A Direct Catalytic Asymmetric Mannich-type Reaction via a Dinuclear Zinc Catalyst: Synthesis of Either *anti*- or *syn*-β-Amino Alcohols

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Supplemental Information

Experimental Section

General

All reactions were performed under an atmosphere of nitrogen or argon, unless otherwise indicated. Solvents were freshly purified by passage through an aluminum column before used. Diethylzinc (Et_2Zn) was purchased from Aldrich (Sure/Seal bottle 1.1 M in toluene). Chiral lingds **1a-c** were synthesized as reported before.[s1]

Flash chromatography was performed on silica gel (EM Science, Kieselgel 60, 230-400 mesh, ASTM) or neutral alumina (Fluka, aluminum Oxide, type 507, Brockmann grade III, 6% hydrate) using compressed air. Radial chromatography on a chromatotron was performed with Merck silica gel 60 F_{254} (Art.7749). Analytical thin layer chromatography was performed using glass-backed plates coated with 0.2 mm silica (E. Merck, DC-Plasrikfolien, kieselgel 60 F_{254}). Melting points were determined in open capillary tubes using a Thomas-Hoover apparatus. NMR spectra were obtained on Varian Germini-200 (200 MHz) and 300 (300 MHz), Mercury-400 (400 MHz) or Unity Inova-500 (500 MHz) instruments and are calibrated to TMS (0 ppm) or residual solvent peak: proton (chloroform 7.26 ppm) and carbon (chloroform 77.1 ppm). Infrared (IR) data were recorded as films on sodium chloride plates on a Perkin-Elmer Paragon 500 FT-IR spectrometer. Elemental analyses (Anal.) were performed by M.-H.-W. Laboratories, Pheonix, Arizona. High resolution mass spectra (HRMS) were obtained from the Mass Spectrometry Resource, School of Pharmacy, University of California-San Francisco on a Kratos MS9 spectrometer. Chiral HPLC analyses were performed on a Thermo Separation Products Spectra Series P-100 or P-200 and UV100 (254 nm) using Chiralcel columns (AD, OD), or Chiralpak column (AS) eluting with heptane/*iso*-propanol mixtures indicated. Optical rotations were measured on a Jasco DIP-1000 digital polarimeter using 5 cm cells and the sodium D line (589 nm) at ambient temperature in the solvent and concentration indicated.

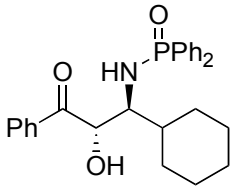
Asymmetric Mannich-type reaction

General procedure for the catalytic asymmetric Mannich-type reaction with Dpp-imine 4 promoted by dinuclear zinc catalyst 2.

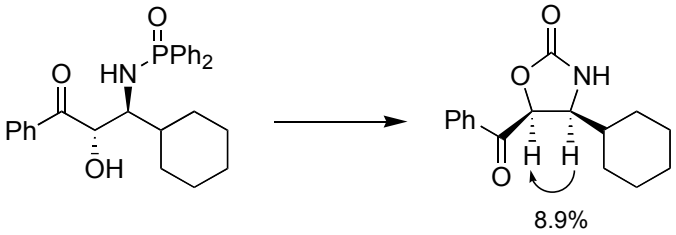
4Å Crushed molecular sieves (60 mg) were flame-dried under vacuum. After cooling down to room temperature, ligand **1a** was added (7 mg, 0.0105 mmol) and nitrogen gas was refilled. THF (0.3 mL) was then added. To this suspension was added dropwise a solution of Et_2Zn (19 μL, 0.021 mmol, 1.1 M in Toluene) at room temperature and continued to stir for 30 minutes. After cooling down to -30 °C, a solution of hydroxyketone **3a** (82 mg, 0.60 mmol) in THF (0.35 mL) and Dpp-imine **4a**[S2-4] (93 mg, 0.3 mmol) in THF (0.35 mL) was added successively. After stirring at -30 °C for 24 hours, the reaction mixture was diluted with Et_2O (6 mL) and then a phosphate buffer (pH = 7) solution (3 mL) was added.

After stirring for 30 minutes, the phases were separated and the aqueous phase was extracted with Et_2O (1 mL x 2). The combined organics were washed with brine (1.5 mL), dried over $MgSO_4$, filtered and concentrated to give a crude mixture of the Mannich adducts. The diastereomeric ratio was determined by ^1H NMR analysis of the crude product. The crude mixture was purified by flash silica gel column chromatography [Petroleum ether/EtOAc 1:1 and then EtOAc 100 %] to yield **5a** [115 mg, 86% yield, *anti*/*syn* = >5:1, 94% ee (*anti* isomer)].

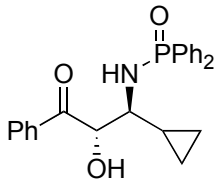
Synthesis of (2*S*, 3*S*)-3-cyclohexyl-2-hydroxy-1-phenyl-3-(*N*-diphenylphosphinoylamino)-1-propa-none (5a)



Compound **5a**: a white solid; m.p. 71-72 °C; R_f 0.39 (EtOAc); t_r = 25.1 min (minor) and 28.0 min (major), (Chiralcel AD, λ = 254 nm, heptane/*i*-PrOH = 84:16, 1.0 mL/min); $[\alpha]_D^{25}$ -2.8 (*c* 1.77, $CHCl_3$, 94% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 8.20-7.94 (m, 4H), 7.92 (dd, *J* = 8.1, 1.3 Hz, 2H), 7.59-7.44 (m, 7H), 7.41 (t, *J* = 8.0 Hz, 2 H), 5.32 (br s, 1H), 5.23 (br d, *J* = 5.0 Hz, 1H), 4.05 (dd, *J* = 12.0, 5.5 Hz, 1H), 3.22-3.12 (m, 1H), 2.11-2.03 (m, 1H), 1.74-1.66 (m, 2H), 1.59-1.50 (m, 2H), 1.50-1.42 (m, 1H), 1.29-1.22 (m, 1H), 1.22-1.11 (m, 1H), 1.10-0.97 (m, 2H), 0.96-0.84 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.6, 134.9, 133.8, 133.0, 132.9, 132.8, 132.2, 132.1, 132.0, 131.6, 129.1, 128.83, 128.78, 128.73, 128.6, 128.5, 75.0, 60.6, 40.3, 40.2, 31.2, 30.2, 26.2, 26.2, 26.1; IR (film): υ = 3331, 1679, 1597, 1439, 1266, 1180, 1123, 1129 cm^{-1}; HRMS (EI) *m/z* 447.1942 [M^+; calcd for $C_{27}H_{30}NO_3P$, 447.1963]. The relative stereochemistry of major diastereomer was determined to be *anti* by NOE observation (8.9%) as shown below, after conversion to the corresponding cyclic carbamate.[s5,s6] The absolute sterochemistry was determined by utilization of the amine in the O-methyl mandelic amide formation.[s7]



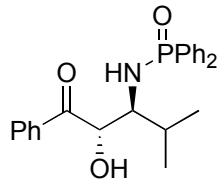
Synthesis of (2*S*, 3*S*)-3-cyclopropyl-2-hydroxy-1-phenyl-3-(*N*-diphenylphosphinoylamino)-1-propanone (5b)



Compound **5b**: a colorless oil; R_f 0.34 (EtOAc); t_r = 11.6 min (major) and 31.7 min (minor), (Chiralcel OD, λ = 254 nm, heptane/*i*-PrOH = 90:10, 1.0 mL/min); $[\alpha]_D^{24}$ +46.3 (c 1.50, $CHCl_3$, 83% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 8.09-7.92 (m, 4H), 7.78 (d, *J* = 7.5 Hz, 2H), 7.60-7.42 (m, 7H), 7.37 (t, *J* = 7.8 Hz, 2H), 5.38 (dd, *J* = 6.5, 2.0 Hz, 1H), 4.40 (d, *J* = 6.5 Hz, 1H), 3.97 (dd, *J* = 11.3, 7.3 Hz, 1H), 2.84-2.74 (m, 1H), 1.04-0.94 (m, 1H), 0.48-0.38 (m, 1H), 0.15-0.08 (m, 1H), -0.35- -0.43 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.3, 134.1, 134.0, 133.4, 132.7, 132.6, 132.5, 132.4, 132.1, 132.0, 131.7, 129.0, 128.8, 128.71, 128.68, 128.6, 128.5, 77.6, 59.7, 12.3, 12.2, 5.0, 3.4; IR (film): υ = 3334, 1681, 1596,

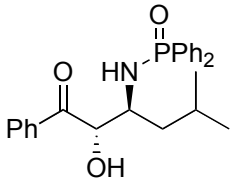
1438, 1268, 1189, 1122, 1073, 967 cm^{-1}; LRMS (ESI) *m/z* 406.2 {$[M+H]^+$; calcd for $C_{24}H_{25}NO_3P$, 406.2}; HRMS (EI) *m/z* 300.1154 {$[M-PhCO]^+$; calcd for $C_{17}H_{19}NO_2P$, 300.1153}.

Synthesis of (2*S*, 3*S*)-2-hydroxy-4-methyl-1-phenyl-3-(*N*-diphenylphosphinoylamino)-1-pentanone (5c)



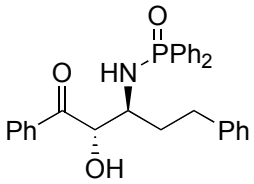
Compound 5c: a colorless oil; R_f 0.13 (Pet. ether/EtOAc 1:1); t_r = 30.2 min (minor; not found) and 35.8 min (major), (Chiralcel AD, λ = 254 nm, heptane/*i*-PrOH = 80:20, 1.0 mL/min); $[\alpha]_D^{24}$ +7.48 (c 3.60, $CHCl_3$, 100% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 8.03-7.94 (m, 4H), 7.90 (dd, *J* = 8.0, 1.0 Hz, 2H), 7.59-7.38 (m, 9H), 5.31 (dd, *J* = 6.8, 2.0 Hz, 1H), 5.06 (br d, *J* = 6.8 Hz, 1H), 4.03 (dd, *J* = 11.5, 5.5 Hz, 1H), 3.26-3.17 (m, 1H), 1.81-1.69 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.69 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 134.6, 133.8, 133.0, 132.8, 132.7, 132.2, 132.1, 132.0, 131.9, 131.8, 130.8, 129.0, 128.8, 128.7, 128.5, 128.4, 75.9, 60.6, 30.4, 30.3, 21.3, 19.7; IR (film): υ = 3331, 1678, 1597, 1438, 1261, 1181, 1124, 1109, 1071 cm^{-1}; LRMS (ESI) *m/z* 408.2 {$[M+H]^+$; calcd for $C_{24}H_{26}NO_3P$, 408.2}; HRMS (EI) *m/z* 302.1287 {$[M-PhCO]^+$; calcd for $C_{17}H_{21}NO_2P$, 302.1310}; Anal. Calcd for $C_{24}H_{26}NO_3P$: C, 70.75; H, 6.43; N, 3.44. Found: C, 70.94; H, 6.34; N, 3.19.

Synthesis of (2*S*, 3*S*)-2-hydroxy-5-methyl-1-phenyl-3-(*N*-diphenylphosphinoylamino)-1-hexanone (5d)



Compound **5d**: a white solid; m.p. 60-61 °C; R_f 0.20 (Pet. ether/EtOAc 1:1, 2 elutions); t_r = 25.7 min (major) and 36.2 min (minor), (Chiralcel AD, λ = 254 nm, heptane/*i*-PrOH = 80:20, 1.0 mL/min); $[\alpha]_D^{24}$ +20.21 (c 4.21, $CHCl_3$, 96% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 8.03-7.96 (m, 4H), 7.85 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.59-7.42 (m, 7H), 7.40 (t, *J* = 7.8 Hz, 2 H), 5.43 (br s, 1H), 4.37 (br s, 1H), 3.69 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.52-3.42 (m, 1H), 1.73-1.62 (m, 1H), 1.51-1.43 (m, 1H), 0.77-0.71 (m, 4H), 0.22 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.2, 134.1, 133.9, 133.2, 132.7, 132.6, 132.4, 132.23, 132.16, 132.03, 131.97, 131.9, 131.3, 128.9, 128.8, 128.7, 128.6, 128.5, 77.7, 60.6, 53.2, 39.9, 39.8, 23.9, 23.7, 21.0; IR (film): υ = 3331, 1679, 1597, 1579, 1439, 1409, 1270, 1189, 1124, 1108, 983 cm^{-1}; HRMS (EI) *m/z* 420.1720 {[M-H]+; calcd for $C_{25}H_{27}NO_3P$, 420.1729}.

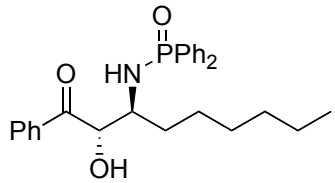
Synthesis of (2*S*, 3*S*)-2-hydroxy-1,5-diphenyl-3-(*N*-diphenylphosphinoylamino)-1-pentanone (5e)



Compound **5e**: a colorless oil; R_f 0.40 (EtOAc); t_r = 17.0 min (major) and 35.1 min (minor), (Chiralcel OD, λ = 254 nm, heptane/*i*-PrOH = 90:10, 1.0 mL/min); $[\alpha]_D^{20}$ +9.31 (c 4.27, $CHCl_3$, 96% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 8.04-7.95 (m, 4H), 7.75 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.62-7.49 (m, 5H), 7.49-7.44

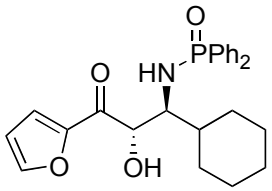
(m, 2H), 7.35 (t, J = 7.8 Hz, 2 H), 7.11-7.02 (m, 3H), 6.87 (dd, J = 8.0, 1.5 Hz, 2H), 5.41 (br s, 1H), 4.32 (br s, 1H), 3.80 (dd, J = 11.8, 6.5 Hz, 1H), 3.53-3.44 (m, 1H), 2.77 (ddd, J = 14.1, 9.5, 5.0 Hz, 1H), 2.35 (ddd, J = 14.1, 9.5, 7.0 Hz, 1H), 1.87-1.77 (m, 1H), 1.42-1.32 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.8, 134.2, 133.5, 133.2, 132.64, 132.56, 132.4, 132.2 br, 132.04, 131.97, 131.4, 128.9, 128.8, 128.75, 128.71, 128.6, 128.3, 128.2, 125.8, 77.5, 54.7, 32.1, 32.04, 31.98; IR (film): υ = 3319, 1684, 1597, 1438, 1267, 1183, 1123 cm^{-1}; HRMS (EI) *m/z* 469.1810 [M^+; calcd for $C_{29}H_{28}NO_3P$, 469.1807].

Synthesis of (2*S*, 3*S*)-2-hydroxy-1-phenyl-3-(*N*-diphenylphosphinoylamino)-1-nonanone (5f)



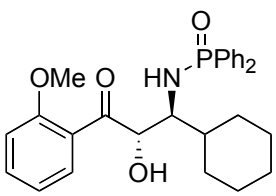
Compound **5f**: a colorless oil; R_f 0.27 (EtOAc); t_r = 9.0 min (major) and 17.3 min (minor), (Chiralcel OD, λ= 254 nm, heptane/*i*-PrOH = 90:10, 1.0 mL/min); $[\alpha]_D^{23}$ +46.2 (c 2.00, $CHCl_3$, 96% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04-7.96 (m, 4H), 7.88 (d, J = 7.0 Hz, 2H), 7.60-7.37 (m, 9H), 5.44 (br s, 1H), 4.30 (br s, 1H), 3.69 (dd, J = 11.8, 6.3 Hz, 1H), 3.48-3.38 (m, 1H), 1.53-1.42 (m, 1H), 1.42-1.32 (m, 1H), 1.17-0.86 (m, 8H), 0.77 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.1, 134.1, 133.8, 132.7, 132.6, 132.4, 132.2, 132.07, 131.98, 131.9, 128.9, 128.8, 128.7, 128.6, 128.5, 77.5, 55.0, 31.5, 30.4, 30.3, 28.9, 26.0, 22.6, 14.1; IR (film): υ = 3331, 1682, 1597, 1439, 1269, 1183, 1124, 1109 cm^{-1}; HRMS (EI) *m/z* 449.2122 [M^+; calcd for $C_{27}H_{32}NO_3P$, 449.2120].

Synthesis of (2*S*, 3*S*)-3-cyclohexyl-1-(2-furyl)-2-hydroxy-3-(*N*-diphenylphosphinoylamino)-1-pro-panone (5g)



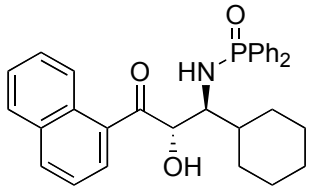
Compound **5g**: a pale yellow oil; R_f 0.46 (EtOAc); t_r = 18.0 min (minor) and 28.2 min (major), (Chiralcel AD, λ = 254 nm, heptane/*i*-PrOH = 80:20, 1.0 mL/min); $[\alpha]_D^{25}$ -14.36 (*c* 1.70, $CHCl_3$, 90% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96-7.86 (m, 4H), 7.56-7.40 (m, 8H), 6.50 (ddd, J = 3.8, 2.0, 0.5 Hz, 1H), 5.93 (br d, J = 8.8 Hz, 1H), 4.86 (br dd, J = 8.8, 2.0 Hz, 1H), 3.93 (dd, J = 12.0, 5.0 Hz, 1H), 3.16-3.06 (m, 1H), 2.10-2.03 (m, 1H), 1.72-1.64 (m, 1H), 1.62-1.50 (m, 3H), 1.50-1.42 (m, 1H), 1.20-0.78 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.1, 151.3, 147.3, 133.0, 132.9, 132.6, 132.3, 132.1, 131.93, 131.85, 131.6, 131.2, 130.2, 128.8, 128.7, 128.6, 128.5, 120.6, 112.5, 74.0, 61.5, 40.54, 40.48, 31.2, 30.4, 26.13, 26.10; IR (film): υ = 3264, 1666, 1566, 1465, 1439, 1389, 1274, 1170, 1124, 1109, 1018, 911 cm^{-1}; HRMS (EI) *m/z* 437.1750 [M^+; calcd for $C_{25}H_{28}NO_4P$, 437.1756].

Synthesis of (2*S*, 3*S*)-3-cyclohexyl-2-hydroxy-1-(2-methoxyphenyl)-3-(*N*-diphenylphosphinoyl-amino)-1-propanone (5h)



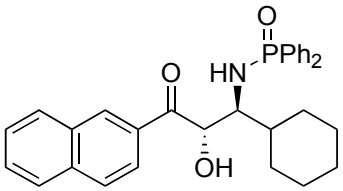
Compound **5h**: a pale yellow oil; R_f 0.26 (EtOAc); t_r = 25.5 min (major) and 31.8 min (minor), (Chiralcel AD, λ = 254 nm, heptane/*i*-PrOH = 80:20, 1.0 mL/min); $[\alpha]_D^{26}$ -3.67 (*c* 1.10, $CHCl_3$, 56% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 11.8, 7.8 Hz, 2H), 7.85 (dd, *J* = 12.0, 8.0 Hz, 2H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.58-7.38 (m, 7H), 6.99 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 5.28 (br dd, *J* = 7.5, 3.0 Hz, 1H), 4.95 (br d, *J* = 7.5 Hz, 1H), 3.77 (dd, *J* = 11.8, 7.3 Hz, 1H), 3.69 (s, 3H), 3.27-3.17 (m, 1H), 2.02-1.92 (m, 1H), 1.74-1.66 (m, 1H), 1.62-1.52 (m, 2H), 1.40-0.92 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.8, 158.2, 134.2, 133.5, 132.5, 132.4, 132.23, 132.16, 132.05, 131.9, 131.5, 130.7, 128.7, 128.6, 128.5, 128.4, 126.2, 120.9, 111.7, 78.7, 59.3, 55.7, 40.82, 40.76, 31.4, 29.6, 26.4, 26.3, 26.1; IR (film): υ = 3334, 1674, 1598, 1486, 1438, 1289, 1247, 1181, 1123, 1109, 1023 cm^{-1}; LRMS (ESI) *m/z* 478.2 {$[M+H]^+$; calcd for $C_{28}H_{33}NO_4P$, 478.2}; HRMS (EI) *m/z* 394.1215 {$[M-c\text{-hexyl}]^+$; calcd for $C_{22}H_{21}NO_4P$, 394.1208}.

Synthesis of (2*S*, 3*S*)-2-hydroxy-4-methyl-1-(1-naphthyl)-3-(*N*-diphenylphosphinoylamino)-1-pen-tanone (5i)



Compound **5i**: a pale yellow oil; R_f 0.34 (EtOAc); t_r = 8.7 min (major) and 14.7 min (minor), (Chiralcel OD, λ = 254 nm, heptane/*i*-PrOH = 90:10, 1.0 mL/min); $[\alpha]_D^{25}$ +8.03 (c 0.71, $CHCl_3$, 88% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (br d, *J* = 9.0 Hz, 1H), 8.04-7.91 (m, 6H), 7.87 (br d, *J* = 9.0 Hz, 1H), 7.62-7.38 (m, 9H), 5.56 (br d, *J* = 2.5 Hz, 1H), 4.79 (br s, 1H), 3.85 (dd, *J* = 11.8, 5.8 Hz, 1H), 3.25-3.16 (m, 1H), 1.80-1.63 (m, 1H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.61 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.4, 134.0, 134.0, 133.2, 132.7, 132.6, 132.2, 132.04, 132.02, 131.97, 131.9, 131.0, 130.4, 129.5, 128.8, 128.7, 128.50, 128.46, 128.40, 126.6, 125.3, 124.6, 78.2, 60.4, 30.4, 30.3, 21.2, 19.5; IR (film): υ = 3331, 1681, 1508, 1439, 1244, 1180, 1070, 946 cm^{-1}; HRMS (EI) *m/z* 457.1789 [M^+; calcd for $C_{28}H_{28}NO_3P$, 457.1807].

Synthesis of (2*S*, 3*S*)-2-hydroxy-4-methyl-1-(2-naphthyl)-3-(*N*-diphenylphosphinoylamino)-1-pen-tanone (5j)



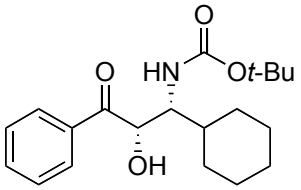
Compound **5j**: a white solid; m.p. 69-70 °C; R_f 0.21 (Pet. ether/EtOAc 1:1); t_r = 7.8 min (major) and 12.1 min (minor), (Chiralcel OD, λ = 254 nm, heptane/*i*-PrOH = 90:10, 1.0 mL/min); $[\alpha]_D^{23}$ -6.51 (c 3.07, $CHCl_3$, 95% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.06-7.92 (m, 6H), 7.87-7.82 (m, 2H), 7.63-7.40 (m, 8H), 5.52 (br s, 1H), 5.14 (br s, 1H), 4.08 (dd, *J* = 12.0, 5.5 Hz, 1H), 3.35-3.26 (m, 1H), 1.86-1.72 (m, 1H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.67 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 135.9, 133.0, 132.8, 132.7, 132.5, 132.28, 132.27, 132.1, 132.04, 132.00, 131.92, 131.90, 131.8, 131.3, 130.7, 130.0, 128.9, 128.8, 128.74, 128.68, 128.5, 128.4, 127.8, 126.9, 124.1, 76.0, 60.8, 30.4, 30.3, 21.3, 19.7; IR (film): υ = 3333, 1676, 1627, 1594, 1469, 1439, 1413, 1388, 1278,

1188, 1121, 1071, 1028, 909 cm^{-1}; Anal. Calcd for $C_{28}H_{28}NO_3P$: C, 73.51; H, 6.17; N, 3.06. Found: C, 73.37; H, 5.94; N, 3.06.

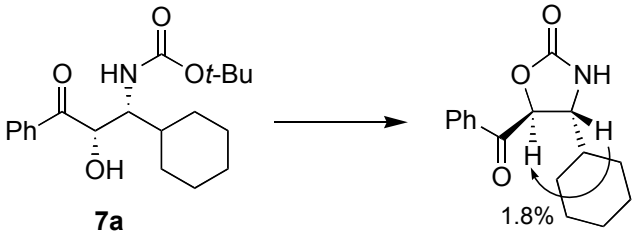
General procedure for the catalytic asymmetric Mannich-type reaction with Boc-imine 6 promoted by dinuclear zinc catalyst 2.

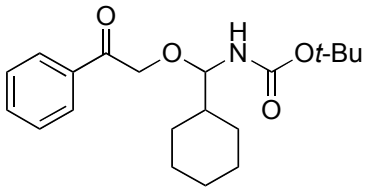
4Å Crushed molecular sieves (60 mg) were flame-dried under vacuum. After cooling down to room temperature, ligand **1a** was added (10 mg, 0.015 mmol) and nitrogen gas was refilled. THF (0.3 mL) was then added. To this suspension was added dropwise a solution of diethylzinc (27 μL, 0.03 mmol, 1.1 M in Toluene) at room temperature and allowed to stir for 30 minutes. A solution of 2-hydroxyacetophenone **3a** (82 mg, 0.60 mmol) in THF (0.35 mL) was then added and stirred for 2 min. After cooling down to -78 °C, a solution of Boc-imine **6a** (63 mg, 0.3 mmol) in THF (0.35 mL) was added successively. After stirring at -78 °C for 30 min, the reaction mixture was warmed up to 5 °C and stirred for 14 h. The reaction mixture was diluted with Et_2O (6 mL) and then a phosphate buffer (pH = 7) solution (3 mL) was added. After stirring for 30 minutes, the phases were separated and the aqueous phase was extracted with Et_2O (1 mL x 2). The combined organics were washed with brine (1.5 mL), dried over $MgSO_4$, filtered and concentrated to give a crude mixture of the Mannich products. The diastereomeric ratio was determined by ^1H NMR analysis of the crude product. The crude mixture was purified by radial chromatography on a 1 mm plate using 1:4 EtOAc/Petroleum ether as eluents to yield desired amino alcohol **7a** (80 mg, 77% yield, *anti*/*syn* = 1:5.4, 94% ee (*syn* isomer)) and undesired compound **8a** (6 mg, 6% yield). The mixture of diastereomers can be separated by radial chromatography on a 1 mm plate using 70:30:1 CH_2Cl_2/Petroleum ether/MeOH.

Synthesis of (2*S*, 3*R*)-3-cyclohexyl-2-hydroxy-1-phenyl-3-(*N*-*tert*-butoxycarbonylamino)-1-propanone (7a)



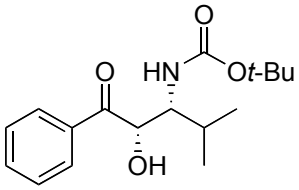
Compound **7a**: a colorless oil; R_f 0.17 (CH_2Cl_2/Pet. ether/MeOH 70:30:1); t_r = 32.1 (major) min and 43.1 min (minor), (Chiralcel AD, λ = 254 nm, heptane/*i*-PrOH = 90:10, 0.8 mL/min); $[\alpha]_D^{23}$ 1.48 (*c* 9.67, $CHCl_3$, 90% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.5 Hz, 0.22x2H, rotamer), 7.83-7.78 (m, 0.78x2H), 7.64-7.55 (m, 1H), 7.53-7.43 (m, 2H), 5.27 (br dd, *J* = 5.0, 1.0 Hz, 0.78H), 5.22 (br d, *J* = 4.5 Hz, 0.22H, rotamer), 4.61 (d, *J* = 10.5 Hz, 0.78H), 4.35 (d, *J* = 10.5 Hz, 0.22H, rotamer), 3.97 (d, *J* = 4.5 Hz, 0.22H, rotamer), 3.93 (d, *J* = 5.0 Hz, 0.78H), 3.82-3.70 (m, 1H), 2.10-2.00 (m, 1H), 1.92-1.55 (m, 6H), 1.46-0.86 (m, 13H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.1, 155.2, 134.0, 133.9, 129.0, 128.9, 128.5, 128.3, 79.2, 72.6, 57.8, 40.3, 30.3, 29.7, 28.2, 27.7, 26.3, 26.14, 26.07; IR (film): υ = 3444 br, 2928, 2853, 1698 br, 1599, 1580, 1498, 1450, 1366, 1269, 1172, 1125, 1054, 1019 cm^{-1}; LRMS (ESI) *m/z* 370.2 {$[M+Na]^+$; calcd for $C_{20}H_{29}NO_4Na$, 370.2}; HRMS (EI) *m/z* 274.1441 {$[M-Ot\text{-}Bu]^+$; calcd for $C_{16}H_{20}NO_3$, 274.1443}. The relative stereochemistry of major diastereomer was determined to be *syn* by NOE observation (1.8%) as shown below, after conversion to the corresponding cyclic carbamate.[s5,s6] The absolute sterochemistry was determined by utilization of the amine in the O-methyl mandelic amide formation.[s7]



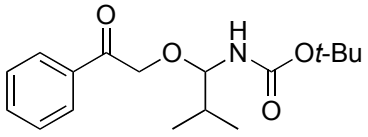


Compound **8a**: a semi white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 7.4 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.45 (dd, *J* = 7.4, 7.4 Hz, 2H), 4.94 (br d, *J* = 10.4 Hz, 1H), 4.86 (s, 2H), 4.83 (dd, *J* = 10.4, 6.4 Hz, 1H), 1.97-1.87 (m, 1H), 1.84-1.72 (m, 2H), 1.70-1.58 (m, 2H), 1.39 (s, 9H), 1.28-1.00 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.7, 156.1, 135.3 133.6, 128.8, 128.1, 86.3, 80.1, 71.1, 53.6, 42.8, 28.7, 28.4, 28.1, 26.51, 26.48, 26.0, 25.9; IR (film): υ = 3345, 2927, 2854, 1704 br, 1599, 1581, 1514, 1450, 1392, 1367, 1292, 1250, 1227, 1173, 1113, 1012, 979 cm^{-1}.

Synthesis of (2*S*, 3*R*)-2-hydroxy-4-methyl-1-phenyl-3-(*N*-*tert*-butoxycarbonylamino)-1-pentanone (7b)



Compound **7b**: a colorless oil; R_f 0.32 (CH_2Cl_2/Pet. etherr/MeOH 70:30:1, 2 elutions); t_r = 5.6 min (major) and 10.4 min (minor), (Chiralcel OD, λ = 254 nm, heptane/*i*-PrOH = 90:10, 1.0 mL/min); $[\alpha]_D^{23}$ -15.27 (*c* 3.05, $CHCl_3$, 90% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.0 Hz, 0.25x2H, rotamer), 7.83 (dd, *J* = 8.5, 1.0 Hz, 0.75x2H), 7.67-7.58 (m, 1H), 7.57-7.46 (m, 2H), 5.27 (dd, *J* = 4.8, 1.3 Hz, 0.75H), 5.23 (d, *J* = 4.8 Hz, 0.25H, rotamer), 4.68 (d, *J* = 10.0 Hz, 0.75H), 4.48 (d, *J* = 11.0 Hz, 0.25H, rotamer), 4.01 (d, *J* = 4.8 Hz, 0.25H, rotamer), 3.96 (d, *J* = 4.8 Hz, 0.75H), 3.80-3.68 (m, 1H), 2.24-1.92 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.9, 155.2, 134.0, 133.9, 129.0, 128.9, 128.5, 128.3, 79.2, 73.1, 58.7, 31.3, 28.4, 28.2, 27.7, 20.1, 19.7, 19.5; IR (film): υ = 3350, 3278, 2932, 2873, 1696 br, 1599, 1503, 1451, 1391, 1366, 1264, 1173, 1089, 1004 cm^{-1}; LRMS (ESI) *m/z* 330.2 {$[M+Na]^+$; calcd for $C_{17}H_{25}NO_4Na$, 330.2}; HRMS (EI) *m/z* 234.1128 {$[M-Ot\text{-}Bu]^+$; calcd for $C_{13}H_{16}NO_3$, 234.1130}.

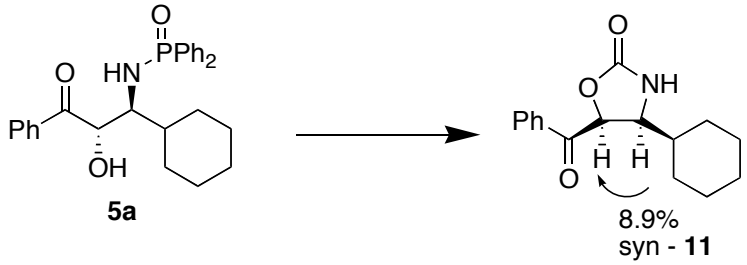


Compound **8b**: a semi white solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, *J* = 7.5 Hz, 2H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.45 (dd, *J* = 7.5, 7.5 Hz, 2H), 4.92 (d, *J* = 10.5 Hz, 1H), 4.88-4.81 (m, 3H), 2.04-1.92 (m, 1H), 1.39 (s, 9H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.98 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ

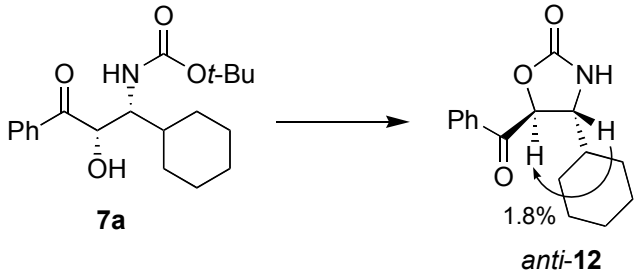
196.6, 155.9, 135.1, 133.4, 128.7, 128.0, 86.7, 80.0, 71.0, 33.1, 28.3, 18.1, 17.4; IR (film): υ = 3347, 2975, 1705 br, 1598, 1504, 1450, 1392, 1367, 1229, 1173, 1111, 1011, 978 cm^{-1}.

Establishment of relative and absolute stereochemistry of the amino alcohol derived from *N*-Dpp and *N*-Boc imine

Determination of the relative stereochemistry of the Mannich adducts[s5,s6]

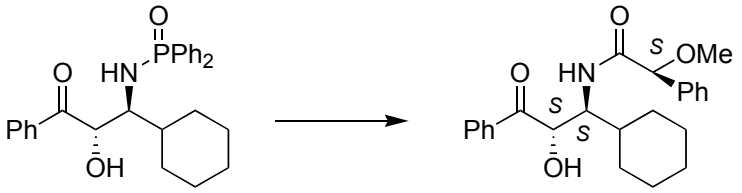


To a stirred solution of **5a** (250 mg, 0.558 mmol) in THF (3 mL) was added conc. HCl (3 mL, 0.69 mmol) at 0 °C. After stirring at room temperature for 1 h, the reaction mixture was basified with K_2CO_3 (pH 10) and extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried over $MgSO_4$. The CH_2Cl_2 solvent was evaporated under reduced pressure (to ~6 mL). After cooling to -78 °C, pyridine (73 μL, 0.90 mmol) and triphosgene (134 mg, 0.45 mmol) in CH_2Cl_2 (0.9 mL) were added slowly and stirred for 30 min at this temperature. The resulting solution was quenched with saturated aqueous $NaHCO_3$ and extracted with ether. The combined organic extracts were washed successively with 1 N HCl, saturated aqueous $NaHCO_3$, brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the resulting residue was purified by silica gel column chromatography (EtOAc/Pet. ether 1:1) to give desired oxazolidinone *syn*-**11** (95 mg, 62 %) as white solid; m.p. 168-170 °C; R_f 0.14 (EtOAc/Pet. ether 1:1); $[\alpha]_D^{26}$ +3.93 (c 1.79, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.96-7.91 (m, 2H), 7.62 (tt, *J* = 7.5, 1.3 Hz, 1H), 7.53-7.47 (m, 2H), 6.62 (br d, *J* = 4.5 Hz, 1H), 5.82 (d, *J* = 8.5 Hz, 1H), 4.05 (dd, *J* = 8.5, 4.5 Hz, 1H), 1.66-1.49 (m, 4H), 1.43-1.32 (m, 2H), 1.06-0.92 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.5, 159.2, 135.5, 134.2, 129.2, 128.4, 80.3, 61.1, 38.6, 30.5, 26.5, 25.9, 25.8, 25.4; IR (film): υ = 3262, 1757, 1694, 1596, 1449, 1226, 1095, 971 cm^{-1}; LRMS (ESI) *m/z* 274.2 {$[M+H]^+$; calcd for $C_{16}H_{20}NO_3$, 274.2}; HRMS (EI) *m/z* 168.1021 {$[M-PhCO]^+$; calcd for $C_9H_{14}NO_2$, 168.1025}. The relative stereochemistry was confirmed by NOE experiment.



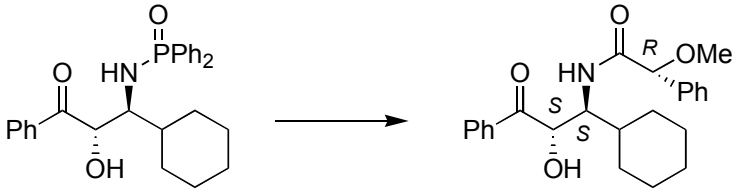
Compound *anti*-**12**: a white solid (87 %); m.p. 92-93 °C; R_f 0.34 (EtOAc/Pet. ether 1:1); $[\alpha]_D^{25}$ +93.18 (c 3.85, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.02-7.94 (m, 2H), 7.62-7.55 (m, 1H), 7.50-7.42 (m, 2H), 7.07 (br s, 1H), 5.34 (d, *J* = 4.8 Hz, 1H), 4.02 (dd, *J* = 5.0, 4.8 Hz, 1H), 1.84-1.44 (m, 6H), 1.29-0.92 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.5, 158.6, 134.2, 134.1, 129.4, 128.9, 79.4, 58.4, 42.3, 28.7, 28.0, 26.0, 25.7, 25.6; IR (film): υ = 3261, 1759, 1692, 1597, 1580, 1449, 1393, 1230, 1184, 1091, 1076, 974 cm^{-1}; HRMS (EI) *m/z* 273.1368 [M^+; calcd for $C_{16}H_{19}NO_3$, 273.1365]. The relative stereochemistry was confirmed by NOE experiment.

Determination of the absolute stereochemistry of the Mannich adducts[s6,s7]



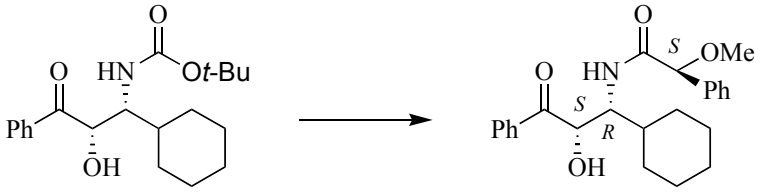
anti-**5a** (*S*)-**13** (*via S*-acid)

To a stirred solution of *anti*-**5a** (100 mg, 0.22 mmol) in THF (1.2 mL) was added conc. HCl (1.2 mL, 0.27 mmol) at 0 °C. After stirring at room temperature for 1 h, the reaction mixture was basified with K_2CO_3 (pH 10) and extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried over $MgSO_4$. The CH_2Cl_2 solvent was evaporated under reduced pressure (to ~2 mL). To a solution of amine in CH_2Cl_2 was then added (*S*)-O-methyl mandelic acid (36 mg, 0.22 mmol), 1-hydroxy benzotrizaole (HOBT) (30 mg, 0.22 mmol), *i*-Pr_2NEt (40 μL, 0.24 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI·HCl) (43 mg, 0.22 mmol), respectively. After stirring for 30 minutes at room temperature, the reaction was diluted with EtOAc (2 mL) and then washed with 1 M HCl (1 mLx2), $NaHCO_3$ (aq. Sat.) (1 mLx2), water (1 mL) and brine (2 mL). The organics were dried over $MgSO_4$, filtered and concentrated to give an oil. Purification by flash chromatography on silica gel [Pet. ether/EtOAc 1:4] afforded a white solid (56 mg, 64%) of the mandelate amide (*S*)-**13** derived from the (*S*)-acid; m.p. 82-83 °C; R_f 0.21 (EtOAc/Pet. ether 1:4); $[\alpha]_D^{25}$ +105.17 (c 1.91, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.61 (tt, *J* = 7.8, 1.2 Hz, 1H), 7.51 (dd, *J* = 8.2, 7.8 Hz, 2H), 7.44-7.30 (m, 5H), 5.22 (dd, *J* = 5.2, 2.8 Hz, 1H), 4.63 (s, 1H), 4.29 (ddd, *J* = 9.3, 6.6, 2.8 Hz, 1H), 4.00 (d, *J* = 5.2 Hz, 1H), 3.37 (s, 3H), 1.86-1.78 (m, 1H), 1.72-1.42 (m, 4H), 1.33-1.24 (m, 1H), 1.22-0.84 (m, 4H), 0.70-0.58 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 170.8, 137.1, 134.3, 133.8, 129.11, 129.06, 128.7, 128.6, 127.2, 84.0, 76.5, 57.2, 56.8, 37.5, 30.6, 29.2, 25.9; IR (film): υ = 3411, 2926, 2852, 1673 br, 1597, 1514, 1450, 1264, 1100, 973 cm^{-1}; LRMS (ESI) *m/z* 418.2 {$[M+Na]^+$; calcd for $C_{24}H_{29}NO_4Na$, 418.2}; HRMS (EI) *m/z* 290.1744 {$[M-COPh]^+$; calcd for $C_{17}H_{24}NO_3$, 290.1756}; Anal. Calcd for $C_{17}H_{24}NO_3$: C, 72.89; H, 7.39; N, 3.54. Found: C, 72.79; H, 7.24; N, 3.34.



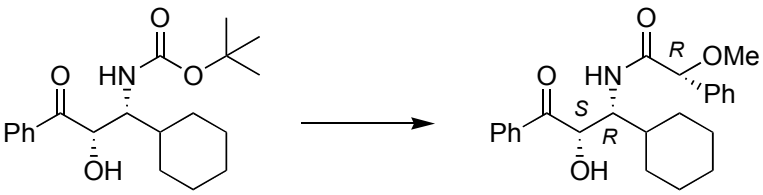
anti-**5a** *(R)*-**13** *(via R-acid)*

Compound (*R*)-**13** derived from the (*R*)-O-methyl mandelic acid: a colorless oil (48 mg, 55%); R_f 0.30 (EtOAc/Pet. ether 1:4); $[\alpha]_D^{25}$ -4.68 (c 2.16, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 8.2, 1.0 Hz, 2H), 7.60 (tt, *J* = 7.7, 1.0 Hz, 1H), 7.49 (dd, *J* = 8.2, 7.7 Hz, 2H), 7.46-7.30 (m, 5H), 5.06 (dd, *J* = 5.0, 2.8 Hz, 1H), 4.68 (s, 1H), 4.33 (ddd, *J* = 9.3, 6.5, 2.8 Hz, 1H), 3.92 (d, *J* = 5.0 Hz, 1H), 3.38 (s, 3H), 1.90-1.82 (m, 1H), 1.74-1.66 (m, 1H), 1.60-1.50 (m, 3H), 1.39-1.31 (m, 1H), 1.23-0.92 (m, 4H), 0.82-0.72 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.4, 170.8, 137.1, 134.3, 133.7, 129.1, 129.0, 128.8, 128.7, 127.4, 83.9, 76.3, 57.2, 56.8, 37.7, 30.7, 29.3, 26.0, 25.9; IR (film): υ = 3412, 2926, 2853, 1674 br, 1598, 1517, 1450, 1268, 1099, 974 cm^{-1}; HRMS (EI) *m/z* 396.2173 {$[M+H]^+$; calcd for $C_{24}H_{30}NO_4$, 396.2175}.



syn-**7a** (*S*)-**14** (*via S*-acid)

To a stirred solution of *syn*-**7a** (140 mg, 0.4 mmol) in THF (2.1 mL) was added conc. HCl (2.1 mL, 0.48 mmol) at 0 °C. After stirring at room temperature for 1 h, the reaction mixture was basified with K_2CO_3 (pH 10) and extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried over $MgSO_4$. The CH_2Cl_2 solvent was evaporated under reduced pressure (to ~3 mL). To a solution of amine in CH_2Cl_2 was then added (*S*)-O-methyl mandelic acid (65 mg, 0.4 mmol), 1-hydroxy benzotrizaole (HOBT) (55 mg, 0.4 mmol), *i*-Pr_2NEt (75 μL, 0.44 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI·HCl) (78 mg, 0.4 mmol), respectively. After stirring for 30 minutes at room temperature, the reaction was diluted with EtOAc (4 mL) and then washed with 1 M HCl (2 mLx2), $NaHCO_3$ (aq. Sat.) (2 mLx2), water (2 mL) and brine (4 mL). The organics were dried over $MgSO_4$, filtered and concentrated to give an oil. Purification by flash chromatography on silica gel [Pet. ether/EtOAc 1:4] afforded a white solid (110 mg, 70%) of the mandelate amide (*S*)-**14** derived from the (*S*)-acid; m.p. 108-109 °C; R_f 0.27 (EtOAc/Pet. ether 1:4); $[\alpha]_D^{24}$ -23.47 (c 3.31, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48-7.42 (m, 3H), 7.41-7.32 (m, 3H), 7.31-7.25 (m, 4H), 6.83 (d, *J* = 10.0 Hz, 1H), 5.29 (dd, *J* = 4.5, 1.0 Hz, 1H), 4.45 (s, 1H), 4.12 (d, *J* = 4.5 Hz, 1H), 4.11-4.06 (m, 1H), 3.29 (s, 3H), 2.15-2.07 (m, 1H), 1.88-1.65 (m, 5H), 1.40-1.14 (m, 4H), 1.11-0.98 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.6, 169.7, 137.0, 133.8, 133.2, 128.6, 128.3, 128.2, 128.1, 127.1, 83.6, 72.2, 57.0, 55.4, 39.8, 30.0, 29.6, 26.1, 26.0, 25.9; IR (film): υ 3411, 2929, 2852, 1683 br, 1598, 1513, 1450, 1268, 1196, 1146, 1100, 991 cm^{-1}; HRMS (EI) *m/z* 396.2174 {[M+H]$^+$; calcd for $C_{24}H_{30}NO_4$, 396.2175}; Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54. Found: C, 72.70; H, 7.19; N, 3.44.



syn-**7a** (*R*)-**14** (*via R*-acid)

Compound (*R*)-**14** derived from the (*R*)-O-methyl mandelic acid: a white solid (99 mg, 63 %); m.p. 59-60 °C; R_f 0.24 (EtOAc/Pet. ether 1:4); $[\alpha]_D^{23}$ 31.35 (c 7.48, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.8 Hz, 2H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.47 (dd, *J* = 7.8, 7.6 Hz, 2H), 7.34-7.21 (m, 5H), 6.83 (d, *J* = 9.8 Hz, 1H), 5.34 (d, *J* = 5.0 Hz, 1H), 4.48 (s, 1H), 4.10 (dd, *J* = 9.8, 9.2 Hz, 1H), 4.05 (d, *J* = 5.0 Hz, 1H), 3.39 (s, 3H), 2.11-2.02 (m, 1H), 1.86-1.68 (m, 2H), 1.67-1.51 (m, 3H), 1.35-1.04 (m, 4H), 0.87-0.77 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 170.1, 137.2, 134.1, 133.4, 128.9, 128.4, 128.3, 128.2, 126.6, 83.7, 72.2, 57.6, 55.6, 40.1, 30.1, 29.3, 26.1, 26.0, 25.8; IR (film): υ = 3411, 2928, 2852, 1682 br, 1598, 1513, 1449, 1268, 1197, 1146, 1100, 990 cm^{-1}; HRMS (EI) *m/z* 396.2183 {[M+H]+; calcd for $C_{24}H_{30}NO_4$, 396.2175}.

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