A Short Catalytic Enantioselective Synthesis of the Vascular Antiinflammatory Eicosanoid (11R,12S)-Oxidoarachidonic Acid

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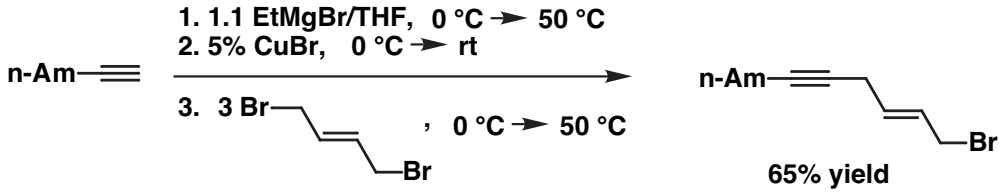
SUPPORTING INFORMATION

EXPERIMENTAL SECTION

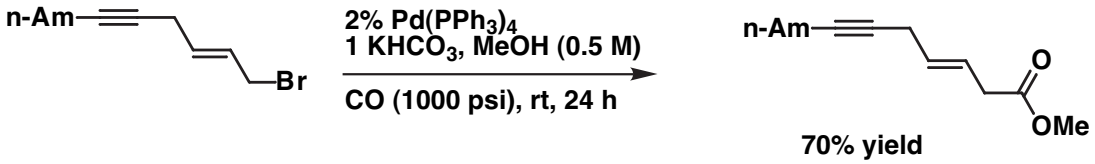
Material and Methods. Unless stated otherwise, reactions were performed in oven dried glassware under a nitrogen or an argon atmosphere, using freshly distilled solvents. Azeotropic drying of starting materials was performed by the addition of dry toluene followed by slow application of full vacuum at room temperature in order to prevent bumping. CuCl and CuBr were recrystallized from concentrated HCl or HBr respectively, and dried under vacuum for 15 h. Benzene (PhH), dichloromethane (CH_2Cl_2), and acetonitrile were distilled from CaH_2 under nitrogen. Hexamethylphosphoramide (HMPA) was distilled from CaH_2 under reduced pressure (0.8 mm Hg). Diethyl ether (Et_2O), tetrahydrofuran (THF), and toluene (PhMe) were distilled from sodium benzophenone ketyl under nitrogen, utilizing sodium dispersion in paraffin. Methanol (MeOH) was distilled from sodium metal. Dimethyl sulfoxide (DMSO) was stirred over flame dried $CaSO_4$ powder overnight and vacuum distilled with bath temperature not higher than 80 °C. All other commercially obtained reagents were used as received. Reaction temperature was

controlled by a Scientific Instruments temperature modulator model 2230. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 pre-coated plates (0.25-mm). Silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. FTIR spectra were recorded as thin films on NaCl plates. Residual solvent peaks were used as an internal chemical shift reference for ^{1}H and ^{13}C NMR spectra. High resolution mass spectral analyses were performed at The Harvard University Mass Spectrometry Centre using electron ionization (EI), chemical ionization (CI), fast-atom bombardment (FAB) or electrospray (ES). Chiralcel HPLC columns were obtained from Daicel Chemical Industries, Ltd. Specific optical rotations ([α]) were measured using a Perkin-Elmer 241 polarimeter at the indicated temperature with a sodium lamp (D line, 589 nm), unless noted otherwise, and are reported in degrees per unit of concentration, c (10 mg/mL), per unit of length (10 cm). $Pd(PPh_3)_4$[1] and trans-1,4-dibromo-2-butene[2] were prepared as previously described. $NaN(SiMe_3)_2$ (1 M in THF) and $KN(SiMe_3)_2$ (0.5 M in PhMe) were purchased from Aldrich.



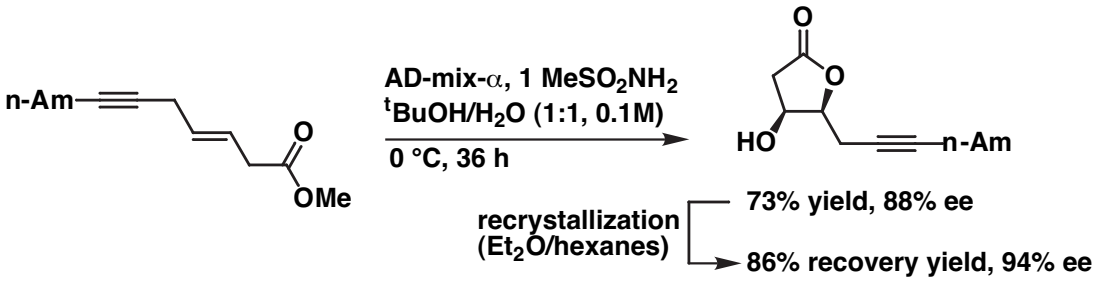
(E)-1-Bromoundec-2-en-5-yne. A freshly prepared solution of EtMgBr in THF (60 mL, 1.1 M, 66 mmol) was added dropwise at 0 °C to a solution of heptyne (7.9 mL, 60 mmol) in THF (12 mL). The mixture was stirred at room temperature for 15 min and then was heated at 50 °C for 1 h. After cooling to 0 °C, a suspension of CuBr (0.86 g, 6.0 mol) in THF (3 mL) was added and the mixture was stirred at 0 °C for 15 min. The resulting mixture was cannulated at 0 °C into a solution of trans-1,4-dibromobutene (38.52 g, 180 mmol) in THF (40 mL) at 0 °C and the resulting reaction mixture was stirred at room temperature for 20 min and then heated at 50 °C for 18 h. The reaction mixture was treated with sat. NH_4Cl (100 mL) and extracted with hexanes (3 x 100 mL). The combined

organic extracts were washed with H_2O, then with brine and dried over Na_2SO_4. After concentration, the residue was dissolved in pentane (40 mL) and the solution was kept in a freezer at -20 °C for 24 h. After filtration, white crystals were washed with -20 °C pentane, and the filtrates were concentrated. The above process was repeated twice more with 30 mL and 25 mL of pentane respectively. The residue was subjected to a vacuum distillation (15 cm-long Vigreux distilling column) to afford a clear, light tan liquid (8.92 g, 65 % yield, bp 75 - 78 °C at 0.7 mm Hg); FTIR 3039, 3018 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.98 (dtt, J = 14.8, 7.6, 1.6 Hz, 1H), 5.76 (dt, J = 14.8, 5.2 Hz, 1H), 3.97 (d, J = 8.0 Hz, 2H), 2.96 (d, J = 2.8 Hz, 2H), 2.20 - 2.15 (m, 2H), 1.50 (quint., J = 7.2 Hz, 2H), 1.38 - 1.30 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.9, 127.6, 83.6, 76.1, 32.9, 31.5, 29.1, 22.6, 22.1, 19.2, 14.5; HRMS (EI) for $[C_{11}H_{17}Br]^+$, m/z calcd 228.0514, found 228.0501.



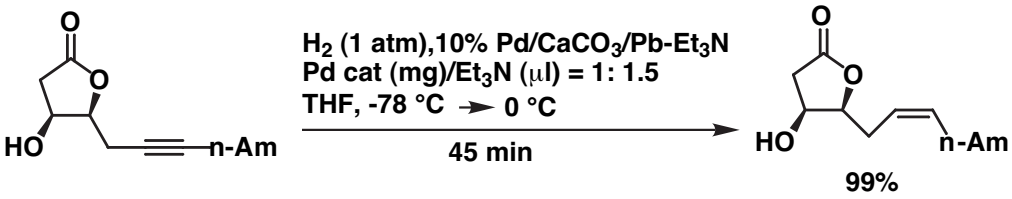
Methyl dodec-3-en-6-ynoate. To a flame-dried Parr bomb was added $Pd(PPh_3)_4$ (231 mg, 0.200 mmol), $KHCO_3$ (100 mg, 10.0 mmol) and MeOH (10.0 mL). The bomb was cooled to -78 °C and the bromide (2.1 mL, 10 mmol) was added. After the bomb was quickly assembled, purged with CO (600 psi) three times and finally the CO pressure was brought to 1000 psi. The reaction mixture was stirred at room temperature for 36 h. After the CO pressure was released, MeOH was removed in vacuo. The residue was partitioned between CH_2Cl_2 (150 mL) and H_2O (100 mL) and the aqueous layer was acidified to pH = 2 by the addition of 2 M HCl. After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. After concentration, the residue was subjected to flash column chromatography (SiO_2 [100 g], EtOAc / hexanes 1 : 30 as eluent) to afford

a light yellow liquid (1.46 g, 70% yield); FTIR 1743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (dtt, J = 15.2, 6.8, 1.6 Hz, 1H), 5.58 (dtt, J = 14.8, 5.6, 1.2 Hz, 1H), 3.69 (s, 3H), 3.08 (dd, J = 6.8, 1.2 Hz, 2H), 2.94 - 2.92 (m, 2H), 2.20 - 2.15 (m, 2H), 1.51 (quint., J = 7.2 Hz, 2H), 1.39 - 1.29 (m, 4H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 129.5, 123.2, 83.0, 76.8, 52.1, 37.9, 31.5, 29.1, 22.6, 22.4, 19.2, 14.4.

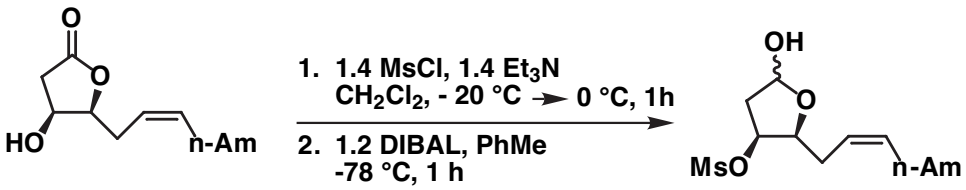


(4S,5S)-4-Hydroxy-5-(oct-2-ynyl)dihydrofuran-2-one. A solution of the ester (3.10 g, 14.9 mmol) in t-BuOH (4.5 mL) was added at 0 °C to a mixture of AD-mix-α (20.9 g) and $CH_3SO_2NH_2$ (1.42 g, 14.9 mmol) in t-BuOH (70 mL) and H_2O (74.5 mL). The resulting mixture was stirred at 0 °C for 36 h, Na_2SO_3 (22.4 g) was added and stirring was continued at room temperature for 1 h. t-BuOH was removed in vacuo and the mixture was extracted with EtOAc (3 x 50 mL) and the combined extracts were washed with brine and dried over Na_2SO_4. After concentration, the residue was subjected to flash column chromatography (SiO_2 [250 g], 1 : 30 EtOAc / CH_2Cl_2 eluent) to afford a very viscous off-white oil of 88% ee, which solidified after storing at -20 °C overnight (2.29 g, 73% yield); FTIR 3452, 1770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.68 (dtd, J = 4.4, 3.8, 1.0 Hz, 1H), 4.50 (ddd, J = 9.4, 5.6, 4.0 Hz, 1H), 2.84 - 2.76 (m, 2H), 2.71 - 2.63 (m, 1H), 2.60 (dd, J = 17.6, 0.8 Hz, 1H), 2.26 (dd, J = 3.8, 0.8 Hz, 1H), 2.17 - 2.11 (m, 2H), 1.51 - 1.47 (m, 2H), 1.36 - 1.31 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 83.9, 82.5, 73.8, 68.5, 38.8, 31.4, 28.8, 22.5, 19.2, 19.0, 14.3; HRMS (CI) for $[C_{12}H_{18}O_3 + NH_4]^+$, m/z calcd 228.1600, found 228.1606; HPLC (chiral) Whelk-O 1 (Regis Technologies) at 23 °C, n = 225 nm (90 : 10 hexane / 2-propanol eluent) retention

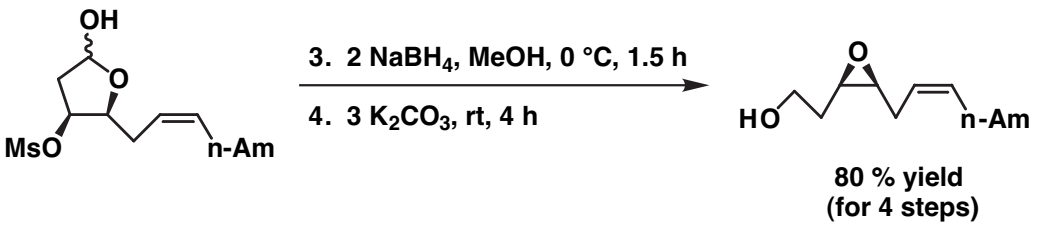
times 21.7 (S, S) and 26.1 (R, R) min at 1 mL/min flow rate. The white solid (1.94 g) was transferred into a flask and 30 mL of hexanes was added. Anhydrous ether was added dropwise to the above mixture while swirling until all solids dissolved. The flask was cooled to -78 °C for 10 min, stored at -20 °C overnight, then 0 °C for 2 h. The clear supernatant (ca 25 mL) was removed by a syringe fitted with a syringe filter. Ether was added to dissolve all the solids and removed in vacuo to afford the title compound as white crystals (1.67 g, 94% ee). $[\alpha]_D^{23}$ -45.0 (c 0.65, acetone).



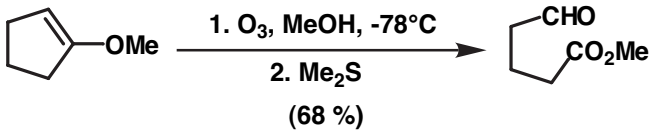
Lindlar catalyst ($Pd/CaCO_3/Pb$, 70 mg) was weighed into a flame-dried 100 mL round-bottom flask, followed by addition of THF (16 mL) and Et_3N (105 μl). The mixture was stirred at rt for 15 min and cooled to -78 °C. After a solution of the alkynol (697 mg, 3.32 mmol) in THF (2 mL + 2 mL [for rinse]) was added, the resulting mixture was degassed and the reaction vessel was flushed with H_2 (1 atm) 6 times at -78 °C. The mixture was stirred at 0 °C under H_2 (1 atm) for 45 min (with careful monitoring of the reaction with $AgNO_3$ impregnated TLC plates in 1 : 2 EtOAc / CH_2Cl_2) and filtered through Celite. Filtrates were concentrated in vacuo to afford the alkenylhydroxylactone as a colorless liquid (700 mg, 99% yield); $[\alpha]_D^{23}$ -44.5 (c 0.65, acetone); FTIR 3456, 1760 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.63 - 5.57 (m, 1H), 5.42 - 5.36 (m, 1H), 4.51 (q, J = 4.5 Hz, 1H), 4.39 (td, J = 7.5, 4.0 Hz, 1H), 2.79 (dd, J = 18.0, 5.5 Hz, 1H), 2.68 - 2.54 (m, 2H), 2.56 (d, J = 18.0 Hz, 1H), 2.09 (q, J = 7.5 Hz, 2H), 1.97 (d, J = 4.5 Hz, 1H), 1.37 (quint, J = 7.0 Hz, 2H), 134 - 1.25 (m, 4H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 134.5, 122.4, 84.2, 69.0, 39.5, 31.8, 29.4, 27.8, 26.9, 22.9, 14.4; HRMS (CI) for $[C_{12}H_{20}O_3 + NH_4]^+$, m/z calcd 230.1756, found 230.1759.



To a solution of the alkenylhydroxylactone (1.14 g, 5.36 mmol, azeotropically dried with PhH [2 x 5 mL]) in CH_2Cl_2 (30 mL) at -20 °C, was added CH_3SO_2Cl (7.5 mmol, 7.5 mL of a 1 M solution in CH_2Cl_2). Et_3N (1.05 mL, 7.5 mmol) was added to the above mixture at -20 °C in 5 min. After the mixture was stirred at 0 °C for 1 h, solvents were removed in vacuo and the resulting white solid was subjected to 0.2 mm vacuum for 20 min. The solid was dissolved in CH_2Cl_2 (150 mL) and washed with distilled H_2O (2 x 50 mL), brine and dried over Na_2SO_4. Solvents were removed in vacuo to afford an off-white solid. The solid was azeotropically dried with PhH (2 x 15 mL) and dissolved in $PhCH_3$ (35 mL). The resulting solution was cooled to -78 °C and DIBAL (6.4 mmol, 6.4 mL / 1 M solution in $PhCH_3$) was added dropwise. After the mixture was stirred at -78 °C for 1 h, the following reagents were sequentially added: MeOH (2.5 mL), ground $Na_2SO_4 \cdot 10H_2O$ (17.3 g), and Celite (3 mL). The suspension was warmed to rt in 1 h and filtered through Celite. The filtrates were concentrated in vacuo to afford the desired lactol (3.2 : 1 mixture of diastereomers) as a colorless liquid; FTIR 3417 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.71 (quint, J = 2.8 Hz, 1H), 5.58 - 5.48 (m, 1H), 5.44 - 5.35 (m, 1H), 5.22 - 5.20 (m, 0.76 H), 5.15 - 5.12 (m, 0.24 H), 4.23 (ddd, J = 7.6, 6.0, 3.4 Hz, 0.76 H), 3.98 (td, J = 7.2, 3.6 Hz, 0.24 H), 3.08 (s, 0.24 x 3H), 3.04 (d, J = 2.8 Hz, 0.76 H), 3.02 (d, J = 1.2 Hz, 0.26 H), 3.03 (s, 0.76 x 3H), 2.61 - 2.27 (m, 4H), 2.08 - 1.96 (m, 2H), 1.39 - 1.24 (m, 6H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for the major isomer δ 133.5, 123.8, 97.2, 81.1, 79.7, 42.2, 38.8, 31.8, 29.5, 27.8, 27.1, 22.9, 14.4; HRMS (CI) for $[C_{13}H_{24}O_5S + NH_4]^+$, m/z calcd 310.1689, found 310.1677.

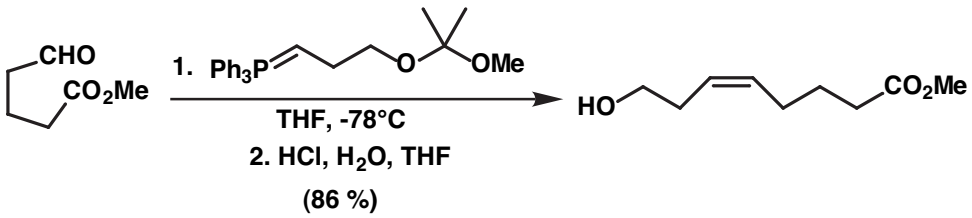


To a solution of the crude mesylate (azeotropically dried with PhH [2 x 10 mL]) in MeOH (40 mL) at 0 °C, was added $NaBH_4$ (405 mg, 10.7 mmol). After the mixture was stirred at 0 °C for 1.5 h, K_2CO_3 (2.22 g, 16.1 mmol) and MeOH (40 mL) were added. The suspension was warmed to rt and stirred at rt for 4 h. Methanol was removed in vacuo and the residue was partitioned between CH_2Cl_2 (100 mL) and H_2O (pH = 7, 100 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 40 mL). The combined CH_2Cl_2 layers were washed with brine and dried over Na_2SO_4. Solvents were removed in vacuo and the residue was subjected to flash chromatography (SiO_2 [50 g], EtOAc / hexanes 45 : 55 with 1% Et_3N as eluent) to afford the epoxyalcohol as a colorless liquid (840 mg, 80% yield from the alkenol). $[\alpha]_D^{23}$ + 8.1 (c 0.60, acetone); FTIR 3419 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.57 - 5.52 (m, 1H), 5.44 - 5.39 (m, 1H), 3.93 - 3.82 (m, 2H), 3.11 (dt, J = 7.5, 4.5 Hz, 1H), 2.98 (q, J = 6.0 Hz, 1H), 2.41 (dt, J = 15.0, 7.25 Hz, 1H), 2.21 (dt, J = 15.0, 7.25 Hz, 1H), 2.06 - 2.02 (m, 2H), 1.94 - 1.87 (m, 1H), 1.78 - 1.71 (m, 1H), 1.61 (s, 1H), 1.39 - 1.25 (m, 6H), 0.89 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.2, 123.6, 60.9, 56.4, 55.3, 31.8, 30.8, 29.5, 27.7, 26.6, 22.9, 14.4; HRMS (CI) for $[C_{12}H_{22}O_2 + NH_4]^+$, m/z calcd 216.1964, found 216.1962.



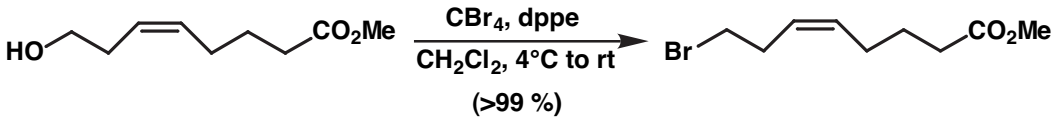
Methyl 5-oxopentanoate.[3a] Ozone was continuously bubbled (using a gas dispersion tube (25 - 50 μ glass frit)) into a solution composed of 1-methoxy-1-cyclopentene[4] (31.73g, 323.3 mmol), pyridine (1 mL) and methanol (300 mL) at -78 °C. The reaction was judged complete after 2 h based on the persistence of the purple color of ozone. The

excess reagent was removed by bubbling nitrogen into the solution. Dimethyl sulfide (120 mL) was added and the solution was stirred at -78 °C for 2 h, -20 °C for 1 h and 4 °C overnight. The mixture was concentrated by rotary evaporation at reduced pressure and the residue was diluted with ether (60 mL) and washed with saturated brine (150 mL). The aqueous layer was extracted further with ether (3 x 60 mL) and the organics were combined, dried (K_2CO_3) and concentrated. Benzene was added and the mixture reconcentrated to effect azeotropic removal of any remaining water. The residue was fractionally distilled and the component boiling at 81 - 82 °C (P = 11 mm Hg) was collected as a colorless liquid (28.0 g, 68 % yield). Spectral data were in agreement with those previously reported;[3b] FTIR 1736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.76 (t, J = 1.2 Hz, 1H), 3.66 (s, 3H), 2.53 (dt, J = 7.2, 1.2 Hz, 2H), 2.37 (t, J = 7.2 Hz, 2H), 1.94 (quint, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 173.2, 51.6, 42.9, 32.9, 17.3.

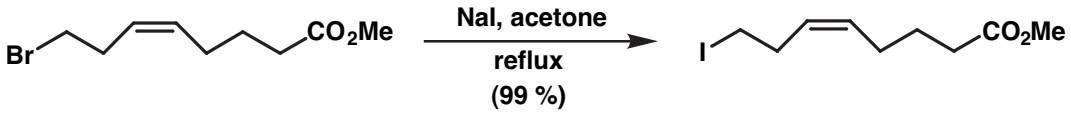


Methyl (5Z)-8-hydroxyoct-5-enoate. A 1.0 M solution of NaHMDS (18.3 mL) in THF was added down the flask wall over a period of 5 min to a stirred slurry of [3-(1-methoxy-1-methylethoxy)propyl]triphenylphosphonium bromide[5] (8.60 g, 18.2 mmol) in THF (42 mL) cooled to -41 °C. The resulting orange mixture was stirred at -41 °C for 30 min prior to cooling to -78 °C. The aldehyde (2.48 g, 19.0 mmol) was introduced down the wall of the flask as a solution in THF (17 mL) over a period of 5 min and the resulting cloudy solution was stirred at -78 °C for 3 h with slow warming to 0 °C over 2 h. A 1 M aqueous solution of HCl (44 mL) was added with stirring at 4 °C for 1 h and the THF was removed by rotary evaporation at 4 °C under reduced pressure (2 mm Hg). The residue was diluted with water (15 mL) and extracted with ethyl acetate (4 x 50 mL). The combined organics were

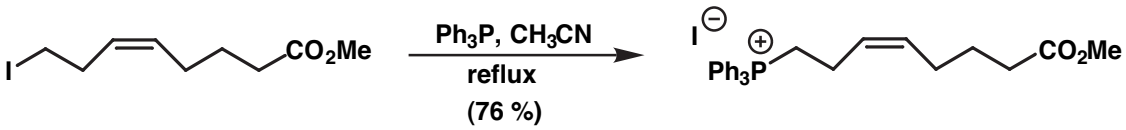
washed with saturated NaCl (50 mL) and saturated $NaHCO_3$ (50 mL) aqueous solutions and dried ($MgSO_4$). The solvent was removed in vacuo and the residue chromatographed on silica gel eluting with a mixture of EtOAc and hexanes (1 : 1) to afford a faint-yellow oil (2.68 g, 86% yield, single isomer (Z) by ^1H NMR); FTIR 3450, 1738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.51 (m, 1H), 5.42 (m, 1H), 3.66 (s, 3H), 3.64 (t, J = 6.4 Hz, 2H), 2.31 (m, 4H), 2.11 (q, J = 7.3 Hz, 2H), 1.70 (quint, J = 7.4 Hz, 2H), 1.55 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 131.7, 126.4, 62.2, 51.6, 33.4, 30.9, 26.7, 24.8; HRMS (CI) for $[C_9H_{20}NO_3 + NH_4]^+$ m/z calcd 190.1442, found 190.1443.



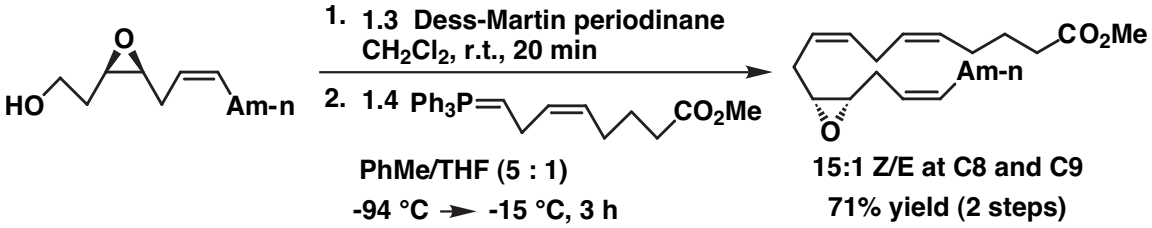
Methyl (5Z)-8-bromooct-5-enoate. Tetrabromomethane (17.5 g, 52.7 mmol) was dissolved in CH_2Cl_2 (23 mL) and added dropwise over 15 min to a 4 °C slurry consisting of methyl (5Z)-8-hydroxyoct-5-enoate (3.03 g, 17.5 mmol) and 1,2-bis(diphenylphosphino)ethane (10.5 g, 26.4 mmol) in CH_2Cl_2 (28 mL). The resulting yellow solution was stirred at rt for 45 min. Additional CH_2Cl_2 (50 mL) was added and the mixture was filtered through a short silica gel plug (washed with CH_2Cl_2) to remove the phosphine oxide by-product. The solvent was removed in vacuo and the residue was chromatographed on silica gel (EtOAc / hexanes (1 : 9)) to provide a colorless oil (4.10 g, >99 % yield); FTIR 1737 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.50 (m, 1H), 5.41 (m, 1H), 3.66 (s, 3H), 3.36 (t, J = 7.0 Hz, 2H), 2.60 (q, J = 7.0 Hz, 2H), 2.32 (t, J = 7.3 Hz, 2H), 2.09 (q, J = 7.3 Hz, 2H), 1.70 (quint, J = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.9, 131.6, 127.0, 51.5, 33.3, 32.4, 30.7, 26.7, 24.6; HRMS (CI) for $[C_9H_{19}BrNO_2 + NH_4]^+$ m/z calcd 252.0599, found 252.0599.



Methyl (5Z)-8-iodooct-5-enoate. Methyl (5Z)-8-bromooct-5-enoate (4.10 g, 17.4 mmol) and NaI (7.88 g, 52.6 mmol) were stirred together in refluxing acetone (45 mL) for 3 h. The mixture was cooled to rt, concentrated in vacuo and the residue suspended in ether and filtered (Celite). The ether solution was passed through a short silica gel plug (washed with ether) and the filtrate was concentrated to afford a light-sensitive brown oil (4.87 g, 99 % yield) that was used in the next step without further purification; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.50 (m, 1H), 5.37 (m, 1H), 3.68 (s, 3H), 3.14 (t, J = 7.3 Hz, 2H), 2.62 (q, J = 7.3 Hz, 2H), 2.32 (t, J = 7.3 Hz, 2H), 2.08 (q, J = 7.3 Hz, 2H), 1.71 (quint, J=7.3 Hz, 2H).



(3Z)-(7-Methoxycarbonylhept-3-enyl)triphenylphosphonium iodide. A mixture of methyl (5Z)-8-iodooct-5-enoate (4.87 g, 17.2 mmol) and triphenylphosphine (6.78 g, 25.8 mmol) was heated together in refluxing acetonitrile (39 mL) for 19 h. Concentration of the reaction mixture in vacuo and chromatography of the residue on silica gel (CH_3OH / CH_2Cl_2 (gradient elution 5 : 95 to 7 : 93)) provided a faint-yellow glass which was subjected to azeotropic distillation (x 2) under reduced pressure with a 2 : 1 mixture of acetonitrile and benzene to remove methanol. Trituration with ethyl acetate and recrystallization from CH_2Cl_2 / EtOAc gave colorless crystals (7.12 g, 76 % yield); mp 110-111°C; IR (CCl_4) 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85 - 7.77 (m, 9H), 7.74 - 7.67 (m, 6H), 5.62 (m, 1H), 5.36 (m, 1H), 3.71 (m, 2H), 3.58 (s, 3H), 2.42 (m, 2H), 2.20 (t, J = 7.3 Hz, 2H), 1.86 (q, J = 7.3 Hz, 2H), 1.58 (quint, J = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.7, 135.11, 135.08, 133.7, 133.6, 131.2, 130.5, 130.4, 126.9, 126.8, 118.3, 117.4, 51.5, 33.2, 26.5, 24.4, 23.3 (d, $J_{C\text{-}P}$=50 Hz), 20.3 (2); HRMS m/z calcd for (M^+-I) $C_{27}H_{30}O_2P$ 417.1982, found 417.1983.



To a solution of the epoxy alcohol (581 mg, 2.93 mmol, azeotropically dried with PhH [2 x 15 mL]) in CH_2Cl_2 (30 mL) was added at 23 °C a clear solution of freshly prepared Dess-Martin periodinane[6] (9.8 mL, 3.8 mmol, 0.39 M in CH_2Cl_2) in 2 min. The clear reaction mixture was stirred at room temperature for 1 h, and diluted with ether (190 mL). The resulting cloudy mixture was poured into a solution of $Na_2S_2O_3.5H_2O$ in sat. $NaHCO_3$ (200 mL). After the two phase mixture was stirred vigorously at room temperature for 15 min, it was extracted with ether (3 x 100 mL). The combined ether layers were washed with sat. $NaHCO_3$, H_2O and brine. After concentration, the residue was azeotropically dried with PhH (3 x 15 mL) to afford the epoxy aldehyde as a colorless liquid, which was ready for the next step.

The triphenylphosphonium salt (2.40 g, 4.4 mmol) was added to a flame-dried 500 mL flask, followed by MeCN (20 mL) and PhH (20 mL). After stirring, a clear solution was formed; then solvents were removed in vacuo. MeCN (8 mL) and PhH (30 mL) were added, the mixture was stirred, and solvents were removed in vacuo. This process was repeated one more time. The resulting viscous oil was put on a high vacuum pump (<0.5 mm Hg) for 20 min with constant turning of the flask. Trituration with PhH (25 mL) returned the material to a solid form that was placed under a high vacuum (<0.5 mm Hg) for 15 min. Under a strong flow of N_2, and white solid along the wall were scraped down. To the white suspension in THF (25 mL) at -78 °C, was added dropwise $KN(SiMe_3)_2$ (7.6 mL, 3.8 mmol, 0.5 M in PhMe) in 10 min. The resulting orange suspension was stirred at -78 °C for 45 min, then -25 °C for 30 min. After the mixture was cooled to -78 °C, PhMe (105 mL) was added in 30 min, then the orange suspension was cooled to -94 °C. A solution of the epoxy aldehyde prepared above in PhMe (6 mL + 2 mL for rinse) was added at -94 °C

over 40 min. The reaction mixture was warmed up to -15 °C in 3 h, treated with pH = 7 buffer (200 mL), and then extracted with EtOAc (3 x 100 mL). The combined EtOAc layers were washed with H_2O, brine and dried over Na_2SO_4. After concentration, the residue was subjected to flash column chromatography (SiO_2 [100 g], 1 : 15 EtOAc / hexanes as eluent) to afford the title compound (15 : 1 Z/E isomers) as a colorless liquid (698 mg, 71% yield); $[\alpha]_D^{23}$ +5.38 (c 1.32, acetone), Lit. $[\alpha]^{23}_D$ +4.94 (c 1.64, acetone); FTIR 1741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.57 - 5.36 (m, 6H), 3.66 (s, 3H), 2.97 - 2.92 (m, 2H), 2.79 (t, J = 5.8 Hz, 2H), 2.44 - 2.37 (m, 2H), 2.31 (t, J = 7.6 Hz, 2H), 2.27 - 2.17 (m, 2H), 2.12 - 2.07 (m, 2H), 2.07 - 2.01 (m, 2H), 1.70 (quint, J = 7.6 Hz, 2H), 1.38 - 1.24 (m, 6H), 0.88 (t, J = 7.0 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 133.1, 130.7, 129.4, 128.6, 124.5, 123.8, 56.8, 56.6, 51.8, 33.7, 31.8, 29.5, 27.7, 26.9, 26.54, 26.49, 26.1, 25.1, 22.9, 14.4; HRMS (CI) for $[C_{21}H_{34}O_3 + NH_4]^+$, m/z calcd 352.2852, found 352.2843.

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