Chiral Zirconium-Catalyzed Asymmetric Hetero Diels-Alder Reactions. Scope, Limitation, Mechanism, and Application to Concise Syntheses of (+)-Prelactone C and (+)-9-Deoxygoniopypyrone

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Supporting Information

Experimental Section

General:

Melting points were uncorrected. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-LA300, JNM-LA400, or JNM-LA500 spectrometer in CDCl_3 unless otherwise noted. Tetramethylsilane (TMS) served as internal standard ($\delta = 0$) for ^1H NMR, and CDCl_3 was used as internal standard ($\delta = 77.0$) for ^{13}C NMR. IR spectra were measured with JASCO FT/IR-610 spectrometers. Optical rotations were measured with a JASCO P-1010 polarimeter. High-performance liquid chromatography was carried out using following apparatuses; SHIMADZU LC-10AT (liquid chromatograph), SHIMADZU SPD-10A (UV detector), and SHIMADZU C-R6A Chromatopac. Mass spectrometry analysis was carried out using SHIMADZU GCMS-QP5050A. High resolution mass spectrometry was carried out using JEOL IMS-SX 102. Column chromatography was conducted on Silica gel 60 (Merck), and preparative thin-layer chromatography was carried out using Wakogel B-5F. Toluene was distilled and dried over MS 4A. *tert*-Butyl methyl ether (*t*BuOMe) was distilled and dried over sodium. Propanol was distilled in the presence of magnesium propoxide and dried over MS4A. Zirconium tetra-*tert*-butoxide ($\text{Zr}(\text{O}^t\text{Bu})_4$) was purchased from Trichemical Laboratory Co., Ltd.

Aldehydes employed were purchased from Tokyo Kasei Kogyo Co., Ltd. and purified by distillation. Starting α,β -unsaturated ketones of employed dienes were synthesized according to literature's methods or similar ones.¹ Dienes **1a**, **1b**, **1d**, **1e**, and **1f** were synthesized according to a standard procedure shown in the following paragraph. Diene **1c** was synthesized by a literature's method using ZnCl_2 and EtMe_2SiCl .^{1g} Diene **1h** was synthesized by an optimized procedure of a literature's method (see the following procedure).^{1h-j} All reactions were carried out under argon atmosphere in well dried glassware.

Typical experimental procedure for asymmetric hetero Diels–Alder reactions using a chiral zirconium catalyst prepared from $\text{Zr}(\text{O}^i\text{Bu})_4$ and (*R*)-3,3'- I_2 BINOL (2a**):** A typical experimental procedure is described for the reaction of benzaldehyde with diene **1c**. To a suspension of (*R*)-3,3'-diiodo-1,1'-binaphthalene-2,2'-diol ((*R*)-3,3'- I_2 BINOL, (*R*)-**2a**, 0.048 mmol) in toluene (0.5 mL) was added $\text{Zr}(\text{O}^i\text{Bu})_4$ (0.040 mmol) in toluene (0.5 mL) at room temperature, and the solution was stirred for 30 min. Then a mixture of propanol (0.32 mmol) and H_2O (0.080 mmol) in toluene (0.3 mL) was added, and the whole was stirred for 3 h at room temperature. After cooling at $-78\text{ }^\circ\text{C}$, benzaldehyde (0.40 mmol) in $t\text{BuOMe}$ (0.35 mL) and diene **1c** (0.48 mmol) in $t\text{BuOMe}$ (0.35 mL) were successively added. After the mixture was warmed to $-20\text{ }^\circ\text{C}$ and stirred for 18 h, saturated aqueous NaHCO_3 (10 mL) was added to quench the reaction. After addition of dichloromethane (CH_2Cl_2 , 10 mL), the organic layer was separated and the aqueous layer was extracted twice with CH_2Cl_2 (10 mL x 2). The organic layers were combined and dried over anhydrous Na_2SO_4 . After filtration and concentration under reduced pressure, the residue was treated with trifluoroacetic acid (TFA, 0.5 mL) in CH_2Cl_2 (8 mL) for 1 h at $0\text{ }^\circ\text{C}$. In the case of the reaction using cinnamaldehyde, scandium triflate ($\text{Sc}(\text{OTf})_3$, 0.040 mmol, 10 mol% to the aldehyde) was used instead of TFA in CH_2Cl_2 at room temperature for 12 h. After the solution was basified with saturated aqueous NaHCO_3 (20 mL), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (10 mL x 2). The organic layers were combined and dried over anhydrous Na_2SO_4 . After filtration and concentration under reduced pressure, the crude product was purified by preparative thin layer chromatography (benzene-ethyl acetate = 20:1) to afford the desired product. The optical purity was

determined by HPLC analysis using a chiral column (see the following analytical data).

Typical experimental procedure for asymmetric hetero Diels–Alder reactions using a chiral zirconium catalyst prepared from $\text{Zr}(\text{O}^i\text{Bu})_4$ and (R) -3,3'- I_2 -6,6'- X_2 BINOL ($\text{X} = \text{I}, \text{C}_2\text{F}_5$): A typical experimental procedure is described for the reaction of benzaldehyde with Danishefsky's diene **1e**. To a suspension of (R) -3,3'-diiodo-6,6'-disubstituted-1,1'-binaphthalene-2,2'-diol ((R) -3,3'- I_2 -6,6'- X_2 BINOL ($\text{X}: \text{C}_2\text{F}_5, \text{I}$), 0.048 mmol) in toluene (0.5 mL) was added $\text{Zr}(\text{O}^i\text{Bu})_4$ (0.040 mmol) in toluene (0.5 mL) at room temperature, and the solution was stirred for 3 h. Then a mixture of propanol (0.32 mmol) and H_2O (0.080 mmol) in toluene (0.3 mL) was added and the whole was stirred for 30 min at room temperature. After cooling at $-78\text{ }^\circ\text{C}$, benzaldehyde (0.40 mmol) in toluene (0.35 mL) and diene **1e** (0.48 mmol) in toluene (0.35 mL) were successively added. After the mixture was warmed to $-20\text{ }^\circ\text{C}$ and stirred for 18 h, saturated aqueous NaHCO_3 (10 mL) was added to quench the reaction. After addition of CH_2Cl_2 (10 mL), the organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2 (10 mL x 2). The organic layers were combined and dried over anhydrous Na_2SO_4 . After filtration and concentration under reduced pressure, the residue was treated with TFA (0.5 mL) in CH_2Cl_2 (8 mL) for 1 h at $0\text{ }^\circ\text{C}$. In the cases of the reactions using α,β -unsaturated aldehydes and diene **1h**, scandium triflate ($\text{Sc}(\text{OTf})_3$, 0.040 mmol, 10 mol% to aldehydes) was used instead of TFA in CH_2Cl_2 at room temperature for 12 h. After the solution was basified with saturated aqueous NaHCO_3 (20 mL), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (10 mL x 2). The organic layers were combined and dried over anhydrous Na_2SO_4 . After filtration and concentration under reduced pressure, the *trans* and *cis* isomers were separated and purified by preparative thin layer chromatography (benzene-ethyl acetate = 20:1). The optical purity of *trans* and *cis* isomers were determined by HPLC analysis using a chiral column (see the following analytical data). In the cases of the reactions with diene **1h**, diastereoselectivities were determined by ^1H NMR analysis of the diastereomer mixtures, and enantioselectivities were determined by HPLC analysis of the diastereomer mixtures.

(R) -2-Phenyl-2,3-dihydro-4*H*-pyran-4-one:² $[\alpha]_{\text{D}}^{26} = -97.1$ (c 0.69, CHCl_3) (97%

ee). lit.)² $[\alpha]_{\text{D}}^{23} = +88.4$ (c 0.529, CHCl_3) (87% ee, *S*-form); IR $[\text{cm}^{-1}]$ 3063, 2902, 1680, 1595, 1496, 1455, 1403, 1270, 1227, 1209; ^1H NMR (CDCl_3) δ 2.66 (dd, 1H, $J = 17, 3.5$ Hz), 2.90 (dd, 1H, $J = 17, 14$ Hz), 5.42 (dd, 1H, $J = 15, 3.7$ Hz), 5.52 (d, 1H, $J = 6.0$ Hz), 7.3-7.4 (m, 5H), 7.48 (d, 1H, $J = 6.0$ Hz); ^{13}C NMR (CDCl_3) δ 43.3, 81.0, 107.3, 126.0, 128.8, 128.9, 137.8, 163.1, 192.1; HPLC, Daicel Chiralcel OD, hexane/*i*PrOH = 40/1, flow rate = 1.0 mL/min : $t_{\text{R}} = 25.1$ min (*S*), $t_{\text{R}} = 30.1$ min (*R*).

2-(*p*-Chlorophenyl)-2,3-dihydro-4*H*-pyran-4-one:² $[\alpha]_{\text{D}}^{19} = -62.4$ (c 0.56, CHCl_3) (84% ee); IR $[\text{cm}^{-1}]$ 3063, 2906, 1907, 1675, 1599, 1494, 1402, 1267, 1227, 1208; ^1H NMR (CDCl_3) δ 2.64 (dd, 1H, $J = 17, 3.7$ Hz), 2.85 (dd, 1H, $J = 17, 14$ Hz), 5.41 (dd, 1H, $J = 14, 3.5$ Hz), 5.53 (d, 1H, $J = 6.1$ Hz), 7.34 (d, 2H, $J = 8.7$ Hz), 7.39 (d, 2H, 8.7 Hz), 7.47 (d, 1H, $J = 6.1$ Hz); ^{13}C NMR (CDCl_3) δ 43.3, 80.2, 107.5, 127.4, 129.0, 134.7, 136.3, 162.9, 191.6; HPLC, Daicel Chiralcel OD, hexane/*i*PrOH = 40/1, flow rate = 1.0 mL/min : $t_{\text{R}} = 27.2$ min (minor), $t_{\text{R}} = 35.9$ min (major); Elemental analysis for $\text{C}_{11}\text{H}_9\text{ClO}_2$, calcd.: C 63.32, H 4.35; found: C 63.36, H 4.58.

(*S*)-2-Phenethyl-2,3-dihydro-4*H*-pyran-4-one:² $[\alpha]_{\text{D}}^{19} = -93.4$ (c 1.34, CHCl_3) (85% ee); IR $[\text{cm}^{-1}]$ 3023, 2931, 2632, 1674, 1599, 1495, 1455, 1402, 1274. ^1H NMR (CDCl_3) δ 1.95 (m, 1H), 2.15 (m, 1H), 2.42 (dd, 1H, $J = 17, 3.8$ Hz), 2.55 (dd, 1H, $J = 17, 13$ Hz), 2.80 (m, 2H), 4.39 (m, 1H), 5.40 (d, 1H, $J = 6.0$ Hz), 7.1-7.3 (m, 5H), 7.38 (d, 1H, $J = 6.1$ Hz); ^{13}C NMR (CDCl_3) δ 30.9, 36.0, 41.8, 78.4, 107.1, 126.2, 128.4, 128.6, 140.6, 163.1, 192.4; HPLC, Daicel Chiralcel OD, hexane/*i*PrOH = 9/1, flow rate = 1.0 mL/min : $t_{\text{R}} = 21.7$ min (*R*), $t_{\text{R}} = 43.8$ min (*S*).

2-(*p*-Tolyl)-2,3-dihydro-4*H*-pyran-4-one: $[\alpha]_{\text{D}}^{19} = -27.5$ (c 0.26, CHCl_3) (92% ee); IR $[\text{cm}^{-1}]$ 2921, 1672, 1596, 1515, 1405, 1271, 1220; ^1H NMR (CDCl_3) δ 2.28 (s, 3H), 2.53 (dd, 1H, $J = 17, 3.5$ Hz), 2.81 (dd, 1H, $J = 17, 15$ Hz), 5.29 (dd, 1H, $J = 14, 3.3$ Hz), 5.43 (dd, 1H, $J = 6.1, 1.3$ Hz), 7.1-7.3 (m, 4H), 7.37 (d, 1H, $J = 6.1$ Hz); ^{13}C NMR (CDCl_3) δ 21.2, 43.3, 81.0, 107.3, 126.1, 129.5, 134.8, 138.9, 163.2, 192.3; HPLC, Daicel Chiralcel OD, hexane/*i*PrOH = 40/1, flow rate = 1.0 mL/min : $t_{\text{R}} = 22.2$ min (minor), $t_{\text{R}} = 27.1$ min (major); EI-HRMS (m/z) calcd. for $\text{C}_{12}\text{H}_{12}\text{O}_2$ (M^+): 188.0837; found: 188.0832; Elemental analysis for $\text{C}_{12}\text{H}_{12}\text{O}_2$, calcd.: C 76.57, H 6.43; found: C 76.29, H 6.57.

2-Pentyl-2,3-dihydro-4*H*-pyran-4-one: $[\alpha]_{\text{D}}^{19} = -131.4$ (c 0.54, CHCl_3) (83% ee);

IR [cm⁻¹] 2935, 2865, 1678, 1599, 1466, 1403, 1274; ¹H NMR (CDCl₃) δ 0.90 (t, 3H, *J* = 6.8 Hz), 1.3 - 1.5 (m, 6H), 1.66 (m, 1H), 1.81 (m, 1H), 2.4–2.5 (m, 1H), 4.4 (m, 1H), 5.4 (dd, 4H, *J* = 5.9, 0.7 Hz), 7.35 (d, 1H, *J* = 6.1 Hz); ¹³C NMR (CDCl₃) δ 13.9, 22.4, 24.4, 31.4, 34.3, 41.8, 79.5, 106.9, 163.3, 192.7; HPLC, Daicel Chiralcel OD, hexane/*i*PrOH = 40/1, flow rate = 0.5 mL/min : *t*_R = 19.0 min (minor), *t*_R = 21.1 min (major); EI-HRMS (m/z) calcd. for C₁₀H₁₆O₂ (M⁺): 168.1150; found: 168.1132.

(*R*)-2-Styryl-2,3-dihydro-4*H*-pyran-4-one:³ [α]_D²³ = –195.2 (c 0.35, CH₂Cl₂) (90% ee); IR [cm⁻¹] 3064, 2914, 1678, 1593, 1493, 1452, 1411, 1271, 1221.

¹H NMR (CDCl₃) δ 2.62 (dd, 1H, *J* = 17, 4.1 Hz), 2.74 (dd, 1H, *J* = 17, 13 Hz), 5.09 (dt, 1H, *J* = 12, 6.6 Hz), 5.47 (d, 1H, *J* = 6.0 Hz), 6.30 (dd, 1H, *J* = 16, 6.6 Hz), 6.72 (d, 1H, *J* = 16 Hz), 7.2–7.4 (m, 5H), 7.41 (d, 1H, *J* = 6.0 Hz); ¹³C NMR (CDCl₃) δ 41.9, 79.7, 107.3, 124.9, 126.7, 128.5, 133.8, 135.6, 162.9, 191.8; HPLC, Daicel Chiralcel OD, hexane/*i*PrOH = 9/1, flow rate = 1.0 mL/min : *t*_R = 22.2 min (*S*), *t*_R = 48.7 min (*R*); EI-HRMS (m/z) calcd. for C₁₃H₁₂O₂ (M⁺): 202.0837; found: 202.0834.

3,5-Dimethyl-2-phenyl-2,3-dihydro-4*H*-pyran-4-one: *trans* isomer: [α]_D²⁶ = –35.1 (c 0.77, CHCl₃) (96% ee); IR [cm⁻¹] 3037, 2926, 1964, 1725, 1670, 1625, 1496, 1455, 1377, 1307, 1272, 1232; ¹H NMR (CDCl₃) *trans* isomer: δ 0.92 (d, 3H, *J* = 6.8 Hz), 1.73 (s, 3H), 2.80 (dq, 1H, *J* = 13, 6.6 Hz), 4.91 (d, 1H, *J* = 13 Hz), 7.31 (s, 1H), 7.3 - 7.5 (m, 5H); *cis* isomer: δ 0.90 (d, 3H, *J* = 7.6 Hz), 1.74 (s, 3H), 2.60 (dq, 1H, *J* = 7.3, 3.2 Hz), 5.47 (d, 1H, *J* = 3.2 Hz), 7.26 (s, 1H), 7.3–7.5 (m, 5H); ¹³C NMR (CDCl₃); *trans* isomer: δ 10.3, 10.7, 44.7, 86.9, 113.1, 127.3, 128.7, 129.0, 137.5, 158.7, 194.9. *cis* isomer: δ 9.9, 10.7, 45.7, 82.9, 112.5, 125.4, 127.9, 128.5, 136.8, 158.8, 197.7; *cis* isomer HPLC, Daicel Chiralcel OD, hexane/*i*PrOH = 40/1, flow rate = 0.6 mL/min : *t*_R = 22.3 min (minor), *t*_R = 27.1 min (major); *trans* isomer HPLC, Daicel Chiralcel OD, hexane/*i*PrOH = 19/1, flow rate = 0.3 mL/min : *t*_R = 29.3 min (minor), *t*_R = 31.2 min (major); *trans* isomer: EI-HRMS (m/z) calcd. for C₁₃H₁₄O₂ (M⁺): 202.0994; found: 202.0993.

3,5-Dimethyl-2-(*p*-chlorophenyl)-2,3-dihydro-4*H*-pyran-4-one: *trans* isomer: [α]_D²⁶ = –59.5 (c 1.03, CDCl₃) (97% ee); IR [cm⁻¹] 2930, 1668, 1630, 1455, 1384, 1306, 1232; ¹H NMR (CDCl₃) *trans* isomer: δ 0.92 (d, 3H, *J* = 6.8 Hz), 1.72 (s, 3H),

2.74 (dq, 1H, $J = 14, 6.8$ Hz), 4.89 (d, 1H, $J = 13$ Hz), 7.30 (s, 1H), 7.3-7.4 (m, 4H); *cis* isomer: δ 0.88 (d, 3H, $J = 7.3$ Hz), 1.74 (s, 3H), 2.56 (dq, 1H, $J = 7.3, 3.2$ Hz), 5.44 (d, 1H, $J = 2.9$ Hz), 7.2-7.4 (m, 5H); ^{13}C NMR (CDCl_3); *trans* isomer: δ 10.3, 10.7, 44.7, 86.0, 113.3, 128.7, 128.9, 134.8, 136.1, 158.5, 194.5; *cis* isomer: δ 9.9, 10.6, 45.5, 82.2, 112.7, 126.8, 128.7, 133.8, 135.3, 158.5, 197.3; *cis* isomer HPLC, Daicel Chiralcel OD, hexane/*i*PrOH = 40/1, flow rate = 0.6 mL/min : $t_R = 14.5$ min (minor), $t_R = 27.8$ min (major); *trans* isomer HPLC, Daicel Chiralcel OD, hexane/*i*PrOH = 19/1, flow rate = 0.3 mL/min : $t_R = 23.9$ min (minor), $t_R = 24.9$ min (major); *trans* isomer: EI-HRMS (m/z) calcd. for $\text{C}_{13}\text{H}_{13}\text{ClO}_2$ (M^+): 236.0604; found: 236.0590; *trans* isomer: Elemental analysis for $\text{C}_{13}\text{H}_{13}\text{ClO}_2$, calcd.: C 65.97, H 5.54; found: C 65.75, H 5.75.

3,5-Dimethyl-2-(*p*-tolyl)-2,3-dihydro-4*H*-pyran-4-one: *trans* isomer: $[\alpha]_{\text{D}}^{23} = -48.6$ (c 1.48, CHCl_3) (90% ee); IR [cm^{-1}] 3445, 2974, 2324, 1671, 1626, 1517, 1456, 1376, 1305, 1270, 1233; ^1H NMR (CDCl_3) *trans* isomer: δ 0.92 (d, 3H, $J = 6.9$ Hz), 1.72 (s, 3H), 2.73 (s, 3H), 2.80 (dq, 1H, $J = 13, 6.8$ Hz), 4.87 (d, 1H, $J = 13$ Hz), 7.2-7.3 (m, 5H); *cis* isomer: δ 0.90 (d, 3H, $J = 7.3$ Hz), 1.73 (s, 3H), 2.37 (s, 3H), 2.57 (dq, 1H, $J = 7.3, 3.3$ Hz), 5.43 (d, 1H, $J = 3.1$ Hz), 7.2-7.3 (m, 4H), 7.37 (s, 1H); ^{13}C NMR (CDCl_3); *trans* isomer: δ 10.4, 10.7, 21.2, 44.6, 86.8, 113.0, 127.3, 129.3, 134.6, 138.9, 158.8, 195.1. *cis* isomer: δ 9.9, 10.7, 21.1, 45.7, 83.0, 112.4, 125.4, 129.1, 133.8, 137.7, 158.9, 197.9; *cis* isomer HPLC, Daicel Chiralcel OD, hexane/*i*PrOH = 40/1, flow rate = 0.6 mL/min : $t_R = 15.7$ min (major), $t_R = 18.1$ min (minor); *trans* isomer HPLC, Daicel Chiralcel OD, hexane/*i*PrOH = 19/1, flow rate = 0.3 mL/min : $t_R = 22.9$ min (major), $t_R = 26.1$ min (minor); *trans* isomer: EI-HRMS (m/z) calcd. for $\text{C}_{14}\text{H}_{16}\text{O}_2$ (M^+): 216.1150; found: 216.1128.

3,5-Dimethyl-2-styryl-2,3-dihydro-4*H*-pyran-4-one: *trans* isomer: $[\alpha]_{\text{D}}^{19} = -28.9$ (c 0.3, CHCl_3) (78% ee); IR [cm^{-1}] 3034, 2816, 2741, 2355, 1675, 1627, 1497, 1450, 1382, 1302; ^1H NMR (CDCl_3) *trans* isomer: δ 1.13 (d, 3H, $J = 7.0$ Hz), 1.69 (s, 3H), 2.57 (dd, 1H, $J = 12, 7.0$ Hz), 4.57 (dd, 1H, $J = 13, 7.7$ Hz), 6.27 (dd, 1H, $J = 16, 7.7$ Hz), 6.71 (d, 1H, $J = 16$ Hz), 7.2-7.4 (m, 6H); *cis* isomer: δ 1.1 (d, 3H, $J = 7.3$ Hz), 1.70 (s, 3H), 2.58 (dd, 1H, $J = 7.3, 3.7$ Hz), 5.01 (dd, 1H, $J = 6.2, 3.7$ Hz), 6.25 (dd, 1H, $J = 16, 6.4$ Hz), 6.74 (d, 1H, $J = 16$ Hz), 7.2-7.4 (m, 6H); ^{13}C NMR (CDCl_3);

trans isomer: δ 10.70, 10.74, 43.9, 85.1, 113.0, 125.3, 126.7, 128.4, 128.7, 135.0, 135.7, 158.4, 194.8. *cis* isomer: δ 10.1, 10.6, 44.1, 82.3, 112.4, 123.2, 126.6, 128.2, 128.6, 133.7, 135.9, 158.3, 196.9; HPLC, Daicel Chiralcel OD, hexane/*i*PrOH = 40/1, flow rate = 1.0 mL/min : *cis* isomer t_R = 12.8 min (minor), t_R = 31.7 min (major); *trans* isomer t_R = 18.7 min (major), t_R = 22.0 min (minor); *trans* isomer: EI-HRMS (m/z) calcd. for C₁₅H₁₆O₂ (M⁺): 228.1150; found: 228.1131.

3,5-Dimethyl-2-phenethyl-2,3-dihydro-4H-pyran-4-one: *trans* isomer: $[\alpha]_D^{22}$ = -121.0 (c 1.01, CHCl₃) (87% ee); IR [cm⁻¹] 3441, 3026, 2927, 1670, 1626, 1496, 1455, 1382, 1311, 1273, 1232; ¹H NMR (CDCl₃) *trans* isomer: δ 1.16 (d, 3H, *J* = 7.1 Hz), 1.67 (s, 3H), 2.02 (dt, 2H, *J* = 14, 7.3 Hz), 2.43 (dt, 1H, *J* = 12, 7 Hz), 2.67-2.93 (m, 2H), 4.01 (m, 1H), 7.2-7.4 (m, 6H); ¹³C NMR (CDCl₃); *trans* isomer: δ 10.7, 30.8, 34.3, 43.5, 82.8, 112.7, 126.0, 128.4, 128.5, 141.2, 158.4, 195.3; HPLC, Daicel Chiralcel OD, hexane/*i*PrOH = 40/1, flow rate = 1.0 mL/min : *cis* isomer t_R = 12.8 min (minor), t_R = 31.7 min (major); *trans* isomer t_R = 18.7 min (major), t_R = 22.0 min (minor); *trans* isomer: EI-HRMS (m/z) calcd. for C₁₅H₁₈O₂ (M⁺): 230.1307; found: 230.1315.

3,5-Dimethyl-2-pentyl-2,3-dihydro-4H-pyran-4-one: *trans* isomer: $[\alpha]_D^{22}$ = -109.0 (c 1.00, CHCl₃) (88% ee); IR [cm⁻¹] 3324, 2929, 2860, 1671, 1628, 1458, 1380, 1312, 1271, 1228; ¹H NMR (CDCl₃) *trans* isomer: δ 0.90 (t, 3H, *J* = 7.1 Hz), 1.11 (d, 3H, *J* = 6.8 Hz), 1.3-1.6 (m, 8H), 1.60 (d, 3H, *J* = 1.0 Hz), 2.35-2.44 (m, 1H), 4.01 (dt, 1H, *J* = 12, 5.6 Hz), 7.21 (s, 1H); ¹³C NMR (CDCl₃); *trans* isomer: δ 10.7, 10.8, 13.9, 22.5, 24.1, 31.6, 32.3, 43.4, 83.8, , 112.4, 158.6, 195.7; *cis* isomer HPLC, Daicel Chiralcel OD, hexane/*i*PrOH = 1000/1, flow rate = 1.0 mL/min : t_R = 13.7 min (minor), t_R = 17.6 min (major); *trans* isomer HPLC, Daicel Chiralcel OB-H, hexane/*i*PrOH = 200/1, flow rate = 0.5 mL/min : t_R = 13.0 min (major), t_R = 14.5 min (minor); *trans* isomer: EI-HRMS (m/z) calcd. for C₁₂H₂₀O₂ (M⁺): 196.1463; found: 196.1464.

3-Benzoyloxy-2-phenyl-2,3-dihydro-pyran-4-one: IR [cm⁻¹] (neat) 3059, 3030, 2875, 1672, 1599, 1455, 1407, 1277, 1225; ¹H NMR (CDCl₃) *cis* isomer: δ 3.69 (dd, 1H, *J* = 2.1, 2.1 Hz), 4.33 (d, 1H, *J* = 12 Hz), 4.62 (d, 1H, *J* = 12 Hz), 5.35 (d, 1H, *J* = 2.1 Hz), 5.55 (dd, 1H, *J* = 6.0, 1.7 Hz), 6.94 (m, 1 H), 7.1-7.4 (m, 8 H), 7.55

(d, 1H, $J = 6.0$ Hz); detectable peaks of *trans* isomer δ 3.97 (d, 1H, $J = 11$ Hz), 4.45 (d, 1H, $J = 12$ Hz), 4.76 (d, 1H, $J = 12$ Hz), 5.26 (d, 1H, $J = 11$ Hz), 5.47 (d, 1H, $J = 5.9$ Hz); ^{13}C NMR (CDCl_3) *cis* isomer: δ 60.4, 72.1, 83.4, 105.1, 126.9, 127.7, 127.9, 128.1, 128.3, 128.6, 134.7, 136.7, 163.5, 190.1; HPLC, Daicel Chiralcel AD, hexane/ i PrOH = 19/1, flow rate = 0.7 mL/min: *cis* isomer $t_R = 13.0$ min (minor), $t_R = 15.1$ min (major); *trans* isomer $t_R = 17.1$ min (minor), $t_R = 20.5$ min (major); EI-HRMS (m/z) calcd. for $\text{C}_{18}\text{H}_{16}\text{O}_3$ (M^+): 280.1099; found: 280.1107.

3-Benzylloxy-2-(4-chlorophenyl)-2,3-dihydro-pyran-4-one: IR [cm^{-1}] (KBr) 3089, 3058, 3030, 2888, 2859, 1731, 1658, 1603, 1492, 1455, 1428, 1402, 1393, 1325, 1288, 1241; ^1H NMR (CDCl_3) *cis* isomer: δ 3.63 (dd, 1H, $J = 1.8, 1.8$ Hz), 4.32 (d, 1H, $J = 12$ Hz), 4.61 (d, 1H, $J = 12$ Hz), 5.29 (d, 1H, $J = 2.2$ Hz), 5.54 (dd, 1H, $J = 6.1, 1.8$ Hz), 6.9-7.0 (m, 2 H), 7.1-7.4 (m, 7H), 7.51 (d, 1H, $J = 6.1$ Hz); detectable peaks of *trans* isomer δ 4.03 (d, 1H, $J = 11$ Hz), 5.18 (d, 1H, $J = 11$ Hz), 5.47 (d, 1H, $J = 5.9$ Hz); ^{13}C NMR (CDCl_3) *cis* isomer: δ 65.3, 76.6, 82.6, 105.2, 127.8, 128.0, 128.1, 128.2, 128.4, 133.2, 134.4, 136.4, 163.2, 189.8; EI-MS [m/z] 314 (M^+), 208 ($\text{M}^+ - \text{C}_7\text{H}_6\text{O}$); HPLC, Daicel Chiralcel AD, hexane/ i PrOH = 19/1, flow rate = 0.4 mL/min: *cis* isomer $t_R = 24.9$ min (minor), $t_R = 31.4$ min (major); *trans* isomer $t_R = 34.0$ min (minor), $t_R = 42.1$ min (major); Elemental analysis for $\text{C}_{18}\text{H}_{15}\text{ClO}_3$, calcd.: C 68.68, H 4.80; found: C 68.38, H 5.02.

3-Benzylloxy-2-(*p*-tolyl)-2,3-dihydro-pyran-4-one: IR [cm^{-1}] (KBr) 3058, 3031, 2900, 2862, 1663, 1601, 1517, 1455, 1410, 1276, 1235; ^1H NMR (CDCl_3) *cis* isomer: δ 2.39 (s, 1H), 3.66 (s, 1H), 4.39 (d, 1H, $J = 12$ Hz), 4.67 (d, 1H, $J = 12$ Hz), 5.28 (s, 1H), 5.51 (d, 1H, $J = 6.1$ Hz), 6.9-7.0 (m, 2 H), 7.1-7.4 (m, 7H), 7.50 (d, 1H, $J = 6.1$ Hz); detectable peaks of *trans* isomer δ 4.16 (d, 1H, $J = 11$ Hz), 4.51 (d, 1H, $J = 12$ Hz), 4.80 (d, 1H, $J = 12$ Hz), 5.28 (d, 1H, $J = 11$ Hz), 5.51 (d, 1H, $J = 5.9$ Hz); ^{13}C NMR (CDCl_3) *cis* isomer: δ 21.2, 72.0, 77.3, 83.3, 105.0, 126.8, 127.6, 127.9, 128.1, 128.9, 131.6, 136.8, 138.3, 163.6, 190.2; EI-MS [m/z] 188 ($\text{M}^+ - \text{C}_7\text{H}_6\text{O}$); HPLC, Daicel Chiralcel AD, hexane/ i PrOH = 19/1, flow rate = 0.5 mL/min: *cis* isomer $t_R = 17.1$ min (minor), $t_R = 19.3$ min (major); *trans* isomer $t_R = 21.0$ min (minor), $t_R = 24.1$ min (major); Elemental analysis for $\text{C}_{19}\text{H}_{18}\text{O}_3$, calcd.: C 77.53, H 6.16; found: C 77.50, H 6.33.

3-Benzylloxy-2-(4-nitrophenyl)-2,3-dihydropyran-4-one: IR [cm^{-1}] (KBr) 3112,

3082, 3030, 2871, 1707, 1665, 1596, 1521, 1347, 1285, 1240; ^1H NMR (CDCl_3) *cis* isomer: δ 3.70 (dd, 1H, $J = 1.8, 1.8$ Hz), 4.30 (d, 1H, $J = 12$ Hz), 4.61 (d, 1H, $J = 12$ Hz), 5.42 (d, 1H, $J = 1.8$ Hz), 5.60 (dd, 1H, $J = 6.0, 1.6$ Hz), 6.8-7.0 (m, 2 H), 7.08 - 7.26 (m, 3H), 7.5-7.6 (m, 3H), 8.1-8.2 (m, 2H); detectable peaks of *trans* isomer δ 4.03 (d, 1H, $J = 12$ Hz), 5.29 (d, 1H, $J = 12$ Hz), 5.53 (d, 1H, $J = 5.9$ Hz); ^{13}C NMR (CDCl_3) *cis* isomer: δ 71.9, 75.9, 85.3, 105.5, 123.4, 127.5, 128.0, 128.2, 136.0, 141.8, 162.7, 189.0; EI-MS [m/z] 219 ($\text{M}^+ - \text{C}_7\text{H}_6\text{O}$); HPLC, Daicel Chiralcel AD, hexane/ i PrOH = 19/1, flow rate = 0.4 mL/min: *cis* isomer $t_R = 24.9$ min (minor), $t_R = 31.4$ min (major); *trans* isomer $t_R = 34.0$ min (minor), $t_R = 42.1$ min (major); Elemental analysis for $\text{C}_{18}\text{H}_{15}\text{NO}_5$, calcd.: N 4.30, C 66.46, H 4.65; found: N 4.27, C 66.17, H 4.86.

3-Benzoyloxy-2-styryl-2,3-dihydro-pyran-4-one: IR [cm^{-1}] (neat) 3058, 3027, 2877, 1671, 1597, 1495, 1453, 1408, 1278, 1224; ^1H NMR (CDCl_3) *cis* isomer: δ 3.71 (dd, 1H, $J = 2.6, 2.6$ Hz), 4.55 (d, 1H, $J = 12$ Hz), 4.80 (d, 1H, $J = 12$ Hz), 4.92 (dd, 1H, $J = 7.0, 2.6$ Hz), 5.48 (dd, 1H, $J = 7.0, 1.5$ Hz), 6.41 (dd, 1H, $J = 16, 7.0$ Hz), 6.75 (d, 1H, $J = 16$ Hz), 7.26-7.44 (m, 11H); detectable peaks of *trans* isomer δ 3.91 (d, 1H, $J = 9.4$ Hz), 4.98 (d, 1H, $J = 12$ Hz), 5.45 (d, 1H, $J = 5.9$ Hz), 6.18 (dd, 1H, $J = 16.0, 6.8$ Hz); ^{13}C NMR (CDCl_3) *cis* isomer: δ 65.3, 72.2, 76.6, 82.3, 105.0, 121.7, 126.8, 127.9, 128.2, 128.3, 128.4, 128.6, 135.1, 135.8, 136.9, 162.9, 190.3; HPLC, Daicel Chiralcel OD-H and Daicel Chiralpak AD (double column), hexane/ i PrOH = 9/1, flow rate = 0.5 mL/min: *cis* isomer $t_R = 45.3$ min (major), $t_R = 57.2$ min (minor); *trans* isomer $t_R = 48.4$ min (minor), $t_R = 60.7$ min (major); EI-HRMS (m/z) calcd. for $\text{C}_{20}\text{H}_{18}\text{O}_3$ (M^+): 306.1256; found: 306.1270.

3-Benzoyloxy-2-phenethyl-2,3-dihydropyran-4-one: IR [cm^{-1}] (neat) 3062, 3026, 2930, 2871, 1669, 1598, 1496, 1455, 1410, 1279, 1235; ^1H NMR (CDCl_3) *cis* isomer: δ 2.00 (m, 1H), 2.35 (m, 1H), 2.5-2.6 (m, 2H), 3.52 (dd, 1H, $J = 2.2, 2.2$ Hz), 4.20 (dt, 1H, $J = 5.4, 2.2$ Hz), 4.47 (d, 1H, $J = 12$ Hz), 4.74 (d, 1H, $J = 12$ Hz), 5.42 (dd, 1H, $J = 5.4, 1.6$ Hz), 7.1-7.4 (m, 11H), 7.57 (s, 1H); detectable peaks of *trans* isomer: δ 3.81 (d, 1H, $J = 9.8$ Hz), 4.36 (dt, 1H, $J = 9.8, 3.4$ Hz), 4.62 (d, 1H, $J = 11$ Hz), 5.00 (d, 1H, $J = 11$ Hz), 5.39 (d, 1H, $J = 5.9$ Hz); ^{13}C NMR (CDCl_3) *cis* isomer: δ 30.5, 30.9, 71.8, 75.5, 77.2, 80.9, 104.9, 126.2, 128.0, 128.4, 128.4, 128.5, 128.5, 137.1, 140.6, 163.0, 190.3; detectable peaks of *trans* isomer: 30.6, 32.0, 73.7,

76.9, 80.9, 104.9, 137.1, 140.6, 162.0, 192.9; HPLC, Daicel Chiralcel AS, hexane/*i*PrOH = 19/1, flow rate = 0.7 mL/min: *cis* isomer t_R = 26.4 min (minor), t_R = 36.8 min (major); *trans* isomer t_R = 20.6 min (minor), t_R = 22.3 min (major); EI-HRMS (*m/z*) calcd. for C₉H₁₄O₃ (M⁺): 308.1412; found: 308.1409.

Asymmetric Synthesis of (+)-Prelactone C

(2*R*, 3*R*)-3-methyl-2-((*E*)-1-propenyl)-2,3-dihydro-4H-pyran-4-one (*trans*-3): To a suspension of (*S*)-3,3',6,6'-tetraiodo-1,1'-binaphthalene-2,2'-diol (**2c**, (*S*)-3,3',6,6'-I₄BINOL, 111.2 mg, 0.141 mmol) in toluene (1.6 mL) was added Zr(O^{*i*}Bu)₄ (36.0 mg, 0.0938 mmol) in toluene (1.0 mL) at room temperature, and the solution was stirred for 3 h. Then a mixture of propanol (67.7 mg, 1.13 mmol) and H₂O (3.4 mg, 0.19 mmol) in toluene (0.3 mL) was added and the whole was stirred for 30 min at room temperature. After cooling at -78 °C, crotonaldehyde (65.7 mg, 0.937 mmol) in ^{*t*}BuOMe (0.9 mL) and diene **1f** (322 mg, 1.41 mmol) in ^{*t*}BuOMe (0.9 mL) were successively added. After the mixture was warmed to -30 °C and stirred for 67 h, saturated aqueous NaHCO₃ was added to quench the reaction. After addition of CH₂Cl₂, the organic layer was separated and the aqueous layer was extracted twice with CH₂Cl₂. The organic layers were combined and dried over anhydrous Na₂SO₄. After filtration and concentration under mildly reduced pressure, the residue was treated with THF-1M aqueous HCl (20:1) for 30 min at 0 °C. Then the solution was basified with saturated aqueous NaHCO₃ and extracted with CH₂Cl₂. The organic layers were combined and dried over anhydrous Na₂SO₄. After filtration and concentration under mildly reduced pressure, the mixture was treated with Sc(OTf)₃ (46.1 mg, 0.937 mmol) in CH₂Cl₂ for 12 h at 0 °C. After usual work-up, the crude product was purified by preparative thin layer chromatography (benzene-ethyl acetate = 30:1) to afford the desired product (**3**, 126 mg, 89%) as a diastereomer mixture. The ratio of *trans* and *cis* isomers was determined by ¹H NMR analysis (*trans*:*cis* = 6:1), and the optical purities were determined by HPLC analysis (*trans* isomer: 93% ee, Daicel Chiralcel AS, hexane/*i*PrOH = 100/1, flow rate = 1.0 mL/min: *trans* isomer t_R = 23.1 min (major), t_R = 19.5 min (minor); *cis* isomer t_R = 30.0 min (major), t_R = 48.0 min (minor)). Then, the *trans*-**3** was separated by column chromatography (silica gel, P.E.-diethyl ether=9:1) and used in the next reaction.

trans-**3**: $[\alpha]_{\text{D}}^{22} = +83.1$ (c 1.35, CHCl_3 , 87% ee); IR $[\text{cm}^{-1}]$ 1677, 1599, 1457, 1409, 1377, 1308, 1285, 1250, 1217; ^1H NMR (CDCl_3) δ 1.04 (d, 3H, $J = 7.1$ Hz), 1.76 (dd, 3H, $J = 6.6, 1.7$ Hz), 2.46 (dq, 1H, $J = 12, 7.1$ Hz), 4.39 (dd, 1H, $J = 12, 8.3$), 5.36 (d, 1H, $J = 5.8$ Hz), 5.57 (ddq, 1H, $J = 15, 8.3, 1.7$ Hz), 5.86 (ddq, 1H, $J = 15, 6.6, 0.7$ Hz), 7.30 (d, 1H, $J = 6.1$ Hz); ^{13}C NMR (CDCl_3) δ 10.6, 17.7, 43.9, 85.5, 106.2, 127.4, 132.9, 162.2, 194.7; EI-HRMS (m/z) calcd. for $\text{C}_9\text{H}_{12}\text{O}_2$ (M^+): 152.0837; found: 152.0831.

(2*R*, 3*S*, 4*S*)-4-Hydroxy-3-methyl-2-((*E*)-1-propenyl)-2,3-dihydro-4*H*-pyrane (4): To a solution of *trans*-**3** (401 mg, 2.64 mmol) in EtOH (36 mL) and CH_2Cl_2 (36 mL), was added sodium borohydride (199 mg, 5.27 mmol) in EtOH (11 mL) at -78°C , and the whole was stirred for 11 h at the same temperature. Then, saturated aqueous NaHCO_3 (20 mL) was added to quench the reaction, and the mixture was filtered to remove insoluble solid. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 in seven times. The CH_2Cl_2 layers were combined and dried over Na_2SO_4 . After filtration and concentration under reduced pressure, the crude product was purified by column chromatography (silica gel, hexane-diethyl ether) to afford the desired product (**4**) (372 mg, 92% yield, the ratio of diastereomeric isomers: 96/4). The diastereomer mixture (230 mg) was purified by recrystallization (CH_2Cl_2 -hexane, at 0°C) to afford the diastereo- and enantiomerically pure product (**4**) (153 mg, 67%, >99% ee). The enantiomeric excess of the product was determined by HPLC analysis (Daicel Chiralpak AD, hexane/*i*PrOH = 1000/1, flow rate = 1.0 mL/min: $t_{\text{R}} = 20.5$ min (major), $t_{\text{R}} = 15.5$ min (minor)) after benzylation using benzoyl chloride and pyridine, DMAP.

Mp 88°C ; $[\alpha]_{\text{D}}^{22} = -88.9$ (c 0.65, THF, >99% ee); IR $[\text{cm}^{-1}]$ (KBr) 3246, 1651, 1457, 1378, 1357, 1335, 1312, 1282, 1268, 1233; ^1H NMR (CDCl_3) δ 0.98 (d, 3H, $J = 6.8$ Hz), 1.38 (d, 1H, $J = 8.0$ Hz), 1.65 (m, 1H), 1.75 (dd, 3H, $J = 6.6, 1.7$ Hz), 3.88 (m, 1H), 4.01 (m, 1H), 4.77 (dd, 1H, $J = 6.1, 2.2$ Hz), 5.49 (ddq, 1H, $J = 15, 8.0, 1.7$ Hz), 5.79 (dq, 1H, $J = 15, 6.4$ Hz), 6.39 (dd, 1H, $J = 6.3, 1.2$ Hz); ^{13}C NMR (CDCl_3) δ 14.9, 17.8, 40.7, 69.1, 81.0, 104.8, 128.9, 130.9, 144.7; EI-HRMS (m/z) calcd. for $\text{C}_9\text{H}_{14}\text{O}_2$ (M^+): 154.0994; found: 154.0997.

(4*R*,5*S*,6*R*)-4-Hydroxy-5-methyl-6-((*E*)-1-propenyl)-tetrahydro-2*H*-pyran-2-one ((+)-Prelactone C, 6): To a suspension of **4** (131 mg, 0.851 mmol), well dried

anhydrous lithium bromide (262 mg, 3.02 mmol), and already dehydrated Dowex® 50W-X2 resin (131 mg) in freshly distilled THF (10 mL) was added a solution of H₂O (92.6 mg, 5.14 mmol) in THF (3.0 mL) at 0 °C, and the whole was stirred at the same temperature for 8 h. Then, triethylamine (0.1 mL) was added to basify the reaction mixture, and the solution was diluted with ethyl acetate and dried over anhydrous Na₂SO₄. After filtrated and concentrated under reduced pressure, the residue was purified by column chromatography (silica gel, ethyl acetate-hexane) to afford the desired hydrated product **5** (115.1 mg, 79%) as a diastereomer mixture. Then, a solution of **5** (109 mg, 0.63 mmol) and Fetizon reagent (Ag₂CO₃/Celite® (0.6 g/1 mmol), 416 mg, 0.69 mmol) in benzene was heated to reflux for 3 h. The whole was cooled to room temperature and filtered to remove precipitate, and the precipitate was washed well with ethyl acetate. The organic layers were combined and concentrated under reduced pressure, the crude product obtained was purified by column chromatography (silica gel, ethyl acetate-hexane) to afford (+)-Prelactone C (**6**) as a pale yellow oil (103.3 mg, 96% yield).

$[\alpha]_D^{24} = +65.4$ (c 0.71, MeOH). [lit.⁴ $[\alpha]_D^{20} = +57.6$ (c 0.5, MeOH)]. IR [cm⁻¹] (neat) 3434, 1730, 1454, 1376, 1244. ¹H NMR (CDCl₃) δ 1.03 (d, 3H, *J*= 6.7 Hz), 1.65 (m, 1H), 1.75 (dd, 3H, *J*= 6.8, 1.6 Hz), 2.49 (dd, 1H, *J*= 17, 8.6 Hz), 2.57 (br, 1H), 2.91 (dd, 1H, *J*= 17, 5.8 Hz), 3.77 (m, 1H), 4.19 (dd, 1H, *J*= 10. 8.6 Hz), 5.43 (ddq, 1H, *J*= 15, 8.2, 1.9 Hz), 5.80 (dq, 1H, *J*= 15, 6.7 Hz). ¹³C NMR (CDCl₃) δ 13.7, 17.6, 39.1, 41.5, 69.5, 84.1, 127.6, 132.4, 170.4. EI-MS [*m/z*] 170 (M⁺), 152 ((M-H₂O)⁺). EI-HRMS (*m/z*) calcd. for C₉H₁₄O₃ (M⁺): 170.0943; found: 170.0972.

Asymmetric Synthesis of (+)-9-deoxygoniopyrnone

(5-Benzyloxy-4-hydroxy-6-phenyltetrahydropyran-2-yl)thioacetic acid S-ethyl ester (7): To a suspension of Sc(OTf)₃ (7.0 mg, 0.014 mmol) in CH₂Cl₂ (0.2mL) was added 3-benzyloxy-2-phenyl-2,3-dihydro-pyran-4-one (19.5 mg, 0.070 mmol, 97% ee) in CH₂Cl₂ (0.4 mL) and the silyl enol ether of *S*-ethyl thioacetate (19.0 mg, 0.11 mmol) in CH₂Cl₂ (0.4 mL) successively at -78 °C. The reaction mixture was stirred for 18h at the same temperature, and water (0.63 μ l) was added to quench the reaction. The mixture was dried directly under reduced pressure (1 mmHg) at room temperature for 1 h to afford the crude Michael adduct. *Trans*-relationship between

the phenyl group and the new stereocenter of the product was confirmed by NOE experiments. To a solution of the crude product in CH₂Cl₂ (3.0 mL) was added dibutyltinhydride (67.0 mg, 0.29 mmol) in CH₂Cl₂ (1.0 mL) at 0 °C, and the whole was stirred for 18h. After H₂O was added to quench the reaction, CH₂Cl₂ (10 mL) was added. The organic layer was separated, and the aqueous layer was extracted twice with CH₂Cl₂ (10 mL x 2). The organic layers were combined and dried over anhydrous Na₂SO₄. After filtration and concentration under reduced pressure, the crude product was purified by preparative thin layer chromatography (hexane-ethyl acetate = 2:1) to afford the mixture of **7a** and **7b** (23.7 mg, 88% yield, **7a/7b** = 63/37).

(2R, 4R, 5S, 6S)-7a: IR [cm⁻¹] (neat) 3453, 3062, 3027, 2924, 1955, 1890, 1678, 1601, 1494, 1455, 1407, 1272. ¹H NMR (CDCl₃) δ 1.27 (t, 3H, *J* = 7.4 Hz), 1.53 (ddd, 1H, *J* = 13, 9.8 Hz), 2.06 (ddd, 1H, *J* = 13, 4.9, 3.0 Hz), 2.71 (dd, 1H, *J* = 15, 4.9 Hz), 2.87 (dd, 1H, *J* = 15, 8.0 Hz), 2.89 (q, 1H, *J* = 7.4 Hz), 3.76 (dd, 1H, *J* = 8.6, 4.9 Hz), 4.02 (m, 1H), 4.20 (dt, 2H, *J* = 8.6, 4.9 Hz), 4.51 (d, 2H, *J* = 11 Hz), 4.65 (d, 2H, *J* = 11 Hz), 5.29 (d, 2H, *J* = 4.9 Hz), 7.2-7.4 (m, 8H), 7.67 (d, 2H, *J* = 7.6 Hz); ¹³C NMR (CDCl₃): δ 14.7, 23.5, 37.1, 49.4, 66.6, 66.8, 72.4, 76.6, 82.4, 127.4, 127.9, 128.2, 128.5, 137.6, 137.8, 196.7. EI-MS [*m/z*] 386 (M⁺). 278 (M⁺-C₇H₈O). EI-HRMS (*m/z*) calcd. for C₁₅H₁₈O₃S (M⁺-C₇H₈O): 278.0977; found: 278.0974.

(2R, 4S, 5S, 6S)-7b: IR [cm⁻¹] (KBr) 3398, 3064, 3028, 2963, 2865, 1950, 1882, 1669, 1498, 1453, 1409, 1353, 1294, 1221. ¹H NMR (CDCl₃) δ 1.20 (t, 3H, *J* = 7.4 Hz), 1.78 (dd, 1H, *J* = 13, 4.9 Hz), 2.10 (ddd, 1H, *J* = 13, 6.1 Hz), 2.85 (dd, 1H, *J* = 14, 7.6 Hz), 2.86 (q, 1H, *J* = 7.4 Hz), 3.04 (dd, 1H, *J* = 14, 7.6 Hz), 3.77 (br, 1H), 3.93 (s, 1H), 4.03 (m, 1H), 4.75 (m, 2H), 7.48 (d, 2H, *J* = 5.4 Hz), 7.2-7.4 (m, 6 H), 7.48 (d, 2H, *J* = 7.3 Hz); ¹³C NMR (CDCl₃): δ 14.6, 23.5, 32.2, 45.5, 66.1, 70.1, 73.8, 75.0, 80.1, 126.4, 127.9, 127.5, 127.8, 128.0, 128.3, 128.4, 137.8, 139.0, 196.4. EI-MS [*m/z*] 386 (M⁺). 278 (M⁺-C₇H₈O). EI-HRMS (*m/z*) calcd. for C₁₅H₁₈O₃S (M⁺-C₇H₈O): 278.0977; found: 278.0987.

((2R, 5R, 6S)-5-Benzoyloxy-4-oxo-6-phenyltetrahydropyran-2-yl)thioacetic acid S-ethyl ester (10): To a suspension of tetrapropylammonium perruthenate (TPAP, 1.4 mg, 0.004 mmol) in CH₂Cl₂ (0.3 mL) were added 4-methylmorpholine *N*-oxide (NMO, 9.0 mg, 0.077 mmol) in CH₂Cl₂ (0.4 mL) and **7b** (9.5 mg, 0.025 mmol) in

CH₂Cl₂ (0.4 mL) successively at 0 °C, and the whole was stirred for 10 h at room temperature. The reaction mixture was filtrated with celite[®], and the precipitate was washed well with CH₂Cl₂. The filtrates were combined and dried over Na₂SO₄. After filtration and concentration under reduced pressure, the crude product was purified by preparative thin layer chromatography (hexane-ethyl acetate = 2:1) to afford the desired product **10** (8.8 mg, 93%). **10**: IR [cm⁻¹] (neat) 3062, 3028, 2927, 2874, 1960, 1888, 1726, 1686, 1496, 1454, 1264, 1215. ¹H NMR (CDCl₃) δ 1.23 (t, 3H, *J* = 7.3 Hz), 1.78 (ddd, 1H, *J* = 14.3, 9.9, 1.1 Hz), 2.39 (ddd, 1H, *J* = 12.6, 6.1 Hz), 2.57 (dt, 1H, *J* = 14.9, 3.7 Hz), 2.75 (dd, 1H, *J* = 12.6, 7.9 Hz), 2.79 (q, 1H, *J* = 7.5 Hz), 4.10 (m, 1H), 4.24 (dd, 1H, *J* = 6.0, 1.1 Hz), 4.53 (d, 1H, *J* = 12.3 Hz), 4.78 (d, 1H, *J* = 12.3 Hz), 5.27 (d, 1H, *J* = 6.0 Hz), 7.1–7.3 (m, 8H), 7.37 (d, 2H, *J* = 8.3 Hz); ¹³C NMR (CDCl₃): δ 14.6, 23.5, 46.0, 48.8, 68.3, 71.3, 72.6, 77.7, 81.2, 127.8, 127.9, 128.0, 128.3, 128.3, 128.4, 128.6, 135.8, 137.1, 195.4, 205.3. EI-MS [*m/z*] 384 (M⁺), 293 (M⁺–C₇H₇), 277 (M⁺–C₇H₇O). EI-HRMS (*m/z*) calcd. for C₁₅H₁₇O₃S (M⁺–C₇H₇O): 277.0898; found: 277.0900.

(–)-(1*R*,5*R*,7*S*,8*R*)-8-Benzylloxy-7-Phenyl-2,6-dibicyclo[3.3.1]nonane-3-one (8): To a suspension of Cu(OTf)₂ (15.8 mg, 0.043 mmol) in CH₃CN (0.5 mL) was added **7a** (7.3 mg, 0.019 mmol) in CH₃CN (1.5 mL) at room temperature, and the reaction mixture was warmed to 60 °C. The whole was stirred for 18 h at the same temperature and quenched with saturated aqueous NaHCO₃ (20 mL). After CH₂Cl₂ (10 mL) was added, the organic layer was separated and extracted with CH₂Cl₂ (10 mL x 2). The organic layers were combined and dried over anhydrous Na₂SO₄. After filtration and concentration under reduced pressure, the crude product was purified by silica gel column chromatography (hexane-ethyl acetate = 3:1) to afford the desired bicyclic product **8** (5.8 mg, 95% yield). The optical purity of **8** was enriched by recrystallization (ethyl acetate–hexane). The optical purity was determined by HPLC analysis using a chiral column. **8**: [α]_D²⁷ = –40.5 (c 0.18, CHCl₃) (>99% ee) [lit.⁵ [α]_D¹⁷ = –40.8 (c 0.15, CHCl₃)]; ¹H NMR (CDCl₃) δ 1.83 (dd, 1H, *J* = 14, 3.9 Hz), 2.63 (ddd, 1H, *J* = 14, 4.2, 2.0 Hz), 2.84 (dd, 1H, *J* = 19, 5.1 Hz), 2.96 (d, 1H, *J* = 19 Hz), 3.65 (d, 1H, *J* = 1.9 Hz), 4.02 (s, 2H), 4.53 (m, 1H), 4.75 (tt, 1H, *J* = 3.9, 1.9 Hz), 4.92 (d, 1H, *J* = 1.9 Hz), 6.92 (m, 2H), 7.2–7.3 (m, 3H), 7.3–7.4 (m, 5H); ¹³C NMR (CDCl₃) : δ 24.6, 36.3, 65.9, 70.4, 73.6, 73.7, 75.0, 126.6,

127.8, 127.9, 128.2, 128.3, 137.0, 137.6, 169.3. HPLC, Daicel Chiralcel OD, hexane/*i*-PrOH = 9/1, flow rate = 1.0 mL/min: t_R = 16.9 min (major), t_R = 18.9 min (minor).

(+)-(1*R*,5*R*,7*S*,8*R*)-8-Hydroxy-7-Phenyl-2,6-dibicyclo[3.3.1]nonane-3-one (9-deoxygoniopyrnone, 9): To a solution of **8** (4.0 mg, 0.012 mmol) in CH₂Cl₂ (1.5 mL) was added TiCl₄ (11.6 mg, 0.061 mmol) in CH₂Cl₂ (0.5 mL) at 0 °C. After stirring at room temperature for 30 min, the reaction was quenched with saturated aqueous NaHCO₃ (20 mL), and the organic layer was separated and extracted CH₂Cl₂ (10 mL x 2). The organic layers were combined and dried over anhydrous Na₂SO₄. After filtration and concentration under reduced pressure, the crude product was purified by silica gel column chromatography (hexane-ethyl acetate = 2:1) to afford **9** (2.7 mg, 96% yield). **9**: [α]_D²⁸ = +11.8 (c 0.1, EtOH) [lit.⁶ [α]_D²² = +12.0 (c 0.1, EtOH)]. ¹H NMR (CDCl₃) δ 1.85 (dd, 1H, J = 14, 3.9 Hz), 2.60 (ddd, 1H, J = 14, 4.2, 2.0 Hz), 2.88 (dd, 1H, J = 19, 5.1 Hz), 3.96 (s, 1H), 4.53 (m, 1H), 4.87 (m, 1H), 4.96 (m, 1H), 7.3 – 7.4 (m, 5H); ¹³C NMR (CDCl₃) δ 24.0, 36.4, 66.1, 68.3, 70.5, 74.7, 126.1, 128.3, 128.9, 136.7, 169.2.

1-*tert*-Butoxy-5-hydroxy-4-methyl-5-phenyl-pent-1-en-3-one (11, aldol intermediate): ¹H NMR (CDCl₃) δ 1.13 (d, 1H, J = 7.1 Hz), 1.33 (s, 9H), 1.66 (s, 3H), 3.26 (dq, 1H, J = 7.1, 6.4 Hz), 3.72 (sbr, 1H), 4.84 (d, 1H, J = 6.4 Hz), 7.2-7.4 (m, 5 H), 7.57 (s, 1H); ¹³C NMR (CDCl₃): δ 8.3, 16.7, 28.2, 46.5, 76.8, 79.6, 117.2, 126.2, 127.4, 128.3, 143.1, 154.7, 204.5.

Syntheses of Danishefsky's dienes

General procedure for synthesis of Danishefsky's diene (1a, 1b, 1d, 1e, and 1f):

To a solution of the corresponding α,β -unsaturated ketone (47.0 mmol) and triethylamine (16.4 mL, 118 mmol) in dried diethyl ether (200 mL) was added trimethylsilyl triflate (TMSOTf, 12.0 g, 54.0 mmol) in dried diethyl ether (10 mL) at 0 °C. The whole was stirred at the same temperature for 5 h, and then diluted with hexane. To the mixture, saturated aqueous NaHCO₃ was added to quench the reaction, the organic layer was separated. The aqueous layer was extracted with hexane, and the organic layers were combined and washed with saturated aqueous NaHCO₃, and water, and brine (twice each). After dried over anhydrous MgSO₄, the mixture was concentrated under reduced pressure, and the residue was distilled to

afford the desired diene. In the case of the synthesis of **1d**, *tert*-butyldimethylsilyl triflate and hexamethylphosphoramide (HMPA, 141 mmol) was used instead of TMSOTf.

(E)-1-Methoxy-3-trimethylsiloxy-1,3-butadiene (1a):^{1a} ¹H NMR (CDCl₃) δ 0.23 (s, 9H), 3.58 (s, 3H), 4.07 (s, 1H), 4.11 (s, 1H), 5.35 (d, 1H, *J* = 12 Hz), 6.83 (d, 1H, *J* = 12 Hz); ¹³C NMR (CDCl₃) δ 0.01, 56.4, 91.1, 103.1, 150.3, 153.9.

(E)-1-*tert*-Butoxy-3-trimethylsiloxy-1,3-butadiene (1b):^{1b,c} IR [cm⁻¹] (neat) 3115, 3064, 2972, 1659, 1589, 1369, 1320, 1256. ¹H NMR (CDCl₃) δ 0.23 (s, 9H), 1.29 (s, 9H), 4.05 (s, 1H), 4.08 (s, 1H), 5.50 (d, 1H, *J* = 12 Hz), 6.82 (d, 1H, *J* = 12 Hz); ¹³C NMR (CDCl₃) δ 0.08, 28.1, 76.7, 91.2, 107.0, 143.9.

(E)-1-*tert*-Butoxy-3-ethyldimethylsiloxy-1,3-butadiene (1c): IR [cm⁻¹] (neat) 3115, 3065, 2979, 2876, 1836, 1660, 1601, 1458, 1370, 1323, 1261. ¹H NMR (CDCl₃) δ 0.20 (s, 6H), 0.69 (q, 2H, *J* = 7.8 Hz), 1.00 (t, 3H, *J* = 7.8 Hz), 1.29 (s, 9H), 4.04 (s, 1H), 4.07 (s, 1H), 5.50 (d, 1H, *J* = 12 Hz), 6.84 (d, 1H, *J* = 12 Hz); ¹³C NMR (CDCl₃) δ -2.1, 6.7, 8.5, 28.1, 76.9, 91.1, 107.0, 143.9, 154.3. EI-HRMS (*m/z*) calcd. for C₁₂H₂₄O₂Si (M⁺): 228.1546; found: 228.1552.

(E)-1-*tert*-Butoxy-3-*tert*-butyldimethylsiloxy-1,3-butadiene (1d):^{1d} ¹H NMR (CDCl₃) δ 0.18 (s, 6H), 0.99 (s, 9H), 1.29 (s, 9H), 4.04 (s, 1H), 4.05 (s, 1H), 5.49 (d, 1H, *J* = 12 Hz), 6.90 (d, 1H, *J* = 12 Hz); ¹³C NMR (CDCl₃) δ -4.7, 18.2, 25.8, 28.1, 76.9, 90.8, 106.9, 144.0, 154.5.

(1E, 3Z)-1-*tert*-Butoxy-2-methyl-3-trimethylsiloxy-1.3-pentadiene (1e):^{1b} ¹H NMR (CDCl₃) δ 0.21 (s, 9H), 1.29 (s, 9H), 1.62 (d, 3H, *J* = 7.0 Hz), 1.68 (d, 3H, *J* = 1.1 Hz), 4.71 (q, 1H, *J* = 7.0 Hz), 6.62 (sbr, 1H); ¹³C NMR (CDCl₃) δ 0.6, 10.4, 11.6, 28.2, 76.2, 101.0, 113.3, 138.2, 150.4. EI-HRMS (*m/z*) calcd. for C₁₂H₂₄O₂Si (M⁺): 228.1546; found: 228.1537.

(1E, 3Z)-1-*tert*-Butoxy-3-trimethylsiloxy-1.3-pentadiene (1f): IR [cm⁻¹] (neat) 3053, 2972, 1661, 1455, 1369, 1330, 1251. ¹H NMR (CDCl₃) δ 0.23 (s, 9H), 1.28 (s, 9H), 1.58 (d, 3H, *J* = 6.8 Hz), 4.58 (q, 1H, *J* = 6.8 Hz), 5.51 (d, 1H, *J* = 12 Hz), 6.63 (d, 1H, *J* = 12 Hz); ¹³C NMR (CDCl₃) δ 0.6, 11.4, 28.1, 76.5, 104.1, 108.7, 141.4, 147.8.

Synthesis of diene 1h

Benzyloxyacetic acid: To benzyl alcohol (400 mL) was added sodium metal (56.8 g, 2.47 mol) in small portions at room temperature, and the whole was heated at 100-120 °C until sodium metal disappeared. The solution was cooled to room temperature, and chloroacetic acid (94.5 g, 1.00 mol) in benzyl alcohol (100 mL) was added over 30 min. The mixture was then heated to reflux for 2 h and cooled to room temperature. After addition of water (400 mL), the aqueous layer was washed with diethyl ether (200 mL x 7), and acidified with a 5M HCl solution (c.a. 300 mL) to pH 1-2 at 0 °C. The aqueous layer was extracted with diethyl ether (200 mL x 4), and the organic layers were combined and washed with water (500 mL x 3) and brine (500 mL x 2), and dried over anhydrous MgSO₄. After filtration and concentration under reduced pressure, the crude product was distilled (155 °C, 4.0 mmHg) to afford benzyloxyacetic acid (133.3 g, 80%). ¹H NMR (CDCl₃) δ 4.12 (s, 2H), 4.61 (s, 2H), 7.27 (m, 5H), 11.29 (s, 1H); ¹³C NMR (CDCl₃) δ 66.3, 73.2, 128.0, 128.2, 128.4, 136.4, 175.7.

Benzyloxyacetyl chloride: To a solution of benzyloxyacetic acid (20.2 g, 122 mmol) in CH₂Cl₂ (130 mL) was added thionyl chloride (53.3 mL, 730 mmol) during 30 min at 0 °C, and the whole was heated to reflux gently for 4 h. After removal of excess thionyl chloride and the solvent under reduced pressure, the crude product obtained was distilled (95 °C, 4.0 mmHg) to afford benzyloxyacetyl chloride (20.2 g, 90%). ¹H NMR (CDCl₃) δ 4.41 (s, 2H), 4.64 (s, 2H), 7.3-7.4 (m, 5H); ¹³C NMR (CDCl₃) δ 73.5, 74.8, 128.1, 128.4, 128.6, 136.1, 171.8.

(1Z, 3E)-1-benzyloxy-4-tert-butoxy-2-trimethylsilyloxy-1,3-butadiene (1h): To a well stirred solution of *tert*-buthyl vinyl ether (3.26 g, 32.5 mmol) and triethylamine (3.29 g, 32.5 mmol) in CH₃CN (6 mL) was added benzyloxyacetyl chloride (5 g, 27.0 mmol) in CH₃CN (3 mL) dropwise over 10 min at room temperature. The temperature was allowed to rise to 80 °C slowly during the addition. The mixture was stirred at 80 °C for 5 h. The solvent was then removed under reduced pressure, and diethyl ether (20 mL) was added to the residue. The precipitated triethylamine hydrochloride was removed by filtration and washed with diethyl ether (10 mL x 2). The organic phases were combined and concentrated under reduced pressure, and the crude mixture obtained was purified by silica gel column chromatography (hexane-ethyl acetate = 15:1) to afford 2-benzyloxy-3-*tert*-butoxy-cyclobutanone (5.11 g, 76%) as a diastereomer mixture. To a solution of 1,1,1,3,3,3-hexamethyldisilazane

(HMDS, 3.59 g, 22.2 mmol) in a THF solution was added *n*-BuLi in hexane (1.58 M, 12.9 mL, 20.4 mmol) at 0 °C. The mixture was stirred for 30 min at the same temperature and cooled to –78 °C. 2-Benzyloxy-3-*tert*-butoxy-cyclobutanone (4.6 g, 18.5 mmol) and trimethylsilyl chloride (TMSCl, 2.21 g, 20.3 mmol) were added successively to the mixture at –78 °C, and the whole was warmed to 0 °C and stirred for 36 h. Then, the solvent was removed under reduced pressure, and the residue was purified by deactivated silica gel (SiO₂/H₂O = 2 (w/w)) column chromatography (hexane-ethyl acetate=15:1) to afford 1-benzyloxy-2-trimethyloxy-4-*tert*-butoxy-1,3-butadiene (**1h**, 4.38 g, 74%) as a single isomer. **1h**: IR [cm⁻¹] (neat) 3064, 3032, 2977, 1950, 1727, 1631, 1497, 1455, 1369, 1249. ¹H NMR (CDCl₃) δ 0.19 (s, 9H), 1.27 (s, 9H), 4.73 (s, 2H), 5.33 (d, 1H, *J* = 12 Hz), 5.62 (s, 1H), 6.60 (d, 1H, *J* = 12 Hz), 7.2-7.4 (m, 5H); ¹³C NMR (CDCl₃) δ 0.4, 28.0, 73.9, 76.4, 104.9, 127.6, 127.6, 127.8, 128.4, 129.3, 133.6, 137.4, 139.9. EI-HRMS (*m/z*) calcd. for C₁₈H₂₈O₃Si (M⁺): 320.1808; found: 320.1817.

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