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Supporting Information

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Stereochemical and Mechanistic Investigations of a Novel Palladium-Catalyzed Annulation Employing Secondary Alkyl Halides

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Contents

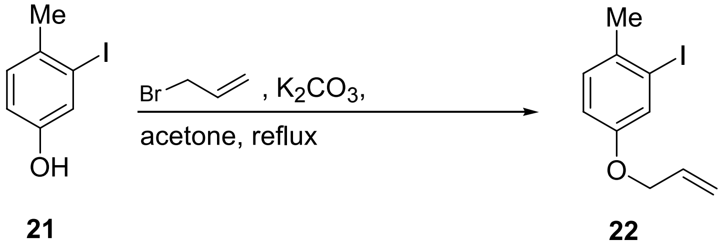
General Experimental

The following includes general experimental procedures, isolation and spectroscopic information for all new compounds. Microwave-assisted reactions were performed in a Biotage (formerly Personal Chemistry) Emrys Liberator model microwave reactor, using Biotage microwave vials (2-5 mL). Melting points were recorded using a Fisher-Johns melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained using either a Varian Gemini 300 MHz, Varian Unity 400 MHz or Varian Unity 500 MHz spectrometer. ^{1}H spectra were referenced to tetramethylsilane (TMS, 0 ppm) and ^{13}C spectra were referenced to chloroform ($CDCl_3$, 77.23 ppm). No special notation is used for equivalent carbons. IR spectra were obtained using a Nicolet DX FT IR spectrometer as thin films on NaCl plates. High-resolution mass spectra were obtained using a VG 70-250S (double focusing) mass spectrometer at 70 eV unless otherwise noted. Chiral HPLC analysis was performed on an Agilent 1100 Series HPLC. Optical rotations were obtained at 589 nm using a Rudolph Autopol IV polarimeter.

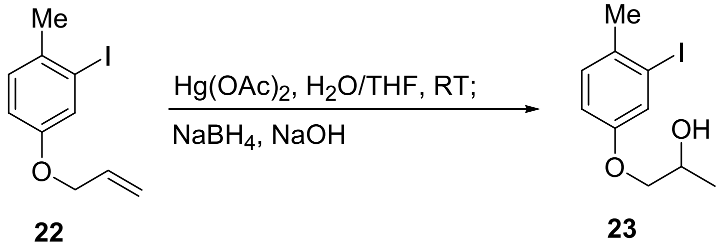
Toluene and tetrahydofuran (THF) were distilled under nitrogen from Na/benzophenone immediately prior to use. Acetonitrile, triethylamine and 1,2-dimethoxyethane (DME) were distilled under nitrogen from CaH_2 immediately prior to use. Methylene chloride (CH_2Cl_2) and diethyl ether (Et_2O) were dried and degassed using a MBRAUN solvent purification system. All other solvents were used as received. Neutral silica (Silicycle, Quebec, Canada) for flash chromatography was used as received. All reagents, metal catalysts and ligands were purchased from Sigma-Aldrich or Strem-Chemical Company and used as received unless otherwise noted. Triphenylphosphine was recrystallized from CH_2Cl_2/EtOH. All reactions were performed under a nitrogen atmosphere unless otherwise noted.

Crystal structure data for ***R*-3**, ***R*-15** and ***S*-16** can be retrieved from the Cambridge Crystallographic Data Centre (CCDC) under deposition numbers CCDC 619351, 627191 and 619350. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_requests/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

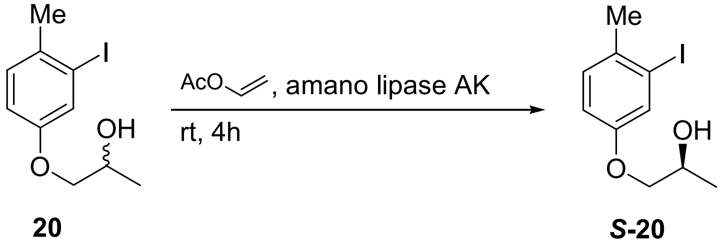
Synthesis of Secondary Alkyl Iodide Substrates



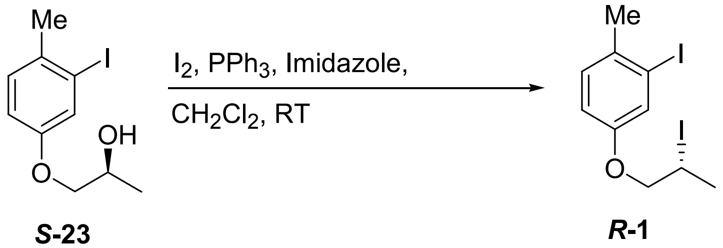
4-Allyloxy-2-iodo-1-methyl-benzene (22). To a solution of 3-iodo-4-methyl-phenol[1] (**21**) (500 mg, 2.14 mmol, 1 equiv) and allyl bromide (775 mg, 6.41 mmol, 3 equiv) in acetone (8 mL) was added K_2CO_3 (591 mg, 4.27 mmol, 2 equiv). The suspension was heated to reflux for 3.0 h. The mixture was then diluted with water and the aqueous layer was extracted with diethyl ether (3×). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography using hexanes/EtOAc (6:1) to afford **22** as a colorless oil (550 mg, 2.01 mmol, 94%). R_f = 0.53 on silica gel (hexanes/EtOAc; 6:1). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 2.35 (s, 3H), 4.48 (m, 2H), 5.28 (m, 1H), 5.39 (m, 1H), 6.02 (m, 1H), 6.81 (dd, *J* = 8.3 Hz, 2.8 Hz, 1H), 7.10 (d, *J* = 8.3 Hz, 1H), 7.37 (d, *J* = 2.8 Hz, 1H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 27.1, 69.3, 101.0, 115.2, 118.1, 125.2, 129.9, 133.2, 133.8, 157.0. **HRMS** calcd for $C_{10}H_{11}IO$ [M^+] 273.9855, found 273.9850. **IR**: $\tilde{\nu}$ = 2907, 1596, 1483, 1280, 1229, 1018, 994 cm^{-1}.



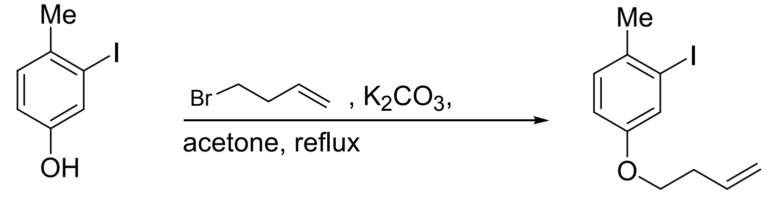
1-(3-Iodo-4-methyl-phenoxy)-propan-2-ol (23). To a bright yellow solution of $Hg(OAc)_2$ (2.7 g, 8.5 mmol, 1.1 equiv) in H_2O (8 mL) and THF (8 mL) was added olefin **22** (2.0 g, 7.7 mmol, 1 equiv). The resulting solution was stirred at ambient temperature until the yellow color disappeared (30 min). A 3 N solution of NaOH (8 mL) was then added to the reaction mixture and stirring was continued for another 30 min. A 0.5 N solution of $NaBH_4$ in 3 N NaOH (15.5 mL, 7.8 mmol, 1 equiv) was then added to the reaction mixture and stirring was continued for an additional hour at ambient temperature. The reaction mixture was then diluted with water and extracted with Et_2O (3×). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography using hexanes/EtOAc (3:1) yielding **23** as a colorless oil (943 mg, 3.4 mmol, 44%). $R_f = 0.09$ on silica gel (hexanes/EtOAc; 3:1). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 1.27 (d, J = 6.5 Hz, 3H), 2.35 (s, 3H), 3.74 (dd, J = 9.3 Hz, 7.7 Hz, 1H), 3.89 (dd, J = 9.3 Hz, 3.2 Hz, 1H), 4.16 (m, 1H), 6.81 (dd, J = 8.3 Hz, 2.8 Hz, 1H), 7.12 (d, J = 8.3 Hz, 1H), 7.37 (d, J = 2.8 Hz, 1H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 18.9, 27.1, 66.4, 73.8, 101.0, 115.0, 125.0, 130.0, 134.1, 157.0. **HRMS** calcd for $C_{10}H_{13}IO_2$ [M^+] 291.9960, found 291.9960. **IR**: $\tilde{\nu}$ = 3372, 2969, 2922, 1596, 1489, 1283, 1235, 1042, 1021 cm^{-1}.



(*S*)-1-(3-Iodo-4-methyl-phenoxy)-propan-2-ol (*S*-22). To a solution of (±)-**20** (1 g, 3.4 mmol, 1 equiv) in vinyl acetate (30 mL) was added amano lipase AK from pseudomonas fluorescens[2] (3 g). The resulting suspension was stirred at ambient temperature for 4 hours. The lipase was filtered from the reaction mixture and washed with several portions of EtOAc. The resulting solution was then concentrated and the crude product was purified by flash chromatography using hexanes/EtOAc (3:1) to afford ***S*-20** as a colorless oil (476 mg, 1.6 mmol, 47% of a theoretical maximum of 50%). **HPLC** (Chiracel-OD, 30°C): wavelength = 254 nm, flow = 1.0 mL/min, hexanes/*i*-propanol = 90:10, t_R = 10.34 min, *ee* = >99%. $[\alpha]_D^{27}$ = 15.9° (c = 2.50 in $CHCl_3$).

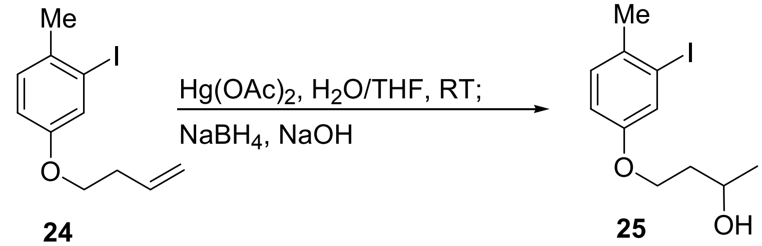


(*R*)-2-Iodo-4-(2-iodo-propoxy)-1-methyl-benzene (*R*-1). A suspension of PPh_3 (525 mg, 2.0 mmol, 1.5 equiv), imidazole (136 mg, 2.0 mmol, 1.5 equiv) and iodine (508 mg, 2.0 mmol, 1.5 equiv) in CH_2Cl_2 (3 mL) was stirred at 0 °C for 15 min. A solution of **23** (390 mg, 1.3 mmol, 1 equiv) in CH_2Cl_2 (3 mL) was added and stirring continued at 0 °C for 30 min. The reaction mixture was allowed to warm to ambient temperature and was stirred at RT for an additional hour. The reaction was quenched with water and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with saturated aqueous sodium thiosulfate, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using 95:5 – 3:1 hexanes/CH_2Cl_2, yielding **1** as a colorless oil (478 mg, 1.2 mmol, 89%). R_f = 0.65 on silica gel (hexanes/EtOAc; 6:1). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 1.99 (d, *J* = 6.5 Hz, 3H), 2.37 (s, 3H), 3.99 (dd, *J* = 9.9 Hz, 7.7 Hz, 1H), 3.89 (dd, *J* = 9.9 Hz, 5.8 Hz, 1H), 4.33 (m, 1H), 6.82 (dd, *J* = 8.3 Hz, 2.8 Hz, 1H), 7.10 (d, *J* = 8.3 Hz, 1H), 7.37 (d, *J* = 2.8 Hz, 1H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 22.0, 24.9, 27.1, 75.3, 101.0, 115.1, 125.3, 130.0, 134.3, 156.4. **HRMS** calcd for $C_{10}H_{12}I_2O$ [M^+] 401.8978, found 401.8981. **IR**: $\tilde{\nu}$ = 2967, 2917, 1594, 1563, 1482, 1455, 1281, 1229, 1012, 861 cm^{-1}. **HPLC** (Chiralpak-OJ, 20°C): wavelength = 230 nm, flow = 1.5 mL/min, heptane, t_R = 11.689 min (–), 13.525 min (+), *ee* = 96%. $[\alpha]_D^{27}$ = -15.3° (*c* = 2.04 in $CHCl_3$).

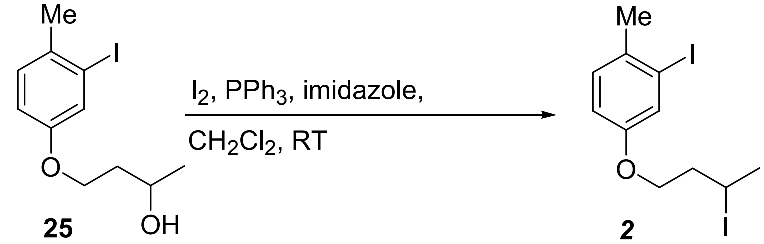


21 **24**

4-But-3-enyloxy-2-iodo-1-methyl-benzene (24). To a solution of **21** (320 mg, 1.37 mmol, 1 equiv) and 4-bromo-1-butene (1.52 mL, 16.4 mmol, 12 equiv) in acetone (5 mL), was added K_2CO_3 (567 mg, 4.10 mmol, 3 equiv). The suspension was then heated to reflux for 2 days. The mixture was diluted with water and the aqueous layer was extracted with diethyl ether (3×). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using hexanes, to afford **24** as a colorless oil (328 mg, 1.1 mmol, 83%). R_f = 0.88 on silica gel (hexanes/EtOAc; 3:1). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 2.36 (s, 3H), 2.51 (ddt, *J* = 1.4 Hz, 1.8 Hz, 6.7 Hz, 2H), 3.96 (t, *J* = 6.7 Hz, 2H), 5.10 (ddt, *J* = 1.4 Hz, 1.8 Hz, 10.3 Hz, 1H), 5.16 (ddt, *J* = 1.4 Hz, 1.8 Hz, 17.2 Hz, 1H), 5.88 (ddt, *J* = 6.7 Hz, 10.3 Hz, 17.2 Hz, 1H), 6.80 (dd, *J* = 2.6 Hz, 8.4 Hz, 1H), 7.10 (dd, *J* = 0.6 Hz, 8.4 Hz, 1H), 7.36 (d, *J* = 2.6 Hz, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 27.1, 33.8, 67.7, 101.1, 114.9, 117.4, 124.9, 129.9, 133.4, 134.5, 157.3. **HRMS** calcd for $C_{11}H_{13}IO$ [M^+] 288.0018, found 288.0011. **IR**: $\tilde{\nu}$ = 3077, 2977, 2919, 2872, 1642, 1597, 1488, 1469, 1285, 1235, 1037, 1021, 991, 912 cm^{-1}.

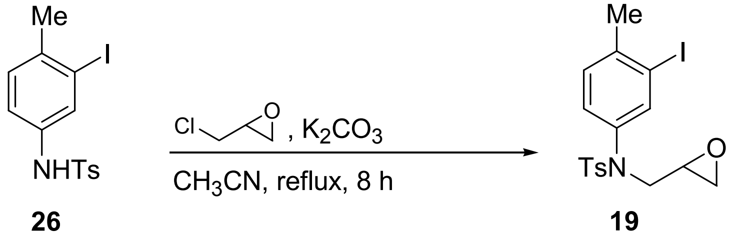


4-(3-Iodo-4-methyl-phenoxy)-butan-2-ol (25). To a bright yellow solution of $Hg(OAc)_2$ (411 mg, 1.3 mmol, 1.2 equiv) in H_2O (1.3 mL) and THF (1.3 mL), was added olefin **24** (310 mg, 1.1 mmol, 1 equiv). The resulting mixture was then stirred at ambient temperature until the yellow color disappeared (15 min). A 3 N solution of NaOH (1.3 mL) was then added to the reaction mixture and stirring was continued for another 30 min. A 0.5 N solution of $NaBH_4$ in 3 N NaOH (1.3 mL, 1.1 mmol, 1 equiv) was added to the reaction mixture and stirring was continued for an additional hour at ambient temperature. The reaction mixture was then diluted with water and extracted with Et_2O (3×). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography using hexanes/EtOAc (6:1 – 3:1) to afford **25** as a colorless oil (286 mg, 0.93 mmol, 86%). R_f = 0.09 on silica gel (hexanes/EtOAc; 6:1). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.24, (d, *J* = 6.3 Hz, 3H), 1.84 – 1.89 (m, 2H), 2.34 (s, 3H), 3.98 – 4.13 (m, 3H), 6.79 (dd, *J* = 2.6 Hz, 8.4 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 7.35 (d, *J* = 2.6 Hz, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 23.8, 27.0, 38.2, 65.9, 66.1, 100.9, 114.8, 124.8, 129.8, 133.6, 157.1. **HRMS** calcd for $C_{11}H_{15}IO_2$ [M^+] 306.0117, found 306.0117. **IR**: $\tilde{\nu}$ = 3361, 2965, 2922, 1597, 1488, 1470, 1286, 1233, 1137, 1051, 1021 cm^{-1}.



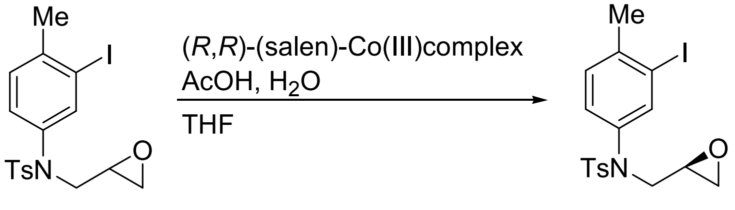
2-Iodo-4-(3-iodo-butoxy)-1-methyl-benzene (2). A suspension of PPh_3 (359 mg, 1.4 mmol, 1.5 equiv), imidazole (93 mg, 1.4 mmol, 1.5 equiv) and iodine (348 mg, 1.4 mmol, 1.5 equiv) in CH_2Cl_2 (2.5 mL) was stirred at 0 °C for 15 min. A solution of **25** (280 mg, 910 μmol, 1 equiv) in CH_2Cl_2 (2.5 mL) was added and stirring continued at 0 °C for 30 min. The reaction mixture was allowed to warm to ambient temperature and was stirred at RT for an additional hour. The reaction was then quenched with water and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with saturated aqueous sodium thiosulfate, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using hexanes/CH_2Cl_2 (95:5), to afford **2** as a pale yellow liquid (357 mg, 858 μmol, 94%). R_f = 0.18 on silica gel (hexanes/CH_2Cl_2, 95:5). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 2.01 (d, *J* = 6.7 Hz, 3H), 2.08 (m, 1 H), 2.20 (m, 1 H), 2.36 (s, 3H), 4.02 (m, 2H), 4.40 (m, 1H), 6.82 (dd, *J* = 8.3 Hz, 2.8 Hz, 1H), 7.12 (d, *J* = 8.3 Hz, 1H), 7.38 (d, *J* = 2.8 Hz, 1H). **^{13}C-**

NMR (75 MHz, $CDCl_3$): δ 25.5, 27.15, 29.3, 42.1, 68.1, 101.1, 114.9, 124.9, 129.9, 133.8, 157.1. **HRMS** calcd for $C_{11}H_{14}IO_2$ [M^+] 415.9140, found 415.9134. **IR**: $\tilde{\nu}$ = 2915, 1595, 1487, 1465, 1284, 1233, 1051, 1021 cm^{-1}.



26 **19**

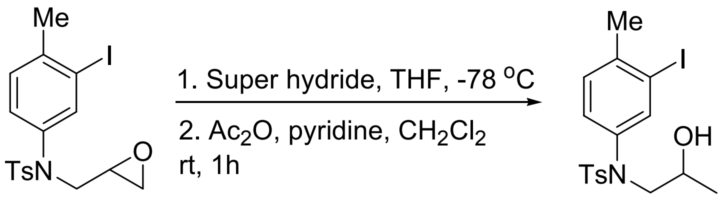
***N*-(3-Iodo-4-methyl-phenyl)-4-methyl-*N*-oxiranylmethyl-benzenesulfonamide (19).** A suspension of *N*-tosyl-3-iodo-4-methyl-aniline (**26**)[3] (200 mg, 516 μmol, 1 equiv), (±)-epichlorohydrin or (*R*)-epichlorohydrin[4] (382 mg, 4.13 mmol, 8 equiv) and potassium carbonate (214 mg, 1.55 mmol, 3 equiv) in CH_3CN (5 mL) was stirred at reflux for 8 hours. The reaction was quenched with water at ambient temperature and the aqueous layer was extracted with diethyl ether (3×). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography using hexanes/EtOAc (3:1) to afford **19** (200 mg, 451 μmol, 87%) as a white solid, mp = 72 – 74°C. R_f = 0.33 on silica gel (hexanes/EtOAc; 3:1). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 2.44 (s, 3H), 2.45 (dd, J = 2.5 Hz, 2.5 Hz, 1H), 2.71 (dd, J = 4.4 Hz, 4.4 Hz, 1H), 3.10 – 3.14 (m, 1H), 3.59 (dd, J = 5.5 Hz, 14.4 Hz, 1H), 3.67 (dd, J = 4.8 Hz, 14.5 Hz, 1H), 7.01 (dd, J = 2.3 Hz, 8.1 Hz, 1H), 7.18 (d, J = 8.1 Hz, 1H), 7.28 (d, J = 8.1 Hz, 2H), 7.45 (d, J = 2.2 Hz, 1H), 7.50 (d, J = 8.5 Hz, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 21.8, 27.9, 45.8, 50.5, 53.8, 100.5, 127.9, 128.8, 129.8, 129.9, 135.1, 138.3, 139.0, 142.0, 144.2. **HRMS** calcd for $C_{17}H_{18}INO_3S$ [M^+] 443.0052, found 443.0050. **IR**: $\tilde{\nu}$ = 3051, 2983, 2922, 1592, 1473, 1344, 1161, 1089, 916, 811 cm^{-1}. For reaction with (*R*)-epichlorohydrin: The enantiomeric excess was determined after the subsequent transformation. $[\alpha]_D^{20}$ = 8.7° (*c* = 1.30 in CH_3OH).



19 ***R*-19**

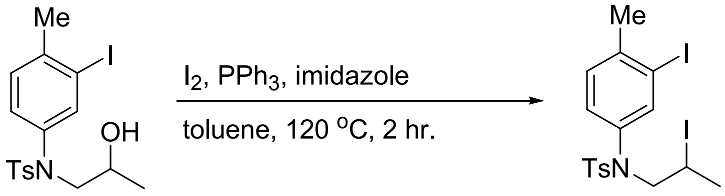
(*R*)-*N*-(3-Iodo-4-methyl-phenyl)-4-methyl-*N*-oxiranylmethyl-benzenesulfonamide (*R*-19).[4] To a solution of (*R*,*R*)-(salen)Co(III) (10.3 mg, 17 μmol, 5 mol%) in CH_2Cl_2 (1 mL) was added acetic acid (10 μL, 170 μmol, 0.5 equiv). The solution was allowed to stir at RT, open to air, for 30 min. The solution was then concentrated in vacuo to give a brown solid. The catalyst residue and ±**19** (150 mg, 340 μmol, 1.0 equiv) were dissolved in THF (1 mL), the reaction mixture was cooled to 0 ºC and H_2O (3.4 μL, 190 μmol, 0.55

eq) was added in one portion. The reaction mixture was allowed to warm to RT and stir for 45 hr. The reaction mixture was concentrated and purified by flash chromatography using hexanes/EtOAc (3:1) to yield ***R*-19** (49 mg, 111 µmol, 65%, 82% ee) as a white solid.



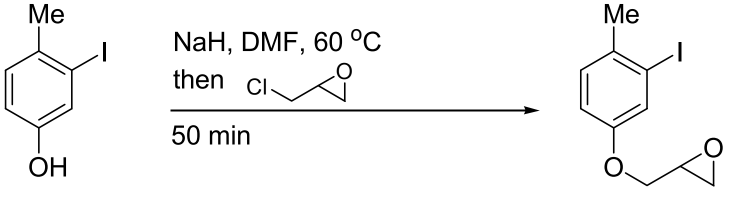
19 **20**

***N*-(2-Hydroxy-propyl)-*N*-(3-iodo-4-methyl-phenyl)-4-methyl-benzenesulfonamide (20).** To a solution of **19** (967 mg, 2.2 mmol, 1 equiv) in THF (20 mL) at –78 ºC was added Super hydride (1 M in THF, 2.6 mL, 2.6 mmol, 1.2 equiv) with a syringe pump, over 1h. The reaction mixture was warmed to RT, quenched with sat. aq. NH_4Cl (10 mL) and diluted with Et_2O (20 mL). The aqueous layer was extracted with Et_2O (3 ×) and the combined organic layers were dried over MgSO4, filtered and concentrated. The crude mixture was chromatographed using hexanes/EtOAc (3:1) to yield **20** as an inseparable mixture of primary and secondary alcohols (1:3). The mixture was dissolved in CH_2Cl_2 (10 mL), treated with pyridine (57 µL, 0.7 mmol, 0.3 equiv) and acetic anhydride (62 µL, 0.7 mmol, 0.3 equiv). The reaction mixture stirred at room temperature for 1 h and was quenched with water (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using hexanes/EtOAc (3:1) to yield **20** (800 mg, 1.8 mmol, 82%) as a thick colorless oil. R_f = 0.17 on silica gel (hexanes/EtOAc; 3:1). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.15 (d, *J* = 6.3 Hz, 3H), 2.33 (bs, 1H), 2.42 (s, 3H), 2.44 (s, 3H), 3.32 (dd, *J* = 3.8 Hz, 13.8 Hz, 1H), 3.53 (dd, *J* = 8.2 Hz, 13.8 Hz, 1H), 3.76 – 3.84 (m, 1H), 7.00 (dd, *J* = 2.2 Hz, 8.4 Hz, 1H), 7.18(d, *J* = 8.4 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 2.2 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 20.5, 21.8, 27.9, 58.8, 65.8, 100.5, 128.0, 128.8, 129.8, 129.9, 134.8, 138.6, 138.8, 142.0, 144.2. **HRMS** calcd for $C_{17}H_{20}INO_3S$ [M^+] 445.020868, found 445.021320. **IR**: $\tilde{\nu}$ = 3520, 2972, 2921, 1593, 1480, 1346, 1164, 1089, 1069, 950, 815 cm^{-1}. **HPLC** (Chiracel-OD-H, 30°C): wavelength = 220 nm, flow = 1.0 mL/min, hexanes/*i*-propanol = 90:10, t_R = 10.33 min (–), 11.64 min (+), *ee* = 91%. $[\alpha]_D^{20}$ = 26.8° (*c* = 1.10 in $CHCl_3$).



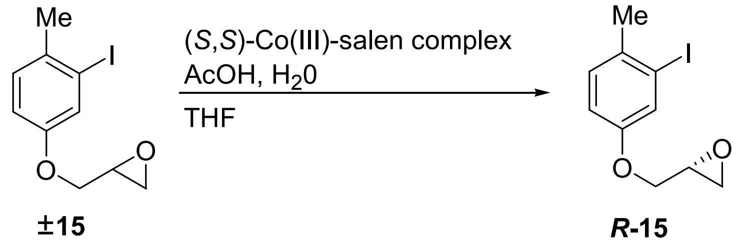
20 **3**

***N*-(3-Iodo-4-methyl-phenyl)-*N*-(2-iodo-propyl)-4-methyl-benzenesulfonamide (3).** A suspension of PPh_3 (496 mg, 1.9 mmol, 1.05 equiv), imidazole (129 mg, 1.9 mmol, 1.05 equiv) and iodine (480 mg, 1.9 mmol, 1.05 equiv) in toluene (10 mL) was stirred at RT for 30 min. A solution of **20** (800 mg, 1.8 mmol, 1 equiv, 88% ee) in toluene (10 mL) was added and stirring continued at 120 °C for 2 hr. The reaction mixture was allowed to cool to ambient temperature. The reaction was then quenched with water and the aqueous layer was extracted with Et_2O (3×). The combined organic layers were washed with saturated aqueous sodium thiosulfate, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using hexanes/EtOAc (6:1), to afford **3** (564 mg, 1.0 mmol, 56%, 89% based on recovered starting material) as a colorless solid, mp = 114 – 116°C. Crystals suitable for x-ray analysis were obtained from diffusion of pentane into a solution of ***R*-3** in THF. R_f = 0.51 on silica gel (hexanes/EtOAc, 3:1). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.92 (d, *J* = 6.8 Hz, 3H), 2.42 (s, 3H), 2.44 (s, 3H), 3.71 (dd, *J* = 9.2 Hz, 13.7 Hz, 1H), 3.82 (dd, *J* = 5.9 Hz, 13.7 Hz, 1H), 3.93-4.02 (m, 1H), 6.98 (dd, *J* = 2.2 Hz, 8.4 Hz, 1H), 7.17 (d, *J* = 8.6 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 2.2 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 21.8, 22.8, 25.3, 27.9, 60.6, 100.6, 128.0, 128.8, 129.8, 130.0, 134.7, 137.6, 138.8, 142.0, 144.2. **HRMS** calcd for $C_{17}H_{19}I_2NO_2S$ [M^+] 554.922605, found 554.921600. **IR**: $\tilde{\nu}$ = 2915, 1476, 1348, 1161, 1086, 1059, 950, 804 cm^{-1}. **HPLC** (Chiralpak AD, 30°C): wavelength = 220 nm, flow = 1.0 mL/min, hexanes/*i*-propanol = 99:1, t_R = 19.99 min (–), 23.08 min (+), *ee* = 80%. $[\alpha]^{20}_D$ = -11.1° (*c* = 3.63 in $CHCl_3$) at 78% ee. CCDC no. 619351.



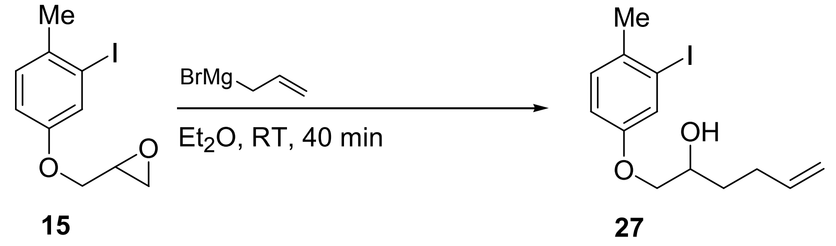
21 **±15**

2-(3-Iodo-4-methyl-phenoxymethyl)-oxirane (15). To a 0 °C solution of **21** (850 mg, 3.63 mmol, 1equiv) in DMF (14 mL) was added NaH (95% suspension in mineral oil, 96 mg, 4.00 mmol, 1.1 equiv). After stirring for 10 min, epichlorohydrin (3.0 mL, 0.83 mL/mmol starting material) was added and the mixture was heated to 60 °C for 50 min. The reaction was quenched with water at ambient temperature and the aqueous layer was extracted with diethyl ether (3×). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography using hexanes/EtOAc (6:1) to yield **15** (950 mg, 3.27 mmol, 90%) as a colorless oil. R_f = 0.35 on silica gel (hexanes/EtOAc; 6:1). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 2.36 (s, 3H), 2.75 (dd, J = 4.6 Hz, 2.7 Hz, 1H), 2.90 (dd J = 4.6 Hz, 4.6 Hz, 1H), 3.33 (m, 1H), 3.90 (dd, J = 11.0 Hz, 5.7 Hz, 1H), 4.19 (dd, J = 11.0 Hz, 2.9 Hz, 1H), 6.83 (dd, J = 8.6 Hz, 2.9 Hz, 1H), 7.12 (d, J = 8.6 Hz, 1H), 7.30 (d, J = 2.9 Hz, 1H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 27.1, 44.8, 50.2, 69.2, 100.9, 115.1, 125.0, 130.0, 134.2, 156.8. **HRMS** calcd for $C_{10}H_{11}IO_2$ [M^+] 289.9804, found 289.9810. **IR**: $\tilde{\nu}$ = 2918, 1595, 1488, 1233 cm^{-1}.

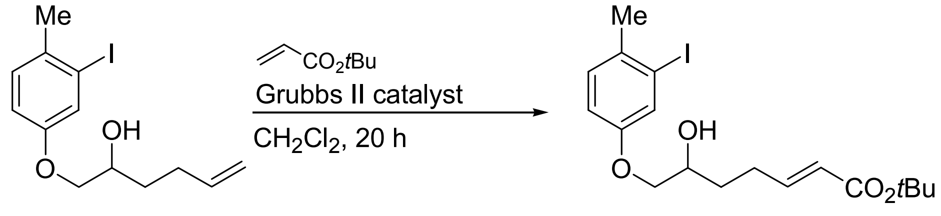


(2*R*)-2-(3-Iodo-4-methyl-phenoxymethyl)-oxirane (*R*-15).[4] To a solution of (±)-**15** (950 mg, 3.27 mmol, 1 equiv), HOAc (7.4 μL, 130 μmol, 4 mol%) and water (32.4 μL 1.80 mmol, 0.55 equiv) in THF (1.5 mL), was added (*S*,*S*)-salen-Co(II)-catalyst (20 mg, 32.7 μmol, 1 mol%). Stirring was continued at ambient temperature in a flask loosely capped with cotton, for 16 h. During this time the reaction mixture became solid. The crude mixture was dissolved in a small portion of CH_2Cl_2 and purified by flash chromatography using hexanes/EtOAc (6:1) to recover ***R*-15** (390 mg, 1.34 mmol, 55%; theoretical maximum yield 50%) as a colorless oil. R_f = 0.35 on silica gel (hexanes/EtOAc; 6:1).

The enantiomeric excess was determined after the subsequent transformation. $[\alpha]_D^{20}$ = –2.3° (c = 1.18 in $CHCl_3$).

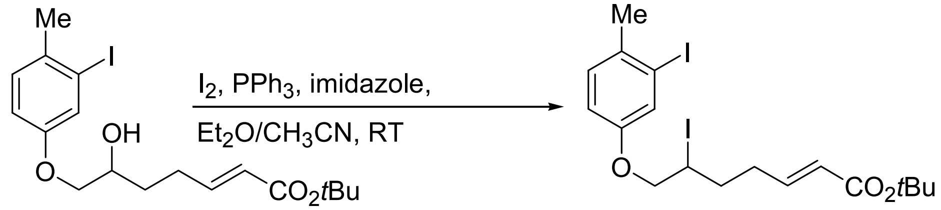


1-(3-Iodo-4-methyl-phenoxy)-hex-5-en-2-ol (27). To a 0 °C solution of **15** (390 mg, 1.34 mmol, 1 equiv) in Et_2O (4.6 mL), was added allyl magnesium bromide (1 M solution in Et_2O, 4.03 mL, 3.0 equiv) dropwise. The resulting suspension was stirred at ambient temperature for 40 min and saturated aqueous NH_4Cl was added at 0 °C. The aqueous layer was extracted with diethyl ether (3×) and the combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography using hexanes/EtOAc (6:1) to afford compound **27** as a colorless oil (420 mg, 1.17 mmol, 94%). R_f = 0.35 on silica gel (hexanes/EtOAc; 6:1). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 1.65 (m, 2H), 2.24 (m, 2H), 2.36 (s, 3H), 3.78 (dd, J = 9.0 Hz, 7.1 Hz, 1H). 3.92 (dd, J = 9.0 Hz, 3.2 Hz, 1H), 3.99 (m, 1H), 5.00 (dd, J = 10.3 Hz, 1.0 Hz, 1H), 5.08 (dd, *J* = 17.1 Hz, 1.6 Hz, 1H), 5.85 (m, 1H), 6.81 (dd, *J* = 8.6 Hz, 2.9 Hz, 1H), 7.11 (d, *J* = 8.6 Hz, 1H), 7.37 (d, *J* = 2.9 Hz, 1H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 27.1, 29.9, 32.3, 69.7, 72.6, 101.0, 114.9, 115.4, 124.9, 130.0, 134.1, 138.2, 157.0. **HRMS** calcd for $C_{13}H_{17}IO_2$ [M^+] 332.0273, found 332.0277. **IR**: $\tilde{\nu}$ = 3384, 2920, 1596, 1487, 1233 cm^{-1}. **HPLC** (Chiracel-OD, 30°C): wavelength = 230 nm, flow = 1.0 mL/min, hexanes/*i*-propanol = 90:10, t_R = 8.07 min (–), 10.84 min (+), *ee* = 84%. $[\alpha]_D^{20}$ = –13.2° (*c* = 1.47 in $CHCl_3$).



27 **16**

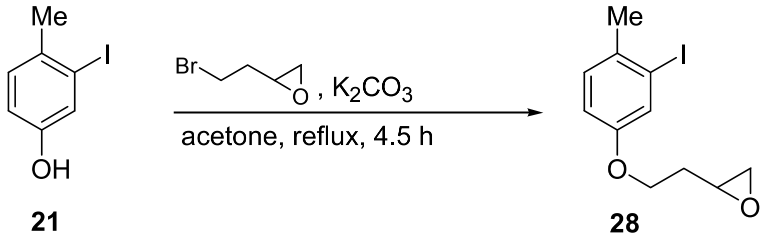
6-Hydroxy-7-(3-iodo-4-methyl-phenoxy)-hept-2-enoic acid *tert*-butyl ester (16). To a solution of **27** (290 mg, 873 μmol, 1.0 equiv) and *tert*-butyl acrylate (1.68 g, 13.0 mmol, 15 equiv) in CH_2Cl_2 (7 mL), was added Grubbs 2nd generation catalyst (74 mg, 87 μmol, 10 mol%). Stirring was continued at ambient temperature for 20 h. The volatiles were then removed under reduced pressure and the crude product was purified by flash chromatography using hexanes/EtOAc (3:1) to afford **16** as a grey oil (310 mg, 717 μmol, 82%). R_f = 0.34 on silica gel (hexanes/EtOAc; 6:1). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.48 (s 9H), 1.71 (m, 2H), 2.36 (s, 3H), 2.42 (m, 2H), 3.79 (dd, *J* = 9.1 Hz, 7.2 Hz, 1H), 3.91 (dd, *J* = 9.1 Hz, 3.2 Hz, 1H), 3.98 (m, 1H), 5.80 (m, 1H), 6.81 (dd, *J* = 8.6 Hz, 2.9 Hz, 1H), 6.88 (ddd, *J* = 15.5 Hz, 6.7 Hz, 6.7 Hz, 1H), 7.11 (d, *J* = 8.6 Hz, 1H), 7.37 (d, *J* = 2.9 Hz, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 27.1, 28.1, 28.3, 31.5, 69.4, 72.5, 80.4, 101.0, 114.9, 123.8, 124.9, 130.0, 134.1, 147.0, 156.8, 166.2. **HRMS** calcd for $C_{18}H_{25}IO_4$ [M^+] 432.0798, found 432.0801. **IR**: $\tilde{\nu}$ = 3443, 2929, 1712, 1596, 1486, 1234 cm^{-1}. **HPLC** (Chiracel-OD, 30°C): wavelength = 230 nm, flow = 1.0 mL/min, hexanes/*i*-propanol = 90:10, t_R = 13.09 min (–), 17.45 min (+), *ee* = 84%. $[\alpha]_D^{20}$ = –7.3° (*c* = 0.66 in $CHCl_3$).



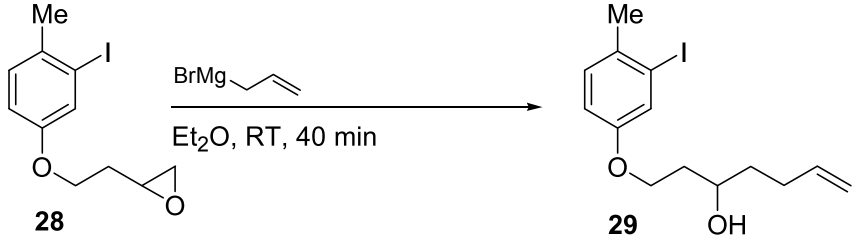
16 **7**

6-Iodo-7-(3-iodo-4-methyl-phenoxy)-hept-2-enoic acid *tert*-butyl ester (7). To a 0 °C solution of PPh_3 (73 mg, 278 μmol, 1.5 equiv) and imidazole (19 mg, 278 μmol, 1.5 equiv) in Et_2O/CH_3CN (1.5 mL, 2:1) was added I_2 (70 mg, 278 μmol, 1.5 equiv). Stirring was continued for 15 min. A solution of **16** (100 mg, 231 μmol, 1.0 equiv) in Et_2O (1 mL) was then added and the mixture was allowed to reach ambient temperature over 4

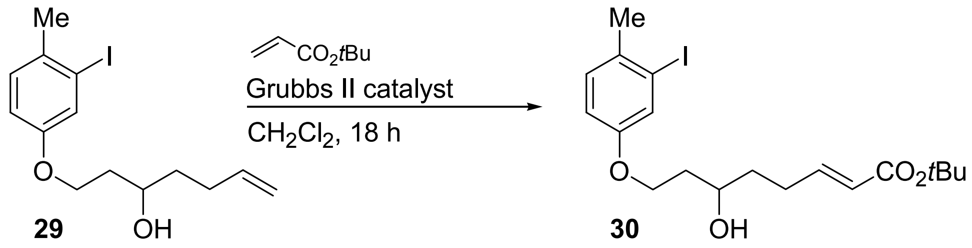
h. The reaction was quenched with water and the aqueous layer was extracted with diethyl ether (3×). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated and the crude product was purified by flash chromatography using hexanes/EtOAc (3:1) to afford **7** as a colourless oil (80 mg, 113 μmol, 80%). R_f = 0.55 on silica gel (hexanes/EtOAc; 3:1). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.48 (s 9H), 2.04 (m, 2H), 2.32 (m, 1H), 2.36 (s, 3H), 2.48 (m, 1H), 4.10 (m, 1H), 4.24 (m, 2H), 5.82 (m, 1H), 6.82 (m, 2H), 7.11 (d, J = 8.6 Hz, 1H), 7.37 (d, J = 2.9 Hz, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 27.1, 28.3, 30.1, 31.8, 34.7, 73.6, 80.5, 101.0, 115.0, 124.4, 125.1, 130.0, 134.4, 145.5, 156.3, 166.0. **HRMS** calcd for $C_{18}H_{24}I_2O_3$ [M^+] 541.9815, found 541.9810. **IR**: $\tilde{\nu}$ = 2974, 1710, 1596, 1483, 1155 cm^{-1}. **HPLC** (Chiracel-OD, 30°C): wavelength = 230 nm, flow = 1.0 mL/min, hexanes/*i*-propanol = 98:02, t_R = 7.27 min (+), 8.22 min (–), *ee* = 82%. $[\alpha]_D^{20}$ = –14.8° (c = 0.50 in $CHCl_3$).



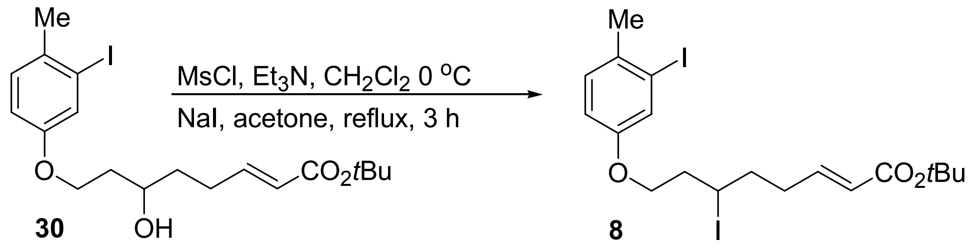
2-[2-(3-Iodo-4-methyl-phenoxy)-ethyl]-oxirane (28). To a solution of **21** (1.0 g, 4.27 mmol, 1.0 equiv) and 2-(2-bromo-ethyl)-oxirane (1.61 g, 10.7 mmol, 2.5 equiv) in acetone (15 mL) was added K_2CO_3 (1.48 g, 10.7 mmol, 2.5 equiv). The suspension was heated to reflux for 4 h. The mixture was diluted with water and the aqueous layer was extracted with diethyl ether (3×). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography using hexanes/EtOAc (6:1) to afford **28** as a colourless oil (860 mg, 2.81 mmol, 66%). R_f = 0.34 on silica gel (hexanes/EtOAc; 3:1). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 1.92, (m, 1H), 2.09 (m, 1H), 2.37 (s, 3H), 2.59 (dd, J = 5.0 Hz, 2.7 Hz, 1H), 2.84 (dd, J = 5.0 Hz, 4.1 Hz, 1H), 3.15 (m, 1H), 6.81 (dd, J = 8.4 Hz, 2.6 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.38 (d, J = 2.6 Hz, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 27.1, 32.6, 47.4, 49.9, 65.1, 101.0, 114.8, 124.9, 129.9, 133.8, 157.1. **HRMS** calcd for $C_{11}H_{13}IO_2$ [M^+] 303.9960, found 303.9955. **IR**: $\tilde{\nu}$ = 2920, 1595, 1483, 1232 cm^{-1}.



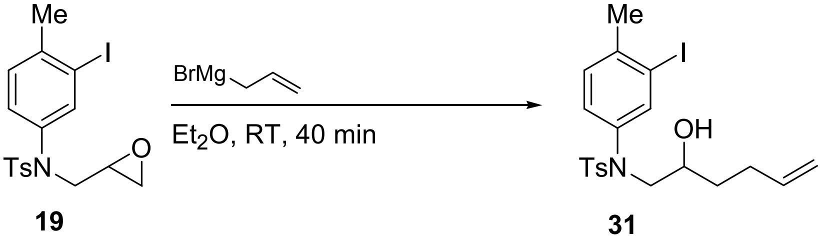
1-(3-Iodo-4-methyl-phenoxy)-hept-6-en-3-ol (29). To a 0 °C solution of **28** (400 mg, 1.32 mmol, 1 equiv) in Et_2O (4.0 mL) was added allyl magnesium bromide (1 M solution in Et_2O, 3.95 mL, 3.0 equiv) dropwise. The resulting suspension was stirred at ambient temperature for 30 min and saturated aqueous NH_4Cl was added slowly at 0°C. The aqueous layer was extracted with diethyl ether (3×) and the combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography using hexanes/EtOAc (6:1) to afford **29** as a colorless oil (333 mg, 962 μmol, 73%). R_f = 0.23 on silica gel (hexanes/EtOAc; 6:1). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 1.61 (m, 1H), 1.90 (m, 2H), 2.10 (d, *J* = 2.5 Hz, 1H), 2.19 (m, 2H), 2.35 (s, 3H), 3.89 (m 1H), 4.08 (m, 2H), 4.98 (m, 1H), 5.06 (m, 1H), 5.85 (m, 1H), 6.80 (dd, *J* = 8.4 Hz, 2.6 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 7.36 (d, *J* = 2.6 Hz, 1H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 27.1, 30.2, 36.6, 36.8, 66.2, 69.5, 101.0, 114,9, 115.2, 124.9, 129.9, 133.8, 138.5, 157.1. **HRMS** calcd for $C_{14}H_{19}IO_2$ [M^+] 346.0430, found 346.0433. **IR**: $\tilde{\nu}$ = 3373, 2920, 1596, 1486, 1234 cm^{-1}.



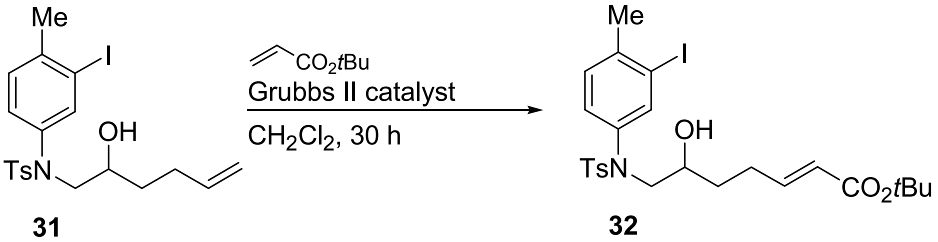
6-Hydroxy-8-(3-iodo-4-methyl-phenoxy)-oct-2-enoic acid *tert*-butyl ester (30). To a solution of **29** (300 mg, 867 μmol, 1.0 equiv) and *tert*-butyl acrylate (1.67 g, 13.0 mmol, 15 equiv) in CH_2Cl_2 (8 mL) was added Grubbs 2nd generation catalyst (37 mg, 43 μmol, 5 mol%). Stirring was continued at ambient temperature for 18 h. The volatiles were removed under reduced pressure and the crude product was purified by flash chromatography using hexanes/EtOAc (3:1) to afford **30** as a grey oil (210 mg, 471 μmol, 55%). R_f = 0.31 on silica gel (hexanes/EtOAc; 3:1). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.48 (s, 9H), 1.65 (m, 3H), 1.91 (m, 2H), 2.10 (d, *J* = 4.0 Hz, 1H), 2.31 (m, 2H), 2.36 (s, 3H), 3.90 (m, 1H), 4.06 (m, 1H), 4.13 (m, 1H), 5.78 (ddd, *J* = 15.6 Hz, 1.6 Hz, 1.6 Hz), 6.80 (dd, *J* = 8.4 Hz, 2.6 Hz, 1H), 6.88 (ddd, *J* = 15.6 Hz, 7.0 Hz, 7.0 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 7.36 (d, *J* = 2.6 Hz, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 27.1, 28.4, 36.0, 36.5, 66.3, 69.4, 80.4, 101.0, 114.9, 123.6, 124.8, 130.0, 133.9, 147.4, 157.0, 166.2. **HRMS** calcd for $C_{19}H_{27}IO_4$ [M^+] 446.0954, found 446.0955. **IR**: $\tilde{\nu}$ = 3443, 2929, 1712, 1596, 1486, 1234 cm^{-1}.



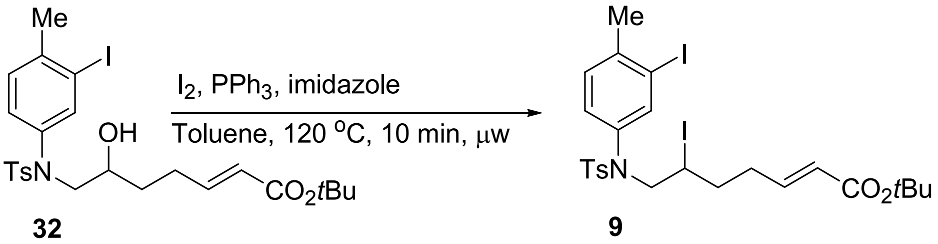
6-Iodo-8-(3-iodo-4-methyl-phenoxy)-oct-2-enoic acid *tert*-butyl ester (8). To a 0 °C solution of **30** (210 mg, 471 μmol, 1.0 equiv) and NEt_3 (0.08 mL, 565 μmol, 1.2 equiv) in CH_2Cl_2 (2 mL), was added MsCl (0.04 mL, 565 μmol, 1.2 equiv) dropwise. Stirring was continued at ambient temperature for 2 h. The solvent was removed under reduced pressure and the residue was dissolved in acetone (4 mL). An excess of NaI (0.6 g) was then added and the suspension was heated to reflux for 3 h. The reaction was quenched with water and the aqueous layer was extracted with diethyl ether (3×). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography using hexanes/EtOAc (3:1) to afford **8** as a colorless oil (230 mg, 414 μmol, 88%). R_f = 0.55 on silica gel (hexanes/EtOAc; 3:1). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 1.49 (s, 9H), 1.84–2.59 (m, 6H), 2.36 (s, 3H), 4.07 (m, 2H), 4.28 (m, 1H), 5.82 (ddd, *J* = 15.6 Hz, 1.6 Hz, 1.6 Hz, 1H), 6.81 (m, 1H), 6.82 (dd, *J* = 8.4 Hz, 2.6 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 7.36 (d, *J* = 2.6 Hz, 1H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 27.1, 28.4, 32.2, 33.4, 39.0, 40.0, 67.8, 80.5, 101.0, 114.9, 124.3, 124.8, 130.0, 133.9, 145.6, 157.0, 166.0. **HRMS** calcd for $C_{19}H_{26}I_2O_3$ [M$^+$] 555.9971, found 555.9972. **IR**: $\tilde{\nu}$ = 2929, 1710, 1596, 1486, 1234 cm^{-1}.



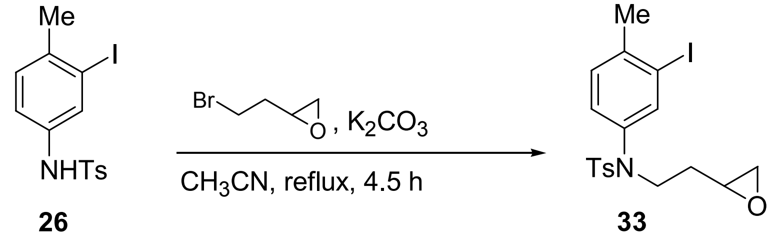
***N*-(2-Hydroxy-hex-5-enyl)-*N*-(3-iodo-4-methyl-phenyl)-4-methyl-benzene-sulfonamide (31).** To a 0 °C solution of **19** (200 mg, 451 μmol, 1 equiv) in Et_2O (3 mL) was added allyl magnesium bromide (1 M solution in Et_2O, 1.35 mL, 1.35 mmol, 3 equiv) dropwise. The resulting suspension was stirred at ambient temperature for 40 min and saturated aqueous NH_4Cl was added slowly at 0 °C. The aqueous layer was extracted with diethyl ether (3×) and the combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography using hexanes/EtOAc (2:1) to afford compound **31** as a colorless oil (200 mg, 412 μmol, 91%). R_f = 0.26 on silica gel (hexanes/EtOAc; 3:1). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.49 – 1.55 (m, 2H), 2.02 – 2.23 (m, 2H), 2.39 (bs, 1H), 2.41 (s, 3H), 2.49 (s, 3H), 3.38 (dd, *J* = 3.7 Hz, 13.8 Hz, 1H), 3.53 (dd, *J* = 8.1 Hz, 13.8 Hz, 1H), 3.64 (bs, 1H), 4.91 – 4.95 (m, 1H), 4.97 (dq, *J* = 1.6 Hz, 17.1 Hz, 1H), 5.76 (ddt, *J* = 6.7 Hz, 10.3 Hz, 17.1 Hz, 1H), 6.99 (dd, *J* = 2.2 Hz, 8.1 Hz, 1H), 7.18 (d, *J* = 8.1 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.42 (d, *J* = 2.2 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 21.8, 27.8, 29.8, 33.6, 57.5, 69.1, 100.5, 115.2, 128.0, 128.8, 129.7, 129.9, 134.8, 138.2, 138.6, 138.8, 141.9, 144.2. **HRMS** calcd for $C_{20}H_{24}INO_3S$ [M$^+$] 485.0522, found 485.0514. **IR**: $\tilde{\nu}$ = 3515, 2920, 2355, 1479, 1347, 1162, 1089 cm^{-1}.



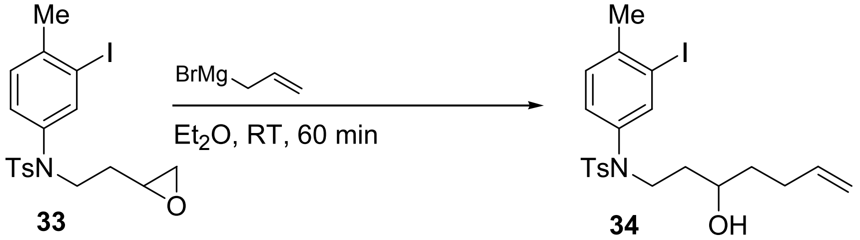
6-Hydroxy-7-[(3-iodo-4-methyl-phenyl)-(toluene-4-sulfonyl)-amino]-hept-2-enoic acid *tert*-butyl ester (32). To a solution of **31** (170 mg, 350 μmol, 1 equiv) and *tert*-butyl acrylate (673 mg, 5.25 mmol, 15 equiv) in CH_2Cl_2 (4 mL) was added Grubbs 2nd generation catalyst (30 mg, 35 μmol, 10 mol%). Stirring was continued at ambient temperature for 30 h. The volatiles were removed under reduced pressure and the crude product was purified by flash chromatography using hexanes/EtOAc (3:1) to afford **32** (150 mg, 256 μmol, 73%) as a white foam, mp = 52 – 54 ºC. R_f = 0.18 on silica gel (hexanes/EtOAc; 3:1). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.47 (s, 9H), 1.55 (q, *J* = 7.2 Hz, 2H), 2.14 – 2.24 (m, 1H), 2.30 – 2.37 (m, 1H), 2.42 (s, 3H), 2.45 (s, 3H), 3.36 (dd, *J* = 3.2 Hz, 13.78 Hz, 1H), 3.54 (dd, *J* = 8.1 Hz, 13.8 Hz, 1H), 3.64 (bs, 1H), 5.70 (d, *J* = 15.5 Hz, 1H), 6.79 (dt, *J* = 7.4 Hz, 15.5 Hz, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 7.19 (d, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.41 (s, 1H), 7.47 (d, *J* = 8.1 Hz, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 21.8, 27.9, 28.2, 28.3, 32.9, 57.6, 69.0, 80.3, 100.6, 123.7, 128.0, 128.8, 129.8, 130.0, 134.7, 138.6, 138.8, 142.1, 144.3, 147.0, 166.1. **HRMS** calcd for $C_{25}H_{32}INNaO_5S$ (ESI) 608.0938, found 608.0948. **IR**: $\tilde{\nu}$ = 3512, 2977, 2929, 1712, 1698, 1694, 1651, 1479, 1348, 1162, 1090, 911, 815, 732 cm^{-1}.



6-Iodo-7-[(3-iodo-4-methyl-phenyl)-(toluene-4-sulfonyl)-amino]-hept-2-enoic acid *tert*-butyl ester (9). A suspension of **32** (188 mg, 320 μmol, 1.0 equiv), iodine (122 mg, 480 μmol, 1.5 equiv), triphenylphosphine (126 mg, 480 μmol, 1.5 equiv) and imidazole (33 mg, 480 μmol, 1.5 equiv) in toluene (4 mL) was heated to 120 °C for 10 min under microwave irradiation. The reaction was quenched with water and the aqueous layer was extracted with diethyl ether (3×) and the combined organic layers were dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using hexanes/EtOAc (9:1) to afford **9** as a white foam (166 mg, 239 μmol, 75%). R_f = 0.59 on silica gel (hexanes/EtOAc; 3:1). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.49 (s, 9H), 1.81 – 1.91 (m, 1H), 2.03 – 2.12 (m, 1H), 2.18 – 2.27 (m, 1H), 2.37 - 2.50 (m, 1H), 2.42 (s, 3H), 2.45 (s, 3H), 3.79 – 3.96 (m, 3H), 5.74 (d, *J* = 15.7 Hz, 1H), 6.77 (dt, *J* = 6.8 Hz, 15.7 Hz, 1H), 6.99 (dd, *J* = 2.2 Hz, 8.2 Hz, 1H), 7.19 (d, *J* = 8.2 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 2.2 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 21.8, 27.9, 28.4, 31.1, 31.7, 34.6, 58.8, 80.4, 100.6, 124.4, 128.0, 129.0, 129.8, 130.1, 134.6, 137.7, 138.6, 142.3, 144.3, 145.4, 165.9. **HRMS** calcd for $C_{25}H_{31}I_2NO_3S$ [M^+] 695.0063, found 695.0081. **IR**: $\tilde{\nu}$ = 2926, 1710, 1653, 1481, 1352, 1163, cm^{-1}.

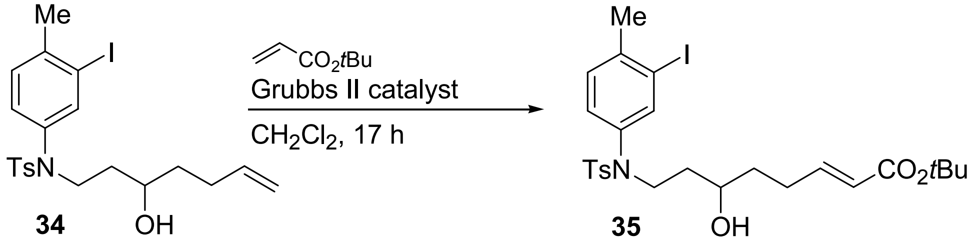


***N*-(3-Iodo-4-methyl-phenyl)-4-methyl-*N*-(2-oxiranyl-ethyl)-benzenesulfonamide (33).** To a solution of **26** (600 mg, 1.55 mmol, 1.0 equiv) and 2-(2-bromo-ethyl)-oxirane (702 mg, 4.65 mmol, 3 equiv) in acetonitrile (6 mL) was added K_2CO_3 (642 mg, 4.65 mmol, 3 equiv). The suspension was heated at reflux for 3.5 h. The mixture was diluted with water and the aqueous layer was extracted with diethyl ether (3×). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography using hexanes/EtOAc (3:1) affording **33** as a colorless oil (700 mg, 1.53 mmol, 98%). R_f = 0.24 on silica gel (hexanes/EtOAc; 3:1). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 1.60 (m, 1H), 1.75 (m, 1H), 2.42 (s, 3H), 2.43 (m, 1H), 2.44 (s, 3H), 2.74 (dd, *J* = 4.6 Hz, 4.6 Hz, 1H), 2.94 (m, 1H), 3.63 (m, 2H), 6.97 (dd, *J* = 8.0 Hz, 2.4 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 2.2 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 21.8, 27.9, 31.8, 47.2, 48.1, 50.0, 100.5, 128.0, 128.7, 129.7, 129.9, 134.8, 137.7, 138.8, 141.8, 144.0. **HRMS** calcd for $C_{18}H_{20}INO_3S$ [M^+] 457.0209, found 457.0203. **IR**: $\tilde{\nu}$ = 2921, 1591, 1481, 1348, 1166 cm^{-1}.

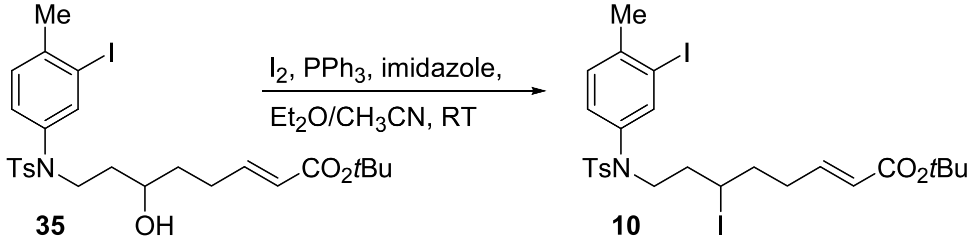


***N*-Tosyl-1-(3-Iodo-4-methyl-phenylamino)-hept-6-en-3-ol (34).** To a 0 °C solution of **33** (700 mg, 1.53 mmol, 1 equiv) in Et_2O (10 mL) was added allyl magnesium bromide (1 M solution in Et_2O, 4.59 mL, 3.0 equiv) dropwise. The resulting suspension was stirred at ambient temperature for 60 min and saturated aqueous NH_4Cl was added at 0 °C. The aqueous layer was extracted with diethyl ether (3×) and the combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography using hexanes/EtOAc (3:1) to afford **34** as a colourless oil (620 mg, 1.24 mmol, 81%). R_f = 0.24 on silica gel (hexanes/EtOAc; 3:1). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 1.50 (m, 4H), 2.15 (m, 2H), 2.37 (d *J* = 5.2 Hz, 1H), 2.43 (s, 3H), 2.44 (s, 3H), 3.38 (m, 1H), 3.85 (m, 2H), 5.00 (m, 2H), 5.82 (m, 1H), 6.97 (dd, *J* = 8.0 Hz, 2.4 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 2.2 Hz, 1H), 7.50

(d, J = 8.2 Hz, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 21.8, 27.9, 30.2, 35.6, 36.4, 47.8, 67.7. 100.5, 115.1, 127.9, 128.9, 129.8, 129.9, 135.1, 137.7, 138.5, 138.9, 141.8, 144.0. **HRMS** calcd for $C_{21}H_{26}INO_3S$ [M^+] 499.0678, found 499.0692. **IR**: $\tilde{\nu}$ = 3533, 2921, 1592, 1481, 1345 cm^{-1}.



***N*-Tosyl-6-hydroxy-8-(3-iodo-4-methyl-phenylamino)-oct-2-enoic acid *tert*-butyl ester (35).** To a solution of **34** (600 mg, 1.20 mmol, 1.0 equiv) and *tert*-butyl acrylate (2.31 g, 18.0 mmol, 15 equiv) in CH_2Cl_2 (9 mL) was added Grubbs 2nd generation catalyst (102 mg, 87 µmol, 10 mol%). Stirring was continued at ambient temperature for 17 h. The volatiles were removed under reduced pressure and the crude product was purified by flash chromatography using hexanes/EtOAc (3:1) to afford **35** as a brown foam (580 mg, 967 µmol, 81%). R_f = 0.15 on silica gel (hexanes/EtOAc; 3:1). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 1.49 (s, 9H), 1.54 (m, 4H), 2.24 (m, 1H), 2.36 (m, 1H), 2.43 (s, 3H), 2.45 (s, 3H), 3.36 (m, 1H), 3.86 (m, 2H), 5.75 (m, 1H), 6.86 (ddd, J = 15.6 Hz, 6.8 Hz, 6.8 Hz, 1H), 6.99 (dd, J = 8.0 Hz, 2.4 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 2.2 Hz, 1H), 7.50 (d, J = 8.2 Hz, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 21.8, 27.9, 28.4, 28.6, 35.6, 47.8, 67.5, 77.4, 80.3, 100.5, 123.5, 127.9, 129.0, 129.8, 130.0, 135.0, 137.7, 138.7, 141.9, 144.1, 147.5, 166.2. **HRMS** calcd for $C_{26}H_{34}INO_5S$ [M^+] 599.1202, found 599.1202. **IR**: $\tilde{\nu}$ = 3446, 2925, 1700, 1346, 1161 cm^{-1}.

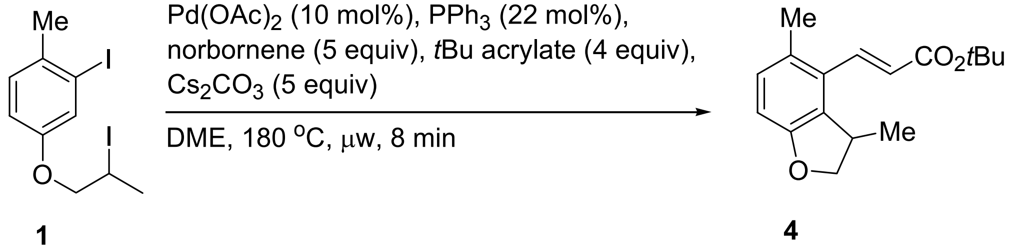


***N*-Tosyl-6-iodo-8-(3-iodo-4-methyl-phenylamino)-oct-2-enoic acid *tert*-butyl ester (10).** To a 0 °C solution of PPh_3 (374 mg, 1.43 mmol, 1.5 equiv) and imidazole (97 mg, 1.43 mmol, 1.5 equiv) in Et_2O/CH_3CN (9.6 mL, 2:1) was added I_2 (362 mg, 1.43 mmol, 1.5 equiv). Stirring was continued for 15 min. A solution of **35** (570 mg, 950 µmol, 1.0 equiv) in Et_2O (6 mL) was added and the mixture was allowed to reach ambient temperature over 4 h. The reaction was quenched with water and the aqueous layer was extracted with diethyl ether (3×). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography using hexanes/EtOAc (3:1) to afford **10** as a colorless oil (640 mg, 902 µmol, 95%). R_f = 0.49 on silica gel (hexanes/EtOAc; 3:1). **^{1}H-NMR** (300 MHz,

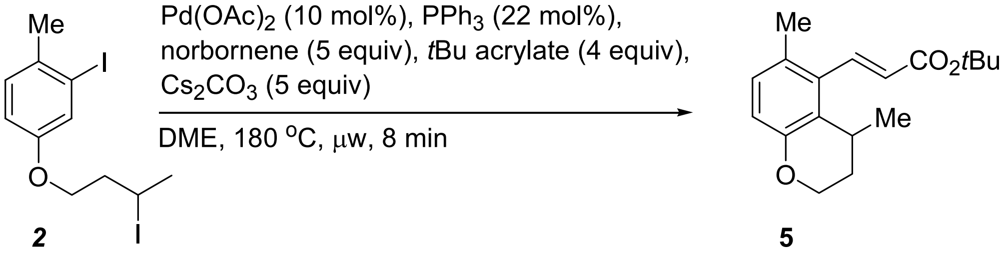
$CDCl_3$): δ 1.48 (m, 9H), 1.78 (m, 1H), 1.95 (m, 3H), 2.27 (m, 1H), 2.37 (m, 1H), 2.42 (s 3H), 2.44 (s, 3H), 3.61 (m, 2H), 4.02 (m, 1H), 5.77 (m, 1H), 6.77 (ddd, *J* = 15.6 Hz, 6.8 Hz, 6.8 Hz, 1H), 6.96 (dd, *J* = 8.0 Hz, 2.4 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 2.2 Hz, 1H), 7.47 (d, *J* = 8.2 Hz, 2H). ^{13}**C-NMR** (75 MHz, $CDCl_3$): δ 21.8, 27.9, 28.3, 32.0, 32.6, 38.7, 39.5, 50.9, 80.5, 100.5, 124.4, 128.0, 128.7, 129.7, 129.9, 134.7, 137.9, 138.6, 141.8, 144.0, 145.4, 165.9. **HRMS** calcd for $C_{26}H_{33}I_2NO_4S$ [M^+] 709.0220, found 709.0220. **IR**: $\tilde{\nu}$ = 2975, 1709, 1592, 1480, 1161 cm^{-1}.

Annulation Reactions

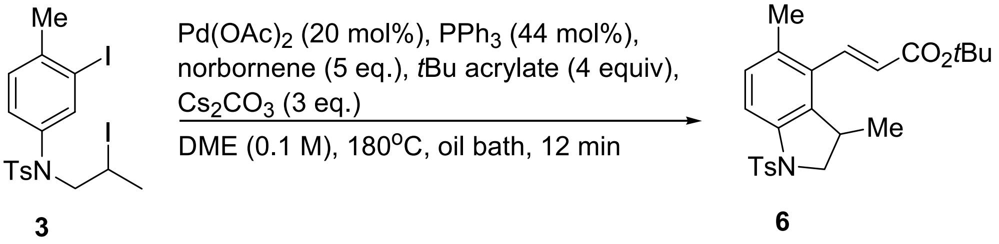
General Procedure for the Annulation Reaction. To a microwave reaction vessel were added the secondary alkyl iodide (0.200 mmol, 1 equiv), Cs_2CO_3 (1.00 mmol, 5 equiv), norbornene (1.00 – 1.40 mmol, 5 - 7 equiv), $Pd(OAc)_2$ (10 – 20 mol%), triphenylphosphine (22 - 44 mol%) and if required, *tert*-butyl acrylate (0.800 mmol, 4 equiv). The vessel was sealed and flushed with N_2. DME (2 - 5 mL) was then added to the reaction and the reaction vessel was subjected to microwave (μw) irradiation or conventional heating in an oil bath at 150 - 180 °C for 5 - 11 min. The mixture was then diluted with ether (4 mL) and quenched with water (4 mL). The aqueous layer was extracted with ether (3×) and the combined organic layers were dried with anhydrous Na_2SO_4 and filtered. Removal of the solvent gave a crude product that was purified by flash chromatography.



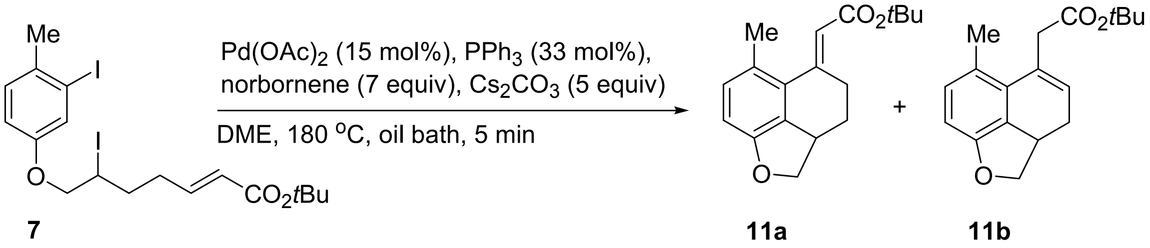
3-(3,5-Dimethyl-2,3-dihydro-benzofuran-4-yl)-acrylic acid *tert*-butyl ester (4). Following the general procedure for the annulation reaction using **1**, 10 mol% $Pd(OAc)_2$, 22 mol% PPh_3, 5 equiv norbornene, 4 equiv *tert*-butyl acrylate and 5 equiv Cs_2CO_3 in DME (0.1 M), for 8 min at 180 °C, in the microwave. Purification by flash chromatography using hexanes/EtOAc (20:1) afforded **4** (44 mg, 159 μmol, 75%) as a colorless oil. R_f = 0.56 on silica gel (hexanes/EtOAc; 20:1). ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ 1.24 (d, *J* = 6.5 Hz, 3H), 1.54 (s, 9H), 2.34 (s, 3H), 3.68 (m, 1H), 4.21 (dd, *J* = 8.7 Hz, 2.3 Hz, 1H), 4.56 (dd, *J* = 8.7 Hz, 8.7 Hz, 1H), 6.18 (d, *J* = 16.3 Hz, 1H), 6.69 (d, *J* = 8.1 Hz, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 7.75 (d, *J* = 16.3 Hz, 1H). ^{13}**C-NMR** (100 MHz, $CDCl_3$): δ 19.9, 20.4, 28.5, 36.7, 78.7, 80.9, 110.4, 124.3, 129.6, 130.7, 130.9, 131.9, 140.8, 158.1, 166.5. **HRMS** calcd for $C_{17}H_{22}O_3$ [M^+] 274.1569, found 274.1575. **IR**: $\tilde{\nu}$ = 2974, 1709, 1634, 1586, 1455, 1307, 1249, 1152, 981, 811 cm^{-1}.



3-(4,6-Dimethyl-chroman-5-yl)-acrylic acid *tert*-butyl ester (5). Following the general procedure for the annulation reaction using **2**, 10 mol% $Pd(OAc)_2$, 22 mol% PPh_3, 5 equiv norbornene, 4 equiv *tert*-butyl acrylate and 5 equiv Cs_2CO_3 in DME (0.1 M), for 8 min at 180 ºC, in the microwave. Purification by flash chromatography using hexanes/Et_2O (98:2) afforded **5** (34 mg, 117 μmol, 49%) as a colorless oil. $R_f = 0.11$ on silica gel (hexanes/Et_2O; 98:2). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.22 (d, J = 7.0 Hz, 3H), 1.55 (s, 9H), 1.66 – 1.73 (m, 1H), 2.10 (tt, J = 5.0 Hz, 13.2 Hz, 1H), 2.26 (s, 3H), 3.10 (dt, J = 6.0 Hz, 13.4 Hz, 1H), 4.15 (dt, J = 2.1 Hz, 12.4 Hz, 1H), 4.20 – 4.24 (m, 1H), 5.98 (dd, J = 0.7, 16.3 Hz, 1H), 6.70 (d, J = 8.3 Hz, 1H), 6.96 (d, J = 8.3 Hz, 1H), 7.76 (d, J = 16.3 Hz, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 20.9, 21.9, 26.0, 28.5, 29.2, 61.4, 80.9, 117.2, 126.2, 126.5, 127.9, 129.7, 134.6, 142.1, 152.2, 166.2. **HRMS** calcd for $C_{18}H_{24}O_3$ [M^+] 288.1725, found 288.1725. **IR**: $\tilde{\nu}$ = 2975, 1710, 1591, 1482, 1151 cm^{-1}.

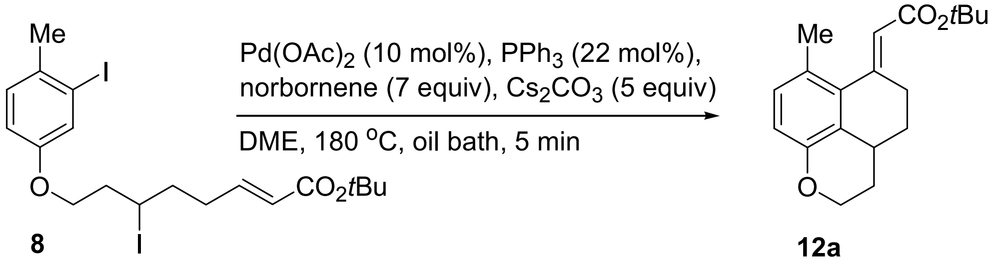


3-[3,5-Dimethyl-1-(toluene-4-sulfonyl)-2,3-dihydro-1*H*-indol-4-yl]-acrylic acid *tert*-butyl ester (6). Following the general procedure for the annulation reaction using **3** (80% ee), 20 mol% $Pd(OAc)_2$, 44 mol% PPh_3, 5 equiv norbornene, 4 equiv *tert*-butyl acrylate and 3 equiv Cs_2CO_3 in DME (0.1 M), for 12 min at 180 ºC, in an oil bath. Purification by flash chromatography using 5 – 20% Et_2O/hexanes afforded **6** (34 mg, 78 μmol, 54%) as a colorless oil. $R_f = 0.50$ on silica gel (20% EtOAc/hexanes). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 0.93 (d, J = 6.9 Hz, 3H), 1.51 (s, 9H), 2.32 (s, 3H), 2.37 (s, 3H), 3.34-3.42 (m, 1H), 3.68 (dd, J = 2.3 Hz, 10.4 Hz, 1H), 3.83 (dd, J = 8.5 Hz, 10.4 Hz, 1H), 6.05 (d, J = 16.4 Hz, 1H), 7.06 (d, J = 8.2 Hz, 1H), 7.23 (d, J = 8.2 Hz, 2H), 7.55 (d, J = 8.2 Hz, 1H), 7.59 (d, J = 16.4 Hz, 1H), 7.68 (d, J = 8.2 Hz, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 20.6, 20.7, 21.7, 28.4, 34.5, 57.5, 81.1, 115.2, 125.2, 127.6, 129.8, 130.7, 131.2, 132.7, 134.0, 136.4, 139.7, 140.2, 144.3, 166.2. **HRMS** calcd for $C_{24}H_{29}NO_4S$ [M^+] 427.181731 found 427.182464. **IR**: $\tilde{\nu}$ = 2974, 1708, 1456, 1356, 1305, 1250, 1167, 1152, 1092, 816, 668 cm^{-1}. **HPLC** (Chiracel-OD-H, 30°C): wavelength = 230 nm, flow= 1.0 mL/min, hexanes/*i*-propanol = 99:1, t_R = 25.61 min (-), 27.64 min (+), *ee* = 63%. $[\alpha]_D^{27}$ = -21.3 ° (c = 2.14 in $CHCl_3$) at 55% ee.



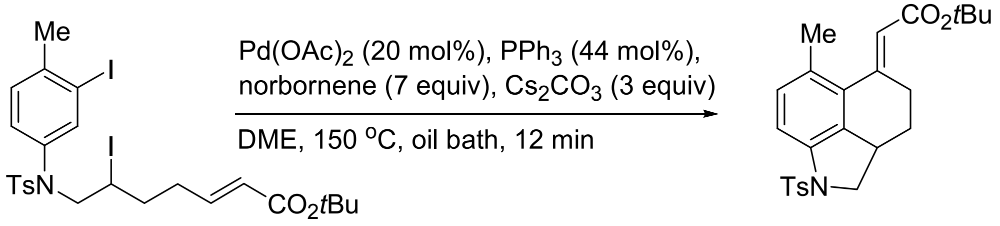
(6-Methyl-2,2*a*,3,4-tetrahydro-naphtho[1,8-*bc*]furan-5-ylidene)-acetic acid *tert*-butyl ester (11a) and (6-Methyl-2*a*,3-dihydro-2*H*-naphtho[1,8-*bc*]furan-5-yl)-acetic acid *tert*-butyl ester (11b). Following the general procedure for the annulation reaction using **7**, 15 mol% Pd(OAc)$_2$, 33 mol% PPh$_3$, 7 equiv norbornene and 5 equiv Cs$_2$CO$_3$ in DME (0.03 M), for 5 min at 180 ºC in an oil bath. Purification by flash chromatography using hexanes/EtOAc (20:1) afforded **11a** (34 mg, 118 µmol, 65%) as a yellow solid (mp = 76 - 78°C), and **11b** as a yellow oil (7 mg, 24 µmol, 13%), respectively. R$_f$ = 0.29 (**11a**) and 0.21 (**11b**) on silica gel (hexanes/EtOAc; 20:1). **Data 11a:** ^{1}**H-NMR** (300 MHz, CDCl$_3$): δ 1.34 (m, 1H), 1.52 (s, 9H), 2.21 (m, 1 H), 2.47 (s, 3H), 3.01 (m, 1H), 3.31 (m, 1H), 3.43 (m, 1H), 4.06 (dd, *J* = 10.2 Hz, 9.0 Hz, 1H), 4.84 (dd *J* = 9.0 Hz, 9.0 Hz, 1H), 6.19 (m, 1H), 6.67 (d, *J* = 8.1 Hz, 1H), 6.99 (d, *J* = 8.1 Hz, 1H). ^{13}**C-NMR** (75 MHz, CDCl$_3$): δ 21.9, 27.3, 28.5, 29.1, 39.0, 78.8, 80.1, 109.4, 119.6, 127.4, 131.5, 131.8, 133.0, 150.2, 156.5, 166.8. **HRMS** calcd for $C_{18}H_{22}O_3$ [M$^+$] 286.1569, found 286.1564. **IR**: $\tilde{\nu}$ = 2976, 1703, 1585, 1482, 1145 cm^{-1}. **HPLC** (Chiracel-OD, 5°C): wavelength = 230 nm, flow = 1.0 mL/min, hexanes/*i*-propanol = 99:01, t_R = 7.23 min (*R*), 7.56 min (*S*), *ee* = 80%. $[\alpha]_D^{27}$ = –101.4° (*c* = 1.01 in CHCl$_3$).

Data for 11b: ^{1}**H-NMR** (300 MHz, CDCl$_3$): δ 1.40 (s, 9H), 2.09 (m, 1H), 2.36 (s, 3H), 2.46 (m, 1H), 3.35 (d, *J* = 17.1 Hz, 1H), 3.57 (m, 1H), 3.70 (d, *J* = 17.1 Hz, 1H), 4.11 (dd, *J* = 11.3 Hz, 8.7 Hz, 1H), 4.81 (dd, *J* = 8.7 Hz, 8.7 Hz, 1H), 5.87 (m, 1H), 6.57 (d, *J* = 8.2 Hz 1H), 6.84 (d, *J* = 8.2 Hz, 1H). ^{13}**C-NMR** (75 MHz, CDCl$_3$): δ 21.1, 28.2, 37.6, 42.4, 79.4, 81.0, 94.6, 108.6, 124.7, 129.2, 129.9, 130.0, 131.3, 132.9, 133.1, 156.0, 171.4. **HRMS** calcd for $C_{18}H_{22}O_3$ [M$^+$] 286.1569, found 286.1562. **IR**: $\tilde{\nu}$ = 2975, 1729, 1459, 11248, 1150 cm^{-1}.



(7-Methyl-3,3*a*,4,5-tetrahydro-2*H*-benzo[*de*]chromen-6-ylidene)-acetic acid *tert*-butyl ester (12a). Following the general procedure for the annulation reaction using **8**, 15 mol% Pd(OAc)$_2$, 33 mol% PPh$_3$, 7 equiv norbornene and 5 equiv Cs$_2$CO$_3$ in DME (0.03 M), for 5 min at 180 ºC in an oil bath. Purification by flash chromatography using pentane/Et$_2$O (98:2) afforded **12a** (44 mg, 146 µmol, 74%) as a colorless oil. R$_f$ = 0.29 on silica gel (hexanes/EtOAc; 20:1). ^{1}**H-NMR** (400 MHz, CDCl$_3$): δ 1.16 (ddd, *J* = 8.1

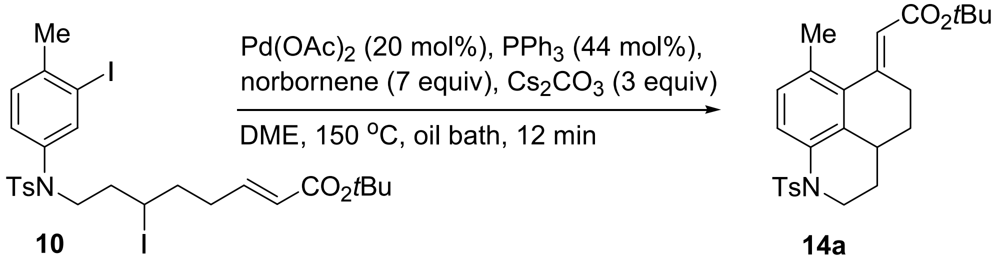
Hz, 12.4 Hz, 24.0 Hz, 1H), 1.51 (s, 9H), 1.62 – 1.73 (m, 1H), 2.01 – 2.10 (m, 2H), 2.38 (s, 3H), 2.51 – 2.60 (m, 1H), 2.79 (dddd, *J* = 1.1 Hz, 3.0 Hz, 8.2 Hz, 18.7 Hz, 1H), 3.48 (dddd, *J* = 1.7 Hz, 7.7 Hz, 11.4 Hz, 26.4 Hz, 1H), 4.02 (ddd, *J* = 1.8 Hz, 10.8 Hz, 12.4 Hz, 1H), 4.29 (ddd, *J* = 3.4 Hz, 3.4 Hz, 11.0 Hz, 1H), 5.82 – 5.83 (m, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 21.1, 27.8, 28.41, 28.6, 29.8, 31.7, 65.7, 80.1, 116.1, 120.8, 126.5, 126.8, 130.6, 136.6, 151.0, 152.7, 166.6. **HRMS** calcd for $C_{19}H_{24}O_3$ [M^+] 300.1725, found 300.1725. **IR**: $\tilde{\nu}$ = 2931, 1704, 1617, 1592, 1483, 1365, 1254, 1146 cm^{-1}.



9

13a

[6-Methyl-1-(toluene-4-sulfonyl)-2,2*a*,3,4-tetrahydro-1*H*-benzo[*cd*]indol-5-ylidene]-acetic acid *tert*-butyl ester (13a). Following the general procedure for the annulation reaction using **9**, 20 mol% $Pd(OAc)_2$, 44 mol% PPh_3, 7 equiv norbornene and 3 equiv Cs_2CO_3 in DME (0.03 M), for 12 min at 150 ºC in an oil bath. Purification by flash chromatography using hexanes/EtOAc (6:1) afforded **13a** (34 mg, 78 µmol, 68%) as a white solid, mp = 166 – 168 ºC. R_f = 0.34 on silica gel (hexanes/EtOAc; 6:1). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.49 (s, 9H), 2.05 – 2.13 (m, 2H), 2.37 (s, 3H), 2.45 (s, 3H), 2.80 – 3.00 (m, 2H), 3.20 – 3.35 (m, 2H), 4.28 (t, *J* = 9.7 Hz, 1H), 6.07 (s, 1H), 7.09 (d, *J* = 8.2 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 21.8, 21.9, 27.3, 28.5, 37.1, 57.4, 80.3, 115.5, 120.2, 127.5, 129.9, 131.1, 132.1, 134.1, 137.0, 138.6, 144.2, 149.5, 166.6. **HRMS** calcd for $C_{25}H_{29}NO_4S$ [M^+] 439.1817, found 439.1812. **IR**: $\tilde{\nu}$ = 2950, 1701, 1610, 1577, 1477, 1458, 1355, 1166, 1144, 912, 812, 733 cm^{-1}.

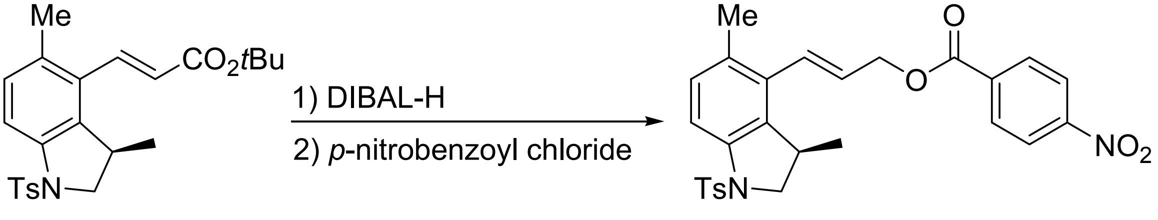


10

14a

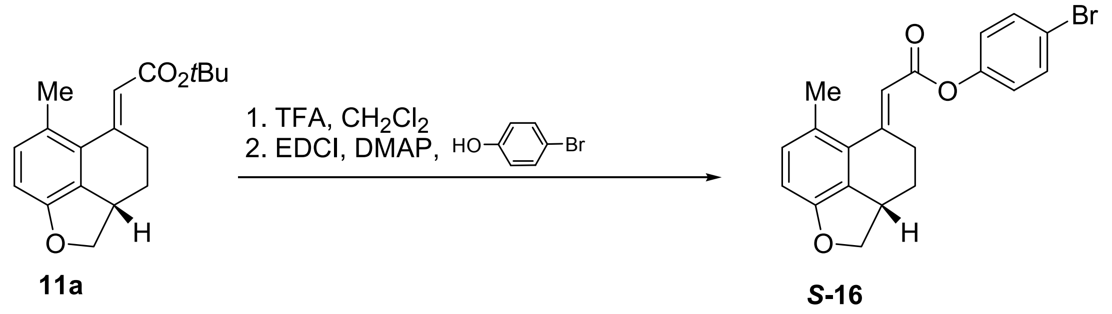
***N*-Tosyl-(7-Methyl-1,2,3,3*a*,4,5-hexahydro-1-aza-phenalen-6-ylidene)-acetic acid *tert*-butyl ester (14a).** Following the general procedure for the annulation reaction using **10**, 20 mol% $Pd(OAc)_2$, 44 mol% PPh_3, 7 equiv norbornene and 3 equiv Cs_2CO_3 in DME (0.03 M), for 12 min at 150 ºC in an oil bath. Purification by flash chromatography using hexanes/EtOAc (6:1) as eluant afforded **14a** (32 mg, 71 µmol, 62%) as a yellow solid, mp = 140 – 142 °C. R_f = 0.27 on silica gel (hexanes/EtOAc; 6:1). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.83 (m 1H), 1.11 (m, 1H), 1.49 (s, 9H), 1.77 (m, 2H), 2.19 (m, 2H), 2.51 (m, 1H), 3.49 (m, 1H), 4.06 (ddd, *J* = 13.9 Hz, 4.4 Hz, 4.4 Hz, 1H), 5.78 (m, 1H), 7.11 (d, *J* = 8.5 Hz, 1H), 7.19 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.2, 2H), 7.70 (d, *J* = 8.5, 1H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 21.1, 21.7, 26.7, 27.7, 28.1, 28.5, 32.5, 45.7, 80.3, 121.2, 123.9, 127.4, 129.7, 129.8, 131.6, 133.1, 133.2, 137.1, 143.8, 152.4, 156.1, 166.4. **HRMS** calcd for $C_{26}H_{31}NO_4S$ [M^+] 453.1974, found 453.1974. **IR**: $\tilde{\nu}$ = 2926, 1701, 1347, 1160, 1143 cm^{-1}.

Synthesis of Structures Solved by X-ray Crystallography



***R*-6** ***R*-15**

4-Nitro-benzoic acid 3-[3,5-dimethyl-1-(toluene-4-sulfonyl)-2,3-dihydro-1*H*-indol-4-yl]-allyl ester (*R*-15). To a solution of *R*-6 (15 mg, 35 μmol, 1 equiv) in CH_2Cl_2 (1 mL), was added DIBAL-H (1 M solution in hexanes, 0.35 mL, 350 μmol, 10 equiv) dropwise over 5 min. The reaction mixture was allowed to stir at ambient temperature for 30 min. The reaction was quenched with water (2 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The resulting yellow oil was dissolved in CH_2Cl_2 (0.5 mL) and 4-nitrobenzoyl chloride (14 mg, 75 μmol, 2.1 equiv) and pyridine were added at ambient temperature. The reaction mixture was stirred for 3 h, after which water was added and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by flash chromatography using hexanes/EtOAc (3:1) to afford compound ***R*-15** (10 mg, 20 μmol, 57%) as a yellow oil. Crystals suitable for x-ray analysis were obtained from diffusion of hexanes into a solution of ***R*-15** in THF. R_f = 0.39 on silica gel (hexanes/EtOAc; 3:1). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 0.94 (d, *J* = 6.9 Hz, 3H), 2.27 (s, 3H), 2.37 (s, 3H), 3.34 – 3.38 (m, 1H), 3.67 (dd, *J* = 10.4 Hz, 2.4 Hz, 1H), 3.84 (dd, *J* = 10.4 Hz, 8.6 Hz, 1H), 5.00 (dd, *J* = 6.5 Hz, 1.1 Hz, 2H), 6.04 (dt, *J* = 16.2 Hz, 6.4 Hz, 1H), 6.69 (d, *J* = 16.2 Hz, 1H), 7.05 (d, *J* = 8.3 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 8.21 (dt, *J* = 8.9 Hz, 2.1 Hz, 2H), 8.30 (dt, *J* = 8.9 Hz, 2.1 Hz, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 20.2, 20.3, 21.7, 34.4, 57.5, 66.7, 114.1, 123.8, 127.6, 127.8, 129.8, 130.3, 130.9, 131.69, 131.74, 132.8, 134.1, 135.3, 135.7, 139.5, 144.2, 150.9, 164.6. **HRMS** calcd for $C_{27}H_{27}N_2O_6S$ (ESI) 507.1584, found 507.1574. **IR**: $\tilde{\nu}$ = 2956, 1722, 1599, 1527, 1351, 1270, 1166, 1093, 719, 667 cm^{-1}. **HPLC** (Chiracel-OD-H, 30°C): wavelength = 254 nm, flow = 1.0 mL/min, hexanes/*i*-propanol = 90:10, t_R = 36.54 min (*S*), 42.57 min (*R*), *ee* = 59%. $[\alpha]_D^{27}$ = −17.3° (*c* = 1.72 in $CHCl_3$). CCDC no. 627191.



(6-Methyl-2,2*a*,3,4-tetrahydro-naphtho[1,8-*bc*]furan-5-ylidene)-acetic acid 4-bromophenyl ester (*S*-16). To a 0 °C solution of **11a** (20 mg, 70 µmol, 1 equiv) in CH_2Cl_2 (2 mL), was added TFA (0.2 mL) slowly. The solution was stirred for 2.5 h at ambient temperature, after which benzene (5 mL) was added and the resulting mixture was placed in liquid nitrogen. The resulting solid was removed from the cooling bath and the solvents sublimed under high vacuum. The resulting white powder was dissolved in CH_2Cl_2 (2 mL) and EDCI (20 mg, 104 µmol, 1.5 equiv), DMAP (1 mg) and *para*-bromo phenol (18 mg, 104 µmol, 1.5 equiv) were added at ambient temperature. The reaction mixture was stirred for 2 h, after which the volatiles were removed under reduced pressure and the crude product was purified by flash chromatography using hexanes/EtOAc (9:1) to afford compound ***S*-17** (16 mg, 42 µmol, 60%) as a yellow solid, mp = 112 - 115°C. Crystals suitable for x-ray analysis were obtained from diffusion of pentane into a solution of ***S*-17** in THF. R_f = 0.33 on silica gel (hexanes/EtOAc; 9:1). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 1.37 (m, 1H), 2.25 (m, 1 H), 2.55 (s, 3H), 3.05 (m, 1H), 3.35 (m, 1H), 3.52 (m, 1H), 4.09 (dd, *J* = 10.2 Hz, 9.0 Hz, 1H), 4.87 (dd *J* = 9.0 Hz, 9.0 Hz, 1H), 6.49 (m, 1H), 6.73 (d, *J* = 8.1 Hz, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 7.05 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.8 Hz, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 22.1, 27.0, 29.8, 39.1, 78.8, 110.4, 115.9, 118.8, 123.8, 127.7, 130.9, 132.2, 132.6, 133.6, 150.0, 155.5, 156.8, 164.9. **HRMS** calcd for $C_{20}H_{17}O_3NaBr$ (ESI) 407.0253, found 407.0265. **IR**: $\tilde{\nu}$ = 2925, 2869, 1732, 1483, 1205, 1134, 1068 cm^{-1}. **HPLC** (Chiracel-OD, 25°C): wavelength = 280 nm, flow = 1.0 mL/min, hexanes/*i*-propanol = 99:01, t_R = 14.99 min (*R*), 16.55 min (*S*), *ee* = 78%. $[\alpha]_D^{27}$ = –94.1° (*c* = 0.86 in $CHCl_3$). CCDC no. 619350.

References

[1] S. Pache, M. Lautens, *Org. Lett.* **2003** *5*, 4827 - 4830.

[2] All commercially available pure or crude *Pseudomonas sp.* lipases possess a stereochemical preference for the (*R*)-configuration at the reaction center of secondary alcohols. C.-H. Wong, G. M. Whitesides in *Enzymes in Synthetic Organic Chemistry, Vol. 12* (Eds.: J. E. Baldwin, P. D. Magnus), Pergamon, New York, 1994, pp. 70-130.

[3] C. Bressy, D. Alberico, M. Lautens, *J. Am. Chem. Soc.* **2005**, *127*, 13148 - 13149.

[4] Prepared by the method described in S. E. Schaus, B. D. Brandes, J.F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 1307 – 1315.