

Electronic Supporting Information

Enantiospecific Bromonium Ion Generation and Intramolecular Capture: A Model System for Asymmetric Bromonium Ion-Induced Polyene Cyclisations†

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Notes ‡, §, ¶, ¥, ††, **, ‡‡, §§, ¶¶, ¥¥, †††, ***, ‡‡‡, §§§, ¶¶¶ and ¥¥¥

‡ We planned to prepare enantiopure bromohydrins from enantiopure epoxides by ring-opening with bromide anion. We were unconcerned about the need to find a regioselective method of ring-opening. In our previous work (reference 13 in the main manuscript) bromohydrins were obtained by ring-opening of enantiopure epoxides with HBr. In the case of terminal epoxides this proceeds stereospecifically, but not regioselectively, giving mixtures (in this case separable) of secondary (with inversion of configuration) and primary (with unchanged configuration at the secondary position) bromides. On activation, stereospecific NGP of the bromide occurs with inversion of configuration so both the bromohydrin derivatives ultimately re-converge into the same bromonium ion. Thus, there is no need for a regioselective epoxide ring-opening method, and indeed, no need necessarily for them to be separable.

§ Here the aromatic nucleus will act as the terminating group for the proposed brominative cyclisation reaction as inspired by the work of Sakakura (see reference 12 in the main manuscript).

¶ The enantiomeric purity was assayed by chiral HPLC methods by reference to a racemic sample (see ESI pp 24-29).

¥ A number of methods were surveyed here to identify the optimum reagent(s) and conditions. Multiple side-products due to rearrangements, elimination and cyclisation were formed under non-optimised conditions (see ESI pp 36-37 for full details). For Couladourous and Vidali see reference 15 in the main manuscript.

†† Acetate **6b** was best prepared from **4b** using TFAA and AcOH (see ESI p 10).

** The measured e.r.'s for **5a**, **5b**, **6a** and **6b** were 92:8, 93:7, 92:8 and 92:8 respectively (see ESI pp 25-28).

‡‡ Preliminary attempts to effect cyclisation were attempted on racemic **5a** and **5b** using protic solvents or Lewis acids, and a variety of outcomes were observed (see ESI pp 33-35 for full details).

§§ A racemic sample of bromocyclohexane **7** could be obtained by direct BDSB-mediated cyclisation of alkene **1** in 63% yield (see ESI pp 10-11).

¥¥ Small quantities of alkene (*ca.* 2-5%) were apparent in the ¹H NMR spectrum of the crude product mixture. Presumably some leakage of ee is occurring by bromonium ion-to-olefin transfer (see reference 14 in the main manuscript). However, two subsequent runs using *ent*-**6a** (e.r. 96:4) gave high yields (95-97%) with undiminished e.r.'s where no alkene was apparent in the ¹H NMR spectrum. Evidently, variable generation of trace quantities of alkene using this substrate leads to variable and unpredictable erosion of ee.

††† Four runs were carried out with this substrate. Product **7** was observed in all cases, along with varying amounts of starting acetate **6b**, 2° acetate **6a**, elimination products and isopropylphenethylketone. Three further subsequent runs with *ent*-**6b** (e.r. 96:4) gave essentially the same results where the enantiomer ratios of the isolated product *ent*-**7** were recorded as 89:11, 63:27 & 90:10. Evidently, the formation of multiple side products leads to variable and unpredictable erosion of ee.

*** The exact structure of a “bromonium ion” of an alkene depends strongly on any substituents and on the solvent, and it is understood that a spectrum of ionic intermediates are possible, of which a cyclic bromonium ion and an open β-bromocarocation are the extremes. See reference 13 in the main manuscript and references cited therein.

‡‡‡ We saw no evidence for trapping of the bromonium ion at the secondary position to form a 5-membered ring.

§§§ The cyclisation of **5b** into **7** may proceed simply through a tertiary carbocation. We have prepared the corresponding *des*-bromo compound and found that it does indeed cyclise under these conditions (see ESI pp 38-39).

¶¶¶ The epoxide ring-opening method produces *ca.* 9% of 5-(4-methoxyphenyl)-2-methylpent-1-en-3-ol, which is carried through in the esterification to give 5-(4-methoxyphenyl)-2-methylpent-1-en-3-yl 2,3,4,5-tetrafluorobenzoate. This material can be removed by treating the mixture with mCPBA followed by chromatography (see ESI pp 30-32 for details). If the cyclisation is conducted in the presence of the allylic ester, *ent*-**7** is obtained in lower yield (53%) with slight erosion of e.r. (92:8). Presumably some leakage of ee is occurring by bromonium ion-to-olefin transfer (see reference 14 in the main manuscript).

¥¥¥ This is the Friedel-Crafts adduct of *ent*-**7** with 1-methylcyclohexene: (*R*)-2-Bromo-7-methoxy-1,1-dimethyl-6-(1-methylcyclohexyl)-1,2,3,4-tetrahydronaphthalene (see ESI p 40).

General experimental

Reagents: Tetrakis(triphenylphosphine)palladium(0) was prepared according to the procedure by Coulson *et al*¹ and stored under nitrogen, without light in the fridge. Triethylamine was distilled from CaH₂ onto activated 4Å molecular sieves. All other reagents were obtained from commercial sources and used as received.

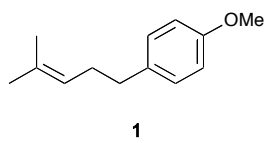
Solvents: All reactions were carried out in anhydrous solvents unless used in combination with H₂O. CH₂Cl₂, THF and toluene were dried by passing through a column of alumina beads. Extraction solvents and chromatography eluents were used as received. MeOH and CH₂Cl₂ were HiPerSolv grade, EtOH was AnalaR grade, and Et₂O, EtOAc, and petroleum ether 40-60 (referred to as PE) were GPR grade. *n*-Hexane and *i*-PrOH for analytical 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 aluminium alloy heating block, or bath temperatures. 4Å Molecular sieves were activated by grinding into a powder and heating under vacuum and then cooling under nitrogen. The phrase, 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 OD-H or CHIRALPAK AD columns detecting at 284 nm. Retention times (*t_R*) are reported in minutes. Analytical TLC was performed on Kieselgel 60 F254 pre-coated aluminium-backed plates which were visualised by ultraviolet light (350 nm) and chemical staining using potassium permanganate solution.

Characterisation: Fourier transform IR spectra were recorded neat using an ATR-IR spectrometer. ¹H, ¹³C and ¹⁹F NMR spectra were recorded on Bruker 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 MS (EI, CI), GCMS and HRMS, were recorded by the Imperial College Department of Chemistry Mass Spectrometry Service.

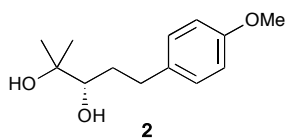
Experimental details and characterising data for compounds 1-3, 4a-b, 5a-b, 6a-b & 7

1-Methoxy-4-(4-methylpent-3-en-1-yl)benzene (1)



Prepared according to the procedure used by Zhao and Loh² and developed by Demuth.³ To a stirred solution of magnesium turnings (2.39 g, 100 mmol) in anhydrous THF (50 mL) was added a few drops of *p*-methoxybenzyl chloride and a few drops of 1,2-dibromoethane to activate the reaction. The reaction could also be started by gentle heating. Subsequently a solution of *p*-methoxybenzyl chloride (11.3 mL, 83 mmol) in anhydrous THF (50 mL) was added dropwise over 30 min maintaining the reflux. After complete addition reflux was continued for 2 h. The mixture was then added dropwise to a freshly prepared solution of 1-bromo-3-methylbut-2-ene (8.0 mL, 67 mmol) and tetrakis(triphenylphosphine)palladium(0) (1.13 g, 0.98 mmol, 1.5 mol%) in THF (50 mL) at 0°C. The reaction mixture was allowed to warm to r.t., stirred for 16h and quenched with ice water (100 mL). The mixture was extracted with Et₂O (2 × 100 mL), washed with water (100 mL), brine (100 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (5:95-15:85 Et₂O:PE) to afford the title product **1** (10.2 g, 80%) as a colourless oil. $R_f = 0.33$ (10:90 EtOAc:PE); IR ν_{\max} 1511, 1243, 1038 cm⁻¹, sp² CH and C=C stretches not observed; ¹H NMR (400 MHz, CDCl₃) δ 7.15 (d, $J = 8.6$ Hz, 2H), 6.87 (d, $J = 8.6$ Hz, 2H), 5.21 (t, $J = 7.1$ Hz, 1H), 3.83 (s, 3H), 2.62 (app. t, $J = 7.8$ Hz, 2H), 2.31 (app. q, $J = 7.8$ Hz, 2H), 1.74 (s, 3H), 1.61 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 157.7, 134.6, 132.1, 129.3, 123.8, 113.7, 55.3, 35.2, 30.3, 25.7, 17.7 ppm; MS (CI⁺, NH₃) m/z 191 [M + H]⁺; HRMS (CI⁺, NH₃) calc'd for C₁₃H₁₉O [M+H]⁺ 191.1436, found 191.1434.

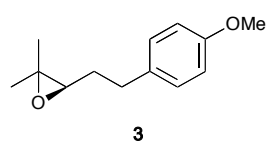
(S)-5-(4-Methoxyphenyl)-2-methylpentane-2,3-diol (2)



According to the method of Sharpless,⁴ to a stirred solution of alkene **1** (2.0 g, 10.5 mmol) and methanesulfonamide (1.0 g, 10.5 mmol) in water (20 mL) and *tert*-butanol (20 mL) was added AD-mix α (14.7 g, 1.4 gmmol⁻¹) at room temperature. The reaction mixture was stirred vigorously for 16 h, was quenched with saturated aqueous Na₂SO₄ solution (60 mL), extracted with EtOAc (2 × 100 mL), washed with brine (100 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (50:50-60:40 EtOAc:PE) to afford the title product **2** (2.17 g, 92%) as a colourless oil. $R_f = 0.37$ (50:50 EtOAc:PE); $[\alpha]_D^{24} -27.6$ (c 1.4, CH₂Cl₂); IR ν_{\max}

3700-3050, 1512, 1244, 1036 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.16 (d, $J = 8.6$ Hz, 2H), 6.86 (d, $J = 8.6$ Hz, 2H), 3.81 (s, 3H), 3.40 (d, $J = 10.5$ Hz, 1H), 2.90 (ddd, $J = 14.3, 9.6, 5.2$ Hz, 1H), 2.65 (ddd, $J = 13.8, 9.3, 7.2$ Hz, 1H), 1.81-1.72 (m, 1H), 1.69-1.59 (m, 1H), 1.21 (s, 3H), 1.17 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 157.9, 134.0, 129.4, 113.9, 77.8, 73.2, 55.3, 33.7, 32.0, 26.6, 23.2 ppm; MS (Cl^+ , NH_3) m/z 242 [$\text{M} + \text{NH}_4$] $^+$; HRMS (Cl^+ , NH_3) calc'd for $\text{C}_{13}\text{H}_{24}\text{NO}_3$ [$\text{M} + \text{NH}_4$] $^+$ 242.1756, found 242.1756; HPLC (CHIRALCEL OD-H; 10% IPA in *n*-hexane; 1.0 mL/min) $t_{\text{R}} = 7.5$ min (major), 9.6 min (minor) – 92:8 e.r. (84% ee). A reference sample of (\pm)-diol **2** was prepared following a modified procedure of Warren.⁵ A solution of potassium ferricyanide (2.60 g, 7.9 mmol), potassium carbonate (1.09 g, 7.9 mmol), $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$ (29 mg, 0.079 mmol), quinuclidine (9 mg, 0.079 mmol, 3 mol%) and methanesulfonamide (250 mg, 2.63 mmol) in water (5 mL) and *tert*-butanol (5 mL) was warmed slightly and stirred until all the solids had dissolved and then allowed to cool to room temperature. Alkene **1** (500 mg, 2.63 mmol) was added and the mixture was stirred vigorously for 16 h. Anhydrous sodium sulphite (3.8 g, 30.2 mmol) was added and the mixture was stirred for 1 h, diluted with water (75 mL) and extracted with CH_2Cl_2 (3×75 mL). The combined organics were washed with aq. NaOH (2M, 100 mL), dried over Na_2SO_4 , concentrated under reduced pressure and chromatographed (50:50-60:40 EtOAc:PE) to afford (\pm)-diol **2** (594 mg, 100%) as a white solid. M.p. 58-62 °C. HPLC (CHIRALCEL OD-H; 10% IPA in *n*-hexane; 1.0 mL/min) $t_{\text{R}} = 7.4$ min, 9.3 min.

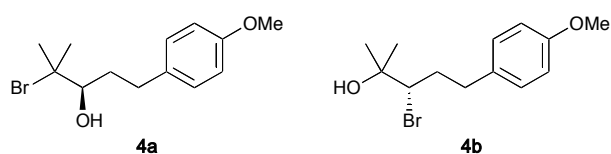
(*R*)-3-(4-Methoxyphenylethyl)-2,2-dimethyloxirane (**3**)



Using a modified procedure of Corey,⁶ to a stirred solution of (*S*)-diol **2** (2.0 g, 8.9 mmol) and triethylamine (2.46 mL, 17.7 mmol) in CH_2Cl_2 (40 mL) at 0°C was added methanesulphonyl chloride (0.89 mL, 11.5 mmol). After 0.5 h the mixture was warmed to room temperature and stirred for 3 h. Additional triethylamine (7.4 mL 53 mmol) was added, the reaction mixture was stirred for 16 h and poured into a suspension of K_2CO_3 (20 g, 145 mmol) in methanol (80 mL). The reaction mixture was stirred for 5 h, concentrated, diluted with water (100 mL), extracted with EtOAc (3×100 mL), washed with 10% aqueous CuSO_4 solution (200 mL) and brine (200 mL), dried over Na_2SO_4 , concentrated under reduced pressure and chromatographed (5:95-15:85 EtOAc:PE) to afford the title product (*R*)-**3** (1.39 g, 76%) as a colourless oil. $R_{\text{f}} = 0.36$ (10:90 EtOAc:PE); $[\alpha]_{\text{D}}^{24} +12.6$ (c 1.1, CH_2Cl_2); IR ν_{max} 1511, 1243, 1035 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), 3.81 (s, 3H),

2.85-2.75 (m, 2H), 2.72-2.63 (m, 1H), 1.93-1.74 (m, 2H), 1.29 (s, 3H) 1.16 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 157.9, 133.5, 129.4, 113.8, 63.9, 58.5, 55.3, 31.8, 31.0, 24.8, 18.6 ppm; MS (Cl^+ , NH_3) m/z 224 [$\text{M} + \text{NH}_4$] $^+$; HRMS (Cl^+ , NH_3) calc'd for $\text{C}_{13}\text{H}_{22}\text{NO}_2$ [$\text{M} + \text{NH}_4$] $^+$ 224.1651, found 224.1660. A reference sample of racemic epoxide **3**⁷ was prepared by epoxidation of alkene **1**. To a solution of alkene **1** (1.0 g, 5.3 mmol) in CH_2Cl_2 (22 mL) at 0 °C was added *meta*-chloroperoxybenzoic acid (1.36 g, 7.9 mmol) in one portion and the mixture was stirred for 16 h. The reaction mixture was quenched with saturated aqueous Na_2SO_3 solution (50 mL), and extracted with CH_2Cl_2 (50 mL). The organic layer was washed with saturated aqueous NaHCO_3 solution (2 \times 100 mL) and brine (100 mL), dried over Na_2SO_4 , concentrated under reduced pressure and chromatographed (10:90 EtOAc:PE) to afford (\pm)-epoxide **3** (1.07 g, 98%) as a colourless oil.

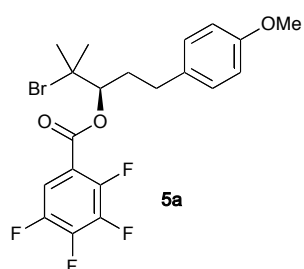
(R)-4-Bromo-1-(4-methoxyphenyl)-4-methylpentan-3-ol (4a) and (S)-3-bromo-5-(4-methoxyphenyl)-2-methylpentan-2-ol (4b)



Following the method of Couladouros and Vidali,⁸ to a solution of (*R*)-epoxide **3** (1.39 g, 6.75 mmol) in *N*-methyl-2-pyrrolidone (2 mL) was added LiBr (763 mg, 8.77 mmol) and PPTS (1.69 g, 6.75 mmol) and stirred at room temperature for 3 h. The reaction was quenched with saturated aqueous NaHCO_3 solution (100 mL), extracted with EtOAc (2 \times 100 mL), washed with brine (100 mL), dried over Na_2SO_4 , concentrated under reduced pressure and chromatographed (10:90-20:80 EtOAc:PE) to yield first 1-(4-methoxyphenyl)-4-methylpentan-3-one⁷ (172 mg, 12%) as a colourless oil, second, bromohydrin **4a** (648 mg, 33%) as a colourless oil, and third, bromohydrin **4b** (1.06 g, 45%) as a colourless oil containing *ca.* 12-15% 5-(4-methoxyphenyl)-2-methylpent-1-en-3-ol.⁹ A sample of analytically pure **4b** was obtained by further careful chromatography. Bromohydrin **4a**: R_f = 0.64 (10:90 EtOAc:PE); $[\alpha]_{\text{D}}^{24}$ +28.5 (*c* 1.4, CH_2Cl_2); IR ν_{max} 3600-3200, 1512, 1244, 1035 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.17 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 3.82 (s, 3H), 3.46 (dd, J = 10.4, 1.8 Hz, 1H), 2.94 (ddd, J = 14.0, 9.4, 4.8 Hz 1H, *H*4), 2.63 (ddd, J = 13.8, 9.0, 7.6 Hz, 1H), 2.20 (br s, 1H), 1.92 (dddd, J = 13.7, 9.4, 7.6, 2.1 Hz, 1H), 1.81 (s, 3H), 1.78-1.67 (m, 1H) 1.74 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 157.9, 133.8, 129.4, 113.9, 78.7, 75.6, 55.3, 33.9, 31.7, 31.2, 28.7 ppm; MS (Cl^+ , NH_3) m/z 306, 304 [$\text{M} + \text{NH}_4$] $^+$; HRMS (Cl^+ , NH_3) calc'd for $\text{C}_{13}\text{H}_{23}\text{NO}_2$ ⁷⁹Br [$\text{M} + \text{NH}_4$] $^+$ 304.0912, found 304.0918; Bromohydrin **4b**: R_f = 0.50 (10:90 EtOAc:PE); $[\alpha]_{\text{D}}^{24}$ -42.0 (*c* 1.1,

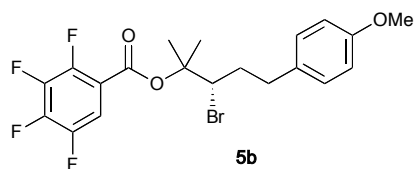
CH₂Cl₂); IR ν_{\max} 3600-3150, 1512, 1244, 1035 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.17 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 3.98 (dd, J = 11.4, 2.1 Hz, 1H), 3.82 (s, 3H), 3.00 (ddd, J = 13.9, 8.4, 4.4, 1H), 2.68 (ddd, J = 13.9, 8.4, 8.3 Hz, 1H), 2.26 (br s, 1H), 2.23-2.13 (m, 1H), 2.11-2.00 (m, 1H) 1.34 (s, 3H), 1.33 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 158.1, 132.7, 129.5, 114.0, 72.5, 70.5, 55.3, 35.9, 33.6, 26.6, 26.0 ppm; MS (CI⁺, NH₃) m/z 306, 304 [M + NH₄]⁺; HRMS (CI⁺, NH₃) calc'd for C₁₃H₂₃NO₂⁷⁹Br [M + NH₄]⁺ 304.0912, found 304.0915. Reference samples of (±)-**4a** and (±)-**4b** were prepared from (±)-**3** using the above procedure.

(R)-2-Bromo-5-(4-methoxyphenyl)-2-methylpentan-3-yl 2,3,4,5-tetrafluorobenzoate (5a)



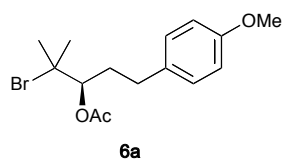
Using the method of Steglich,¹⁰ to a stirred solution of secondary alcohol **4a** (50 mg, 0.18 mmol) in CH₂Cl₂ (1 mL) was added 2,3,4,5-tetrafluorobenzoic acid (41 mg, 0.21 mmol), DMAP (6 mg, 0.052 mmol, 30 mol%) and DCC (47 mg, 0.23 mmol). After 1 h the reaction mixture was diluted with Et₂O, filtered through a silica plug, concentrated under reduced pressure and chromatographed (5:95-20:80 EtOAc:PE) to afford bromo tetrafluorobenzoate **5a** (71 mg, 88%) as a colourless oil. R_f = 0.34 (5:95 EtOAc:PE); $[\alpha]_D^{24}$ +16.5 (c 1.2, CH₂Cl₂); IR ν_{\max} 1725 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.63 (dddd, J = 10.5, 8.4, 6.0, 2.5 Hz, 1H), 7.12 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 5.33 (dd, J = 10.2, 1.8 Hz 1H), 3.79 (s, 3H), 2.67 (app. t, J = 7.8 Hz, 2H), 2.32-2.23 (m, 1H), 2.18-2.07 (m, 1H) 1.81 (s, 3H), 1.80 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 161.5, 158.0, 148.0 (dd, J = 262, 12 Hz), 146.4 (dd, J = 250, 10 Hz), 144.0 (ddd, J = 232, 14, 14 Hz), 141.0 (ddd, J = 228, 14, 14 Hz) 114.6 (m), 113.8, 113.4 (dd, J = 21, 3 Hz), 81.5, 65.6, 55.1, 32.9, 31.6, 30.3 ppm; ¹⁹F NMR (377 MHz, CDCl₃) δ -153.2 (t, J = 20 Hz, 1F), -146.9 (m, 1F), -137.7 (m, 1F), -133.5 (m, 1F) ppm; MS (CI⁺, NH₃) m/z 482, 480 [M + NH₄]⁺; HRMS (CI⁺, NH₃) calc'd for C₂₀H₂₃NO₃⁷⁹BrF₄ [M + NH₄]⁺ 480.0797, found 480.0803; HPLC (CHIRALPAK AD; 0.25% IPA in *n*-hexane; 0.5 mL/min) t_R = 19.8 min (minor), 22.0 min (major) – 92:8 e.r. (84% ee). A reference sample of (±)-**5a** was prepared from (±)-**4a** using the above procedure. HPLC (CHIRALPAK AD; 0.25% IPA in *n*-hexane; 0.5 mL/min) t_R = 19.8 min, 22.4 min.

(S)-3-Bromo-5-(4-methoxyphenyl)-2-methylpentan-2-yl 2,3,4,5-tetrafluorobenzoate (5b)



Using the method of Steglich,¹⁰ to a stirred solution of tertiary alcohol **4b** (250 mg, 0.87 mmol, 1 eq) in CH₂Cl₂ (1 mL) was added 2,3,4,5-tetrafluorobenzoic acid (338 mg, 1.78 mmol, 2 eq), DMAP (32 mg, 0.262 mmol, 30 mol%) and DCC (538 mg, 2.61 mmol, 3 eq). After 16 h the reaction mixture was diluted with Et₂O, filtered through a silica plug, concentrated under reduced pressure and chromatographed (5:95-20:80 EtOAc:PE) to afford tetrafluorobenzoate ester **5b** (300 mg, 62%) as a white solid containing *ca.* 15% 5-(4-methoxyphenyl)-2-methylpent-1-en-3-yl tetrafluorobenzoate. A sample of analytically pure **5b** was obtained by further careful chromatography. Bromo tetrafluorobenzoate **5b**: *R_f* = 0.3 (5:95 EtOAc:PE); m.p. 72-75 °C; [α]_D²⁴ -37.3 (*c* 1.5, CH₂Cl₂); IR *v*_{max} 1729 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.55 (dddd, *J* = 10.5, 8.4, 6.0, 2.5 Hz, 1H), 7.16 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.51 (dd, *J* = 11.3, 1.9 Hz), 3.83 (s, 3H), 3.03 (ddd, *J* = 13.4, 8.6, 4.5 Hz, 1H), 2.70 (ddd, *J* = 13.9, 8.3, 8.3 Hz, 1H), 2.25-2.15 (m, 1H) 2.13-2.03 (m, 1H) 1.74 (s, 3H), 1.72 (s, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 160.4, 158.1, 147.8 (dddd, *J* = 262, 11, 4, 2 Hz), 146.4 (dddd, *J* = 249, 11, 4, 2 Hz), 143.4 (dddd, *J* = 261, 16, 12, 3 Hz), 141.2 (dddd, *J* = 248, 17, 12, 4 Hz) 132.5, 129.5, 115.8 (m), 113.9, 113.3 (dd, *J* = 20, 3 Hz), 86.1, 61.3, 55.2, 35.5, 33.3, 24.1, 23.1 ppm; ¹⁹F NMR (377 MHz, CDCl₃) δ -153.5 (t, *J* = 20 Hz, 1F), -147.6 (m, 1F), -138.0 (m, 1F), -134.4 (m, 1F) ppm MS (Cl⁺, NH₃) *m/z* 482, 480 [M + NH₄]⁺; HRMS (Cl⁺) calc'd for C₂₀H₂₃NO₃⁷⁹BrF₄ [M + NH₄]⁺ 480.0797, found 480.0821; HPLC (CHIRALCEL OD-H; 0.25% IPA in *n*-hexane; 1.0 mL/min) *t_R* = 16.9 min (major), 20.2 min (minor) – 93:7 e.r. (86% ee). A reference sample of (±)-**5b** was prepared from (±)-**4b** using the above procedure. M.p. 74-77 °C; HPLC (CHIRALCEL OD-H; 0.25% IPA in *n*-hexane; 1.0 mL/min) *t_R* = 16.9 min, 19.8 min.

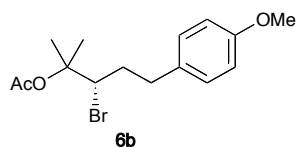
(R)-4-Bromo-1-(4-methoxyphenyl)-4-methylpentan-3-yl acetate (6a)



Using the method of Steglich,¹⁰ to a stirred solution of secondary alcohol **4a** (250 mg, 0.87 mmol) in CH₂Cl₂ (5 mL) was added acetic acid (0.06 mL, 1.05 mmol, 1.2 eq), DMAP (32 mg, 0.26 mmol, 30 mol%) and DCC (233 mg, 1.13 mmol, 1.3 eq). After 16 h the reaction mixture was diluted

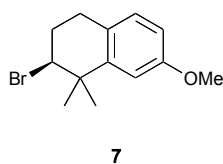
with Et₂O, filtered through a silica plug, concentrated under reduced pressure and chromatographed (5:95-20:80 EtOAc:PE) to afford the bromoacetate **6a** (272 mg, 95%) as a colourless oil. $R_f = 0.38$ (15:85 EtOAc:PE); $[\alpha]_D^{24} +8.7$ (c 1.3, CH₂Cl₂); IR ν_{\max} 1739 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.14 (d, $J = 8.6$ Hz, 2H), 6.86 (d, $J = 8.6$ Hz, 2H), 5.05 (dd, $J = 10.3, 2.1$ Hz, 1H), 3.82 (s, 3H), 2.68-2.52 (m, 2H), 2.20-2.10 (m, 1H), 2.16 (s, 3H) 2.03-1.92 (m, 1H), 1.74 (s, 3H) 1.73 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 170.6, 158.0, 133.2, 129.3, 113.9, 79.1, 66.5, 55.3, 33.3, 31.5, 30.6, 30.4, 20.9 ppm; MS (CI⁺, NH₃) m/z 348, 346 [M + NH₄]⁺; HRMS (CI⁺, NH₃) calc'd for C₁₅H₂₅NO₃⁷⁹Br [M+NH₄]⁺ 346.1018, found 346.1017; HPLC (CHIRALCEL OD-H; 1% IPA in *n*-hexane; 1.0 mL/min) $t_R = 7.6$ min (major), 10.7 min (minor) – 92:8 e.r. (84% ee). A reference sample of (±)-**6a** was prepared from (±)-**4a** using the above procedure. HPLC (CHIRALCEL OD-H; 1% IPA in *n*-hexane; 1.0 mL/min) $t_R = 7.6$ min, 10.7 min.

(S)-3-Bromo-5-(4-methoxyphenyl)-2-methylpentan-2-yl acetate (**6b**)



Using a modified procedure of Murai¹¹ to a stirred solution of tertiary alcohol **4b** (100 mg, 0.35 mmol) and acetic acid (0.02 mL, 0.35 mmol) in CH₂Cl₂ (1 mL) was added trifluoroacetic anhydride (0.29 mL, 2.09 mmol) and stirred at room temperature for 4 h. The reaction was quenched with saturated aqueous NaHCO₃ solution (20 mL) and extracted with CH₂Cl₂ (20 mL). The organic layer was washed with brine (20 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (10:90-20:80 Et₂O:PE) to give bromoacetate **6b** (73 mg, 64%) as a colourless oil. $R_f = 0.34$ (10:90 EtOAc:PE); $[\alpha]_D^{24} -41.9$ (c 2.1, CH₂Cl₂); IR ν_{\max} 1734 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.16 (d, $J = 8.6$ Hz, 2H), 6.88 (d, $J = 6.8$ Hz, 2H), 4.58 (dd, $J = 11.2, 2.0$ Hz, 1H), 3.82 (s, 3H), 3.01 (ddd, $J = 13.9, 9.3, 4.5$ Hz, 1H), 2.65 (ddd, $J = 13.9, 9.4, 7.3$ Hz, 1H), 2.18-2.06 (m, 1H), 2.05-1.95 (m, 1H), 2.02 (s, 3H), 1.59 (s, 3H), 1.57 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 170.2, 158.1, 132.9, 129.4, 114.0, 83.2, 61.9, 55.3, 35.6, 33.6, 24.2, 23.1, 22.3 ppm; MS (CI⁺, NH₃) m/z 348, 346 [M + NH₄]⁺; HRMS (CI⁺, NH₃) calc'd for C₁₅H₂₅NO₃⁷⁹Br [M+NH₄]⁺ 346.1018, found 346.1019; HPLC (CHIRALCEL OD-H; 0.25% IPA in *n*-hexane; 1.0 mL/min) $t_R = 12.1$ min (major), 13.6 min (minor) – 92:8 e.r. (84% ee). A reference sample of (±)-**6b** was prepared by mixing equal amounts of (*S*)-**4b** and (*R*)-**4b**, which were then acetylated using the above procedure. HPLC (CHIRALCEL OD-H; 0.25% IPA in *n*-hexane; 1.0 mL/min) $t_R = 12.1$ min, 13.7 min.

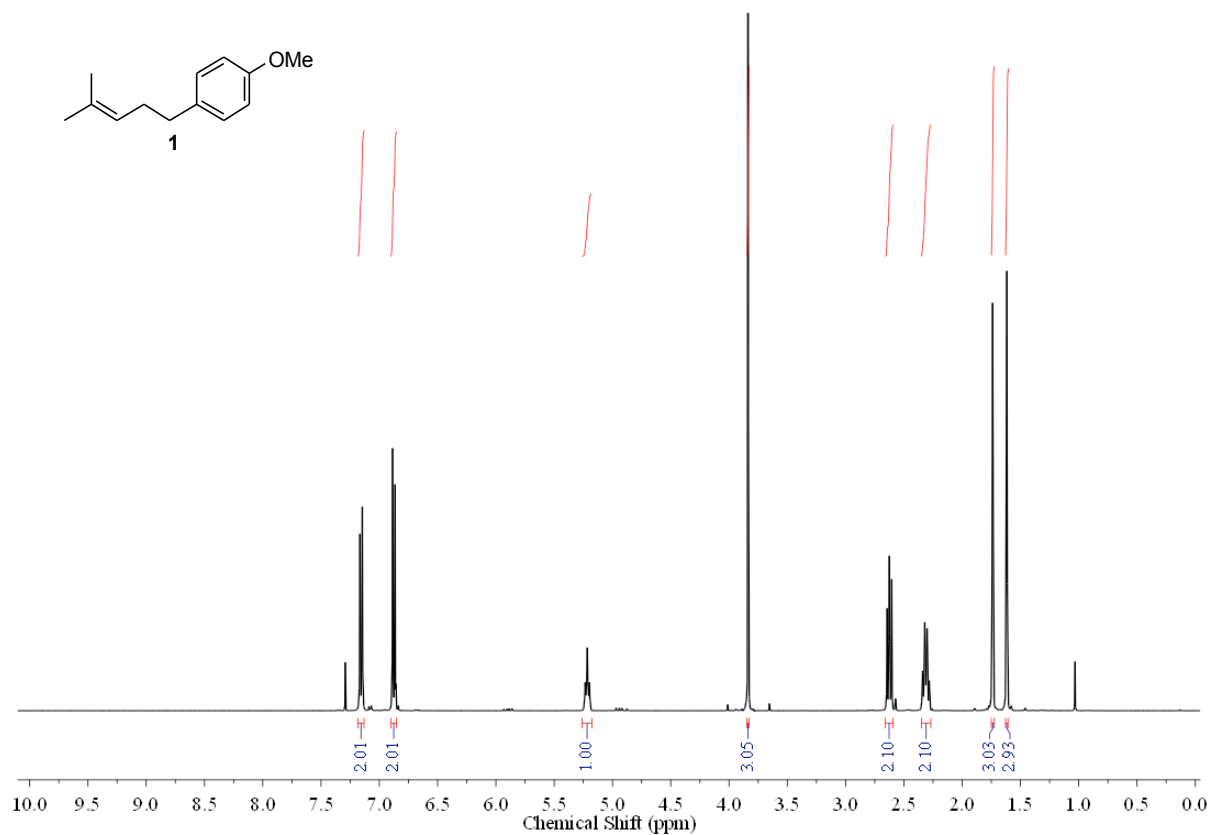
(S)-2-Bromo-7-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalene (7)



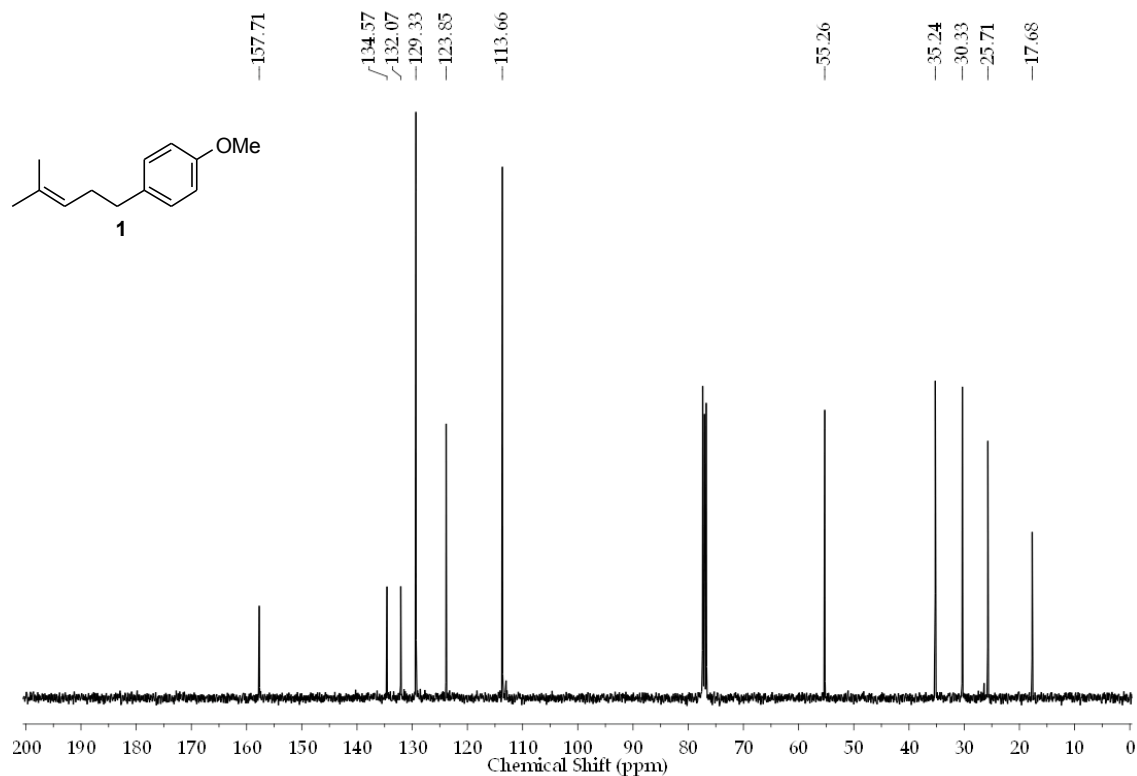
General procedure (See Table in main paper). To a stirred solution of substrate (0.2 mmol) in CH₂Cl₂ (2 mL) at -14 °C was added a solution of triflic acid (5-30 mol%) in CH₂Cl₂ (1 mL). The reaction was allowed to warm to room temperature and stirred overnight or heated to reflux. The reaction was quenched with a saturated aqueous solution of NaHCO₃, extracted with CH₂Cl₂, washed with brine, dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (10:90-15:85 CH₂Cl₂:PE) to afford bromide **7** as a pale yellow oil. $R_f = 0.64$ (40:60 CH₂Cl₂:PE); $[\alpha]_D^{24} -5.9$ (c 2.1, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.03 (d, $J = 8.5$ Hz, 1H), 6.93 (d, $J = 2.6$ Hz, 1H), 6.76 (dd, $J = 8.5, 2.6$ Hz, 1H), 4.47 (dd, $J = 9.2, 3.1$ Hz, 1H), 3.84 (s, 3H), 3.03 (ddd, $J = 16.8, 6.0, 6.0$ Hz, 1H) 2.95-2.85 (m, 1H), 2.52-2.33 (m, 2H), 1.50 (s, 6H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 158.1, 144.3, 129.8, 125.9, 112.3, 111.8, 64.8, 55.3, 39.9, 30.5, 30.1, 28.8, 28.4 ppm; MS (CI⁺, NH₃) m/z 288, 286 [M + NH₄]⁺; HRMS (CI⁺, NH₃) calc'd for C₁₃H₂₁NO⁷⁹Br [M + NH₄]⁺ 286.0807, found 286.0815. HPLC (CHIRALCEL OD-H; 1% IPA in *n*-hexane; 1.0 mL/min) $t_R = 5.1$ min (major), 7.2 min (minor) – 91:9 e.r. (82% ee). A reference sample of (±)-bromide **7** was prepared by direct brominative cyclisation of alkene **1** using the method of Snyder and Treitler.¹² To a stirred solution of alkene **1** (100 mg, 0.53 mmol) in CH₃NO₂ (4 mL) at -25°C was added quickly a solution of BDSB (289 mg, 0.53 mmol) in CH₃NO₂ (2 mL) and stirred for 15 min. The reaction was quenched with a 1:1 mixture of 5% aqueous NaHCO₃ and 5% aqueous Na₂SO₃ (20 mL) solution and stirred for 15 min before being poured into water (20 mL), extracted with CH₂Cl₂ (2 × 20 mL), dried over MgSO₄, concentrated under reduced pressure and chromatographed (PE) to afford (±)-bromide **7** (88 mg, 63%) as a pale yellow oil. HPLC (CHIRALCEL OD-H; 1% IPA in *n*-hexane; 1.0 mL / min) $t_R = 5.2$ min, 7.2 min.

^1H and ^{13}C NMR spectra for compounds 1-3, 4a-b, 5a-b, 6a-b and 7 including ^{13}C NMR spectra displaying bromine isotopic shifts for 4a and 4b;

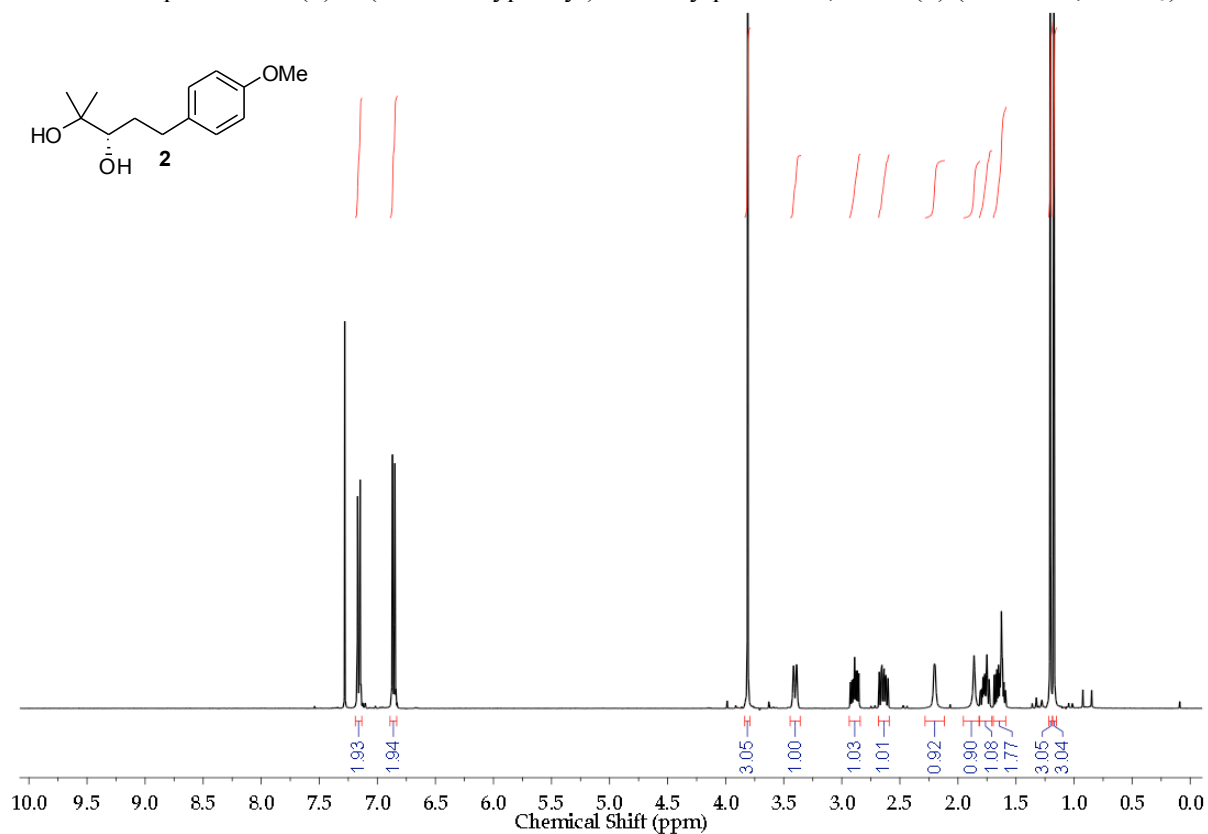
^1H NMR Spectrum of 1-Methoxy-4-(4-methylpent-3-en-1-yl)benzene (**1**) (400 MHz, CDCl_3)



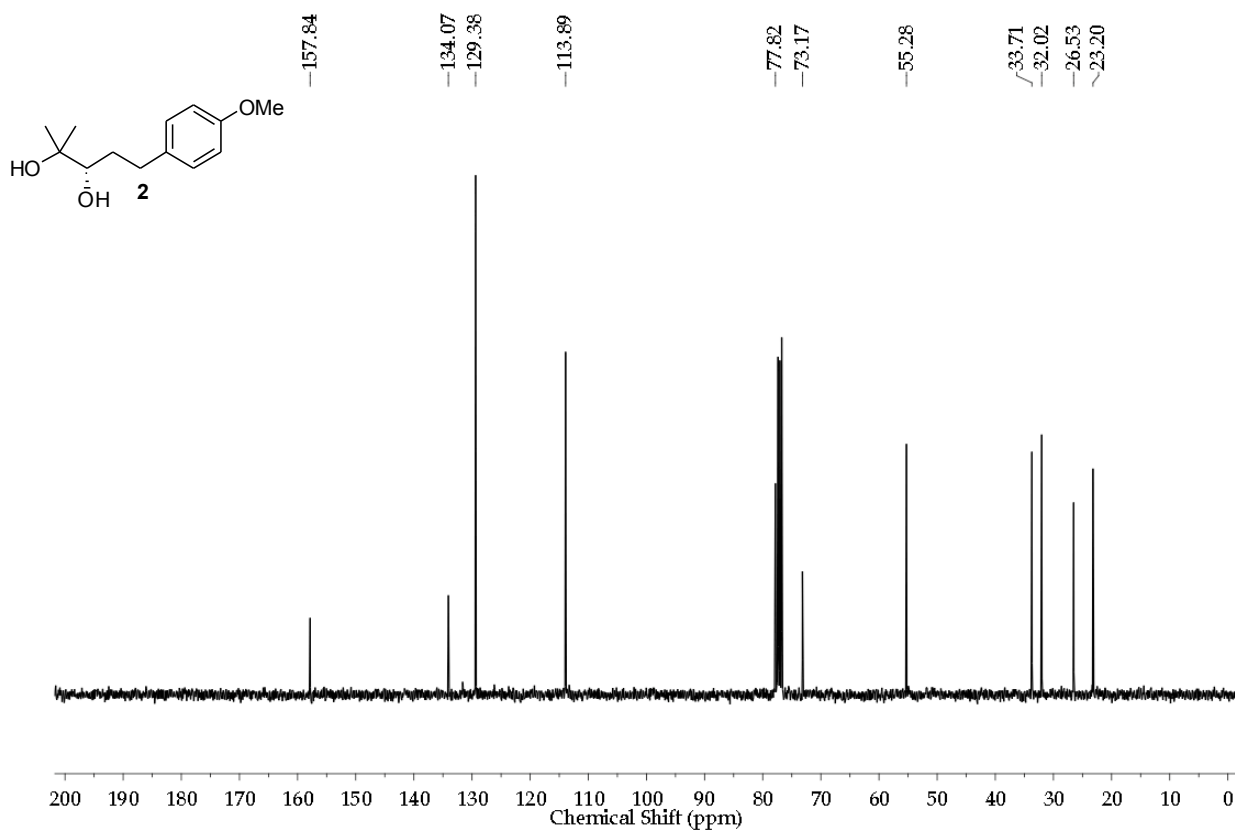
^{13}C NMR Spectrum of 1-Methoxy-4-(4-methylpent-3-en-1-yl)benzene (**1**) (100 MHz, CDCl_3)



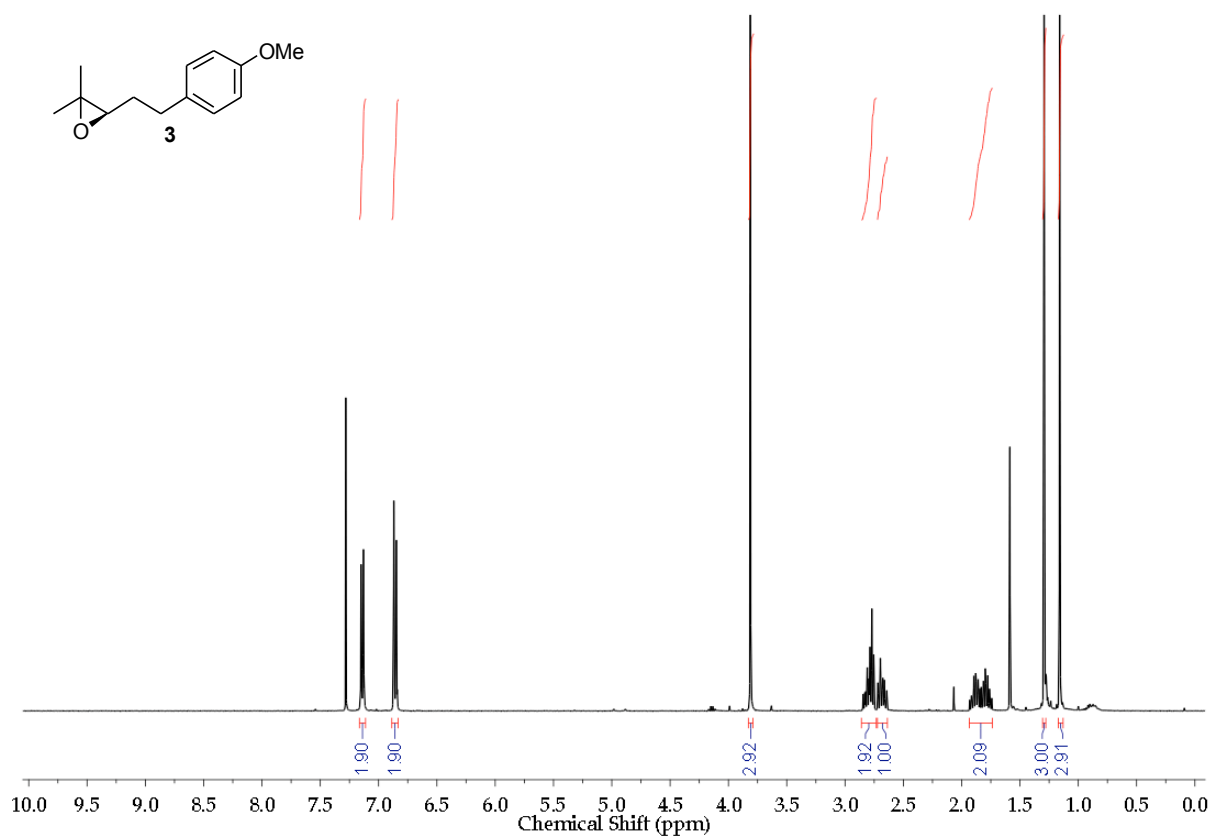
^1H NMR Spectrum of (*S*)-5-(4-Methoxyphenyl)-2-methylpentane-2,3-diol (**2**) (400 MHz, CDCl_3)



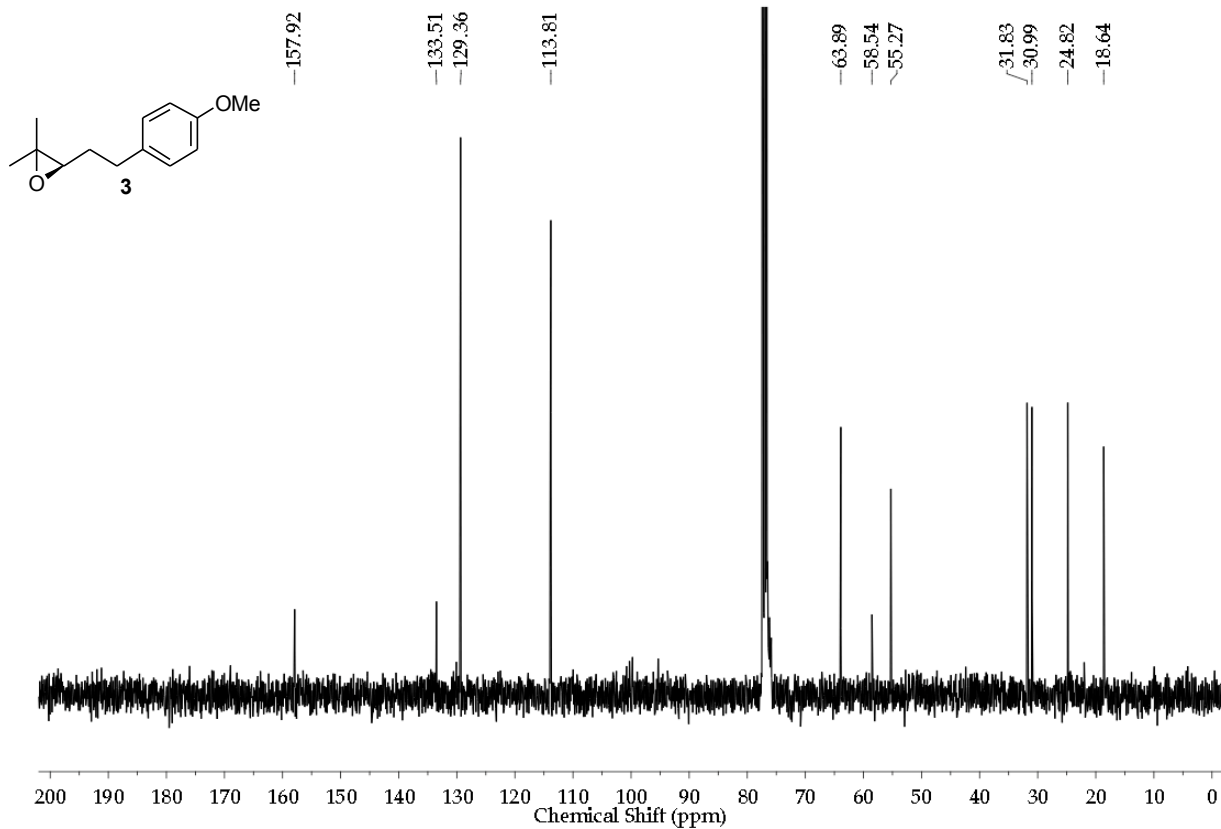
^{13}C NMR Spectrum of (*S*)-5-(4-Methoxyphenyl)-2-methylpentane-2,3-diol (**2**) (100 MHz, CDCl_3)



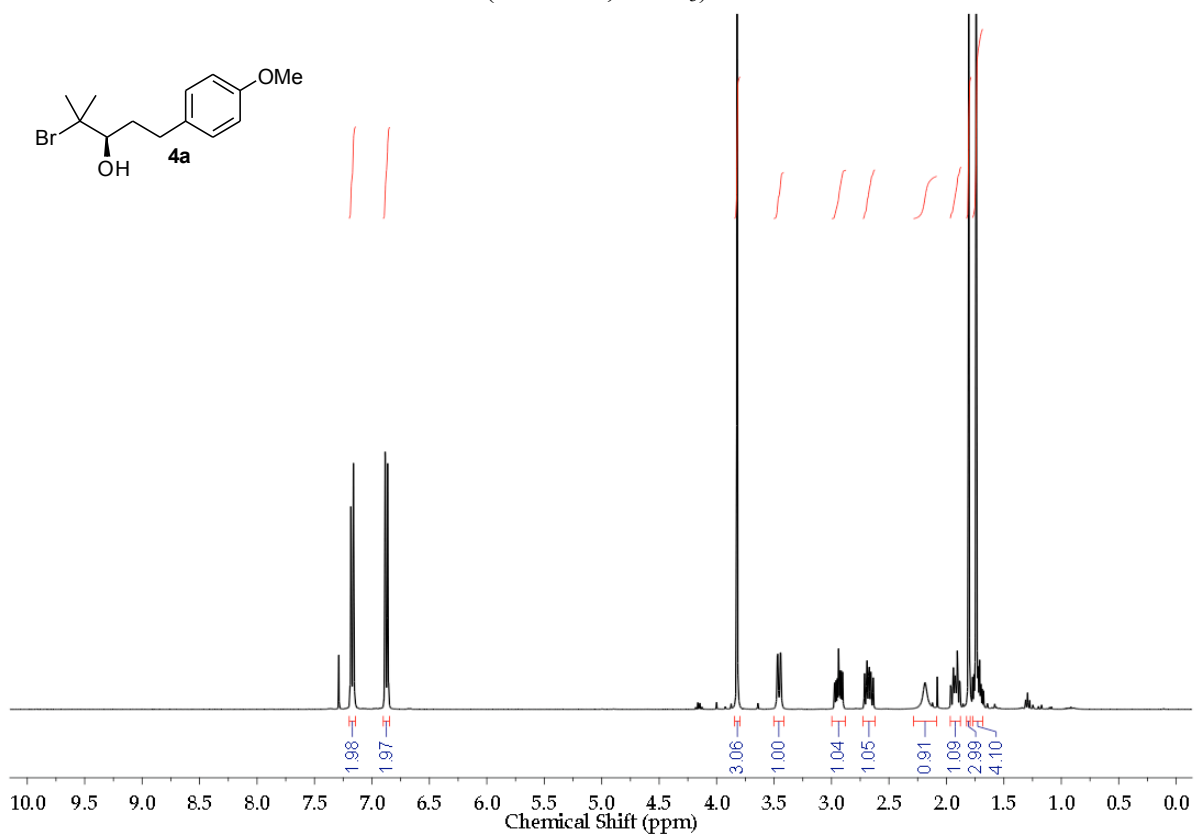
¹H NMR Spectrum of (*R*)-3-(4-Methoxyphenylethyl)-2,2-dimethyloxirane (**3**) (400 MHz, CDCl₃)



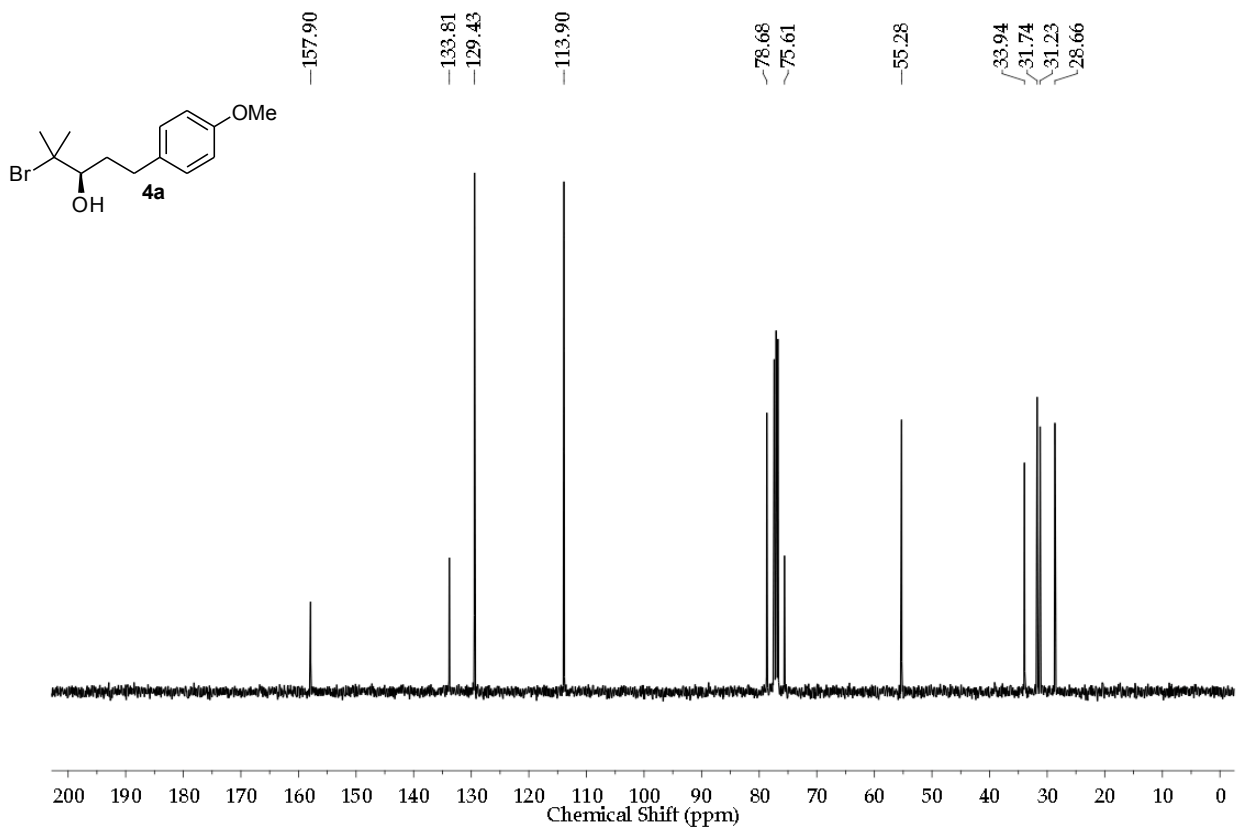
¹³C NMR Spectrum of (*R*)-3-(4-Methoxyphenylethyl)-2,2-dimethyloxirane (**3**) (100 MHz, CDCl₃)



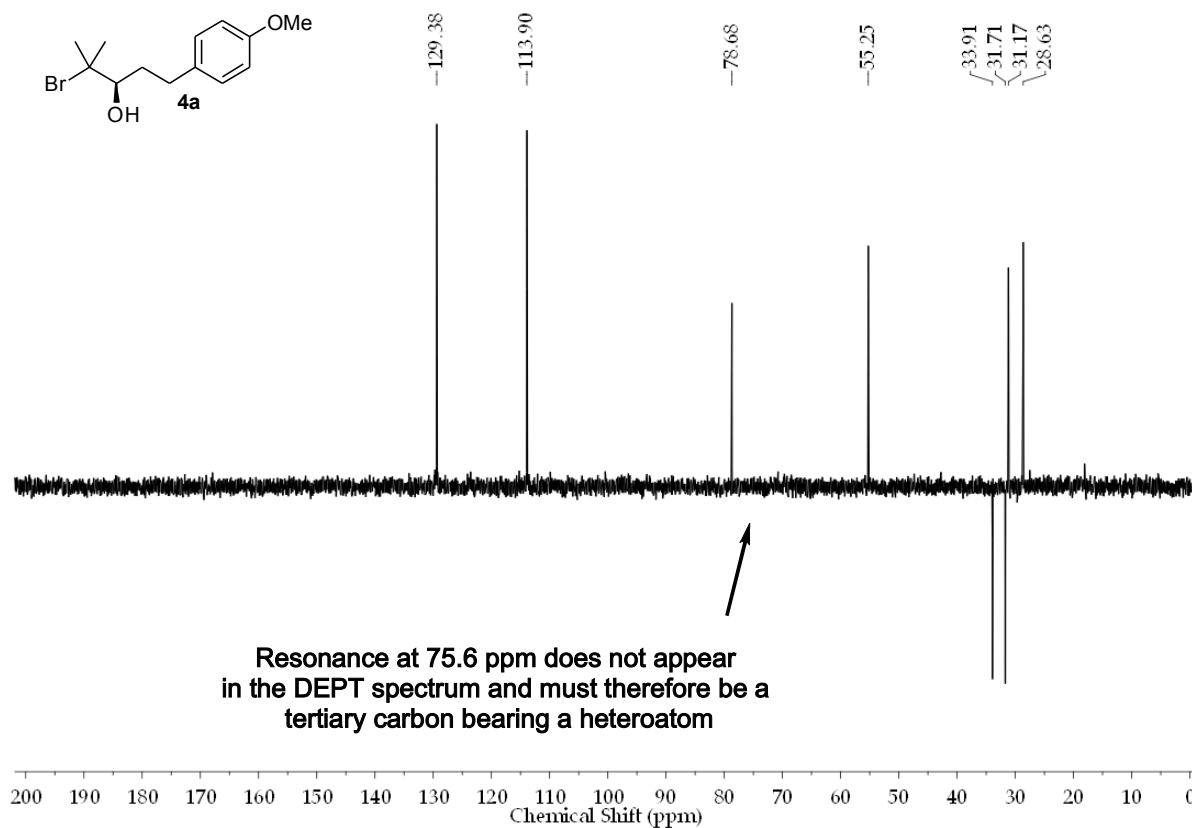
¹H NMR Spectrum of (*R*)-4-Bromo-1-(4-methoxyphenyl)-4-methylpentan-3-ol (**4a**)
(400 MHz, CDCl₃)



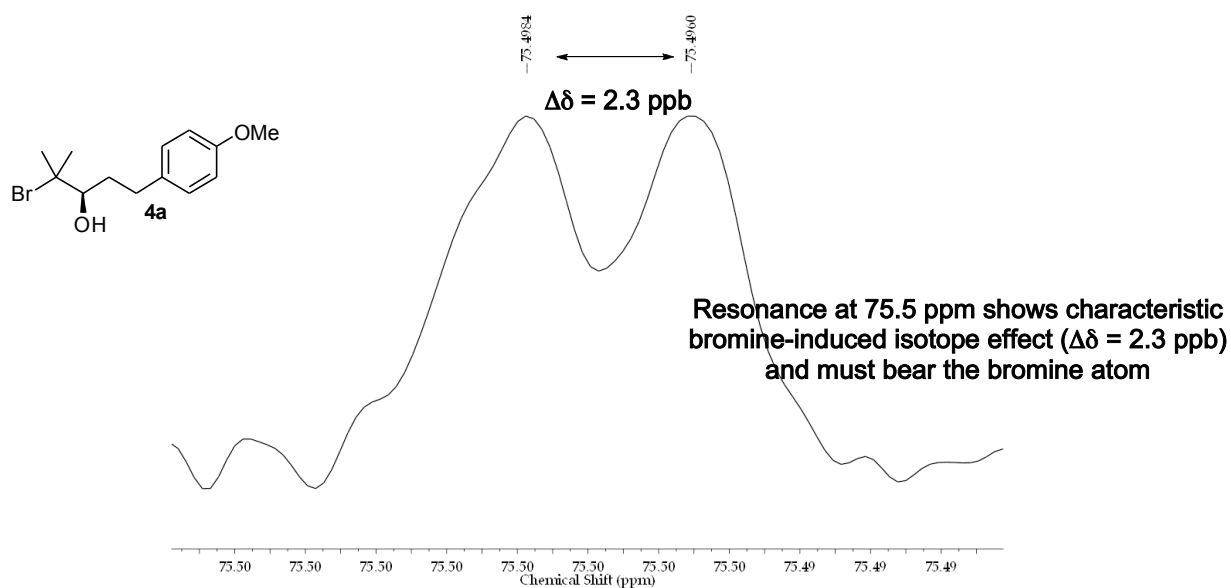
¹³C NMR Spectrum of (*R*)-4-Bromo-1-(4-methoxyphenyl)-4-methylpentan-3-ol (**4a**)
(100 MHz, CDCl₃)



DEPT-135 NMR Spectrum of (*R*)-4-Bromo-1-(4-methoxyphenyl)-4-methylpentan-3-ol (**4a**) (100 MHz, CDCl₃)

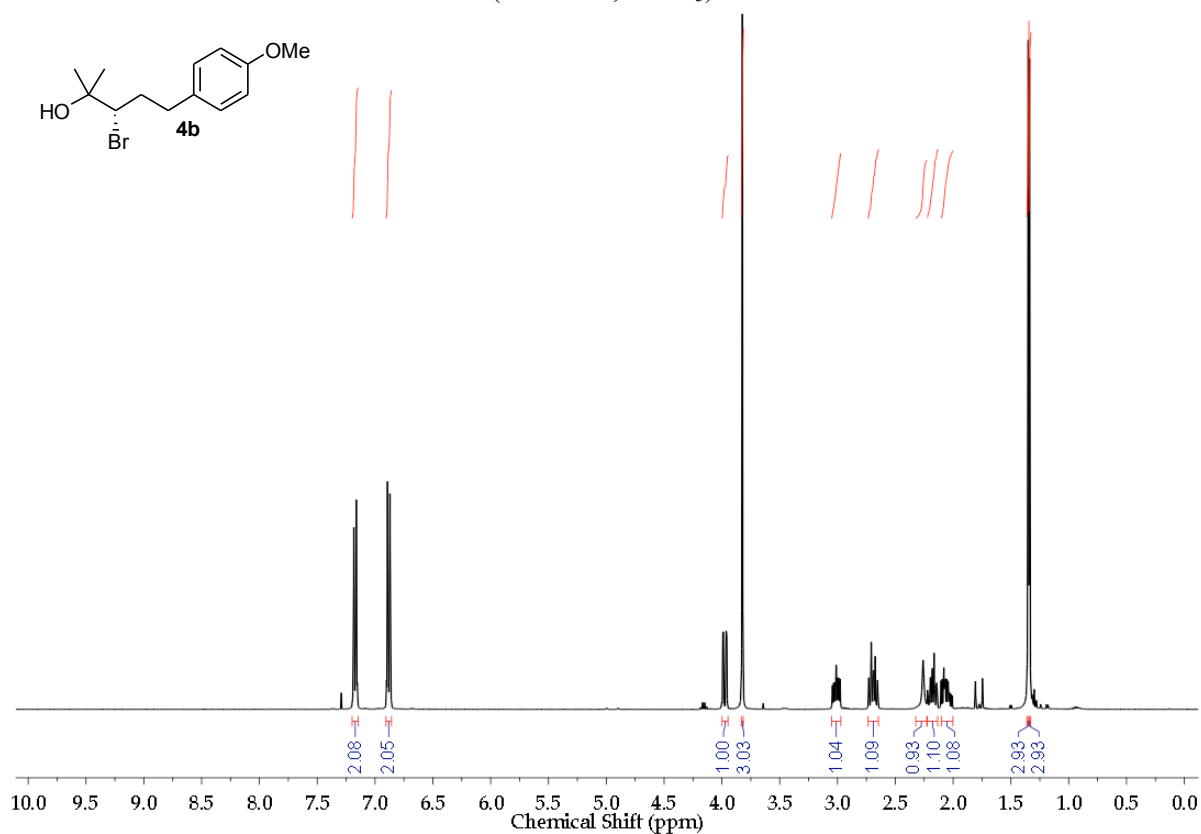


Bromine induced isotopic shift in ¹³C NMR Spectrum of (*R*)-4-Bromo-1-(4-methoxyphenyl)-4-methylpentan-3-ol (**4a**) (125 MHz, CDCl₃)

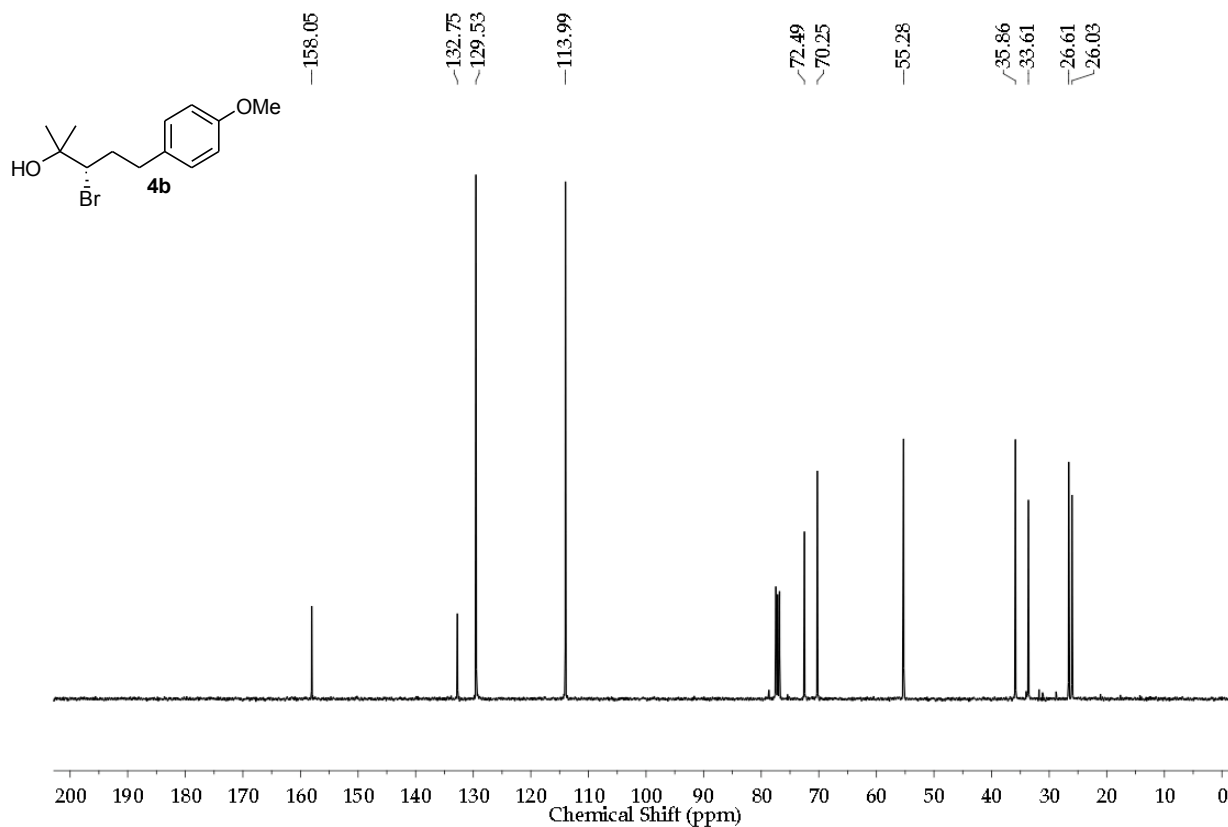


$\delta \text{ 75.5 (CBr) ppm; } \Delta\delta (\text{C}^{79}\text{Br, C}^{81}\text{Br}) = 2.3 \text{ ppb}$

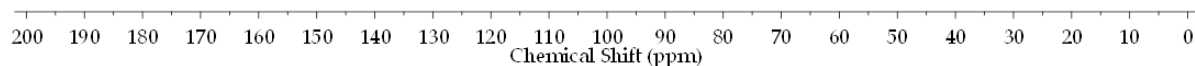
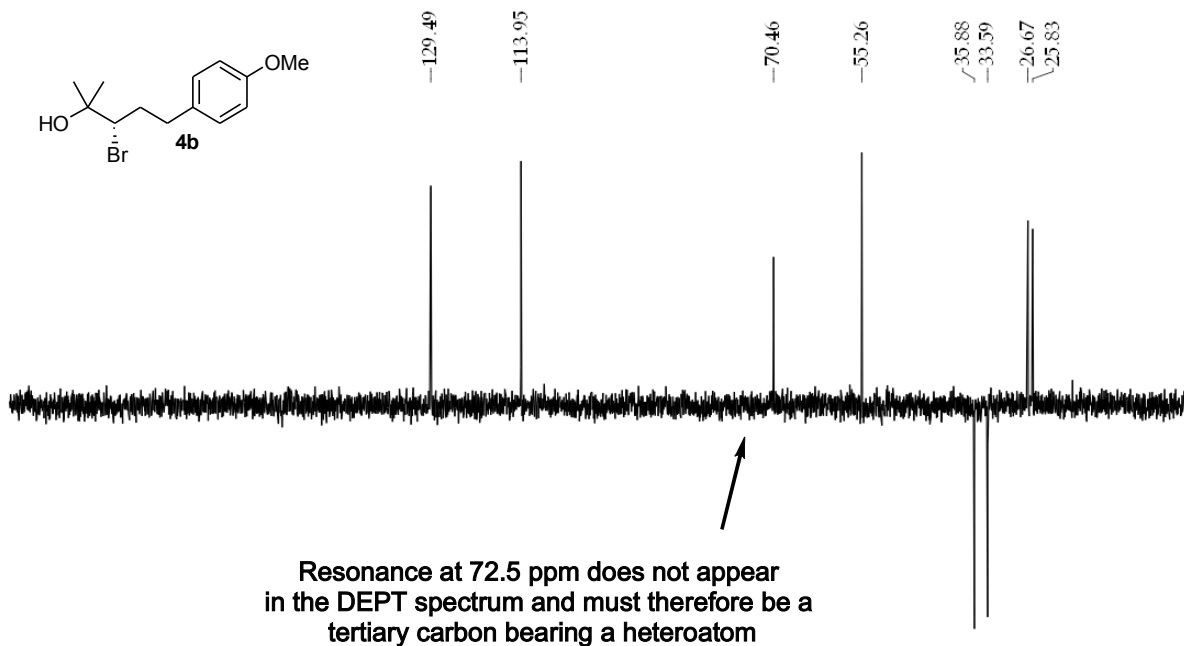
^1H NMR Spectrum of (*S*)-3-Bromo-5-(4-methoxyphenyl)-2-methylpentan-2-ol (**4b**)
(400 MHz, CDCl_3)



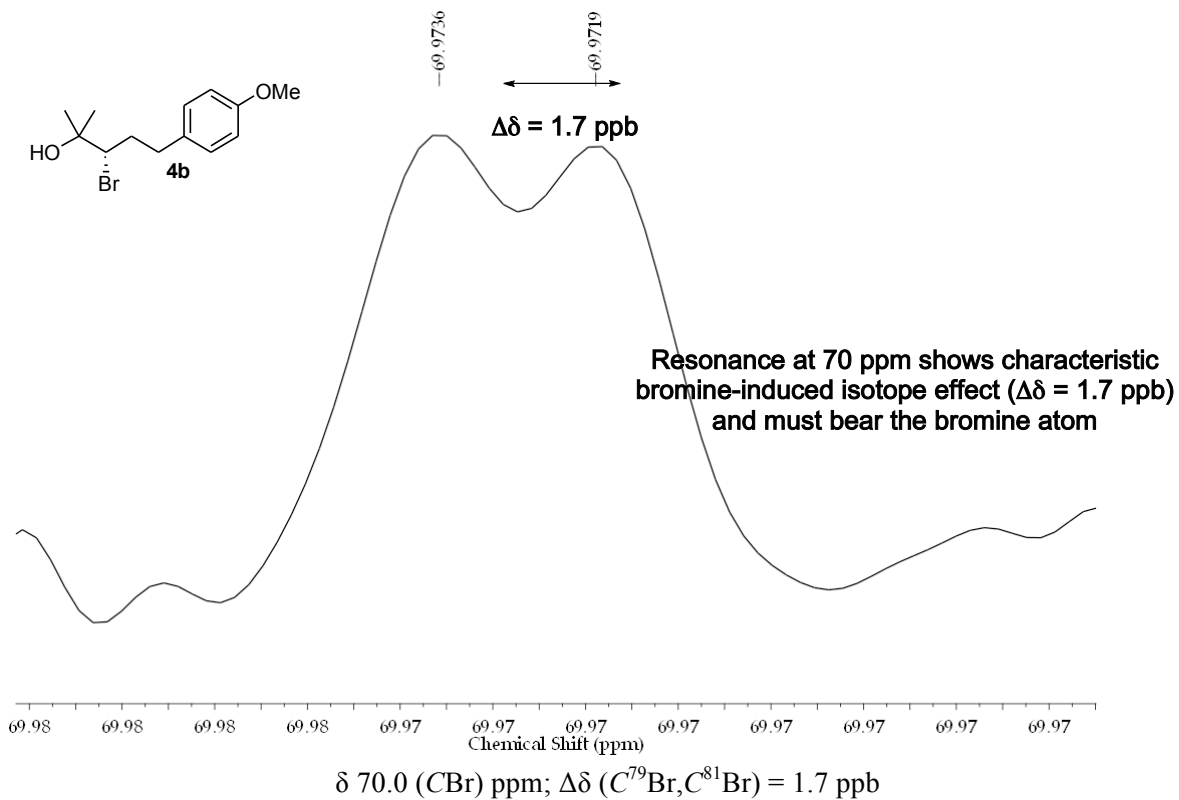
^{13}C NMR Spectrum of (*S*)-3-Bromo-5-(4-methoxyphenyl)-2-methylpentan-2-ol (**4b**)
(100 MHz, CDCl_3)



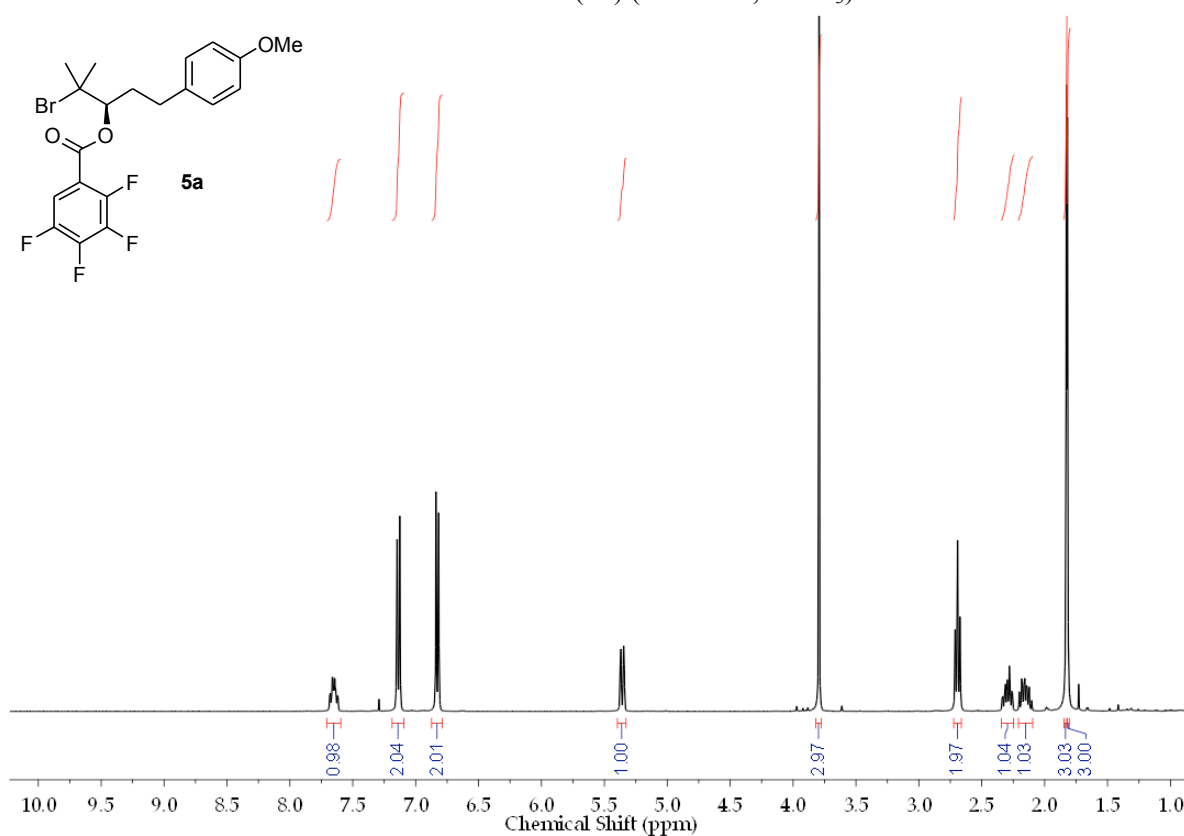
DEPT-135 NMR Spectrum of (*S*)-3-Bromo-5-(4-methoxyphenyl)-2-methylpentan-2-ol (**4b**)
(100 MHz, CDCl₃)



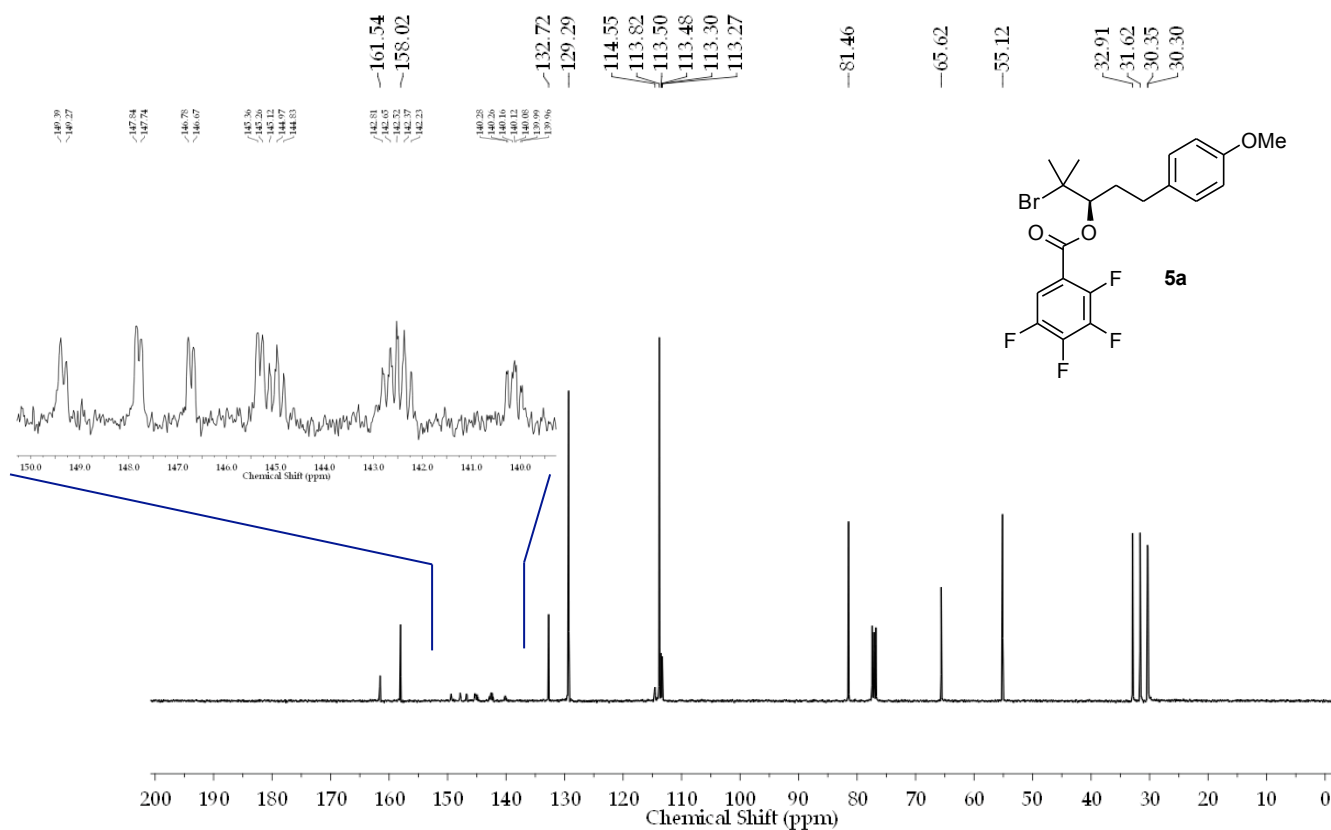
Bromine induced isotopic shift in ¹³C NMR Spectrum of (*S*)-3-Bromo-5-(4-methoxyphenyl)-2-methylpentan-2-ol (**4b**) (125 MHz, CDCl₃)



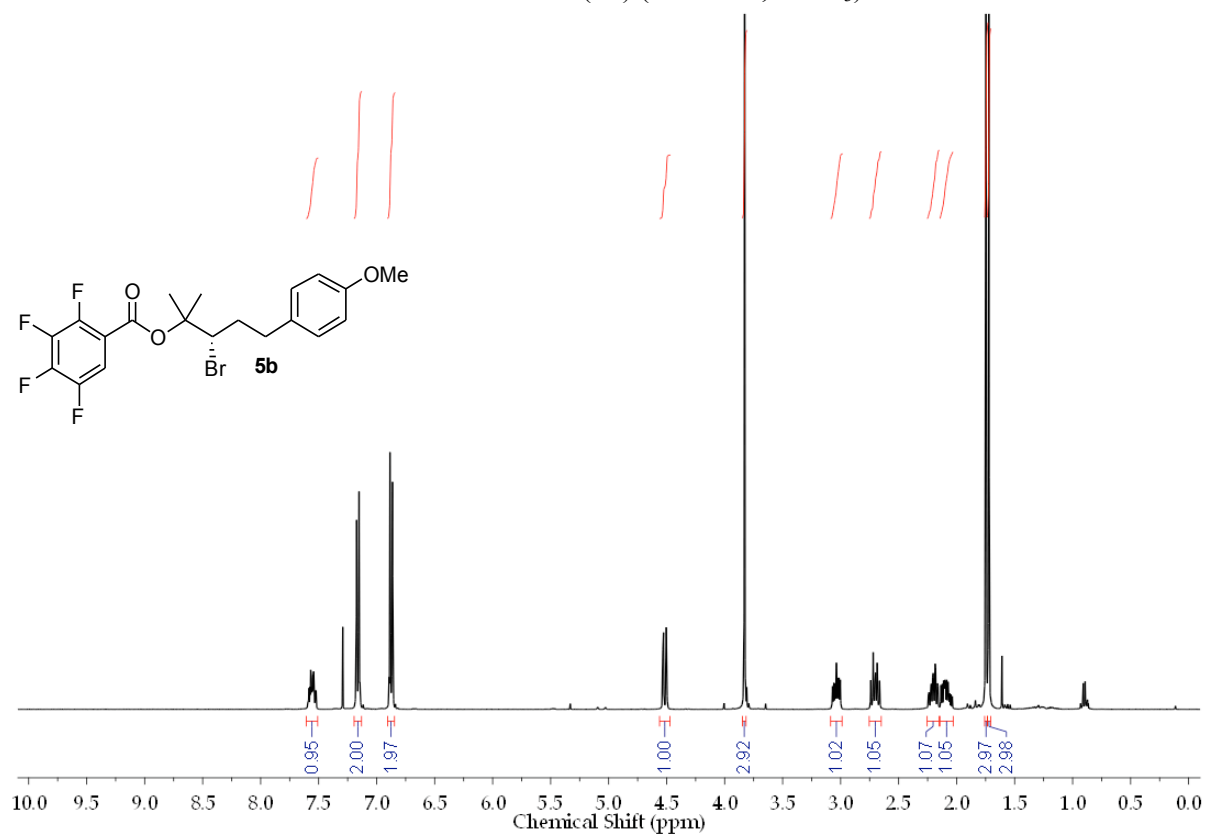
^1H NMR Spectrum of (*R*)-2-Bromo-5-(4-methoxyphenyl)-2-methylpentan-3-yl 2,3,4,5-tetrafluorobenzoate (**5a**) (400 MHz, CDCl_3)



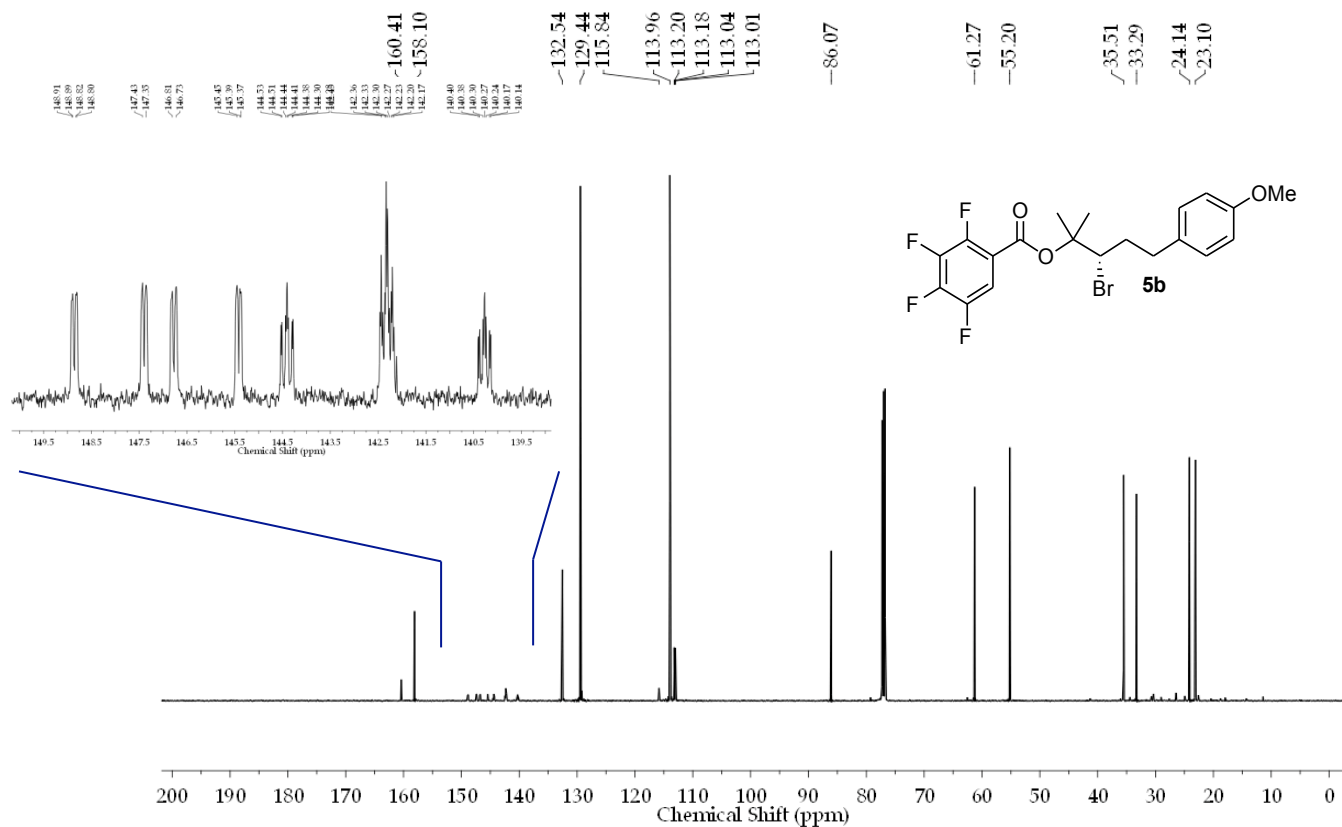
^{13}C NMR Spectrum of (*R*)-2-Bromo-5-(4-methoxyphenyl)-2-methylpentan-3-yl 2,3,4,5-tetrafluorobenzoate (**5a**) (100 MHz, CDCl_3)



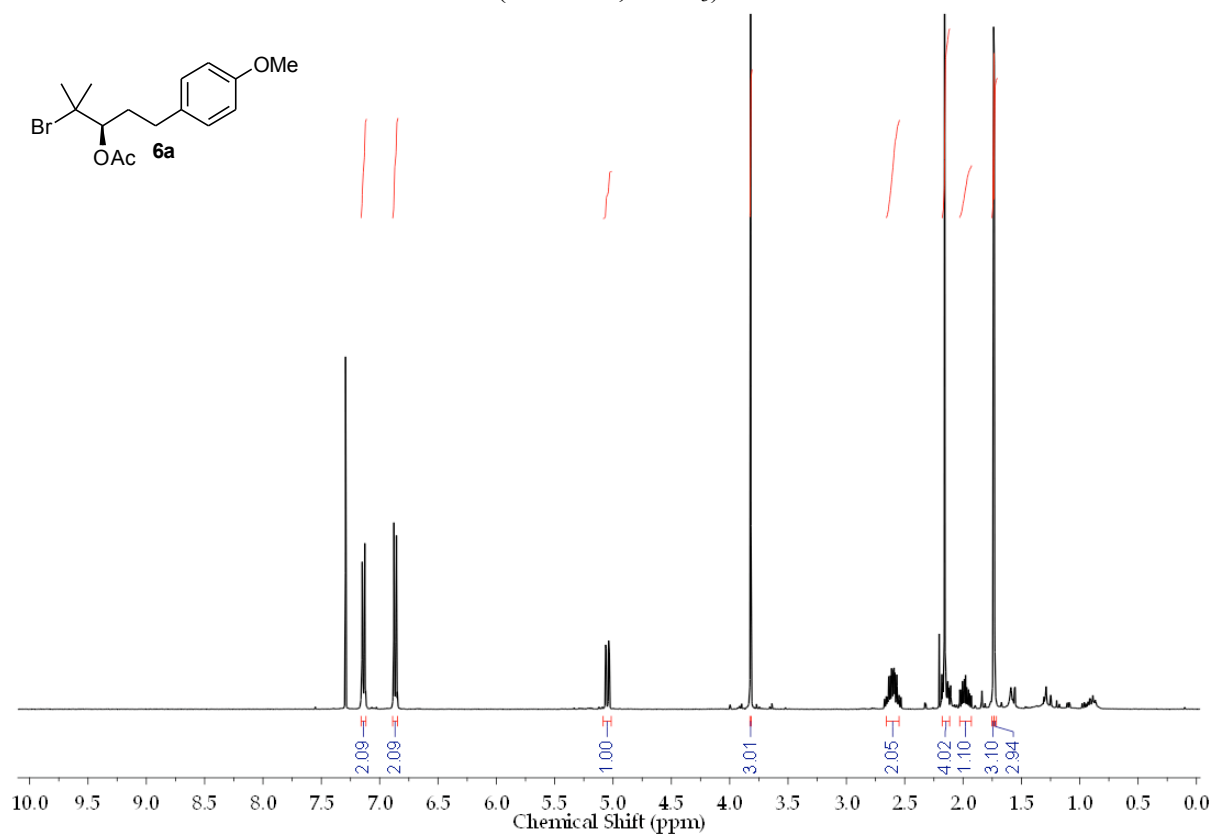
^1H NMR Spectrum of (*S*)-3-Bromo-5-(4-methoxyphenyl)-2-methylpentan-2-yl 2,3,4,5-tetrafluorobenzoate (**5b**) (400 MHz, CDCl_3)



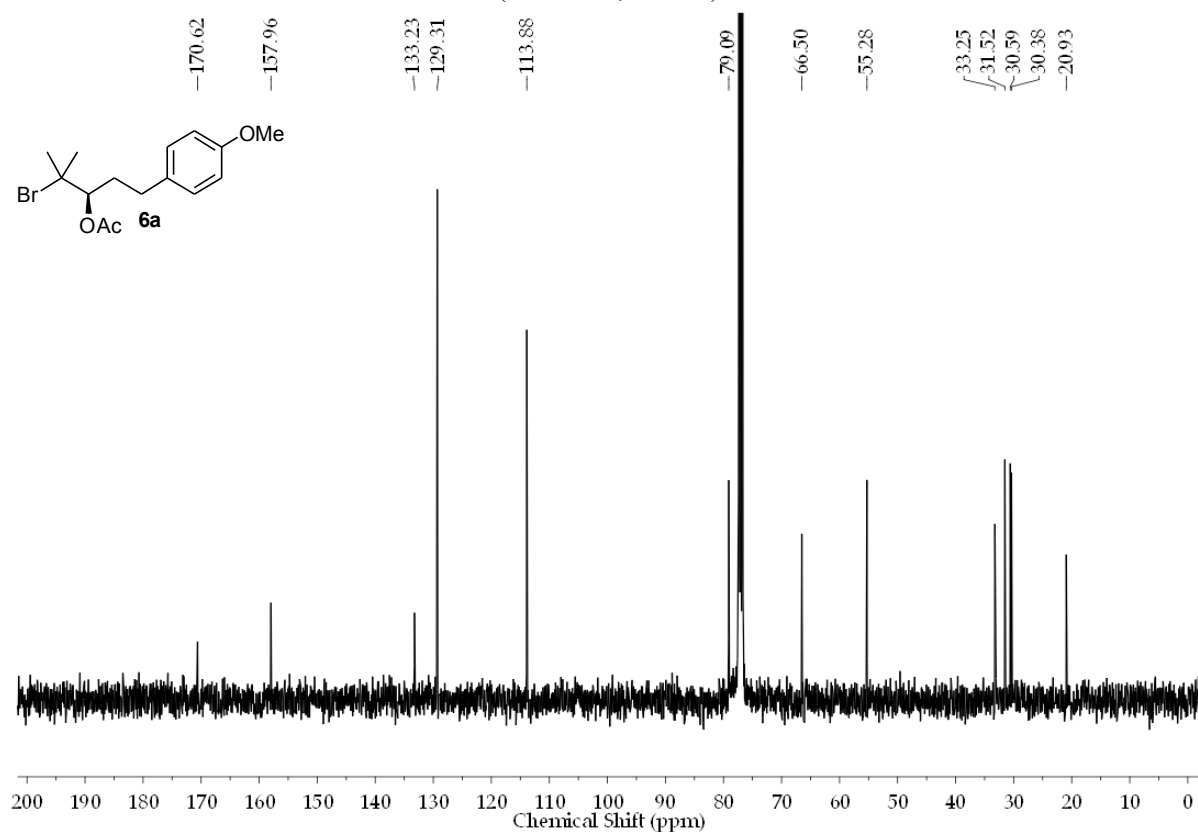
^{13}C NMR Spectrum of (*S*)-3-Bromo-5-(4-methoxyphenyl)-2-methylpentan-2-yl 2,3,4,5-tetrafluorobenzoate (**5b**) (100 MHz, CDCl_3)



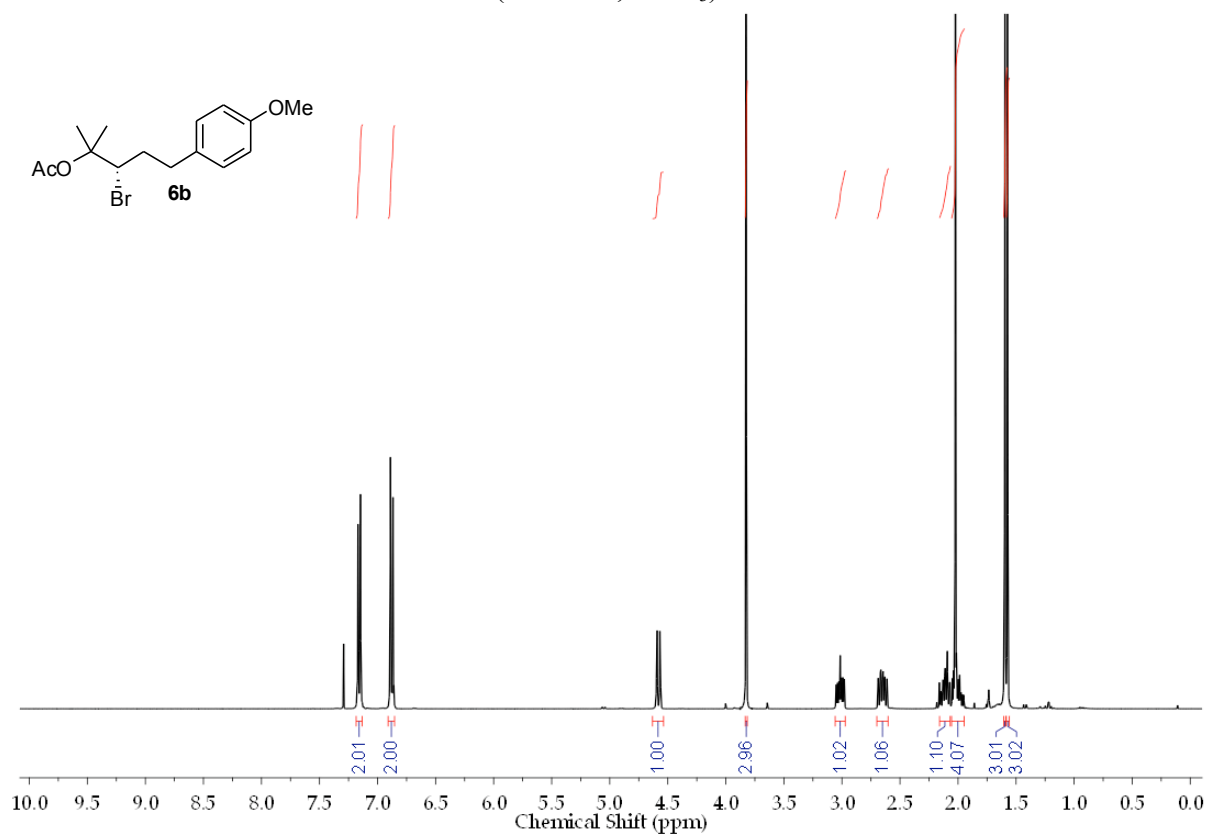
¹H NMR Spectrum of (*R*)-4-Bromo-1-(4-methoxyphenyl)-4-methylpentan-3-yl acetate (**6a**)
(400 MHz, CDCl₃)



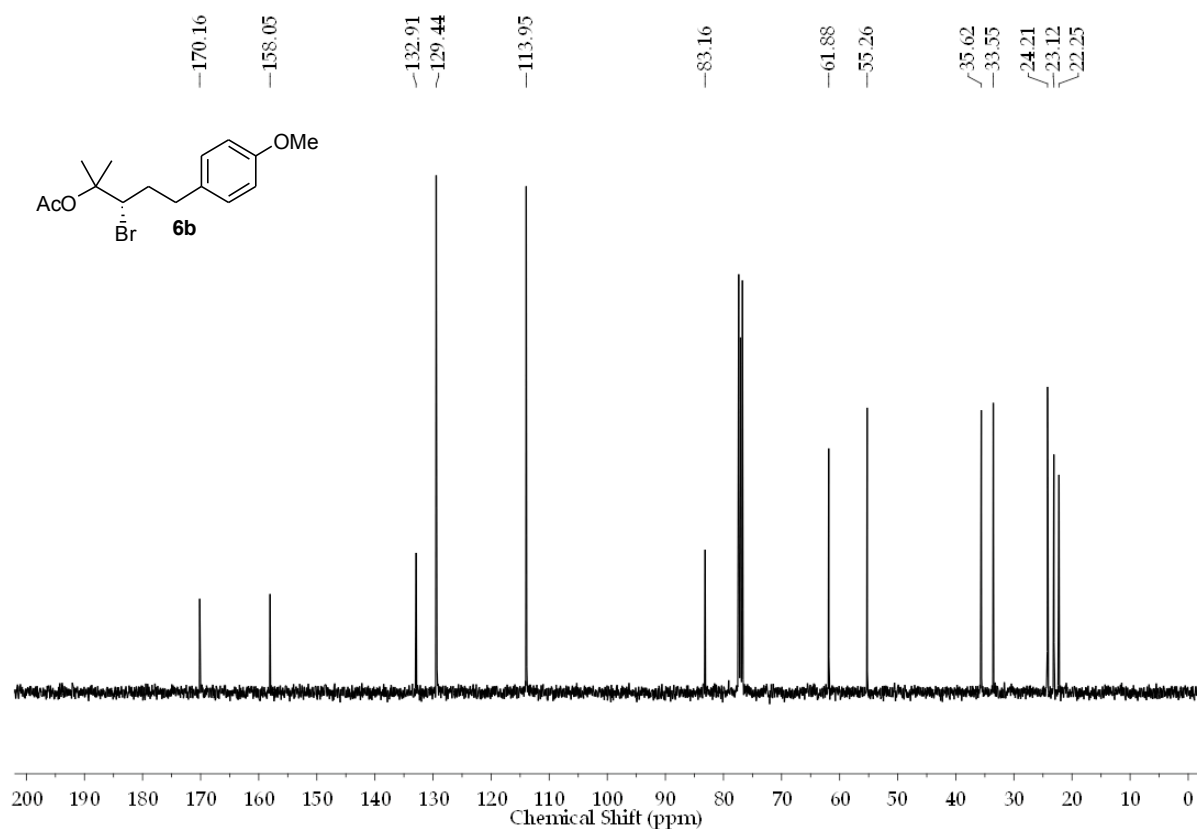
¹³C NMR Spectrum of (*R*)-4-Bromo-1-(4-methoxyphenyl)-4-methylpentan-3-yl acetate (**6a**)
(100 MHz, CDCl₃)



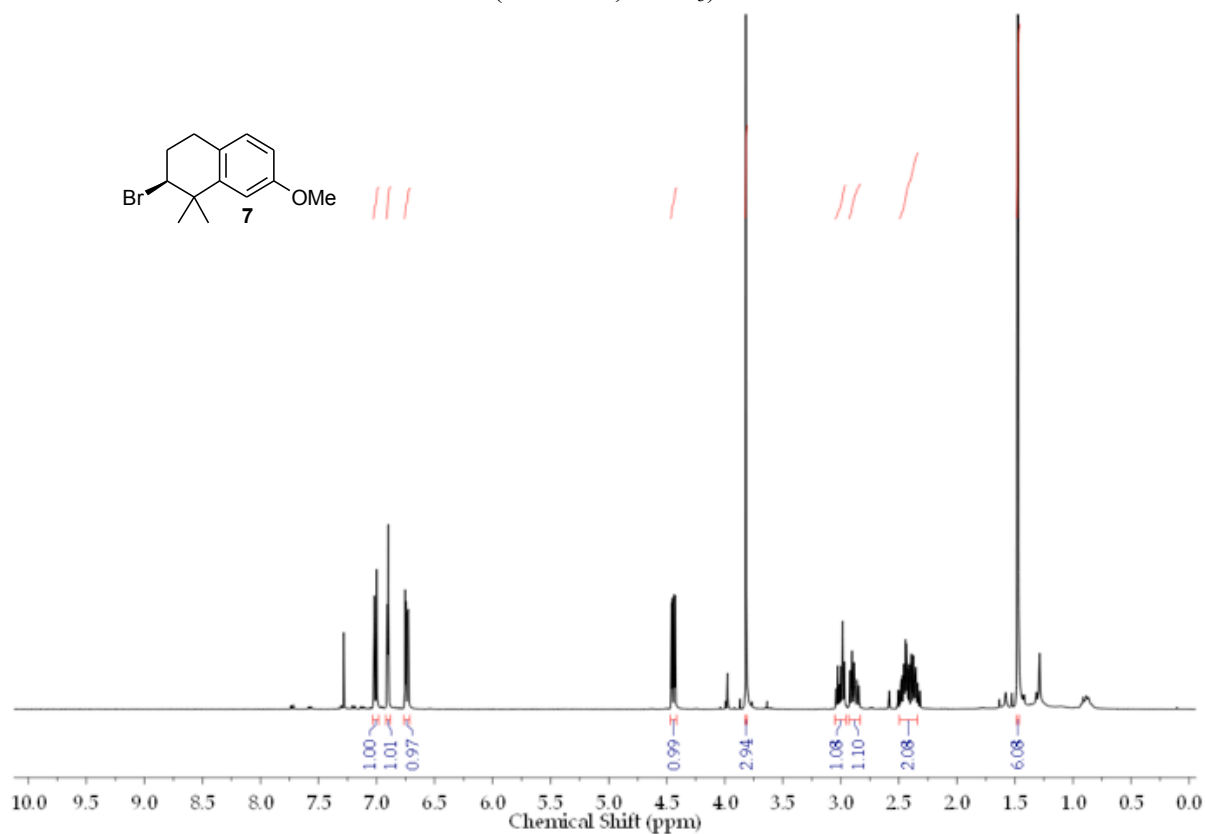
^1H NMR Spectrum of (*S*)-3-Bromo-5-(4-methoxyphenyl)-2-methylpentan-2-yl acetate (**6b**)
(400 MHz, CDCl_3)



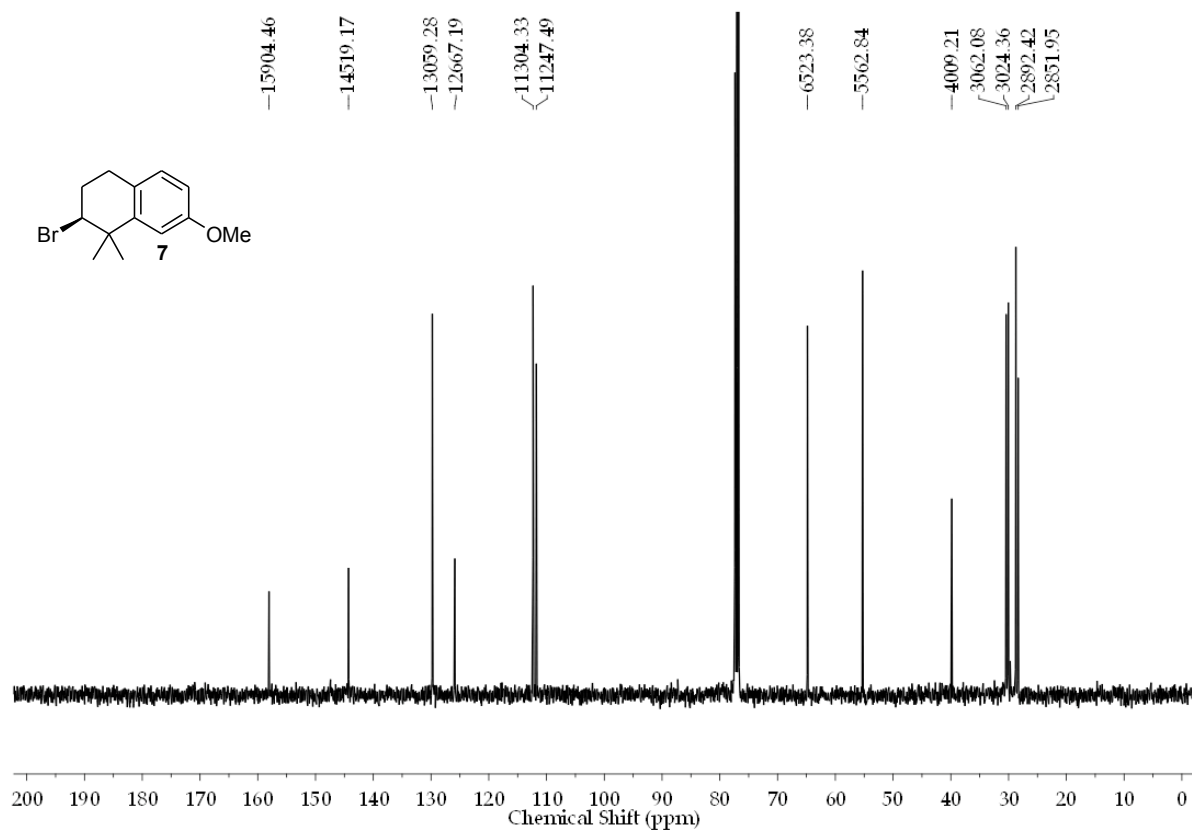
^{13}C NMR Spectrum of (*S*)-3-Bromo-5-(4-methoxyphenyl)-2-methylpentan-2-yl acetate (**6b**)
(100 MHz, CDCl_3)



¹H NMR Spectrum of (*S*)-2-Bromo-7-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalene (**7**)
(400 MHz, CDCl₃)

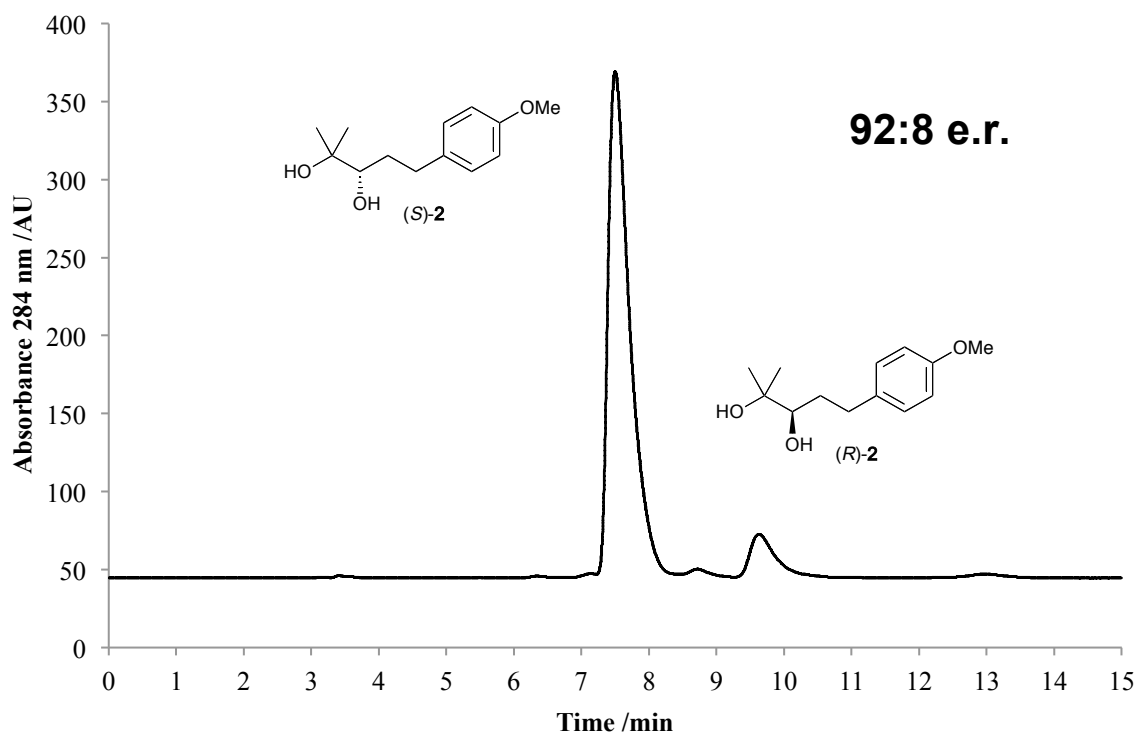
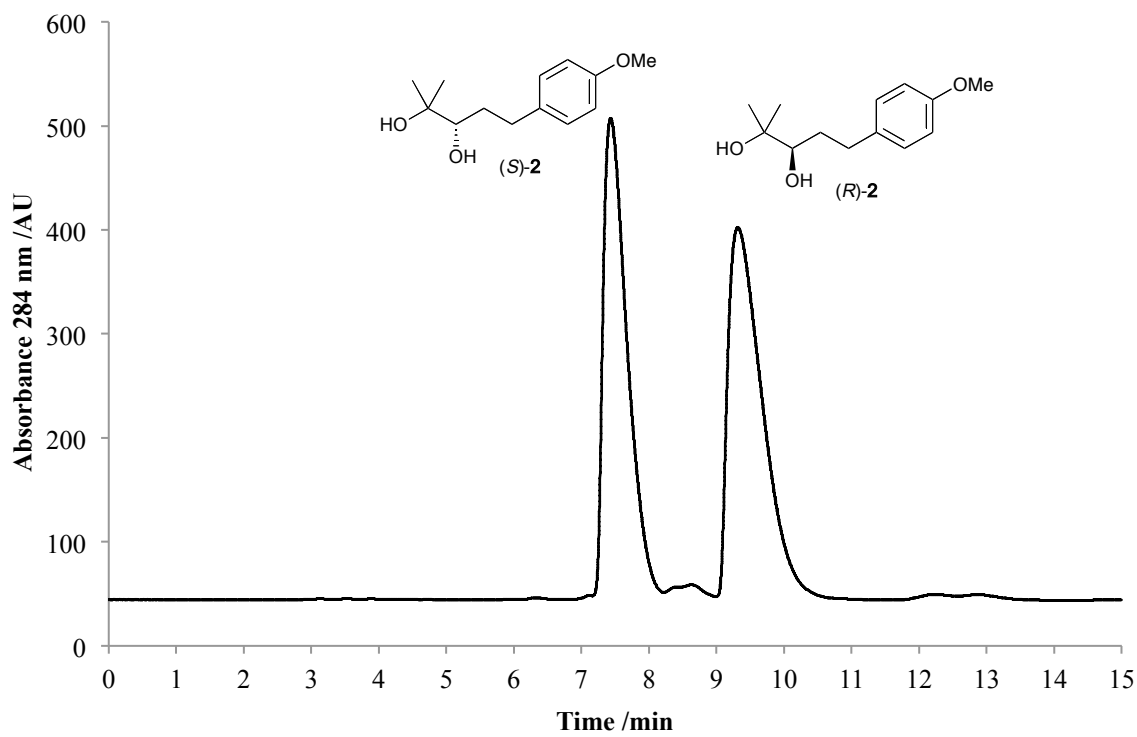


¹³C NMR Spectrum of (*S*)-2-Bromo-7-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalene (**7**)
(100 MHz, CDCl₃)

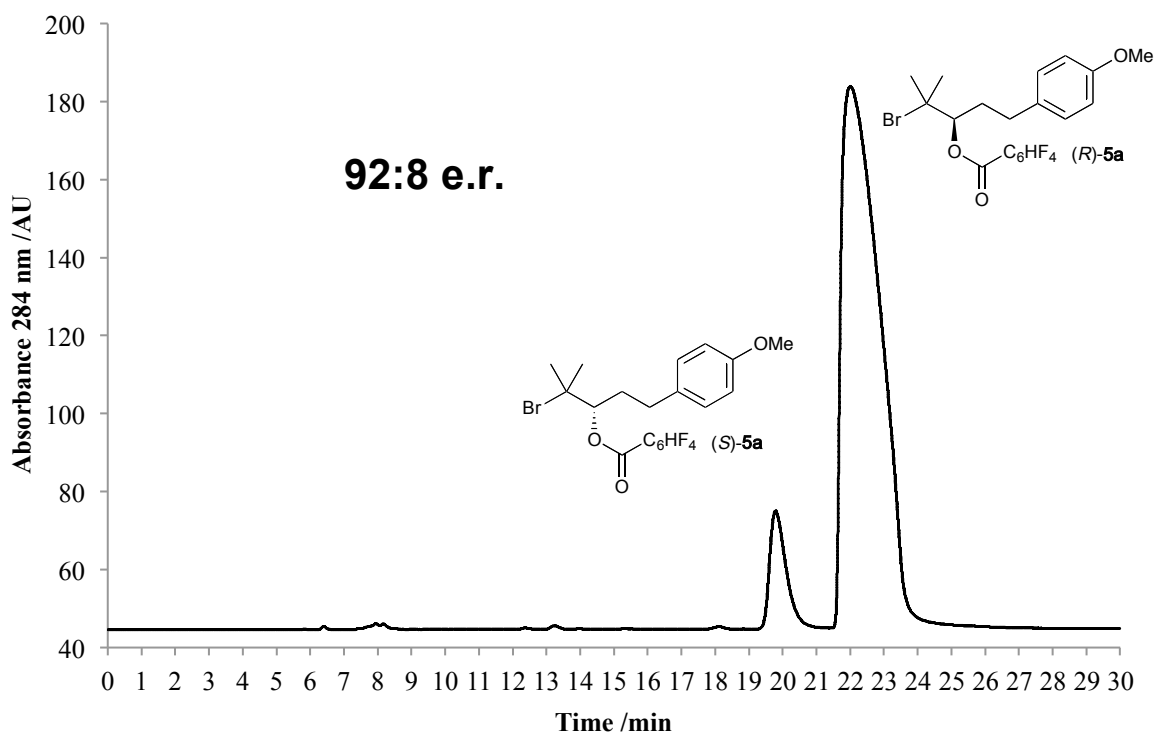
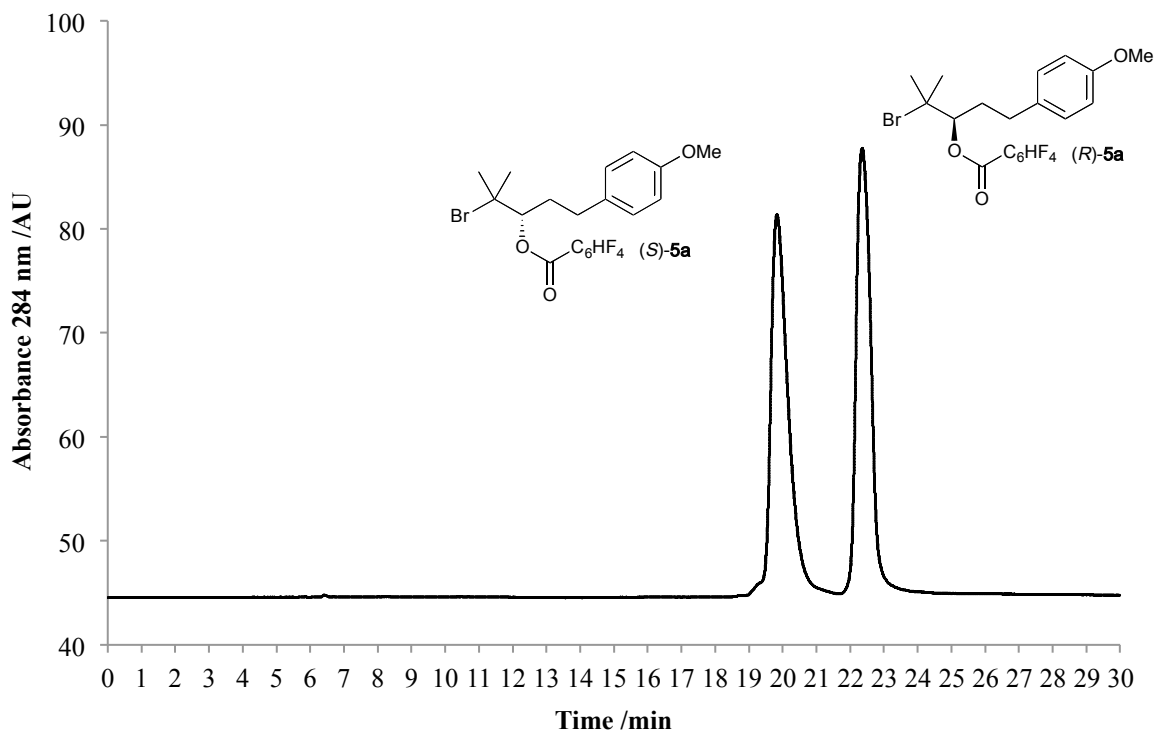


Determination of enantiomer ratios (e.r.) by HPLC

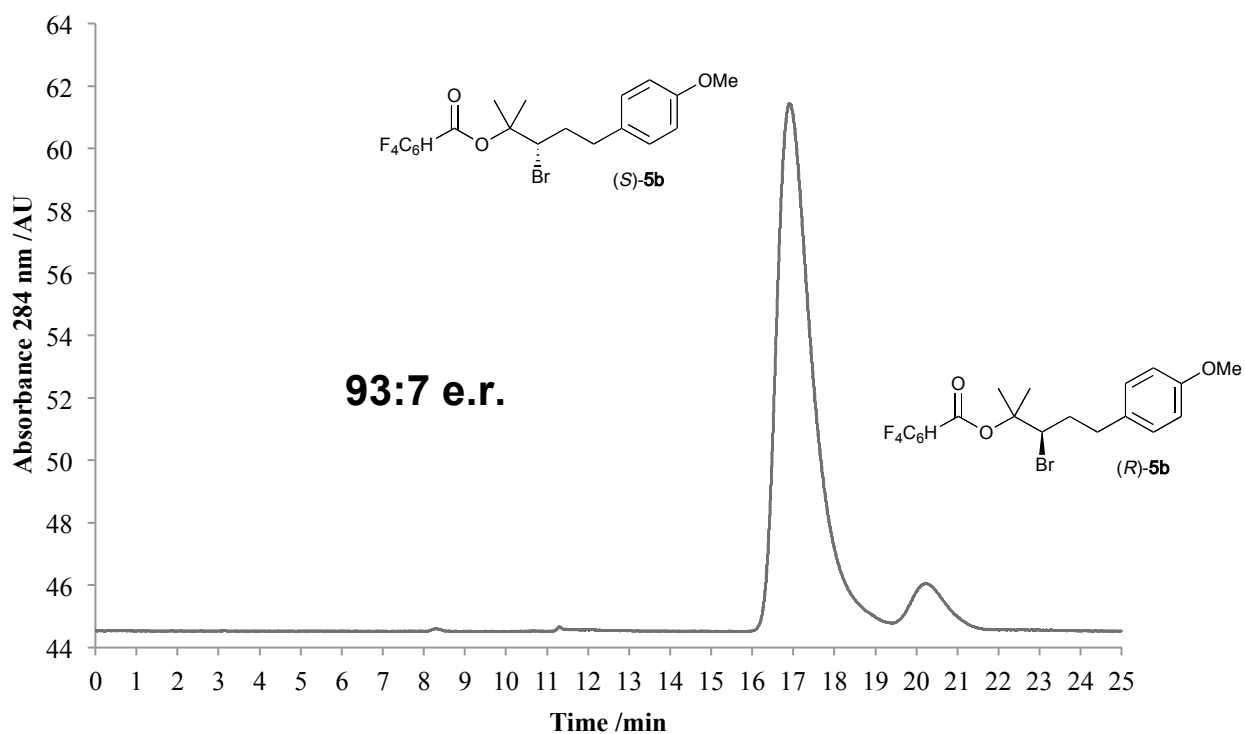
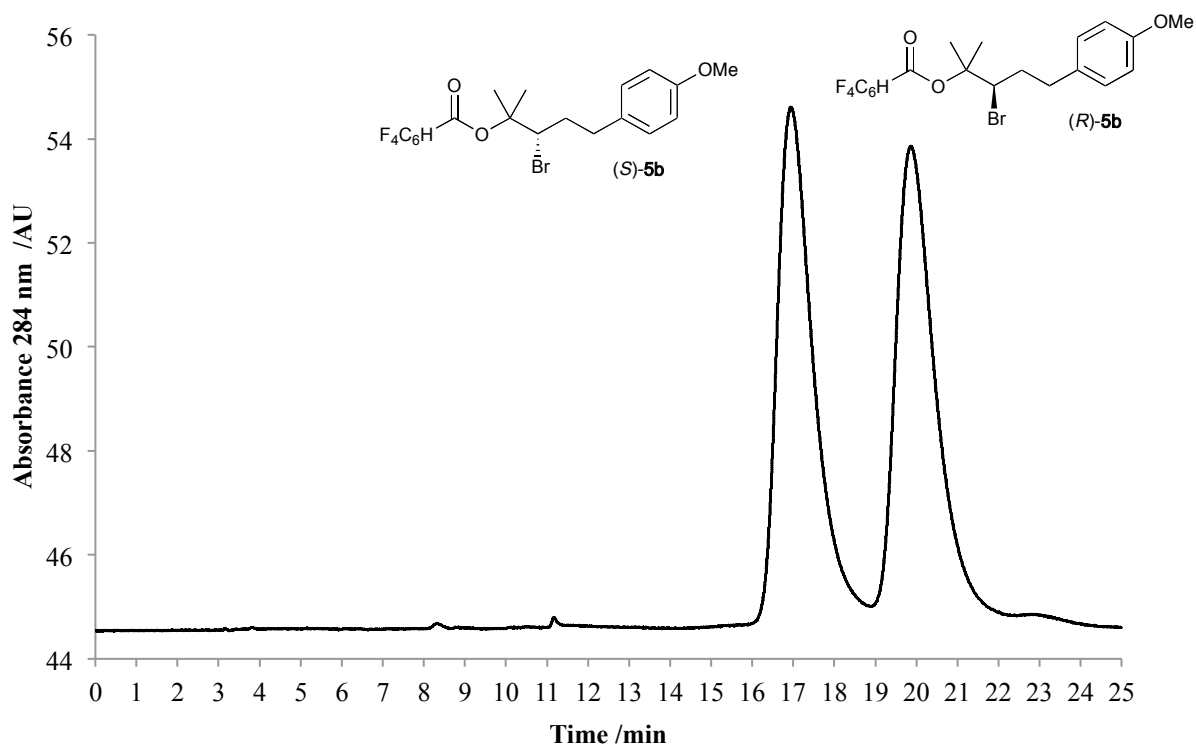
HPLC determination of enantiomeric purity of (*S*)-5-(4-methoxyphenyl)-2-methylpentane-2,3-diol (**2**) by reference to a racemic sample



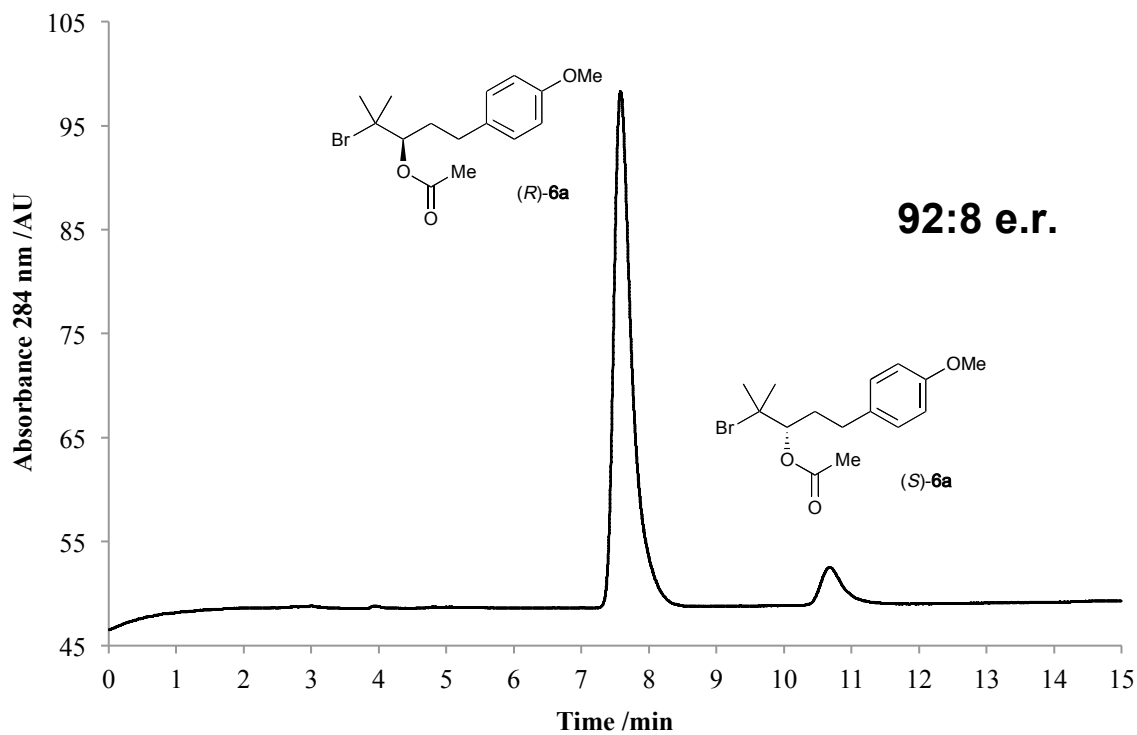
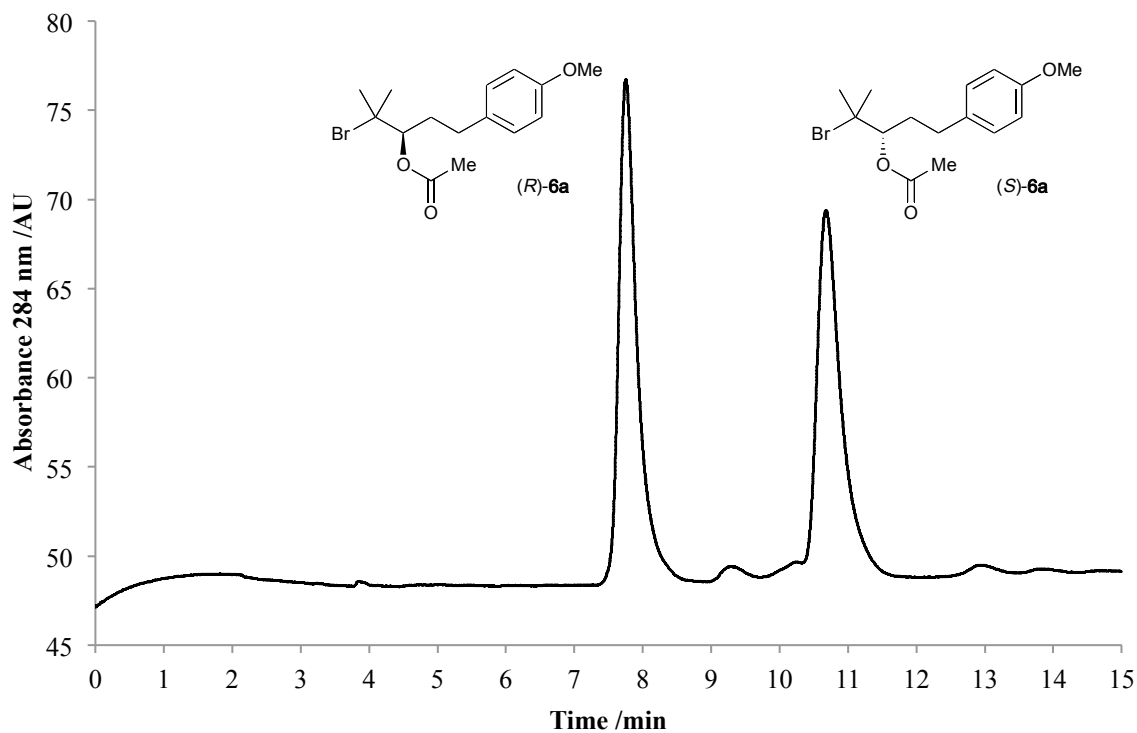
HPLC determination of enantiomeric purity of (*R*)-2-bromo-5-(4-methoxyphenyl)-2-methylpentan-3-yl 2,3,4,5-tetrafluorobenzoate (**5a**) by reference to a racemic sample



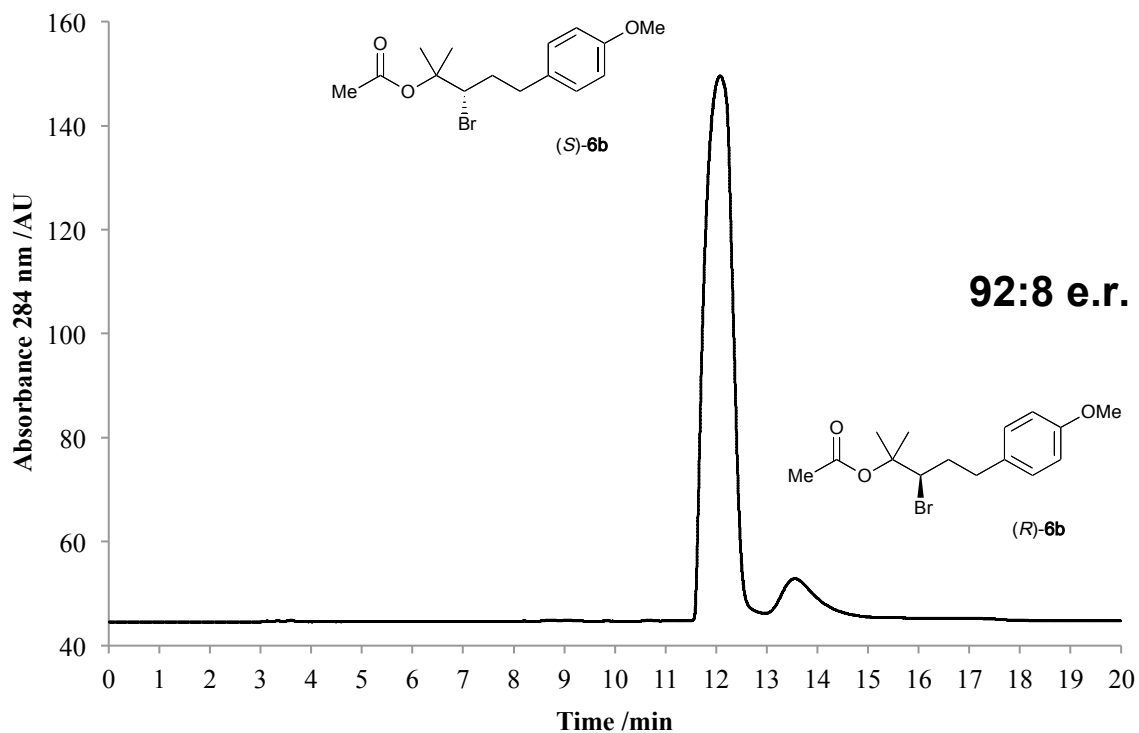
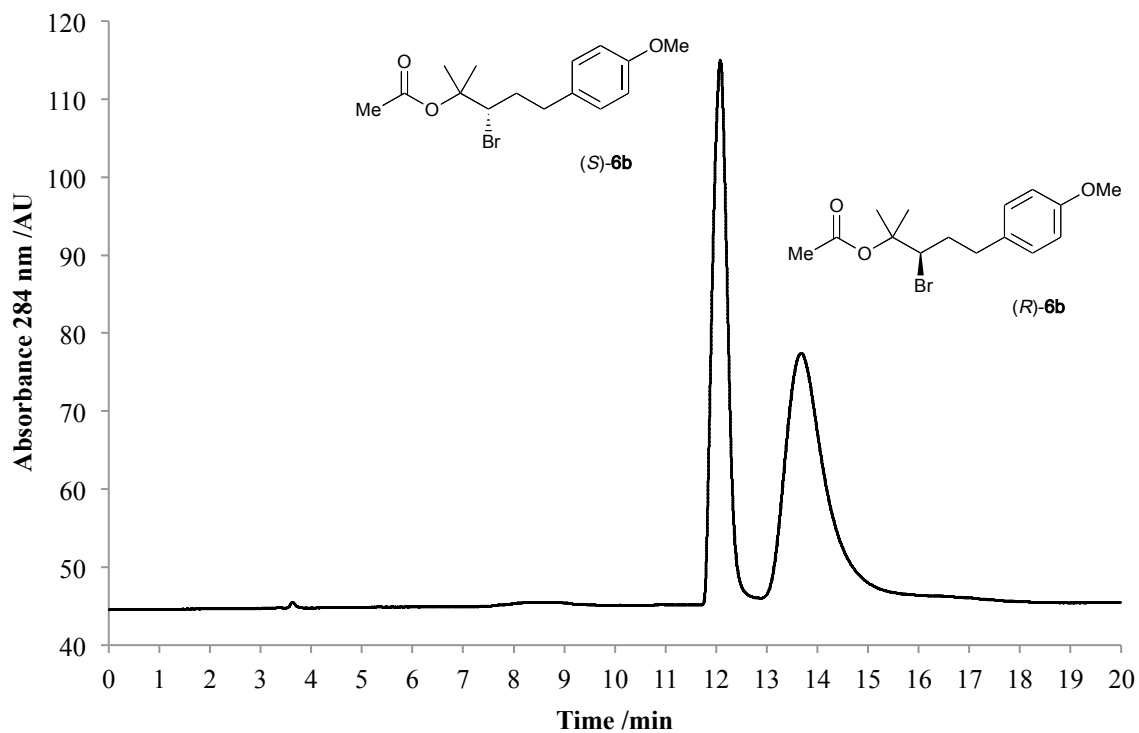
HPLC determination of enantiomeric purity of (*S*)-3-bromo-5-(4-methoxyphenyl)-2-methylpentan-2-yl 2,3,4,5-tetrafluorobenzoate (**5b**) by reference to a racemic sample



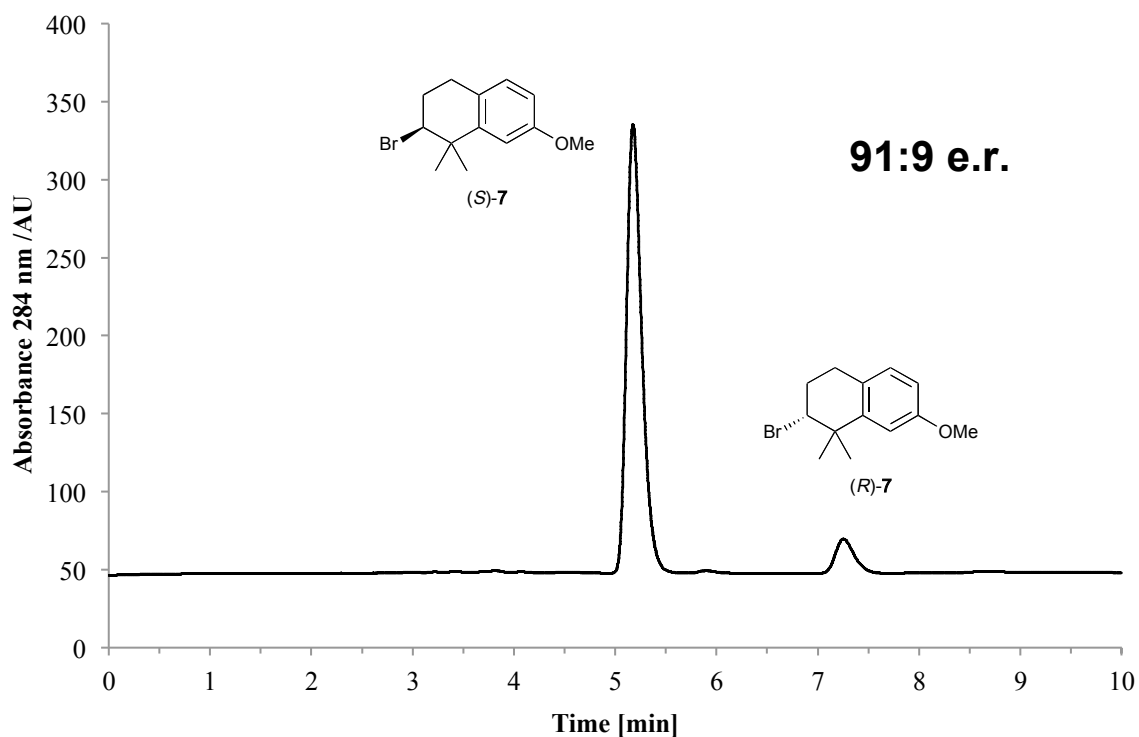
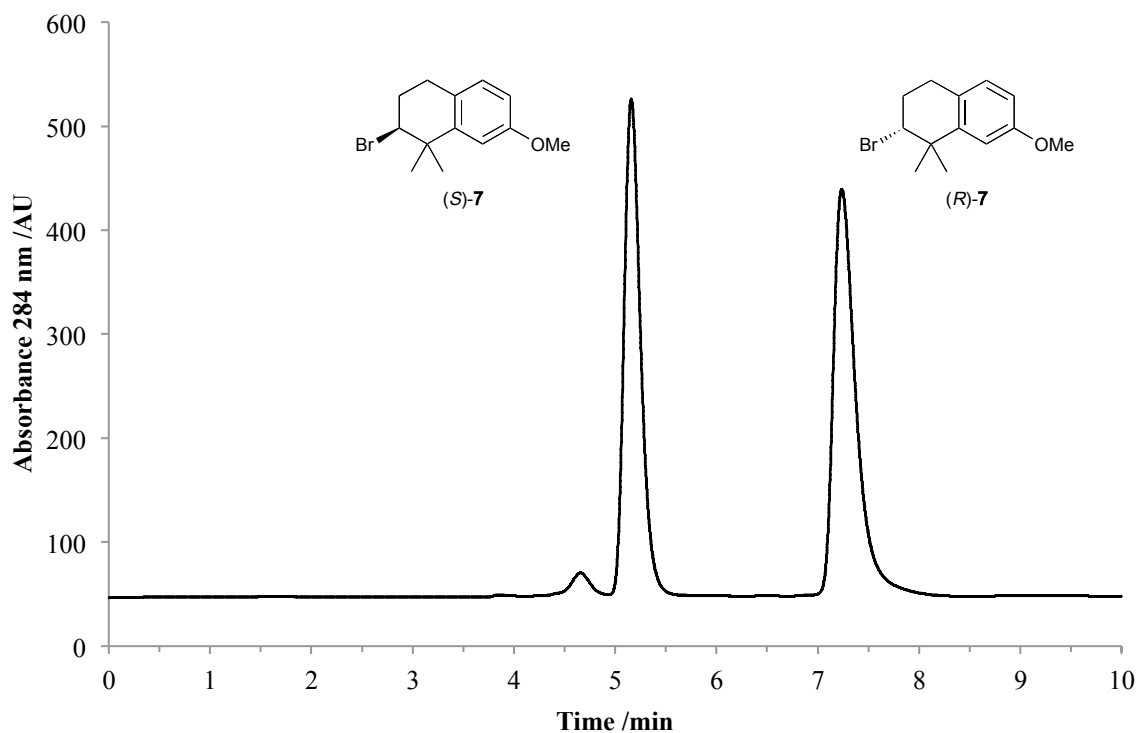
HPLC determination of enantiomeric purity of (*R*)-4-bromo-1-(4-methoxyphenyl)-4-methylpentan-3-yl acetate (**6a**) by reference to a racemic sample



HPLC determination of enantiomeric purity of (*S*)-3-bromo-5-(4-methoxyphenyl)-2-methylpentan-2-yl acetate (**6b**) by reference to a racemic sample

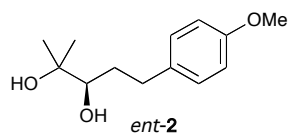


HPLC determination of enantiomeric purity of (*S*)-2-bromo-7-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalene (**7**) by reference to a racemic sample



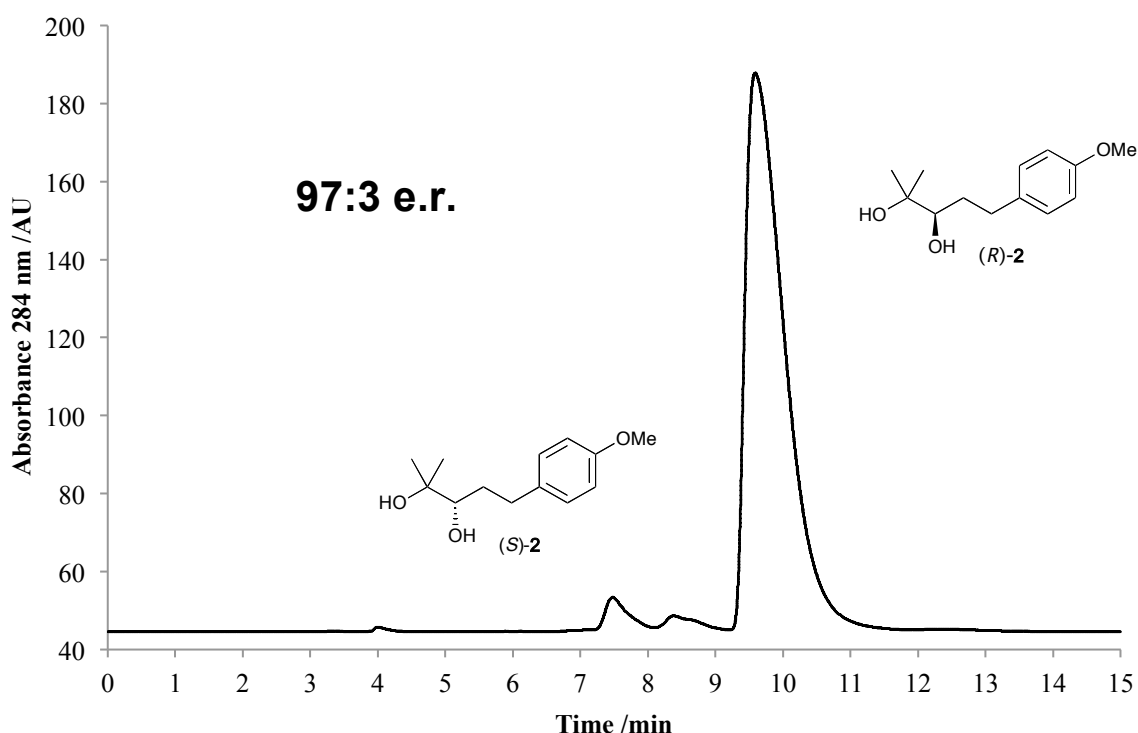
Details for preparation of *ent-7*

(*R*)-5-(4-Methoxyphenyl)-2-methylpentane-2,3-diol (*ent-2*)



According to the method of Sharpless,⁴ to a stirred solution of alkene **1** (1.5 g, 7.9 mmol) and methanesulfonamide (750 mg, 7.9 mmol) in water (15 mL) and *tert*-butanol (15 mL) was added AD-mix β (11.0 g, 1.4 gmmol⁻¹) at room temperature. The reaction mixture was stirred vigorously for 16 h, quenched with saturated aqueous Na₂SO₄ solution (40 mL), extracted with EtOAc (2 × 75 mL), washed with brine (75 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (50:50-60:40 EtOAc:PE) to afford the title product **2** (1.76 g, 99%, 94% e.e.) as a white solid. m.p. 42-44°C; [α]_D²⁴ +31.8 (*c* 1.1, CH₂Cl₂). All other data identical to that of diol **2** (see ESI p3-4).

HPLC determination of enantiomeric purity of (*R*)-5-(4-methoxyphenyl)-2-methylpentane-2,3-diol (*ent-2*) by reference to a racemic sample (see ESI p22).



(R)-2-Bromo-7-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalene (*ent*-7)

Following the method used for the preparation of epoxide **3** (see ESI p4), *ent*-**2** (1.76 g, 7.9 mmol) was converted into (*S*)-epoxide *ent*-**3** (53%, 858 mg) as a colourless oil: $[\alpha]_{\text{D}}^{24} -14.8$ (*c* 1.7 CH₂Cl₂). Following the method of Couladouros and Vidali,⁸ to a solution of (*S*)-epoxide **3** (858 mg, 4.17 mmol) in *N*-methyl-2-pyrrolidone (1.2 mL) was added LiBr (471 mg, 5.41 mmol) and PPTS (1.05 g, 4.17 mmol) and stirred at room temperature for 4 h. Additional LiBr (72 mg, 0.83 mmol) and PPTS (209 mg, 0.83 mmol) was added and stirred for a further 2 h. The reaction was quenched with saturated aqueous NaHCO₃ solution (50 mL), extracted with EtOAc (2 × 50 mL), washed with brine (50 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (10:90-20:80 EtOAc:PE) to yield a 4:5 mixture of bromohydrins *ent*-**4a** and *ent*-**4b** (860 mg, 72%) as a colourless oil containing *ca.* 9% 5-(4-methoxyphenyl)-2-methylpent-1-en-3-ol.⁹ The spectral data for *ent*-**4a** and *ent*-**4b** were identical to those of **4a** and **4b** (see ESI p5-6).

This mixture was then esterified under the same conditions as used for **5a/5b** (ESI p 6-7) to produce a 4:5 mixture of tetrafluorobenzoates *ent*-**5a** and *ent*-**5b** (644 mg, 95%) as a white oily solid containing *ca.* 8% 5-(4-methoxyphenyl)-2-methylpent-1-en-3-yl 2,3,4,5-tetrafluorobenzoate. The spectral data for *ent*-**5a** and *ent*-**5b** were identical to those of **5a** and **5b** (see ESI p6-7).

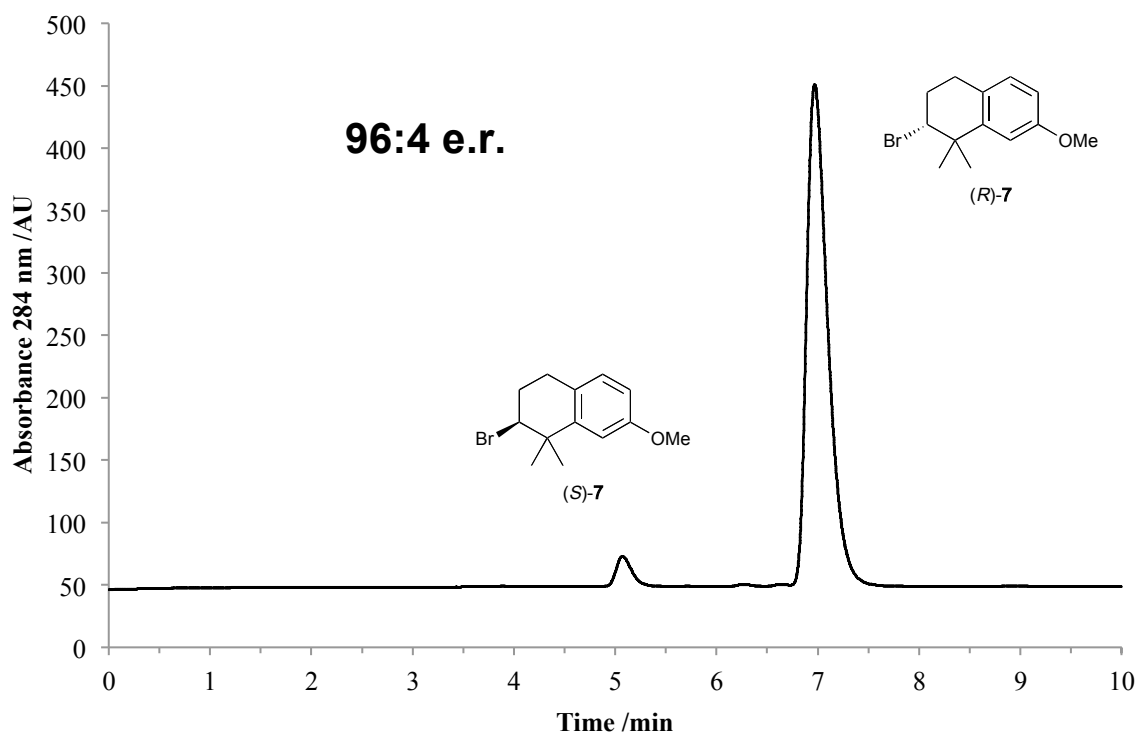
To a stirred solution of this mixture (200 mg, 0.44 mmol) in CH₂Cl₂ (6 mL) at -14 °C was added a solution of triflic acid (11 μL, 0.13 mmol, 30 mol%) in CH₂Cl₂ (2.8 mL). The reaction was allowed to warm to room temperature and stirred for 7 h. The reaction was quenched with a saturated aqueous solution of NaHCO₃ (2 × 25 mL), extracted with CH₂Cl₂ (20 mL), washed with brine (25 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (10:90-15:85 CH₂Cl₂:PE) to afford bicycle *ent*-**7** (63 mg, 53%, 84% e.e.) as a pale yellow oil.

In order to avoid deterioration of the e.r. in the cyclisation process to *ent*-**7**, purification of tetrafluorobenzoates *ent*-**5a** and *ent*-**5b** is required. To remove 5-(4-methoxyphenyl)-2-methylpent-1-en-3-yl 2,3,4,5-tetrafluorobenzoate a stirred solution of the mixture (200 mg, 0.44 mmol) in CH₂Cl₂ (4 mL) was added *m*CPBA (74 mg, 0.43 mmol) and stirred at room temperature for 16 h. The reaction was quenched with a saturated aqueous solution of Na₂SO₃ (25 mL), extracted with CH₂Cl₂ (20 mL), washed with an aqueous solution of

NaHCO₃ (25 mL), brine (25 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (10:90-25:75 Et₂O:PE) to afford tetrafluorobenzoates *ent*-**5a** and *ent*-**5b** (143 mg, 72%) as a 1:1 mixture as a white solid.

To a stirred solution of a 1:1 mixture of analytically pure tetrafluorobenzoates *ent*-**5a** and *ent*-**5b** (143 mg, 0.31 mmol) in CH₂Cl₂ (4.3 mL) at -14 °C was added a solution of triflic acid (8.2 μL, 0.09 mmol, 30 mol%) in CH₂Cl₂ (2 mL). The reaction was allowed to warm to room temperature and stirred for 2 h then heated at reflux for 2 h. The reaction was quenched with a saturated aqueous solution of NaHCO₃ (2 × 25 mL), extracted with CH₂Cl₂ (20 mL), washed with brine (25 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (10:90-15:85 CH₂Cl₂:PE) to afford bromide *ent*-**7** (70 mg, 84%, 92% e.e.) as a colourless oil. [α]_D²⁴ +6.1 (*c* 1.1, CH₂Cl₂). All other spectral data identical to bromide **7** (see ESI p9).

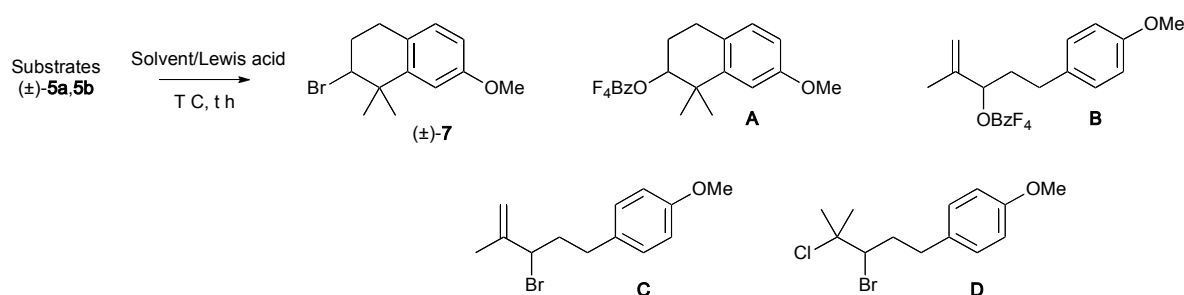
HPLC determination of enantiomeric purity of (*R*)-2-bromo-7-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalene (*ent*-**7**) by reference to a racemic sample (see ESI p27).



Preliminary investigations for cyclisation of (±)-**5a** and **5b** into **7**

We had recently observed the spontaneous formation of a bromonium ion on standing from an isolable 1-bromo-2-tetrafluorobenzoate.¹³ We reasoned that **5a** and/or **5b** may also spontaneously generate a bromonium ion by solvolysis. Accordingly, a range of solvents and conditions were explored using racemic **5a** and/or **5b** (ESI Table 1).

ESI Table 1. Attempted cyclisation of (±)-**5a** or (±)-**5b** into (±)-**7**



Entry	Substrate ^a	Solvent/ Lewis acid	T	t	SM ^b	7 ^c	A ^c	B ^c	C ^c	D ^c
1	5a	CDCl ₃	61°C	3h	100 ^d	0	0	0	0	0
2	5a	CD ₃ NO ₂	100°C	3h	100 ^d	0	0	0	0	0
3	5a	HFIP	60°C	16h	0	0	39 ^e	26 ^e	0	0
4	5b	HFIP	60°C	16h	<i>complicated mixture of components</i>					
5	5a	NFTB	45°C	16h	100 ^d	0	0	0	0	0
6	5b	NFTB	45°C	16h	<i>complicated mixture of components</i>					
7	5a	HCO ₂ H	101°C	6h	<i>complicated mixture of components</i>					
8	5b	HCO ₂ H	101°C	6h	<i>complicated mixture of components</i>					
9	5a	BF ₃ .OEt ₂ ^f	-40°C	0.5h	100 ^d	0	0	0	0	0
10	5b	BF ₃ .OEt ₂ ^f	-40°C	0.5h	80 ^g	0	0	0	20 ^g	0
11	5a	TiCl ₄ ^f	-78°C	1h	100 ^d	0	0	0	0	0
12	5b	TiCl ₄ ^f	-78°C	1h	5	55 ^g	0	0	0	12 ^g
13	5a	Me ₂ AlCl ^f	-78°C	16h	20	33 ^g	0	0	0	23 ^g
14	5b	Me ₂ AlCl ^f	-78°C to r.t.	4h	7	18 ^g	0	0	0	35 ^g
15	5a	TMSOTf ^f	-78°C	6h	95	0	0	0	0	0
16	5b	TMSOTf ^f	-78°C	6h	0	44	0	0	0	0
17	5b	TMSOTf ^{f,h}	-78°C to r.t.	96h	100	0	0	0	0	0

^a Racemic substrates; ^b Recovered starting material after column chromatography; ^c isolated yield after chromatography; ^d inspection of the ¹H NMR spectrum after work-up revealed no reaction and only recovered starting material; ^e inseparable mixture of components; ^f Performed in CH₂Cl₂ with 1.0 equivalent of Lewis acid; ^g relative ratio of products by inspection of the ¹H NMR spectrum after work-up; ^h 1 equivalent of 2,6-di-*tert*-butylpyridine was added.

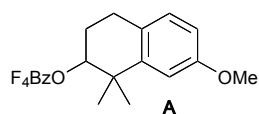
No product was observed in chloroform (Table 1, entry 1) or nitromethane (entry 2) after heating secondary benzoate **5a** at reflux for 3h. Denmark¹⁴ has shown that enantiopure bromonium ions can be generated from 1,2-bromotosylates in hexafluoroisopropanol (HFIP), a polar solvent of strong ionising power and low nucleophilicity. Jamison *et al*¹⁵ found that it also facilitated bromonium ion initiated epoxide-opening cascades. Accordingly, HFIP could reasonably be foreseen to promote bromonium ion formation and cyclization of bromo-tetrafluorobenzoate **5a**. However utilising HFIP as a solvent at 60°C (entry 3) gave non-bromine containing compounds **A** (39%) and **B** (26%). These must result from solvent assisted *bromide* extraction to produce a tertiary carbocation (which may be stabilised anchimerically by the benzoate). This may then cyclise to form **A** or eliminate to form **B**. Under the same conditions tetrafluorobenzoate **5b** (entry 4) produced a complex mixture of products. The use of nonafluoro *tert*-butanol (NFTB) or formic acid as the solvent was also unsuccessful in promoting clean cyclisation of **5a/5b** to product **7** (entries 5-8).

Attention then turned to the attempted cyclisation of **5a/5b** using stoichiometric quantities of oxophilic Lewis acids in dichloromethane at low temperature (entries 9-14). Boron trifluoride etherate was essentially ineffective under these conditions, although **5b** gave some eliminated product **C**. Titanium tetrachloride (**5b** only) and dimethyl aluminium chloride (**5a** and **5b**) were able to effect the desired cyclisation, but the chloride containing product **D** was formed as well which was inseparable from the product. Trimethylsilyl triflate (entries 15,16) showed promising activity but control experiments with added non-nucleophilic base (entry 17) showed that adventitious triflic acid must be the active constituent.

Characterising data for compounds **A-D**:

(±)-7-Methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl
tetrafluorobenzoate (**A**)

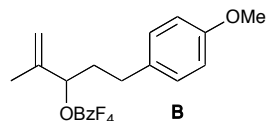
2,3,4,5-



As an inseparable mixture with **B** after column chromatography.
Colourless oil: $R_f = 0.45$ (10:90 EtOAc:PE); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.64-7.54 (m, 1H) 7.05 (d, $J = 8.5$ Hz, 1H), 6.90 (d, $J = 2.6$

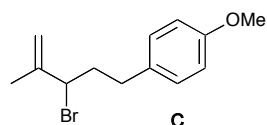
Hz, 1H), 6.75 (dd, $J = 8.4, 2.7$ Hz, 1H), 5.37 (dd, $J = 8.0, 3.3$ Hz 1H), 3.83 (s, 3H), 2.99-2.84 (m, 2H), 2.08-1.98 (m, 2H), 1.41 (s, 3H), 1.40 (s, 3H) ppm. GCMS (Cl^+ , NH_3) $t_R = 23.9$ min, m/z 400 $[\text{M} + \text{NH}_4]^+$.

(±)-5-(4-Methoxyphenyl)-2-methylpent-1-en-3-yl 2,3,4,5-tetrafluorobenzoate (B)



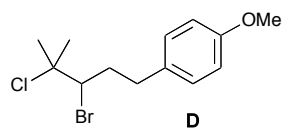
As an inseparable mixture with **A** after column chromatography. Colourless oil: $R_f = 0.45$ (10:90 EtOAc:PE); ^1H NMR (400 MHz, CDCl_3) δ 7.64-7.54 (m, 1H) 7.12 (d, $J = 8.6$ Hz, 2H), 6.84 (d, $J = 8.6$ Hz, 2H), 5.47 (dd, $J = 7.2, 6.0$ Hz, 1H), 5.08 (s, 1H), 5.03-5.01 (s, 1H), 3.80 (s, 3H), 2.71-2.65 (m, 2H), 2.22-2.00 (m, 2H), 1.83 (s, 3H) ppm. GCMS (Cl^+ , NH_3) $t_R = 23.3$ min, m/z 400 $[\text{M} + \text{NH}_4]^+$.

1-(3-Bromo-4-methylpent-4-enyl)-4-methoxybenzene (C)



Colourless oil: $R_f = 0.62$ (40:60 CH_2Cl_2 :PE); ^1H NMR (400 MHz, CDCl_3) δ 7.15 (d, $J = 8.6$ Hz, 2H) 6.88 (d, $J = 8.6$ Hz, 2H), 5.08 (s, 1H), 5.08 (s, 1H), 4.93 (s, 1H), 4.50 (dd, $J = 8.1, 6.7$ Hz, 1H), 3.82 (s, 3H), 2.80-2.58 (m, 2H), 2.40-2.22 (m, 1H) 2.20-2.10 (m, 2H), 2.22-2.00 (m, 2H), 1.89 (s, 3H) ppm. GCMS (Cl^+ , NH_3) $t_R = 20.5$ min, m/z 288, 286 $[\text{M} + \text{NH}_4]^+$.

(±)-1-(3-Bromo-4-chloro-4-methylpentyl)-4-methoxybenzene (D)

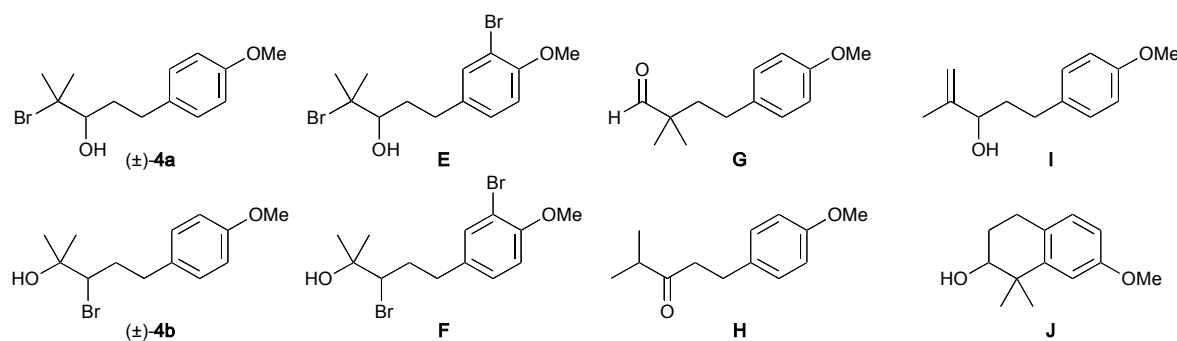


As an inseparable mixture with **7** after column chromatography. Colourless oil; $R_f = 0.64$ (40:60 CH_2Cl_2 :PE); ^1H NMR (400 MHz, CDCl_3) δ 7.22-7.17 (m, 2H), 6.90-6.86 (m, 2H), 4.03 (dd, $J = 11.3, 1.6$, 1H), 3.83 (s, 3H), 2.71 (m, 2H), 2.66-2.56 (m, 1H), 2.09 (m, 1H), 1.79 (s, 3H), 1.70 (s, 3H) ppm; GCMS (Cl^+ , NH_3) $t_R = 21.0$ min, m/z 326, 324, 322, $[\text{M} + \text{NH}_4]^+$.

Optimisation of anionic bromide ring-opening of epoxide **3**

Optimisation of anionic bromide epoxide opening was performed using (±)-**3**, obtained by mCPBA epoxidation of alkene **1** (see ESI p5). The aim was to discover a high yielding method to give access to both bromohydrin regioisomers.

ESI Table 2. Optimisation of anionic bromide ring-opening of epoxide **3**^a



Entry	Reagent	Solvent (T, t)	SM	4a + 4b ^b (4a : 4b)	E + F ^b (E : F)	G ^b	H ^b	I ^b	J ^b
1	PPh ₃ /Br ₂ ^c	CH ₂ Cl ₂ (r.t., 16h)	0	42 (69:31)	42 (79:21)	0	0	0	0
2	PPh ₃ /Br ₂ ^d	CH ₂ Cl ₂ (r.t., 16h)	0	50 (60:40)	10 (100:0)	0	0	0	0
3	(<i>n</i> -hexyl) ₄ NBr	HFIP (reflux, 12h)	12	0	0	8 ^e	28 ^e	14	20
4	Bu ₄ NBr/Mg(NO ₃) ₂	CH ₂ Cl ₂ (reflux, 6h)	35	39 (38:62)	0	0	7	10	0
5	Me ₂ SBr ⁺ Br ⁻	MeCN (r.t., 0.5h)	0	46 (63:37)	0	0	0	0	0
6	LiBr, PPTS	NMP (r.t., 3h)	6	44 (41:59)	0	0	6	8	0

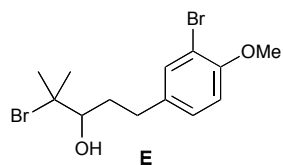
^a All reactions performed with racemic epoxide **3**; ^b isolated yield after chromatography (value in parenthesis is ratio as determined by inspection of the ¹H NMR spectrum); ^c ratio of **3**: PPh₃: Br₂ = 1:1.1:1.1; ^d ratio of **3**: PPh₃: Br₂ = 1:1.3:1.1; ^e Inseparable mixture of components – compounds identified by inspection of ¹H NMR spectrum.

The use of a 1:1 mixture of triphenylphosphine and molecular bromine as described by Palumbo et al¹⁶ gave the desired bromohydrins (±)-**4a** and **4b** along with equimolar quantities of aromatic bromination adducts **E** and **F** (Table 2, entry 1). The aromatic bromide adducts could be reduced to ca. 10% by the use of excess triphenyl phosphine (entry 2). The

attempted use of tetrahexylammonium bromide in HFIP (entry 3) resulted instead in the formation of aldehyde **G**,⁸ ketone **H**,⁸ allylic alcohol **I**⁹ and cycloadduct **J**⁸ where presumably the solvent promotes epoxide ring opening by hydrogen bonding but competitive elimination, rearrangement and/or cyclisation are faster than attack by bromide anion. Using the conditions of Suh et al,¹⁷ gave the desired bromohydrins along with ketone **H** and alkene **I** (entry 4). The use of bromodimethylsulphonium bromide as described by Das¹⁸ gave the desired bromohydrins (\pm)-**4a** and **4b** cleanly (entry 5). The method of Couladorous⁸ using inexpensive lithium bromide (entry 6) became the method of choice to access both regioisomeric bromohydrins.

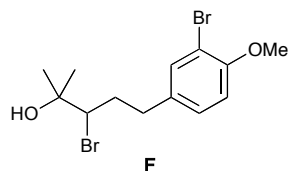
Characterising data for compounds E-F:

(\pm)-4-Bromo-1-(3-bromo-4-methoxyphenyl)-4-methylpentan-3-ol (E)



Colourless oil. $R_f = 0.50$ (10% EtOAc in pet. spirit); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.43 (d, $J = 2.2$ Hz, 1H), 7.18-7.13 (m, 1H), 6.89-6.84 (m, 1H), 3.90 (s, 3H), 3.43 (dd, $J = 10.5, 2.0$ Hz, 1H), 2.92 (ddd, $J = 14.1, 9.5, 4.8$ Hz, 1H), 2.72-2.60 (m, 1H), 1.90 (dddd, $J = 13.7, 9.4, 7.5, 1.9$ Hz, 1H), 1.81 (s, 3H), 1.74 (s, 3H), 1.75-1.64 (m, 1H) ppm; $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 154.2, 135.4, 133.2, 128.5, 112.0, 111.5, 78.5, 75.4, 56.3, 31.4, 31.2, 28.6, 21.1 ppm; MS (Cl^+) m/z 304, 302 [$\text{M}-\text{Br} + \text{NH}_4$]⁺.

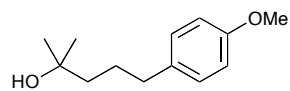
(\pm)-3-Bromo-5-(3-bromo-4-methoxyphenyl)-2-methylpentan-2-ol (F)



Colourless oil. $R_f = 0.42$ (10:90 EtOAc:PE); IR ν_{max} 3462, 1256, 1056, cm^{-1} ; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.43 (d, $J = 2.1$ Hz, 1H), 7.15 (dd, $J = 8.3, 2.1$ Hz, 1H), 6.86 (d, $J = 8.4$ Hz, 1H), 3.96 (dd, $J = 11.4, 2.1$ Hz, 1H), 3.91 (s, 3H), 2.99 (ddd, $J = 13.9, 8.6, 4.5$ Hz, 1H), 2.66 (dt, $J = 14.0, 8.3$ Hz, 1H), 2.23-2.11 (m, 1H), 2.10-1.99 (m, 1H) 1.35 (s, 6H) ppm; $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 154.4, 134.4, 133.3, 128.5, 112.0, 111.6, 72.5, 70.0, 56.3, 35.7, 33.3, 26.7, 25.9 ppm; MS (Cl^+ , NH_3) m/z 386, 384, 382 [$\text{M} + \text{NH}_4$]⁺; HRMS (Cl^+) calc'd for $\text{C}_{13}\text{H}_{22}\text{NO}_2$ $^{79}\text{Br}_2$ 382.0017 [$\text{M} + \text{NH}_4$]⁺. Found: 382.0013.

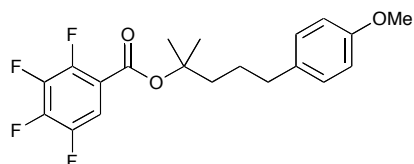
Procedures and data for preparation and cyclisation of *des*-bromo 4b

5-(4-Methoxyphenyl)-2-methylpentan-2-ol¹⁹



Prepared according to a modified procedure of Sarandeses *et al.*²⁰ To a stirred solution of alkene **1** (250 mg, 1.3 mmol) in THF:H₂O (20 mL 1:1) was added mercury(II) trifluoroacetate (618 mg, 1.45 mmol). The mixture was stirred at r.t. for 1.5 h, and aqueous NaOH solution (20 mL, 3 M) was added, followed by a solution of NaBH₄ (55 mg, 1.4 mmol, 1.1 eq) in aqueous NaOH solution (2 mL, 3 M). After stirring for a further 0.5 h, brine (20 mL) was added and the mixture extracted with Et₂O (3 × 30 mL), dried over Na₂SO₄, concentrated and chromatographed (20:80-50:50 EtOAc:PE) to yield the title product (177 mg, 65%) as a colourless oil. $R_f = 0.26$ (20:80 EtOAc PE); IR ν_{\max} 3600-3100 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.13 (d, $J = 8.6$ Hz, 2H), 6.86 (d, $J = 8.6$ Hz, 2H), 3.82 (s, 3H), 2.60 (t, $J = 7.6$ Hz, 2H) 1.75-1.64 (m, 2H) 1.60-1.50 (m, 2H) 1.23 (s, 6H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 157.7, 134.6, 129.3, 113.7, 70.9, 55.3, 43.5, 35.4, 29.3, 26.5 ppm; MS (CI⁺, NH₃) m/z 226 [M + NH₄]⁺; HRMS (CI⁺, NH₃) calc'd for C₁₃H₂₄NO₂ [M+NH₄]⁺ 226.1807, found 226.1808.

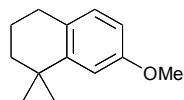
5-(4-Methoxyphenyl)-2-methylpentan-2-yl 2,3,4,5-tetrafluorobenzoate



Using the method of Steglich,¹⁰ to a stirred solution of tertiary alcohol 5-(4-methoxyphenyl)-2-methylpentan-2-ol (85 mg, 0.41 mmol, 1 eq) in CH₂Cl₂ (2 mL) was added 2,3,4,5-tetrafluorobenzoic acid (159 mg, 0.82 mmol, 2 eq), DMAP (15 mg, 0.12 mmol, 30 mol%) and DCC (253 mg, 1.23 mmol, 3 eq). After 16 h the reaction mixture was diluted with Et₂O, filtered through a silica plug, concentrated and chromatographed (5:95-15:85 Et₂O:PE) to afford the title product (131 mg, 83%) as a colourless oil. $R_f = 0.52$ (10:90 Et₂O:PE); IR ν_{\max} 1716 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.54 (dddd, $J = 10.5, 8.4, 6.0, 2.5$ Hz, 1H), 7.12 (d, $J = 8.6$ Hz, 2H), 6.86 (d, $J = 8.6$ Hz, 2H), 3.82 (s, 3H), 2.62 (t, $J = 7.6$ Hz, 2H), 1.98-1.90 (m, 2H), 1.78-1.62 (m, 2H), 1.59 (s, 6H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 161.0, 157.8, 147.9 (dddd, $J = 262, 11, 4, 2$ Hz), 146.4 (dddd, $J = 249, 11, 4, 2$ Hz), 143.1 (dddd, $J = 261, 16, 12, 3$ Hz), 141.2 (dddd, $J = 248, 17, 12, 4$ Hz), 134.1, 129.1, 116.6, 113.8, 113.1 (d, $J = 20$ Hz), 85.7, 55.2, 40.6, 35.1, 26.0, 25.9

ppm; MS (Cl^+ , NH_3) m/z 402 $[\text{M} + \text{NH}_4]^+$; HRMS (Cl^+ , NH_3) calc'd for $\text{C}_{20}\text{H}_{24}\text{NO}_3\text{F}_4$ $[\text{M} + \text{NH}_4]^+$ 402.1692, found 402.1707.

7-Methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalene¹⁹



To a solution of 5-(4-methoxyphenyl)-2-methylpentan-2-yl 2,3,4,5-tetrafluorobenzoate (120 mg, 0.31 mmol) in CH_2Cl_2 (2 mL) at $-14\text{ }^\circ\text{C}$ was added a solution of triflic acid (30 mol%) in CH_2Cl_2 (1 mL) and stirred at room temperature for 6 h. Workup using the usual method afforded the title compound (51 mg, 85%) as a pale yellow oil. $R_f = 0.43$ (20:80 CH_2Cl_2 :PE); IR ν_{max} 1236, 1047 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.04 (d, $J = 8.4$ Hz, 1H), 6.95 (d, $J = 2.7$ Hz, 1H), 6.74 (dd, $J = 8.4, 2.7$ Hz, 1H), 3.86 (s, 3H), 2.78 (t, $J = 6.3$ Hz, 2H), 1.90-1.83 (m, 2H), 1.75-1.70 (m, 2H), 1.36 (s, 6H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 157.8, 147.1, 129.9, 128.4, 112.2, 111.0, 55.2, 39.3, 34.1, 31.9, 30.0, 19.9 ppm; MS (Cl^+ , NH_3) m/z 191, $[\text{M} + \text{H}]^+$; HRMS (Cl^+ , NH_3) calc'd for $\text{C}_{13}\text{H}_{19}\text{O}$ $[\text{M} + \text{H}]^+$ 191.1436, found 191.1437. 5-(4-Methoxyphenyl)-2-methylpentan-2-ol was also found to cyclise at reflux using this method to give the title compound (88%).

Details of experiment for cyclisation of *ent*-6a in the presence of added 1-methylcyclohexene

To a stirred solution of secondary acetate **6a** (50 mg, 0.15 mmol, 1 eq.) and 1-methylcyclohexene (0.018 mL, 0.15 mmol, 1 eq.) in CH₂Cl₂ (0.078 M) was added a solution of triflic acid in CH₂Cl₂ (0.05 M) -14 °C and heated at reflux for 3 h. The reaction was quenched with a saturated aqueous solution of NaHCO₃, extracted with CH₂Cl₂, washed with brine, dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (10:90-15:85 CH₂Cl₂:PE) to give first (*R*)-2-Bromo-7-methoxy-1,1-dimethyl-6-(1-methylcyclohexyl)-1,2,3,4-tetrahydro naphthalene (30 mg, 53%) as a colourless oil: [α]_D²⁴ + 7.0 (*c* 0.4, CH₂Cl₂); R_f = 0.5 (10:90 CH₂Cl₂:PE); ¹H NMR (400 MHz, CDCl₃) δ 6.92 (s, 1H), 6.81 (s, 1H), 4.44 (dd, *J* = 9.7, 3.7 Hz, 1H), 3.82 (s, 3H), 2.97-2.82 (m, 2H), 2.48-2.33 (m, 2H), 2.05-1.95 (m, 2H), 1.78-1.68 (m, 2H), 1.63-1.45 (m, 6H), 1.47 (s, 3H), 1.45 (s, 3H), 1.28 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 157.3, 141.0, 136.4, 127.7, 125.0, 110.1, 65.4, 55.2, 39.6, 37.6, 36.9, 30.7, 30.0, 29.3, 28.5, 26.7, 24.9, 22.8 ppm; MS (CI⁺, NH₃) *m/z* 384, 382 [M + NH₄]⁺; HRMS (CI⁺) calc'd for C₂₀H₃₃NO⁷⁹Br [M + NH₄]⁺ 382.1746, found 382.1752; and second bicycle *ent*-7 (14 mg, 34%) as a colourless oil: HPLC (CHIRALCEL OD-H; 1% IPA in *n*-hexane; 1.0 mL/min) *t*_R = 5.1 min (minor), 7.2 min (major) – 94:6 e.r. (88% ee).

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