Direct Vinylogous Mannich-type Reactions via Ring-Opening and Rearrangement of Vinyloxiranes

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Supporting Information

General. Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR spectrometer, SPECTRUM 1000. ^1H and ^{13}C NMR spectra was measured on a Varian Gemini 2000 or Mercury 300 (^1H : 300 MHz, ^{13}C : 75 MHz) spectrometer. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF₂₅₄ on aluminium sheet) were used. The products were purified by preparative column chromatography on silica gel (60Å, ultrapure silica gel, SILICYCLE). The high-resolution mass spectra (HRMS) analysis was accomplished at the Department of Chemistry, University of Toronto (EI and ESI). Reactions were conducted in appropriate round-bottomed flask with magnetic stirring bars under an atmosphere of dry nitrogen. Tetrahydrofuran (THF) was distilled from benzophenoneketyl prior to use. $\text{Sc}(\text{OTf})_3$ was purchased from Strem Chemicals, Inc. 2-Methyl-2-vinyloxirane **1** was purchased from Sigma-Aldrich Canada Ltd.

Preparation of 2: To a mixture of aldehyde or glyoxalate (1.0-1.5 equiv) and aminodiphenylmethane (1.0 equiv) in CH_2Cl_2 (0.5 M) was added MgSO_4 (5 equiv) at room temperature. After stirring for a few hours, the resulting mixture was filtered and the filtrate was concentrated. Purification of the residue by chromatography on silica gel (hexane/ Et_2O as eluent) and/or recrystallization from hexane or hexane-benzene gave imine **2**.

Ethyl *N*-benzhydryliminoethanoate (2a)¹ : colorless crystals; mp = 52-54 °C (hexane); ¹H NMR (300 MHz, CDCl₃) δ 7.77 (1H, s, CH=N), 7.36-7.24 (10H, m, Ar-H), 5.68 (1H, s, CHPh₂), 4.34 (2H, q, *J* = 7.2 Hz, CH₂CH₃), 1.35 (3H, t, *J* = 7.2 Hz, CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 163.1, 153.7, 141.5, 128.6, 127.8, 127.5, 77.4, 61.8, 14.1; IR (film) 3058, 3024, 2983, 2935, 2901, 1745, 1718, 1647, 1599, 1490, 1453, 1371, 1300, 1205, 1096, 1032, 967, 858, 746, 699 cm⁻¹; HRMS (EI) calcd for C₁₇H₁₆NO₂ ([M-H]⁺): 266.1181, Found: 266.1177.

***N*-Benzylidenebenzhydramine (2b)^{2,4}** : colorless crystals; mp = 103-104 °C (hexane-benzene); ¹H NMR (300 MHz, CDCl₃) δ 8.43 (1H, s, CH=N), 7.86-7.83 (2H, m, Ar-H), 7.43-7.39 (7H, m, Ar-H), 7.34-7.29 (4H, m, Ar-H), 7.22 (2H, tt, *J* = 7.2, 1.5 Hz, Ar-H), 5.60 (1H, s, CHPh₂); ¹³C NMR (75 MHz, CDCl₃) δ 160.8, 143.9, 136.3, 130.7, 128.51, 128.46, 128.4, 127.7, 127.0, 77.9; IR (film) 3078, 3058, 3031, 2922, 2853, 1633, 1599, 1579, 1490, 1450, 1378, 1314, 1273, 1215, 1072, 1028, 906, 882, 851, 821, 750, 695 cm⁻¹; HRMS (EI) calcd for C₂₀H₁₇N (M⁺): 271.1361, Found: 271.1357.

***N*-(4-Chlorobenzylidene)benzhydramine (2c)³** : colorless crystals; mp = 80-81 °C (hexane); ¹H NMR (300 MHz, CDCl₃) δ 8.34 (1H, s, CH=N), 7.78 (2H, dt, *J* = 8.7, 2.1 Hz, Ar-H), 7.40-7.30 (10H, m, Ar-H), 7.23 (2H, tt, *J* = 7.2, 1.2 Hz, Ar-H), 5.59 (1H, s, CHPh₂); ¹³C NMR (75 MHz, CDCl₃) δ 159.4, 143.7, 136.7, 134.8, 129.6, 128.8, 128.5, 127.6, 127.0, 77.8; IR (film) 3078, 3058, 3024, 2846, 1643, 1596, 1490, 1450, 1375, 1269, 1215, 1167, 1086, 1025, 1011, 848, 821, 763, 743, 699 cm⁻¹; HRMS (EI) calcd for C₂₀H₁₆ClN (M⁺): 305.0971, Found: 305.0976.

***N*-(2-Chlorobenzylidene)benzhydramine (2d)⁴** : colorless crystals; mp = 115-116 °C (hexane-benzene); ¹H NMR (300 MHz, CDCl₃) δ 8.89 (1H, s, CH=N), 8.26-8.23 (1H, m, Ar-H), 7.42-7.38 (4H, m, Ar-H), 7.37-7.29 (7H, m, Ar-H), 7.23 (2H, tt, *J* = 7.2, 1.5 Hz, Ar-H), 5.66 (1H, s, CHPh₂); ¹³C NMR (75 MHz, CDCl₃) δ 157.5, 143.7, 135.3, 133.2, 131.6, 129.7, 128.8, 128.5, 127.6, 127.1, 126.9, 78.3; IR (film) 3078, 3058, 3017, 2922, 2853, 1630, 1596, 1490, 1443, 1378, 1266, 1120, 1052, 1021, 848, 760, 743, 699 cm⁻¹; HRMS (EI) calcd for C₂₀H₁₆ClN (M⁺): 305.0971, Found: 305.0963.

N-(2-Trifluoromethylbenzylidene)benzhydramine (2e) : colorless crystals; mp = 52-54 °C (hexane); ^1H NMR (300 MHz, CDCl_3) δ 8.80 (1H, q, J = 2.7 Hz, $\text{CH}=\text{N}$), 8.41 (1H, d, J = 7.8 Hz, Ar-H), 7.67 (1H, d, J = 7.8 Hz, Ar-H), 7.60 (1H, t, J = 7.8 Hz, Ar-H), 7.51 (1H, t, J = 7.8 Hz, Ar-H), 7.41-7.38 (4H, m, Ar-H), 7.36-7.30 (4H, m, Ar-H), 7.24 (2H, tt, J = 7.2, 1.5 Hz, Ar-H), 5.68 (1H, s, CHPh_2); ^{13}C NMR (75 MHz, CDCl_3) δ 157.1, 143.3, 134.2, 131.9, 130.2, 129.3, 128.7, 128.5, 127.6, 127.1, 125.9, 125.5 (q, J = 5.7 Hz), 78.3; IR (film) 3058, 3024, 2915, 2840, 1636, 1596, 1579, 1490, 1450, 1392, 1314, 1273, 1167, 1120, 1055, 1032, 848, 767, 739, 699 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{21}\text{H}_{16}\text{F}_3\text{N}$ (M^+): 338.1157, Found: 338.1167.

N-(4-Methoxybenzylidene)benzhydramine (2f)⁴ : colorless crystals; mp = 111-112 °C (hexane-benzene); ^1H NMR (300 MHz, CDCl_3) δ 8.35 (1H, s, $\text{CH}=\text{N}$), 7.78 (2H, dt, J = 8.7, 2.4 Hz, Ar-H), 7.41-7.36 (4H, m, Ar-H), 7.34-7.29 (4H, m, Ar-H), 7.22 (2H, tt, J = 7.2, 1.5 Hz, Ar-H), 6.92 (2H, dt, J = 8.7, 2.4 Hz, Ar-H), 5.56 (1H, s, CHPh_2), 3.84 (3H, s, OMe); ^{13}C NMR (75 MHz, CDCl_3) δ 161.7, 160.0, 144.1, 130.0, 129.3, 128.4, 127.7, 126.9, 113.9, 77.8, 55.3; IR (film) 3078, 3051, 3024, 2962, 2922, 2840, 1626, 1609, 1575, 1511, 1490, 1456, 1382, 1307, 1246, 1167, 1103, 1079, 1028, 913, 831, 763, 739, 702 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{21}\text{H}_{19}\text{NO}$ (M^+): 301.1467, Found: 301.1470.

Cyclohexyl N-benzhydryliminoethanoate (2g) : colorless crystals; mp = 117-118 °C (hexane); ^1H NMR (300 MHz, CDCl_3) δ 7.76 (1H, s, $\text{CH}=\text{N}$), 7.33-7.23 (10H, m, Ar-H), 5.68 (1H, s, CHPh_2), 4.94 (1H, tt, J = 9.3, 4.5 Hz, OCH), 1.97-1.87 (2H, m), 1.81-1.70 (2H, m), 1.60-1.18 (6H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 162.4, 154.2, 154.1, 141.8, 128.8-128.4 (m), 127.9, 127.7, 127.3, 74.6, 74.1, 52.4, 52.3, 31.4 (br), 25.2 (br), 23.7 (br); IR (film) 3078, 3058, 3024, 2928, 2853, 1732, 1647, 1599, 1490, 1446, 1382, 1361, 1293, 1215, 1032, 1011, 936, 909, 858, 760, 699 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{21}\text{H}_{22}\text{NO}_2$ ($[\text{M}-\text{H}]^+$): 320.1651, Found: 320.1657.

(-)-8-Phenylmenthyl N-benzhydryliminoethanoate (2h) : colorless viscous oil; ^1H NMR (300 MHz, CDCl_3) δ 7.38-7.19 (12H, m, Ar-H), 7.03 (2H, t, J = 7.5 Hz, Ar-H), 6.93 (1H, t, J = 7.5 Hz, Ar-H), 6.84 (1H, s, $\text{CH}=\text{N}$), 5.40 (1H, s, CHPh_2), 4.95 (1H, td, J = 10.5, 4.5 Hz, OCH), 2.10 (1H, ddd, J = 12.3, 10.5, 3.6 Hz),

1.94-1.76 (2H, m), 1.73-1.64 (1H, m), 1.58-1.42 (1H, m), 1.32 (3H, s, CPh(CH₃)₂), 1.29-0.92 (3H, m), 1.22 (3H, s, CPh(CH₃)₂), 0.87 (3H, d, *J* = 6.6 Hz, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 161.7, 154.0, 151.4, 142.0, 141.9, 128.5, 127.9, 127.8, 127.7, 127.4, 127.3, 125.4, 125.0, 77.6, 75.4, 50.5, 41.4, 39.5, 34.5, 31.3, 28.9, 26.3, 23.8, 21.7; IR (film) 3085, 3058, 3024, 2956, 2922, 2867, 1742, 1711, 1643, 1599, 1494, 1450, 1368, 1297, 1198, 1130, 1089, 1028, 998, 909, 848, 763, 699 cm⁻¹; HRMS (EI) calcd for C₃₁H₃₅NO₂ (M⁺): 453.2668, Found: 453.2680.

General procedure for direct vinylogous Mannich-type reactions via ring-opening and rearrangement of vinyloxiranes : To a solution of **2** (0.50 mmol) and 2-methyl-2-vinyloxirane **1** (74 μL, 0.75 mmol) in THF (1.0 mL) was added Sc(OTf)₃ (25 mg, 0.050 mmol) at 0 °C under a N₂ atmosphere and the mixture was allowed to warm to 50 °C. After stirring for 10-30 min, the resulting mixture was quenched with saturated NaHCO₃ at room temperature. Extractive work up and purification of the residue by column chromatography on silica gel (hexane/Et₂O or EtOAc as eluent) gave the corresponding amino aldehyde **3**.

(2E)-N-Benzhydryl-5-amino-5-ethoxycarbonyl-2-methylpent-2-en-1-nal (3a) : colorless crystals; mp = 53-54 °C (hexane-Et₂O); ¹H NMR (300 MHz, CDCl₃) δ 9.43 (1H, s, CHO), 7.43-7.19 (10H, m, Ar-H), 6.55 (1H, td, *J* = 7.2, 1.5 Hz, 3-CH), 4.83 (1H, s, CHPh₂), 4.21 (2H, q, *J* = 7.2 Hz, CH₂CH₃), 3.38 (1H, t, *J* = 6.6 Hz, 5-CH), 2.72 (1H, ddd, *J* = 15.6, 7.2, 6.6 Hz, 4-CH₂), 2.65 (1H, dt, *J* = 15.6, 7.2, 6.6 Hz, 4-CH₂), 2.29 (1H, s, NH), 1.74 (3H, d, *J* = 0.6 Hz, CH₃), 1.27 (3H, t, *J* = 7.2 Hz, CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 194.8, 174.2, 149.3, 143.8, 142.4, 141.0, 128.6, 128.5, 127.6, 127.4, 127.3, 127.1, 65.6, 61.1, 58.2, 33.1, 14.3, 9.4; IR (film) 3324, 3058, 3024, 2976, 2935, 2846, 1728, 1684, 1643, 1490, 1453, 1368, 1334, 1266, 1188, 1130, 1025, 841, 746, 705 cm⁻¹; HRMS (EI) calcd for C₂₂H₂₅NO₃ (M⁺): 351.1834, Found: 351.1833.

(2E)-N-Benzhydryl-5-amino-2-methyl-5-phenylpent-2-en-1-nal

(3b) : yellow viscous oil; ^1H NMR (300 MHz, CDCl_3) δ 9.35 (1H, s, CHO), 7.40-7.17 (15H, m, Ar-H), 6.48 (1H, td, $J = 7.2, 1.2$ Hz, 3-CH), 4.63 (1H, s, CHPh_2), 3.69 (1H, t, $J = 7.2$ Hz, 5-CH), 2.77 (1H, ddd, $J = 15.0, 7.2, 7.2$ Hz, 4- CH_2), 2.66 (1H, ddd, $J = 15.0, 7.2, 7.2$ Hz, 4- CH_2), 1.97 (1H, br, NH), 1.65 (3H, d, $J = 1.2$ Hz, CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 195.0, 151.2, 144.2, 143.1, 142.8, 140.6, 128.7, 128.6, 128.4, 127.7, 127.5, 127.20, 127.15, 127.0, 126.9, 63.7, 59.3, 37.7, 9.3. IR (film) 3324, 3058, 3024, 2922, 2840, 1681, 1643, 1599, 1490, 1450, 1358, 1242, 1195, 1103, 1072, 1025, 913, 865, 760, 746, 699 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{25}\text{H}_{25}\text{NO}$ (M^+): 356.2014, Found: 356.2015.

(2E)-N-Benzhydryl-5-amino-2-methyl-5-(4-chlorophenyl)pent-2-en-1-nal (3c)

: pale yellow viscous oil; ^1H NMR (300 MHz, CDCl_3) δ 9.35 (1H, s, CHO), 7.36-7.22 (12H, m, Ar-H), 7.18 (2H, d, $J = 8.4$ Hz, Ar-H), 6.43 (1H, td, $J = 7.2, 1.2$ Hz, 3-CH), 4.58 (1H, s, CHPh_2), 3.69 (1H, t, $J = 7.2$ Hz, 5-CH), 2.75 (1H, ddd, $J = 15.0, 7.2, 7.2$ Hz, 4- CH_2), 2.63 (1H, ddd, $J = 15.0, 7.2, 7.2$ Hz, 4- CH_2), 1.94 (1H, br, NH), 1.65 (3H, s, CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 194.9, 150.3, 143.9, 142.8, 141.2, 140.8, 133.2, 129.0, 128.9, 128.6, 128.5, 128.3, 127.6, 127.3, 127.1, 63.7, 58.7, 37.6, 9.4; IR (film) 3324, 3058, 3024, 2922, 2853, 1684, 1647, 1596, 1487, 1453, 1409, 1358, 1089, 1028, 1011, 865, 828, 746, 702 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{25}\text{H}_{24}\text{ClNO}$ (M^+): 389.1546, Found: 389.1542.

(2E)-N-Benzhydryl-5-amino-2-methyl-5-(2-chlorophenyl)pent-2-en-1-nal (3d)

: colorless viscous oil; ^1H NMR (300 MHz, CDCl_3) δ 9.37 (1H, s, CHO), 7.43 (1H, d, $J = 7.2$ Hz, Ar-H), 7.37-7.19 (13H, m, Ar-H), 6.50 (1H, t, $J = 7.2$ Hz, 3-CH), 4.58 (1H, s, CHPh_2), 4.25 (1H, t, $J = 6.9$ Hz, 5-CH), 2.72 (2H, dd, $J = 7.2, 6.9$ Hz, 4- CH_2), 2.15 (1H, br, NH), 1.64 (3H, s, CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 195.0, 150.7, 144.0, 142.9, 139.7, 133.7, 130.0, 128.54, 128.51, 128.4, 127.7, 127.3, 127.2, 127.13, 127.08, 64.0, 56.1, 36.2, 9.3; IR (film) 3324, 3058, 3024, 2922, 2853, 2710, 1684, 1643, 1494, 1450, 1361, 1246, 1191, 1103, 1032, 865, 756, 705 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{25}\text{H}_{24}\text{ClNO}$ (M^+): 389.1546, Found: 389.1542.

(2E)-N-Benzhydryl-5-amino-2-methyl-5-(2-trifluoromethylphenyl)pent-2-en-1-nal (3e)

: colorless viscous oil; ^1H NMR (300 MHz,

CDCl₃) δ 9.41 (1H, s, CHO), 7.82 (1H, d, J = 7.5 Hz, Ar-H), 7.65 (1H, d, J = 7.5 Hz, Ar-H), 7.62 (1H, t, J = 7.5 Hz, Ar-H), 7.40 (1H, t, J = 7.5 Hz, Ar-H), 7.34-7.18 (10H, m, Ar-H), 6.54 (1H, t, J = 7.2 Hz, 3-CH), 4.57 (1H, s, CHPh₂), 4.29 (1H, t, J = 6.9 Hz, 5-CH), 2.64 (2H, dd, J = 7.2, 6.9 Hz, 4-CH₂), 2.10 (1H, s, NH), 1.66 (3H, s, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 195.0, 150.5, 144.1, 142.7, 140.9, 132.4, 128.5, 128.4, 127.5, 127.4, 127.34, 127.25, 127.19, 127.1, 125.9 (q, J = 6.0 Hz), 122.3, 64.1, 54.8, 38.2, 9.3; IR (film) 3331, 3058, 3024, 2922, 2819, 2710, 1684, 1643, 1490, 1453, 1310, 1245, 1157, 1123, 1059, 1038, 919, 862, 770, 746, 702 cm⁻¹; HRMS (EI) calcd for C₂₆H₂₄F₃NO (M⁺): 423.1810, Found: 423.1804.

(2E)-N-Benzhydryl-5-amino-2-methyl-5-(4-methoxyphenyl)pent-2-en-1-al (3f) : pale yellow viscous oil; ¹H NMR (300 MHz, CDCl₃) δ 9.41 (1H, s, CHO), 7.40-7.25 (10H, m, Ar-H), 7.21 (2H, d, J = 8.7 Hz, Ar-H), 6.96 (2H, d, J = 8.7

Hz, Ar-H), 6.53 (1H, td, J = 7.2, 1.5 Hz, 3-CH), 4.69 (1H, s, CHPh₂), 3.90 (3H, s, OMe), 3.71 (1H, t, J = 7.2 Hz, 5-CH), 2.83 (1H, ddd, J = 15.0, 7.2, 7.2 Hz, 4-CH₂), 2.70 (1H, ddd, J = 15.0, 7.2, 7.2 Hz, 4-CH₂), 1.98 (1H, br, NH), 1.72 (3H, s, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 195.1, 151.4, 144.3, 143.1, 140.5, 138.7, 134.7, 128.6, 128.4, 128.3, 128.0, 127.7, 127.2, 127.0, 114.1, 63.6, 58.6, 55.3, 37.8, 9.3; IR (film) 3317, 3058, 3024, 2997, 2949, 2928, 2833, 1681, 1643, 1606, 1511, 1490, 1453, 1358, 1300, 1246, 1174, 1106, 1028, 919, 868, 831, 746, 699 cm⁻¹; HRMS (EI) calcd for C₂₆H₂₇NO₂ (M⁺): 385.2120, Found: 385.2116.

(2E)-N-Benzhydryl-5-amino-5-cyclohexyloxycarbonyl-2-methylpent-2-en-1-al (3g) : colorless viscous oil; ¹H NMR (300 MHz, CDCl₃) δ 9.42 (1H, s, CHO), 7.43-7.18 (10H, m, Ar-H), 6.54 (1H, td, J = 7.2, 1.2 Hz, 3-CH), 4.90-4.80 (1H,

m, OCH), 4.83 (1H, s, CHPh₂), 3.35 (1H, t, J = 6.6 Hz, 5-CH), 2.72 (1H, ddd, J = 14.7, 7.2, 6.6 Hz, 4-CH₂), 2.63 (1H, ddd, J = 14.7, 7.2, 6.6 Hz, 4-CH₂), 2.29 (1H, br, NH), 1.94-1.65 (4H, m), 1.74 (3H, d, J = 0.9 Hz, CH₃), 1.60-1.51 (1H, m), 1.50-1.21 (5H, m); ¹³C NMR (75 MHz, CDCl₃) δ 194.9, 173.7, 149.5, 143.8, 142.4, 140.9, 128.59, 128.55, 127.6, 127.4, 127.3, 127.2, 73.7, 65.6, 58.3, 42.7, 40.8, 33.2, 31.7, 31.6, 25.2, 23.7, 9.4; IR (film) 3317, 3058, 3024, 2928, 2853, 1728, 1684, 1643, 1490, 1450, 1351, 1334, 1263, 1195, 1120, 1028, 1011, 960, 919, 838, 811, 790, 746, 702 cm⁻¹; HRMS (EI) calcd for C₂₆H₃₁NO₃ (M⁺): 405.2304, Found: 405.2310.

(2E)-N-Benzhydryl-5-amino-5-[(S)-8-phenylmenthyloxy]carbonyl]-2-methylpent-2-en-1-al (3h) : colorless viscous oil; ^1H NMR (300 MHz, CDCl_3 , 5-(*S*)/5-(*R*) = 11:1 mixture) δ 9.41 (0.08H, s, CHO), 9.38 (0.92H, s, CHO), 7.43-7.17 (11H, m, Ar-H), 7.12-7.06 (2H, m, Ar-H), 6.94-6.82 (2H, m,

Ar-H), 6.41 (0.05H, t, $J = 5.4$ Hz, 3-CH), 6.30 (0.95H, t, $J = 5.4$ Hz, 3-CH), 4.81 (1H, s, CHPh_2), 4.78 (1H, dt, $J = 10.8, 3.9$ Hz, OCH), 2.81 (1H, t, $J = 5.4$ Hz, 5-CH), 2.34 (1H, ddd, $J = 11.4, 5.4, 5.4$ Hz, 4- CH_2), 2.24 (1H, ddd, $J = 11.4, 5.4, 5.4$ Hz, 4- CH_2), 2.08-1.99 (1H, m), 2.03 (1H, br, NH), 1.94-1.87 (1H, m), 1.80-1.70 (1H, m), 1.66 (3H, s, 2- CH_3), 1.55-1.47 (1H, m), 1.31-1.08 (2H, m), 1.22 (3H, s, $\text{CPh}(\text{CH}_3)_2$), 1.17 (3H, s, $\text{CPh}(\text{CH}_3)_2$), 0.95-0.80 (2H, m), 0.88 (3H, d, $J = 4.8$ Hz, menthol- CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 194.9, 173.4, 151.9, 150.3, 144.0, 142.6, 140.3, 128.6, 127.8, 127.6, 127.4, 127.35, 127.28, 125.0, 124.9, 76.1, 65.6, 57.8, 50.3, 41.4, 39.3, 34.5, 32.9, 31.3, 28.7, 26.4, 23.9, 21.7, 9.4; IR (film) 3324, 3085, 3024, 2956, 2922, 1721, 1687, 1647, 1494, 1453, 1365, 1337, 1266, 1198, 1130, 1086, 1028, 981, 909, 845, 763, 743, 699 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{36}\text{H}_{43}\text{NO}_3$ (M^+): 537.3243, Found: 537.3236. The configuration was determined according to a literature.⁵ The imino (-)-8-phenylmenthol ester formed *S-cis* conformation in reaction conditions. Accordingly, the nucleophile attacks the imino carbon from the front side of the *S-cis* conformer, since the back side is blocked by an aromatic ring.

S-cis

***cis*-5-Methylpipecolinic acid ethyl ester (4a)** : To a solution of **3a** (199 mg, 0.566 mmol) in MeOH (5.7 mL) was added 10% Pd-C (30 mg) and the mixture was stirred for 4 h at room temperature under a H_2 atmosphere. The resulting mixture was filtered through a pad of Celite

and the filtrate was concentrated. The residue was purified by column chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 30:1$ to $15:1$ as eluent) to afford **4a** as a colorless oil (81.0 mg, 0.473 mmol, 84% yield, *cis/trans* = >20:1 determined by ^1H NMR analysis). ^1H NMR (300 MHz, CDCl_3 , *cis/trans* = >20:1 mixture) δ 4.20 (1H, q, $J = 7.2$ Hz, CH_2CH_3), 3.54 (1H, dd, $J = 4.8, 4.8$ Hz, 2-CH), 3.24 (<0.05H, dd, $J = 11.4, 3.0$ Hz, 6- CH_2), 3.04

(<0.05H, d, $J = 11.4$ Hz, 6-CH₂), 2.83 (>0.95H, ddd, $J = 11.7, 3.6, 1.2$ Hz, 6-CH₂), 2.50 (>0.95H, dd, $J = 11.7, 8.7$ Hz, 6-CH₂), 2.15 (1H, br, NH), 2.06 (1H, ddd, $J = 13.5, 9.0, 4.8$ Hz, 3-CH₂), 1.83-1.60 (3H, m, 3-CH₂ and 4-CH₂), 1.29 (3H, t, $J = 7.2$ Hz, CH₂CH₃), 1.18-1.05 (1H, m, 5-CH), 0.88 (3H, d, $J = 6.6$ Hz, 5-CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 174.1, 60.6, 56.3, 50.6, 30.2, 30.1, 26.1, 18.9, 14.2; IR (film) 3352, 2949, 2928, 2867, 1731, 1453, 1375, 1266, 1201, 1157, 1130, 1059, 1025, 906, 885, 862, 756 cm⁻¹; HRMS (EI) calcd for C₉H₁₇NO₂ (M⁺): 172.1338, Found: 172.1341.

Determination of configuration of *cis*-isomer 4a : To a suspension of LiAlH₄ (61 mg, 1.6 mmol) in Et₂O (2.4 mL) was added a solution of **4a** (138 mg, 0.806 mmol) in Et₂O (1.6 mL) at 0 °C and the mixture was stirred for 30 min at room temperature. The resulting mixture was quenched with NaF (0.27 g, 6.4 mmol) and H₂O (86 μ L, 4.8 mmol) at 0 °C and stirred for a few hours at room temperature. The white solid was removed by filtration and the filtrate was concentrated. The residue was dissolved in THF (4.0 mL), treated with NaHCO₃ (0.34 g, 4.0 mmol) and methylchloroformate (75 μ L, 0.97 mmol) at 0 °C. After stirring for 1 h at room temperature, the mixture was filtered. The filtrate was concentrated and the residue was dissolved in CH₂Cl₂ (4.0 mL). The solution was treated with Et₃N (134 μ L, 0.97 mmol) and triphenylmethylechloride (270 mg, 0.97 mmol) at 0 °C. After stirring for 2 h at room temperature, the volatiles were removed by evaporation and purification of the residue by column chromatography on silica gel (hexane/EtOAc = 7:1 to 4:1 as eluent) gave *cis*-*N*-methoxycarbonyl-5-methyl-2-triphenyl-methoxymethylpiperidine (**4d**, 31.5 mg, 0.073 mmol, 9% yield) as a colorless viscous oil. ¹H NMR (300 MHz, CDCl₃, 65: 35 mixture of rotamers) δ 7.43 (6H, d, $J = 6.9$ Hz, Ar-H), 7.32-7.20 (9H, m, Ar-H), 4.64 (0.35H, br, 2-CH), 4.44 (0.65H, br, 2-CH), 3.95 (0.65H, d, $J = 13.5$ Hz, 6-CH₂), 3.79 (0.35H, br, 6-CH₂), 3.72 (3H, s, COOCH₃), 3.27-3.15 (1H, m), 3.12-3.00 (1H, m), 2.18-2.01 (1H, m), 1.79-1.69 (1H, m), 1.67-1.57 (1H, m), 1.52-1.38 (2H, m), 0.97-0.70 (4H, m); ¹³C NMR (75 MHz, CDCl₃, mixture of rotamers) δ 156.5, 156.1, 144.0, 128.6, 127.7, 126.9, 86.5, 61.2, 61.0, 52.5, 50.0, 49.4, 46.7, 46.4, 30.9, 28.2, 25.9, 25.5, 19.9. IR (film) 3058, 3017, 2949, 2922, 2867, 1698, 1443, 1409, 1375, 1341, 1317, 1266, 1215, 1191, 1171, 1150, 1076, 1032, 987, 899, 763, 743, 702 cm⁻¹; HRMS (ESI) calcd for C₂₈H₃₁NO₃Na [(M+Na)⁺]: 452.2196, Found: 452.2195. In the literature⁶, the *trans*-isomer of **4d** was assigned based on a shift at 16.6 ppm in the ¹³C NMR spectrum attributed to the 5-Me substituent. The configuration of **4a** was assigned based by this data.

Cyclization of 3a in benzene under hydrogenation conditions : The same procedure described above using benzene instead of MeOH. Purification by column chromatography on silica gel (hexane/Et₂O = 30:1 to 15:1 as eluent) gave **4b** and **4c**.

***cis*-N-Benzhydryl-5-methylpipecolinic acid ethyl ester (4b) :**

cis/trans = >20:1 determined by ¹H NMR analysis. colorless viscous oil; ¹H NMR (300 MHz, CDCl₃, *cis/trans* = >20:1 mixture) δ 7.47 (2H, d, *J* = 7.2 Hz, Ar-H), 7.33-7.14 (8H, m, Ar-H), 5.12 (>0.95H, s, CHPh₂), 5.04 (<0.05H, s, CHPh₂), 4.09 (1H, q, *J* = 7.2 Hz, CH₂CH₃), 4.08 (1H, q, *J* = 7.2 Hz, CH₂CH₃), 3.45 (1H, dd, *J* = 5.4, 2.7 Hz, 2-CH), 3.17 (<0.05H, dd, *J* = 7.8, 4.5 Hz, 6-CH₂), 2.91 (<0.05H, d, *J* = 7.8 Hz, 6-CH₂), 2.66 (>0.95H, dd, *J* = 11.7, 4.8 Hz, 6-CH₂), 2.56 (>0.95H, dd, *J* = 11.7, 11.0 Hz, 6-CH₂), 2.01 (1H, dddd, *J* = 13.6, 6.0, 6.0, 2.7 Hz, 3-CH₂), 1.81 (1H, dddd, *J* = 13.6, 13.6, 5.4, 3.9 Hz, 3-CH₂), 1.72-1.58 (2H, m, 4-CH₂), 1.21 (3H, t, *J* = 7.2 Hz, CH₂CH₃), 1.02-0.87 (1H, m, 5-CH), 0.76 (3H, d, *J* = 6.6 Hz, 5-CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 173.5, 144.2, 142.3, 128.44, 128.40, 127.5, 127.0, 126.6, 71.9, 59.5, 57.2, 53.1, 31.2, 29.9, 28.7, 19.6, 14.3; IR (film) 3058, 3024, 2949, 2922, 2867, 1728, 1596, 1490, 1450, 1371, 1300, 1273, 1266, 1181, 1154, 1133, 1021, 984, 967, 919, 743,

702 cm⁻¹; HRMS (EI) calcd for C₂₂H₂₇NO₂ (M⁺): 337.2042, Found: 337.2043. The configuration of **4b** was determined by conversion to **4a** under hydrogenation conditions (Pd-C, MeOH, room temperature).

***N*-Benzhydryl-5-methyl-1,2,3,4-tetrahydro-pyridine-2-carboxylic acid ethyl ester (**4c**)** :

pale yellow viscous oil; ¹H NMR (300 MHz, CDCl₃) δ 7.36-7.20 (10H, m, Ar-H), 5.68 (1H, s, 6-CH), 5.38 (1H, s, CHPh₂), 4.14 (1H, q, *J* = 7.2 Hz, CH₂CH₃), 4.13 (1H, q, *J* = 7.2 Hz, CH₂CH₃), 3.73 (1H, dd, *J* = 3.6, 3.6 Hz, 2-CH), 2.19-2.10 (1H, m, 3-CH₂), 1.95-1.79 (3H, m, 3-CH₂ and 4-CH₂), 1.51 (3H, s, 5-CH₃), 1.24 (3H, t, *J* = 7.2 Hz, CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 173.3, 141.6, 141.0, 128.9, 128.6, 128.5, 128.3, 127.3, 127.1, 126.8, 104.5, 70.0, 60.5, 57.2, 25.0, 24.4, 21.0, 14.3; IR (film) 3058, 3023, 2976, 2956, 2915, 2881, 1735, 1664, 1599, 1490, 1446, 1368, 1337, 1269, 1171, 1123, 1059, 1025, 987, 923, 858, 743, 699 cm⁻¹; HRMS (EI) calcd for C₂₂H₂₅NO₂ (M⁺): 335.1885, Found: 335.1888.

(2*E*)-*N*-Benzhydryl-5-amino-5-cyclohexyloxycarbonyl-2-(4-methoxyphenyl)-2-en-1-nal (6**)** :

The reaction was performed by the same procedure described above using 2-(4-methoxyphenyl)-3-vinyloxirane⁷ **5** (2.0 equiv, 1:1 mixture of isomers) instead of **1**. pale yellow viscous oil; ¹H NMR (300 MHz, CDCl₃) δ 9.62 (1H, s, CHO), 7.41 (2H, d, *J* = 7.8 Hz, Ar-H), 7.36-7.17 (8H, m, Ar-H), 7.10 (2H, dt, *J* = 8.7, 2.4 Hz, Ar-H), 6.92 (2H, dt, *J* = 8.7, 2.4 Hz, Ar-H), 6.73 (1H, t, *J* = 7.2 Hz, 3-CH), 4.87-4.77 (1H, m, OCH), 4.80 (1H, s, CHPh₂), 3.82 (3H, s, OCH₃), 3.34 (1H, dd, *J* = 7.2, 6.3 Hz, 5-CH), 2.80-2.61 (2H, m, 4-CH₂), 2.24 (1H, br, NH), 1.90-1.18 (10H, m); ¹³C NMR (75MHz, CDCl₃) δ 193.7, 173.5, 159.4, 151.0, 144.8, 143.8, 142.4, 130.7, 130.6, 128.6, 128.5, 127.6, 127.4, 127.3, 127.1, 124.2, 113.8, 113.7, 73.6, 65.5, 58.5, 55.2, 33.8, 31.7, 31.5, 25.2, 23.6; IR (film) 3324, 3058, 3024, 2935, 2853, 1725, 1687, 1606, 1511, 1453, 1412, 1334, 1290, 1246, 1178, 1133, 1032, 967, 909, 834, 743, 702 cm⁻¹; HRMS (EI) calcd for C₃₂H₃₅NO₄

(M⁺): 497.2566, Found: 497.2574.

***N*-Benzhydryl-5-(4-methoxyphenyl)-1,2,3,4-tetrahydro-pyridine-2-carboxylic acid cyclohexyl ester (7)** : A solution of **6** (278 mg, 0.558 mmol) in EtOAc (5.6 mL) was stirred for 4 h in the presence of 10% Pd-C (30 mg) at room temperature under a H₂ atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (hexane/Et₂O = 20:1 to 10:1 as eluent) and the enamine **7** was obtained as a pale yellow viscous oil (215 mg, 0.446 mmol, 80% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.36-7.23 (10H, m, Ar-H), 6.98 (2H, dt, *J* = 8.7, 2.4 Hz, Ar-H), 6.73 (2H, dt, *J* = 8.7, 2.4 Hz, Ar-H), 6.43 (1H, s, 6-CH), 5.58 (1H, s, CHPh₂), 4.88-4.78 (1H, m, OCH), 3.87 (1H, dd, *J* = 4.5, 3.9 Hz, 2-CH), 3.73 (3H, s, OCH₃), 2.46-2.18 (3H, m), 2.04-1.91 (1H, m), 1.90-1.62 (4H, m), 1.57-1.20 (6H, m); ¹³C NMR (75MHz, CDCl₃) δ 172.4, 156.6, 140.7, 140.6, 134.6, 129.3, 128.62, 128.56, 128.44, 128.42, 127.54, 127.47, 123.8, 113.8, 105.7, 73.1, 70.2, 57.8, 55.3, 31.6, 25.4, 25.1, 23.65, 23.62, 21.3; IR (film) 3058, 3024, 2935, 2853, 1728, 1630, 1511, 1450, 1399, 1365, 1280, 1242, 1178, 1133, 1072, 1038, 923, 824, 746, 699 cm⁻¹; HRMS (EI) calcd for C₃₂H₃₅NO₃ (M⁺): 481.2617, Found: 481.2612.

***cis*-N-Benzhydryl-5-(4-methoxyphenyl)pipecolinic acid cyclohexyl ester (8)** : A solution of enamine **7** (194 mg, 0.403 mmol) was dissolved in THF (2.0 mL) and treated with NaBH₃CN (51 mg, 0.81 mmol) at 0 °C. To the resulting mixture was added AcOH (0.81 mL) and the solution was stirred for 30 min at the same temperature. After stirring for 30 min more at room temperature, the resulting mixture was treated with saturated NaHCO₃. The reaction was extracted with Et₂O and the combined extracts were washed with saturated NaHCO₃ and brine, dried over Na₂SO₄ and concentrated. Purification of the residue by chromatography on silica gel (hexane/Et₂O = 20:1 to 10:1) gave **8** as a colorless viscous oil (188 mg, 0.389 mmol, 97% yield, *cis/trans* = >20:1 determined by ¹H NMR analysis). ¹H NMR (300 MHz, CDCl₃, *cis/trans* = >20:1 mixture) δ 7.47 (2H, d, *J* = 7.2 Hz, Ar-H), 7.35 (2H, d, *J* = 7.2 Hz, Ar-H), 7.27-7.19 (4H, m, Ar-H), 7.18-7.10 (2H, m, Ar-H), 7.06 (2H, dd, *J* = 9.0, 2.4 Hz, Ar-H), 6.77 (2H, dd, *J* = 9.0, 2.4 Hz, Ar-H), 5.17 (>0.95H, s, CHPh₂), 5.10 (<0.05H, s, CHPh₂), 4.87-4.78 (1H, m, OCH), 3.76 (<0.15H, s, OCH₃), 3.74 (>2.85H, s,

OCH₃), 3.51 (1H, dd, $J = 5.1, 2.1$ Hz, 2-CH), 3.05 (1H, t, $J = 11.7$ Hz, 6-CH₂), 2.87-2.72 (2H, m, 5-CH and 6-CH₂), 2.13 (1H, ddd, $J = 13.2, 6.0, 3.3$ Hz), 2.00-1.63 (6H, m), 1.59-1.22 (7H, m); ¹³C NMR (75MHz, CDCl₃) δ 172.9, 158.0, 143.9, 142.3, 136.9, 128.5, 128.44, 128.41, 128.1, 127.4, 127.0, 126.7, 113.6, 72.09, 72.06, 57.1, 55.2, 52.4, 42.2, 31.75, 31.68, 28.8, 25.4, 23.7; IR (film) 3058, 3024, 2935, 2853, 1721, 1609, 1511, 1490, 1450, 1358, 1300, 1246, 1181, 1147, 1117, 1069, 1035, 1011, 991, 923, 842, 787, 743, 702 cm⁻¹; HRMS (EI) calcd for C₃₂H₃₇NO₃ (M⁺): 483.2773, Found: 483.2767.

***cis*-5-(4-Methoxyphenyl)pipecolinic acid ethyl ester**

(9) : To a solution of **8** (180 mg, 0.371 mmol) in MeOH (3.7 mL) and EtOAc (0.74 mL) was added a 1M HCl solution in MeOH (0.74 mL, 0.74 mmol, prepared from *conc* HCl and MeOH) and 10% Pd-C (39 mg) at room

temperature. The mixture was stirred for 2 h under a H₂ atmosphere and filtered through a pad of Celite. After excess MeOH was removed by evaporation, the solution was treated with saturated NaHCO₃. The mixture was extracted with Et₂O and the combined extracts were washed with saturated NaHCO₃ and brine. The solution was dried over Na₂SO₄ and concentrated. The residue was purified by chromatography on silica gel (CH₂Cl₂/MeOH = 30:1 to 15:1) and **9** was obtained as a pale yellow viscous oil (107 mg, 0.337 mmol, 91% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.12 (2H, dt, $J = 8.4, 2.4$ Hz, Ar-H), 6.83 (2H, dt, $J = 8.4, 2.4$ Hz, Ar-H), 4.94-4.84 (1H, m, OCH), 3.78 (3H, s, OCH₃), 3.66 (1H, dd, $J = 5.1, 2.7$ Hz, 2-CH), 2.97 (1H, ddd, $J = 11.7, 3.9, 1.2$ Hz, 6-CH₂), 2.89 (1H, dd, $J = 11.7, 10.8$ Hz, 6-CH₂), 2.72 (1H, tt, $J = 10.8, 3.9$ Hz, 5-CH), 2.43 (1H, br, NH), 2.29 (1H, ddd, $J = 13.5, 6.6, 3.9$ Hz), 1.97-1.80 (4H, m), 1.79-1.68 (2H, m), 1.64-1.24 (7H, m); ¹³C NMR (75MHz, CDCl₃) δ 173.5, 158.0, 136.7, 128.0, 113.7, 73.0, 55.4, 55.2, 49.9, 41.6, 31.7, 31.6, 28.9, 26.8, 25.3, 23.7; IR (film) 3345, 2928, 2853, 1721, 1609, 1511, 1453, 1354, 1300, 1242, 1195, 1157, 1120, 1110, 1059, 1035, 1015, 926, 916, 828, 783, 770, 743 cm⁻¹; HRMS (EI) calcd for C₁₉H₂₈NO₃ ([M+H]⁺): 318.2069, Found: 318.2076.

Determination of configuration in **8 and **9**** : The configurations were determined by another experimental result. Treatment of amino aldehyde **6** under a H₂ atmosphere in acidic conditions (AcOH) gave **9** in only one step with excellent diastereoselectivity. The yield was low due to the sensitivity of the substrate or intermediate under acidic condition (35%). It is expectable that the reaction proceeded via the same intermediate with

hydrogenation of **3a**. Based on the result, the configurations of **8** and **9** were also determined.

Determination of *cis/trans* diastereoselectivities of **4a**, **4b** or **8**, **9** by ^1H NMR analysis:

To determine the *cis/trans* diastereoselectivities, a mixture of the *cis* and *trans*-isomer was prepared by epimerization of the corresponding amino acid ester using excess LiHMDS (5 equiv) in THF. In each case, the amount of the *trans*-isomer increased after epimerization.

***trans*-5-Methylpipecolinic acid ethyl ester (*trans*-4a)** : The following shifts were assigned to the *trans*-isomer. ^1H NMR (300 MHz, CDCl_3) δ 3.24 (dd, $J = 11.4, 3.0$ Hz, 6- CH_2), 3.04 (d, $J = 11.4$ Hz, 6- CH_2),

***trans*-*N*-Benzhydryl-5-methylpipecolinic acid ethyl ester (*trans*-4b)** : The following shifts were assigned to the *trans*-isomer. ^1H NMR (300 MHz, CDCl_3) δ 5.04 (s, CHPh_2), 3.17 (dd, $J = 7.8, 4.5$ Hz, 6- CH_2), 2.91 (d, $J = 7.8$ Hz, 6- CH_2).

***trans*-*N*-Benzhydryl-5-(4-methoxyphenyl)pipecolinic acid cyclohexyl ester (*trans*-8)** :

The following shifts were assigned to the *trans*-isomer. ^1H NMR (300 MHz, CDCl_3) δ 5.10 (s, CHPh_2), 3.76 (s, OCH_3).

***trans*-5-(4-Methoxyphenyl)pipecolinic acid ethyl ester (*trans*-9)** : This isomer could not be assigned cleanly by ^1H NMR analysis.

2-Methyl-3-butenal: Prepared according to a literature⁸ using crotyl bromide instead of allyl bromide. colorless oil; ^1H NMR (300 MHz, CDCl_3) δ 9.60 (1H, d, $J = 1.2$ Hz, CHO), 5.83 (1H, ddd, $J = 17.5, 10.5, 7.2$ Hz, $\text{CH}_2=\text{CH}$), 5.31-5.29, 5.27-5.24 and 5.20-5.19 (2H, m, $\text{CH}_2=\text{CH}$ and $\text{CH}_2=\text{CH}$), 3.09 (1H, dqdd, $J = 7.2, 6.6, 2.7, 1.2$ Hz, CHCHO), 1.23 (3H, d, $J = 6.6$ Hz, CH_3); ^{13}C NMR (75MHz, CDCl_3) δ 201.7, 134.4, 118.2, 50.8, 12.9; IR (film) 3085, 2976, 2935, 2874, 2812, 2717, 1728, 1633, 1453, 1416, 1392, 1269, 1113, 994, 923, 783, 736 cm^{-1} .

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