Supporting Information

© Copyright Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, 2007
Supporting Information

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

Hiroyuki Kakei, Riichiro Tsuji, Takashi Ohshima, Hiroyuki Morimoto, Shigeki Matsunaga, and Masakatsu Shibasaki*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan); E-mail: mshibasa@mol.f.u-tokyo.ac.jp

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 1H NMR and 125.65 MHz for 13C NMR. Chemical shifts in CDCl3 were reported downfield from TMS (= 0 ppm) for 1H NMR. For 13C NMR, chemical shifts were reported downfield from TMS (= 0 ppm) or in the scale relative to CHCl3 (77.00 ppm for 13C 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(OiPr)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(OiPr)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)-Ethyl 5-phenylpent-2-enoate (2m): colorless oil; IR (neat) ν 1720, 1654, 1267, 1197, 700 cm⁻¹; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) δ 14.2, 26.9, 32.3, 60.2, 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 C₁₅H₁₇O₂⁺ [M+H]⁺: 205.1229. Found 205.1232.

(2E,6Z)-Ethyl 7-phenylhexa-2,6-dienote (2n): colorless oil; IR (neat) ν 1720, 1654, 1266, 700 cm⁻¹; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 C₁₅H₁₉O₂⁺
(E)-Ethyl 7-oxo-7-phenylhept-2-enoate (2o): colorless oil; IR (neat) v 1718, 1686, 1367, 1201, 691 cm⁻¹; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 C₁₅H₁₉O₃⁺ [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⁻¹; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 C₁₅H₂₀O₄⁺ [M⁺]: 264.1362. Found 264.1364, for C₁₅H₂₁O₄⁺ [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 Na₂SO₄. After removing solvent under reduced pressure, the residue was purified by flash column chromatography (SiO₂, 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 (SiO₂, hexane/ethyl acetate = 100/1 to 50/1) to give methyl ester 2u (1.31 g, 96%) as a colorless oil.


(2E, 6Z)-Methyl 7-phenylhepta-2,5-dienoate (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 (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 C₁₅H₁₇O₃⁺ [M+H]⁺: 233.1172. Found 233.1171.


General Procedure for Catalytic Asymmetric Epoxidation of α,β-Unsaturated Esters Using Y(OiPr)₃: Biphenyldiol 1a : Ph₃As(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(OiPr)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$_2$SO$_4$. 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, $t_R$ 31.6 min (2S,3R)-isomer) and 38.0 min (2R,3S)-isomer, detection at 254 nm]; $[\alpha]_b^{24}$ = -158.8 (c 1.06 CHCl$_3$). lit. $[\alpha]_b^{25}$ +160.1 [c 1.15, CHCl$_3$, 96% ee, (2S,3R)]. See: ref $^{[7b]}$. *J. Am. Chem. Soc.* 2002, 124, 8792.

**Methyl (2R,3S)-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]; $[\alpha]_b^{20}$ = -132.6 (c 0.44 CHCl$_3$). lit. $[\alpha]_b^{25}$ = -111.8 [c 1.17, CHCl$_3$, (2R,3S) (92% ee)]. Known compound, see: *J. Am. Chem. Soc.* 2001, 123, 9474.

**Ethyl (2R,3S)-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$^{-1}$; $^{1}$H 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, $J = 8.1$, 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, 127.8, 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+Na]$^+$: 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]; $[\alpha]_b^{24}$ = -170.3 (c 1.50 CHCl$_3$).

**Ethyl (2R,3S)-3-naphthalen-1-yl-oxirane-2-carboxyate (3d):** colorless oil; IR (neat) ν 3059, 2982, 1748, 1200, 800, 776 cm$^{-1}$; $^{1}$H 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+Na]$^+$: 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 CHCl₃).

**Ethyl (2R,3S)-3-(3-chlorophenyl)oxirane-2-carboxylate (3e):** colorless oil; IR (neat) \(v\) 2984, 1748, 1444, 1286, 1028, 786, 687 cm\(^{-1}\); \(^1\)H NMR (CDCl₃) \(\delta\) 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); \(^1\)C NMR (CDCl₃) \(\delta\) 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\(_3\)Cl\(^+\) [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 CHCl₃).

**Ethyl (2R,3S)-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 CHCl₃). Known compound, see: *J. Am. Chem. Soc.* 2002, 124, 8792.

**Ethyl (2R,3S)-3-(4-acetylphenyl)oxirane-2-carboxylate (3g):** colorless oil; IR (neat) \(v\) 2984, 1748, 1685, 1266, 1202, 1026 cm\(^{-1}\); \(^1\)H NMR (CDCl₃) \(\delta\) 1.34 (t, \(J = 7.2\) Hz, 3H), 2.61 (s, 3H), 3.51 (d, \(J = 1.8\) Hz, 1H), 4.16 (d, \(J = 1.8\) Hz, 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); \(^1\)C NMR (CDCl₃) \(\delta\) 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 CHCl₃).

**Ethyl (2R,3S)-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 CHCl₃). Known compound, see: *J. Am. Chem. Soc.* 2002, 124, 8792.
Ethyl (2R,3S)-3-(4-methoxyphenyl)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$_3$). Known compound, see: J. Am. Chem. Soc. 2002, 124, 8792.

Ethyl (2R,3S)-3-furan-3-yl-oxirane-2-carboxyate (3j): white-yellow solid; IR (KBr) $\nu$ 3141, 2985, 1731, 1424, 1308, 1164, 1026, 903, 876, 774 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_9$H$_{11}$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 (2R,3S)-3-pyridin-3-yl-oxirane-2-carboxylate (3k): yellow oil; IR (neat) $\nu$ 2984, 1747, 1288, 1204, 1025, 893, 799, 712 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_3$N$^+$ [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 (2R,3S)-3-thiophen-3-yl-oxirane-2-carboxylate (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 (2R,3S)-3-(2-phenylethyl)oxirane-2-carboxylate (3m): colorless oil; IR (neat) ν 1749, 1454, 1370, 1198, 1030, 803 cm⁻¹; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 C₁₃H₁₇O₂⁺ [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, tᵣ 8.8 min (major) and 9.3 min (minor), detection at 254 nm]; [α]D²² –39.4 (c 1.29 CHCl₃).

Ethyl (2R,3S)-3-[(3Z)-4-phenyl-3-butenyl]oxirane-2-carboxylate (3n): colorless oil; IR (neat) ν 1748, 1446, 1197, 1094 cm⁻¹; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) δ 14.1, 24.8, 31.6, 53.0, 57.9, 61.5, 126.8, 128.2, 130.1, 130.5, 137.1, 169.1; ESI-MS m/z 269 [M+Na]⁺; HR-MS [FAB(+)] calcd for C₁₅H₁₉O₃⁺ [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, tᵣ 10.0 min (minor) and 23.1 min (major), detection at 254 nm]; [α]D²² –13.1 (c 1.04 CH₂Cl₂).

Ethyl (2R,3S)-3-(4-oxo-4-phenylbutyl)oxirane-2-carboxylate (3o): colorless oil; IR (neat) ν 1748, 1685, 1200, 691 cm⁻¹; ¹H NMR (CDCl₃) 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, 1H), 7.55-7.58 (m, 1H), 7.95-7.97 (m, 2H); ¹³C NMR (CDCl₃) 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 C₁₅H₁₉O₄⁺ [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, tᵣ 35.4 min (minor) and 38.0 min (major), detection at 254 nm]; [α]D²² –25.2 (c 0.98 CHCl₃).

Ethyl (2R,3S)-3-[2-(4-Methoxybenzyloxy)ethyl]oxirane-2-carboxylate (3p): colorless oil; IR (neat) ν 2929, 1748, 1612, 1370, 819 cm⁻¹; ¹H NMR (CDCl₃) 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); 13C 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 15H20O5 [M]+: 280.1311. Found 280.1311, for C 15H21O5 [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]; [α] 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(OiPr)3: (S)-binol : Ph3P(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(OiPr)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 Na2SO4. After removing solvent under reduced pressure, the residue was purified by flash chromatography (SiO2, hexane/ethyl acetate = 100/1 to 50/1) to give epoxy ester 3r (89.5 mg, 87%) as a colorless 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]; [α] D 25 –44.4 (c 1.47 CHCl 3). lit. [α] D 25 –33.5 [c 0.82, CHCl3, (83% ee)] Known compound, see: J. Am. Chem. Soc. 2001, 123, 9474.

Methyl (2R,3S)-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]; [α] D 25 –23.0 (c 0.55, CHCl3). lit. [α] D 25 –33.5 [c 0.82, CHCl3, (83% ee)] Known compound, see: Tetrahedron. 2003, 59, 10485.

Methyl (2R,3S)-3-[(3Z)-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]; \([\alpha]_D^{20} –20.0 \) (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 (2R,3S)-3-(4-oxo-4-phenylbutyl)oxirane-2-carboxylate (3u):** pale yellow solid: IR (KBr) ν 2923, 1752, 1684, 1448, 1204 cm\(^{-1}\); \(^1\)H 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); \(^1^3\)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 excess 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 (2S,3R) and 18.3 min (2R, 3S), 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), (2R,3S)]. Known compound, see: J. Am. Chem. Soc. 2001, 123, 9474.

**Dihedral angle calculation:**

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 nBuLi (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, FeCl₃ (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 Na₂SO₄. After removing solvent under reduced pressure, 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 CH₂Cl₂ (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 H₂O. The water layer was extracted with ether (x 2). The combined organic layers were washed with brine, dried over Na₂SO₄, 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.
(aS,R)-6,6’-[(Propylene)dioxy]biphenyl-2,2'-diol (8): (aS,R)-8 was synthesized by the following literature. See: *Org. Lett.*, 2000, 2, 1319.

To a suspension of 2,2’,6,6’-tetrahydroxybiphenyl (7) (1.77 g, 8.12 mmol) and Cs₂CO₃ (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 Na₂SO₄ and concentrated under reduced pressure. Purification of the residue by flash column chromatography (SiO₂, 5-40% ethyl acetate in hexane) gave (aS,R)-8 (1.43 g, 68%).

(aS,R)-2,2’-[Oxybis(ethylene)dioxy]-6,6’-[(propylene)dioxy]biphenyl (9): To a mixture of (aS,R)-8 (600 mg, 2.4 mmol) and K₂CO₃ (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 Na₂SO₄. After removing solvent under reduced pressure, the residue was purified by flash column chromatography (SiO₂, hexane/ethyl acetate = 20/1 to 4/1) to give (aS,R)-9 (558.0 mg, 70%) as a colorless solid.

IR (KBr) ν 2959, 2927, 2858, 1589, 1459, 1442, 1274, 1242, 1222, 1136, 1096, 1082, 838, 751, 723 cm⁻¹; ¹H NMR (CDCl₃) 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), 4.61-4.63 (m, 2H), 5.73-5.74 (m, 2H), 6.19-6.23 (m, 2H); ¹³C NMR (CDCl₃) 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 C₁₉H₂₁O₅⁺ [M+Na]^+: 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 (aS,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 Na₂SO₄. After concentration
under reduced pressure, the residue was purified by flash column chromatography (SiO₂, 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, tᵣ 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 Na₂SO₄. After removing solvent under reduced pressure, the residue was purified by flash column chromatography (SiO₂, 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 (CDCl₃) 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); ¹³C NMR (CDCl₃) 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, tᵣ 14.0 min (R)] and 21.3 min (S), detection at 254 nm]; [α]D₂² +136.2 [c 0.89 CHCl₃ (99% ee)]; ESI-MS m/z 311 [M+Na]⁺; HR-MS [FAB(+)] calcd for C₁₆H₁₇O₅⁺ [M+H]⁺: 289.1076. Found 289.1080.
Scheme SI-2 Synthesis of (−)-ragaglitazar

Reagents and conditions: a) 10 (1 equiv), 11 (1 equiv), K₂CO₃ (2 equiv), xylene, 130 °C, 23 h, 83%; b) Y(O)Pr₃ (5 mol %), (R)-1a (5 mol %), Ph₃As(O) (5 mol %), TBHP (1.2 equiv), THF, RT, 48 h; c) Pd/C (10 mol %), H₂, ethyl acetate, RT, 24 h, 64% (2 steps from 12); d) Et₃O⁺BF₄⁻, proton sponge, CH₂Cl₂, 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 K₂CO₃ (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. NH₄Cl was added and the solution was extracted with ethyl acetate (x 2). The combined organic layers were washed with H₂O and brine, and dried over Na₂SO₄. After removing solvent under reduced pressure, the residue was purified by flash column chromatography (SiO₂, 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 (CDCl₃) 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); ¹³C NMR (CDCl₃) δ 43.9, 51.6, 63.7, 111.6, 114.9, 115.6, 115.7, 115.8, 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 C₂₅H₂₁O₄N₁⁺ [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-i-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 H₂ 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 (SiO₂, 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 (CDCl₃) 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); ¹³C NMR (CDCl₃); 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 C₂₄H₂₃O₅N₁⁺ [M]: 405.1571. Found 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, tᵣ 28.6 min (R)] and 31.1 min (S), detection at 254 nm); [α]D²⁶ –7.7 [c 1.02 CHCl₃ (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 CH₂Cl₂ was added triethylxonium tetrafluoroborate (1 M in CH₂Cl₂, 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 (SiO₂, hexane/ethyl acetate = 10/1) to give 15 (31.7 mg, 82%). [α]D²⁹ –13.3 [c 0.39 CHCl₃ (98% ee)] lit. [α]D²⁵ –9.6 [c 1.9, CHCl₃, (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$_2$O 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$_2$O and brine, and dried over Na$_2$SO$_4$. After concentration in vacuo, (–)-ragaglitazar was obtained (17.4 mg, 98%). [α]$^25$ –9.6 [c 0.54 CHCl$_3$] lit. [α]$^25$ –8.7 [c 1.0, CHCl$_3$, (95% ee)] Known compound, see: J. Org. Chem. 2005, 70, 9470.