

Enantioselective Total Synthesis of (+)-Salvileucalin B

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Supporting Information 1 (Experimental Procedures):

Table of Contents

1. General Considerations	S3
2. Procedures for substrate synthesis	S5

General. Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), diethyl ether (Et_2O), acetonitrile (MeCN), toluene and benzene were dried by passing through activated alumina columns. Dimethylformamide (DMF) was dried over activated molecular sieves, MeOH was distilled over magnesium oxide and dichloroethane (DCE) was distilled over calcium hydride. All other commercially obtained reagents were used as received. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm). Flash column chromatography was performed either as described by Still et al. (Still, W. C., Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.) using silica gel (partical size 0.032-0.063) purchased from Silicycle or using pre-packaged RediSep[®]Rf columns on a CombiFlash Rf system (Teledyne ISCO Inc.). Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. Microwave experiments were performed using a Biotage Initiator[®] microwave reactor. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz respectively) or a Varian Inova 500 (at 500 MHz and 125 MHz respectively), and are reported relative to internal CHCl_3 (^1H , $\delta = 7.26$) or CDHCl_2 (^1H , $\delta = 5.32$), and CDCl_3 (^{13}C , $\delta = 77.0$) or CD_2Cl_2 (^{13}C , $\delta = 53.8$). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained from the Caltech Mass Spectral Facility. Preparative HPLC was performed with an Agilent 1100 Series HPLC utilizing an Agilent Zorbax RX-SIL $5\mu\text{m}$ column (9.4 x 250 mm). Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing Chiralcel OD-H columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd with visualization at 220 nm. Analytical HPLC was performed on an Agilent 1290 Infinity Eclipse Plus C_{18} $1.8\mu\text{m}$ column (2.1 x 50 mm). Melting points were determined using a Büchi B-545 capillary melting point apparatus and the values reported are uncorrected.

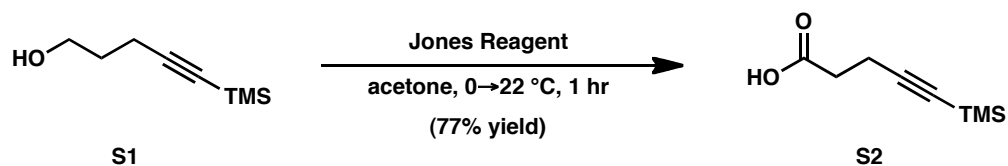
Catalyst abbreviations:

Cu(hfacac) 2 Copper(II) hexafluoroacetylacetonate (Aldrich)

RuCp*(cod)Cl Chloro(1,5-cyclooctadiene)(pentamethylcyclopentadienyl)

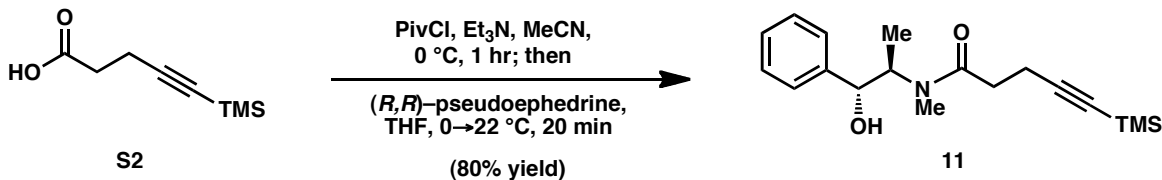
ruthenium(II) (Strem Chemicals)

Preparation of Carboxylic Acid S2



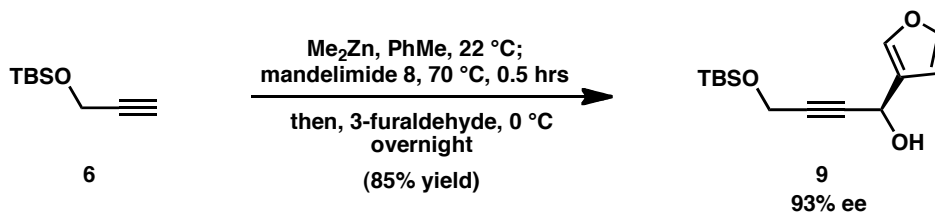
To a 250 mL round-bottom flask containing acetone (15 mL) at 0 °C was added Jones reagent (21.4 mL, 64 mmol, approximately 3M). Alcohol **S1** (4.55 g, 29.1 mmol) in acetone (50 mL) was added dropwise via cannula to the vigorously stirred Jones reagent solution at 0 °C over 35 minutes. Upon completion of the addition the resulting thick green slurry was warmed to 22 °C, and stirred for 1 hour. After consumption of the starting material (TLC analysis), the reaction was quenched with isopropanol (2 mL). The reaction was filtered through a plug of celite and washed with 10 x 20 mL portions of acetone. The combined filtrates were concentrated *in vacuo*, and the resulting residue was partitioned between Et₂O and water. The aqueous layer was separated, back-extracted twice with Et₂O, and then basified with solid potassium carbonate and sodium bicarbonate such that the pH did not exceed 10 (Note: a pH exceeding 10 can result in silyl cleavage, the product of which is difficult to separate from **S2**). The basic aqueous layer was washed once with Et₂O, then acidified to pH 1 with aqueous 1M HCl and extracted three times with Et₂O. The combined organic layers were dried over MgSO₄, filtered, and concentrated *in vacuo* to provide 3.85 g (77% yield) of acid **S2** as a white solid. ¹H NMR (300 MHz, CDCl₃) δ 2.65 – 2.50 (m, 4H), 0.13 (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 176.65, 104.52, 85.69, 77.25, 76.75, 33.16, 15.49, -0.00. IR (NaCl/thin film): 3017, 2928, 2858, 2173 cm⁻¹; HRMS (EI⁺) calc'd for C₇H₁₁O₂Si [M – CH₃]⁺ 155.0528, found 155.0555.

Preparation of Amide 11



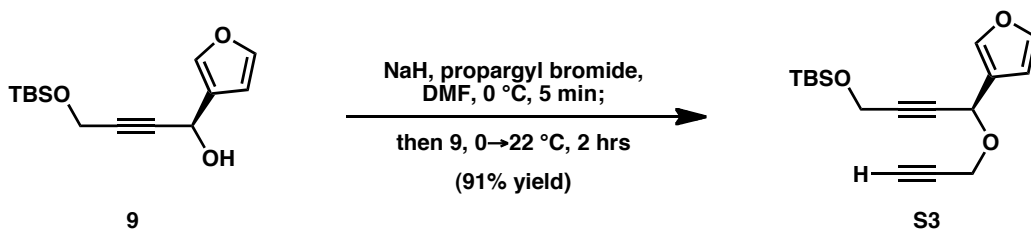
To a flame-dried 500 mL round-bottom flask under N₂ containing acid **S2** (3.18 g, 18.7 mmol) was added MeCN (80 mL). After cooling to 0 °C, triethylamine (6.5 mL, 46.8 mmol) and pivaloyl chloride (2.35 mL, 19.0 mmol) were added successively, resulting in the formation of a thick yellow slurry, which was stirred for 1 hour at the same temperature. In a separate flask, (*R,R*)-pseudoephedrine was dissolved in THF (80 mL) under N₂, and transferred via cannula to the mixed anhydride at 0 °C. The reaction was warmed to 22 °C over 1.5 hours, and quenched with water and aqueous 1M HCl after consumption of starting material (TLC analysis). The volatiles were concentrated *in vacuo*, and the residue was partitioned between EtOAc and brine. The aqueous layer was separated and backextracted once with EtOAc, and the combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (0 → 50% EtOAc/hexanes) to provide 4.75 g (80% yield) of amide **11** as a light yellow oil. $[\alpha]_D^{25} -76.1^\circ$ (*c* 0.96, CH₂Cl₂); ¹H NMR (3:1 rotamer ratio, asterisk denotes minor peaks, 500 MHz, CDCl₃) δ 7.43 – 7.26 (m, 10H), 4.58 (t, *J* = 7.6 Hz, 2H), 4.49 (s, 1H), 4.03* (dd, *J* = 8.7, 6.9 Hz, 1H), 2.92* (s, 3H), 2.85 (s, 3H), 2.74 (m, 1H), 2.65 – 2.44 (m, 7H), 1.09 (d, *J* = 6.9 Hz, 3H), 0.99* (d, *J* = 6.8 Hz, 3H), 0.15* (s, 9H), 0.14 (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 173.26, 172.16*, 142.19, 141.06*, 128.73, 128.47*, 128.40, 127.75, 126.88, 126.42, 106.53*, 105.94, 85.03, 84.78*, 77.20*, 76.41, 75.48*, 58.29*, 58.16, 33.41, 32.74*, 32.47*, 26.83*, 16.13*, 15.92, 15.37*, 14.43, 0.12*, 0.06. IR (NaCl/thin film): 3392, 3064, 3031, 2959, 2899, 2176 cm⁻¹; HRMS (FAB+) calc'd for C₁₈H₂₈NO₂Si [M+H]⁺ 318.1889, found 318.1896.

Preparation of Propargyl Alcohol 9



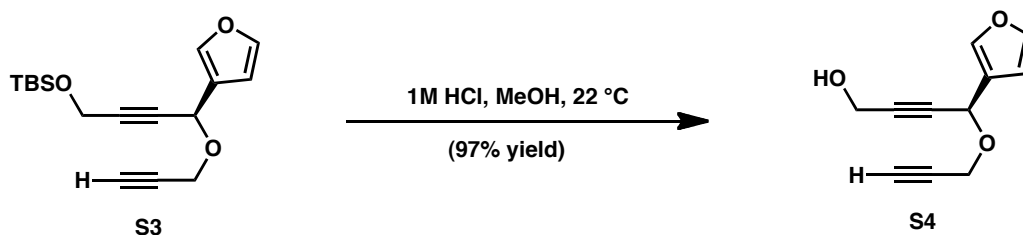
To a flame-dried 1L flask under N₂ were added PhMe (110 mL), alkyne **6** (25.6 mL, 126 mmol) and Me₂Zn (100 mL, 120 mmol, 1.2M in PhMe) successively at 22 °C. The clear solution was stirred for 30 minutes at 22 °C. To a separate flame-dried 500 mL flask was added the mandelamide **8** (3.06 g, 12 mmol) and PhMe (110 mL), followed by heating to 70 °C to effect complete dissolution of the solids. This clear solution was transferred via cannula to the zinc-acetylide solution at 22 °C. After heating at 70 °C for 30 minutes the reaction was cooled to 0 °C and neat 3-furaldehyde (2.60 mL, 30 mmol) was added dropwise. The reaction was allowed to warm to 22 °C over 12 hours. After consumption of starting material (TLC analysis) the reaction (yellow slurry) was cooled to 0 °C and quenched carefully with aqueous 1M HCl (125 mL) until vigorous bubbling ceased (CAUTION! Methane gas evolves). The aqueous layer was separated and back-extracted three times with PhMe. The combined organics layers were dried over Na₂SO₄, concentrated *in vacuo*, and purified by silica gel chromatography (0 → 30% EtOAc/hexanes) to provide 6.9 g (85% yield, 93% ee) of alcohol **9** as a light yellow oil. The enantiomeric excess was determined by chiral HPLC analysis (OD-H, 1 mL/min, 10% IPA in hexanes, λ = 220 nm). [α]_D²⁵ +7.5° (c 1.78, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 7.52 (dt, *J* = 1.7, 0.9 Hz, 1H), 7.40 (t, *J* = 1.7 Hz, 1H), 6.51 (dd, *J* = 1.8, 0.9 Hz, 1H), 5.43 (br s, 1H), 4.39 (d, *J* = 1.8 Hz, 2H), 0.91 (s, 9H), 0.12 (s, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 143.55, 140.12, 126.24, 109.11, 83.88, 83.85, 57.29, 51.65, 25.76, 18.25, -5.18. IR (NaCl/thin film): 3367, 2955, 2930, 2886, 2858 cm⁻¹; HRMS (FAB+) calc'd for C₁₄H₂₁O₃Si [M+H]⁺-H₂ 265.1260, found 265.1265.

Preparation of propargyl ether S3



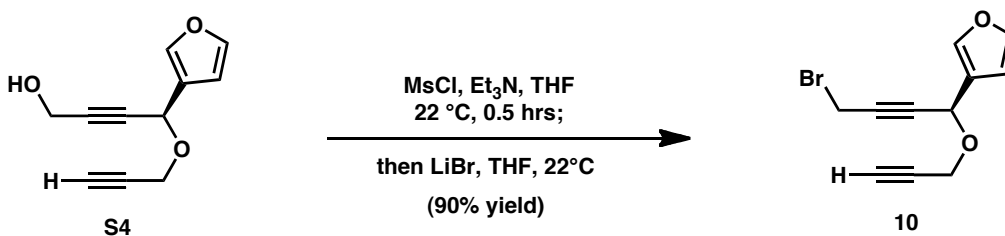
To a flame-dried 250 mL flask in a glovebox was added sodium hydride (95%, 388 mg, 15.3 mmol). The flask was removed from the box and placed under N₂ on the bench. DMF (45 mL) was charged to the flask, and the grey suspension was cooled to 0 °C. Propargyl bromide (80% wt PhMe, 4.9 mL, 43.8 mmol) was added to the NaH slurry, immediately after which alcohol **9** (3.89 g, 14.6 mmol) in DMF (30 mL) was transferred to the reaction via cannula. The orange suspension was warmed to 22 °C and allowed to stir for 2 hours. After consumption of starting material (TLC analysis) the reaction was quenched with saturated aqueous NH₄Cl and the aqueous layer extracted five times with hexane. The combined organic layers were dried over Na₂SO₄, concentrated *in vacuo*, and purified by silica gel chromatography (0 → 10% EtOAc/hexanes) to provide 4.0 g (91% yield) of propargyl ether **S3** as a light yellow oil. $[\alpha]_D^{25} +60.4^\circ$ (*c* 1.55, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 7.53 (dt, *J* = 1.7, 0.9 Hz, 1H), 7.40 (t, *J* = 1.7 Hz, 1H), 6.50 (dd, *J* = 1.8, 0.6 Hz, 1H), 5.43 – 5.41 (m, 1H), 4.40 (d, *J* = 1.7 Hz, 2H), 4.34 (dd, *J* = 15.7, 2.4 Hz, 1H), 4.25 (dd, *J* = 15.7, 2.4 Hz, 1H), 2.45 (t, *J* = 2.4 Hz, 1H), 0.91 (s, 9H), 0.12 (s, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 143.52, 141.11, 123.38, 109.53, 85.49, 80.92, 79.15, 74.86, 62.53, 54.91, 51.66, 25.76, 18.25, -5.18. IR (NaCl/thin film): 3297, 3146, 2955, 2929, 2893, 2857, 2114 cm⁻¹; HRMS (EI+) calc'd for C₁₇H₂₄O₃Si [M]⁺ 304.1495, found 304.1446.

Preparation of alcohol S4



To a 250 mL flask containing propargyl ether **S3** (4.00 g, 13.2 mmol) was added aqueous 1M HCl (400 μ L). The clear yellow reaction was stirred open to air at 22 $^\circ$ C for 4 hours, at which point TLC analysis indicated full consumption of starting material. The reaction was neutralized and dried with solid NaHCO_3 and Na_2SO_4 , filtered, concentrated and purified by silica gel chromatography (0 \rightarrow 40% EtOAc/hexanes) to provide 2.43 g (97% yield) of alcohol **S4** as a yellow oil. $[\alpha]_D^{25} +78.3^\circ$ (*c* 3.40, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3) δ 7.54 (dt, $J = 1.6, 0.8$ Hz, 1H), 7.41 (t, $J = 1.7$ Hz, 1H), 6.50 (dd, $J = 1.8, 0.7$ Hz, 1H), 5.43 (br s, 1H), 4.37 (dd, $J = 6.2, 1.6$ Hz, 2H), 4.33 (dd, $J = 15.7, 2.4$ Hz, 1H), 4.24 (dd, $J = 15.7, 2.4$ Hz, 1H), 2.47 (t, $J = 2.4$ Hz, 1H), 1.58 (t, $J = 6.3$ Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 143.60, 141.12, 123.01, 109.37, 84.97, 81.78, 78.95, 75.10, 62.38, 54.88, 50.73. IR (NaCl/thin film): 3400, 3292, 3148, 2914, 2861, 2117 cm^{-1} ; HRMS (EI+) calc'd for $\text{C}_{11}\text{H}_{10}\text{O}_2$ $[\text{M}]^+$ 190.0630, found 190.0614

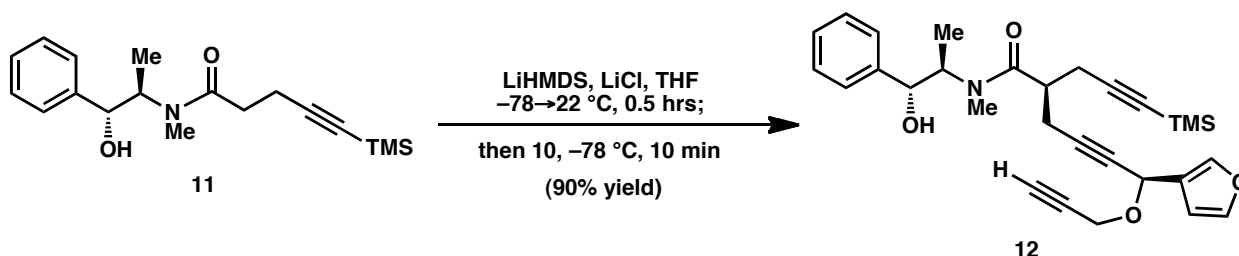
Preparation of bromide 10



To a flame-dried 1 L flask under N_2 containing alcohol **S4** (3.33 g, 17.5 mmol) was added THF (300 mL), MsCl (1.50 mL, 19.3 mmol) and Et_3N (2.93 mL, 21.0) at 22 $^\circ$ C. Upon addition of Et_3N a slurry immediately resulted, and this was stirred for 35 minutes. In a separate flame-dried 1 L flask LiBr (6.09 g, 70.1 mmol) was dissolved in THF (50 mL). The mesylate solution was transferred via a fritted funnel to the flask

containing LiBr/THF with a THF (50 mL) wash. The resulting murky orange solution was stirred under N₂ at 22 °C for 12 hours, after which time most of the THF was concentrated *in vacuo*, and the residue was diluted with brine and extracted three times with hexane. The combined organics layers were dried over Na₂SO₄, concentrated *in vacuo*, and purified by silica gel chromatography (0 → 10% EtOAc/hexanes) to provide 4.0 g (90% yield) of bromide **10** as a light yellow oil. $[\alpha]_D^{25} +73.5^\circ$ (*c* 1.57, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 7.55 (dt, *J* = 1.6, 0.8 Hz, 1H), 7.41 (t, *J* = 1.7 Hz, 1H), 6.50 (dd, *J* = 1.7, 0.7 Hz, 1H), 5.44 (br s, 1H), 4.32 (dd, *J* = 15.7, 2.4 Hz, 1H), 4.24 (dd, *J* = 15.7, 2.4 Hz, 1H), 3.98 (d, *J* = 1.9 Hz, 2H), 2.48 (t, *J* = 2.4 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 143.66, 141.20, 122.89, 109.42, 83.13, 81.71, 78.93, 75.13, 62.43, 55.04, 13.72. IR (NaCl/thin film): 3293, 3148, 3007, 2957, 2904, 2856, 2117 cm⁻¹; HRMS (EI+) calc'd for cationic fragment C₈H₆OBr [M - ⁻OCH₂CCH]⁺ 196.9602, found 196.9637.

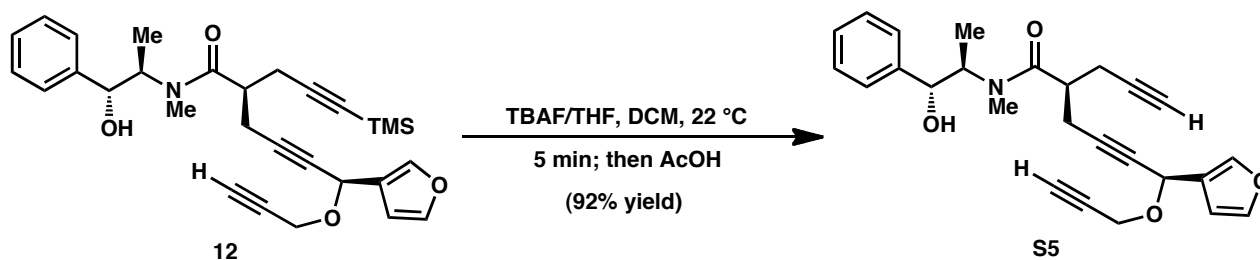
Preparation of triyne **12**



To a flame-dried 250 mL flask in a glovebox was added LHMDS (97%, 3.28 g, 19.6 mmol) and LiCl (1.72 g, 40.5 mmol). The flask was sealed and placed under N₂ on the bench. THF (10 mL) was added at 22 °C, and the thin slurry was cooled to -78 °C. To a 100 mL flask containing amide **11** (3.00 g, 9.45 mmol) THF (60 mL) was charged, and the solution was cannula transferred to the LHMDS/LiCl solution at -78 °C. The light copper colored solution was warmed to 22 °C, and held at this temperature for 30 minutes. The reaction was re-cooled to -78 °C, and bromide **10** (1.71g, 6.75 mmol) in THF (20 mL) was cannula transferred to the amide enolate with a 10 mL THF wash. After 10 minutes the reaction was judged complete by TLC, and was quenched with aqueous saturated NH₄Cl and extracted three times with EtOAc. The combined organic layers were dried over Na₂SO₄, concentrated *in vacuo*, and purified by silica gel

chromatography (0 → 40% EtOAc/hexanes) to provide 3.29 g (90% yield) of triyne **12** as a light yellow oil. $[\alpha]_D^{25} -4.2^\circ$ (*c* 3.25, CH₂Cl₂); ¹H NMR (2.5:1 rotamer ratio, asterisk denotes minor peaks, 500 MHz, CDCl₃) δ 7.55* (s, 1H), 7.49 – 7.48 (m, 1H), 7.41 – 7.26 (m, 12H), 6.51* (dd, *J* = 1.7, 0.6 Hz, 1H), 6.46 (dd, *J* = 1.7, 0.6 Hz, 1H), 5.37* (br s, 1H), 5.32 (br s, 4H), 4.62 – 4.51 (m, 3H), 4.34 – 4.25 (m, 3H), 4.18 (dd, *J* = 15.7, 2.4 Hz, 2H), 3.75 – 3.60 (br s, 2H), 3.35* (app qnt, *J* = 7.4 Hz, 1H), 3.14 (app qnt, *J* = 7.4 Hz, 1H), 2.98 (s, 3H), 2.96* (s, 3H), 2.64 – 2.48 (m, 8H), 2.45 – 2.42 (m, 2H), 1.06 – 1.01 (m, 6H), 0.15 (s, 9H), 0.08* (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 174.67, 173.91*, 143.53, 143.49*, 141.84, 141.32, 141.13*, 141.04, 128.73, 128.39*, 128.34, 127.76, 126.84, 126.60, 123.61*, 123.58, 109.58*, 109.42, 103.98*, 103.69, 86.81, 86.34*, 85.17*, 84.20, 79.35*, 79.14, 78.25, 78.11*, 75.89, 75.40*, 74.88, 74.83*, 62.62*, 62.49, 58.42*, 58.26, 54.78, 54.65*, 40.93, 40.27*, 32.62, 30.70, 29.65*, 27.44, 23.26*, 23.13, 22.15*, 21.71, 16.02*, 14.30, -0.02*, -0.08. IR (NaCl/thin film): 3400, 3294, 3146, 3062, 3029, 2959, 2901, 2856, 2281, 2228, 2174, 2115, 1625 cm⁻¹; HRMS (EI+) calc'd for cationic fragment C₂₂H₂₈NO₃Si [M – ⁻CH₂Ph]⁺ 382.1833, found 382.1819.

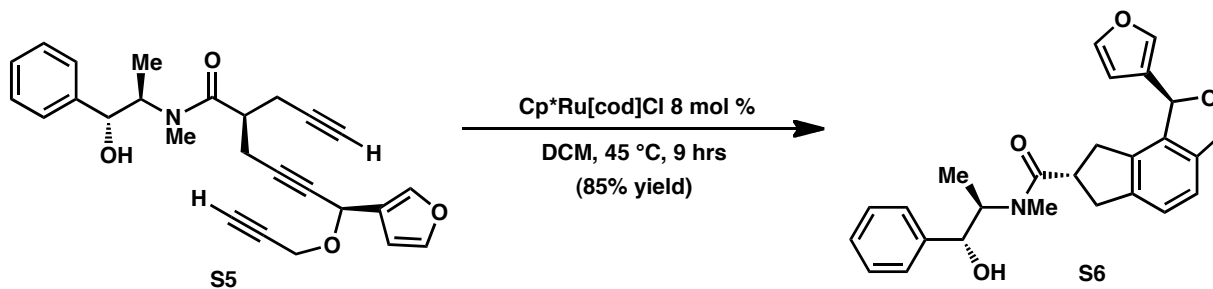
Preparation of triyne **S5**



To a 100 mL flask containing triyne **12** (3.42 g, 6.98 mmol) was added DCM (50 mL). TBAF (1M THF, 7.12 mL, 7.12 mmol) was charged to the yellow solution at 22 °C, resulting in an immediate color change to light brown. After 5 minutes TLC analysis indicated complete consumption of starting material, and the reaction was quenched with acetic acid (450 μL). The solvent was removed *in vacuo*, and the residue was purified by silica gel chromatography (0 → 40% EtOAc/hexanes) to provide 2.77 g (92% yield) of triyne **S5** as a light yellow oil. $[\alpha]_D^{25} -8.1^\circ$ (*c* 1.75, CH₂Cl₂); ¹H NMR (2.5:1 rotamer ratio, asterisk denotes minor peaks, 500 MHz, CDCl₃) δ 7.55 – 7.54* (m, 1H), 7.48 (dt, *J*

= 1.5, 0.8 Hz, 1H), 7.40 – 7.25 (m, 12H), 6.50* (d, $J = 1.1$ Hz, 1H), 6.46 (dd, $J = 1.7, 0.6$ Hz, 1H), 5.36* (br s, 1H), 5.32 (br s, 1H), 4.64 (s, 1H), 4.57 (d, $J = 8.4$ Hz, 2H), 4.33 – 4.24 (m, 2H), 4.24 – 4.15 (m, 3H), 3.61 (br s, 1H), 3.31* (app qnt, $J = 7.0$ Hz, 1H), 3.15 (app qnt, $J = 7.3$ Hz, 1H), 2.96 (s, 3H), 2.95* (s, 3H), 2.70 – 2.39 (m, 12H), 2.04 (t, $J = 2.6$ Hz, 1H), 1.96* (t, $J = 2.6$ Hz, 1H), 1.04* (d, $J = 6.7$ Hz, 3H), 1.00 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 174.44, 173.64*, 143.53, 143.48*, 141.64, 141.27, 141.20*, 141.01, 128.72, 128.36, 127.82, 126.78*, 126.61, 123.63*, 123.56, 109.56, 109.40, 85.05*, 83.98, 81.48*, 81.38, 79.33*, 79.11, 78.35, 78.18*, 77.20*, 75.86, 75.40*, 74.89, 74.83*, 70.29, 70.01*, 62.61*, 62.46, 58.21*, 57.64, 54.78, 54.66*, 40.76, 40.06*, 32.15, 27.51*, 21.95*, 21.70*, 21.62, 21.59, 15.84*, 14.22. IR (NaCl/thin film): 3394, 3290, 2977, 2913, 2848, 2590, 2228, 2114, 1622 cm^{-1} ; HRMS (EI+) calc'd for $\text{C}_{26}\text{H}_{27}\text{NO}_4$ [M] $^+$ 417.1940, found 417.1939.

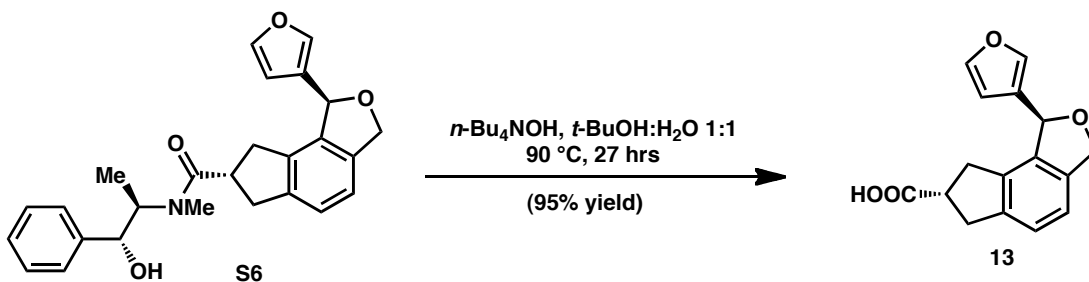
Preparation of arene S6



To a flame-dried 500 mL flask containing triyne **S5** (2.70 g, 6.47 mmol) was added DCM (100 mL). In a glovebox, $\text{Cp}^*\text{Ru}[\text{cod}]\text{Cl}$ (50 mg, 0.13 mmol) was dissolved in DCM (10 mL), and the clear brown catalyst solution was added in one portion to the triyne at 45 °C. After 2 hours an additional 50 mg of catalyst (2 mol %) was charged as a DCM solution, and this was repeated two times until the starting material was completely consumed (HPLC analysis, 4 x 2 mol % catalyst additions total). The solvent was then concentrated *in vacuo*, and the residue was purified by silica gel chromatography (0 → 50% EtOAc/hexanes) to provide 2.3 g (85% yield) of arene **S6** as a yellow oil. $[\alpha]_{\text{D}}^{25} - 9.7^\circ$ (c 0.86, CH_2Cl_2); ^1H NMR (2.2:1 rotamer ratio, asterisk denotes minor peaks, 500 MHz, CDCl_3) δ 7.49* (s, 1H), 7.45 (s, 1H), 7.43* (t, $J = 1.5$ Hz, 1H), 7.37 (t, $J = 1.7$ Hz, 1H), 7.36 – 7.22 (m, 10H), 7.16 – 7.11 (m, 2H), 7.09 – 7.04 (m, 2H), 6.27* (d, $J = 1.1$

Hz, 1H), 6.22 (d, $J = 1.2$ Hz, 1H), 6.12 (br s, 2H), 5.22 (dd, $J = 11.9, 1.7$ Hz, 2H), 5.10 (d, $J = 11.9$ Hz, 2H), 4.64 – 4.59 (m, 1H), 4.57 (d, $J = 8.6$ Hz, 1H), 4.49 (s, 1H), 4.07 – 3.97 (m, 1H), 3.53* (app qnt, $J = 8.5$ Hz, 1H), 3.40 (app tt, $J = 8.9, 7.0$ Hz, 1H), 3.26 – 3.04 (m, 5H), 2.94* (s, 3H), 2.93 – 2.89 (m, 1H), 2.88 (s, 3H), 2.73* (dd, $J = 16.3, 8.9$ Hz, 1H), 2.64 (dd, $J = 16.3, 9.0$ Hz, 1H), 1.11 (d, $J = 6.9$ Hz, 3H), 1.03* (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 176.89, 175.40*, 143.59, 143.55*, 142.35, 141.70, 141.12*, 140.74, 140.69, 137.92, 137.85*, 136.48*, 136.42, 136.27*, 135.70, 128.74, 128.48*, 128.35, 127.63, 126.75, 126.29, 125.66*, 125.57, 123.76, 123.65*, 119.20, 119.01*, 109.44*, 109.32, 77.20*, 77.16, 76.46, 75.46*, 72.77, 58.47, 58.19*, 41.77, 41.60*, 36.42*, 35.96, 34.13*, 33.66, 32.71, 27.23*, 15.52*, 14.34. IR (NaCl/thin film): 3391, 3131, 3058, 3028, 2916, 2849, 1622 cm^{-1} ; HRMS (EI+) calc'd for $\text{C}_{26}\text{H}_{27}\text{NO}_4$ $[\text{M}]^+$ 417.1940, found 417.1959.

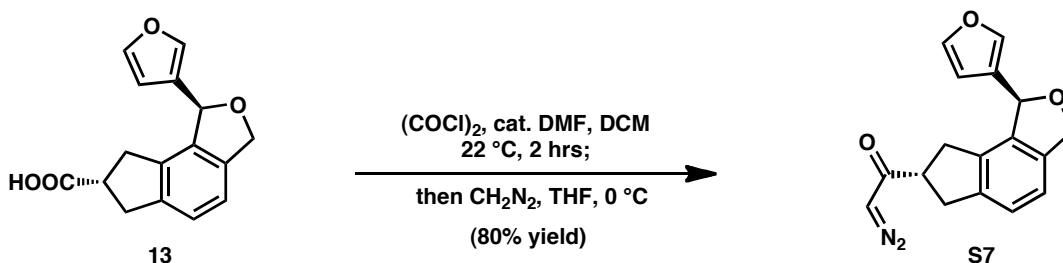
Preparation of acid 13



To a 500 mL flask open to air was added arene **S6** (2.45 g, 5.87 mmol), *t*-BuOH (70 mL), and water (70 mL). To this colorless clear solution was added *n*-Bu₄NOH (1.5 M in H₂O, 11.74 mL, 17.61 mmol), and the reaction was heated to 90 °C for 27 hours. At this time HPLC analysis indicated a 99:1 ratio of starting material to product, and the clear yellow reaction was cooled to 0 °C and quenched with an aqueous 5:1 mixture of NaH₂PO₄/NaHSO₄ (approximately pH=2.5). After a reaction pH of < 3 was achieved, most of the *t*-BuOH was concentrated *in vacuo*. The mixture was then extracted with EtOAc until HPLC analysis confirmed no remaining product in the aqueous layer. The combined organic layers were dried over MgSO₄, concentrated *in vacuo*, and purified by silica gel chromatography (0 → 70% EtOAc/hexanes) to provide 1.50 g (95% yield) of acid **13** as a 10:1 ratio of inseparable diastereomers. $[\alpha]_{\text{D}}^{25} +96.1^\circ$ (*c* 1.95, CH₂Cl₂); ^1H

NMR (10:1 diastereomer ratio, asterisk denotes minor peaks 500 MHz, CDCl₃) δ 7.47 (s, 1H), 7.44* (s, 1H), 7.38 (t, *J* = 1.5 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 7.09 (d, *J* = 7.7 Hz, 2H), 6.23* (d, *J* = 1.5 Hz, 1H), 6.22 (dd, *J* = 1.8, 0.7 Hz, 1H), 6.13 (s, 2H), 5.22 (d, *J* = 12.1 Hz, 2H), 5.10 (d, *J* = 11.8 Hz, 2H), 3.38 – 3.17 (m, 6H), 3.01 (dd, *J* = 16.8, 6.5 Hz, 2H), 2.83 (dd, *J* = 16.4, 8.9 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 181.07, 180.84*, 143.71, 141.43, 141.40*, 140.74, 140.65*, 138.06*, 138.03, 136.50, 136.39*, 135.28, 125.30, 123.88, 119.38, 109.27*, 109.21, 77.19*, 77.15, 72.66, 43.70*, 43.17, 35.48*, 35.42, 33.76*, 33.34. IR (NaCl/thin film): 3122, 3076, 3027, 2951, 2853, 2744, 2655, 2565, 1731, 1705 cm⁻¹; HRMS (FAB+) calc'd for C₁₆H₁₃O₄ [M+H]⁺-H₂ 269.0814, found 269.0816.

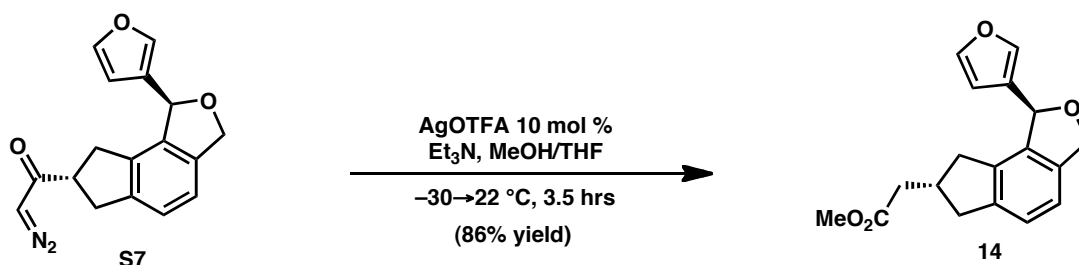
Preparation of diazo ketone S7



To a flame-dried 250 mL flask containing acid **13** (1.47 g, 5.44 mmol, 10:1 ratio diastereomers) was added DCM (60 mL), 1 drop of DMF, and (COCl)₂ (933 μL, 10.9 mmol) at 22 °C. A clear deep red solution resulted, and steady gas evolution occurred for 15 minutes. After 2 hours the solvent was concentrated *in vacuo*, and the red residue was placed under argon. NMR analysis confirmed complete conversion of the acid to the acid chloride. The acid chloride was then dissolved in THF (70 mL), and in a separate Erlenmeyer flask 250 mL of an ethereal diazomethane solution was dried briefly over KOH at 0 °C. This was carefully decanted into a separate oven-dried Erlenmeyer at 0 °C, and placed under nitrogen. The acid chloride/THF solution was cannula transferred over 10 minutes to the yellow diazomethane (excess) solution at 0 °C, which resulted in a steady gas evolution. The murky brown reaction was held for 20 minutes at the same temperature, after which time TLC analysis indicated full consumption of the starting material. The reaction was quenched with AcOH until bubbling subsided, and the

volatiles were concentrated *in vacuo*. The residue was purified by silica gel chromatography (0 → 30% EtOAc/hexanes) to provide 1.28 g (80% yield) of diazo ketone **S7** as a yellow solid. The product was determined to be a 10:1 mixture of separable diastereomers. The major diastereomer was separated from a small sample (preparative HPLC) for characterization. $[\alpha]_D^{25} +175.7^\circ$ (*c* 0.98, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 7.46 (s, 1H), 7.38 (dd, *J* = 2.4, 1.0 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 6.22 (dd, *J* = 1.8, 0.7 Hz, 1H), 6.12 (br s, 1H), 5.25 (br s, 1H), 5.22 (dd, *J* = 12.1, 1.9 Hz, 1H), 5.09 (d, *J* = 12.0 Hz, 1H), 3.33 – 3.08 (m, 3H), 2.95 (dd, *J* = 16.4, 6.1 Hz, 1H), 2.73 (dd, *J* = 16.4, 9.1 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 196.10, 143.68, 141.51, 140.70, 138.16, 136.61, 135.43, 125.47, 123.87, 119.37, 109.26, 77.12, 72.71, 53.90, 49.20, 35.53, 33.39. IR (NaCl/thin film): 3090, 2942, 2913, 2848, 2228, 2104, 1635 cm⁻¹; HRMS (FAB+) calc'd for C₁₇H₁₃N₂O₃ [M+H]⁺-H₂ 293.0926, found 293.0932.

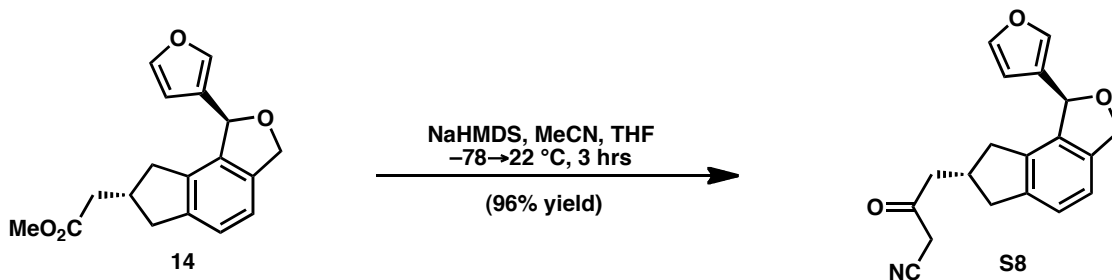
Preparation of methyl ester **14**



To a flame-dried 250 mL flask containing diazo ketone **S7** (1.22 g, 4.14 mmol, 10:1 ratio diastereomers) was added THF (110 mL) and MeOH (12.0 mL). The flask was covered in foil and cooled to -30 °C. To a N₂ purged 25 mL conical flask protected from light was added silver trifluoroacetate (91 mg, 0.414 mmol), followed by Et₃N (1.73 mL, 12.42 mmol) with vigorous stirring at 22 °C. (Note: vigorous stirring during Et₃N addition is critical to ensure dissolution of silver salt. Lack of stirring can result in a brown silver clump and incomplete dissolution. When dissolved a clear tan solution is obtained). The Et₃N/AgOTFA solution was added in one portion to the clear yellow diazo ketone solution at -30 °C. The reaction was slowly warmed to 23 °C over 3.5 hours (starting material consumed by TLC), after which time clear red/brown solution was

present with a silver mirror. The reaction was quenched with 1 mL of aqueous 1M HCl, and diluted with 50 mL Et₂O. The aqueous layer was separated and back-extracted twice Et₂O, and the combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. The crude brown residue was purified (0→30% EtOAc/hexanes), yielding 1.07 g (86% yield) of methyl ester **14** as a white solid. The product was determined to be a 10:1 mixture of separable diastereomers. The major diastereomer was separated from a small sample (preparative HPLC) for characterization. $[\alpha]_D^{25} +97.1^\circ$ (*c* 0.92, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 7.43 – 7.41 (m, 1H), 7.37 (t, *J* = 1.8 Hz, 1H), 7.15 (d, *J* = 7.7 Hz, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 6.22 (dd, *J* = 1.8, 0.6 Hz, 1H), 6.11 (br s, 1H), 5.21 (dd, *J* = 11.9, 1.5 Hz, 1H), 5.09 (d, *J* = 11.9 Hz, 1H), 3.67 (s, 3H), 3.13 (dd, *J* = 15.8, 7.8 Hz, 1H), 2.84 (apt spt, *J* = 7.0 Hz, 1H), 2.74 (dd, *J* = 16.1, 8.0 Hz, 1H), 2.63 (dd, *J* = 15.8, 6.4 Hz, 1H), 2.43 (d, *J* = 7.4 Hz, 2H), 2.36 (dd, *J* = 16.0, 6.3 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 173.17, 143.65, 142.62, 140.63, 137.79, 136.65, 136.39, 125.58, 124.06, 118.97, 109.32, 77.21, 72.70, 51.53, 39.78, 38.37, 36.29, 35.93. IR (NaCl/thin film): 3438, 3142, 3121, 2996, 2953, 2894, 2840, 1723 cm⁻¹; HRMS (FAB+) calc'd for C₁₇H₁₃N₂O₃ [M+H]⁺-H₂ 297.1127, found 297.1126.

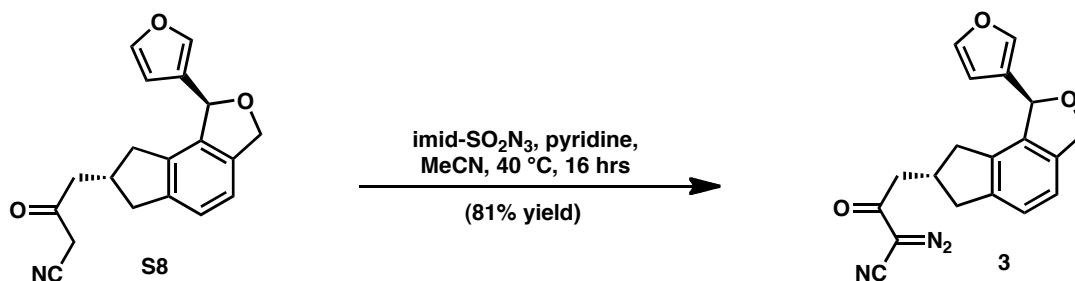
Preparation of keto nitrile S8



To a flame-dried 100 mL flask containing methyl ester **14** (1.05 g, 3.52 mmol, 10:1 ratio diastereomers) was added THF (50 mL). To a separate flame-dried 250 mL flask in the glovebox was added NaHMDS (1.42 g, 7.75 mmol). The flask was then sealed and put under N₂ on the bench. THF (25 mL) was charged to the NaHMDS, and the light yellow solution was cooled to -78 °C. Anhydrous MeCN (440 μL, 8.45 mmol) was added via syringe to the NaHMDS solution, and stirred at -78 °C for 20 minutes. The methyl ester **14** solution was transferred via cannula to the sodio-acetonitrile solution

with a 10 mL THF wash. The reaction was allowed to warm to 0 °C over 1.5 hours, at which point TLC analysis indicated complete consumption of starting material. The reaction was quenched with aqueous saturated NH₄Cl, and diluted with brine and Et₂O. The aqueous layer was separated and back-extracted twice with Et₂O. The combined organics were washed with brine, dried (MgSO₄) and concentrated *in vacuo*. The crude residue was purified (0→45% EtOAc/hexanes) to provide 1.04 g (96% yield) of keto nitrile **S8** as an approximate 10:1 mixture of inseparable diastereomers. $[\alpha]_D^{25} +92.5^\circ$ (*c* 2.25, CH₂Cl₂); ¹H NMR (10:1 diastereomer ratio, asterisk denotes minor peaks 500 MHz, CDCl₃) δ 7.43* (d, *J* = 1.1 Hz, 1H), 7.42 (s, 1H), 7.38 (t, *J* = 1.7 Hz, 2H), 7.15 (d, *J* = 7.6 Hz, 2H), 7.07 (d, *J* = 7.6 Hz, 2H), 6.21 (dd, *J* = 1.8, 0.6 Hz, 2H), 6.12* (s, 1H), 6.10 (s, 1H), 5.21 (dd, *J* = 11.9, 1.5 Hz, 2H), 5.09 (d, *J* = 11.9 Hz, 2H), 3.42 (s, 2H), 3.40* (s, 2H), 3.17 (dd, *J* = 15.8, 7.8 Hz, 2H), 2.92 – 2.82 (m, 2H), 2.80 – 2.74 (m, 6H), 2.56 (dd, *J* = 15.8, 6.0 Hz, 2H), 2.30 (dd, *J* = 16.2, 5.9 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 196.76, 196.69*, 143.65, 143.59*, 142.23*, 142.10, 140.55, 137.91, 137.80*, 136.68, 136.62*, 136.10*, 135.86, 125.71*, 125.46, 124.06, 123.94*, 119.13, 119.08*, 113.63, 109.22, 77.20*, 77.12, 72.71*, 72.62, 47.76, 47.39*, 38.21, 38.13*, 36.33*, 36.14, 34.91*, 34.26, 32.14. IR (NaCl/thin film): 3139, 3076, 3025, 2942, 2913, 2847, 2259, 2183, 1729 cm⁻¹; HRMS (FAB+) calc'd for C₁₉H₁₆NO₃ [M+H]⁺-H₂ 306.1130, found 306.1137.

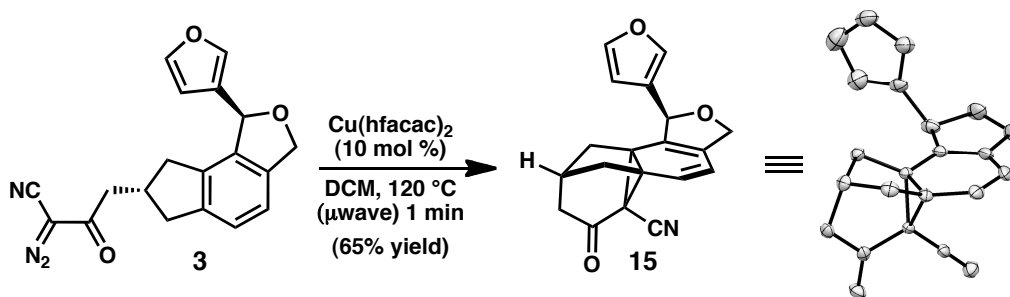
Preparation of diazo keto nitrile **3**



To a 500 mL flask containing keto nitrile **S8** (975 mg, 3.18 mmol, approximately 10:1 ratio diastereomers) and imidazole sulfonyl azide (715 mg, 4.13 mmol) was added MeCN (100 mL). The headspace was purged with N₂, and pyridine (1.41 mL, 17.50 mmol) was added in one portion, resulting in a hazy yellow solution. The reaction was

heated to 40 °C, and after 1 hour became orange in color. After heating an additional 13 hours the TLC analysis indicated full consumption of starting material. The volatiles were removed *in vacuo*, and the residue was purified by flash chromatography (0→30% EtOAc/hexanes), yielding 858 mg (81% yield) of diazo keto nitrile **3** (yellow oil) as a 10:1 mixture of inseparable diastereomers. $[\alpha]_D^{25} +87.0^\circ$ (*c* 2.80, CH₂Cl₂); ¹H NMR (10:1 diastereomer ratio, asterisk denotes minor peaks 500 MHz, CDCl₃) δ 7.43 (s, 2H), 7.38 (t, *J* = 1.7 Hz, 2H), 7.16 (d, *J* = 7.6 Hz, 2H), 7.08 (d, *J* = 7.6 Hz, 2H), 6.21 (dd, *J* = 1.7, 0.7 Hz, 2H), 6.11 (br s, 2H), 5.22 (dd, *J* = 11.9, 1.5 Hz, 2H), 5.10 (d, *J* = 11.9 Hz, 2H), 3.17 (dd, *J* = 15.8, 7.9 Hz, 2H), 2.98 – 2.85 (m, 2H), 2.81 – 2.69 (m, 6H), 2.63 (dd, *J* = 15.8, 6.1 Hz, 2H), 2.37 (dd, *J* = 16.2, 6.0 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 189.22, 143.61, 142.18*, 142.01, 140.56, 140.54*, 137.95, 137.82*, 136.68, 136.59*, 136.08*, 135.81, 125.65*, 125.48, 124.03, 123.90*, 119.12, 119.07*, 109.23, 108.30*, 77.20*, 77.10, 72.69*, 72.61, 57.46, 44.88, 44.56*, 38.20, 38.11*, 36.40*, 36.12, 35.81*, 35.23. IR (NaCl/thin film): 3487, 3330, 3131, 3073, 3024, 2943, 2904, 2846, 2459, 2249, 2221, 2129, 1883, 1673 cm⁻¹; HRMS (FAB+) calc'd for C₁₉H₁₄N₃O₃ [M+H]⁺-H₂ 332.1035, found 332.1028.

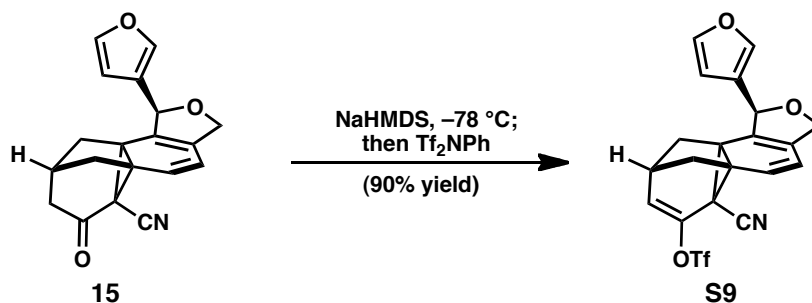
Preparation of Norcaradiene 15



A 20 mL microwave vial was charged with Cu(hfacac)₂ (14.9 mg, 0.03 mmol), sealed, and purged with N₂. To a flame-dried 25 mL flask containing diazo β -ketonitrile **3** (100 mg, 0.30 mmol, 10:1 mixture diastereomers) was charged DCM (15 mL). The diazo solution was then transferred via syringe into the sealed microwave vial. The vial was placed into the microwave reactor and heated to 120 °C for 1 minute (ramp from 22 °C to 120 °C required 1.5 minutes). TLC analysis confirmed consumption of the starting

material, and the solvent was removed *in vacuo*. The crude residue was purified by flash chromatography (gradient elution, 0 → 60% EtOAc/Hexanes), yielding norcaradiene **15** (60 mg, 65% yield, single diastereomer) as a white crystalline solid. m.p. 197-199 °C; $[\alpha]_D^{25} + 185.8^\circ$ (*c* 0.18, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 7.53 (dd, *J* = 1.5, 0.8 Hz, 1H), 7.42 (td, *J* = 1.7, 0.6 Hz, 1H), 6.45 (d, *J* = 9.4 Hz, 1H), 6.34 (dd, *J* = 1.7, 0.8 Hz, 1H), 6.31 (d, *J* = 9.4 Hz, 1H), 5.98 (t, *J* = 4.9 Hz, 1H), 4.91 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.88 (dd, *J* = 12.5, 4.5 Hz, 1H), 2.32 – 2.20 (m, 3H), 2.14 (d, *J* = 12.8 Hz, 1H), 2.12 – 2.06 (m, 1H), 1.73 (d, *J* = 13.3 Hz, 1H), 1.68 (ddd, *J* = 13.4, 5.0, 1.5 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 199.2, 144.0, 140.9, 135.8, 131.1, 125.4, 125.4, 123.0, 112.0, 109.2, 79.3, 73.6, 51.6, 46.9, 43.24, 35.7, 34.5, 29.9, 26.2; IR (NaCl/thin film): 2937, 2848, 2239, 1694, 1343, 1034 cm⁻¹; HRMS (FAB+) calc'd for C₁₉H₁₆O₅N [M+H]⁺ 306.1130 found 306.1136. **Note:** Short reaction time allows for rapid throughput of material, thus facilitating scale-up.

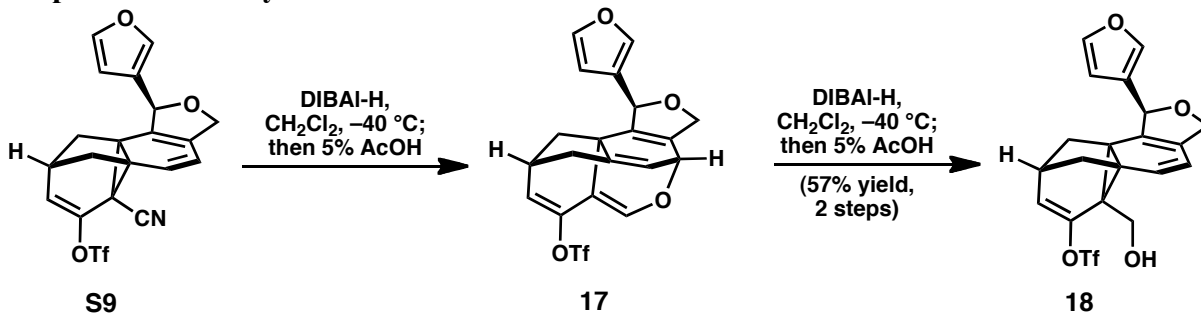
Preparation of Vinyl Triflate S9



To a solution of β-ketonitrile **15** (30.0 mg, 0.10 mmol) in THF (20 mL) cooled to -78 °C was added NaHMDS (20.0 mg, 0.11 mmol) in THF (1 mL). The resulting orange solution was stirred under N₂ for 30 minutes, after which time Tf₂NPh (43.0 mg, 0.12 mmol) in THF (1 mL) was added in one portion. After 40 minutes the reaction mixture was quenched by addition of saturated aqueous NaHCO₃ at -78 °C and warmed up to 23 °C. The resulting mixture was diluted with saturated aqueous NaCl (20 mL) and extracted with diethyl ether (3 x 40 mL). The combined ethereal solution was dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (gradient elution, 0 → 50% Hexanes/ EtOAc)

to give 39 mg (90% yield) of **S9** as a yellow oil. $[\alpha]_D^{25} + 168.4^\circ$ (c 2.50, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3) δ 7.49 (dd, $J = 1.7, 0.9$ Hz, 1H), 7.40 (td, $J = 1.7, 0.6$ Hz, 1H), 6.41 (d, $J = 9.4$ Hz, 1H), 6.33 (ddd, $J = 1.7, 0.9, 0.4$ Hz, 1H), 6.17 (d, $J = 9.4$ Hz, 1H), 5.99 (d, $J = 8.3$ Hz, 1H), 5.91 (t, $J = 5.0$ Hz, 1H), 4.89 (m, 2H), 2.59 (dtt, $J = 8.3, 4.9, 0.5$ Hz, 1H), 1.78 (dd, $J = 12.5, 5.0$ Hz, 1H), 1.53 (d, $J = 12.9$ Hz, 1H), 1.40 (dd, $J = 12.9, 5.0$ Hz, 1H), 1.10 (d, $J = 12.9$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 143.9, 140.9, 137.0, 135.4, 128.6, 125.2, 123.4, 123.2, 118.6 (q, $J = 318$ Hz), 115.5, 111.8, 109.1, 79.3, 73.8, 44.4, 39.7, 31.1, 29.4, 27.6, 16.7; IR (NaCl/thin film): 2935, 2854, 2240, 1654, 1506, 1425, 1212 cm^{-1} ; HRMS (ES+) calc'd for $\text{C}_{20}\text{H}_{15}\text{F}_3\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$ 438.0623, found 438.0641.

Preparation of Vinyl Triflate **18**



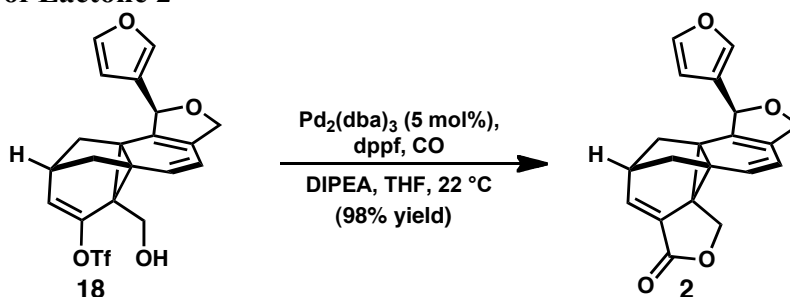
To a flame-dried flask under N_2 containing a solution of vinyl triflate **S9** (25.0 mg, 0.06 mmol) in DCM (10 mL) was added DIBAL-H (24.0 mg, 0.17 mmol) in DCM (1 mL) at -30°C . After 30 minutes, reaction was complete (TLC analysis) and was quenched with 5% aqueous AcOH (5 mL) (**Warning**: H_2 evolution). The reaction mixture was warmed up to room temperature and stirred vigorously for 30 minutes (clear biphasic mixture resulted). The organic layer was separated and stirred with dilute aqueous NaHCO_3 solution (5 mL, 1:1 H_2O : aqueous saturated NaHCO_3) to remove traces of AcOH. This organic layer was separated, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to yield 27.0 mg crude rearranged product **17** as pale yellow oil, which turns darker upon standing. (**Warning**: rearranged product **17** is extremely unstable and should be used for the next step immediately; it should be kept under argon and away from light as often as possible during workup). A small portion of the rearranged product **17** was purified by preparative HPLC for analytical purposes to

give rearranged product **17** as a clear oil (retention time 4.6 minutes, 15% EtOAc/Hexanes), which was immediately dissolved in CD₂Cl₂ under argon for NMR analysis. ¹H NMR (600 MHz, CD₂Cl₂) δ 7.41 (br s, 1H), 7.40 (app t, *J* = 1.7 Hz, 1H), 6.50 (s, 1H), 6.27 (dt, *J* = 1.7, 0.7 Hz, 1H), 5.78 (br d, *J* = 4.1 Hz, 1H), 5.75 (d, *J* = 7.4 Hz, 1H), 5.53 (dt, *J* = 4.0, 2.0 Hz, 1H), 5.50 (t, *J* = 2.2 Hz, 1H), 4.59 (dt, *J* = 13.5, 1.7 Hz, 1H), 4.53 (dt, *J* = 13.5, 1.7 Hz, 1H), 2.71 (td, *J* = 7.0, 4.1 Hz, 1H), 2.32 (br d, *J* = 17.8 Hz, 1H), 2.16 – 2.02 (m, 2H), 1.73 (dd, *J* = 10.4, 4.2 Hz, 1H); HRMS (EI+) calc'd for C₂₀H₁₅F₃O₆S [M]⁺ 440.0541, found 440.0523. A completely clean ¹³C NMR could not be obtained on the purified material due to the rapid decomposition. ¹³C NMR, HSQC and HMBC spectra could be obtained, however, on mostly pure compound directly from the workup. ¹³C NMR (125 MHz, CD₂Cl₂) δ 144.16, 141.98, 141.48, 140.43, 139.16, 135.15, 130.34, 123.91, 120.28, 118.90 (q, *J* = 320 Hz), 116.43, 109.70, 108.83, 85.38, 74.53, 69.95, 57.85, 41.31, 36.26, 33.88.

The rearranged product **17** was dissolved in benzene and concentrated under reduced pressure, dried under vacuum for 10 minutes, backfilled with Ar, dissolved in dry DCM (10 mL). The resulting solution was cooled to –30 °C and treated with DIBAL-H (24.0 mg, 0.17 mmol) in DCM (1 mL). After 15 minutes, reaction was complete (TLC analysis) and was carefully quenched (H₂ evolution) with 5% aqueous AcOH (5 mL). When gas evolution ceased, the reaction mixture was warmed up to room temperature and stirred vigorously for 30 minutes (a clear biphasic mixture formed). The organic layer was separated and stirred with dilute aqueous NaHCO₃ solution (5 mL, 1:1 H₂O saturated aqueous NaHCO₃) to remove traces of AcOH. This organic layer was separated, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to yield crude yellow oil. This residue was purified by preparative HPLC (40% Hexanes/EtOAc, retention time 4 minutes) to give 14.3 mg (57% yield, two steps) of **18** as a clear oil. [α]_D²⁵ + 81.1° (*c* 3.1, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 7.45 (d, *J* = 1.4, 0.9 Hz, 1H), 7.38 (td, *J* = 1.7, 0.5 Hz, 1H), 6.38 (ddd, *J* = 1.8, 0.9, 0.4 Hz, 1H), 6.15 (d, *J* = 9.5 Hz, 1H), 6.12 (d, *J* = 9.5 Hz, 1H), 5.95 (d, *J* = 8.2 Hz, 1H), 5.90 (dd, *J* = 9.2, 4.0 Hz, 1H), 4.87 (dd, *J* = 12.3, 5.6 Hz, 1H), 4.75 (dd, *J* = 12.3, 3.7 Hz, 1H), 3.68 (dd, *J* = 12.8, 5.2

Hz, 1H), 3.58 (dd, $J = 12.8, 6.6$ Hz, 1H), 2.38 (dt, $J = 8.9, 4.5$ Hz, 1H), 1.56 (dd, $J = 12.0, 4.8$ Hz, 1H), 1.48 (dd, $J = 6.7, 5.3$ Hz, 1H), 1.44 (d, $J = 11.9$ Hz, 1H), 1.23 (dd, $J = 12.3, 4.8$ Hz, 1H), 1.02 (d, $J = 12.4$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 143.62, 143.55, 140.4, 132.3, 130.7, 125.8, 125.6, 121.0, 118.4 (q, $J = 317.5$ Hz), 116.1, 109.3, 80.1, 73.7, 56.0, 39.4, 34.1, 32.70, 30.8, 27.5, 24.2; IR (NaCl/thin film): 3436, 2930, 2895, 2855, 1653, 1505, 1417, 1208 cm^{-1} ; HRMS (FAB+) calc'd for $\text{C}_{20}\text{H}_{18}\text{F}_3\text{O}_6\text{S}$ $[\text{M}+\text{H}]^+$ 443.0776, found 443.0792.

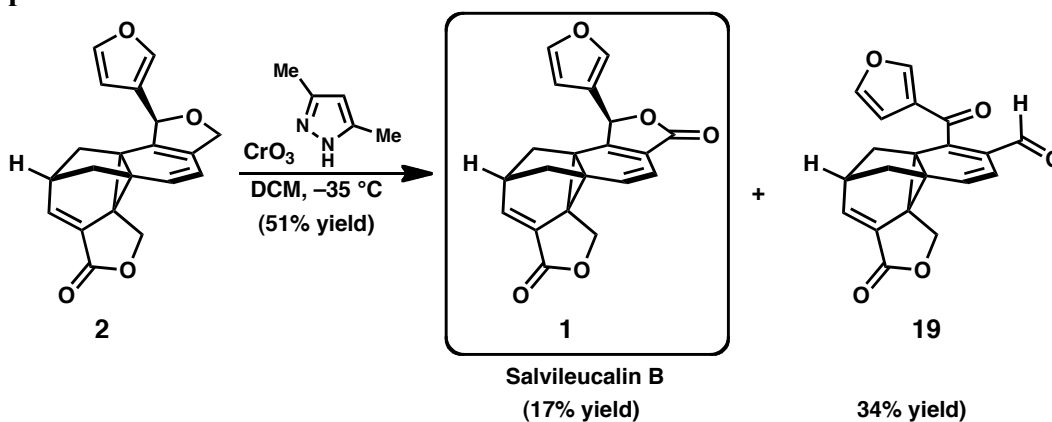
Preparation of Lactone 2



To an oven-dried 20-mL vial, equipped with a stir bar, septum and CO balloon, was added solution of vinyl triflate **18** (7.0 mg, 16 μmol) in dry THF (4 mL). CO was allowed to bubble through the solution for 5 minutes. Triethylamine (9.0 μL , 64 μmol) was added, followed by dppf (1.6 mg, 1.6 μmol) in THF (0.4 mL) and $\text{Pd}_2(\text{dba})_3$ in THF (0.8 mL). The resulting yellow solution was gently warmed up to 40 °C under CO atmosphere. After 40 minutes the reaction was complete (LCMS analysis) and was passed through short pug of silica-gel, which was washed with EtOAc (3 x 5 mL). The resulting filtrate was concentrated under reduced pressure, and the crude residue was purified by preparative HPLC (40% EtOAc/Hexanes, retention time 3.9 minutes) to give 5.2 mg (98% yield) of **2** as a clear oil, which solidifies when stored. $[\alpha]_D^{25} + 91.4^\circ$ (c 2.6, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.43 (dd, $J = 1.3, 1.0$ Hz, 1H), 7.39 (td, $J = 1.7, 0.5$ Hz, 1H), 7.01 (d, $J = 7.0$ Hz, 1H), 6.30 (ddd, $J = 1.9, 0.8, 0.4$ Hz, 1H), 6.23 (d, $J = 9.4$ Hz, 1H), 6.05 (d, $J = 9.4$ Hz, 1H), 5.85 (t, $J = 4.4$ Hz, 1H), 4.90 (dd, $J = 12.0, 5.4$ Hz, 1H), 4.81 (dd, $J = 12.0, 3.6$ Hz, 1H), 3.94 (d, $J = 10.2$ Hz, 1H), 3.90 (d, $J = 10.2$ Hz, 1H), 2.73 (dt, $J = 7.0, 4.8$ Hz, 1H), 1.64 (dd, $J = 12.0, 4.8$ Hz, 1H), 1.28 (dd, $J = 12.4, 4.8$ Hz, 1H), 1.23 (d, $J = 12.0$ Hz, 1H), 0.84 (d, $J = 12.3$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ

169.1, 143.8, 140.7, 132.7, 131.0, 129.8, 125.4, 124.9, 124.7, 119.5, 109.1, 79.8, 74.0, 66.9, 39.6, 34.5, 31.6, 29.8, 27.8, 23.6; IR (NaCl/thin film): 2956, 2927, 2852, 1761, 1653, 1506, 1231, 1156 cm^{-1} ; HRMS (EI+) calc'd for $\text{C}_{20}\text{H}_{16}\text{O}_4$ $[\text{M}]^+$ 320.1049, found 320.1052.

Preparation of Salvileucalin B 1



In a glove box a stirred suspension of finely grinded CrO_3 (27.0 mg, 0.27 mmol)¹ in DCM (7 mL) at $-35\text{ }^\circ\text{C}$ was charged with a solution of 1,3-dimethylpyrazole (52.0 mg, 0.54 mmol) in DCM (4 mL). After 30 minutes complete dissolution of the CrO_3 was observed. To this clear dark orange solution ($\text{CrO}_3 \cdot \text{DMP}$ complex) was added solution of **2** (8.6 mg, 0.03 mmol) in DCM (2 mL). After 3 hours dark brown solution was allowed to warm up to $23\text{ }^\circ\text{C}$ and loaded directly onto a 50 g silica column (no solvent evaporation). Elution with Hexanes/EtOAc (1:2) afforded crude mixture of salvileucalin B (**1**) and keto-aldehyde **19** as a yellow oil. Further purification was achieved by preparative HPLC (2:3 EtOAc/Hexanes) to yield 1.5 mg (17% yield) of salvileucalin B (**1**) as a clear oil and ketoaldehyde **19** 3.0 mg (34% yield) as yellow oil.

Synthetic Salvileucalin B (**1**): $[\alpha]_{\text{D}}^{25} + 40.8^\circ$ (c 0.14, CHCl_3); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.58 (s, 1H), 7.45 (t, $J = 1.4$ Hz, 1H), 7.15 (d, $J = 7.0$ Hz, 1H), 6.63 (d, $J = 9.5$ Hz, 1H), 6.24 (d, $J = 9.5$ Hz, 1H), 6.22 (dd, $J = 2.0, 0.7$ Hz, 1H), 6.10 (s, 1H), 3.96 (d, $J = 10.5$ Hz, 1H), 3.79 (d, $J = 10.5$ Hz, 1H), 2.85 (dt, $J = 6.9, 4.7$ Hz, 1H), 1.72 (dd, $J = 12.2, 4.7$ Hz, 1H), 1.37 (dd, $J = 12.4, 4.8$ Hz, 1H), 1.33 (d, $J = 12.3$ Hz, 1H), 1.00 (d, $J =$

¹ CrO_3 was dried under vacuum over P_2O_5 for 12 hours.

12.4 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.0, 168.1, 154.2, 144.5, 142.2, 134.3, 126.3, 123.8, 122.6, 119.2, 118.0, 108.3, 75.9, 66.3, 42.4, 36.6, 31.5, 29.6, 27.3, 25.7; IR (NaCl/thin film): 2952, 2913, 2848, 1754, 1352, 1295, 1233; HRMS (EI+) calc'd for $\text{C}_{20}\text{H}_{14}\text{O}_5$ $[\text{M}]^+$ 334.0841, found 334.0840.

Keto-Aldehyde **19**: $[\alpha]_{\text{D}}^{25} - 210.1^\circ$ (*c* 0.24, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.58 (s, 1H), 7.44 (s, 1H), 7.15 (d, $J = 7.0$ Hz, 1H), 6.63 (d, $J = 9.5$ Hz, 1H), 6.23 (d, $J = 9.5$ Hz, 1H), 6.21 (s, 1H), 6.10 (s, 1H), 3.96 (d, $J = 10.5$ Hz, 1H), 3.79 (d, $J = 10.5$ Hz, 1H), 2.84 (dt, $J = 9.2, 4.6$ Hz, 1H), 1.71 (dd, $J = 12.2, 4.7$ Hz, 1H), 1.36 (dd, $J = 12.4, 4.8$ Hz, 1H), 1.33 (d, $J = 12.3$ Hz, 1H), 1.00 (d, $J = 12.4$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 187.4, 187.3, 168.1, 149.5, 146.7, 145.6, 134.5, 133.0, 128.8, 125.7, 123.7, 119.4, 108.3, 66.5, 42.9, 40.1, 31.0, 29.90, 28.7, 27.2; IR (NaCl/thin film): 3030, 2957, 2928, 2851, 2754, 1760, 1683, 1657, 1557, 1233 cm^{-1} ; HRMS (ESI) calc'd for $\text{C}_{20}\text{H}_{15}\text{O}_5$ $[\text{M}+\text{H}]^+$ 335.0914, found 335.0920.

Comparison of spectroscopic data for natural² and synthetic salvileucalin B

¹H NMR Data (both spectra are referenced to CHCl₃ at 7.27 ppm)

Reported	Synthetic
7.59 (br. s, 1H)	7.59 (s, 1H),
7.44, (br. dd, 1H)	7.46 (t, <i>J</i> = 1.4 Hz, 1H)
7.16 (d, <i>J</i> = 7.0 Hz, 1H)	7.16 (d, <i>J</i> = 7.0 Hz, 1H)
6.62 (d, <i>J</i> = 9.6 Hz, 1H)	6.64 (d, <i>J</i> = 9.5 Hz, 1H)
6.25 (d, <i>J</i> = 9.6 Hz, 1H)	6.25 (d, <i>J</i> = 9.5 Hz, 1H)
6.22 (br. s, 1H)	6.23 (dd, , <i>J</i> = 2.0, 0.7 Hz 1H)
6.13 (1H, s)	6.11 (s, 1H)
3.95 (d, <i>J</i> = 10.5 Hz, 1H)	3.97 (d, <i>J</i> = 10.5 Hz, 1H)
3.80 (d, <i>J</i> = 10.5 Hz, 1H)	3.80 (d, <i>J</i> = 10.5 Hz, 1H)
2.85 (1H, br ddd)	2.86 (dt, <i>J</i> = 6.9, 4.7 Hz, 1H)
1.72 (dd, <i>J</i> = 12.2, 4.7 Hz, 1H)	1.73 (dd, <i>J</i> = 12.2, 4.7 Hz, 1H)
1.38 (dd, , <i>J</i> = 12.4, 4.7 Hz, 1H)	1.38 (dd, <i>J</i> = 12.4, 4.8 Hz, 1H)
1.33 (d, <i>J</i> = 12.2 Hz, 1H)	1.34 (d, <i>J</i> = 12.3 Hz, 1H)
1.01 (d, <i>J</i> = 12.4 Hz, 1H)	1.01 (d, <i>J</i> = 12.4 Hz, 1H)

¹³C NMR Data (both spectra are referenced to CDCl₃ at 77.0 ppm)

Reported	Synthetic
170.0	170.0
168.1	168.1
154.3	154.2
144.5	144.5
142.2	142.2
134.3	134.3
126.3	126.3
123.7	123.8
122.6	122.6
119.2	119.2
117.9	118.0
108.2	108.3
75.9	75.9
66.3	66.3
42.3	42.4
36.6	36.6
31.4	31.5
29.6	29.6
27.3	27.3
25.7	25.7

² Data extracted from the supporting information of the isolation paper: Aoyagi, Y.; Yamazaki, A.; Nakatsugawa, C.; Fukaya, H.; Takeya, K.; Kawauchi, S.; Izumi, H. *Org. Lett.* **2008**, *10*, 4429.