Supporting Information

Efficient Two-step Conversion of α,β -Unsaturated Aldehydes to Optically Active γ -Oxy- α,β -Unsaturated Nitriles and its Application to Total Synthesis of (+)-Patulolide C

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Experimental Section

General: Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. NMR spectra were recorded on a JEOL JNM-LA500 spectrometer, operating at 500 MHz for ^1H NMR and 125.65 MHz for ^{13}C NMR. Chemical shifts in CDCl_3 were reported downfield from TMS (= 0) or in the scale relative to CHCl_3 (7.24 ppm) for ^1H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to CHCl_3 (77.0 ppm for ^{13}C NMR) as an internal reference. Optical rotations were measured on a JASCO P-1010 polarimeter. EI mass spectra were measured on JMS-BU20 GCmate. ESI mass spectra were measured on Waters-ZQ4000. Column chromatography was performed with silica gel Merck 60 (230–400 mesh ASTM). The enantiomeric excess (ee) was determined by HPLC analysis and GC analysis. HPLC was performed on JASCO HPLC systems consisting of the following: pump, 880-PU or PU-980; detector, 875-UV or UV-970, measured at 254 nm; column, DAICEL CHIRALCEL OD, OD-H, OJ, and DAICEL CHIRALPAK AD-H; mobile phase, hexane–2-propanol; flow rate, 1.0 mL/min. GC was performed on Shimadzu GC-14A with Varian Chirasil DEX CB column (0.25 mm x 25 m); carrier gas, nitrogen (4 kPa). Reactions were carried out in dry solvents under an argon atmosphere, unless otherwise stated. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. $\text{Y}[\text{N}(\text{Si}(\text{CH}_3)_2)_3]$ was purchased from Aldrich. Other reagents were purified by the usual methods.

Procedure for Preparation of the (S)-Yttrium-Lithium₃-tris(binaphthoxide) Complex (YLB 1) :

To a stirred solution of (S)-BINOL (1.237 g, 4.32 mmol) in THF (20 mL) at 0 °C, was added BuLi (2.72 mL, 4.32 mmol, 1.59 M in hexanes). To the resulting suspended mixture was added a solution of $\text{Y}[\text{N}(\text{Si}(\text{CH}_3)_2)_3]$ (820 mg, 1.44 mmol) in THF (20 mL). After stirring for 10 min at room temperature, the solvents were removed under reduced pressure. The residue was dissolved in THF (48 mL), and H_2O (78 μL , 4.32 mmol) was added to give (S)-YLB 1- H_2O solution (30 mM, in THF).

General Procedure for Enantioselective Cyanation Reaction of Aldehyde Promoted by (S)-YLB 1:

To tris(2,6-dimethoxyphenyl)phosphine oxide (27.5 mg, 0.06 mmol) in a test tube was added the (S)-YLB 1- H_2O solution (2.0 mL, 0.06 mmol, 30 mM in THF). The solution was stirred at room temperature. After completely dissolving phosphine oxide, BuLi (0.06 mmol) was added to the mixture. The mixture solution was cooled down to $-78\text{ }^\circ\text{C}$, α,β -unsaturated aldehyde **3a** (0.6 mmol) and ethyl cyanofomate **2** (0.72 mmol) was added and stirred at $-78\text{ }^\circ\text{C}$. After stirring for 3 h, 1 M HCl was added to the solution and organic component was extracted with diethyl ether. Organic layer was washed with brine, dried over Na_2SO_4 . After evaporating solvent, the residue was purified by silica gel flash column chromatography to give the product **4a** (118 mg, 0.60 mmol, y. 100%) as colorless oil.

(2R,3E)-2-Ethoxycarboxy-3-heptenenitrile (**4a**):

colorless oil; IR (neat) ν 1757, 1251 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.90 (t, $J = 7.3$ Hz, 3H), 1.32 (dd, $J = 7.2, 7.2$ Hz, 3H), 1.40–1.47 (m, 2H), 2.07–2.12 (m, 2H), 4.21–4.30 (m, 2H), 5.54–5.59 (m, 1H), 5.65 (dd, $J = 6.7, 0.9$ Hz, 1H), 6.16 (ddt, $J = 15.3, 6.7, 0.9$ Hz,

1H); ^{13}C NMR (CDCl_3) δ 13.7, 14.3, 21.6, 34.1, 65.1, 65.5, 115.5, 119.9, 141.3, 153.5; EI-MS m/z 197 $[\text{M}]^+$, 169 $[\text{M}-\text{CH}_2\text{CH}_2]^+$; $[\alpha]_{\text{D}}^{23}$ -11.5 (c 2.17, CH_3Cl) (92% ee); Anal. Calcd for $\text{C}_{10}\text{H}_{15}\text{O}_3\text{N}$; C, 60.90; H, 7.67; N, 7.10; O, 24.33. Found: C, 60.88; H, 7.78; N, 7.07; GC, injection temp. 230 $^\circ\text{C}$; initial column temp. 120 $^\circ\text{C}$; detection temp. 250 $^\circ\text{C}$; retention time (t_{R}) of 14.4 min (major), 15.9 min (minor).

(2*R*,3*E*)-2-(Ethoxycarboxy)-6-phenyl-3-

hexenenitrile (4b): colorless oil; IR (neat) ν 2934, 1756, 1372, 1251 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.33 (dd, $J = 7.3, 7.3$ Hz, 3H), 2.44 (q, $J = 7.3$ Hz, 2H), 2.73 (t, $J = 7.3$ Hz, 2H), 4.21-4.31 (m, 2H), 5.58 (dd, $J = 6.7, 15.3$ Hz, 1H), 5.64 (d, $J = 6.7$ Hz, 1H), 6.21 (dt, $J = 6.7, 15.3$ Hz, 1H), 7.15 (d, $J = 7.4$ Hz, 2H), 7.19 (t, $J = 7.4$ Hz, 1H), 7.28 (t, $J = 7.4$ Hz, 2H); ^{13}C NMR (CDCl_3) δ 14.1, 33.7, 34.6, 64.8, 65.4, 115.2, 120.3, 126.2, 128.3, 128.5, 140.1, 140.6, 153.3; ESI-MS (m/z) 282 $[\text{M}+\text{Na}]^+$; $[\alpha]_{\text{D}}^{24.8}$ -17.1 (c 1.20, CHCl_3) (91% ee); HPLC (DAICEL CHIRALCEL OD-H, 2-propanol/hexane = 1/99, flow 1.0 mL/min; detection at 220 nm) t_{R} 28.0 min (major), 29.8 min (minor).

(2*R*,3*E*)-2-(Ethoxycarboxy)-4-cyclohexyl-3-butenenitrile

(4c): colorless oil; IR (neat) ν 2927, 2853, 1757, 1261 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.04-1.29 (m, 6H), 1.32 (dd, $J = 7.0, 7.0$ Hz, 3H), 1.63-1.74 (m, 4H), 2.00-2.08 (m, 1H), 4.21-4.30 (m, 2H), 5.51 (ddd, $J = 1.5, 6.7, 15.6$ Hz, 1H), 5.64 (d, $J = 6.7$ Hz, 1H), 6.10 (dd, $J = 6.7, 15.6$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 14.1, 25.7, 25.9, 31.9, 40.2, 65.2, 65.4, 115.4, 117.3, 146.5, 153.0; ESI-MS (m/z) 260 $[\text{M}+\text{Na}]^+$; $[\alpha]_{\text{D}}^{24.3}$ -12.6 (c 1.24, CHCl_3) (93% ee); GC (injection temp. 250 $^\circ\text{C}$; column temp. 150 $^\circ\text{C}$; detection temp. 250 $^\circ\text{C}$) t_{R} 39.2 min (major), 40.7 min (minor).

(2*R*,3*E*)-2-Ethoxycarboxy-4-phenyl-3-butenenitrile (4d):

colorless oil; IR (neat) ν 1756, 1250 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.34 (dd, $J = 7.0, 7.0$ Hz, 3H), 4.24-4.33 (m, 2H), 5.88 (dd, $J = 6.8, 1.3$ Hz, 1H), 6.22 (dd, $J = 15.9, 6.8$ Hz, 1H), 6.98 (d, $J = 15.9$ Hz, 1H), 7.31-7.37 (m, 3H), 7.41-7.42 (m, 2H); ^{13}C NMR (CDCl_3) δ 14.1, 65.0, 65.1, 115.1, 117.8, 127.2, 128.9, 129.5, 134.2, 138.4, 153.4; $[\alpha]_{\text{D}}^{22.4}$ -17.2 (c 2.02, CHCl_3) (88% ee); Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{O}_3\text{N}$; C, 67.52; H, 5.67; N, 6.06; O, 20.75. Found: C, 67.25; H, 5.83; N, 5.96; HPLC (DAICEL CHIRALCEL OD, 2-propanol/hexane 1/99, flow 1.0 mL/min, detection at 254 nm) t_{R} 52.0 min (*S*) and 68.7 min (*R*). Absolute configuration was determined after converting into corresponding 2-hydroxyacid methyl ester; **Methyl (*R*)-2-hydroxy-4-phenyl-3-butenate**: colorless oil; ^1H NMR (CDCl_3) δ 3.72 (brs, 1H), 3.82 (s, 3H), 4.83 (dd, $J = 5.6, 1.6$ Hz, 1H), 6.22 (dd, $J = 15.6, 5.6$ Hz, 1H), 6.79 (dd, $J = 15.6, 1.6$ Hz, 1H), 7.23-7.26 (m, 1H), 7.29-7.32 (m, 2H), 7.37-7.38 (m, 2H); ^{13}C NMR (CDCl_3) δ 53.0, 71.28, 125.2, 126.7, 128.1, 128.6, 132.4, 136.0, 173.8; $[\alpha]_{\text{D}}^{24}$ -32.8 (c 0.9, CHCl_3) [lit. $[\alpha]_{\text{D}}^{24}$ -67.7 (c 0.05 M, CHCl_3 for *R* enantiomer). Lit. H.-T. Yu, H. Simon, *Tetrahedron*, **1991**, 47, 9035.

General Procedure for [3,3]-Sigmatropic Rearrangement:

Thermal Rearrangement: A solution of **4a** (197.2 mg, 1.0 mmol) in 1,2,4-trichlorobenzene (5 mL) was stirred for 12 h at 200 $^\circ\text{C}$. After cooling to the room temperature, the reaction mixture was poured into silica gel column, eluted with hexane until removal of the reaction solvent. Then, the silica gel was washed with diethyl ether to

give rearrangement products. After evaporating under reduced pressure, *trans*-**5a**/*cis*-**5a** ratio was determined by ^1H NMR (86/14). Further purification by silica gel column chromatography (hexane/diethyl ether 10/1) afforded **5a** as colorless oil (99%).

Pd(II)-Promoted Rearrangement: To a stirred solution of **4a** (197.2mg, 1.0 mmol) in 1.0 mL of anhydrous THF in a test tube at room temperature, was added $\text{PdCl}_2(\text{PhCN})_2$ (19.2 mg, 0.05 mmol). After stirring for 24 h at 50 °C, the reaction mixture was quenched with 1 M HCl, extracted with diethyl ether (5 mL $\times$ 3), washed with brine and dried over Na_2SO_4 . After evaporating under reduced pressure, *trans*-**5a**/*cis*-**5a** ratio was determined by ^1H NMR (96/4). Purification by silica gel column chromatography (hexane/diethyl ether 10/1) afforded **5a** (90%).

(CH₃)₃SiOTf-Promoted Rearrangement: To a stirred solution of **4a** (197.2mg, 1.0 mmol) in 1.0 mL of anhydrous toluene in a test tube at room temperature, was added (CH₃)₃SiOTf (163.4 μL , 1.0 mmol). After stirring for 48 h at the same temperature, the reaction mixture was quenched with 1 M HCl, extracted with diethyl ether (5 mL $\times$ 3), washed with brine and dried over Na_2SO_4 . After evaporating under reduced pressure, *trans*-**5a**/*cis*-**5a** ratio was determined by ^1H NMR (89/11). Purification by silica gel column chromatography (hexane/diethyl ether 10/1) afforded **5a** (82%).

(4*R*,2*E*)-4-Ethoxycarboxy-2-heptenenitrile (*trans*-5a**):** colorless oil; IR (neat) ν 2963, 2227, 1748, 1374, 1256 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.92 (t, J = 7.2 Hz, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1.33-1.41 (m, 2H), 1.58-1.72 (m, 2H), 4.19 (q, J = 7.2 Hz, 2H), 5.16-5.21 (m, 1H), 5.56 (dd, J = 1.5, 16.5 Hz, 1H), 6.62 (dd, J = 5.5, 16.5 Hz, 1H); ^{13}C NMR (CDCl_3) δ 13.6, 14.1, 18.0, 35.5, 64.5, 75.7, 100.9, 116.5, 151.3, 154.2; ESI-MS (m/z) 220 [$\text{M}+\text{Na}$] $^+$; $[\alpha]_{\text{D}}^{24.5}$ -11.3 (c 0.82, CHCl_3) (92% ee); GC (injection temp. 250 °C; column temp. 100 °C; detection temp. 250 °C) t_{R} 45.7 min (minor), 49.2 min (major).

(4*S*,2*Z*)-4-Ethoxycarboxy-2-heptenenitrile (*cis*-5a**):** colorless oil; IR (neat) ν 2925, 2224, 1748, 1372, 1256 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.95 (t, J = 7.3 Hz, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1.35-1.50 (m, 2H), 1.59-1.66 (m, 1H), 1.76-1.84 (m, 1H), 4.20 (q, J = 7.2 Hz, 2H), 5.40-5.46 (m, 1H), 5.47 (d, J = 11.3 Hz, 1H), 6.37 (dd, J = 8.3, 11.3 Hz, 1H); ^{13}C NMR (CDCl_3) δ 13.7, 14.2, 18.0, 35.7, 64.4, 75.8, 101.3, 113.8, 114.7, 150.9; ESI-MS (m/z) 220 [$\text{M}+\text{Na}$] $^+$; $[\alpha]_{\text{D}}^{24.4}$ -32.6 (c 0.23, CHCl_3) (92% ee); GC (injection temp. 250 °C; column temp. 100 °C; detection temp. 250 °C) t_{R} 37.0 min (major), 39.2 min (minor).

(4*R*,2*E*)-4-Ethoxycarboxy-6-phenyl-2-hexenenitrile (*trans*-5b**):** colorless oil; IR (neat) ν 2934, 2227, 1748, 1373, 1258 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.32 (t, J = 7.0 Hz, 3H), 1.93-2.08 (m, 2H), 2.64-2.74 (m, 2H), 4.21 (q, J = 7.0 Hz, 2H), 5.17-5.21 (m, 1H), 5.57 (dd, J = 1.5, 16.5 Hz, 1H), 6.62 (dd, J = 5.5, 16.5 Hz, 1H), 7.14 (d, J = 7.4 Hz, 2H), 7.20 (t, J = 7.4 Hz, 1H), 7.28 (t, J = 7.4 Hz, 2H); ^{13}C NMR (CDCl_3) δ 14.2, 30.9, 35.1, 64.6, 75.2, 101.3, 116.4, 126.4, 128.3, 128.6, 140.0, 150.9, 154.1; ESI-MS (m/z) 282 [$\text{M}+\text{Na}$] $^+$; $[\alpha]_{\text{D}}^{24.9}$ -11.9 (c 1.99, CHCl_3) (91% ee); HPLC (DAICEL CHIRALCEL OD-H, 2-propanol/hexane = 1/9, flow 1.0 mL/min; detection at 220 nm) t_{R} 19.8 min (major), 24.9 min (minor).

(4*S*,2*Z*)-4-Ethoxycarboxy-6-phenyl-2-hexenenitrile (*cis*-5b**):** colorless oil; IR

(neat) ν 2934, 2224, 1748, 1372, 1260 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.32 (t, $J = 7.0$ Hz, 3H), 1.94-2.17 (m, 2H), 2.66-2.81 (m, 2H), 4.22 (q, $J = 7.0$ Hz, 2H), 5.43-5.47 (m, 1H), 5.47 (d, $J = 11.5$ Hz, 1H), 6.39 (dd, $J = 7.8, 11.5$ Hz, 1H), 7.14 (d, $J = 7.4$ Hz, 2H), 7.19 (t, $J = 7.4$ Hz, 1H), 7.28 (t, $J = 7.4$ Hz, 2H); ^{13}C NMR (CDCl_3) δ 14.2, 31.0, 35.4, 64.6, 75.5, 101.4, 114.6, 126.3, 128.3, 128.6, 140.2, 150.5, 154.1; ESI-MS (m/z) 282 $[\text{M}+\text{Na}]^+$; $[\alpha]_{\text{D}}^{24.7} -3.2$ (c 2.88, CHCl_3) (91% ee); HPLC (DAICEL CHIRALCEL OD-H, 2-propanol/hexane = 1/9, flow 1.0 mL/min; detection at 220 nm) t_{R} 9.4 min (minor), 10.8 min (major).

(4R,2E)-4-Ethoxycarboxy-4-cyclohexyl-2-butenenitrile

(*trans*-5c): colorless oil; IR (neat) ν 2931, 2856, 2227, 1748, 1372, 1255 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.97-1.25 (m, 6H), 1.30 (t, $J = 7.5$ Hz, 3H), 1.61-1.75 (m, 5H), 4.18 (q, $J = 7.5$ Hz, 2H), 5.00 (dt, $J = 1.5, 5.7$ Hz, 1H), 5.54 (dd, $J = 1.5, 16.2$ Hz, 1H), 6.63 (dd, $J = 5.7, 16.2$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 14.2, 25.7, 26.0, 28.0, 28.3, 41.5, 64.5, 79.9, 101.0, 116.5, 150.4, 154.3; ESI-MS (m/z) 260 $[\text{M}+\text{Na}]^+$; $[\alpha]_{\text{D}}^{24.3} -7.9$ (c 1.12, CHCl_3) (92% ee); HPLC (DAICEL CHIRALCEL OD-H, 2-propanol/hexane = 1/99, flow 1.0 mL/min; detection at 220 nm) t_{R} 9.0 min (major), 11.2 min (minor).

(4S,2Z)-4-Ethoxycarboxy-4-cyclohexyl-2-butenenitrile

(*cis*-5c): colorless oil; IR (neat) ν 2931, 2855, 2223, 1748, 1371, 1254 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.04-1.25 (m, 6H), 1.30 (t, $J = 7.1$ Hz, 3H), 1.64-1.86 (m, 5H), 4.19 (q, $J = 7.1$ Hz, 2H), 5.21 (t, $J = 8.6$ Hz, 1H), 5.51 (d, $J = 11.3$ Hz, 1H), 6.34 (dd, $J = 8.6, 11.3$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 14.2, 25.6, 25.7, 26.0, 28.0, 28.1, 41.5, 64.4, 79.9, 102.3, 114.8, 149.6, 154.3; ESI-MS (m/z) 260 $[\text{M}+\text{Na}]^+$; $[\alpha]_{\text{D}}^{24.4} +52.9$ (c 0.80, CHCl_3) (93% ee); GC (inject temperature, 250 $^{\circ}\text{C}$; detection temperature, 250 $^{\circ}\text{C}$; column temperature, 150 $^{\circ}\text{C}$) t_{R} 29.7 min (minor), 30.7 min (major).

(4S,2E)-4-Ethoxycarboxy-4-phenyl-2-butenenitrile

(*trans*-5d): colorless oil; IR (neat) ν 2985, 2228, 1749, 1372, 1256 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.28 (t, $J = 7.2$ Hz, 3H), 4.13-4.24 (m, 2H), 5.67 (dd, $J = 1.5, 16.5$ Hz, 1H), 6.17 (dd, $J = 1.5, 4.6$ Hz, 1H), 7.31-7.40 (m, 5H); ^{13}C NMR (CDCl_3) δ 14.1, 64.7, 100.8, 116.3, 127.3, 129.1, 129.4, 135.4, 150.3, 153.8; ESI-MS (m/z) 254 $[\text{M}+\text{Na}]^+$; $[\alpha]_{\text{D}}^{24.9} -87.9$ (c 1.62, CHCl_3) (91% ee); HPLC (DAICEL CHIRALCEL OD-H, 2-propanol/hexane = 1/9, flow 1.0 mL/min; detection at 220 nm) t_{R} 9.3 min (major), 11.7 min (minor).

(4R,2Z)-4-Ethoxycarboxy-4-phenyl-2-butenenitrile

(*cis*-5d): colorless oil; IR (neat) ν 2985, 2223, 1749, 1371, 1254 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.30 (t, $J = 7.0$ Hz, 3H), 4.16-4.26 (m, 2H), 5.48 (d, $J = 11.0$ Hz, 1H), 6.43 (d, $J = 8.3$ Hz, 1H), 6.60 (dd, $J = 8.3, 11.0$ Hz, 1H), 7.34-7.43 (m, 5H); ^{13}C NMR (CDCl_3) δ 14.2, 64.7, 101.0, 114.7, 126.7, 129.1, 129.3, 136.4, 149.6, 153.8; ESI-MS (m/z) 254 $[\text{M}+\text{Na}]^+$; $[\alpha]_{\text{D}}^{24.9} -146.6$ (c 0.97, CHCl_3) (90% ee); HPLC (DAICEL CHIRALCEL OD-H, 2-propanol/hexane = 1/9, flow 0.5 mL/min; detection at 220 nm) t_{R} 17.5 min (minor), 19.4 min (major).

Determination of Absolute Configuration:

Absolute configuration of *trans*-5a was determined to be *R* after converting to the

known γ -hydroxy- α,β -unsaturated carboxylic acid as shown in the scheme below. $[\alpha]_D^{28.6} -23.3$ (c 0.24, CHCl_3); Lit. $[\alpha]_D^{28.6} -20.3$ (1%, CHCl_3 solution) for *R*. Allevi, P.; Anastasia, M.; Ciuffreda, P.; Sanvito, A. M. *Tetrahedron Asymmetry*, **1993**, 4, 1397.

Determination of Absolute Configuration (1)

Absolute configuration of *cis*-**5a** was determined to be *S* by comparison of optical rotation of 4-ethoxycarboxy-heptanenitrile derived from *trans*-**5a** and *cis*-**5a** as shown in scheme below.

Determination of Absolute Configuration (2)

Total Synthesis of (+)-Patulolide C:

(2*S*, 3*E*)-2-Ethoxycarboxy-11-oxo-dodec-3-enenitrile

(4e): To a stirred solution of **3e** (547 mg, 3.0 mmol) and (*R*)-YLB catalyst (0.3 mmol, prepared by the procedure of a literature cited in ref 3) in THF (20 mL) was added ethyl cyanoformate **2** (0.36 mL, 3.6 mmol) at -78°C . After stirring for 5 h at the same temperature, the reaction mixture was quenched with 1M HCl, extracted with diethyl ether (25 mL $\times$ 3), washed with brine and dried over Na_2SO_4 . The solvent was evaporated under reduced pressure and the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate 6/1) to afford **4e** (776 mg, 92%) as colorless oil; IR (neat) ν 2932, 2857, 1757, 1715, 1372, 1251, 1005 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.23-1.30 (m, 4H), 1.31 (dd, $J = 7.0$, 7.0 Hz, 3H), 1.37-1.42 (m, 4H), 1.51-1.57 (m, 2H), 2.06-2.12 (m, 2H), 2.11 (s, 3H), 2.40 (t, $J = 7.3$ Hz, 2H), 4.25 (dq, $J = 2.0$, 7.0 Hz, 2H), 5.55 (dd, $J = 6.7$, 15.3 Hz, 1H), 5.64 (d, $J = 6.7$ Hz, 1H), 6.15 (dt, $J = 6.7$, 15.3 Hz, 1H); ^{13}C NMR (CDCl_3) δ 14.1, 23.6, 28.0, 28.8, 28.8, 29.9, 31.8, 43.6, 64.9, 65.4, 115.4, 119.7, 141.2, 153.4, 209.1; ESI-MS (m/z) 304 $[\text{M}+\text{Na}]^+$; HRMS (FAB) calcd. for $\text{C}_{15}\text{H}_{24}\text{NO}_4$ (282.1705) $[\text{M}+\text{H}]^+$, found 282.1703; $[\alpha]_D^{21.8} +8.0$ (c 0.74, EtOH) (87% ee); HPLC (DAICEL CHIRALCEL OJ-H, 2-propanol/hexane = 20/80, flow 1.0 mL/min; detection at 254 nm) t_R 20.9 min (major), 32.3 min (minor).

(2*E*, 4*S*)-4-Ethoxycarboxy-11-oxo-dodec-2-enenitrile

(5e): A solution of **4e** (281.4 mg, 1.0 mmol) in 1,2,4-trichlorobenzene (3 mL) was stirred for 6 h at 190°C . After cooling to the room temperature, the reaction mixture was poured into silica gel column, eluted with hexane until removal of the reaction solvent. Then, the silica gel was washed with diethyl ether to collect the reaction products. After evaporating under reduced pressure, the residue was purified by

silica gel column chromatography (hexane/ethyl acetate 6/1) to afford *trans*-**5e** (84%) and *cis*-**5e** (15%) as colorless oil; IR (neat) ν 2935, 2860, 2226, 1747, 1714, 1373, 1257, 1008 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.26-1.35 (m, 6H), 1.30 (t, $J = 7.0$ Hz, 3H), 1.50-1.56 (m, 2H), 1.60-1.68 (m, 2H), 2.10 (s, 3H), 2.39 (t, $J = 7.5$ Hz, 2H), 4.18 (q, $J = 7.0$ Hz, 2H), 5.16 (ddd, $J = 1.5, 5.5, 16.5$ Hz, 1H), 5.55 (dd, $J = 1.5, 16.5$ Hz, 1H), 6.61 (dd, $J = 5.5, 16.5$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 14.1, 23.5, 24.3, 28.8, 28.9, 29.9, 33.4, 43.5, 64.5, 75.8, 100.9, 116.4, 151.2, 154.1, 209.0; ESI-MS (m/z) 304 $[\text{M}+\text{Na}]^+$; HRMS (FAB) calcd. for $\text{C}_{15}\text{H}_{24}\text{NO}_4$ (282.1705) $[\text{M}+\text{H}]^+$, found 282.1703; $[\alpha]_{\text{D}}^{24.3} = -7.1$ (c 0.90, EtOH) (87% ee); HPLC (DAICEL CHIRALCEL OJ-H, 2-propanol/hexane = 20/80, flow 1.0 mL/min; detection at 254 nm) t_{R} 18.7 min (major), 23.1 min (minor).

(2*E*, 4*S*)-4-(*tert*-Butyldimethylsiloxy)-11-oxo-dodec-2-enenitrile (7):

To a solution of *trans*-**5e** (215.2 mg, 0.8 mmol) in MeOH (5 mL), was added 10% K_2CO_3 solution (5 mL). After stirring at room temperature for 2 h, the reaction mixture was quenched with 1 M HCl, extracted with ethyl acetate ($\times 3$), washed with brine and dried over Na_2SO_4 . The solvent was evaporated under reduced pressure to give crude **6**, which was used for next step without further purification. To a solution of crude **6** in anhydrous DMF (5 mL), was added TBSCl (301 mg, 1.6 mmol) and imidazole (272 mg, 3.2 mmol). After stirring at room temperature for 12 h, the reaction mixture was quenched by addition of saturated aqueous NaHCO_3 , extracted with diethyl ether ($\times 3$), washed with brine and dried over Na_2SO_4 . The solvent was evaporated under reduced pressure, and then chromatographed (ether-hexane 1:6) to afford **7** (92%) as colorless oil; IR (neat) ν 2931, 2857, 2224, 1716, 1362, 1255, 1092 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.00 (s, 3H), 0.03 (s, 3H), 0.87 (s, 9H), 1.26 (brs, 6H), 1.46-1.54 (m, 4H), 2.10 (s, 3H), 2.38 (t, $J = 7.3$ Hz, 2H), 4.24-4.26 (m, 1H), 5.55 (dd, $J = 1.8, 16.2$ Hz, 1H), 6.71 (dd, $J = 3.8, 16.2$ Hz, 1H); ^{13}C NMR (CDCl_3) δ -4.9, -4.8, 18.1, 23.6, 24.3, 25.7, 29.0, 29.3, 29.9, 36.8, 43.6, 71.3, 98.3, 117.6, 157.4, 209.1; ESI-MS (m/z) 346 $[\text{M}+\text{Na}]^+$; HRMS (FAB) calcd. for $\text{C}_{18}\text{H}_{34}\text{NO}_2\text{Si}$ (324.2359) $[\text{M}+\text{H}]^+$, found 324.2358; $[\alpha]_{\text{D}}^{24.8} = +2.5$ (c 1.35, EtOH) (87% ee); HPLC (DAICEL CHIRALCEL OD, 2-propanol/hexane = 10/90, flow 1.0 mL/min; detection at 254 nm) t_{R} 20.1 (minor), 26.3 (major).

(2*E*, 4*S*, 11*R*)-11-Hydroxy-4-(*tert*-butyldimethylsiloxy)-dodec-2-enenitrile (8):

To a solution of **7** (194.1 mg, 0.6 mmol) in anhydrous toluene (1.2 mL) at -78°C , was added (*S*)-CBS (0.18 mmol, 1 M in toluene) and catecholborane (1.2 mmol, 1 M in THF). After stirring at the same temperature for 20 h, the reaction mixture was quenched with MeOH, warmed to room temperature, diluted with ether, washed with brine and dried over Na_2SO_4 . The solvent was evaporated under reduced pressure and then chromatographed (ethyl acetate-hexane 1:6) to afford **8** (95%) as inseparable mixture with 11*S*-isomer; colorless oil; IR (neat) ν 3398, 2929, 2857, 2224, 1464, 1255, 1096 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.01 (s, 3H), 0.04 (s, 3H), 0.88 (s, 9H), 1.21-1.50 (m, 12H), 3.73-3.80 (m, 1H), 4.25-4.29 (m, 1H), 5.57 (dd, $J = 2.0, 16.0$ Hz, 1H), 6.73 (dd, $J = 3.8, 16.0$ Hz, 1H); ^{13}C NMR (CDCl_3) δ -4.9, -4.8, 15.3, 18.1, 23.5, 24.4, 25.6, 29.5, 36.9, 39.2, 65.8, 68.1, 71.4, 98.3, 117.6, 157.5; ESI-MS (m/z) 348 $[\text{M}+\text{Na}]^+$; HRMS (FAB) calcd. for $\text{C}_{18}\text{H}_{36}\text{NO}_2\text{Si}$ (326.2515) $[\text{M}+\text{H}]^+$, found 326.2508.

(2*E*, 4*S*, 11*R*)-11-Hydroxy-4-(*tert*-butyldimethylsiloxy)-2-dodecenecarboxylic acid (9):

To a solution of **8** (162.8 mg, 0.5 mmol) in anhydrous toluene (8 mL) at -78°C , was slowly added DIBAL (1.5 mmol, 1.01 M in toluene). After stirring at the same temperature for 3 h, the reaction mixture was quenched by dropwise addition of water, warmed to room temperature,

extracted with ethyl acetate ($\times 3$), washed with brine and dried over Na_2SO_4 . The solvent was evaporated under reduced pressure to give crude aldehyde, which was used for next step without further purification. To a solution of crude aldehyde in $t\text{BuOH-H}_2\text{O}$ (4:1, 5 mL), was added 2-methyl-2-butene (0.5 mL), NaH_2PO_4 (1.5 mmol) solution (1 mL) and 80% NaClO_2 (1.5 mmol). After stirring at room temperature for 5 h, the reaction mixture was quenched by addition of Na_2SO_3 , extracted with ethyl acetate (10 mL $\times 3$), washed with brine and dried over Na_2SO_4 . The solvent was evaporated under reduced pressure, and then chromatographed (ethyl acetate-hexane 1:3) to afford **9** (72%) as inseparable mixture with 11S-isomer; colorless oil; IR (neat) ν 3394, 2929, 2857, 1698, 1256, 1094 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.01 (s, 3H), 0.04 (s, 3H), 0.88 (s, 9H), 1.16 (d, $J = 6.1$ Hz, 3H), 1.23-1.55 (m, 12H), 3.73-3.80 (m, 1H), 4.25-4.29 (m, 1H), 5.56 (dd, $J = 2.0, 16.0$ Hz, 1H), 6.72 (dd, $J = 3.8, 16.0$ Hz, 1H); ^{13}C NMR (CDCl_3) δ -4.9, -4.8, 18.1, 23.5, 24.4, 25.6, 25.7, 29.5, 29.5, 68.1, 71.4, 98.3, 117.6, 157.5; ESI-MS (m/z) 367 $[\text{M}+\text{Na}]^+$; HRMS (FAB) calcd. for $\text{C}_{18}\text{H}_{37}\text{O}_4\text{Si}$ (345.2461) $[\text{M}+\text{H}]^+$, found 345.2455.

(2E, 4S, 11R)-4-(tert-Butyldimethylsiloxy)-2-dodecen-11-olide (10**):**

To a stirred solution of 2-methyl-6-nitrobenzoic anhydride (82.6 mg, 0.24 mmol) and DMAP (58.7 mg, 0.48 mmol) in anhydrous CH_2Cl_2 (160 mL) at room temperature, was added **9** (68.9 mg, 0.2 mmol) in anhydrous CH_2Cl_2 (40 mL) slowly over 16 h by means of a syringe pump. Stirring was continued for 2 h and the solvent was evaporated under reduced pressure. The residue was quenched with saturated aqueous NaHCO_3 , neutralized with 1M HCl, extracted with diethyl ether, washed with brine, dried over Na_2SO_4 , and chromatographed (diethyl ether-hexane) to give isolated **10** (68%) as colorless oil. **10** was isolated from 11S-isomer (16%); ^1H NMR (CDCl_3) δ 0.01 (s, 3H), 0.02 (s, 3H), 0.87 (s, 9H), 1.10-1.72 (m, 12H), 1.25 (d, $J = 6.4$ Hz, 3H), 4.41-4.44 (m, 1H), 5.03-5.09 (m, 1H), 6.06 (dd, $J = 15.9$ Hz, 1H), 6.74 (dd, $J = 5.5, 15.9$ Hz, 1H); ^{13}C NMR (CDCl_3) δ -5.0, -4.8, 18.2, 19.2, 20.4, 22.1, 25.8, 28.0, 28.5, 32.5, 36.5, 71.1, 72.8, 121.1, 152.3, 168.7; ESI-MS (m/z) 349 $[\text{M}+\text{Na}]^+$; $[\alpha]_{\text{D}}^{22.5} = -22.4$ (c 0.72, EtOH) (98% ee); HPLC (DAICEL CHIRALPAK AD-H, 2-propanol/hexane = 1/300, flow 0.5 mL/min; detection at 220 nm) t_{R} 11.0 (major), 14.7 (minor).

(2E, 4S, 11R)-4-Hydroxy-2-dodecen-11-olide

((+)-Patulolide C (11**)):** To a stirred anhydrous THF (2 mL) solution of **10** (32.7 mg 0.1 mmol) at 0 $^{\circ}\text{C}$, was added excessive HF-Py (1 mL). After stirring for 2 h at room temperature, the reaction mixture was quenched with saturated aqueous NaHCO_3 , neutralized with 1M HCl, extracted with diethyl ether ($\times 3$), washed with brine, dried over Na_2SO_4 , and chromatographed to give **11** (99%) as a colorless oil. all the spectral data matched well with the reported data; $[\alpha]_{\text{D}}^{22.5} = +5.0$ (c 0.32, EtOH).

Statistical Asymmetric Amplification:

In the total synthesis of (+)-patulolide C, two catalytic asymmetric reactions were utilized to improve the ee value of the product. Because the positions of two chiral centers (C-4 and C-11) are relatively far away, remote stereocontrol is rather unlikely with asymmetric reduction with (*S*)-CBS. Ee for C-4 was 87% (4*S*/4*R* = 93.5/6.5). Ee for C-4, C-11 was 98% (4*S*, 11*R* / 4*R*, 11*S* = 99/1). Dr ratio for **10** was 81/19 (4*S*, 11*R* + 4*R*, 11*S* / 4*R*, 11*R* + 4*S*, 11*S* = 81/19). From these three values, ee value for C-11 (4*S*, 11*R* + 4*R*, 11*R* / 4*R*, 11*S* + 4*S*, 11*S*) was calculated to be 86/14 (72% ee). The ee value for CBS-reduction was matched well with the result obtained by the model compound (2-octanone), which afforded alcohol in 75% ee with 30 mol % of (*S*)-CBS at -78 $^{\circ}\text{C}$ for 20 h.

	C-4:S	C-4:R
C-11:R	4 <i>S</i> ,11 <i>R</i>	4 <i>R</i> ,11 <i>R</i>
C-11:S	4 <i>S</i> ,11 <i>S</i>	4 <i>R</i> ,11 <i>S</i>

$4S,11R + 4S,11S / 4R,11R + 4R,11S = 93.5/6.5$ (87% ee at C-4)

$4S,11R / 4R,11S = 99/1$ (98% ee for **10**)

$4S,11R + 4R,11S / 4R,11R + 4S,11S = 81/19$ (dr for **10**)

Thus, enantiomeric ratio at C-11 is

$4S,11R + 4R,11R / 4R,11S + 4S,11S = 86/14$ (by calculation) (72% ee).