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Supporting Information

Supporting Information

Catalytic Asymmetric Epoxidation of α,β-Unsaturated Esters Using Chiral Yttrium-Biaryldiol Complexes

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Experimental

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 ^{1}H NMR and 125.65 MHz for ^{13}C NMR. Chemical shifts in $CDCl_3$ were reported downfield from TMS (= 0 ppm) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported downfield from TMS (= 0 ppm) or in the scale relative to $CHCl_3$ (77.00 ppm for ^{13}C NMR) as an internal reference. Optical rotations were measured on a JASCO P-1010 polarimeter. ESI mass spectra were measured on Waters micromass ZQ. The enantiomeric excess (ee) was determined by HPLC analysis. HPLC was performed on JASCO HPLC systems consisting of the following: pump, PU-986 or PU-2080; detector, UV-970 or UV-2075, measured at 210 nm or 254 nm; column, DAICEL CHIRALPAK AS-H, DAICEL CHIRALPAK AD-H, DAICEL CHIRALCEL OD-H; mobile phase, hexane–2-propanol; flow rate, 0.4-1 mL/min. Reactions were carried out in dry solvents under an argon atmosphere, unless otherwise stated. $RE(O\textit{i}Pr)_3$ was purchased from Kojundo Chemical Laboratory Co., LTD., 5-1-28, Chiyoda, Sakado-shi, Saitama 350-0214, Japan (Fax: +81-492-84-1351, sales@kojundo.co.jp). Same grade $Y(O\textit{i}Pr)_3$ is also commercially available from Aldrich [cat No. 2172-12-5]. MS 4Å (Molecular Sieve UOP 4A, powder) was purchased from Fluka. Other reagents were purified by the usual methods.

Synthesis of α,β-unsaturated ethyl esters 2

α,β-Unsaturated ethyl esters were prepared by standard Horner-Emmons-Wadsworth reaction of corresponding aldehydes.

(*E*)-Methyl 3-phenylacrylate (2a). See: *J. Org. Chem.* **2004**, *69*, 4216.

(*E*)-Ethyl 3-phenylacrylate (2b). See: *J. Org. Chem.* **2004**, *69*, 4216.

(*E*)-Ethyl 3-naphthalen-1-yl-acrylate (2c). See: *J. Org. Chem.* **1989**, *54*, 3963.

(*E*)-Ethyl 3-naphthalen-2-yl-acrylate (2d). See: *Tetrahedron* **1996**, 52, 1943.

(*E*)-Ethyl 3-(3-chlorophenyl)acrylate (2e). See: *J. Org. Chem.* **2002**, *67*, 5320.

(*E*)-Ethyl 3-(4-chlorophenyl)acrylate (2f). See: *J. Am. Chem. Soc.* **2002**, *124*, 8792.

(*E*)-Ethyl 3-(4-acetylphenyl)acrylate (2g). See: *J. Org. Chem.* **2003**, *68*, 2929.

(*E*)-Ethyl 3-(4-methylphenyl)acrylate (2h). See: *J. Am. Chem. Soc.* **1990**, *112*, 4324.

(*E*)-Ethyl 3-(4-methoxyphenyl)acrylate (2i). See: *J. Org. Chem.* **2004**, *69*, 4216.

(*E*)-Ethyl 3-furan-3-yl-2-acrylate (2j): See: *J. Org. Chem.* **1998**, *63*, 4489.

(*E*)-Ethyl 3-pyridin 3-yl-2-acrylate (2k): See: *J. Org. Chem.* **1994**, *59*, 2537.

(*E*)-Ethyl 3-thiophene 3-yl-2-acrylate (2l): See: *Tetrahedron* **1989**, 45, 4103.

(*E*)-Ethyl 5-phenylpent-2-enoate (2m): colorless oil; IR (neat) ν 1720, 1654, 1267, 1197, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (t, *J* = 7.0 Hz, 3H), 2.49-2.54 (m, 2H), 2.76 (t, *J* = 8.0 Hz, 2H), 4.17 (q, *J* = 7.0 Hz, 2H), 5.83 (dt, *J* = 15.5, 2.0 Hz, 1H), 7.00 (dt, *J* = 15.5, 7.0 Hz, 1H), 7.17-7.21 (m, 3H), 7.27-7.30 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.2, 33.9, 34.3, 60.14, 121.8, 126.1, 128.2, 128.4, 140.7, 148.0, 166.5; ESI-MS *m/z* 227 $[M+Na]^+$; HR-MS [FAB(+)] calcd for $C_{13}H_{17}O_2^+$ $[M+H]^+$: 205.1229. Found 205.1232.

(2*E*,6*Z*)-Ethyl 7-phenylhexa-2,6-dienote (2n): colorless oil; IR (neat) ν 1720, 1654, 1266, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, *J* = 7.5 Hz, 3H), 2.34 (dt, *J* = 7.5, 6.8 Hz, 2H), 2.50 (dt, *J* = 7.5, 6.8 Hz, 2H), 4.17 (q, *J* = 7.0 Hz, 2H), 5.62 (m, 1H), 5.83 (d, *J* = 16.0 Hz, 1H), 6.47 (d, *J* = 11.5 Hz, 1H), 6.96 (m, 1H), 7.21-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.2, 26.9, 32.3, 60.2, 121.8, 126.7, 128.1, 128.6, 129.9, 130.8, 137.2, 148.0, 166.5; ESI-MS *m/z* 253 $[M+Na]^+$; HR-MS [FAB(+)] calcd for $C_{15}H_{19}O_2^+$

[M+H]$^+$:231.1385. Found 231.1381.

(*E*)-Ethyl 7-oxo-7-phenylhept-2-enoate (2o): colorless oil; IR (neat) ν 1718, 1686, 1367, 1201, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, *J* = 7.0 Hz, 3H), 1.90-1.96 (m, 2H), 2.29-2.34 (m, 2H), 3.00 (t, *J* = 7.5 Hz, 2H), 4.18 (q, *J* = 7.0 Hz, 2H), 5.84-5.88 (m, 1H), 6.97 (dt, *J* = 14.5, 7.5 Hz, 1H), 7.45-7.48 (m, 2H), 7.54, (m, 1H), 7.94 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.2, 22.3, 31.4, 37.4, 60.2, 121.2, 127.9, 128.6, 133.1, 136.7, 148.15, 166.51, 199.47; ESI-MS *m/z* [M+Na]$^+$ 269; HR-MS [FAB(+)] calcd for $C_{15}H_{19}O_3^+$ [M+H]$^+$: 247.1334. Found 247.1336.

(*E*)-Ethyl 5-(4-methoxybenzyloxy)pent-2-enoate (2p): colorless oil; IR (neat)□ 1717, 1512, 1247, 1095, 820 cm cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, *J* = 7.5 Hz, 3H), 2.49 (dd, *J* = 13.0, 6.5 Hz, 2H), 3.55 (t, *J* = 6.5 Hz, 2H), 3.80 (s, 3H), 4.18 (q, 7.5 Hz, 2H), 4.45 (s, 2H), 5.88 (dt, *J* = 16.0, 2.0 Hz, 1H), 6.88 (m, 2H), 6.96 (dt, *J* = 16.0, 7.0 Hz, 1H), 7.25 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.3, 32.6, 55.2, 60.2, 67.9, 72.7, 113.8, 122.8, 129.31, 130.1, 145.6, 159.2, 166.4; ESI-MS *m/z* 287 [M+Na]$^+$; HR-MS [FAB(+)] calcd for $C_{15}H_{20}O_4^+$ [M$^+$]:264.1362. Found 264.1364, for $C_{15}H_{21}O_4^+$ [M+H]$^+$: 265.1447. Found 265.1439.

Synthesis of α,β-unsaturated methyl esters 2

α,β-Unsaturated ethyl esters were prepared by Knoevenagel condensation reaction of aldehydes, and then the obtained (*E*)-α,β-unsaturated carboxylic acids were converted into methyl ester.

Typical Procedure for Synthesis of α,β-Unsaturated Methyl Esters 2

Knoevenagel Condensation Reaction

To a mixture of malonic acid (2.08 g, 20.0 mmol) and pyperidine (235 μL, 2.38 mmol) in pyridine (5.8 mL) at room temperature was added cyclohexanecarboxaldehyde (1.12 g, 10.0 mmol). The reaction mixture was heated to 130 °C and refluxed for 4 h. After complete consumption of the starting material, the reaction mixture was cooled to room temperature and quenched by 1 M HCl. The water layer was extracted with ether (x 2). The combined organic layers were washed with brine, and dried over Na_2SO_4. After removing solvent under reduced pressure, the residue was purified by flash column chromatography (SiO_2, hexane/ethyl acetate = 5/1) to give (*E*)-3-cyclohexyl-acrylic acid (1.25 g, 81%) as a colorless solid.

Methyl Esterification

To a solution of 3-cyclohexyl-acrylic acid (1.25 g, 8.11 mmol) in MeOH (16.2 mL) at 0 °C was added trimethylsilyl diazomethane (9.0 mL in hexane, 18.0 mmol). The reaction mixture was warmed to 0 °C and stirred for 1 h at 0 °C. After complete consumption of the starting material, most of the solvent was removed by distillation under reduced pressure. The residue was purified by flash column chromatography (SiO_2, hexane/ethyl acetate = 100/1 to 50/1) to give methyl ester **2u** (1.31 g, 96%) as a colorless oil.

(*E*)-Methyl 5-phenylpent-2-enoate (2q): See: *J. Org. Chem.* **1990**, *55*, 1928.

(*E*)-Methyl 7-phenylhept-2-enoate (2r):See: *Bioorg.Med. Chem.* **1999**, *7*, 3003.

(2*E*, 6*Z*)-Methyl 7-phenylhepa-2,5-dienote (2s):See: *Tetrahedron* **1989,** *45*, 7835.

(*E*)-Methyl 7-oxo-7-phenylhept-2-enoate (2t): colorless oil; IR (neat) ν 2950, 1685, 1528, 1437, 1043, 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.91-1.96 (m, 2H), 2.30-2.34 (m, 2H), 3.00 (t, *J* = 7.2 Hz, 2H), 3.72 (s, 3H), 5.87 (dt, *J* = 15.6, 1.5 Hz, 1H), 6.98 (dt, *J* = 15.6, 6.9 Hz, 1H), 7.45-7.47 (m, 2H), 7.55-58, (m, 1H), 7.93-7.95 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.4, 31.5, 51.4, 121.6, 128.0, 128.6, 133.0, 136.9, 148.4, 166.9, 199.5; ESI-MS *m/z* $[M+Na]^+$ 255; HR-MS [FAB(+)] calcd for $C_{14}H_{17}O_3^+$ $[M+H]^+$: 233.1172. Found 233.1171.

(*E*)-Methyl 3-cyclohexylprop-2-enoate (2u):See: *J. Org. Chem.* **1975**, 40, 3237.

General Procedure for Catalytic Asymmetric Epoxidation of α,β-Unsaturated Esters Using $Y(O\mathit{i}Pr)_3$: Biphenyldiol 1a : $Ph_3As(O)$ = 1:1:1 Complex.

MS 4Å was dried for 3 h at 180 °C under reduced pressure (0.7 kPa) [Caution: activation of MS 4Å is important to achieve good reactivity]. To a mixture of MS 4Å (250 mg), biphenyldiol **1a** (7.2 mg, 0.025 mmol), and triphenylarsine oxide (8.1 mg, 0.025 mmol) in THF (1.125 mL), was added $Y(O\mathit{i}Pr)_3$ (0.125 mL, 0.025 mmol, 0.2 M solution in THF) at room temperature. After being stirred for 45 min at room temperature, TBHP (0.375 mL, 1.5 mmol, 4.0 M solution in toluene) was added. After being stirred for 10 min, ester **2b** (220.3 mg, 1.25 mmol) was added and the mixture was stirred at room temperature. After complete consumption of the starting material

(36 h), the reaction mixture was diluted with ethyl acetate (10 mL) and quenched with 2% citric acid (2.5 mL). The water layer was extracted with ethyl acetate (10 mL x 2). The combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4. After removing solvent under reduced pressure, the residue was purified by flash column chromatography (SiO_2, hexane/ethyl acetate = 100/1 to 50/1) to give epoxy ester **3b** (212.7 mg, 89%) as a colorless oil. The enantiomeric excess of **3b** was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AD-H, *i*-PrOH/hexane 2/98, flow rate 0.4 mL/min, t_R 31.5 min (*2S,3R*) and 38.0 min (*2R,3S*), detection at 254 nm]; $[\alpha]_D^{24}$ –158.8 (c 1.06 $CHCl_3$). lit. $[\alpha]_D^{25}$ +160.1 [*c* 1.15, $CHCl_3$, 96% ee, (2*S*,3*R*)]. See: ref [7b]. *J. Am. Chem. Soc*. **2002**, *124*, 8792.

Methyl (2*R*,3*S*)-3-phenyloxirane-2-carboxylate (3a): The enantiomeric excess of **3a** was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AD-H, *i*-PrOH/hexane 2/98, flow rate 0.4 mL/min, t_R 31.6 min ((*2S,3R*)-isomer)) and 38.0 min ((*2R,3S*)-isomer), detection at 254 nm]; $[\alpha]_D^{20}$ –132.6 (c 0.44 $CHCl_3$). lit. $[\alpha]_D^{25}$ –111.8 [*c* 1.17, $CHCl_3$, (2*R*,3*S*) (92% ee)]. Known compound, see: *J. Am. Chem. Soc*. **2001**, *123*, 9474.

Ethyl (2*R*,3*S*)-3-naphthalen-2-yl-oxirane-2-carboxyate (3c): white solid; IR (KBr) ν 2985, 1749, 1369, 1316, 1235, 1207, 1022, 907, 867, 831, 809, 783, 755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (t, *J* = 7.3 Hz, 3H), 3.60 (d, *J* = 1.5 Hz, 1H), 4.25-4.33 (m, 3H), 7.29 (d, *J* = 8.1, 1.4 Hz, 1H), 7.46-7.49 (m, 2H), 7.79-7.81 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.0, 56.7, 58.1, 61.7, 122.3, 125.8, 126.4, 126.5, 127.7, 127.7, 128.5, 132.2, 132.9, 133.4, 168.1; ESI-MS *m/z* 265 $[M+Na]^+$; HR-MS [FAB(+)] calcd for $C_{15}H_{15}O_3^+$ $[M+H]^+$: 243.1021. Found 243.1022. The enantiomeric excess of **3c** was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AD-H, *i*-PrOH/hexane 2/98, flow rate 0.4 mL/min, t_R 39.8 min (minor) and 48.7 min (major), detection at 254 nm]; $[\alpha]_D^{24}$ –170.3 (c 1.50 $CHCl_3$).

Ethyl (2*R*,3*S*)-3-naphthalen-1-yl-oxirane-2-carboxyate (3d): colorless oil; IR (neat) ν 3059, 2982, 1748, 1200, 800, 776 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (t, *J* = 7.2 Hz, 3H), 3.52 (d, *J* = 1.7 Hz, 1H), 4.34-4.36 (m, 2H), 4.72 (d, *J* = 1.7 Hz, 1H), 7.44 (m, 4H), 7.40 (dd, *J* =8.3, 1.8 Hz, 1H), 7.82 (m, 1H), 7.88 (m, 1H), 8.04 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.9, 55.9, 56.2, 61.8, 122.5, 122.7, 125.3, 126.1, 126.6, 128.7, 128.9, 131.0, 131.1, 133.2, 168.4; ESI-MS *m/z* 265 $[M+Na]^+$; HR-MS [FAB(+)] calcd for $C_{15}H_{15}O_3^+$ $[M+H]^+$: 243.1021. Found 243.1025. The enantiomeric excess of **3d** was determined by

chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AD-H, *i*-PrOH/hexane 5/95, flow rate 1.0 mL/min, t_R 7.3 min (minor) and 8.9 min (major), detection at 254 nm]; $[\alpha]_D^{23}$ +16.1 (c 0.85 $CHCl_3$).

Ethyl (2*R*,3*S*)-3-(3-chlorophenyl)oxirane-2-carboxylate (3e): colorless oil; IR (neat) ν 2984, 1748, 1444, 1286, 1202, 1028, 786, 687 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (t, *J* = 7.2 Hz, 3H), 3.46 (d, *J* = 1.7 Hz, 1H), 4.07 (d, *J* = 1.7 Hz, 1H), 4.24-4.32 (m, 2H), 7.18 (ddd, *J* = 6.7, 3.1, 1.8 Hz, 1H), 7.27-7.30 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 13.9, 56.5, 56.9, 61.7, 123.9, 125.6, 128.9, 129.8, 134.5, 137.0, 167.6; ESI-MS *m/z* 249 $[M+Na]^+$; HR-MS [FAB(+)] calcd for $C_{11}H_{12}O_3Cl^+$ $[M+H]^+$: 227.0475. Found 227.0476. The enantiomeric excess of **3e** was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AD-H, *i*-PrOH/hexane 2/98, flow rate 0.4 mL/min, t_R 28.1 min (major) and 31.2 min (minor), detection at 254 nm]; $[\alpha]_D^{23}$ –157.9 (c 1.69 $CHCl_3$).

Ethyl (2*R*,3*S*)-3-(4-chlorophenyl)oxirane-2-carboxylate (3f): The enantiomeric excess of **3f** was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALCEL OD-H, *i*-PrOH/hexane 2/98, flow rate 1.0 mL/min, t_R 8.7 min (major) and 9.6 min (minor), detection at 254 nm]; $[\alpha]_D^{23}$ –155.7 (c 1.37 $CHCl_3$). Known compound, see: *J. Am. Chem. Soc.* **2002**, *124*, 8792.

Ethyl (2*R*,3*S*)-3-(4-acetylphenyl)oxirane-2-carboxylate (3g): colorless oil; IR (neat) ν 2984, 1748, 1685, 1266, 1202, 1026 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (t, *J* = 7.2 Hz, 3H), 2.61 (s, 3H), 3.51 (d, *J* = 1.8 Hz, 1H), 4.16 (d, *J* = 1.8Hz, 1H), 4.26-4.34 (m, 2H), 7.40 (dd, *J* =8.3, 1.8 Hz, 1H), 7.40 (dd, *J* =8.3, 1.8 Hz, 1H), 7.96 (dd, *J* =8.3, 1.8 Hz, 1H), 7.96 (dd, *J* =8.3, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 26.6, 56.8, 57.2, 61.8, 125.9, 128.5, 137.4, 140.1, 167.6, 197.3; ESI-MS *m/z* 257 $[M+Na]^+$; HR-MS [FAB(+)] calcd for $C_{13}H_{15}O_4^+$ $[M+H]^+$: 235.0970. Found 235.0968. The enantiomeric excess of **3g** was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AD-H, *i*-PrOH/hexane 1/9, flow rate 1.0 mL/min, t_R 14.8 min (major) and 16.3 min (minor), detection at 254 nm]; $[\alpha]_D^{23}$ –164.4 (c 0.46 $CHCl_3$).

Ethyl (2*R*,3*S*)-3-(4-methylphenyl)oxirane-2-carboxylate (3h): The enantiomeric excess of **3h** was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AD-H, *i*-PrOH/hexane 5/95, flow rate 1.0 mL/min, t_R 7.5 min (minor) and 8.8 min (major), detection at 254 nm]; $[\alpha]_D^{24}$ –174.4 (c 1.14 $CHCl_3$). Known compound, see: *J. Am. Chem. Soc.* **2002**, *124*, 8792.

Ethyl (2*R*,3*S*)-3-(4-methoxylphenyl)oxirane-2-carboxylate (3i): The enantiomeric excess of **3i** was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALCEL OD-H, *i*-PrOH/hexane 5/95, flow rate 1.0 mL/min, t_R 8.9 min ((*2R,3S*-isomer)) and 10.4 min ((*2S,3R*)-isomer), detection at 254 nm]; $[\alpha]_D^{23}$ –153.3 (c 1.11 $CHCl_3$). lit. $[\alpha]_D^{25}$ +143.2 [*c* 1.15 $CHCl_3$ (90% ee, (2*S*,3*R*))]. Known compound, see: *J. Am. Chem. Soc.* **2002**, *124*, 8792.

Ethyl (2*R*,3*S*)-3-furan-3-yl-oxirane-2-carboxyate (3j): white-yellow solid; IR (KBr) ν 3141, 2985, 1731, 1424, 1308, 1164, 1026, 903, 876, 774 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (t, *J* = 7.0 Hz, 3H), 3.58 (d, *J* = 2.0 Hz, 1H), 4.04 (d, *J* = 2.0 Hz, 1H), 4.24-4.32 (m, 2H), 6.29 (dd, *J* = 1.8, 0.6 Hz, 1H), 7.40-7.41 (m, 1H), 7.57 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 51.8, 55.4, 61.8, 107.7, 120.9, 142.1, 143.9, 168.3; ESI-MS *m/z* 205 $[M+Na]^+$; HR-MS [FAB(+)] calcd for $C_9H_{11}O_4^+$ $[M+H]^+$: 183.0657. Found 183.0654. The enantiomeric excess of **3j** was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AD-H, *i*-PrOH/hexane 5/95, flow rate 1.0 mL/min, t_R 9.1 min (major) and 10.2 min (minor), detection at 210 nm]; $[\alpha]_D^{23}$ –93.8 (c 0.83 $CHCl_3$).

Ethyl (2*R*,3*S*)-3-pyridin-3-yl-oxirane-2-carboxyate (3k): yellow oil; IR (neat) ν 2984, 1747, 1288, 1204, 1025, 893, 799, 712 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (t, *J* = 7.2 Hz, 3H), 3.56 (d, *J* = 1.7 Hz, 1H), 4.16 (d, *J* = 1.7 Hz, 1H), 4.26-4.34 (m, 2H), 7.32 (ddd, *J* = 7.9, 4.9, 0.7 Hz, 1H), 7.58 (ddd, *J* = 7.9, 1.8, 1.8 Hz, 1H), 8.60-8.62 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.8, 55.6, 56.3, 61.7, 123.3, 130.6, 132.8, 147.8, 150.0, 167.4; ESI-MS *m/z* 216 $[M+Na]^+$; HR-MS [FAB(+)] calcd for $C_{10}H_{12}O_3N^+$ $[M+H]^+$: 194.0817. Found 194.0818. The enantiomeric excess of **3k** was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AD-H, *i*-PrOH/hexane 1/1, flow rate 1.0 mL/min, t_R 7.4 min (major) and 8.6 min (minor), detection at 254 nm]; $[\alpha]_D^{24}$ –153.2 (c 0.85 $CHCl_3$).

Ethyl (2*R*,3*S*)-3-thiophen-3-yl-oxirane-2-carboxyate (3l): The enantiomeric excess of **3l** was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALCEL OD-H, *i*-PrOH/hexane 5/95, flow rate 1.0 mL/min, t_R 10.8 min (minor) and 26.5 min (major), detection at 254 nm]; $[\alpha]_D^{23}$ –139.0 (c 0.98 $CHCl_3$). Known compound, see: *J. Heterocyclic Chem.* **1964**, *11*, 242.

Ethyl (2*R*,3*S*)-3-(2-phenylethyl)oxirane-2-carboxylate (3m): colorless oil; IR (neat) ν 1749, 1454, 1370, 1198, 1030, 803 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (t, *J* = 7.0 Hz, 3H), 1.86-2.01 (m, 2H), 2.73-2.76 (m, 2H), 3.16-3.22 (m, 2H), 4.17-4.25 (m, 2H), 7.18-7.22 (m, 3H), 7.28-7.31 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.1, 31.9, 33.2, 53.2, 57.8, 61.5, 126.2, 128.3, 140.5, 169.1; ESI-MS *m/z* 243 $[M+Na]^+$; HR-MS [FAB(+)] calcd for $C_{13}H_{17}O_2^+$ $[M+H]^+$: 221.1178 Found 221.1178. The enantiomeric excess of **3m** was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AD-H, *i*-PrOH/hexane 2/98, flow rate 1.0 mL/min, t_R 8.8 min (major) and 9.3 min (minor), detection at 254 nm]; $[\alpha]_D^{22}$ –39.4 (c 1.29 $CHCl_3$).

Ethyl (2*R*,3*S*)-3-[(3Z)-4-phenyl-3-butenyl]oxirane-2-carboxylate (3n): colorless oil; IR (neat) ν 1748, 1446, 1197, 1094 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, *J* = 7.0 Hz, 3H), 1.68-1.85 (m, 2H), 2.08-2.54 (m, 2H), 3.18 (ddd, *J* = 6.0, 4.5, 2.0 Hz 1H), 3.23 (m, 2H), 4.16-4.27 (d, *J* = 2.0 Hz, 1H), 5.65 (dt, *J* = 11.5, 7.5 Hz, 2H), 6.48 (d, *J* = 11.5 Hz, 1H), 7.21-7.25 (m, 3H), 7.32-7.35 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.1, 24.8, 31.6, 53.0, 57.9, 61.5, 126.8, 128.2, 128.6, 130.1, 130.5, 137.1, 169.1; ESI-MS *m/z* 269 $[M+Na]^+$; HR-MS [FAB(+)] calcd for $C_{15}H_{19}O_3^+$ $[M+H]^+$: 247.1335 Found 247.1336. The enantiomeric excess of **3n** was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALCEL OD-H, *i*-PrOH/hexane 2/98, flow rate 1.0 mL/min, t_R 10.0 min (minor) and 23.1 min (major), detection at 254 nm]; $[\alpha]_D^{22}$ –13.1 (c 1.04 CH_2Cl_2).

Ethyl (2*R*,3*S*)-3-(4-oxo-4-phenylbutyl)oxirane-2-carboxylate (3o): colorless oil; IR (neat) ν 1748, 1685, 1200, 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (t, *J* = 7.0 Hz, 3H), 1.60-1.67 (m, 1H), 1.81-1.98 (m, 3H), 3.07 (t, *J* = 7.0 Hz 2H), 3.19-3.22 (m, 1H), 3.24 (d, *J* = 2.0 Hz, 1H), 4.18-4.29 (m, 2H), 7.45-7.48 (m, 2H), 7.55-7.58 (m, 1H), 7.95-7.97 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.2, 30.7, 37.4, 52.8, 58.1, 61.6, 127.9, 133.1, 136.7, 169.1, 199.4; ESI-MS *m/z* 285 $[M+Na]^+$; HR-MS [FAB(+)] calcd for $C_{15}H_{19}O_4^+$ $[M+H]^+$: 263.1283 Found 263.1279. The enantiomeric excess of **3o** was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AD-H, *i*-PrOH/hexane 2/98, flow rate 1.0 mL/min, t_R 35.4 min (minor) and 38.0 min (major), detection at 254 nm]; $[\alpha]_D^{22}$ –25.2 (c 0.98 $CHCl_3$).

Ethyl (2*R*,3*S*)-3-[2-(4-Methoxybenzyloxy)ethyl]oxirane-2-carboxylate (3p): colorless oil; IR (neat) ν 2929, 1748, 1612, 1370, 819 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (t, *J* = 7.0 Hz, 3H), 1.82 (ddd, *J* = 14.5, 11.5, 5.5 Hz, 1H), 1.95-2.02 (m, 1H), 3.27 (d, *J* = 1.9 Hz 1H), 3.30 (ddd, *J* = 6.0, 4, 2.0 Hz, 1H) , 3.80 (s, 1H), 4.17-4.28 (m, 2H), 4.44 (dd, *J* =

14.0, 11.5 Hz, 2H), 6.86-6.89 (m, 2H), 7.24-7.27 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.1, 31.9, 53.0, 55.2, 56.2, 61.5, 66.0, 72.8, 113.8, 129.3, 130.1, 159.2, 169.1; ESI-MS *m/z* 303 $[M+Na]^+$; HR-MS [FAB(+)] calcd for $C_{15}H_{20}O_5^+$ $[M^+]$:280.1311. Found 280.1311, for $C_{15}H_{21}O_5^+$ $[M+H]^+$: 281.1389. Found 281.1386. The enantiomeric excess of **3p** was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AD-H, *i*-PrOH/hexane 2/98, flow rate 1.0 mL/min, t_R 20.1 min (major) and 21.3 min (minor), detection at 254 nm]; $[\alpha]_D^{22}$ –13.7 [c 2.95 $CHCl_3$ (96% ee)].

General Procedure for the Catalytic Asymmetric Epoxidation of α,β-Unsaturated Esters Using the Y(O*i*Pr)$_3$: (*S*)-binol : Ph$_3$P(O) = 1:1:2 Complex.

To a stirred mixture of MS 4A [500 mg (1000 mg/mmol of starting material); MS 4A was dried for 3 h at 180 °C under reduced pressure.] (*S*)-binol was added (14.3 mg, 0.05 mmol) and triphenylphosphine oxide (27.8 mg, 0.1 mmol) as a THF solution (5.0 mL), and then Y(O*i*Pr)$_3$ (0.250 mL, 0.05 mmol, 0.2 M solution in THF) was added to the reaction mixture at room temperature. After being stirred for 45 min at the same temperature, TBHP (0.150 mL, 0.5 mmol, 4.0 M solution in toluene) was added. After being stirred for 10 min, **2q** (95.0 mg, 0.5 mmol) was added directly and the mixture was stirred at room temperature. After 24 h, the reaction mixture was diluted with ethyl acetate (20 mL) and quenched with 2% citric acid (10 mL). The water layer was extracted with ethyl acetate (20 mL), the combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4. After removing solvent under reduced pressure, the residue was purified by flash chromatography (SiO_2, hexane/ethyl acetate = 100/1 to 50/1) to give epoxy ester **3r** (89.5 mg, 87%) as a cololess oil. The enantiomeric excess of **3r** was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AD-H, *i*-PrOH/hexane 2/98, flow rate 1.0 mL/min, t_R 9.2 min (*2R,3S*) and 10.9 min (*2S,3R*), detection at 254 nm]; $[\alpha]_D^{25}$ –44.4 (c 1.47 $CHCl_3$). lit. $[\alpha]_D^{25}$ –33.5 [*c* 0.82, $CHCl_3$, (83% ee)]. Known compound, see: *J. Am. Chem. Soc*. **2001**, *123*, 9474.

Methyl (2*R*,3*S*)-3-(4-phenylbutyl)oxirane-2-carboxylate (3s): The enantiomeric excess of **3s** was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AD-H, *i*-PrOH/hexane 1/99, flow rate 1.0 mL/min, t_R 12.1 min (major) and 14.0 min (minor), detection at 254 nm]; $[\alpha]_D^{25}$ –23.0 (c 0.55, $CHCl_3$). lit. $[\alpha]_D^{24}$ –24.6 [*c* 1.70, $CHCl_3$, (99% ee)] Known compound, see: *Tetrahedron*. **2003**, *59*, 10485.

Methyl (2*R*,3*S*)-3-[(3*Z*)-4-phenyl-3-butenyl]oxirane-2-carboxylate (3t): The

enantiomeric excess of **3t** was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AD-H, *i*-PrOH/hexane 1/9, flow rate 0.5 mL/min, t_R 18.9 min (major) and 20.2 min (minor), detection at 254 nm]; $[\alpha]_D^{29}$ –20.0 (c 0.68, $CHCl_3$). lit. $[\alpha]_D^{24}$ –13.7 [*c* 0.54, $CHCl_3$, (82% ee)] Known compound, see: *Tetrahedron*. **2003**, *59*, 10485.

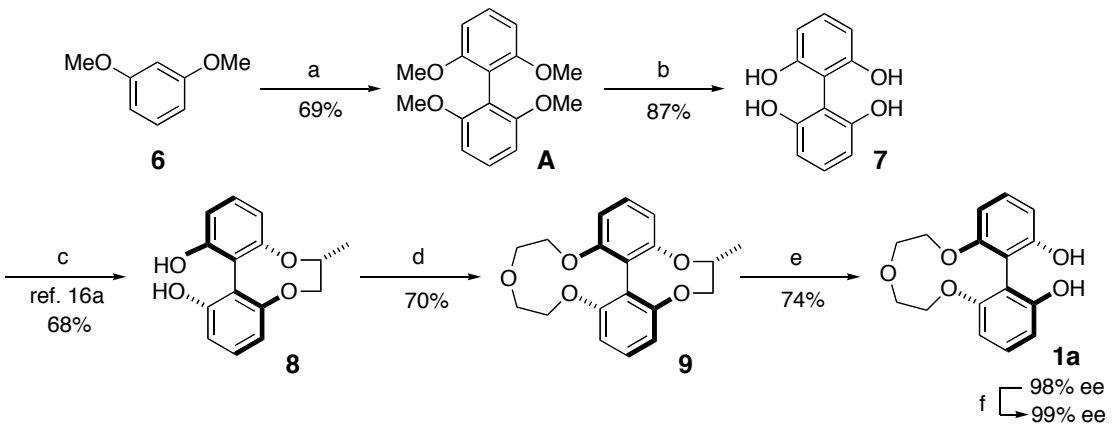
Methyl (2*R*,3*S*)-3-(4-oxo-4-phenylbutyl)oxirane-2-carboxylate (3u): pale yellow solid: IR (KBr) ν 2923, 1752, 1684, 1448, 1204 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.53-1.60 (m, 1H), 1.73-1.80 (m, 1H), 1.84-1.90 (m, 2H), 2.99 (t, *J* = 7.0 Hz, 2H), 3.13-3.16 (m, 1H), 3.19 (d, *J* = 1.9 Hz, 1H), 3.70 (s, 1H), 7.38-7.39 (m, 2H), 7.47-7.51 (m, 1H), 7.87-7.89 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.2, 30.7, 37.5, 52.4, 52.7 58.1, 127.9, 128.6, 133.1, 136.8, 169.5, 199.3; ESI-MS *m/z* 271 $[M+Na]^+$; HR-MS [FAB(+)] calcd for $C_{15}H_{19}O_4^+$ $[M+H]^+$: 263.1283 Found 263.1279. The enantiomeric excess of **3u** was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AD-H (x2), *i*-PrOH/hexane 1/19, flow rate 1.0 mL/min, t_R 44.9 min (minor) and 46.2 min (major), detection at 254 nm]; $[\alpha]_D^{26}$ –23.2 (c 0.54 $CHCl_3$).

Methyl (*2R,3S*)-3-Cyclohexyloxiranecatboxyrate (3v): The enantiomeric ex
cess of **3v** was determined by chiral stationary-phase HPLC analysis after conversion to corresponding 4-methoxy benzyl ester (DAICEL CHIRALPAK AD, *i*-PrOH/Hexane 1/9, flow rate 0.5 mL/min, t_R 15.5 min (2*S*,3*R*) and 18.3 min (2*R*, 3*S*), detection at 254 nm);]; $[\alpha]_D^{26}$ –26.2 [c 0.328 $CHCl_3$]. lit. $[\alpha]_D^{25}$ –24.8 [*c* 1.27, $CHCl_3$, (88% ee), (2*R*,3*S*)]. Known compound, see: *J. Am. Chem. Soc*. **2001**, *123*, 9474.

Dihedral angle calculation:

Dihedral angles of ligands **1a**-**1h** were estimated by calculation using the B3LYP method with 6-31G* as basis sets. See, (a) Becke, A. D. *J. Chem. Phys*. **1993**, *98*, 5648. (b) Lee, C. T.; Yang, W. T.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. (c) Kong, J.; White, C. A.; Krylov, A. I.; Sherrill, C. D.; Adamson, R. D.; Furlani, T. R.; Lee, M. S.; Lee, A. M.; Gwaltney, S. R.; Adams, T. R.; Ochsenfeld, C.; Gilbert, A. T. B.; Kedziora, G. S.; Rassolov, V. A.; Maurice, D. R.; Nair, N.; Shao, Y.; Besley, N. A.; Maslen, P. E.; Dombroski, J. P.; Daschel, H.; Zhang, W.; Korambath, P. P.; Baker, J.; Byrd, E. F. C.; Van Voorhis, T.; Oumi, M.; Hirata, S.; Hsu, C.-P.; Ishikawa, N.; Florian, J.; Warshel, A.; Johnson, B. G.; Gill, P. M. W.; Head-Gordon, M.; Pople, J. A. *J. Computational Chem*. **2000**, *21*, 1532. Spartan'02 for Mac Wavefunction, Inc.; Irvine, CA.

Scheme SI-1 Synthesis of 1a



a) i) *n*BuLi, TMEDA, THF, –78 to 0°C, 4 h; ii) $FeCl_3$, 0°C to RT, 2 h; b) BBr_3, CH_2Cl_2 –78°C to RT;
c) (*S*)-1,2-propanediol bismesylate, $CsCO_3$, DMF, 80°C, 16 h; d) Br-$(CH_2)_2$-O-$(CH_2)_2$-Br, K_2CO_3, DMF, 80 °C, 9 h;
e) LDBB, THF, 0°C, 1 h

2,2',6,6'-Tetramethoxybiphenyl (A): To a mixture of 1,3-dimethoxybenzene **6** (27.6 g, 200 mmol) and TMEDA (36.3 mL, 240 mmol) in THF at –78 °C was slowly added a solution of *n*BuLi (1.5 M in hexane,140 mL, 210 mmol). After being stirred for 2 h at –78 °C, the reaction mixture was warmed to 0 °C. After being stirred for 1 h 0 °C, $FeCl_3$ (38.9 g, 240 mmol) was added, and the reaction mixture was warmed to room temperature. After 36 h, *aq*. 1 M HCl was added and the resulting solid (target molecule **A**) was collected by filtration. The filtrate was extracted with diethyl ether (x 3), washed with brine, and dried over Na_2SO_4. After removing solvent under reduced pressure, the residue was washed with ethyl acetate to give the biphenyldiol **A**. 2,2',6,6'-tetramethoxybiphenyl **(A)** was obtained in 69% total yield (19.0 g). **A** was used for the next step without further purification.

2,2',6,6'-Tetrahydroxybiphenyl (7): To a solution of 2,2',6,6'-tetramethoxybiphenyl (**A**) (11.1 g, 42.7 mmol) in CH_2Cl_2 (215 mL) at –78 °C was slowly added boron tribromide (50 g, 200 mmol). The reaction mixture was gradually warmed to room temperature over 2 h, and stirred for 24 h at room temperature. After complete consumption of the starting material, the reaction mixture was quenched by H_2O. The water layer was extracted with ether (x 2). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give 2,2',6,6'-tetrahydroxybiphenyl (**7**) as a yellow solid (7.67 g, 87%). **7** is the known compound see: *Org. Lett.* **2000**, *2*, 1319.

(a*S*,*R*)-6,6'-[(Propylene)dioxy]biphenyl-2.2'-diol (8): (a*S*,*R*)-**8** was synthesized by the following literature. See: *Org*. *Lett*. **2000**, *2*, 1319.
To a suspention of 2,2',6,6'-tetrahydroxybiphenyl (**7**) (1.77 g, 8.12 mmol) and Cs_2CO_3 (6.08 g, 18.67 mmol) in DMF (232 mL) at 80 °C was added slowly a solution of (*S*)-propanediol bis(mesylate) (1.89 g, 8.12 mmol) in DMF (81 mL) over 4 h. The resulting suspension was stirred further for 12 h at 80 °C. Most of the solvent was removed by distillation under reduced pressure. The residue was poured into aqueous 1 M HCl and extracted with diethyl ether. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by flash column chromatography (SiO_2, 5-40% ethyl acetate in hexane) gave (a*S*,*R*)-**8** (1.43 g, 68%).

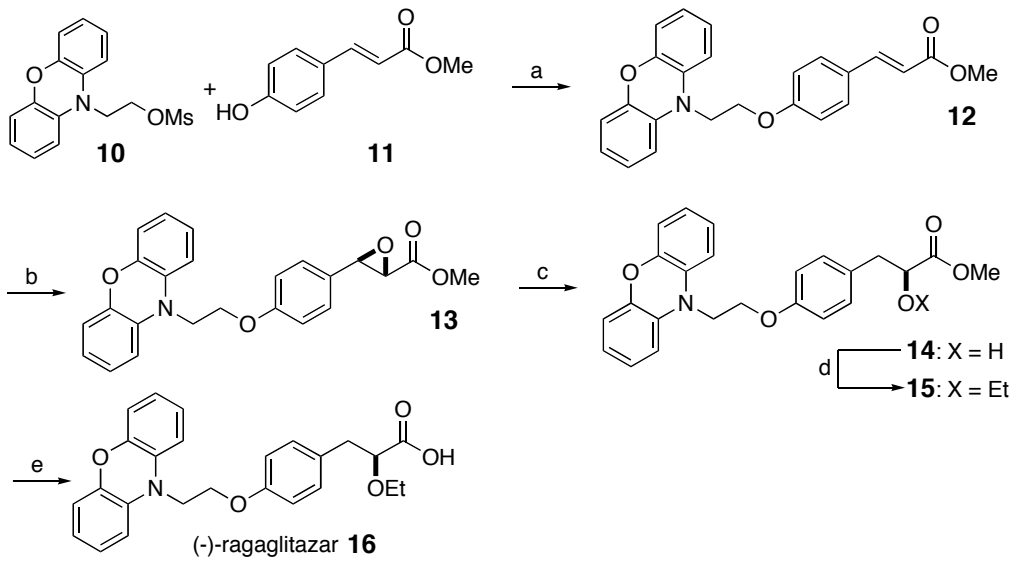
(a*S*,*R*)-2.2-[Oxybis(ethylene)dioxy]-6,6'-[(propylene)dioxy]biphenyl (9): To a mixture of .(a*S*,*R*)-**8** (600 mg, 2.4 mmol) and K_2CO_3 (720 mg, 5.52 mmol) in DMF (150 mL) at 80 °C was added a solution of 2-bromoethyl ether (553 μL, 4.8 mmol) in DMF (4 mL) during 4 h by using syringe pump and stirred for 5 h at the same temperature. After the reaction mixture was cooled down to room temperature, aqueous 1 M HCl was added and the solution was extracted with benzene (x 3). The combined organic layers were washed with brine, and dried over Na_2SO_4. After removing solvent under reduced pressure, the residue was purified by flash column chromatography (SiO_2, hexane/ethyl acetate = 20/1 to 4/1) to give (a*S*,*R*)-**9** (558.0 mg, 70%) as a colorless solid. IR (KBr) ν 2959, 2927, 2858, 1589, 1574, 1459, 1442, 1274, 1242, 1222, 1136, 1096, 1082, 838, 751, 723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (d, *J* = 6.4 Hz, 3H), 3.62-3.66 (m, 1H), 3.77-3.81 (m, 2H), 3.84-3.88 (m, 2H), 4.08-4.12 (m, 2H), 4.15-4.19 (m, 1H), 4.25-4.29 (m, 3H), 6.61-6.63 (m, 2H), 6.73-6.74 (m, 2H), 7.19-7.23 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 17.2, 69.7, 69.7, 72.5, 72.5, 78.9, 80.6, 107.4, 107.5, 114.8, 114.8, 117.8, 117.8, 129.2, 129.3, 156.2, 156.2, 160.0, 160.4 ESI-MS *m/z* 351 $[M+Na]^+$; HR-MS [FAB(+)] calcd for $C_{19}H_{21}O_5^+$ $[M+H]^+$: 329.1389. Found 329.1387.

Synthesis of (*S*)-6,6'-[oxybis(ethylene)dioxy]biphenyl-2,2'-diol (1a): A solution of lithium 4,4'-di-*tert*-butylbiphenyl (LDBB) in THF (0.34 M) was prepared by the reaction of Li (140 mg, 20 mmol) with 4,4'-di-*tert*-butylbiphenyl (16.9 mmol) in THF (50 mL) at 0 °C. To a reaction flask containing (a*S*,*R*)-**9** (656.0 mg, 2 mmol) at 0 °C was added the LDBB solution in THF (25 mL). After being stirred for 1 h, *aq*. 1 M HCl was added and the solution was extracted with diethyl ether (x 3). The combined organic layers were washed with brine, and dried over Na_2SO_4. After concentration

under reduced pressure, the residue was purified by flash column chromatography (SiO_2, hexane/ethyl acetate = 20/1 to 3/1) to give (*S*)-**1a** (426.3 mg, 74%, 98% ee) as a colorless solid. The enantiomeric excess of (*S*)-**1a** was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALCEL OD-H, *i*-PrOH/hexane 1/4, flow rate 1.0 mL/min, t_R 14.0 min (*R*) and 21.3 min (*S*), detection at 254 nm].

Enantiomeric Enrichment of (*S*)-1a: To a reaction flask containing (*S*)-**1a** (225.6 mg, 0.78 mmol) and quinine (127.0 mg, 0.39 mmol) was added ethanol (1.56 mL). The mixture suspension was heated until the mixture turned to clear solution and was settled at room temperature for 12 h to afford (*S*)-**1a**-quinine complex. To a mixture of *aq.* 1 M HCl and diethyl ether, was added the obtained crystal of (*S*)-**1a**-quinine complex, the mixture was stirred for 15 min at room temperature, and the solution was extracted with diethyl ether (x 2). The combined organic layers were washed with brine, and dried over Na_2SO_4. After removing solvent under reduced pressure, the residue was purified by flash column chromatography (SiO_2, hexane/ethyl acetate = 20/1 to 3/1) to give (*S*)-**1a** (167.8 mg, 74%, 99% ee) as a colorless solid. (*S*)-**1a**: IR (KBr) ν 3387, 2929, 1600, 1579, 1459, 1254, 1187, 1131, 1087, 779 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.66 (dd, *J* = 12.7, 6.3 Hz, 2H), 3.75 (dd, *J* = 12.7, 5.6 Hz, 2H), 4.08 (dd, *J* = 12.2, 5.6 Hz, 2H), 4.23 (dd, *J* = 12.2, 6.3 Hz, 2H), 5.15 (br-s, 2H), 6.48 (d, *J* = 8.3 Hz, 2H), 6.62 (d, *J* = 8.3 Hz, 2H), 7.18 (dd, *J* = 8.3, 8.3 Hz, 1H), 7.19 (dd, *J* = 8.3, 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 69.9, 72.0, 105.6, 108.7, 109.1, 130.1, 154.4, 157.4. The enantiomeric excess of (*S*)-**1a** was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALCEL OD-H, *i*-PrOH/hexane 1/4, flow rate 1.0 mL/min, t_R 14.0 min (*R*)] and 21.3 min (*S*), detection at 254 nm]; $[\alpha]_D^{22}$ +136.2 [c 0.89 $CHCl_3$ (99% ee)]; ESI-MS *m/z* 311 $[M+Na]^+$; HR-MS [FAB(+)] calcd for $C_{16}H_{17}O_5^+$ $[M+H]^+$: 289.1076. Found 289.1080.

Scheme SI-2 Synthesis of (–)-ragaglitazar



Reagents and conditions: a) **10** (1 equiv), **11** (1 equiv), K_2CO_3 (2 equiv), xylene, 130 °C, 23 h, 83%; b) $Y(OiPr)_3$ (5 mol %), (*R*)-**1a** (5 mol %), $Ph_3As(O)$ (5 mol %), TBHP (1.2 equiv), THF, RT, 48 h; c) Pd/C (10 mol %), H_2, ethyl acetate, RT, 24 h, 64% (2 steps from **12**); d) $Et_3O^+BF_4^-$, proton sponge, CH_2Cl_2, 0 °˜C, 82%; e) 3 M *aq.* NaOH, MeOH, RT, 4 h, 98%.

3-[4-(2-Phenoxazin-10-yl-ethoxy)-phenyl]-acrylic acid methyl ester (12): To a mixture of *p*-hydroxy cinnamic acid methyl ester **11** (0.623 g, 3.5 mmol) and K_2CO_3, (0.967 g, 7.0 mmol) in xylene (12 mL) was added 2-(Phenoxazin-10-yl)ethyl methanesulfonate **10** (1.06 g, 3.5 mmol). The mixture was stirred at 130 °C for 23 h. After the reaction mixture was cooled down to room temperature, *sat. aq.* NH_4Cl was added and the solution was extracted with ethyl acetate (x 2). The combined organic layers were washed with H_2O and brine, and dried over Na_2SO_4. After removing solvent under reduced pressure, the residue was purified by flash column chromatography (SiO_2, hexane/ethyl acetate = 10/1) to give **12** (1.13 g, 83%) as a yellow solid: IR (neat) ν 3065, 2950, 1718, 1604, 1509, 1380, 1256, 1173, 1037, 822, 723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.98 (s, 3H), 3.99 (t, *J* = 6.8 Hz, 2H), 4.22 (t, *J* = 6.8 Hz, 2H), 6.31 (d, *J* = 15.9 Hz, 1H), 6.61-6.68 (m, 6H), 6.78-6.82 (m, 2H), 6.88-6.90 (m, 2H), 7.45-7.47 (m, 2H), 7.64 (d, *J* = 15.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 43.9, 51.6, 63.7, 111.6, 114.9, 115.6, 115.6, 115.7, 121.4, 121.5, 123.6, 127.7, 129.7, 129.8, 133.1, 144.3, 144.9, 144.9, 167.7, 169.9; ESI-MS *m/z* $[M+Na]^+$ 410; HR-MS [FAB(+)] calcd for $C_{24}H_{21}O_4N_1^+$ $[M]^+$: 387.1465. Found 387.1476.

(*S*)-2-Hydroxy-3-[4-(2-phenoxazin-10-yl-ethoxy)-phenyl]-propionic acid methyl ester (14): MS 4A was dried for 3 h at 180 °C under reduced pressure. To a mixture of

MS 4A (150 mg), (*R*)-biphenyldiol **1a** (4.32 mg, 0.015 mmol) and triphenylarsine oxide (4.83 mg, 0.015 mmol) in THF (0.675 mL) at room temperature, was added $Y(O\text{-}i\text{-}Pr)_3$ (75 μL, 0.015 mmol, 0.2 M solution in THF). After being stirred for 45 min at room temperature, TBHP (90 μL, 0.36 mmol, 4.0 M solution in toluene) was added. After being stirred for 10 min, **12** (116.2 mg, 0.3 mmol) was added and the mixture was stirred at room temperature. After 48 h, the reaction mixture was passed through short pad silica gel (eluted with 50 mL of ethyl acetate), and the eluate was concentrated under reduced pressure to afford crude epoxide **13**. To the crude mixture, was added dry ethyl acetate (3 mL) and Pd/C (31.8 mg, 0.03 mmol). The reaction mixture was stirred at room temperature for 24 h under H_2 atmosphere (1 atm). After dilution with ethyl acetate, the resulting mixture was filtered by short pad of celite (eluted with 50 mL ethyl acetate. After evaporation, the residue was purified by flash column chromatography (SiO_2, hexane/ethyl acetate = 10/1 to 5/1) to give **14** (77.4 mg, 64%, 98% ee in 2 steps from **12**) as a yellow oil: IR (neat) ν 3497, 3065, 2979, 1729, 1510, 1490, 1376, 1274, 1245, 1106, 741 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.71 (m, 3H), 2.90 (dd, J = 14.0, 6.4 Hz, 2H), 3.05 (dd, J = 14.0, 4.6 Hz, 1H), 3.94 (t, J = 6.8 Hz, 2H), 4.15 (t, J = 6.8 Hz, 2H), 4.40 (m, 1H), 6.60-6.68 (m, 6H), 6.77-6.83 (m, 4H), 7.10-7.12 (m, 2H); ^{13}C NMR ($CDCl_3$); 39.6, 43.9, 52.4, 63.4, 72.3, 111.6, 114.4, 115.5, 121.3, 123.6, 128.9, 130.5, 133.1, 144.8, 157.4, 174.5; ESI-MS *m/z* $[M+Na]^+$ 428; HR-MS [FAB(+)] calcd for $C_{24}H_{23}O_5N_1^+$ $[M]^+$: 405.1571. Found 387.405.1570. The enantiomeric excess of (*S*)-**14** was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AD-H, *i*-PrOH/hexane 1/9, flow rate 1.0 mL/min, t_R 28.6 min (R)] and 31.1 min (*S*), detection at 254 nm); $[\alpha]_D^{26}$ –7.7 [c 1.02 $CHCl_3$ (98% ee)].

(*S*)-2-Ethoxy-3-[4-(2-phenoxazin-10-yl-ethoxy)-phenyl]-propionic acid methyl ester (15): To a mixture of **14** (35.9 mg, 0.089 mmol) and proton sponge (84.9 mg, 0.445 mmol) in dry CH_2Cl_2 was added triethyloxonium tetrafuluoroborate (1 M in CH_2Cl_2, 440 μL, 0.445 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 48 h. The mixture was passed through short pad of silica gel (eluted with 50 mL of ethyl acetate), and the eluate was evaporated. The residue was purified by flash column chromatography (SiO_2, hexane/ethyl acetate = 10/1) to give **15** (31.7 mg, 82%). $[\alpha]_D^{29}$ –13.3 [c 0.39 $CHCl_3$ (98% ee)] lit. $[\alpha]_D^{25}$ –9.6 [*c* 1.9, $CHCl_3$, (95% ee)] Known compound, see: *J. Org. Chem.* **2005**, *70*, 9470.

(–)-ragaglitazar (16): To a mixture of **15** (18.4 mg, 0.0423 mmol) in MeOH (400 μL), was added 3 M NaOH (350 μL) at room temperature. After being stirred for 4 h at room

temperature, H_2O was added, and washed with diethyl ether. The water layer was acidified with 1 M HCl, and the solution was extracted by ethyl acetate (x 3) The combined organic layers were washed with H_2O and brine, and dried over Na_2SO_4. After concentration in *vacuo,* (–)-ragaglitazar was obtained (17.4 mg, 98%). $[\alpha]_D^{29}$ –9.6 [c 0.54 $CHCl_3$] lit. $[\alpha]_D^{25}$ –8.7 [*c* 1.0, $CHCl_3$, (95% ee)] Known compound, see: *J. Org. Chem.* **2005**, *70*, 9470.

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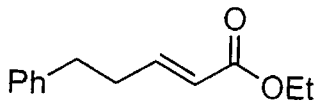

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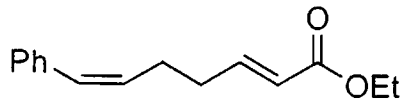

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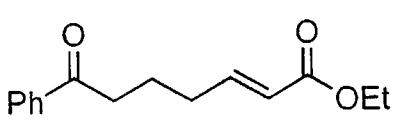

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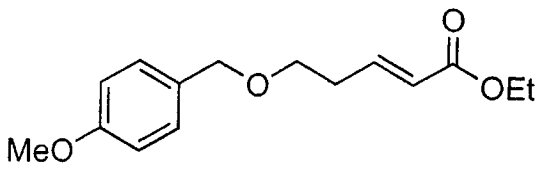

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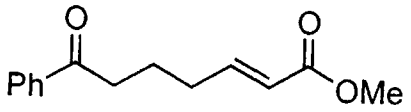

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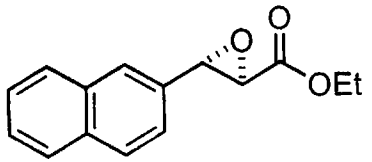

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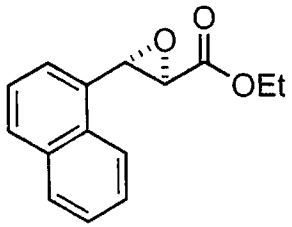

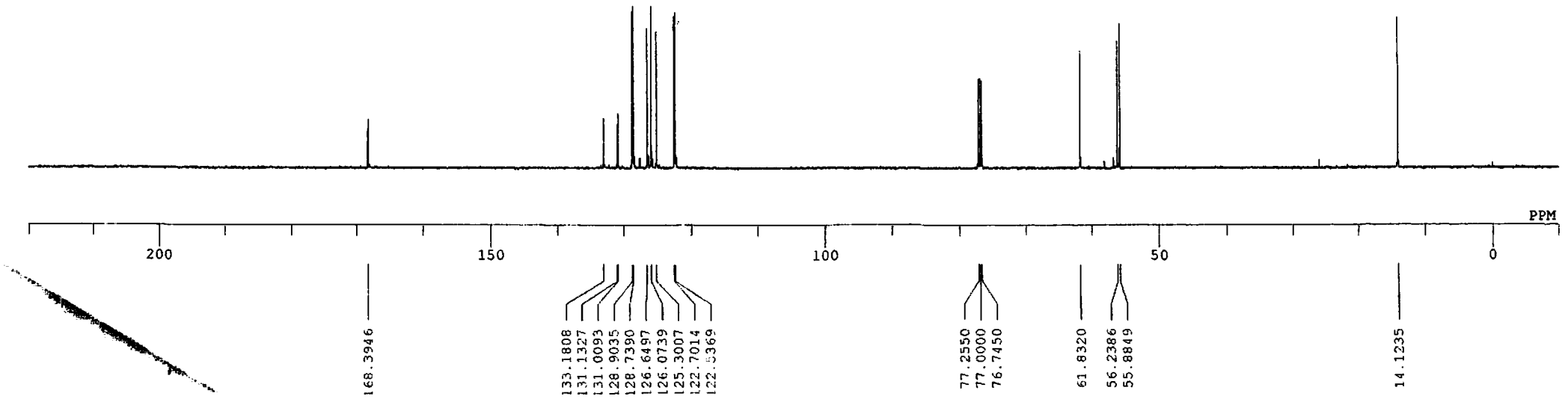

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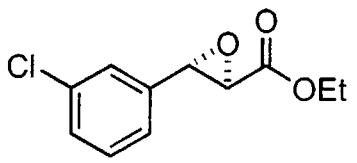

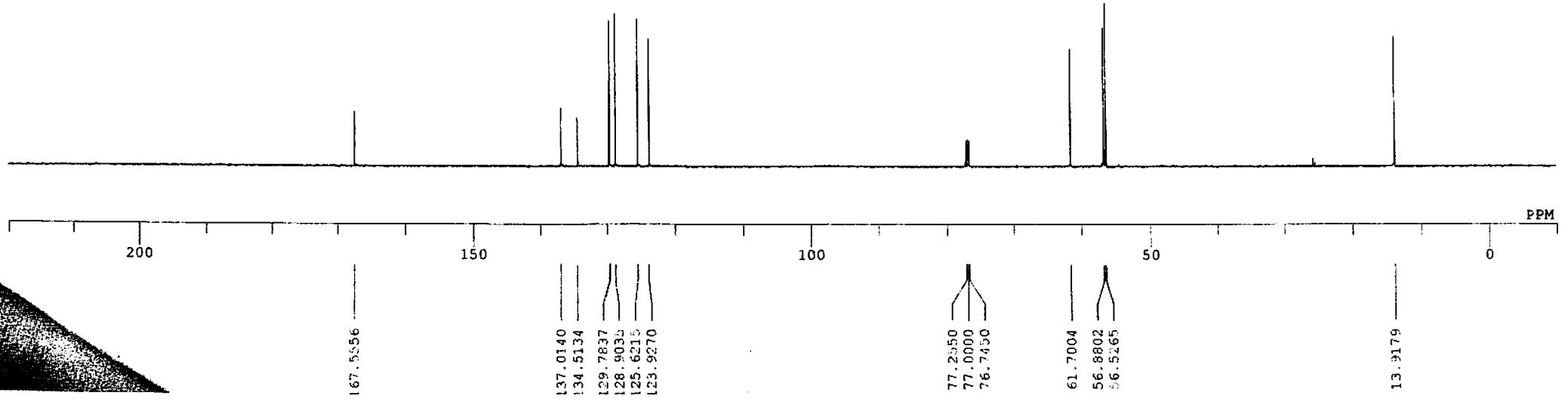

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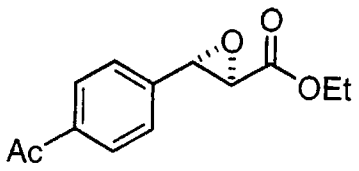

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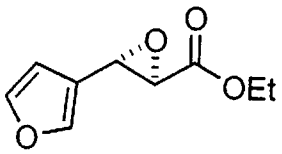

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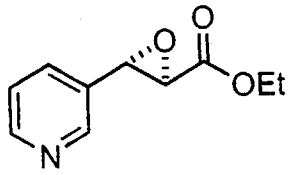

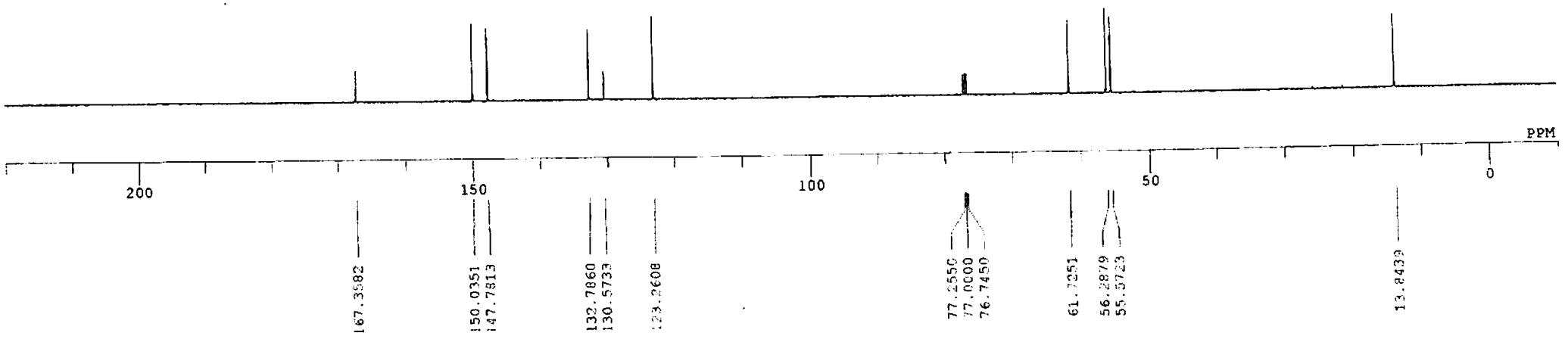

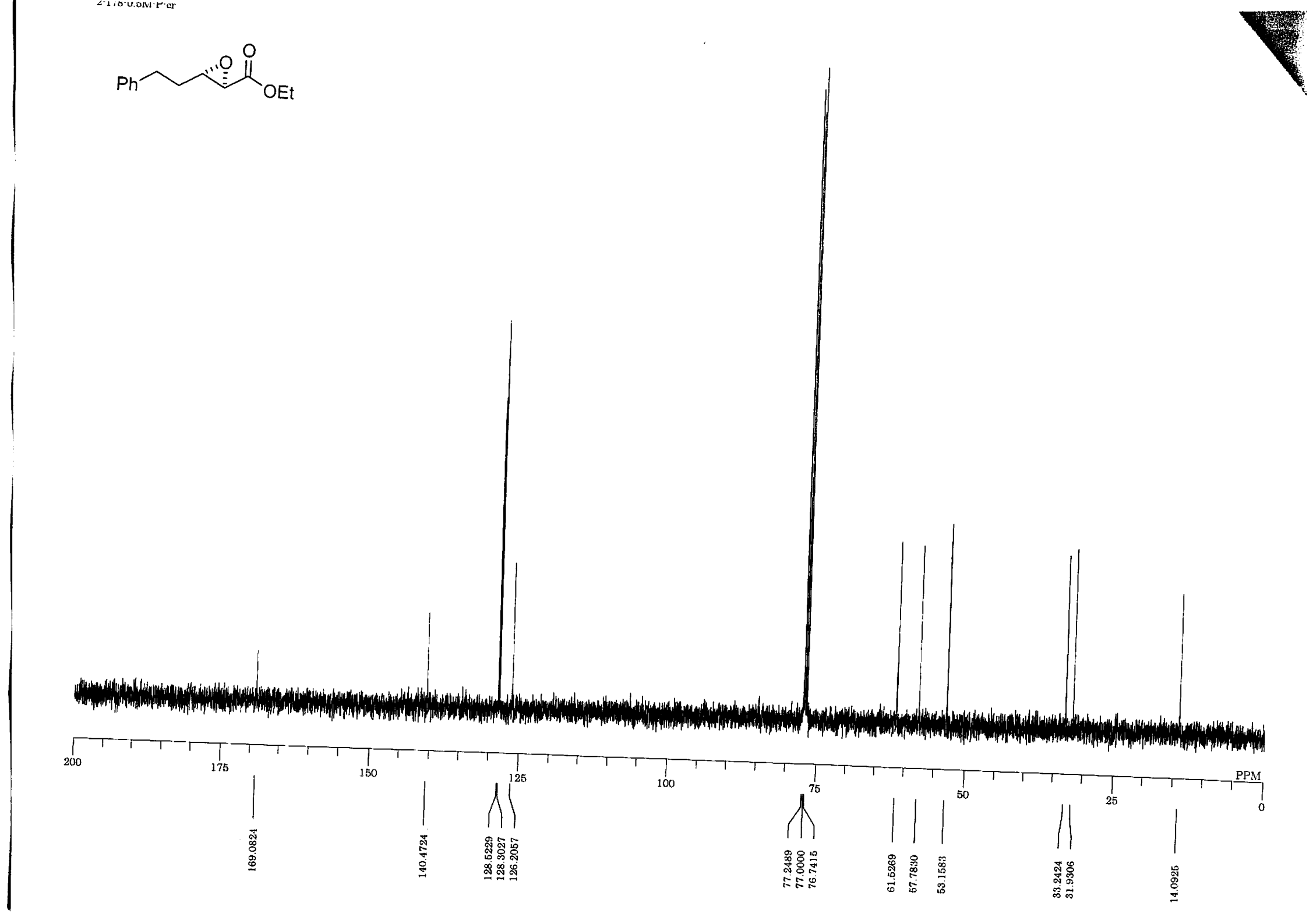
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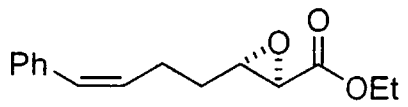

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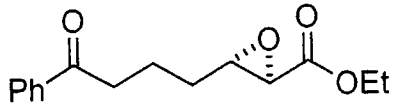

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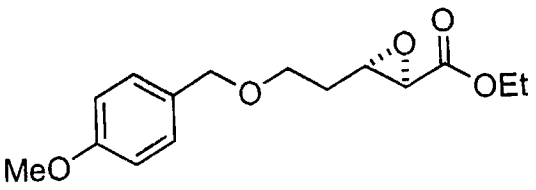
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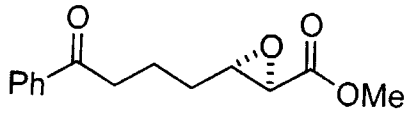

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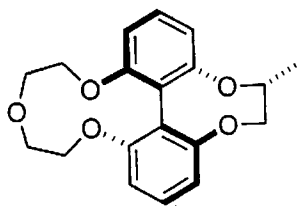

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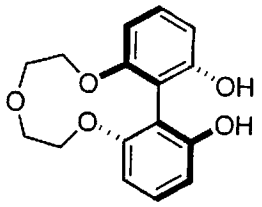

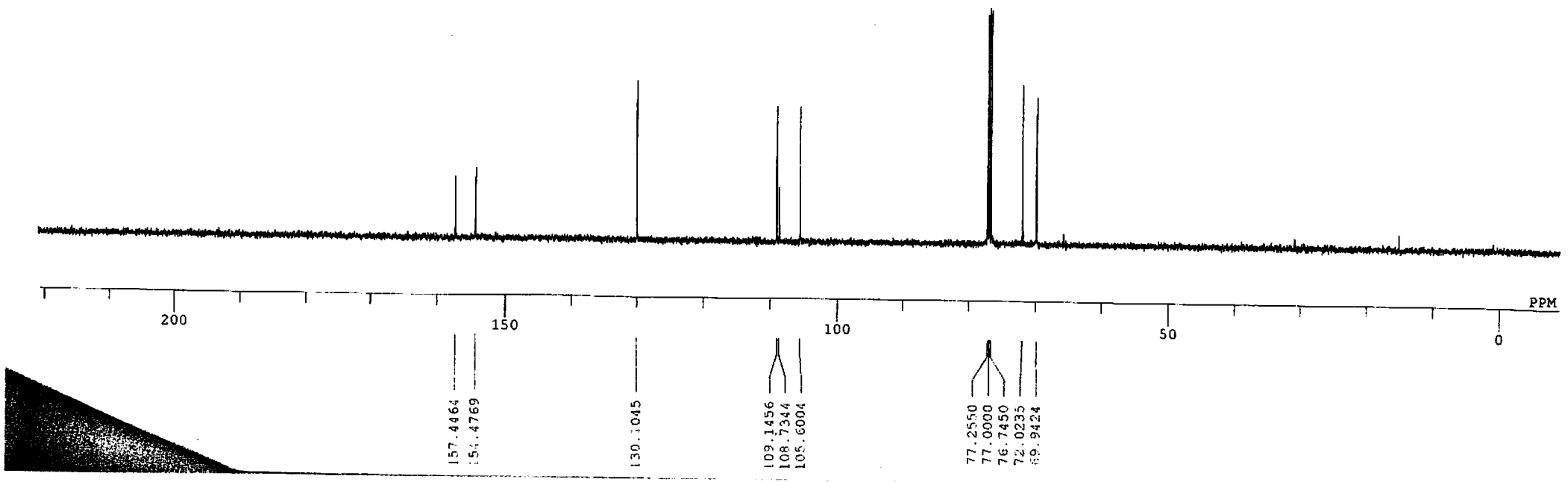

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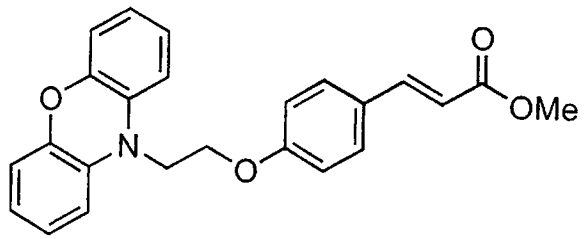

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