Hydrocarbon Oxidation *vs.* C-C Bond Forming Approaches for Efficient Syntheses of Oxygenated Molecules.

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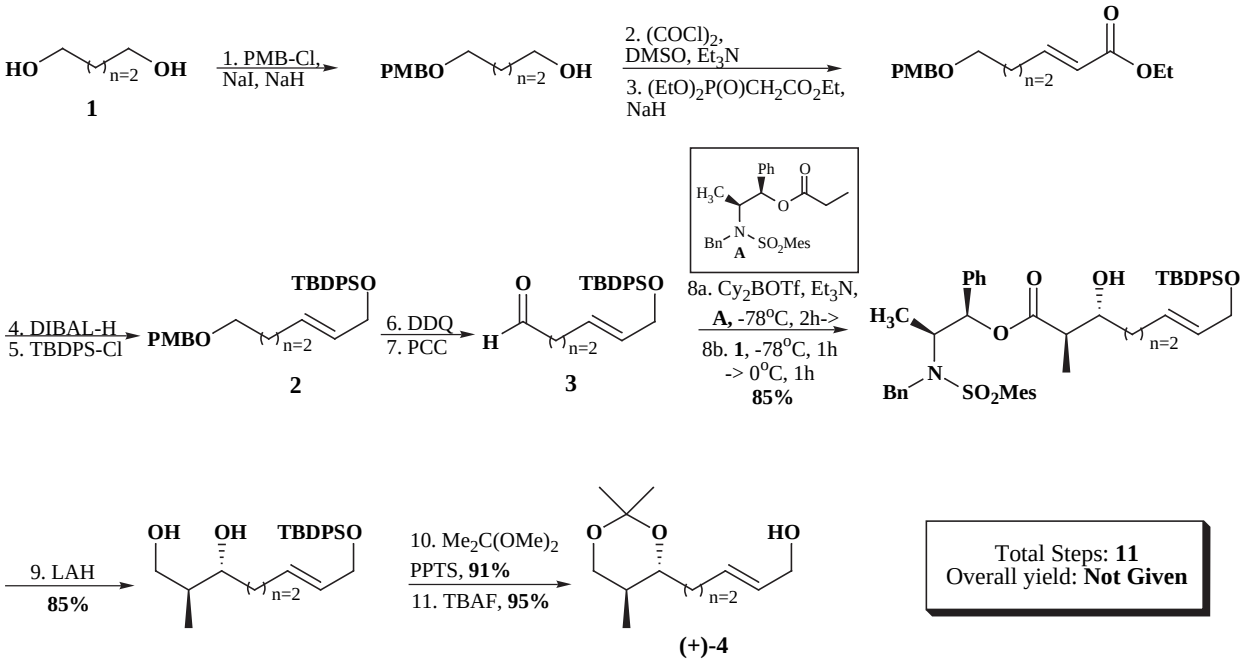
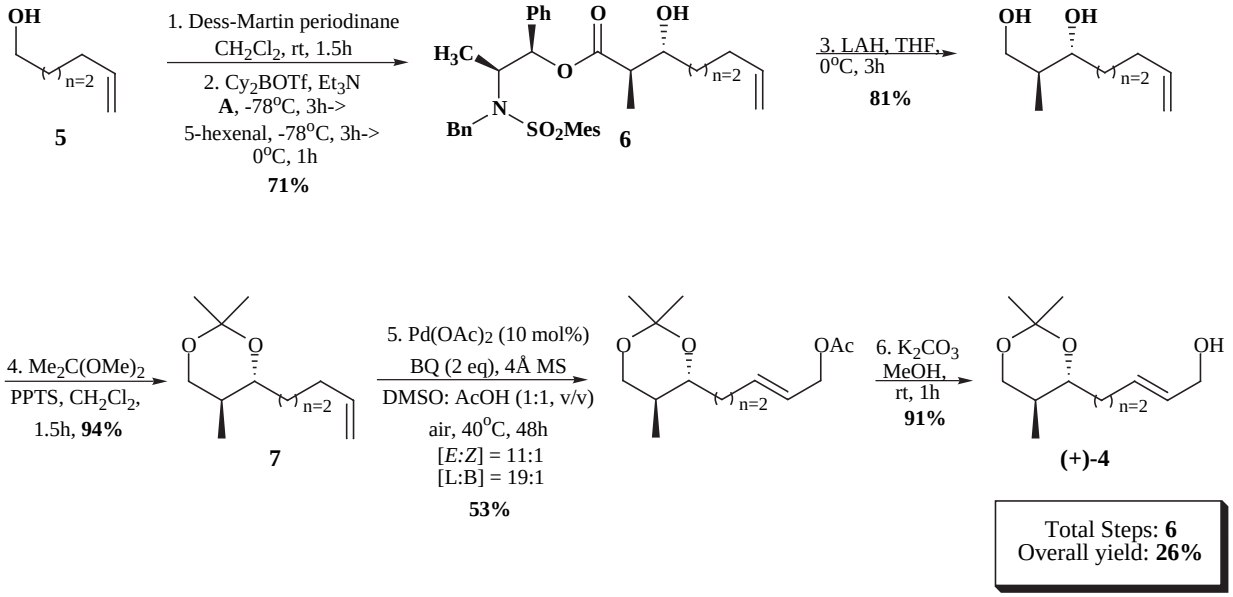
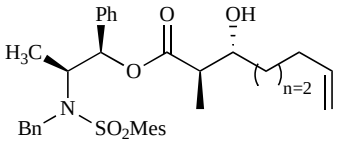
General Information: All allylic oxidation reactions were conducted in 40 mL VWRbrand borosilicate glass vials with a teflon-lined solid cap under an air atmosphere. Vials were used as received (no cleansing or drying was done prior to reaction). All commercially obtained reagents for the allylic oxidation reaction (Sigma-Aldrich Chemical Company, unless otherwise stated) were used as received: anhydrous (Sure/Seal) DMSO; 4Å (powdered, <5 micron) activated molecular sieves; 1,4-benzoquinone; glacial acetic acid (Mallinckrodt Chemicals); $Pd(OAc)_2$ (Strem Chemicals). $Pd(OAc)_2$ was stored in a glove box under a nitrogen atmosphere and weighed out under an air atmosphere prior to use. Solvents tetrahydrofuran (THF), diethyl ether (Et_2O), and methylene chloride (CH_2Cl_2) were purified prior to use by passage through a bed of activated alumina (Glass Contour, Laguna Beach, California). Methanol (MeOH) was distilled from magnesium. Anhydrous N,N-dimethylformamide (DMF) (Sure/Seal) was obtained from Sigma-Aldrich and used as received. (-)-*B*-Methoxydiisopinocampheylborane was obtained from Sigma-Aldrich. Propionic acid (*1R, 2S*)-2-[N-benzyl-N-(mesitylenesulfonyl)amino]-1-phenylpropyl ester was obtained from TCI-US Chemical Company. Dess-Martin periodinane was obtained from Sigma-Aldrich. Dicyclohexylboron triflate (Cy_2BOTf) was prepared according to the published procedure.[1] Isobutyraldehyde was distilled at 65°C external temperature (760 mm Hg) before use. Achiral gas chromatographic (GC) analyses were performed on Agilent Technologies 6890N Series instrument equipped with FID detectors using a HP-5 (5%-Phenyl)-methylpolysiloxane column (30m, 0.32mm, 0.25μm). Linear to branched allylic acetate ratios [L:B] were determined by GC analysis of the crude and were not corrected for small response factor variations. Retention times for the branched isomers were determined by independent synthesis using the previously described literature procedure.[2] Chiral GC analysis was performed on Agilent 5890 Series instrument equipped with FID detectors using a cyclodex-β column (30m, 0.25mm, 0.25μm). Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized with UV and potassium permanganate staining. Flash column chromatography was performed as described by Still et al.[3] using EM reagent silica gel 60 (230-400 mesh). ^{1}H NMR spectra were recorded on a Varian Mercury-400 (400 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; coupling constant(s) in Hz; integration. Ratios of *E* to *Z* isomers for the allylic acetates and allylic alcohols were determined by ^{1}H NMR analysis of the crude upon workup and are based on integration of the allylic hydrogens of the acetoxy- or hydroxy-bearing carbon of the two isomers. Proton-decoupled ^{13}C- NMR spectra were recorded on a Varian Mercury-400 (100 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm). IR spectra were recorded as thin films on NaCl plates on a Matterson FTIR 3000 and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra were obtained at the Harvard University Mass Spectrometry Laboratory. Optical rotations were measured using a 2 mL cell with a 1 dm path length on a Jasco DIP 370 digital polarimeter. Optical rotations were obtained with a sodium lamp and are reported as follows: $[\alpha]_{\lambda}^{T\,^oC}$ (c = g/100 mL, solvent).

Previously Reported HWE Olefination Route to Miyakolide C_6-C_{13} Fragment Precursor (+)-4:[4]



Oxidation Route to Miyakolide C_6-C_{13} Fragment Precursor (+)-4:

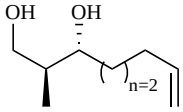




Anti-Aldol Adduct 6:[4,5] A flame-dried 250 mL round bottom flask was charged sequentially with a stir bar and Dess-Martin periodinane (4.73 g, 11.15 mmol). A solution of 5-hexen-1-ol (1.10 mL, 9.29 mmol) in CH_2Cl_2 (60 mL) was added *via* cannula. The reaction was allowed to stir at room temperature for 1.5 h then diluted with saturated aq. $NaHCO_3$ (45 mL) and $Na_2S_2O_3$ (11.0 g). The reaction mixture was allowed to stir for 10 min. then the aqueous and organic layers were separated. The organic layer was washed with 1.0M KOH (3 x 50 mL) and H_2O (1 x 50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* (-15°C at 52 mm Hg) to a 35 mL solution of crude 5-hexenal in CH_2Cl_2. This was used directly in the aldol addition.

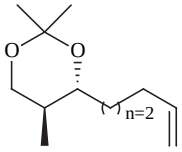
A flame-dried 500 mL round bottom flask was charged sequentially with a stir bar, propionic acid (*1R, 2S)*-2-[N-benzyl-N-(mesitylenesulfonyl)-amino]-1-phenylpropyl ester **A** (5.12 g, 10.68 mmol) and CH_2Cl_2 (90 mL). The solution was cooled to –78°C and was charged with Et_3N (3.6 mL, 25.64 mmol). A flame-dried 100 mL round bottom flask was sequentially charged with a stir bar, CH_2Cl_2 (50 mL) and Cy_2BOTf[1] (1.4M in hexanes, 21.37 mmol). The Cy_2BOTf solution was cooled to –78°C then added to **A** dropwise *via* cannula. The reaction mixture was allowed to stir at –78°C for 3h. The 5-hexenal solution was cooled to –78°C then added to the boron enolate dropwise *via* cannula. The reaction was allowed to stir at –78°C for 3h then 0°C for 1h. The reaction was quenched with pH 7 buffer (50 mL), MeOH (100 mL), then 30 wt % aq. H_2O_2 (50 mL). The reaction mixture was warmed to room temperature then allowed to stir vigorously overnight. The next day the aqueous and organic layers were separated and the aqueous layer was extracted with CH_2Cl_2 (1 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by SiO_2 flash chromatography (10% EtOAc/hexanes) provided the desired anti-aldol adduct (3.83g, 6.64 mmol, 71% yield over 2 steps) with trace amounts of cyclohexanol impurity remaining. Note: the mass of the undesired cyclohexanol impurity (determined by ^{1}H NMR) was subtracted from the total mass before calculating the reported yield. No other anti- or syn- diastereomers were observed by ^{1}H-NMR.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17-7.30 (m, 8H), 6.88 (m, 4H) 5.84 (d, *J* = 4.4 Hz, 1H), 5.78 (ddt, *J* = 16.8, 10.4, 6.4 Hz, 1H), 4.99 (dm, *J* = 17.2, 1H), 4.94 (dm, *J* = 10.4 Hz, 1H), 4.75 (d, *J* = 16.4 Hz, 1H), 4.53 (d, *J* = 16.4 Hz, 1H), 4.12 (m, 1H), 3.63 (m, 1H), 2.48 (s, 6H), 2.47 (m, 1H), 2.28 (s, 3H), 2.05 (m, 2H), 1.35-1.60 (m, 4H), 1.18 (d, *J* = 7.2 Hz, 3H), 1.13 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 142.5, 140.2, 138.5, 138.4, 138.1, 133.3, 132.1, 128.4 (d), 128.3, 127.9, 127.6, 127.2, 125.9, 114.7, 78.2, 72.9, 56.7, 48.2, 45.4, 33.7, 33.5, 24.6, 22.9, 20.8, 14.1, 13.4; IR (film, cm^{-1}): 3524 (br), 2978, 2936, 2857, 1740, 1605, 1454, 1323, 1154. HRMS (ESI) *m/z* calc'd for $C_{34}H_{44}NO_5S$ $[M+H]^+$: 578.2940, found 578.2943.



(2*S*,3*R*)-2-Methyloct-7-ene-1,3-diol: A flame-dried 500 mL round bottom flask was charged sequentially with a stir bar, lithium aluminum hydride (LAH) powder (573 mg, 15.10 mmol), and THF (45 mL). The LAH suspension was cooled to 0°C. A solution of aldol adduct (1.45 g, 2.52 mmol) in THF (27 mL) was cooled to 0°C and added dropwise *via* cannula to the lithium aluminum hydride suspension. The reaction was allowed to stir at 0°C for 3h. The reaction was quenched with EtOAc (100 mL) and saturated aq. Rochelle's salt (100 mL). The mixture was allowed to warm to room temperature then stirred for 3h. The aqueous and organic layers were separated. The aqueous layer was extracted with EtOAc (4 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by SiO_2 flash chromatography (45% EtOAc/hexanes) provided the desired diol (321.3 mg, 2.03 mmol, 81% yield) as a pale yellow, viscous oil.

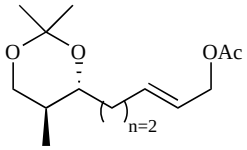
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 16.8, 10.4, 6.4 Hz, 1H), 5.01 (dm, *J* = 17.2 Hz, 1H), 4.95 (dm, *J* = 10.0 Hz, 1H), 3.76 (dd, *J* = 11.0, 4.0 Hz, 1H), 3.60 (dd, *J* = 10.8, 7.2 Hz, 1H), 3.55 (dt, *J* = 7.8, 2.4 Hz, 1H), 3.05 (br s, 2H), 2.08 (m, 2H), 1.70 (m, 1H), 1.58 (m, 2H), 1.45 (m, 2H), 0.87 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 114.6, 77.1, 67.6, 39.8, 34.7, 33.7, 24.4, 13.9; IR (film, cm^{-1}): 3347 (br), 3077, 2936, 1642, 1458. HRMS (CI, NH_3) *m/z* calc'd for $C_9H_{22}NO_2$ $[M+NH_4]^+$: 176.1651, found 176.1660; $[\alpha]_D^{26}$ = +28.8° (c = 0.98, $CHCl_3$).



7

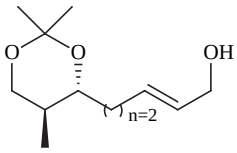
(4*R*,5*S*)-2,2,5-Trimethyl-4-(pent-4-enyl)-1,3-dioxane 7: A flame-dried 200 mL round bottom flask was charged sequentially with a stir bar and pyridinium *p*-toluene sulfonate (116.5 mg, 0.46 mmol). A solution of (2*S*,3*R*)-2-methyloct-7-ene-1,3-diol (293.5 mg, 1.85 mmol) in CH_2Cl_2 (40 mL) was added dropwise *via* cannula. The reaction was allowed to stir at room temperature for 1 h. The reaction was quenched with saturated $NaHCO_3$ (20 mL). The aqueous and organic layers were separated and the aqueous layer was extracted with CH_2Cl_2 (1 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* at –15°C. Purification by SiO_2 flash chromatography (5% Et_2O/*n*-pentane) provided the desired acetonide (346.0 mg, 1.74 mmol, 94% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 16.8, 10.0, 6.8 Hz, 1H), 5.00 (dm, *J* = 17.0 Hz, 1H), 4.94 (dm, *J* = 10.0 Hz, 1H), 3.67 (dd, *J* = 11.6, 5.2 Hz, 1H), 3.45 (t, *J* = 11.2 Hz, 1H), 3.42 (dt, *J* = 10.0, 2.0 Hz, 1H), 2.05 (m, 2H), 1.62 (m, 1H), 1.42 (s, 3H), 1.39 (m, 2H), 1.38 (s, 3H), 1.29 (m, 2H), 0.73 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 114.4, 98.1, 74.8, 66.2, 34.0, 33.7, 32.4, 29.8, 24.2, 19.1, 12.7; IR (film, cm^{-1}): 3077, 2994, 2940, 2853, 1642, 1460, 1381, 1368, 1267, 1202. HRMS (CI, NH_3) *m/z* calc'd for $C_{12}H_{26}NO_2$ $[M+NH_4]^+$: 216.1964, found 216.1966; $[\alpha]_D^{26}$ = +41.2° (c = 1.00, $CHCl_3$).



(*E*)-5-[(4*R*,5*S*)-2,2,5-Trimethyl-1,3-dioxan-4-yl]pent-2-enyl acetate : A 40 mL borosilicate glass vial was charged with the following solids: $Pd(OAc)_2$ (22.4 mg, 0.1 mmol), benzoquinone (217 mg, 2.0 mmol), and 4Å MS (217 mg). To the solids vial was sequentially added DMSO (2.5 mL) and (2*S*,3*R*)-2-methyloct-7-ene-1,3-acetonide **2** (198.3 mg, 1.0 mmol). DMSO (0.5 mL) was used to rinse any residual acetonide to the bottom of the vial. The vial was then charged with AcOH (3.0 mL) and a stir bar, capped, and allowed to heat at 40°C. Aliquots were taken at t = 24h and 48h to determine the linear (*E*)-allylic acetate:branched acetate isomeric ratio [L:B]. After 48h the reaction was quenched with saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with H_2O (2 x 100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a brown oil. Crude product: 24h: [L:B] = 34:1; 48h: [L:B] = 20:1, [E:Z] = 12:1. *Immediate* purification by SiO_2 flash chromatography (10% EtOAc/hexanes) provided the desired linear (*E*)-allylic acetate as a yellow oil. After column: (run 1: 134.6 mg, 0.53 mmol, 53% yield; run 2: 130.6 mg, 0.51 mmol, 51% yield; run 3: 139.5 mg, 0.54 mmol, 54% yield; average yield: 53%). After column: [L:B] = 19:1, [E:Z] = 11:1.

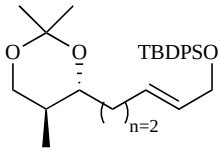
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (dt, *J* = 15.4, 6.6 Hz, 1H), 5.58 (dt, *J* = 15.2, 6.8 Hz, 1H), 4.50 (d, *J* = 6.8 Hz, 2H), 3.67 (dd, *J* = 11.2, 5.2 Hz, 1H), 3.48 (t, *J* = 11.2 Hz, 1H), 3.42 (dt, *J* = 2.4, 9.4 Hz, 1H), 2.23 (m, 1H), 2.10 (m, 1H), 2.05 (s, 3H), 1.66 (m, 2H), 1.45 (m, 1H), 1.40 (s, 3H), 1.37 (s, 3H), 0.73 (d, *J* = 6.8 Hz, 3H); Z isomer: 4.63 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 136.1, 124.1, 98.2, 74.0, 66.1, 65.2, 34.0, 32.0, 29.7, 27.6, 21.0, 19.1, 12.7; IR (film, cm^{-1}): 2992, 2944, 2855, 1742, 1460, 1381, 1368, 1233, 1202. HRMS (ESI) *m/z* calc'd for $C_{14}H_{25}O_4$ $[M+H]^+$: 257.1753, found 257.1750; $[\alpha]_D^{27}$ = +40.7° (c = 0.97, $CHCl_3$).



(+)-4

(*E*)-5-[(4*R*,5*S*)-2,2,5-Trimethyl-1,3-dioxan-4-yl]pent-2-en-1-ol (+)-4:[4] A 50 mL round bottom flask was charged sequentially with a stir bar, (*E*)-6-(2*S*,3*R*)-2-methyloct-6-ene-1,3-acetonide-7-acetate (85.4 mg, 0.33 mmol), MeOH (2.5 mL), and potassium carbonate (K_2CO_3) (92.0 mg, 0.66 mmol). The reaction was allowed to stir at room temperature for 1h then diluted with Et_2O (150 mL). The Et_2O layer was washed with saturated NH_4Cl (5 mL) and H_2O (5 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by SiO_2 flash chromatography (30% EtOAc/hexanes) provided the desired linear (*E*)-allylic alcohol (64.9 mg, 0.30 mmol, 91% yield) as a yellow oil. After column: no branched alcohol was observed by ^{1}H NMR or GC; [E:Z] = 11:1.

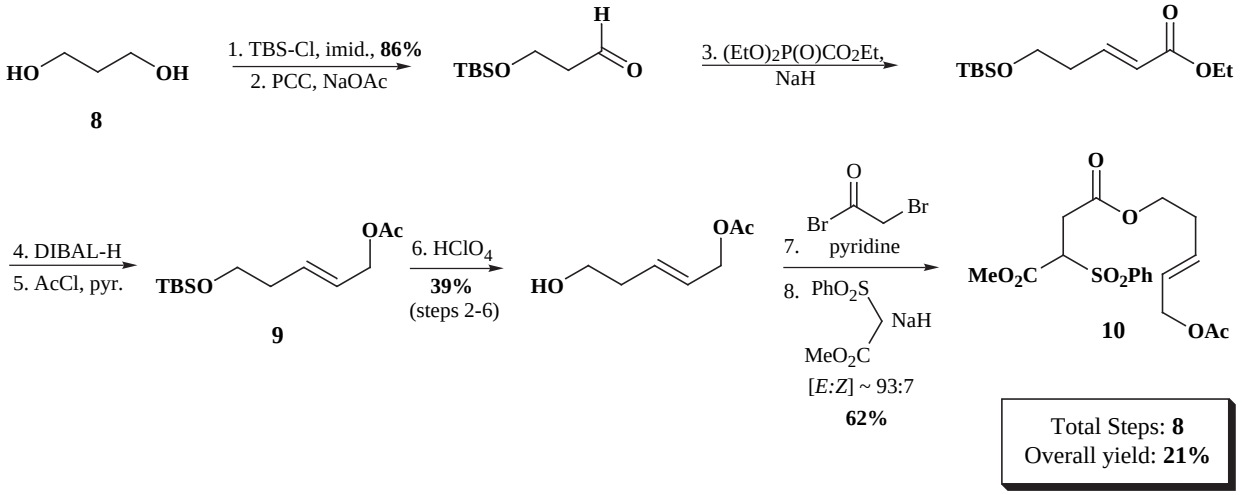
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 (m, 2H), 4.08 (br m, 2H), 3.68 (dd, *J* = 11.6, 5.2 Hz, 1H), 3.48 (t, *J* = 11.2 Hz, 1H), 3.44 (dt, *J* = 2.4, 9.6 Hz, 1H), 2.23 (m, 1H), 2.07 (m, 1H), 1.66 (m, 2H), 1.65 (br s, 1H), 1.45 (m, 1H), 1.41 (s, 3H), 1.38 (s, 3H), 0.73 (d, *J* = 6.8 Hz, 3H); Z isomer: 4.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.9, 129.2, 98.2, 74.1, 66.1, 63.8, 34.0, 32.3, 29.8, 27.6, 19.1, 12.7; IR (film, cm^{-1}): 3383 (br), 2992, 2938, 2855, 1460, 1383, 1267. HRMS (ESI) *m/z* calc'd for $C_{12}H_{23}O_3$ $[M+H]^+$: 215.1647, found 215.1651; $[\alpha]_D^{27}$ = +42.3° (c = 1.00, $CHCl_3$).



***tert*-Butyldiphenyl[(*E*)-5-[(4*R*,5*S*)-2,2,5-trimethyl-1,3-dioxan-4-yl]pent-2-enyloxy]silane:** [4] We confirmed the absolute and relative stereochemistry of **(+)-3** by converting it to its TBDPS-ether and comparing the rotation and spectroscopic properties with those reported for the identical compound by Masamune and coworkers.[4a] A 25 mL round bottom flask was charged sequentially with a stir bar, (**+)-3** (40.4 mg, 0.19 mmol), CH_2Cl_2 (1.0 mL), *tert*-butylchlorodiphenylsilane (54 μL, 0.21 mmol), imidazole, (19.3 mg, 0.28 mmol), and DMAP (1.2 mg, 0.01 mmol). The reaction was allowed to stir for 5 h. The reaction was quenched with saturated NH_4Cl (5 mL). The aqueous and organic layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by SiO_2 flash chromatography (5% EtOAc/hexanes) provided the desired silyl-protected linear (*E*)-allylic alcohol (68.9 mg, 0.15 mmol, 81% yield) as a viscous, yellow oil.

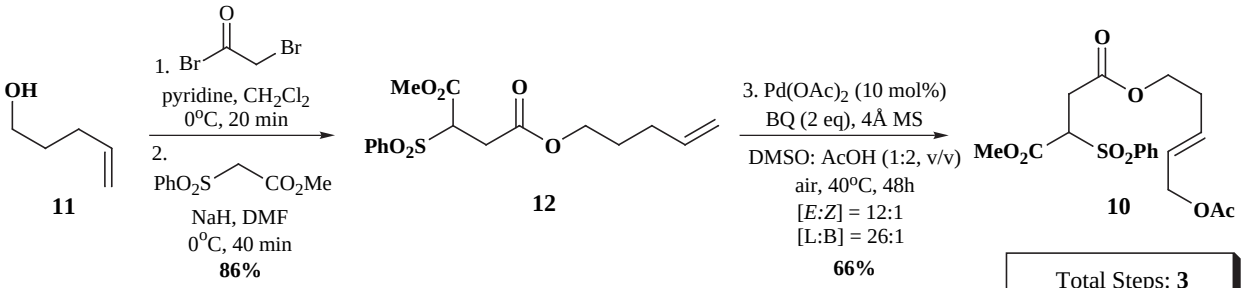
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.39 (m, 6 H), 5.65 (dt, *J* = 15.6, 6.2 Hz, 1H), 5.56 (dt, *J* = 15.2, 4.8 Hz, 1H), 4.15 (d, *J* = 4.8 Hz, 2H), 3.68 (dd, *J* = 11.6, 5.2 Hz, 1H), 3.48 (t, *J* = 11.2 Hz, 1H), 3.44 (dt, *J* = 2.4, 9.4 Hz, 1H), 2.20 (m, 1H), 2.08 (m, 1H), 1.64 (m, 2H), 1.44 (m, 1H), 1.40 (s, 3H), 1.38 (s, 3H), 1.05 (s, 9H); 0.74 (d, *J* = 6.4 Hz, 3H); Z isomer: 4.26 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 133.9, 130.7, 129.5, 129.2, 127.6, 98.2, 74.0, 66.2, 64.6, 34.1, 32.4, 29.8, 27.5, 26.8, 19.2 (d), 12.7; MS (ESI) *m/z* calc'd for $C_{28}H_{40}O_3Si$ $[M+NH_4]^+$: 470.3, found 470.6; $[\alpha]_D^{27}$ = +25.4° (c = 0.56, $CHCl_3$). Literature value: $[\alpha]_D^{24}$ = +23.6° (c = 0.56, $CHCl_3$).[4a]

Previously Reported HWE Olefination Route to Macrolide Precursor 10:[6]

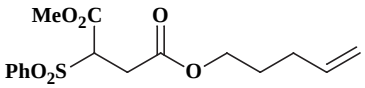


Total Steps: **8**
Overall yield: **21%**

Oxidation Route to Macrolide Precursor 10:



Total Steps: **3**
Overall yield: **57%**

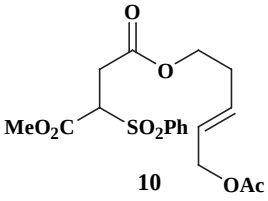


12

1'-Penten-5'-yl 3-benzenesulfonyl-3-carbomethoxypropanoate: A flame-dried 25 mL round bottom flask was charged sequentially with a stir bar, 4-penten-1-ol (250 μL, 2.42 mmol), CH_2Cl_2 (5 mL), and pyridine (600 μL, 7.44 mmol). The solution was cooled to 0°C then bromoacetyl bromide (300 μL, 3.45 mmol) was added dropwise *via* syringe over 5 min. The reaction was allowed to stir at 0°C for 20 min then diluted with Et_2O (30 mL) and allowed to warm to room temperature. The reaction mixture was washed with 10% HCl (2 x 8 mL) and saturated $NaHCO_3$ (2 x 8 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the crude bromoacetate as a dark yellow oil (521 mg).

A flame-dried 25 mL round bottom flask was charged sequentially with sodium hydride (201.9 mg, 8.41 mmol), DMF (4 mL), and methyl phenylsulfonylacetate (1.55 mL, 9.47 mmol). The reaction mixture was allowed to stir at room temperature for 3 h then cooled to 0°C. A solution of crude bromoacetate (521 mg) in DMF (2.5 mL) was cooled to 0°C. The enolate solution was added *via* cannula to the bromoacetate solution. The reaction was allowed to stir at 0°C for 40 min then diluted with Et_2O (40 mL) and allowed to warm up to room temperature. The reaction mixture was washed with H_2O (4 x 10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by SiO_2 flash chromatography (48.5:48.5:3 hexane:$CHCl_3$:acetone) provided the desired β-sulfonyl acetate ester (709.4 mg, 2.08 mmol, 86% yield) as a light yellow, viscous oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd J = 8.4, 1.2 Hz, 2H), 7.73 (t, J = 7.2, 1H), 7.61 (t, J = 7.2 Hz, 2H), 5.78 (m, 1H), 5.01 (m, 2H), 4.45 (dd, J = 9.6, 5.2 Hz, 1H), 4.10 (m, 2H), 3.68 (s, 3H), 3.12 (m, 2H), 2.10 (m, 2H), 1.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 165.4, 137.1, 137.0, 134.6, 129.2, 129.1, 115.5, 66.3, 65.0, 53.2, 31.2, 29.8, 27.5; IR (film, cm^{-1}): 3069, 2955, 2851, 1742, 1449, 1327, 1211, 1152. HRMS (ESI) *m/z* calc'd for $C_{16}H_{21}O_6S$ $[M+H]^+$: 341.1059, found 341.1057.

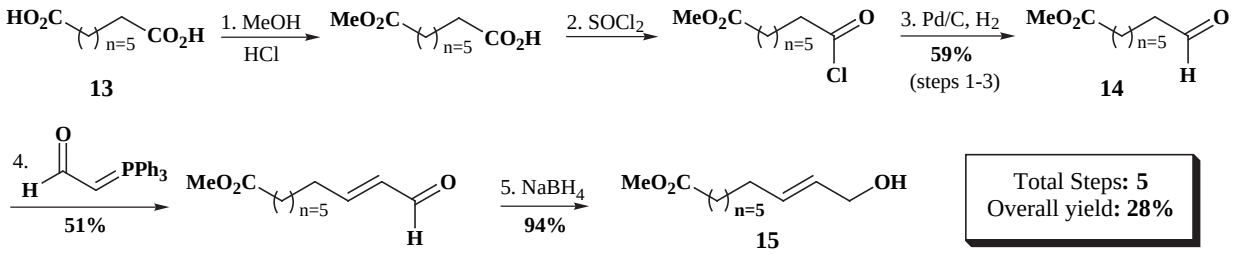


10

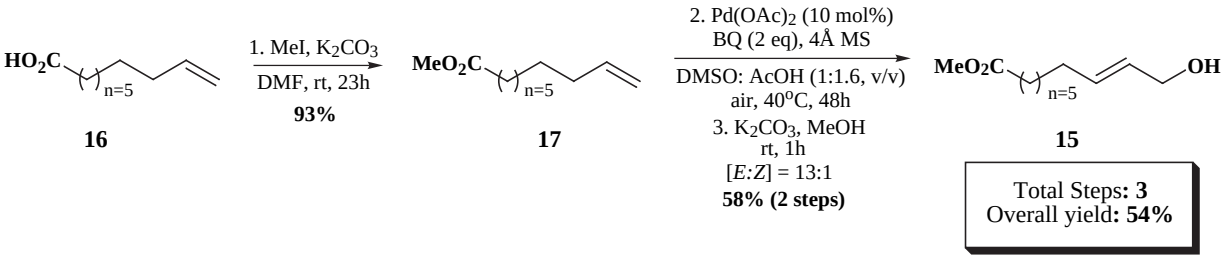
(*E*)-1'-Acetoxy-2'-penten-5'-yl-3-benzenesulfonyl-3-carbomethoxy-propanoate (10):[6] A 40 mL borosilicate glass vial was charged with the following solids: $Pd(OAc)_2$ (22.4 mg, 0.1 mmol), benzoquinone (217 mg, 2.0 mmol), and 4Å MS (217 mg). To the solids vial was sequentially added a solution of 1'-penten-5'-yl 3-benzenesulfonyl-3-carbomethoxypropanoate **(**340.4 mg, 1.0 mmol) in DMSO (2 mL) and AcOH (4 mL). The vial was charged with a stir bar, capped and allowed to heat at 40°C. Aliquots were taken at t = 24h and 48h to determine [L:B]. After 48h the reaction was quenched with saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with H_2O (2 x 100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a brown oil. Purification by SiO_2 flash chromatography (47.5:47.5:5 hexanes:$CHCl_3$:acetone) provided the desired linear (*E*)-allylic acetate as a yellow, viscous oil. Crude product 24h: [L:B] = 38:1; 48h: [L:B] = 26:1, [E:Z] = 13:1. After column (run 1: 253mg, 0.64 mmol, 64% yield; run 2: 260.2mg, 0.65 mmol, 65% yield; run 3: 270.3mg, 0.68 mmol, 68% yield; average yield: 66%). After column: [L:B] = 26:1, [E:Z] = 12:1.

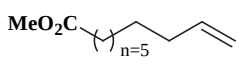
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 8.4, 0.8 Hz, 2H), 7.72 (tt, *J* = 7.2, 1.2 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 2H), 5.67 (m, 2H), 4.51 (d, *J* = 5.2 Hz, 2H), 4.43 (dd, *J* = 9.6, 5.2 Hz, 1H), 4.13 (m, 2H), 3.67 (s, 3H), 3.12 (m, 2H), 2.37 (bq, *J* = 6.4Hz, 2H), 2.06 (s, 3H); Z isomer: 4.60 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 169.5, 165.4, 137.0, 134.6, 130.3, 129.3, 129.1, 127.1, 66.3, 64.6, 64.4, 53.2, 31.4, 31.1, 20.9; IR (film, cm^{-1}): 2957, 1740, 1449, 1327, 1235, 1152. HRMS (ESI) *m/z* calc'd for $C_{18}H_{23}O_8S$ $[M+H]^+$: 399.1113, found 399.1118.

Previously Reported Stabilized Wittig Olefination Route to 8,9-Leukotriene C_3 Precursor 15:[7]



Oxidation Route to 8,9-Leukotriene C_3 Precursor 15:



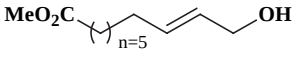


17

Methyl-9-decenoate 17:[8] A flame-dried 100 mL round bottom flask was charged sequentially with a stir bar, 9-decenoic acid (2.03g, 11.8 mmol), DMF (7 mL), and potassium carbonate (2.92g, 21.2 mmol). Methyl iodide (3.3mL, 53.0mmol) was added dropwise *via* syringe and the mixture was allowed to stir at room temperature for 23h. The reaction was then diluted with CH_2Cl_2 (30 mL) and quenched with saturated NH_4Cl

(50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 200 mL) and the combined organic layers were washed with water (2 x 150 mL). The combined organic layers were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by SiO_2 flash chromatography (3% EtOAc/hexanes) provided the pure product (2.03g, 11.0 mmol, 93% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 17.2, 10.4, 6.4 Hz, 1H), 4.98 (dd, *J* = 17.2, 1.6 Hz, 1H), 4.92 (dd, *J* = 10.0, 1.0 Hz, 1H), 3.66 (s, 3H), 2.30 (t, *J* = 7.6 Hz, 2H), 2.03 (m, 2H), 1.61 (m, 2H), 1.25-1.40 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 139.1, 114.2, 51.4, 34.1, 33.7, 29.1, 28.9, 28.8, 24.9; IR (film, cm^{-1}): 2928, 2857, 1742, 1642, 1437, 1248, 1198, 1171. HRMS (CI, NH_3) *m/z* calc'd for $C_{11}H_{24}NO_2$ $[M+NH_4]^+$: 202.1807, found 202.1807.

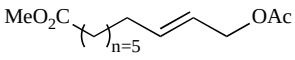


15

Methyl 10-hydroxy-(*E*)-dec-8-enoate 15 : [9]: A 40 mL borosilicate glass vial was charged with the following solids: $Pd(OAc)_2$ (22.4 mg, 0.1 mmol), benzoquinone (217 mg, 2.0 mmol), and 4Å MS (217 mg). To the solids vial was sequentially added DMSO (2.3 mL), 9-methyl decenoate **(**184.3 mg, 1.0 mmol), and AcOH (3.7 mL). The vial was charged with a stir bar, capped and allowed to heat at 40°C. Aliquots were taken at t = 24h and 48h to determine [L:B]. After 48h the reaction was quenched with saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with H_2O (2 x 100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a brown oil. Linear acetate crude product 48h: [L:B] = 11:1, [E:Z] = 13:1.

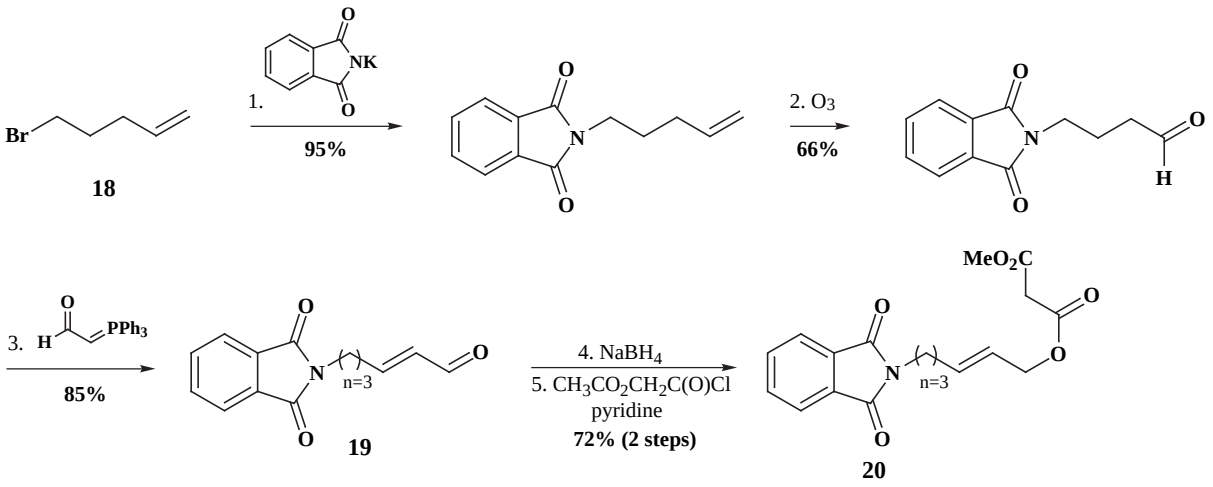
Crude product was taken on without purification. A flame-dried 25 mL round bottom flask was charged with a stir bar and potassium carbonate (415 mg, 3.0 mmol). A solution of the crude linear acetate in MeOH (3.5 mL) was added *via* cannula. The reaction was allowed to stir at room temperature for 1h then diluted with Et_2O (150 mL). The Et_2O layer was washed with saturated NH_4Cl (5 mL), H_2O (5 mL), and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by SiO_2 flash chromatography (25% EtOAc/hexanes) provided the desired linear (*E*)-allylic alcohol as a yellow, viscous oil. Linear alcohol crude product: [L:B] = 13:1 (by ^{1}H NMR), [E:Z] = 13:1. After column (run 1: 118.1 mg, 0.59 mmol, 59% yield; run 2: 119.1 mg, 0.59 mmol, 59% yield; run 3: 111.8 mg, 0.56 mmol, 56% yield; average yield: 58%). After column: No branched product observed by ^{1}H NMR or GC), [E:Z] = 13:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (m, 2H), 4.08 (d, *J* = 5.2 Hz, 2H), 3.66 (s, 3H), 2.30 (t, *J* = 7.6Hz, 2H), 2.03 (m, 2H), 1.61 (m, 2H), 1.24-1.42 (m, 6H); Z isomer: 4.19 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 133.2, 129.0, 63.8, 51.4, 34.0, 32.1, 29.0, 28.8, 28.7, 24.8; IR (film, cm^{-1}): 3401 (br), 2928, 2857, 1740, 1437, 1366, 1254, 1202, 1175. HRMS (ESI) *m/z* calc'd for $C_{11}H_{21}O_3$ $[M+H]^+$: 201.1491, found 201.1487.



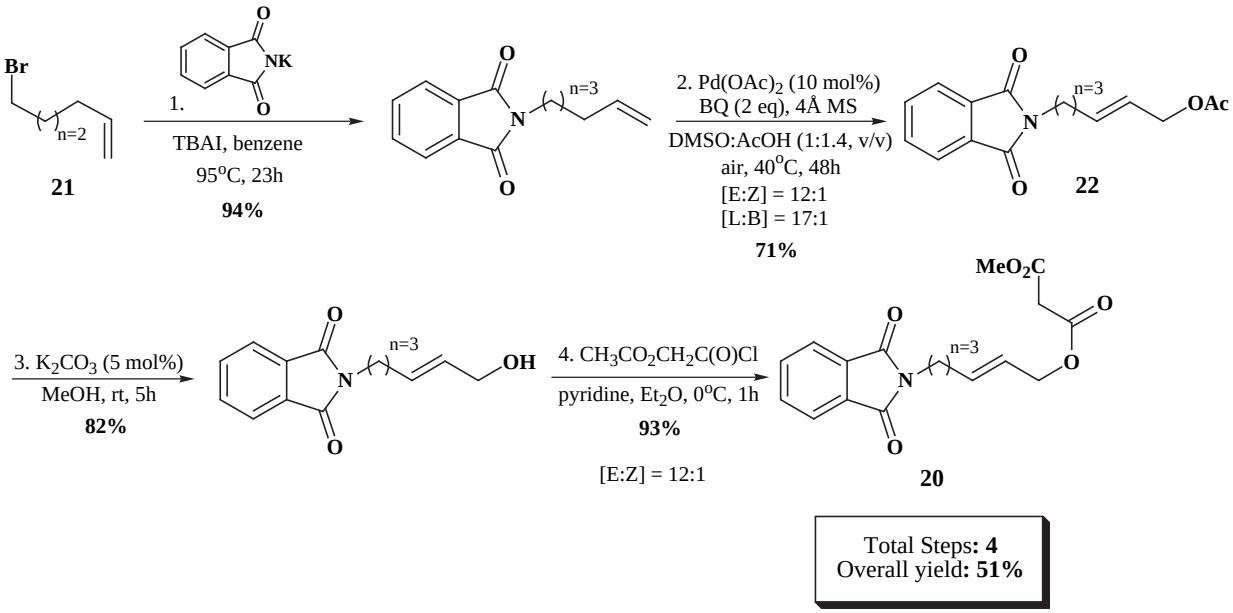
Characterization of methyl 10-acetoxy-(*E*)-dec-8-enoate:[9] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (dt, *J* = 15.6, 6.8 Hz, 1H), 5.55 (dt, *J* = 15.2, 6.4 Hz, 1H), 4.50 (d, *J* = 6.0 Hz, 2H), 3.66 (s, 3H), 2.30 (t, *J* = 7.6 Hz, 2H), 2.06 (s, 3H), 2.03 (m, 2H), 1.61 (m, 2H), 1.25-1.40 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 170.8, 136.4, 123.8, 65.2, 51.4, 34.0, 32.1, 28.9, 28.7, 28.6, 24.8, 21.0; HRMS (ESI) *m/z* calc'd for $C_{13}H_{23}O_4$ $[M+H]^+$: 243.1596, found 243.1591.

Previously Reported Stabilized Wittig Olefination Route to Isoretronecanol Precursor 20:[10]

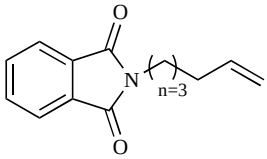


Total Steps**: 5**
Overall yield**: 38%**

Oxidation Route to Isoretronecanol Precursor 20:



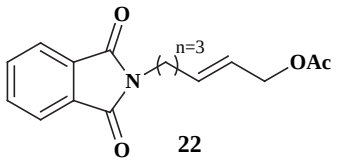
Total Steps**: 4**
Overall yield**: 51%**



N-(5-Hexenyl)phthalimide:[11] A flame-dried 100 mL round bottom flask was sequentially charged with a stir bar, tetrabutylammonium iodide (45.2mg, 0.14 mmol), potassium phthalimide (2.1g, 11.2 mmol), and benzene (40 mL). 6-bromo-1-hexene (750 μL, 5.6 mmol) was added dropwise *via* syringe and the suspension was allowed to stir at 95°C for 23h. The suspension was cooled to 23°C, diluted with ether (45 mL), filtered through celite, then concentrated *in vacuo*. Purification by SiO_2 flash chromatography (15% EtOAc/hexanes) provided the pure product (1.21 g, 5.28 mmol, 94% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.6, 2.8 Hz, 2H), 7.71 (dd, *J* = 5.4, 2.8 Hz, 2H), 5.78 (ddt, *J* = 16.8, 10.0, 6.4 Hz, 1H), 5.00 (dd, *J* = 17.2, 1.6 Hz, 1H), 4.94 (dd, *J* = 10.4, 1.6 Hz, 1H), 3.69 (t, *J* = 7.2 Hz, 2H), 2.09 (m, 2H), 1.69 (m, 2H), 1.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 138.2, 133.8, 132.1, 123.1, 114.8,

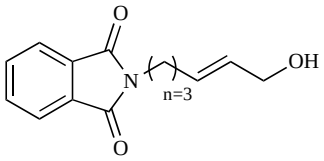
37.8, 33.2, 28.0, 26.1; IR (film, cm^{-1}): 3077, 2976, 2938, 2861, 1773, 1711, 1642, 1615, 1466, 1439, 1397, 1371. HRMS (CI) *m/z* calc'd for $C_{14}H_{16}NO_2$ $[M+H]^+$: 230.1181, found 230.1188.



22

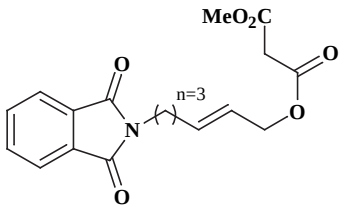
(*E*)-6-Phthalimidohex-2-enyl acetate 22: A 40 mL borosilicate glass vial was charged with the following solids: $Pd(OAc)_2$ (22.4 mg, 0.1 mmol), benzoquinone (217 mg, 2.0 mmol), and 4Å MS (217 mg). To the solids vial was sequentially added a solution of N-(5-hexenyl)phthalimide **(**184.3 mg, 1.0 mmol) in DMSO (2.5 mL), and AcOH (3.5 mL). The vial was charged with a stir bar, capped and allowed to heat at 40ºC. Aliquots were taken at t = 24h and 48h to determine [L:B]. After 48h the reaction was quenched with saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with H_2O (2 x 100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a brown oil. Purification by SiO_2 flash chromatography (20% EtOAc/hexanes) provided the desired linear (*E*)-allylic acetate. Crude product 24h: [L:B] = 29:1; 48h: [L:B] = 17:1, [E:Z] = 12:1. After column: (run 1: 206.8 mg, 0.72 mmol, 72% yield; run 2: 199.5 mg, 0.69 mmol, 69% yield; run 3: 206.1 mg, 0.72 mmol, 72% yield; average yield: 71%). After column: [L:B] = 17:1, [E:Z] = 12:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 5.4, 3.6 Hz, 2H), 7.71 (dd, *J* = 5.4, 3.2 Hz, 2H), 5.77 (dt, *J* = 15.6, 6.4 Hz, 1H), 5.61 (dt, *J* = 15.6, 6.4 Hz, 1H), 4.47 (dd, *J* = 6.4, 0.8 Hz, 2H), 3.69 (t, *J* = 7.2 Hz, 2H), 2.13 (m, 2H), 2.05 (s, 3H), 1.79 (m, 2H); Z isomer: 4.60 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 168.4, 134.5, 133.9, 132.1, 124.8, 123.2, 64.9, 37.5, 29.5, 27.6, 21.0; IR (film, cm^{-1}): 2942, 1771, 1736, 1711, 1615, 1468, 1439, 1397, 1370, 1235. HRMS (ESI) *m/z* calc'd for $C_{16}H_{18}NO_4$ $[M+H]^+$: 288.1236, found 288.1230.



(*E*)-6-Phthalimidohex-2-ene-1-ol:[10] A flame-dried 25 mL round bottom flask was charged with a stir bar and potassium carbonate (3.8 mg, 0.03 mmol). A solution of the linear (*E*)-6-phthalimidohex-2-enyl acetate (88.4 mg, 0.31 mmol) in MeOH (4.0 mL) was added *via* cannula. The reaction was allowed to stir at room temperature for 5h then concentrated *in vacuo*. The residue was diluted in Et_2O (100 mL) then was washed with H_2O (2 x 5 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by SiO_2 flash chromatography (42.5:42.5:15 hexane:$CHCl_3$:acetone) provided the desired linear (*E*)-allylic alcohol (61.8 mg, 0.25 mmol, 82% yield) as a white solid. No branched alcohol observed by ^{1}H NMR. [E:Z] = 11:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.2, 3.2 Hz, 2H), 7.70 (dd, *J* = 5.2, 2.8 Hz, 2H), 5.67 (m, 2H), 4.05 (s, 2H), 3.69 (t, *J* = 7.2 Hz, 2H), 2.10 (m, 2H), 1.79 (m, 2H), 1.44 (br s, 1H); Z isomer: 4.14 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 133.9, 132.1, 131.4, 130.1, 123.2, 63.6, 37.4, 29.4, 27.7; IR (film, cm^{-1}): 3437 (br), 2940, 2864, 1771, 1711, 1615, 1468, 1439, 1398, 1370. HRMS (ESI) *m/z* calc'd for $C_{14}H_{16}NO_3$ $[M+H]^+$: 246.1130, found 246.1132.

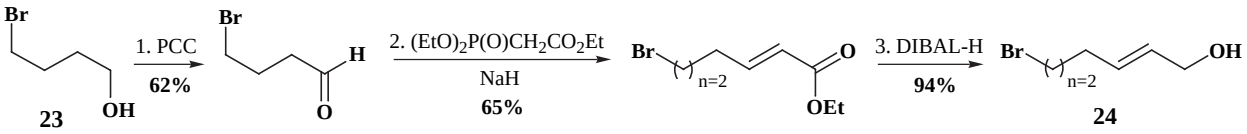


20

(*E*)-6-Phthalimidohex-2-ene-1-ol carbomethoxyacetate 20:[10] A flame-dried 25 mL round bottom flask was sequentially charged with a stir bar, (*E*)-6-phthalimidohex-2-ene-1-ol (68.5 mg, 0.28 mmol), Et_2O (3.0 mL), and pyridine (45 μL, 0.56 mmol). The reaction mixture was cooled to 0ºC then methyl-3-chloro-3-oxopropionate (45 μL, 0.42 mmol) was added dropwise *via* syringe. The reaction was allowed to stir at 0ºC for 1 h then quenched by the addition of H_2O (2.0 mL). The reaction mixture was allowed to warm to room temperature then the aqueous and organic layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by SiO_2 flash chromatography (25% EtOAc/hexanes) provided the desired product (89.4 mg, 0.26 mmol, 93% yield) as a viscous, yellow oil. [E:Z] = 12:1

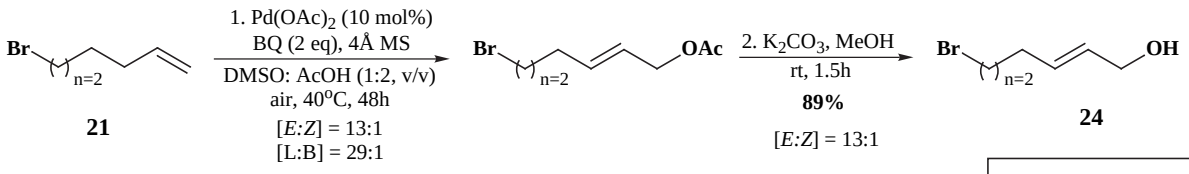
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.4, 3.2 Hz, 2H), 7.71 (dd, *J* = 5.4, 3.2 Hz, 2H), 5.78 (dt, *J* = 15.6, 6.8 Hz, 1H), 5.60 (dt, *J* = 15.2, 6.8 Hz, 1H), 4.55 (d, *J* = 6.6 Hz, 2H), 3.74 (s, 3H), 3.68 (t, *J* = 7.2 Hz, 2H), 3.37 (s, 2H), 2.12 (m, 2H), 1.78 (m, 2H); Z isomer: 4.68 (br d, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 166.9, 166.2, 135.2, 133.9, 132.1, 124.2, 123.2, 66.0, 52.5, 41.3, 37.4, 29.5, 27.6; IR (film, cm^{-1}): 2951, 1753, 1734, 1711, 1439, 1398, 1371, 1337, 1275. HRMS (ESI) *m/z* calc'd for $C_{18}H_{20}NO_6$ $[M+H]^+$: 346.1290, found 346.1287.

Previously Reported HWE Olefination Route to (-)-Swainsonine Precursor 24:[12]

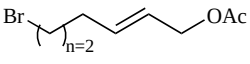


Total Steps**: 3**
Overall yield**: 38%**

Oxidation Route to (-)-Swainsonine Precursor 24:

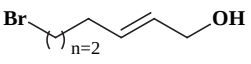


Total Steps**: 2**
Overall yield**: 57%**



(*E*)-6-Bromohex-2-enyl acetate:[13] A 40 mL borosilicate glass vial was charged with the following solids: $Pd(OAc)_2$ (22.4 mg, 0.1 mmol), benzoquinone (217 mg, 2.0 mmol), and 4Å MS (217 mg). To the solids vial was sequentially added the following: DMSO (2 mL), 6-bromo-1-hexene (163.1 mg, 1.0 mmol), and AcOH (4 mL). The vial was charged with a stir bar, capped and allowed to heat at 40°C. Aliquots were taken at t = 24h, 48h, and 72h to determine [L:B]. After 72h the reaction was quenched with saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with H_2O (2 x 100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* at 0°C to give a brown oil. Purification by SiO_2 flash chromatography (10% Et_2O/*n*-pentane) provided the desired linear (*E*)-allylic acetate as a light yellow oil. Crude product 24h: [L:B] = 32:1; 48h: [L:B] = 30:1; 72h: [L:B] = 29:1, [E:Z] = 14:1. After column: (run 1: 149.0 mg, 0.67 mmol, 67%; run 2: 138.3 mg, 0.63 mmol, 63%; run 3 138.5 mg, 0.63 mmol, 63% yield; average yield: 64%) [L:B] = 29:1, [E:Z] = 13:1

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (dt, *J* = 15.2, 6.4 Hz, 1H), 5.63 (dt, *J* = 15.2, 6.4 Hz, 1H), 4.51 (d, *J* = 6.0 Hz, 2H), 3.40 (t, *J* = 6.8 Hz, 2H), 2.23 (m, 2H), 2.06 (s, 3H), 1.95 (m, 2H); Z isomer: 4.64 (d, *J* = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 133.9, 125.4, 64.9, 32.9, 31.7, 30.5, 21.0; IR (film, cm^{-1}): 3017, 2938, 2851, 1740, 1441, 1381, 1366, 1240. HRMS (CI, NH_3) *m/z* calc'd for $C_8H_{17}BrNO_2$ $[M+NH_4]^+$: 238.0443, found 238.0455.

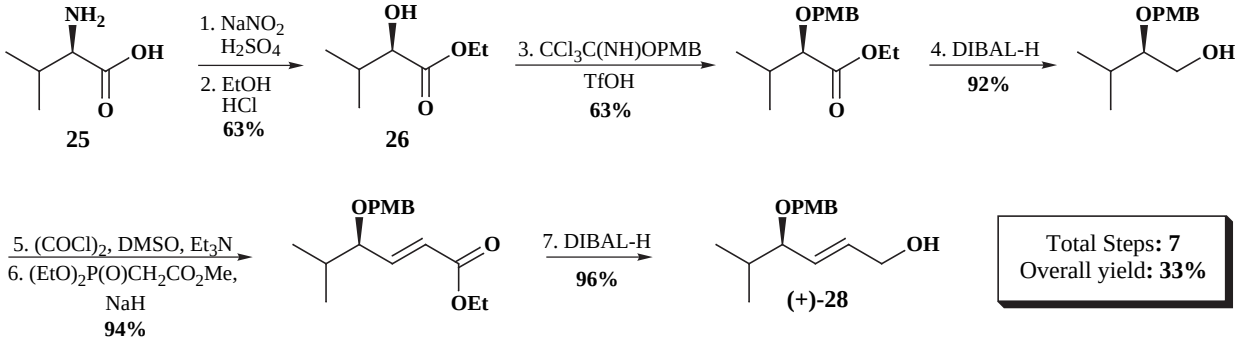


24

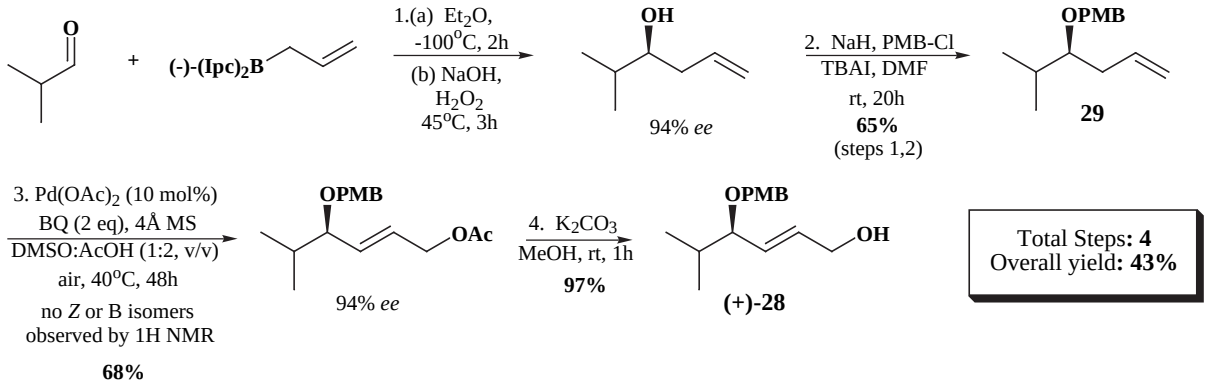
(*E*)-6-Bromohex-2-en-1-ol 24:[12] A 25 mL round bottom flask was charged sequentially with a stir bar, (*E*)-6-bromohex-2-enyl acetate (125.6 mg, 0.57 mmol), MeOH (2.5 mL), and potassium carbonate (78.5 mg, 0.57 mmol). The reaction was allowed to stir at room temperature for 1.5h then diluted with Et_2O (150 mL). The Et_2O layer was washed with saturated NH_4Cl (5 mL), H_2O (5 mL), and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* at 0°C. Purification by SiO_2 flash chromatography (30% Et_2O/*n*-pentane) provided the desired linear (*E*)-allylic alcohol (90.1 mg, 0.50 mmol, 89% yield) as a yellow oil. After column: No branched alcohol observed by ^{1}H NMR or GC. [*E:Z*] = 13:1

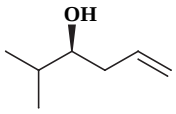
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (dt, *J* = 15.4, 5.4 Hz, 1H), 5.65 (dt, *J* = 15.2, 6.0 Hz, 1H), 4.10 (d, *J* = 4.4 Hz, 2H), 3.41 (t, *J* = 6.8 Hz, 2H), 2.22 (m, 2H), 1.95 (m, 2H), 1.37 (br s, 1H); Z isomer: 4.23 (d, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.7, 130.4, 63.5, 33.1, 31.9, 30.5; IR (film, cm^{-1}): 3331, 3009, 2934, 2866, 1670, 1437, 1267, 1244. HRMS (CI, NH_3) *m/z* calc'd for $C_6H_{15}BrNO$ $[M+NH_4]^+$: 196.0337, found 196.0343.

Previously Reported HWE Olefination Route to Tautomycin C_{17}-C_{26} Fragment (+)-28:[14]



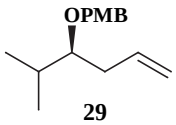
Oxidation Route to Tautomycin C_{17}-C_{26} Fragment (+)-28:





(*S*)-2-Methylhex-5-en-3-ol:[15] A flame-dried 100 mL round bottom flask was sequentially charged with a stir bar, (-)-*B*-methoxydiisopinocampheylborane (4.56 g, 14.53 mmol), and Et_2O (14 mL). The solution was cooled to 0°C then allylmagnesium bromide (14 mL, 1.0 M in Et_2O) was added dropwise *via* syringe. The reaction mixture was warmed to room temperature and allowed to stir for 1h during which time a white solid crashed out. The Et_2O was removed under high vacuum and the residue was dissolved in *n*-pentane (25 mL). The suspension was filtered under nitrogen using Schlenk line techniques and washed with *n*-pentane (25 mL). The *n*-pentane was removed under high vacuum and the residue was dissolved in Et_2O (29 mL). The borane solution was cooled to –100°C. A solution of isobutyraldehyde (1.1 mL, 12.11 mmol) in Et_2O (12 mL) was cooled to –78°C and added dropwise *via* cannula down the side of the flask in an area that was submerged in the –100°C bath. The reaction was allowed to stir at –100°C for 2h. The reaction was quenched with 5 mL 3N NaOH at –100°C and allowed to warm to room temperature over 1h. The reaction mixture was charged with 10 mL 30% H_2O_2. The reaction mixture was heated to reflux for 3h then cooled to room temperature. The aqueous and organic layers were separated and the aqueous layer was extracted with Et_2O (15 mL). The combined organic layers were washed with H_2O (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* at –15°C to give a clear residue. Kugelrohr distillation (100°C, 6 torr) provided the allylic alcohol (1.47 g) in 94% *ee* (see "Determination of Enantiomeric Excess" section) with α-pinene and trace isopinocampheol impurities.

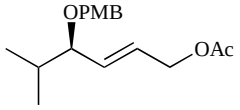
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (m, 1H), 5.18-5.10 (m, 2H), 3.39 (m, 1H), 2.32 (m, 1H), 2.11 (m, 1H), 1.69 (m, 1H), 0.94 (d, *J* = 5.2 Hz, 3H), 0.93 (d, *J* = 5.2 Hz, 3H).



29

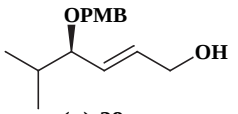
(*S*)-3-(*p*-Methoxybenzyloxy)-2-methyl-5-hexene 29: A flame-dried 100 mL round bottom flask was sequentially charged with a stir bar, sodium hydride (445.8 mg, 18.58 mmol), tetrabutylammonium iodide (171.5 mg, 0.46 mmol), and DMF (20 mL). The suspension was cooled to 0°C. A solution of an aliquot of the allylic alcohol (1.32 g) in DMF (40 mL) was cooled to 0°C then added *via* cannula. The reaction mixture was allowed to stir at 0°C for 30 min. 4-Methoxybenzyl chloride (PMB-Cl) (2.4 mL, 17.46 mmol) was added *via* syringe. The reaction mixture was allowed to warm to room temperature then allowed to stir for 21h. The reaction was quenched with MeOH (300 μL) and allowed to stir for 30 min. The reaction was diluted with H_2O (100 mL) and extracted with Et_2O (3 x 150 mL). The combined organic layers were washed with H_2O (2 x 125 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by SiO_2 flash chromatography (3% EtOAc/hexanes) provided the desired PMB-protected homoallylic alcohol (1.65 g, 7.03 mmol, 65% over 2 steps) with trace amounts of PMB-protected isopinocampheol impurity. Note: the mass of the undesired isopinocampheol impurity (determined by ^{1}H NMR) was subtracted from the total mass before calculating the reported yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.88 (ddt, *J* = 17.2, 10.4, 7.2 Hz, 1H), 5.09 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.04 (d, *J* = 10.0 Hz, 1H), 4.50 (d, *J* = 10.8, 1H), 4.42 (d, *J* = 11.2 Hz, 1H), 3.80 (s, 3H), 3.17 (app q, *J* = 6.0 Hz, 1H), 2.29 (m, 2H), 1.86 (m, 1H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 135.7, 131.1, 129.3, 116.4, 113.6, 83.5, 71.4, 55.2, 35.2, 30.9, 18.4, 18.2; IR (film, cm^{-1}): 3075, 2959, 2936, 2909, 2872, 2837, 1640, 1615, 1588, 1514, 1466, 1302, 1248. HRMS (EI) *m/z* calc'd for $C_{15}H_{22}O_2$: 234.1620, found 234.1627



(4*R*, 2 *E*)-4-(*p*-Methoxybenzyloxy)-5-methylhex-2-enyl acetate: A 40 mL borosilicate glass vial was charged with the following solids: $Pd(OAc)_2$ (22.4 mg, 0.1 mmol), benzoquinone (217 mg, 2.0 mmol), and 4Å MS (217 mg). To the solids vial was sequentially added a solution of homoallylic ether **9 (**172.5 mg, 0.94 mmol) in DMSO (2 mL), and AcOH (4 mL). The vial was charged with a stir bar, capped and allowed to heat at 40°C. After 48h the reaction was quenched with saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with H_2O (2 x 100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a brown oil. Crude product 48h: No (Z)-linear or branched acetate observed by ^{1}H NMR or GC. Purification by SiO_2 flash chromatography (10% EtOAc/hexanes) provided the desired linear (*E*)-allylic acetate as a viscous, yellow oil with no degradation of enantiomeric purity (see "Determination of Enantiomeric Excess" section below). After column: (run 1: 191.1 mg, 0.65 mmol, 70% yield; run 2: 202.7 mg, 0.69 mmol, 74% yield; run 3: 183.1 mg, 0.63 mmol, 67% yield; run 4: 175.7 mg, 0.60 mmol, 64% yield, run 5: 176.3 mg, 0.60 mmol, 64% yield; average yield: 68% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 9.2 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.72 (dt, *J* = 15.6, 6.0 Hz, 1H), 5.65 (dd, *J* = 15.8, 7.6 Hz, 1H), 4.61 (d, *J* = 4.8 Hz, 2H), 4.51 (d, *J* = 11.2 Hz, 1H), 4.26 (d, *J* = 12.0 Hz, 1H), 3.80 (s, 3H), 3.43 (t, *J* = 7.2 Hz, 1H), 2.09 (s, 3H), 1.78 (m, 1H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 159.0, 133.7, 130.9, 129.2, 127.5, 113.7, 84.2, 70.0, 64.3, 55.2, 32.7, 21.0, 18.7, 18.4; IR (film, cm^{-1}): 3077, 2928, 2857, 1742, 1642, 1460, 1362, 1248, 1200, 1171. HRMS (ESI) *m/z* calc'd for $C_{17}H_{28}NO_4$ $[M+NH_4]^+$: 310.2018, found 310.2017; $[\alpha]_D^{29}$ = +43.3° (c = 1.00, $CHCl_3$).



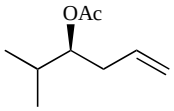
(+)-28

(4*R*, 2 *E*)-4-(*p*-Methoxybenzyloxy)-5-methylhex-2-en-1-ol 28[14a] A 25 mL round bottom flask was charged sequentially with a stir bar, the linear (*E*)-allylic acetate (139.6 mg, 0.48 mmol), MeOH (2.0 mL), and potassium carbonate (329 mg, 2.38 mmol). The reaction was allowed to stir at room temperature for 1h then diluted with Et_2O (150 mL). The Et_2O layer was washed with saturated NH_4Cl (5 mL), H_2O (5 mL), and brine (5 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo* at 0°C. Purification by SiO_2 flash chromatography (30% EtOAc/hexanes) provided the desired linear (*E*)-allylic alcohol (116.5 mg, 0.47 mmol, 97% yield, 94% *ee*) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.80 (dt, *J* = 15.6, 5.6 Hz, 1H), 5.60 (ddt, *J* = 15.6, 8.0, 1.2 Hz, 1H), 4.51 (d, *J* = 11.6 Hz, 1H), 4.28 (d, *J* = 11.6 Hz, 1H), 4.20 (br t, *J* = 4.8 Hz, 2H), 3.80 (s, 3H), 3.44 (t, *J* = 7.2 Hz, 1H), 1.78 (m, 1H), 1.44 (-OH, 1H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 132.8, 131.0, 130.7, 129.2, 113.7, 84.4, 69.9, 63.1, 55.2, 32.7, 18.7, 18.4; IR (film, cm^{-1}): 3374 (br), 2959, 2934, 2870, 2837, 1613, 1514, 1466, 1302, 1248, 1173. HRMS (EI) *m/z*

calc'd for $C_{15}H_{22}O_3$: 250.1569, found 250.1571; $[\alpha]_D^{29}$ = +42.8° (c = 1.00, $CHCl_3$). Literature value: $[\alpha]_D^{27}$ = +41.8° (c = 1.00, $CHCl_3$).[14a]

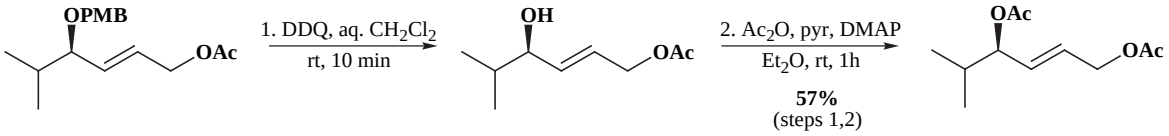
Determination of Enantiomeric Excess:

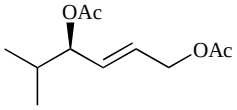


(3*S*)-2-Methylhex-5-en-3-yl acetate : A portion of the homoallylic alcohol was acetylated to check the enantiomeric excess of the allylation step. A 25 mL round bottom flask was sequentially charged with the homoallylic alcohol (74.2 mg, 0.65 mmol), Et_2O (3.0 mL), pyridine (105 μL, 1.30 mmol, 1.30 mmol), acetic anhydride (120 μL, 1.30 mmol), and DMAP (7.9 mg, 0.07 mmol). The reaction was allowed to stir at room temperature for 30 minutes. The reaction was quenched with 1.0 M HCl (1 mL). The aqueous and organic layers were separated and the organic layer was washed with 1.0 M HCl (2 x 3 mL) and H_2O (1 x 3 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* at 0°C. Purification by SiO_2 flash chromatography (3% Et_2O/hexanes) provided the desired homoallylic acetate (76.2 g, 0.49 mmol, 75%) with trace amounts of acetylated isopinocampheol impurity.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (ddt, *J* = 17.0, 10.0, 7.2 Hz, 1H), 5.07 (dm, *J* = 17.2 Hz, 1H), 5.04 (dm, *J* = 10.0 Hz, 1H), 4.77 (m, 1H), 2.29 (m, 2H), 2.04 (s, 3H), 1.84 (m, 1H), 0.91 (d, *J* = 6.8 Hz, 6H).

Enantiomeric excess was determined by chiral GC analysis (Cyclodex-β, 50°C, isothermal); major enantiomer t_R=12.1 min, minor enantiomer t_R=11.8 min; 94% *ee*.





(4*R*,2*E*)-4-(Acetoxy)-5-methylhex-2-enyl acetate: A portion of the PMB-protected (*E*)-allylic acetate was transformed into the acetate-protected (*E*)-allylic acetate for enantiomeric excess determination. A 25 mL round bottom flask was charged sequentially with a stir bar, (4*R*)-(*p*-methoxybenzyloxy)-5-methyl-(2*E*)-hexen-1-acetate (19.0 mg, 0.07 mmol), CH_2Cl_2 (330 μL), H_2O (20 μL), and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (15.5 mg, 0.07 mmol). The reaction was allowed to stir at room temperature for 10 min then diluted with CH_2Cl_2 (20 mL). The organic layer was washed with H_2O (3 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by SiO_2 flash chromatography (20% EtOAc/hexanes) provided the desired linear allylic alcohol (12.3 mg, mass above theoretical yield). A 25 mL round bottom flask containing the entire mixture of linear allylic alcohol (12.3 mg) was charged with a stir bar, Et_2O (0.5 mL), pyridine (11 μL, 0.13 mmol), acetic anhydride (12 μL, 0.13 mmol), and DMAP (1.0 mg, 0.01 mmol). The reaction was allowed to stir at room temperature for 1h then diluted with Et_2O (20 mL) and quenched with 1.0 M HCl (0.1 mL). The organic layer was washed with 1.0 M HCl (1 x 3 mL) and H_2O (1 x 3 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by SiO_2 flash chromatography (20% EtOAc/hexanes) provided the desired acetate-protected linear (*E*)-allylic acetate (7.9 mg, 0.04 mmol, 57% yield, 2 steps) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (dt, *J* = 16.0, 5.2 Hz, 1H), 5.67 (dd, *J* = 15.6, 6.8 Hz, 1H), 5.07 (t, *J* = 6.4 Hz, 1H), 4.55 (d, *J* = 5.2 Hz, 2H), 2.06 (s, 6H), 1.86 (m, 1H), 0.90 (d, *J* = 6.4 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 170.3, 130.8, 127.3, 78.1, 64.1, 31.9, 21.1, 20.9, 18.0, 17.9. Enantiomeric excess was determined by chiral GC analysis (Cyclodex-β, 95°C, isothermal); major enantiomer t_R=28.2 min, minor enantiomer t_R=26.6 min; 94% *ee*.

References:

(1) Abiko, A. *Org. Synth. Collective Vol. X* **2004**, 103. The alternative isolation procedure (paper note 14) for Cy_2BOTf was used.
(2) Chen, M.S.; White. M.C *J. Am. Chem. Soc.* **2004**, *126*, 1346.
(3) Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(4) (a) Yoshimitsu, T.; Song, J.J.; Wang, G.; Masamune, S. *J. Org. Chem.* **1997**, *62*, 8978. (b) Route to aldehyde **1** from 1,4-butanediol was obtained from a personal communication with Dr. Takehiko Yoshimitsu.
(5) Abiko, A.; Liu, J.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586.
(6) Trost, B.M.; Verhoeven, T.R. *J. Am. Chem. Soc.* **1980**, *102*, 4743.
(7) (a) Baker, S.R.; Boot, J.R.; Morgan, S.E.; Osborne, D.J.; Ross, W.J.; Schrubsall, P.R. *Tetrahedron Lett.* **1983**, *24*, 4469. (b) Pennington, F.C.; Celmer, W.D.; McLamore, W.M.; Bogert, V.V.; Solomons, I.A. *J. Am. Chem. Soc.* **1953**, *75*, 109.
(8) Bartra, M.; Vilarrasa, J. *J. Org. Chem*, **1991**, *56*, 5132.
(9) Spectral information for **5**: Ranganathan, D.; Ranganathan, S.; Mehrotra, M.M. *Tetrahedron* **1980**, *36*, 1869.
(10) Danishefsky, S.; McKee, R.; Singh, R.K. *J. Am. Chem. Soc.* **1977**, *99*, 4783.
(11) Barlin, G.B.; Ireland, S.J.; Jiravinyu, C.; Nguyen, T.M.T.; Kotecka, B.; Ricekmann, K.H. *Aust. J. Chem.* **1993**, *46*, 1695.
(12) Swainsonine: (a) Hunt, J.A.; Roush, W.R. *J. Org. Chem.* **1997**, *62*, 1112. Overall yield for olefination route to **5** starting from commercial 4-bromobutanol. (b) Vedejs, E.; Arnost, M.J.; Hagan, J.P. *J. Org. Chem.* **1979**, *44*, 3230.
(13) Shimada, T.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 471.
(14) (a) Tsuboi, K.; Ichikawa, Y.; Naganawa, A.; Isobe, M.; Ubukata, M.; Isono, K. *Tetrahedron*, **1997**, *53*, 5083. (b) Ichikawa, Y.; Tsuboi, K.; Naganawa, A.; Isobe, M. *Synlett*, **1993**, 907.
(15) Racherla, U.S.; Brown, H.C. *J. Org. Chem.* **1991**, *56*, 401.