6, 31.2, 31.5, 32.2, 38.6, 40.6, 40.7, 51.9, 69.6, 125.1, 126.3, 126.6, 129.7, 135.4, 149.4; HRMS (DART) calcd for $C_{17}H_{23}^+$ [M-Br]$^+$ 227.1800, found 227.1806; Anal. calcd. for $C_{17}H_{23}Br$: C, 66.45; H, 7.55. Found: C, 66.37; H, 7.54.

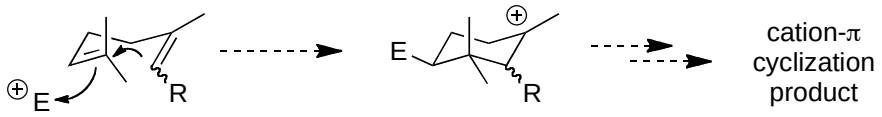
Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with *Prudent Practices in the Laboratory*. National Academy Press: Washington, DC, 1995.

3. Discussion

Cation-π cyclizations are an important class of reactions for the rapid and stereoselective generation of molecular complexity.[2] As shown simplistically in Scheme 1, these reactions are initiated by electrophilic activation of an alkene, an event that then induces one or more ring constructions via the sequential attack of up to several suitably disposed

olefins. To date, synthetic chemists have developed the means to effectively utilize proton,[3] oxygen,[4] iodine,[5] sulfur,[6] selenium,[6] mercury,[7] and transition metals such as gold,[8] palladium,[9] and platinum[10] as initiators for these cyclizations, forming up to 5 new rings at once.[11]



Scheme 1. Simplified form of a cation-π cyclization

Despite significant effort, however, challenges remain in initiating cation-π cyclizations with electrophilic bromine. Such a transformation would be of value given the existence of hundreds of brominated natural products that could be accessed from such an event as well as the potential ability to use the installed bromine atom as a handle to further elaborate the cyclized product. In nature, such reactions are achieved by a number of marine microorganisms that possess enzymes containing highly oxidized iron or vanadium metal centers that convert bromide into bromonium in a localized, highly controlled environment.[12] In the laboratory, by contrast, molecular bromine, *N*-bromosuccinimide, and 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCO),[13] the most common sources of electrophilic bromine available to synthetic chemists, fail to broadly initiate cation-π cyclizations. Instead, numerous side-products and over-halogenated materials are typically formed in lieu of the desired material.[14] For example, none of these halogen sources can successfully effect the cyclization of electron-poor substrates, even if the R group in Scheme 1 is only moderately electron-withdrawing (such as CH_2OAc).

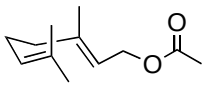
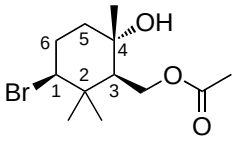
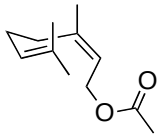
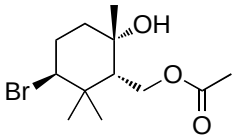
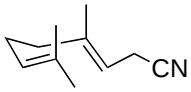
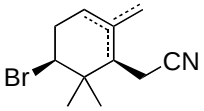
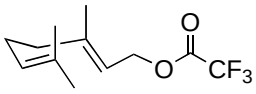
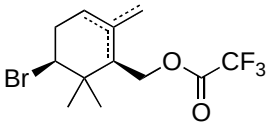
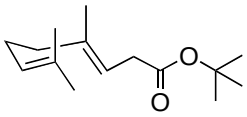
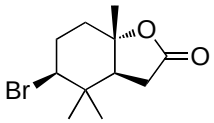
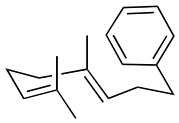
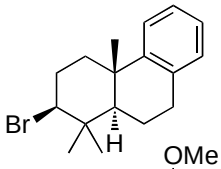
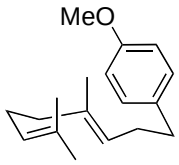
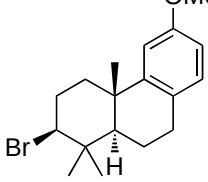
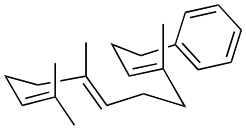
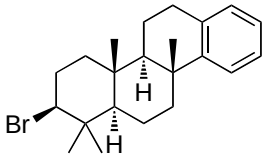
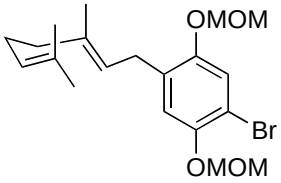
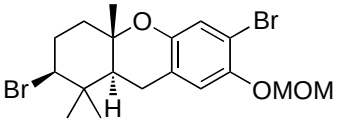
Attempts in our laboratory to use chiral bromodialkylsulfonium bromides for asymmetric bromination reactions (though unsuccessful) led to the discovery that reagents formed by sequestering the bromide anion of such species with the highly halophilic Lewis acid $SbCl_5$ could successfully initiate bromonium-induced cation π-cyclizations. An investigation of several dialkyl, diaryl, and alkyl-aryl bromosulfonium complexes of this type culminated in the observation that **1** (BDSB) was the best candidate given its solubility profile, stability, and ease of synthesis.[15] As illustrated in the procedure above, this reagent is readily prepared in large quantities from relatively inexpensive starting materials. Additionally, no discrete purification step is required, since the product crystallizes smoothly from the

reaction solution. An additional benefit of **1** is its air-stability, as it can be easily weighed and otherwise manipulated on the bench.

As illustrated by several selected examples from our investigations in Table 1, BDSB (**1**) has significant substrate scope for cation-π cyclization, successfully cyclizing an array of polyenes derived from geraniol, farnesol, and nerol, whether electron-rich or deficient. Moreover, BDSB is capable of achieving cyclizations cleanly even when bromination of an electron-rich aromatic ring could be considered a competitive pathway. The reaction is presumed to proceed via a synchronous process given the observation that *E*-olefins yield *trans*-ring junctions while *Z*-olefins result in *cis*-ring junctions (for instance, entries 1 and 2), in line with the Stork-Eschenmoser hypothesis.[2] In terms of experimental execution, though reactions are easily set up and reaction times are only a few minutes, it is critical to use an appropriate reaction concentration to achieve optimal yield. On small scale (0.1 mmol), reaction yields are generally quite good at concentrations as high as 0.1 M. However, when scaling above such amounts, higher dilution is necessary to obtain equivalent yields (as is often the case for cation-π cyclizations).[16] For instance, on gram scale, reaction concentrations of 0.01 M are optimal; pleasingly, although more solvent is needed, it can be easily recovered and recycled as noted above.

In conclusion, we have developed a novel source of electrophilic bromine that is capable of initiating bromonium-induced cation-π cyclizations in good yields with a variety of terpene-derived substrates.

Table 1. Exploration of Reaction Scope

Entry	Starting Material	Product	**Yield**[b] (%) [Rxn Temp (°C)]
1[c]			**80** [0]
2			**71** [0]
3[d]			**73** [23]
4[d]			**56** [23]
5			**79** [0]
6			**75** [-25]
7			**76** [-25]
8[e]			**58** [-25]
9			**67** [-25]

[a] All reactions performed on a 0.1 mmol scale at 0.05 M in CH_3NO_2 with 1.1 equivalents of **1** for 5 minutes. [b] Isolated yields. [c] Isolated as a 3.8:1 mixture of separable diastereomers at the C-4 position. [d] Isolated alkene mixtures. [e] CH_3SO_3H added to enhance yield of tetracyclic product.

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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Bromine; (7726-95-6)

Diethyl sulfide: Ethane, 1,1'-thiobis-; (352-93-2)

Bromodiethylsulfonium Bromopentachloroantimonate: Sulfonium, bromodiethyl-, (OC-6-22)-bromopentachloroantimonate(1-) (1:1); (1198402-81-1)

Antimony pentachloride; (7647-18-9)

Geraniol: 2,6-Octadien-1-ol, 3,7-dimethyl-, (2E)-; (106-24-1)

Diethyl chlorophosphate: Phosphorochloridic acid, diethyl ester; (814-49-3)

Pyridine; (110-86-1)

Homogeranylbenzene: Benzene, [(3E)-4,8-dimethyl-3,7-nonadienyl]-; (22555-66-4)

Benzylmagnesium chloride: Magnesium, chloro(phenylmethyl)-; (6921-34-2)

Phenanthrene, 2-bromo-1,2,3,4,4a,9,10,10a-octahydro-1,1,4a-trimethyl-, (2R,4aR,10aS)-rel-: (1198206-88-0)

Scott A. Snyder pursued his undergraduate education at Williams College. He then obtained his Ph.D. with Professor K. C. Nicolaou at The Scripps Research Institute, during which time he co-authored *Classics in Total Synthesis II.* Scott then trained with Professor E. J. Corey at Harvard University. Since August of 2006, Scott has been an Assistant Professor of Chemistry at Columbia University where his group seeks to explore chemical space through natural product total synthesis. Recent honors include a Camille and Henry Dreyfus New Faculty Award, an Eli Lilly Grantee Award, an NSF CAREER Award, a Cottrell Scholar Award, a JSPS travel fellowship, and a Columbia University Presidential Teaching Award.

Daniel S. Treitler was born in Denville, New Jersey, in 1985. He earned a Bachelors Degree in Biology from Cornell University in 2007, with undergraduate research experience in polymer chemistry in the group of Professor Geoffrey Coates as well as with Novomer, LLC. He is currently in his third year of an organic chemistry Ph.D. at Columbia University as an NSF Predoctoral Fellow, where his research in the group of Professor Scott Snyder has focused broadly on halogenation reactions, particularly cation-π cyclizations.

Nobuhiro Satoh was born in 1984 in Sapporo, Japan. He received his M.S. degree under the direction of Professor Tohru Fukuyama at University of Tokyo in 2008, where he is currently pursuing a Ph.D. degree. His research interest is total synthesis of natural products.