An Enantiospecific Polyene Cyclization Initiated by an Enantiomerically Pure Bromonium Ion

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ABSTRACT Dimethylaluminum triflate-mediated activation of tetrafluorobenzoates of enantiomerically pure bromohydrins results in enantiospecific polyene cyclizations. The initiation of cyclization by enantiomerically pure bromonium ions and subsequent propagation is not subject to catastrophic erosion of enantiomeric purity by any intramolecular or intermolecular bromonium ion-to-alkene transfer. *Chirality 25:692–700, 2013.*

KEY WORDS: bromonium ion; polyene cyclization; enantiospecific

INTRODUCTION

Since the advance of the Stork-Eschenmoser hypothesis,[1–3] cation-initiated polyene cyclizations as inspired by the enzymatic conversions of squalene to hopene and oxidosqualene to lanosterol have attracted much synthetic attention,[4–6] with enantioselective variants now representing the state of the art.[7–15] With the continued isolation[16–29] of complex single enantiomer brominated (poly)cyclic terpenoid natural products containing the signature α-bromo-β,β-dimethylcyclohexane motif from marine sources,[30–34] a consensus has arisen that nature employs enzyme-mediated bromonium ion initiated asymmetric polyene cyclizations to so construct them (Fig. 1).[35] While van Tamelen and Hessler[36] demonstrated the first direct brominative cyclization of polyene methyl farnesate with NBS nearly 50 years ago, the products were necessarily racemic and formed in very low yields (ca. 5%). Over the next 30 years a number of other direct brominative polyene cyclizations have further been reported using a variety of (achiral) reagent-solvent combinations.[37–48] The low yields generally obtained in these cyclizations must arise in part from the requirement of the reagent to react regioselectively with the olefin at the terminus of the polyene chain. The recent introduction of the powerful bromodiethylsulphonium bromopentachloroantimonate reagent, BDSB, by Snyder and co-workers now allows for highly efficient bromonium ion initiated polyene cyclizations to give bi- tri-, and even tetracyclic adducts, albeit still as racemates.[41–51,*] Snyder and colleagues have also recently reported a two-step mimic for direct, asymmetric bromonium-induced polyene cyclizations using a chiral Hg(II) salt to mediate the initial cyclization.[52] However, the demonstration of an enantiospecific, nonenzymatic-mediated, polyene cyclization initiated by an enantiopure bromonium ion remains unreported.[†]

In contemplating such an asymmetric bromonium ion-initiated polyene cyclization, challenges in each of the fundamental steps of initiation and propagation arise (Fig. 2), and a suitable group must also be chosen to terminate the polyene cyclization. In any initiation step, an enantiopure bromonium ion must be formed regioselectively at the terminus alkene of the polyene. Currently, there is no widely applicable method for the formation of enantiopure bromonium ions by direct bromination of a simple trisubstituted alkene (even before considering the required regioselectivity of the process).[53–57] In the propagation step(s) intramolecular and/or intermolecular bromonium ion-to-alkene transfer[58,59] must be avoided, where Denmark et al. have recently demonstrated that racemization of enantiopure bromonium ions via bromonium ion-to-olefin transfer with an added alkene is competitive with *intermolecular* capture by anionic nucleophiles.[60] Since by definition a polyene cyclization substrate will always contain alkene functional groups, it is not unreasonable to ask if such asymmetric cyclizations are therefore inherently compromised when not under enzymatic control. Thus, methods for the initiation of polyene cyclizations with enantiopure bromonium ions are required to be developed, so that the extent of the racemization via either intramolecular or intermolecular bromonium ion-to-alkene transfer can be assessed. An enantiomerically pure bromonium ion was generated in the formation of a vicinal bromochloride in the total synthesis of (+)-intricatetraol.[61] Lewis acid-mediated carbocyclizations of (racemic) 1,2-bromohydrins (3° alcohol and/or esterified derivatives, 2° bromide) have been demonstrated previously,[62–66] and a cyclization of an enantiopure 1,2-bromohydrin (3° alcohol, 2° bromide) to an enantiopure 1-bromo-2,2,4-trimethylcyclohexane has been reported,[67] but bromonium ions were not invoked. Herein, as an extension of our previous work, we report the formation of an enantiopure bromonium ion at the terminus of a polyene by suitable activation of an enantiopure bromohydrin,[68,69] thereby initiating polyene cyclization to produce tricyclic carbocycles with the characteristic α-bromo-β,β-dimethylcyclohexane motif of (poly)cyclic naturally occurring terpenoids. Under these

*Chiral versions of BDSB are also reported in Ref. 50. However, no asymmetric induction was observed in the cyclization of a representative polyene.
†Chiral phosphoramidites at stoichiometric loading have delivered high enantiomeric excess for direct iodonium-induced polyene cyclizations (up to 95% ee) using NIS as the electrophilic halide source. With NBS as the halide source instead to effect a bromonium-ion induced cyclization, the asymmetric induction dropped off markedly (36% ee) (Ref. 10).

Additional Supporting Information may be found in the online version of this article.

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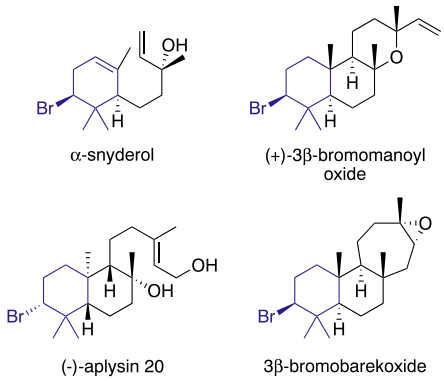


Fig. 1. Selected single enantiomer terpenoid natural products containing the α-bromo-β,β-dimethylcyclohexane motif (highlighted in blue) considered to arise via bromonium ion-initiated polyene cyclization.

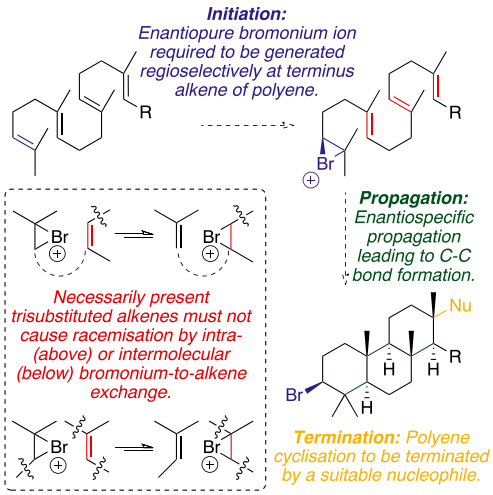


Fig. 2. Challenges for enantiospecific polyene cyclization initiated by an enantiopure bromonium ion.

conditions—*even with a necessarily present trisubstituted alkene in the cyclization substrates*—the brominated tricyclic carbocycles are isolated in high enantiomeric excess. Racemization via either intramolecular or intermolecular bromonium ion-to-alkene transfer is evidently not in operation, and the cyclizations proceed enantiospecifically.

MATERIALS AND METHODS

General Experimental

Reagents. 4-Methoxybenzyl chloride was prepared from 4-methoxybenzyl alcohol according to a procedure by Yadav and colleagues.[70] Bromodiethylsulphide pentachloroantimonybromide (BDSB) was prepared according to the procedure by Snyder and Treitler.[51] Pyridine was distilled from CaH_2. Methanesulphonamide was purified by recrystallization from EtOH. All other regents were obtained from commercial sources and used as received.

Solvents. All reactions were carried out in anhydrous solvents unless used in combination with H_2O. CH_2Cl_2, Et_2O, and THF were dried by passing through a column of alumina beads. *N*-Methyl-2-pyrrolidone was purified by distillation and stored over 4Å molecular sieves. All other reaction solvents, extraction solvents, and chromatography eluents were used as received. MeOH and CH_2Cl_2 were HiPerSolv grade, EtOH was AnalaR grade, and Et_2O, EtOAc, and petroleum ether 40-60 (referred to as PE) were GPR grade. *n*-Hexane and *i*-PrOH for analytical high-performance liquid chromatography (HPLC) were HPLC grade and used as received.

Experimental techniques. Reactions were carried out in oven-dried glassware under an inert atmosphere of nitrogen, unless otherwise stated. Air and moisture-sensitive reagents were transferred by syringe. Reaction temperatures other than room temperature were recorded as aluminum alloy heating block, or bath temperatures. Concentrated under reduced pressure refers to rotary evaporation. Brine refers to a saturated aqueous solution of NaCl. Column chromatography was performed on silica gel, particle size 40-63 μm unless otherwise stated. Chiral HPLC was performed on CHIRALCEL OJ or CHIRALPAK AD columns detecting at 284 nm. Retention times (t_R) are reported in minutes. Analytical thin-layer chromatography (TLC) was performed on Kieselgel 60 F254 precoated aluminum-backed plates visualized by ultraviolet light (350 nm) and/or chemical staining using potassium permanganate solution. Silver nitrate-doped silica gel was obtained after slurrying silica in aqueous $AgNO_3$ solution (0.1 M, 4 $mL g^{-1}$ silica) and concentrating under reduced pressure azeotroping with toluene until dryness.

Characterization. Fourier transform IR spectra were recorded neat using an ATR-IR spectrometer. ^1H, ^{13}C and ^{19}F NMR spectra were recorded on Brüker AV400 and AV500 spectrometers at 400 MHz and 500 MHz, and 100 MHz and 125 MHz, and 377 (AV500 only) MHz, respectively. Chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to the residual solvent resonance. Coupling constants (*J*) are quoted in Hertz (Hz). Low-resolution mass spectroscopy (MS) (EI, CI), gas chromatography MS (GCMS), and high-resolution MS (HRMS) were recorded by the Imperial College Department of Chemistry Mass Spectrometry Service.

(*E*)-1-(4,8-Dimethylnona-3,7-dienyl)-4-methoxybenzene (1). Prepared according to a modified procedure of Snyder and Treitler.[49] To a stirred solution of geraniol (23 mL, 133 mmol) and pyridine (32 mL, 398 mmol) in diethyl ether (80 mL) at −15 °C was added diethyl chlorophosphate (29 mL, 199 mmol) and the mixture was allowed to warm to room temperature over 5 h. The reaction mixture was quenched with 1M aqueous HCl solution (250 mL), extracted with ethyl acetate (2 × 250 mL), washed with saturated aqueous $NaHCO_3$ solution (2 × 250mL), brine (250 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give geranyl diethyl phosphate as a colorless oil (46 g) which was used directly without purification. To magnesium turnings (7.6 g, 318 mmol) stirred in anhydrous THF (200 mL) was added a portion of 4-methoxybenzyl chloride (2.0 mL, 15 mmol), where the reaction could be started by gentle heating. Subsequently, a solution of 4-methoxybenzyl chloride (19.5 mL, 144 mmol) in anhydrous THF (200 mL) was added dropwise over 1 h at such a rate as to maintain reflux. After complete addition, reflux was continued for 2 h. The reaction mixture was cooled to -40 °C and added dropwise via cannula to a stirred solution of geranyl diethyl phosphate (23 g, 80 mmol) in anhydrous THF (250 mL) at -40 °C and allowed to warm to room temperature over 16 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (300 mL), extracted with diethyl ether (2 × 300 mL), washed with saturated aqueous $NaHCO_3$ solution (300 mL), brine (300 mL), dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed (0:1-1:3 CH_2Cl_2:PE) to afford the title compound **1** as a mixture of constitutional isomers with branched diene **1a** in 19:1 ratio (12.7 g, 49 mmol, 61%) as a colorless oil. A second run on the same scale afforded the title product **1** as a mixture of constitutional isomers with **1a** in ratio 35:1 (14.0 g, 54 mmol, 68%). The purity of **1** could be increased to >98% by fractional distillation of the combined diene mixtures (27 g, 26:1 **1**:**1a**). Distillation (200 °C, 0.003 mmHg) collecting the fraction at 70 °C was enriched in branched isomer **1a** and the distillation residue was linear diene **1** (8.2 g, 32 mmol). Diene **1**: R_f = 0.35 (15% CH_2Cl_2 in PE); IR ν_{max} 2919, 2854, 1612, 1584 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.24 (t, *J* = 7.1 Hz, 1H), 5.19-5.13 (m, 1H), 3.82 (s, 3H), 2.60 (t, *J* = 7.8 Hz, 2H), 2.34 (q, *J* = 8.5 Hz, 2H), 2.17-2.02 (m, 4H), 1.75 (s, 3H), 1.67 (s, 3H), 1.62 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 135.7, 134.6, 131.3, 129.4, 124.4, 123.7, 113.7, 55.3, 39.8, 35.3, 30.2,

26.8, 25.7, 17.7, 16.0 ppm; MS (CI^+) *m/z* 276 $[M+NH_4]^+$; HRMS (CI^+) calcd. for $C_{18}H_{27}O$ $[M+H]^+$ 259.2062. Found: 259.2050. An analytically pure sample of branched diene **1a** could be obtained after silver nitrate-doped silica gel chromatography (0:1-3:7 Et_2O:PE).

(*E*)-1-(2,6-Dimethyl-2-vinylhept-5-enyl)-4-methoxybenzene (1a). R_f = 0.35 (15% CH_2Cl_2 in PE); IR ν_{max} 2920, 2854, 1612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 5.76 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.10-5.05 (m, 1H), 5.00 (dd, *J* = 10.8, 1.4 Hz, 1H), 4.82 (dd, *J* = 17.6, 1.4 Hz, 1H), 3.79 (s, 3H), 2.54 (m, 2H), 1.91 (q, *J* = 8.0 Hz, 2H), 1.67 (s, 3H), 1.58 (s, 3H), 1.37-1.25 (m, 2H), 0.94 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 146.6, 131.6, 131.0, 130.6, 125.0, 112.9, 112.1, 55.2, 47.2, 40.8, 40.4, 25.7, 23.1, 21.9, 17.6 ppm; MS (CI^+) *m/z* 276 $[M+NH_4]^+$; HRMS (CI^+) calcd. for $C_{18}H_{30}NO$ $[M+NH_4]^+$ 276.2327. Found: 276.2328.

(2*R,4a*R**,10a*S**)-2-Bromo-6-methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (2*R**,4a*R**,10a*S**)-(2) by direct brominative cyclization of polyene 1 with BDSB.** Bromide (2*R**,4a*R**,10a*S**)-**2** was prepared by direct brominative cyclization of diene **1** using the method of Snyder and Treitler.[49] To a stirred solution of alkene **1** (100 mg, 0.39 mmol) in CH_3NO_2 (6 mL) at -25 °C was added quickly a solution of BDSB (213 mg, 0.39 mmol) in CH_3NO_2 (2 mL) and stirred for 5 min. The reaction mixture was quenched with a 1:1 mixture of 5% aqueous $NaHCO_3$ and 5% aqueous Na_2SO_3 solution (20 mL) and stirred for 15 min before being poured into water (20 mL), extracted with CH_2Cl_2 (2 × 20 mL), dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed (PE) to afford bromide (2*R**,4a*R**,10a*S**)-**2** (88 mg, 68%) as a white solid: m.p. 86-87 °C. R_f = 0.64 (40:60 CH_2Cl_2:PE); IR ν_{max} 2933, 2851, 1611 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, *J* = 8.3 Hz, 1H,), 6.77 (d, *J* = 2.8 Hz, 1H), 6.71 (dd, *J* = 8.3, 2.8 Hz, 1H), 4.07 (dd, *J* = 12.5, 4.1 Hz, 1H), 3.80 (s, 3H), 2.98-2.76 (m, 2H) 2.48-2.23 (m, 3H), 1.98 (ddt, *J* = 13.4, 7.0, 2.2 Hz, 1H), 1.88-1.75 (m, 1H), 1.69-1.56 (m, 1H), 1.48 (dd, *J* = 12.1, 2.2 Hz, 1H), 1.27 (s, 3H), 1.18 (s, 3H), 1.09 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 150.0, 129.9, 127.0, 111.2, 110.2, 68.8, 55.3, 51.3, 40.1, 39.9, 38.1, 31.6, 30.6, 30.0, 24.8, 20.8, 18.3 ppm; MS (CI^+, NH_3) *m/z* 354, 356 $[M+NH_4]^+$; HRMS (CI^+, NH_3) calcd. for $C_{18}H_{29}NO^{79}Br$ $[M+NH_4]^+$ 354.1433, found 354.1433. HPLC (CHIRALPAK AD; 1% IPA in *n*-hexane; 1.0 mL/min) t_R = 4.9 min, 5.7 min.

(+)-(*R*,*E*)-9-(4-Methoxyphenyl)-2,6-dimethylnon-6-ene-2,3-diol (3). According to the method of Sharpless,[71] to a stirred solution of AD-mix β (22.3 g, 1.4 $gmmol^{-1}$) and methanesulphonamide (1.5 g, 16 mmol) in water (40 mL) and *tert*-butanol (40 mL) at 0 °C was added alkene **1** (4.1 g, 16 mmol). The reaction mixture was stirred vigorously for 16 h, quenched with saturated aqueous sodium sulfite solution (50 mL), extracted with EtOAc (2 × 100 mL), washed with brine (100 mL), dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed (1:1-3:2 EtOAc:PE) to afford first unreacted diene **1** (1.64 g, 6.3 mmol, 40%), the title product **3** (1.16 g, 4.3 mmol, 27%, 67% based on recovered starting material) as a colorless oil, and tetraol **3a** (1.27 g, 3.9 mmol, 24%) as a white solid. Diol **3**: R_f = 0.42 (1:1 EtOAc:PE); $[\alpha]_D^{24}$ = +12.3 (*c* 1.9, CH_2Cl_2); IR ν_{max} 3600-3100, 2931, 2858, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.26 (br t, *J* = 7.1 Hz, 1H), 3.81 (s, 3H), 3.32 (dd, *J* = 10.5. 2.0 Hz, 1H), 2.63 (t, *J* = 7.6 Hz, 2H), 2.38-2.19 (m, 3H), 2.15-2.01 (m, 3H), 1.64-1.55 (m, 1H) 1.60 (s, 3H), 1.44 (m, 1H), 1.21 (s, 3H), 1.18 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 135.5, 134.4, 129.4, 124.5, 113.7, 78.1, 73.0, 55.3, 36.7, 35.1, 30.1, 29.6, 26.4, 23.2, 15.9 ppm; MS (CI^+, NH_3) *m/z* 310 $[M+NH_4]^+$; HRMS (CI^+, NH_3) calcd. for $C_{18}H_{32}NO_3$ $[M+NH_4]^+$ 310.2382. Found: 310.2384; HPLC (CHIRALCEL OJ; 10% IPA in *n*-hexane; 1.0 mL/min) t_R = 16.2 min (major), 18.2 min (minor) – e.r. 99:1. In a run using AD - mix α, (*S*)-diol *ent*-**3** was obtained: $[\alpha]_D^{24}$ = - 5.9 (*c* 1.0, CH_2Cl_2); HPLC (CHIRALCEL OJ; 10% IPA in *n*-hexane; 1.0 mL/min) t_R = 15.9 min (minor), 17.1 min (major) – e.r. 6:94.

(+)-(3*R*,6*R*,7*R*)-2,6-Dimethyl-9-(4-methoxyphenyl)nonane-2,3,6,7-tetraol (3a). m.p. 130-131°C. $[\alpha]_D^{24}$ = +20.0 (*c* 1.0, EtOH); R_f = 0.28 (1:1 EtOH:PE); IR ν_{max} 3600-3100, 2972, 2952 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.4 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 3.81 (s, 3H), 3.41 (d, *J* = 9.6 Hz, 1H), 3.30 (d, *J* = 9.6 Hz, 1H), 3.29 (br s, 2H), 2.90 (ddd, *J* = 13.8, 8.8, 4.9 Hz, 1H), 2.65 (dt, *J* = 13.7, 8.2 Hz, 1H), 2.53 (br s, 1H), 2.20 (br s, 1H), 1.81-1.56 (m, 5H), 1.48-1.37 (m, 1H), 1.21 (s, 3H), 1.17 (s, 3H), 1.13 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 134.2, 129.4, 113.9, 78.9, 74.6, 73.2, 55.3, 50.7, 35.6, 33.6, 31.9, 26.5, 25.0, 23.3, 20.6 ppm; MS (CI^+, NH_3) *m/z* 344 $[M+NH_4]^+$; HRMS (CI^+, NH_3) calcd. for $C_{18}H_{31}O_5$ $[M+H]^+$ 327.2171. Found: 327.2164. A reference sample of (±)-diol **3** was prepared following a modified procedure of Warren and colleagues.[72] To a solution of potassium ferricyanide (383 mg, 1.16 mmol), potassium carbonate (161 mg, 1.16 mmol), $K_2OsO_4.2H_2O$ (4 mg, 0.012 mmol), quinuclidine (1 mg, 0.012 mmol), and methanesulphonamide (37 mg, 0.39 mmol) in water (2.5 mL) and *tert*-butanol (2.5 mL) at 0 °C was added olefin **1** (100 mg, 0.39 mmol) and stirred vigorously for 2 h. The reaction mixture was quenched with a saturated aqueous solution of sodium sulfite (10 mL), extracted with EtOAc (2 × 20 mL), washed with brine (40 mL), dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed (1:1-3:2 EtOAc:PE) to afford (±)-diol **3** (21 mg, 19%) as a colorless oil. HPLC (CHIRALCEL OJ; 10% IPA in *n*-hexane; 1.0 mL/min) t_R = 16.5 min, 17.8 min.

(-)-(*S*,*E*)-3-[-6-(4-Methoxyphenyl)-3-methylhex-3-enyl]-2,2-dimethyloxirane (4). Using a modified procedure of Corey et al.,[73] to a stirred solution of (*R*)-diol **3** (840 mg, 2.88 mmol) and pyridine (0.46 mL, 5.75 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added methanesulphonyl chloride (0.29 mL, 3.72 mmol). After 0.5 h the mixture was allowed to warm to room temperature and stirred for 3 h. Additional pyridine (1.38 mL 17.7 mmol) was added and the reaction mixture stirred for 16 h. The reaction mixture was poured into a suspension of K_2CO_3 (6.63 g, 48 mmol) in methanol (25 mL), stirred for 6 h, concentrated under reduced pressure, diluted with water (50 mL), extracted with EtOAc (2 × 50 mL), washed with 10% aqueous $CuSO_4$ solution (100 mL), brine (100 mL), dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed (1:19-1:4 EtOAc:PE) to afford the title product (*S*)-**4** (565 mg, 83%) as a colorless oil: R_f = 0.34 (1:9 EtOAc:PE); $[\alpha]_D^{24}$ -2.5 (*c* 1.6, CH_2Cl_2); IR ν_{max} 2958, 2925, 2835, 1612, 1586 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.26 (tq, *J* = 5.8, 1.5 Hz, 1H), 3.81 (s, 3H), 2.72 (app. t, *J* = 6.3 Hz, 1H), 2.62 (t, *J* = 7.5 Hz, 2H), 2.32 (app. q, *J* = 7.6 Hz, 2H), 2.24-2.06 (m, 2H), 1.78-1.62 (m, 2H), 1.61 (s, 3H) 1.33 (s, 3H) 1.29 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 134.8, 134.3, 129.3, 124.3, 113.7, 64.1, 58.3, 55.2, 36.3, 35.1, 30.2, 27.5, 24.9, 18.8, 16.0 ppm; MS (CI^+, NH_3) *m/z* 292 $[M+NH_4]^+$; HRMS (CI^+, NH_3) calcd. for $C_{18}H_{27}O_2$ $[M+H]^+$ 275.2011, found 275.2011.

(-)-(*S*,*E*)-2-Bromo-9-(4-methoxyphenyl)-2,6-dimethylnon-6-en-3-ol (5a) and (+)-(R,E)-3-bromo-9-(4-methoxyphenyl)-2,6-dimethylnon-6-en-2-ol (5b). Following the method of Couladouros and Vidali,[67] to a solution of (*S*)-epoxide **4** (200 mg, 0.73 mmol) in *N*-methyl-2-pyrrolidone (0.22 mL) was added LiBr (99 mg, 0.95 mmol) and PPTS (183 mg, 0.73 mmol) and stirred at room temperature for 4 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (15 mL), extracted with EtOAc (2 × 15 mL), washed with brine (30 mL), dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed (1:9-1:4 EtOAc:PE) to yield first (*E*)-9-(4-methoxyphenyl)-2,6-dimethylnon-6-en-3-one (10 mg, 5%) as a colorless oil, second bromohydrin **5a** (66 mg, 25%) as a colorless oil, and third, bromohydrin **5b** (119 mg, 46%) as a colorless oil. Bromohydrin **5a**: R_f = 0.32 (1:9 EtOAc:PE); $[\alpha]_D^{24}$ -10.6 (*c* 1.3, CH_2Cl_2); IR ν_{max} 3600-3200, 2958, 2926, 2855, 2835, 1612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.27 (tq, *J* = 6.8, 1.4 Hz, 1H), 3.82 (s, 3H), 3.40 (dd, *J* = 10.1, 3.0 Hz, 1H), 2.63 (t, *J* = 7.5 Hz 2H), 2.37-2.25 (m, 3H), 2.17-2.05 (m, 2H), 1.82 (s, 3H), 1.81-1.72 (m, 1H), 1.75 (s, 3H), 1.59 (s, 3H), 1.49 (dddd, *J* = 14.0, 10.3, 8.8, 5.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 135.1, 134.4, 129.4, 124.6, 113.7, 79.0, 75.4, 55.3, 36.4, 35.1, 31.1, 30.1 (×2), 28.9, 16.0 ppm; MS (CI^+, NH_3) *m/z* 374, 372 $[M+NH_4]^+$; HRMS (CI^+, NH_3) calcd. for $C_{18}H_{31}NO_2^{79}Br$ $[M+NH_4]^+$ 372.1538, found 372.1538. Bromohydrin **5b**: R_f = 0.24 (1:9 EtOAc:PE); $[\alpha]_D^{24}$ +35.1 (c 1.3, CH_2Cl_2); IR ν_{max} 3600-3250, 2925, 2854, 1612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.29 (t, *J* = 7.3 Hz, 1H), 3.95 (dd, *J* = 11.6, 1.9 Hz, 1H), 3.82 (s, 3H), 2.63 (td, *J* = 7.4, 3.4 Hz, 2H), 2.39-2.27 (m, 3H), 2.24 (s, 1H),

2.15 (dt, J = 14.9, 8.2 Hz, 1H), 1.97 (dtd, J = 16.2, 8.0, 1.8 Hz, 1H), 1.85-1.74 (m, 1H), 1.56 (s, 3H), 1.354 (s, 3H), 1.347 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 134.3, 133.7, 129.4, 125.5, 113.7, 72.5, 70.8, 55.3, 38.2, 35.1, 31.8, 30.2, 26.6, 25.9 15.8 ppm; MS (CI^+, NH_3) m/z 374, 372 $[M+NH_4]^+$; HRMS (CI^+, NH_3) calcd. for $C_{18}H_{31}NO_2^{79}Br$ $[M+NH_4]^+$ 372.1538, found 372.1540.

(-)-(*S,E*)-2-Bromo-9-(4-methoxyphenyl)-2,6-dimethylnon-6-en-3-yl 2,3,4,5-tetrafluorobenzoate (6a). Using the method of Neises and Steglich,[74] to a stirred solution of secondary alcohol **5a** (380 mg, 1.07 mmol) in CH_2Cl_2 (7.5 mL) was added 2,3,4,5-tetrafluorobenzoic acid (228 mg, 1.18 mmol), DMAP (39 mg, 0.321 mmol, 30 mol%) and DCC (287 mg, 1.39 mmol). After 4 h the reaction mixture was filtered through a silica plug eluting with Et_2O, concentrated under reduced pressure, and chromatographed (0:1-3:17 Et_2O:PE) to afford bromo tetrafluorobenzoate **6a** (520 mg, 92%) as a colorless oil. R_f = 0.34 (5:95 EtOAc:PE); $[\alpha]_D^{24}$ -22.0 (*c* 1.1, CH_2Cl_2); IR ν_{max} 2935, 2861, 2362, 2344, 1729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dddd, J = 10.3, 8.3, 6.0, 2.4 Hz, 1H), 7.13 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 5.27 (d, J = 9.9 Hz 1H), 5.22 (t, J = 7.0 Hz, 1H), 3.82 (s, 3H), 2.61 (app. t, J = 7.7 Hz, 2H), 2.37-2.19 (m, 2H), 2.10-2.03 (m, 3H) 1.99-1.85 (m, 1H), 1.83 (s, 3H), 1.82 (s, 3H) 1.58 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 157.7, 148.0 (dddd, J = 262, 11, 3, 1 Hz), 146.6 (dddd, J = 249, 10, 4, 2 Hz), 143.6 (dddd, J = 262, 17, 13, 3 Hz), 141.4 (dddd, J = 255, 17, 12, 3 Hz) 134.3, 134.0, 129.4, 125.1, 114.7 (m), 113.7, 113.4 (dd, J = 21, 3 Hz), 81.5, 65.8, 55.2, 36.0, 35.0, 30.44, 30.35, 30.15, 29.3, 15.9 ppm; ^{19}F NMR (377 MHz, $CDCl_3$) δ -153.1 (t, J = 20 Hz, 1F), -147.0 (m, 1F), -137.6 (m, 1F), -133.6 (m, 1F) ppm; MS (CI^+, NH_3) m/z 548, 546 $[M+NH_4]^+$; HRMS (EI^+) calcd. for $C_{25}H_{27}O_3^{79}BrF_4$ $[M]^+$ 530.1080, found 530.1080.

(+)-(*R,E*)-3-Bromo-9-(4-methoxyphenyl)-2,6-dimethylnon-6-en-2-yl 2,3,4,5-tetrafluorobenzoate (6b). Using the method of Neises and Steglich,[74] to a stirred solution of tertiary alcohol **5b** (350 mg, 0.99 mmol) in CH_2Cl_2 (7.5 mL) was added 2,3,4,5-tetrafluorobenzoic acid (383 mg, 1.97 mmol), DMAP (36 mg, 0.30 mmol, 30 mol%), and DCC (610 mg, 2.96 mmol). After 16 h further 2,3,4,5-tetrafluorobenzoic acid (191 mg, 0.98 mmol), DMAP (36 mg, 0.30 mmol, 30 mol%), and DCC (305 mg, 1.48 mmol) was added and stirred for 5 h, passed through a plug of silica, and chromatographed (0:1-2:3 CH_2Cl_2:PE) to afford tetrafluorobenzoate ester **6b** (316 mg, 60%) as a colorless oil. R_f = 0.3 (5:95 EtOAc:PE); $[\alpha]_D^{24}$ +14.4 (*c* 1.4, CH_2Cl_2); IR ν_{max} 2931, 2858, 2362, 1719 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.56 (m, 1H), 7.15 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 5.34 (t, 6.80 Hz, 1H), 4.54 (dd, J = 11.5, 1.9 Hz, 1H), 3.81 (s, 3H), 2.66 (t, J = 7.6 Hz, 2H), 2.44-2.26 (m, 3H) 2.21 (dt, J = 13.8, 8.0 Hz, 1H), 2.09-2.00 (m, 1H) 1.94-1.85 (m, 1H) 1.79 (s, 3H), 1.76 (s, 3H), 1.60 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.5, 157.7, 147.8 (dddd, J = 262, 11, 4, 2 Hz), 146.4 (dddd, J = 249, 10, 4, 2 Hz), 143.4 (dddd, J = 262, 17, 13, 3 Hz), 141.3 (dddd, J = 255, 17, 12, 3 Hz), 134.3, 133.6, 129.3, 125.7, 116.0 (m), 113.6, 113.2 (dd, J = 21, 2 Hz), 86.2, 61.6, 55.2, 37.8, 35.0, 31.5, 30.2, 24.1, 23.3, 15.8 ppm; ^{19}F NMR (377 MHz, $CDCl_3$) δ -153.5 (t, J = 20 Hz, 1F), -147.7 (tt, J = 19, 8 Hz, 1F), -138.0 (dt, J = 22, 12 Hz, 1F), -134.5 (m, 1F) ppm; MS (CI^+, NH_3) m/z 548, 546 $[M+NH_4]^+$; HRMS (EI^+) calcd. for $C_{25}H_{27}NO_3^{79}BrF_4$ $[M]^+$ 530.1080, found 530.1082.

(-)-(2*R*,4a*R*,10a*S*)- and (-)-(2*R*,4a*S*,10a*R*)-2-Bromo-6-methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrenes (2) from cyclization of bromotetrafluorobenzoates 6a and 6b. Cyclization of tertiary bromide **6a**: To a stirred solution of Me_3Al (2M in hexanes, 0.25 mL, 0.5 mmol) in CH_2Cl_2 (2 mL) at –78 °C was added a solution of trifluoromethanesulphonic acid (43 μL, 0.5 mmol) in CH_2Cl_2 (4 mL) and stirred at –78 °C for 0.5 h and 0 °C for 0.5 h. The white suspension of Me_2AlOTf was recooled to –78 °C and a solution of bromo tetrafluorobenzoate **6a** (50 mg, 0.292 mmol) in CH_2Cl_2 (2 mL) was added dropwise at –78 °C. The reaction was allowed to warm to room temperature over 16 h, quenched with aqueous HCl solution (1M, 10 mL), extracted with CH_2Cl_2 (2 × 10 mL), washed with saturated aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL), dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed (0:1-3:7 CH_2Cl_2:PE) to afford first monocycles **7** as an inseparable mixture of at least two endocyclic and two exocyclic alkenes (6 mg, 19%) as a colorless oil, R_f = 0.39 (1:4 CH_2Cl_2:PE), and second bromides (2*R*,4a*R*,10a*S*)-**2** and (2*R*,4a*S*,10a*R*)-**2** as an inseparable mixture of diastereoisomers (d.r. 3:1, 8 mg, 25%) as a white solid: m.p. 92-93 °C; R_f = 0.64 (40:60 CH_2Cl_2:PE). The major diastereoisomer (2*R*,4a*R*,10a*S*)-**2** was identical to that produced in the BDSB mediated cyclization of polyene **1**, and the minor diastereoisomer (2*R*,4a*S*,10a*R*)-**2** was identified in the mixture by its characteristic ^{1}H NMR signal at 4.42 (1H, CHBr) ppm as a broad singlet (see SI 11 for ^{1}H and ^{13}C NMR spectra). Data for (2*R*,4a*S*,10a*R*)-**2** [as 1:3 mixture with bromide (2*R*,4a*R*,10a*S*)-**2**]: ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.01 (d, J = 8.3 Hz, 1H,), 6.84 (d, J = 2.8 Hz, 1H), 6.71 (dd, J = 8.3, 2.8 Hz, 1H), 4.42 (br s, 1H), 3.81 (s, 3H), 2.94-2.75 (m, 2H), 2.42-2.38 (m, 1H), 2.21-2.06 (m, 3H), 1.89 (dd, J = 12.4, 2.5 Hz, 1H), 1.82-1.67 (m, 2H), 1.22 (s, 3H), 1.12 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 150.5, 129.8, 127.1, 111.0, 110.0, 69.1, 55.3, 43.5, 38.4, 37.8, 33.4, 32.9, 29.1, 28.7, 25.5, 22.2, 18.5 ppm; GCMS (EI^+) m/z 337, 335 $[M-H]^+$. The diastereoisomers were inseparable by standard column chromatography on silica gel, but could be separated by preparative HPLC (Prep Si; *n*-hexane; 5 mL/min) t_R = 145 min [(2*R*,4a*S*,10a*R*)-**2**], 165 min [(2*R*,4a*R*,10a*S*)-**2**]. Bromide (2*R*,4a*R*,10a*S*)-**2**: $[\alpha]_D^{24}$ -100 (*c* 0.04, CH_2Cl_2)[‡]; HPLC (CHIRALPAK AD; 1% IPA in *n*-hexane; 1.0 mL/min) t_R = 4.7 min (minor), 5.4 min (major), e.r. 98:2. Bromide (2*R*,4a*S*,10a*R*)-**2**: $[\alpha]_D^{24}$ -43 (*c* 0.01, CH_2Cl_2) [‡]; HPLC (CHIRALPAK AD; 1% IPA in *n*-hexane; 1.0 mL/min) t_R = 4.7 min (major), 6.1 min (minor), e.r. 98:2. Cyclization of secondary bromide **6b** (135 mg, 0.254 mmol) was conducted as above using 2.5 equivalents of Me_2AlOTf to afford first monocycles **7** as an inseparable mixture of at least two endocyclic and two exocyclic alkenes (21 mg, 25%) as a colorless oil, R_f = 0.39 (1:4 CH_2Cl_2:PE), and second bromides (2*R*,4a*R*,10a*S*)-**2** and (2*R*,4a*S*,10a*R*)-**2** as an inseparable mixture of diastereoisomers (d.r. 3:1, 30 mg, 35%) as a white solid. The diastereomers were separated by preparative HPLC (Prep Si; *n*-hexane; 5 mL/min) t_R = 145 min and [(2*R*,4a*S*,10a*R*)-**2**] and 165 min [(2*R*,4a*R*,10a*S*)-**2**]. Bromide (2*R*,4a*R*,10a*S*)-**2**: HPLC (CHIRALPAK AD; 1% IPA in *n*-hexane; 1.0 mL/min) t_R = 4.7 min (minor), 5.4 min (major), e.r. 98:2. Bromide (2*R*,4a*S*,10a*R*)-**2**: HPLC (CHIRALPAK AD; 1% IPA in *n*-hexane; 1.0 mL/min) t_R = 4.7 min (major), 6.1 min (minor), e.r. 98:2.

(-)-(4a*S*,10a*S*)- and (+)-(4a*S*,10a*S*)-6-methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a -octahydrophenanthrenes (8) from reduction of a 3:1 mixture of (-)-(2*R*,4a*R*,10a*S*)- and (-)-(2*R*,4a*S*,10a*R*)-2-Bromo-6-methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrenes (2). Using the method of Chatgilialoglu and colleagues,[75] to a stirred solution of (2*R*,4a*R*,10a*S*)-**2** and (2*R*,4a*S*,10a*R*)-**2** (d.r. 3:1, 15 mg, 45 μmol) in toluene (2 mL) was added tris(trimethylsilyl)silane (16.5 μL, 53 μmol) and azobisisobutyronitrile (0.73 mg, 40 μmol) and heated to 90 °C for 2 h. The mixture was allowed to cool, concentrated under reduced pressure, and chromatographed (0:1-3:7 CH_2Cl_2:PE) to give *trans*-decalin **8** (5 mg, 43%) as a single diastereoisomer as a colorless oil. R_f = 0.42 (20:80 CH_2Cl_2:PE); $[\alpha]_D^{24}$ -23.0 (*c* 0.26, CH_2Cl_2); lit.[76] (4a*S*,10a*S*)-**8** $[\alpha]_D$ +64.0 (*c* 1.0, $CHCl_3$); IR ν_{max} 2997, 2924, 2852, 1686, 1609 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (d, J = 8.3 Hz, 1H), 6.81 (d, J = 2.7 Hz, 1H), 6.66 (dd, J = 8.3, 2.7 Hz, 1H), 3.78 (s, 3H), 2.88 (ddd, J = 16.8, 6.9, 1.3 Hz, 1H), 2.78 (ddd, J = 16.8, 11.2, 7.4 Hz, 1H), 2.24 (br d, J = 12.6 Hz, 1H), 1.86 (dddd, J = 13.3, 7.5, 2.0, 2.0 Hz, 1H), 1.80-1.57 (m, 3H), 1.48 (br d, J = 13.2 Hz, 1H), 1.41 (td, J = 13.1, 3.7 Hz, 1H), 1.32 (dd, J = 12.5, 2.3 Hz, 1H), 1.23 (dd, J = 13.7, 4.0 Hz, 1H), 1.21 (s, 3H), 0.97 (s, 3H), 0.95 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 151.5, 129.7, 127.5, 110.7, 110.2, 55.3, 50.3, 41.7, 38.8, 38.0, 33.5, 33.3, 29.6, 24.8, 21.7, 19.3, 19.1 ppm; MS (CI^+, NH_3) m/z 259 $[M+H]^+$; HRMS (CI^+, NH_3) calcd. for $C_{18}H_{27}O$ $[M+H]^+$ 259.2062, found 259.2071. HPLC (CHIRALPAK AD; 1% IPA in *n*-hexane; 1.0 mL/min) t_R = 4.12 min [(4a*S*,10a*S*)-**8**], 4.72 min [(4a*R*,10a*R*)-**8**], e.r. 25:75.

RESULTS AND DISCUSSION

Polyene **1**[49] (Fig. 3) was selected as the basic carbon framework for our investigations, with the enantiopure

[‡]The concentration of this solution is very dilute and the absolute magnitude of this measurement is liable to a large error.

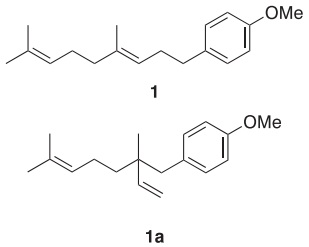
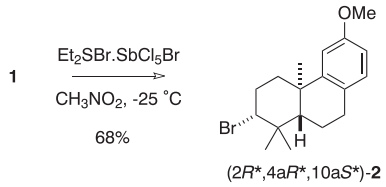


Fig. 3. Polyene **1** and isomer **1a**.



Scheme 1. BDSB mediated cyclization of polyene **1** into racemic tricyclic bromide (2*R**,4a*R**,10a*S**)-**2**.

bromonium ion to be formed on the terminus alkene, the second, internal alkene acting as the propagating olefin, and the polyene cyclization to be terminated by the aromatic nucleus. Diene **1** could be prepared by the palladium(0) catalyzed coupling of *p*-methoxybenzyl magnesium chloride with geranyl bromide,[77] but in our hands variable and significant quantities of the inseparable branched regioisomer **1a** were also observed.[§] The noncatalyzed coupling of the same Grignard reagent with geranyl diethyl phosphate as described by Synder[49] gave significantly improved regioselectivity.[¶] The direct action of BDSB on diene **1** as described by Synder[49] gave racemic tricyclic bromide (2*R**,4a*R**,10a*S**)-**2** (Scheme 1) in good yield as a single diastereoisomer, which in our hands proved to be crystalline. Single crystal x-ray determination (Fig. 4) of tricyclic bromide (2*R**,4a*R**,10a*S**)-**2** confirms the formation of the two six-membered carbocyclic rings as a *trans*-fused decalin ring system, and also the equatorial positioning of the bromine atom.

To the end of generating enantiopure bromohydrins,[69–78] high purity diene **1**** was first dihydroxylated using AD-mix β[71] in good regioselectivity to give diol (*R*)-**3**, in excellent

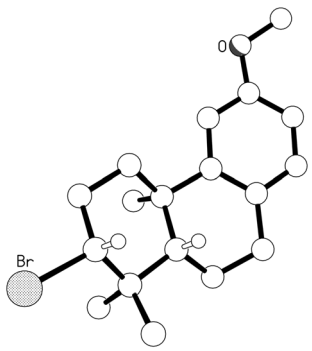
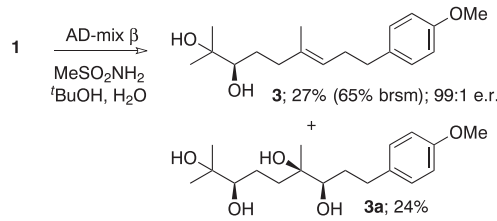


Fig. 4. The crystal structure of (2*R**,4a*R**,10a*S**)-**2**. Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre (CCDC 928846.). Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, United Kingdom (Fax: 44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).



Scheme 2. Asymmetric dihydroxylation of diene **1**.

enantioselectivity (*R*)-**3**; e.r. 99:1)[††] along with unavoidable formation of tetraol (3*R*,6*R*,7*R*)-**3a** (Scheme 2). The absolute configuration of diol (*R*)-**3** was assigned on the basis of the Sharpless mnemonic.[71,79] Diol (*R*)-**3** was converted stereospecifically into epoxide (*S*)-**4** by the Corey et al. method,[73] followed by stereospecific (but non-regioselective) epoxide ring-opening by bromide anion[55] providing the separable regioisomeric bromohydrins (*S*)-**5a** and (*R*)-**5b** (Scheme 3). The regioisomeric bromohydrins (*S*)-**5a** and (*R*)-**5b** were assigned on the basis of their distinctive chemical shifts at 3.40 and 3.95 ppm in their ^{1}H NMR spectra, respectively, where two regioisomeric bromohydrins of a trisubstituted alkene were previously distinguished unambiguously by bromide induced ^{13}C isotopic shifts.[69]

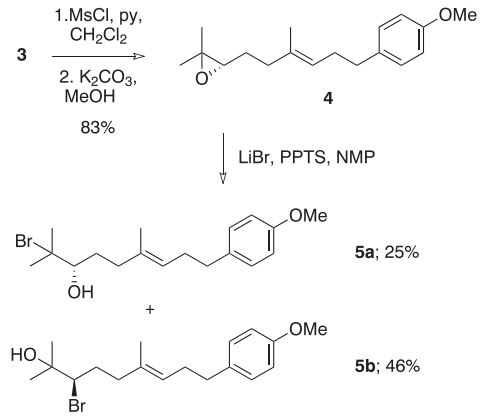
In our previous work with non-alkene-containing substrates,[69] and on the basis of an earlier observation where we had observed the spontaneous formation of a bromonium ion from a 1-bromo-2-tetrafluorobenzoate on standing,[80] enantiopure bromonium ions had been generated by first converting enantiopure bromohydrins into 2,3,4,5-tetrafluorobenzoates, followed by activation with catalytic amounts of triflic acid. While we were confident that the corresponding tetrafluorobenzoates of bromohydrins (*S*)-**5a** and (*R*)-**5b** could be synthesized, the presence of the acid-sensitive trisubstituted alkenes in these substrates would render the use of triflic acid to subsequently generate bromonium ions undoubtedly problematic. Nevertheless, knowing that a suitable Lewis acid should offer an alternative activation mode, tetrafluorobenzoates (*S*)-**6a** (92%) and (*R*)-**6b** (60%) (Fig. 5) were prepared from alcohols (*S*)-**5a** and (*R*)-**5b**, respectively, by Steglich esterification[74] with 2,3,4,5-tetrafluorobenzoic acid. On activation—and stereospecific

[§]In multiple runs the ratio of **1**:**1a** was found to vary unpredictably from 35:1 to 10:1. The two isomers could not be separated by simple column chromatography.

[¶]In two 80 mmol batch reactions, the ratio of **1**:**1a** was determined to be 19:1 and 35:1. Analytically pure **1a** could be obtained from silver nitrate-doped silica gel column chromatography. The purity of **1** could be improved to >98% by a fractional distillation process (see Experimental).

[**]High purity diene **1** free from branched **1a** was found to be essential for subsequent HPLC enantiomeric excess determination of products. The branched isomers were inseparable at all stages of the subsequent synthesis and overlapped and/or obscured the minor and/or major enantiomer signal in the HPLC analyses. This was especially problematic since the asymmetric dihydroxylation of diene **1** is so highly enantioselective (99:1 e.r.), and therefore high purity was required for accurate ee assessment. Moreover, in dihydroxylation runs using lower purity diene **1**, the branched isomer actually *accumulated* (e.g., in multiple runs using dienes **1**:**1a** in a 13:1 ratio, the ratio of linear diol **3** to its inseparable branched diol counterpart was 5:1). Evidently, while **3** could be further dihydroxylated to tetraol **3a** thus depleting the amount of **3**, the terminal alkene of the branched isomer diol was more resistant to further dihydroxylation.

[††]The enantiomeric purity was assayed by chiral HPLC methods (see Supporting Information).



Scheme 3. Synthesis of enantiopure bromohydrins (*S*)-**5a** and (*R*)-**5b**.

displacement of the activated leaving group by neighboring group participation of the bromide—each of (*S*)-**6a** and (*R*)-**6b** should re-converge on the same *R*-configured enantiomerically pure bromonium ion **A** (Fig. 5).

Attempted bromonium ion initiated cyclization of (*S*)-**6a** or (*R*)-**6b** with catalytic quantities of triflic acid,[69] led, as predicted (vide supra), to extensive decomposition, and previous attempts to generate bromonium ions from vicinal bromo tetrafluorobenzoates of trisubstituted alkenes by solvolysis were unsuccessful[69] and not pursued in this study. Lewis acid activation was then explored, where the use of alkyl aluminum reagents as Lewis acids that lead to rigorously proton-free solutions[81] was expected to be beneficial (oxophilic Lewis acid metal halides were rejected as potential mediators of the cyclization on the basis that hydrohalic acids would be generated during the course of the reaction), and preliminary studies with stoichiometric quantities of $Yb(OTf)_3$ and/or $Eu(fod)_3$ in CH_2Cl_2 or chlorobenzene were ineffective in initiating the cyclization even at elevated temperatures and/or under microwave irradiation. The use of stoichiometric quantities of trimethylaluminum to mediate the cyclization was found to be ineffective, leading to decomposition of both of the substrates (*S*)-**6a** or (*R*)-**6b**. Some cyclization adduct was observed using dimethylaluminum chloride as the Lewis acid activator, but a bromochloride was also observed as the major product, where intermolecular attack of any incipient bromonium ion by anionic chloride from the Lewis acid is evidently competing.[‡‡] The use of the Lewis acid dimethylaluminum triflate, incorporating the non-nucleophilic triflate anion—first reported in the 1980s[82] and only infrequently employed[83]—on either bromide (*S*)-**6a** (5 eq. Me_2AlOTf)[§§] or (*R*)-**6b** (2.5 eq. Me_2AlOTf)[§§] led to clean and complete conversion of substrates into cyclization adducts (Scheme 4).[¶¶] *** In both cases, enantiopure bromide (2*R*,4a*R*,10a*S*)-**2** (e.r. 98:2)[††] was provided as a 3:1 mixture with diastereomeric enantiopure bromide (2*R*,4a*S*,10a*R*)-**2** (e.r. 98:2),[††,†††] along with monocyclization adducts **7**.,[‡‡‡] [§§§]

The relative configuration of (2*R*,4a*R*,10a*S*)-**2** had already been established by x-ray crystallography (Fig. 4) from direct BDSB mediated cyclization of polyene **1** (Scheme 1), and the assignment of absolute configuration follows from an *R*-configured bromonium ion. The relative configuration of (2*R*,4a*S*,10a*R*)-**2** was established by $(Me_3Si)_3SiH$ mediated dehalogenation of a 3:1 mixture of (2*R*,4a*R*,10a*S*)-**2** and (2*R*,4a*S*,10a*R*)-**2** diastereomers with essentially quantitative conversion (43% isolated yield) to give a *single* diastereomeric *trans*-decalin **8** (Scheme 5). The observed 3:1 e.r. for *trans*-decalin **8** allows assignment of the absolute configurations as (4a*R*,10a*R*)-**8** and (4a*S*,10a*S*)-**8** from (2*R*,4a*R*,10a*S*)-**2** and (2*R*,4a*S*,10a*R*)-**2**, respectively. The absolute configurations were confirmed by comparison of the negative sign of optical rotation for the 3:1 enantiomeric mixture of (4a*R*,10a*R*)-**8** and (4a*S*,10a*S*)-**8** with the rotation already reported for (+)-(4a*S*,10a*S*)-**8**.[76]

Evidently, the bromonium ion initiated cyclizations described herein (Scheme 4) are proceeding enantiospecifically via enantiomerically pure bromonium ions[68,¶¶¶,****] without problematic intramolecular or intermolecular bromonium ion-to-alkene transfer.[53] We invoke a chair-like conformation **C** in the cyclization leading to (2*R*,4a*R*,10a*S*)-**2**, and a boat-like conformation **B** in the cyclization leading to (2*R*,4a*S*,10a*R*)-**2** (Fig. 6), each with the same absolute configuration of the bromonium ion (*R*-configured).[¶¶¶,****]

CONCLUSION

In conclusion, we have demonstrated the first enantiospecific polyene cyclizations initiated by enantiopure bromonium ions. We have identified the stoichiometric use of dimethylaluminum triflate to activate tetrafluorobenzoates of enantiopure bromohydrins to initiate such processes, where other Lewis and Brönsted acids fail. Notably, under

[‡‡]From a run using 131 mg of a mixture of **6a** and **6b** (1:2) 9 mg of cyclization adducts **2** (d.r. 3:1) were isolated after extensive column chromatography. A noncyclized bromochloride (24 mg) was obtained with a characteristic mass spectrometry isotope pattern of 390 (82%), 392 (100%), 394 (49%) $(M+NH_4)^+$.

[§§]The use of less equivalents of Me_2AlOTf led to incomplete consumption of starting tetrafluorobenzoates. Evidently the 2° benzoate **6a** is less readily activated than the 3° benzoate **6b**.

[¶¶]The use of $MeAl(OTf)_2$ as prepared from Me_3Al and 2TfOH in CH_2Cl_2 led to decomposition of the substrates.

[***]Inspection of the ^1H NMR spectrum of the crude reaction mixtures show that all starting material has cleanly been converted to product. The relatively low isolated yields (scheme 4) reflect the difficult chromatographic purification/separation of these non-polar compounds.

[†††]The two diastereoisomers were not separable by column chromatography, but could be separated by preparative HPLC. This enabled the enantiomeric purity of each to be established without interference from the other (see Supporting Information).

[‡‡‡]A mixture of inseparable monocyclisation adducts **7** could be isolated by column chromatography after cyclization. Inspection of the alkene region of the ^1H NMR spectrum reveals two monocycles with exocyclic methylene groups [δ_H 5.03 (s, 1H), 4.79 (s, 1H), and 4.90 (s, 1H), 4.17 (s, 1H) in a 3:1 ratio respectively] and two monocycles with endocyclic trisubstituted alkenes [δ_H 5.27 (br s, 1H), and 5.20 (br s, 1H) in a 3:1 ratio, respectively]. The endocyclic:exocyclic alkenes ratio is 1.5:1.

[§§§]Attempts to convert the isolated monocyclic alkene mixture **7** into tricyclic adducts **2** with chlorosulphonic acid in nitromethane as previously demonstrated by Sakakura et al. (Ref. 10) in a similar system, led instead to extensive decomposition.

[¶¶¶]The exact structure of a "bromonium ion" of an alkene will depend strongly on the substitution pattern of the alkene, the solvent, and its counterion. It is understood that a cyclic bromonium ion and an open β-bromocarbocation represent the two extremes of a spectrum of ionic intermediates that are possible.

[****]The enantiospecific cyclization of tertiary bromide (*S*)-**6a** requires the intermediacy of an *R*-configured enantiomerically pure bromonium ion by stereospecific NGP displacement of the tetrafluorobenzoate group, whereas cyclization of secondary bromide (*R*)-**6b** may proceed instead directly via a tertiary carbocation. The near identical product distributions for each substrate as observed by inspection of the crude reaction mixtures by ^1H NMR implicate a single common intermediate *viz.* a bromonium ion.

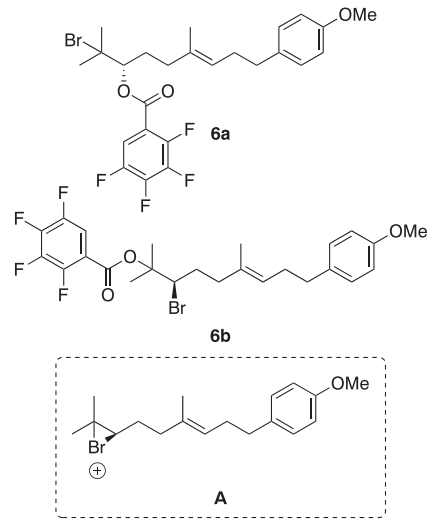
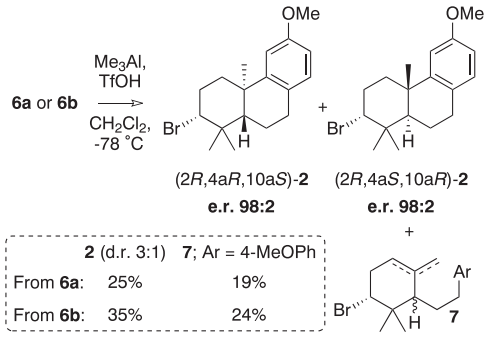
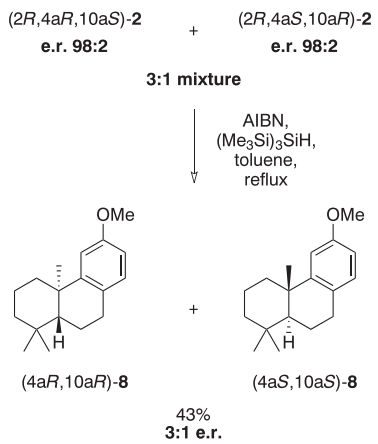


Fig. 5. Tetrafluorobenzoates (*S*)-**6a** and (*R*)-**6b** as precursors to the same enantiomerically pure bromonium ion **A**.



Scheme 4. Enantiospecific cyclization of tetrafluorobenzoates (*S*)-**6a** and (*R*)-**6b** with stoichiometric dimethylaluminum triflate.



Scheme 5. Correlation of absolute and relative configurations by reduction of a 3:1 diastereomeric bromide mixture **2** to *trans*-decalin **8**.

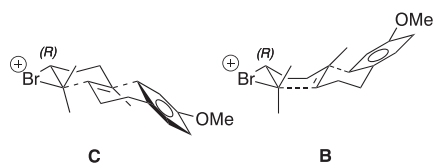


Fig. 6. Chair-like **C** and boat-like **B** geometries in the cyclizations leading to (2*R*,4a*R*,10a*S*)-**2** and (2*R*,4a*S*,10a*R*)-**2**, respectively.

the reported cyclization conditions, any intramolecular or intermolecular bromonium ion-to-alkene transfer is evidently not in operation. Further work will require the identification of other Lewis acid-leaving group combinations to improve overall yields of polycyclic products and to expand the substrate scope.

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