SUPPORTING INFORMATION

Stereoselective Synthesis of 2,6-Disubstituted 3-Piperidinols: Application to the Expedient Synthesis of (+)-Julifloridine.

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General information. Experimental procedures and characterization data for new compounds. ^1H , ^{13}C and ^{19}F NMR spectra of selected compounds.

General Information. Unless otherwise stated, reactions were run under argon atmosphere with rigid exclusion of moisture from reagents and glassware using standard techniques for manipulating air-sensitive compounds.¹ All glassware were rinsed with a base bath, left to stand for 15 min., washed with water, then acetone and stored in the oven and/or were flame-dried under an argon atmosphere prior to use.² Dichloromethane, diethyl ether, tetrahydrofuran and methanol were obtained by filtration through drying columns on a GlassContour system (Irvine, CA). Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel (Merck 60 F₂₅₄). Visualization of the developed chromatogram was performed by UV and aqueous potassium permanganate. Flash column chromatography was performed using 230-400 mesh silica (EM Science or Silicycle). Melting points were obtained on a Buchi melting point apparatus and are uncorrected. Optical rotations were determined with a Perkin-Elmer 341 polarimeter at 589 nm. Data are reported as follows: $[\alpha]_D^{20}$ (observed rotation x volume (mL)/[length (dm) x mass (g)]), concentration (c in g/100 mL), and solvent. Nuclear magnetic resonance spectra were recorded either on a Bruker AV 300, AMX 300, AV 400, ARX 400 or DMX 600 spectrometer. Chemical shifts for ¹H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sx = sextet, sp = septet, o = octet, m = multiplet and br = broad), coupling constant in Hz, integration. Chemical shifts for ¹³C NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of the solvent resonance as the internal standard. All ¹³C NMR spectra were obtained with complete proton decoupling. When ambiguous, proton and carbon assignments were established using homonuclear decoupling, COSY, NOESY, HMQC, HMBC and DEPT experiments. Chemical shifts for ¹⁹F NMR spectra are recorded in parts per million from fluorotrichloromethane using trifluoroacetic acid resonance as the internal standard. Infrared spectra were recorded with a Perkin Elmer Spectrum One FTIR. High resolution mass spectra were performed by the Centre régional de spectroscopie de masse de l'Université de Montréal. Low resolution mass spectra were performed on a Agilent 1100 Series LC/MSD. Combustion analyses were performed by the Laboratoire d'analyse élémentaire de l'Université de Montréal.

Reagents: Unless otherwise stated, commercial reagents were used without purification. Triflic anhydride was distilled over a small amount of P₂O₅. Pyridine and isopropanol were distilled over calcium hydride. Dimethyldioxirane solution in acetone was prepared according to literature procedure, redistilled over potassium carbonate³ and titrated with thioanisole before use. *t*-BuLi, methyl- and phenylmagnesium bromide were purchased from Strem Chemicals. Diethylzinc was purchased from Akzo-Nobel. 2.0 M dimethylzinc in toluene was purchased from Aldrich Co. Anhydrous zinc bromide was used to prepare organozinc bromides. Amides **15**, **15a** and 2-substituted 1,2-dihydropyridines **11b-11e** were prepared according to literature procedure.⁴

(1) Shriver, D. F.; Drezdson, M. A. *The manipulation of air-sensitive compounds*; 2nd Edition ed.; Wiley: New York, 1986.

(2) Waldemar, A.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, 124, 2377.

(3) Considerable loss in yield (ca. 20%) occurs when redistillation is omitted.

(4) Charette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. J. *Am. Chem. Soc.* **2001**, 123, 11829-11830.

Experimental Procedures and Characterization Data.

***N*-{[(1*S*)-1-[(benzyloxy)methyl]-2-methylpropyl]-*N*-{[(1*E*)-phenyl[(2*S*)-2-phenylpyridin-1(2*H*)-yl]methylene}amine (11a).** The amide **15a** (1.5 g, 5.0 mmol) was dissolved in 25 mL of dichloromethane. Pyridine (1.2 mL, 1.2 g, 15 mmol) was added and the mixture was cooled to -40°C . Triflic anhydride (1.0 mL, 1.7 g, 6.0 mmol) was added dropwise, the mixture was warmed to -10°C and stirred at that temperature for 48 hours. In a separate flask, phenyllithium (12.5 mL, 12.5 mmol, 1.0 M in diethyl ether, containing lithium bromide⁵) was cooled to $0-5^\circ\text{C}$ in an ice bath and solid magnesium bromide diethyl etherate (3.3 g, 12.5 mmol) was added rapidly in one portion *via* septum. The suspension was warmed to room temperature, stirred 60 min and then charged in a syringe. The pyridinium salt was cooled to -30°C and the freshly prepared phenylmagnesium bromide (containing 2 equivalents of lithium bromide) was added over a period of 75 min *via* syringe pump. The mixture was stirred at -30°C for 4.5 h then the reaction was quenched by addition of a solution of saturated sodium bicarbonate. The mixture was transferred to a separatory funnel and extracted three times with dichloromethane. The combined organic phases were dried with sodium sulfate, filtered and concentrated under reduced pressure. Flash chromatography of the oily residue (gradient 0-10% EtOAc/hexane) afforded 1.7 g of **11a** (77%) as a pale yellow oil. R_f 0.47 (10 % EtOAc/hexane); $[\alpha]_D^{20} = -633$ (c 1.29, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz) δ 7.60 (d, $J = 6.2$, Hz, 2H), 7.45-7.24 (m, 9H), 7.20-7.12 (m, 4H), 6.53 (br s, 1H), 6.16 (br s, 1H), 6.03 (dd, $J = 9.3$, 5.5 Hz, 1H), 5.70 (dd, $J = 9.2$, 5.8 Hz, 1H), 4.92 (t, $J = 6.2$ Hz, 1H), 4.18 (s, 2H), 3.48 (dd, $J = 9.2$, 4.5 Hz, 1H), 3.19 (t, $J = 8.5$ Hz, 1H), 3.06 (dt, $J = 7.4$, 4.4 Hz, 1H), 1.76 (dsp, $J = 4.9$, 6.5 Hz, 1H), 0.95 (d, $J = 6.7$ Hz, 3H), 0.81 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 157.0, 144.5, 139.1, 133.0, 129.9, 129.2, 128.9, 128.7, 128.6, 128.5, 128.3 (2), 128.2 (2), 127.7 (2), 127.3, 127.0 (3), 121.2, 121.1, 100.2, 73.7, 73.2, 64.0, 56.1, 30.8, 20.3, 17.9; FTIR (neat) 3029, 2956, 1629, 1599, 1571, 1333, 1106, 697 cm^{-1} ; HRMS (ES) calcd for $\text{C}_{30}\text{H}_{33}\text{N}_2\text{O}$ ($M + \text{H}$)⁺: 437.2593, found 437.2580.

***N*-{[(1*S*)-1-[(benzyloxy)methyl]-2-methylpropyl]-*N*-{[(1*E*)-phenyl[(2*S*)-2-phenyl-3,4-dihydropyridin-1(2*H*)-yl]methylene}amine (12a).** The dihydropyridine derivative **11a** (2.2 g, 5.1 mmol) was dissolved in 17 mL of acetonitrile. The palladium catalyst (160 mg of 10 wt. % Pd/C, 0.15 mmol Pd) was added and the mixture purged three times with hydrogen atmosphere. The mixture was stirred for 2 hours at room temperature under hydrogen atmosphere (1.0 bar), then filtered through Celite®, rinsed with CH_2Cl_2 and concentrated under reduced pressure. Flash

(5) Prepared from bromobenzene and lithium wire (1% sodium content) following a known procedure: Cocker, W.; Geraghty, N. W. A.; Shannon, P. V. R. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2241-2243.

chromatography of the oily residue (gradient 0-25% EtOAc/hexane) afforded 1.8 g of **12a** (77%) as a pale yellow solid: Mp 45 °C; R_f 0.27 (10 % EtOAc/hexane); $[\alpha]_D^{20} = -58.6$ (c 2.08, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz) δ 7.33-7.17 (m, 14H), 6.96 (br s, 1H), 6.58 (br s, 1H), 5.59 (br s, 1H), 4.60 (br t, 1H), 4.16 (s, 2H), 3.35 (dd, $J = 9.4, 4.7$ Hz, 1H), 3.10 (t, $J = 8.9$ Hz, 1H), 2.90 (dt, $J = 7.3, 4.8$, 1H), 2.12-2.05 (m, 2H), 1.92 (br d, $J = 16$ Hz, 1H), 1.82 (dd, $J = 9.8, 7.8$ Hz, 1H), 1.70 (dsp, $J = 5.2, 6.6$ Hz, 1H), 0.84 (d, $J = 6.7$ Hz, 3H), 0.74 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 157.0, 143.8, 139.3, 133.7, 129.1, 128.6, 128.4 (3), 128.3 (3), 128.1 (2), 127.6 (2), 127.3, 126.2 (3), 101.5, 73.8, 73.1, 63.9, 54.4, 30.9, 28.0, 20.3, 18.4, 18.0; FTIR (neat) 3062, 2954, 1619, 1598, 1340, 1268, 1107, 697 cm^{-1} ; LRMS (APCI) calcd for $\text{C}_{30}\text{H}_{35}\text{N}_2\text{O}$ ($M + \text{H}$) $^+$: 439.3, found 439.3; Anal. calcd for $\text{C}_{30}\text{H}_{34}\text{N}_2\text{O}$: C, 82.15; H, 7.81; N, 6.39, found C, 82.10; H, 8.11; N, 6.06.

***N*-{[(1*S*)-1-[(methoxy)methyl]-2-methylpropyl]-*N*-{[(1*E*)-[(2*R*)-2-methyl-3,4-dihydropyridin-1(2*H*)-yl](phenyl)methylene}amine (**12b**).** The dihydropyridine derivative **11b** (602 mg, 2.02 mmol) was dissolved in 6.75 mL of acetonitrile. The palladium catalyst (11 mg of 10 wt. % Pd/C, 0.10 mmol) was added and the mixture purged three times with hydrogen atmosphere. The mixture was stirred for 2 hours at room temperature under hydrogen atmosphere (1.0 bar), then filtered through Celite®, rinsed with CH_2Cl_2 and concentrated under reduced pressure. Flash chromatography of the oily residue (gradient 0-25% EtOAc/hexane) afforded 569 mg of **12b** (86 %) as a pale yellow oil. R_f 0.20 (10 % EtOAc/hexane); $[\alpha]_D^{20} = -143$ (c 3.92, C_6H_6); ^1H NMR (CD_2Cl_2 , 600 MHz) δ 7.40 (dt, $J = 7.2, 1.3$ Hz, 2H), 7.36 (tt, $J = 7.2, 1.6$ Hz, 1H), 7.20 (br s, 1H), 7.11 (br s, 1H), 6.10 (br s, 1H), 4.59 (br s, 1H), 4.46 (br t, 1H), 3.39 (dd, $J = 9.5, 5.3$ Hz, 1H), 3.24 (dd, $J = 9.2, 7.2$ Hz, 1H), 3.23 (s, 3H), 2.83 (dt, $J = 6.9, 4.9$ Hz, 1H), 2.18 (m, 1H), 1.97 (dt, $J = 14.2, 5.5$ Hz, 1H), 1.80 (tt, $J = 12.5, 5.3$ Hz, 1H), 1.70 (dd, $J = 12.5, 5.3$ Hz, 1H), 1.64 (dsp, $J = 6.9, 4.9$ Hz, 1H), 1.13 (d, $J = 6.2$ Hz, 3H), 0.83 (d, $J = 6.6$ Hz, 3H), 0.71 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (C_6D_6 , 100 MHz) δ 157.4, 134.7, 130.1, 129.4, 128.9 (3), 128.0, 100.4, 77.1, 64.2, 59.3, 46.3, 31.8, 27.7, 20.7, 19.0, 18.5, 16.5; FTIR (neat) 3063, 1614, 1597, 1343, 1111, 768, 702 cm^{-1} ; LRMS (APCI) calcd for $\text{C}_{19}\text{H}_{29}\text{N}_2\text{O}$ ($M + \text{H}$) $^+$: 301.2, found 301.2; Anal. calcd for $\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}$: C, 75.96; H, 9.39; N, 9.32, found C, 75.63; H, 9.69; N, 9.23.

***N*-{[(1*E*)-[(2*R*)-2-ethyl-3,4-dihydropyridin-1(2*H*)-yl](phenyl)methylene]-*N*-{[(1*S*)-1-[(methoxy)methyl]-2-methylpropyl]-amine (**12c**).** The dihydropyridine derivative **11c** (1.65 g, 5.29 mmol) was dissolved in 18 mL of acetonitrile. The palladium catalyst (155 mg of 10 wt. % Pd/C, 0.15 mmol) was added and the mixture purged three times with hydrogen atmosphere. The mixture was stirred for 2 hours at room temperature under hydrogen atmosphere (1.0 bar), then filtered through Celite®, rinsed with CH_2Cl_2 and concentrated under reduced pressure. Flash chromatography of the oily residue (gradient 0-25% EtOAc/hexane) afforded 0.96 g of **12c** (58 %)

as a pale yellow oil. R_f 0.23 (25 % EtOAc/hexane); $[\alpha]_D^{20} = -175$ (c 1.50, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz) δ 7.42-7.32 (m, 3H), 7.19 (d, $J = 6.1$ Hz, 1H), 7.10 (d, $J = 5.6$ Hz, 1H), 6.05 (br s, 1H), 4.58 (br s, 1H), 4.42 (br t, $J = 6.2$ Hz, 1H), 3.42 (dd, $J = 9.5, 5.5$ Hz, 1H), 3.23 (s, 3H), 3.22 (dd, $J = 9.5, 7.3$ Hz, 1H), 2.89 (dt, $J = 6.5, 5.3$ Hz, 1H), 2.11 (dddd, $J = 17.4, 12.8, 6.1, 2.4, 1.8$ Hz, 1H), 1.99-1.87 (m, 2H), 1.80-1.63 (m, 3H), 1.47 (dq, $J = 14.4, 7.4, 4.5$ Hz, 1H), 0.91 (t, $J = 7.5$ Hz, 3H), 0.87 (d, $J = 6.8$ Hz, 3H), 0.74 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 157.2, 134.3, 128.9, 128.8, 128.5, 128.3 (2), 127.7, 100.4, 76.3, 63.2, 59.0, 50.9, 30.8, 23.7, 23.1, 20.3, 18.5, 17.7, 10.8; FTIR (neat) 3064, 2959, 1617, 1598, 1345, 1113, 702 cm^{-1} ; LRMS (APCI) calcd for $\text{C}_{20}\text{H}_{31}\text{N}_2\text{O}$ ($M + \text{H}$) $^+$: 315.2, found 315.3; Anal. calcd for $\text{C}_{20}\text{H}_{30}\text{N}_2\text{O}$: C, 76.39; H, 9.62; N, 8.91, found C, 76.55; H, 9.90; N, 8.66.

***N*-{[(1*S*)-1-[(methoxy)methyl]-2-methylpropyl]-*N*-{[(1*E*)-[2-(2-furyl)-3,4-dihydropyridin-1(2*H*)-yl](phenyl)methylene}amine (12d).** The dihydropyridine derivative **11d** (482 mg, 1.38 mmol) was dissolved in 4.7 mL of acetonitrile. The palladium catalyst (40 mg of 10 wt. % Pd/C, 0.037 mmol Pd) was added and the mixture purged three times with hydrogen atmosphere. The mixture was stirred for 1 hour at room temperature under hydrogen atmosphere (1.0 bar), then filtered through Celite®, rinsed with CH_2Cl_2 and concentrated under reduced pressure. Flash chromatography of the oily residue (gradient 0-25% EtOAc/hexane) afforded 381 mg of **12d** (79%) as a pale yellow oil. R_f 0.42 (25 % EtOAc/hexane); $[\alpha]_D^{20} = -113$ (c 2.79, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz) δ 7.33-7.45 (m, 3H), 7.30 (bs, 1H), 7.24 (bd, $J = 5.4$, 1H), 7.05 (br s, 1H), 6.42 (br s, 1H), 6.30 (dd, $J = 3.2, 1.8$ Hz, 1H), 6.15 (dt, $J = 3.2, 1.0$ Hz, 1H), 5.64 (br s, 1H), 4.56 (br s, 1H), 3.35 (dd, $J = 9.5, 5.1$ Hz, 1H), 3.16 (s, 3H), 3.11 (dd, $J = 9.6, 7.3$ Hz, 1H), 2.88 (dt, $J = 7.1, 5.0$ Hz, 1H), 2.27 (bd, $J = 6.4$ Hz, 1H), 1.95 (m, 3H), 1.69 (dsp, $J = 6.8, 5.0$ Hz, 1H), 0.89 (d, $J = 6.8$ Hz, 3H), 0.75 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 156.8, 155.6, 140.8, 133.6, 128.9, 128.6 (3), 128.3, 127.2, 110.2, 106.0, 101.4, 76.0, 63.6, 59.1, 49.2, 30.8, 25.5, 20.3, 19.2, 18.0; FTIR (neat) 3062, 1622, 1599, 1344, 1303 cm^{-1} ; HRMS (FAB) calcd for $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_2$ (M) $^+$: 352.2167, found 352.2151; Anal. calcd for $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_2$: C, 74.97; H, 8.01; N, 7.95, found C, 74.61; H, 8.31; N, 7.91.

***N*-{[(1*S*)-1-[(methoxy)methyl]-2-methylpropyl]-*N*-{[(1*E*)-phenyl[2-phenyl-3,4-dihydropyridin-1(2*H*)-yl]methylene}amine (12e).** The dihydropyridine derivative **11e** (2.6 g, 7.2 mmol) was dissolved in 24 mL of acetonitrile. The palladium catalyst (160 mg of 10 wt. % Pd/C, 0.15 mmol Pd) was added and the mixture purged three times with hydrogen atmosphere. The mixture was stirred for 3 hours at room temperature under hydrogen atmosphere (1.0 bar), then filtered through Celite®, rinsed with CH_2Cl_2 and concentrated under reduced pressure. Flash chromatography of the oily residue (gradient 0-25% EtOAc/hexane) afforded 2.0 g of **12e** (78%) as a colorless oil. R_f 0.33 (25 % EtOAc/hexane); $[\alpha]_D^{20} = -67.9$ (c 2.97, C_6H_6); ^1H NMR (C_6D_6 , 300

MHz) δ 7.43 (br s, 1H), 7.29 (d, J = 7.3 Hz, 2H), 7.20 (t, J = 7.3 Hz, 3H), 7.09 (t, J = 7.2 Hz, 2H), 7.05-6.90 (br m, 3H), 5.80 (br s, 1H), 4.55 (br s, 1H), 3.28 (dd, J = 8.5, 4.1 Hz, 1H), 3.15-2.98 (m, 2H), 2.93 (s, 3H), 2.01 (tt, J = 12.7, 5.0 Hz, 1H), 1.90-1.65 (m, 4H), 1.03 (d, J = 6.7 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H); ^{13}C NMR (C_6D_6 , 75 MHz) δ 157.3, 144.4, 134.5, 129.8, 128.9, 128.8, 128.6 (5), 126.8 (2), 126.8, 101.8, 76.6, 64.3, 59.0, 55.1, 31.5, 28.5, 20.7, 18.9, 18.5; FTIR (neat) 3062, 3028, 1621, 1598, 1340, 1301, 1114, 987, 699 cm^{-1} ; LRMS (APCI) calcd for $\text{C}_{24}\text{H}_{31}\text{N}_2\text{O}$ ($\text{M} + \text{H}$) $^+$: 363.2, found 363.2. Anal. calcd for $\text{C}_{24}\text{H}_{30}\text{N}_2\text{O}$: C, 79.52; H, 8.34; N, 7.73, found C, 79.32; H, 8.58; N, 7.77.

(2R,3R,6S)-1-[(E)-((1S)-1-[(benzyloxy)methyl]-2-methylpropyl)imino)(phenyl)methyl]-2-methoxy-6-phenylpiperidin-3-ol (13a). The tetrahydropyridine derivative **12a** (314 mg, 0.717 mmol) was dissolved in 4.8 mL THF, 3.0 mL of dry methanol (2.4 g, 75 mmol) was added and the mixture was cooled to $-78\text{ }^\circ\text{C}$. A $-78\text{ }^\circ\text{C}$ solution of dimethyldioxirane (8.5 mL of a 0.093 M solution in acetone, 0.79 mmol) was added rapidly using a syringe, the mixture stirred at $-78\text{ }^\circ\text{C}$ for 2 hours and concentrated under reduced pressure. Flash chromatography of the oily residue (gradient 10-50% EtOAc/hexane containing 1% Et_3N) afforded 286 mg of **13a** (82%) as a colorless oil. R_f 0.22 (50 % EtOAc/hexane); $[\alpha]_D^{20}$ = 96.1 (c 3.27, MeOH); ^1H NMR (CD_3OD , 400 MHz) δ 7.40 (dd, J = 5.7, 2.0 Hz, 3H), 7.33-7.22 (m, 7H), 7.15 (t, J = 7.3 Hz, 2H), 7.06 (t, J = 8.6 Hz, 3H), 4.59 (dd, J = 9.3, 4.1 Hz, 1H), 4.48 (d, J = 2.8 Hz, 1H), 3.98 (d, J = 12.1 Hz, 1H), 3.91 (d, J = 12.1 Hz, 1H), 3.81 (m, 1H), 3.43 (s, 3H), 3.16 (td, J = 6.4, 4.0 Hz, 1H), 2.48 (dd, J = 9.6, 7.3 Hz, 1H), 2.16 (dd, J = 9.5, 6.2 Hz, 1H), 2.03 (dt, J = 12.6, 4.2 Hz, 1H), 1.85 (qd, J = 11.4, 3.8 Hz, 1H), 1.80-1.63 (m, 3H), 0.81 (d, J = 6.9 Hz, 3H), 0.72 (d, J = 6.8 Hz, 3H); ^{13}C NMR (CD_3OD , 100 MHz) δ 161.9, 148.1, 140.0, 135.3, 130.4 (2), 130.0, 129.5 (2), 129.3 (2), 129.0 (2), 128.7 (2), 128.5, 127.4 (2), 126.8, 90.6, 73.4, 72.7, 71.4, 63.9, 58.5, 57.4, 33.7, 31.3, 27.5, 20.9, 17.9; FTIR (neat) 3566, 3435, 3028, 2954, 1633, 1599, 1453, 1271, 1076, 700 cm^{-1} ; LRMS (ES) calcd for $\text{C}_{31}\text{H}_{39}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$: 487.3, found 487.3; Anal. calcd for $\text{C}_{31}\text{H}_{38}\text{N}_2\text{O}_3$: C, 76.51; H, 7.87; N, 5.76, found C, 76.41; H, 8.10; N, 5.64.

(2R,3R,6S)-1-[(E)-((1S)-1-[(benzyloxy)methyl]-2-methylpropyl)imino)(phenyl)methyl]-2-methoxy-6-phenylpiperidin-3-yl acetate (14a). The tetrahydropyridine derivative **12a** (370 mg, 0.84 mmol) was dissolved in 5.6 mL of THF, 3.4 mL of dry methanol (2.7 g, 84 mmol) was added and the mixture was cooled to $-78\text{ }^\circ\text{C}$. A $-78\text{ }^\circ\text{C}$ solution of dimethyldioxirane (17 mL of a 0.053 M solution in acetone, 0.88 mmol) was added rapidly using a syringe and the mixture stirred at $-78\text{ }^\circ\text{C}$ for 1 hour. The volatiles were removed under reduced pressure and 2 mL of pyridine, 1 mL of acetic anhydride and 2 mg of DMAP were added and the mixture was stirred at room temperature

for 16 hours. The solution was then cooled to 0 °C, sodium bicarbonate was added and stirring was continued for 30 minutes. The aqueous phase was extracted three times with dichloromethane, the organic phase was dried with magnesium sulfate, filtered and concentrated under reduced pressure. Flash chromatography of the oily residue (gradient 10-25% EtOAc/hexane) afforded 400 mg of **14a** (89%) as a colorless oil. R_f 0.50 (50 % EtOAc/hexane); $[\alpha]_D^{20} = 101.6$ (c 4.19, MeOH); ^1H NMR (CD_3OD , 400 MHz) δ 7.41 (m, 3H), 7.32-7.23 (m, 7H), 7.17 (t, $J = 7.4$ Hz, 2H), 7.11-7.05 (m, 3H), 4.94 (ddd, $J = 10.7, 5.1, 2.9$ Hz, 1H), 4.68 (dd, $J = 9.3, 4.2$ Hz, 1H), 4.63 (d, $J = 2.6$ Hz, 1H), 3.99 (d, $J = 12.1$ Hz, 1H), 3.92 (d, $J = 12.1$ Hz, 1H), 3.35 (s, 3H), 3.11 (td, $J = 6.4, 4.1$ Hz, 1H), 2.56 (dd, $J = 10.4, 6.6$ Hz, 1H), 2.22 (dd, $J = 9.5, 5.5$ Hz, 1H), 2.14 (dt, $J = 13.0, 4.5$ Hz, 1H), 2.01-1.93 (m, 1H), 1.97 (s, 3H), 1.91-1.77 (m, 2H), 1.66 (dsp, $J = 6.8, 4.2$ Hz, 1H), 0.79 (d, $J = 6.9$ Hz, 3H), 0.72 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (CD_3OD , 100 MHz) δ 172.1, 161.3, 147.6, 140.0, 134.9, 130.3 (2), 130.0, 129.4 (2), 129.2 (2), 129.1 (2), 128.6 (2), 128.4, 127.3 (2), 126.8, 87.7, 74.0, 73.4, 72.9, 64.8, 58.2, 57.2, 32.7, 31.3, 24.4, 21.1, 20.9, 18.0; FTIR (neat) 3027, 1735, 1630, 1236, 1071, 698 cm^{-1} ; LRMS (ES) calcd for $\text{C}_{33}\text{H}_{41}\text{N}_2\text{O}_4$ ($M + \text{H}$) $^+$: 529.3, found 529.3; Anal. calcd for $\text{C}_{33}\text{H}_{40}\text{N}_2\text{O}_4$: C, 74.97; H, 7.63; N, 5.30, found C, 74.90; H, 7.60; N, 5.15.

(2R,3R,6S)-1-[(E)-((1S)-1-[(benzyloxy)methyl]-2-methylpropyl)imino)(phenyl)methyl]-2-isopropoxy-6-phenylpiperidin-3-yl acetate (14b**)**. The tetrahydropyridine derivative **12a** (52 mg, 0.12 mmol) was dissolved in 0.8 mL of THF, 0.93 mL of dry isopropanol (0.73 g, 12 mmol) was added and the mixture was cooled to -78 °C. A -78 °C solution of dimethyldioxirane (1.7 mL of a 0.079 M solution in acetone, 0.13 mmol) was added rapidly using a syringe and the mixture stirred at -78 °C for 2 hours. The volatiles were removed under reduced pressure and 1 mL of pyridine, 0.5 mL of acetic anhydride and 2 mg of DMAP were added and the mixture was stirred at room temperature for 16 hours. The solution was then cooled to 0 °C, sodium bicarbonate was added and stirring was continued for 30 minutes. The aqueous phase was extracted three times with dichloromethane, the organic phase was dried with magnesium sulfate, filtered and concentrated under reduced pressure. Flash chromatography of the oily residue (gradient 10-25% EtOAc/hexane) afforded 62 mg of **14b** (92%) as a colorless oil. R_f 0.35 (25 % EtOAc/hexane); $[\alpha]_D^{20} = 94.6$ (c 4.65, C_6H_6); ^1H NMR (C_6D_6 , 300 MHz) δ 7.42 (d, $J = 7.2$ Hz, 2H), 7.32 (d, $J = 7.4$ Hz, 2H), 7.20-7.10 (m, 9H), 7.04 (t, $J = 7.3$ Hz, 2H), 5.13 (ddd, $J = 10.8, 5.3, 3.1$ Hz, 1H), 5.04 (d, $J = 3.0$ Hz, 1H), 4.81 (dd, $J = 9.7, 4.4$ Hz, 1H), 4.06 (d, $J = 12.1$ Hz, 1H), 4.00 (sp, $J = 6.1$ Hz, 1H), 3.98 (d, $J = 12.1$ Hz, 1H), 3.48 (td, $J = 6.3, 4.0$ Hz, 1H), 2.72 (dd, $J = 9.2, 6.1$ Hz, 1H), 2.43 (dd, $J = 9.2, 6.9$ Hz, 1H), 2.22 (dq, $J = 11.3, 5.0$ Hz, 1H), 2.10-1.91 (m, 2H), 1.90-1.75 (m, 2H), 1.57 (s, 3H), 1.28 (d, $J = 6.2$ Hz, 3H), 0.90 (d, $J = 5.8$ Hz, 3H), 0.89 (d, $J = 6.9$ Hz, 3H), 0.88 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (C_6D_6 , 75 MHz) δ 169.9, 159.5, 147.0, 140.0, 134.5, 129.9 (2), 129.3, 128.9, 128.7 (3), 128.5 (2), 127.9 (2), 127.6, 127.0 (2), 126.2, 82.8, 72.9, 72.7, 72.5, 69.2, 63.6, 56.4, 31.7, 31.1, 24.5, 24.2, 22.1, 21.0, 20.8, 18.0; FTIR (neat) 3029, 1736, 1631, 1241, 700 cm^{-1} ; LRMS (APCI) calcd for $\text{C}_{35}\text{H}_{45}\text{N}_2\text{O}_4$ ($M + \text{H}$) $^+$: 557.3, found 557.3; Anal. calcd for $\text{C}_{35}\text{H}_{44}\text{N}_2\text{O}_4$: C, 75.51; H, 7.97; N, 5.03, found C, 75.28; H, 8.11; N, 4.97.

(2*R*,3*R*,6*S*)-1-[(*E*)-{[(1*S*)-1-[(benzyloxy)methyl]-2-methylpropyl]imino}(phenyl)methyl]-2-[(4-bromobenzyl)oxy]-6-phenylpiperidin-3-yl acetate (14c**)**. The tetrahydropyridine derivative **12a** (85 mg, 0.19 mmol) and 4-bromobenzyl alcohol (72 mg, 0.39 mmol) were dissolved in 1.3 mL THF and the mixture was cooled to 0-5 °C using an ice bath. A -78 °C solution of dimethyldioxirane⁶ (3.8 mL of a 0.057 M solution in acetone, 0.21 mmol) was added rapidly using a syringe. The mixture was allowed to warm to room temperature and was stirred for 14 hours. The volatiles were then removed under reduced pressure and 1 mL of pyridine, 0.5 mL of acetic anhydride and 2 mg of DMAP were added. The mixture was stirred at room temperature for 18 hours, and then cooled to 0-5 °C. 5 mL of a saturated sodium bicarbonate solution was added and stirring was continued for 30 minutes. The aqueous phase was extracted three times with dichloromethane, the organic phase was dried with magnesium sulfate, filtered and concentrated under reduced pressure. Flash chromatography of the oily residue (gradient 10-25% EtOAc/hexane) afforded 79 mg of **14c** (60%) as a colorless oil. R_f 0.50 (25 % EtOAc/hexane); $[\alpha]_D^{20} = 43.1$ (c 2.65, C_6H_6); 1H NMR (C_6D_6 , 400 MHz) δ 7.33-7.25 (m, 6H), 7.18-7.00 (m, 13H), 5.17 (ddd, $J = 10.5, 5.0, 2.8$ Hz, 1H), 5.08 (d, $J = 2.7$ Hz, 1H), 4.81 (dd, $J = 9.6, 4.1$ Hz, 1H), 4.58 (d, $J = 12.1$ Hz, 1H), 4.44 (d, $J = 12.1$ Hz, 1H), 3.99 (d, $J = 12.1$ Hz, 1H), 3.91 (d, $J = 12.1$ Hz, 1H), 3.38 (td, $J = 5.8, 5.0$ Hz, 1H), 2.70 (dd, $J = 9.2, 5.7$ Hz, 1H), 2.36 (dd, $J = 9.1, 7.1$ Hz, 1H), 2.12 (dd, $J = 10.8, 4.7$ Hz, 1H), 2.01 (dt, $J = 13.6, 4.2$ Hz, 1H), 1.89-1.74 (m, 3H), 1.48 (s, 3H), 0.89 (d, $J = 6.9$ Hz, 3H), 0.86 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (C_6D_6 , 75 MHz) δ 169.7, 159.8, 147.1, 139.9, 138.8, 134.3, 132.0 (2), 131.5, 129.7 (2), 129.5 (2), 129.3, 128.8, 128.7, 128.6 (2), 128.5 (2), 127.9 (2), 127.6, 126.8 (2), 126.3, 86.2, 73.1, 72.8, 72.7, 71.1, 63.6, 56.8, 32.3, 31.1, 24.2, 20.9, 20.9, 18.1; FTIR (neat) 3061, 3029, 1737, 1634, 1238, 1070, 700 cm^{-1} ; LRMS (APCI) calcd for $C_{39}H_{44}BrN_2O_4$ ($M + H$)⁺: 683.2 and 685.2, found 683.2 and 685.2; Anal. calcd for $C_{39}H_{43}BrN_2O_4$: C, 68.51; H, 6.34; N, 4.10, found C, 68.47; H, 6.49; N, 4.03.

(2*R*,3*R*,6*S*)-1-[(*E*)-{[(1*S*)-1-[(benzyloxy)methyl]-2-methylpropyl]imino}(phenyl)methyl]-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-6-phenylpiperidin-3-yl acetate (14d**)**. The tetrahydropyridine derivative **12a** (83 mg, 0.19 mmol) and phthalimide (56 mg, 0.38 mmol) were dissolved in 1.3 mL THF and the mixture was cooled to 0-5 °C using an ice bath. A -78 °C solution of dimethyldioxirane (3.7 mL of a 0.057 M solution in acetone, 0.21 mmol) was added rapidly using a syringe. The mixture was allowed to warm to room temperature and was stirred for 14 hours. The volatiles were then removed under reduced pressure and 1 mL of pyridine, 0.5 mL of acetic

(6) The dimethyldioxirane solution was redistilled over potassium carbonate to minimize the water content and to afford higher yields. It is also imperative that the glassware be previously washed with base bath. See p. S-2.

anhydride and 2 mg of DMAP were added. The mixture was stirred at room temperature for 18 hours, and then cooled to 0-5 °C. 5 mL of a saturated sodium bicarbonate solution was added and stirring was continued for 30 minutes. The aqueous phase was extracted three times with dichloromethane, the organic phase was dried with magnesium sulfate, filtered and concentrated under reduced pressure. Flash chromatography of the oily residue (gradient 10-25% EtOAc/hexane) afforded 94 mg of **14d** (77%) as colorless oil which foams under high vacuum. R_f 0.25 (25 % EtOAc/hexane); $[\alpha]_D^{20} = 37.6$ (c 1.83, C_6H_6); 1H NMR (C_6D_6 , 300 MHz) δ 7.53 (dd, 5.5, 3.0 Hz, 2H), 7.20-7.05 (m, 7H), 7.00 (t, 6.4 Hz, 5H), 6.93 (m, 3H), 6.90 (dd, $J = 5.5, 3.0$ Hz, 2H), 6.85 (bd, $J = 4.2$ Hz, 1H), 5.68 (dt, $J = 12.1, 4.8$ Hz, 1H), 5.31 (t, $J = 6.8$ Hz, 1H), 3.63 (s, 2H), 3.13 (ddd, $J = 7.2, 5.3, 4.0$ Hz, 1H), 2.74 (dd, $J = 9.1, 5.5$ Hz, 1H), 2.65 (dq, $J = 11.5, 6.6$ Hz, 1H), 2.47 (dd, $J = 8.9, 7.4$ Hz, 1H), 2.20 (tdd, $J = 12.1, 9.1, 6.6$ Hz, 1H), 1.83-1.71 (m, 2H), 1.71 (s, 3H), 1.62 (dq, $J = 11.6, 6.0$ Hz, 1H), 1.08 (d, $J = 6.8$ Hz, 3H), 0.84 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (C_6D_6 , 75 MHz) δ 169.7, 169.2 (2), 159.5, 148.6, 139.9, 134.0 (2), 133.9 (2), 133.0, 129.1, 128.9 (3), 128.7 (3), 128.5 (2), 127.6 (2), 127.5, 126.7 (2), 126.6, 123.3 (2), 73.5, 72.6, 69.8, 64.4, 63.2, 57.8, 31.1 (2), 23.6, 20.9 (2), 17.9; FTIR (neat) 3089, 3062, 3032, 1775, 1739, 1715, 1627, 1366, 1311, 1231, 700 cm^{-1} ; LRMS (APCI) calcd for $C_{40}H_{42}N_3O_5$ ($M + H$) $^+$: 644.3, found 644.2; Anal. calcd for $C_{40}H_{41}N_3O_5$: C, 74.63; H, 6.42; N, 6.53, found C, 74.29; H, 6.38; N, 6.20.

(2R,3R,6S)-1-[(E)-[(1S)-1-[(benzyloxy)methyl]-2-methylpropyl]imino](phenyl)methyl]-2-methyl-6-phenylpiperidin-3-ol (13e). Anhydrous zinc bromide (260 mg, 1.16 mmol) was dissolved in 8 mL THF and the solution was cooled to 0-5 °C using an ice bath. Methylmagnesium bromide (0.40 mL of a 2.80 M solution in ether) was added. The resulting white suspension was warmed to room temperature, stirred for 30 minutes and cooled to -78 °C. In a separate flask, the tetrahydropyridine derivative **12a** (97 mg, 0.22 mmol) was dissolved in 1.5 mL THF and the solution was cooled to -78 °C. A -78 °C solution of dimethyldioxirane (5.1 mL of a 0.048 M solution in acetone, 0.24 mmol) was added rapidly using a syringe and the mixture was stirred at -78 °C for 5 minutes. The previously prepared methylzinc bromide at -78 °C was transferred via canula and the suspension was stirred at -78 °C for 3 hours. The reaction was quenched by addition of saturated ammonium chloride (5 mL) and the mixture was warmed to room temperature. Zinc salts were dissolved upon addition of ammonium hydroxide 28% (10 mL) and the aqueous phase was extracted three times with diethyl ether. The organic phase was dried with potassium carbonate, filtered and concentrated under reduced pressure. Flash chromatography of the oily residue (gradient 10-50% EtOAc/hexane containing 1% NEt_3) afforded 70 mg of **13e** (67%) as a colorless oil. R_f 0.20 (EtOAc); $[\alpha]_D^{20} = -3.09$ (c 3.93, $CHCl_3$); 1H NMR ($CDCl_3$, 400 MHz) δ 8.00-7.60 (br s, 1H), 7.50-7.42 (m, $J = 8.4$ Hz, 4H), 7.42-7.36 (m, $J = 7.0$ Hz, 4H), 7.36-7.28 (m, $J = 7.4$ Hz, 6H), 7.22 (t, $J = 7.0$ Hz, 1H), 4.64 (d, $J = 11.8$ Hz, 1H), 4.56 (d, $J = 11.8$ Hz, 1H), 4.39 (br s, 1H), 3.72 (br s, 1H), 3.68 (dd, $J = 8.8, 4.8$ Hz, 1H), 3.57 (t, $J = 8.3$ Hz, 1H), 3.30 (m, 2H), 2.25 (ddt, $J = 13.9, 12.2, 4.7$ Hz, 1H), 1.96 (dq, $J = 14.1, 3.4$ Hz, 1H), 1.89-1.73 (m, 3H), 1.68 (d, $J = 7.1$ Hz, 3H), 0.89 (d, $J = 6.8$ Hz, 3H), 0.76 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.9, 140.6, 139.0, 134.6, 129.1 (2), 128.7 (3), 128.4 (4), 127.9 (2), 127.6, 126.7 (2), 126.6, 73.6 (2), 70.3, 64.4, 58.7, 53.9, 31.3, 30.0, 21.5, 19.8, 18.0, 16.5; FTIR (neat) 3341, 3170, 3061, 3029, 1615, 1596, 1494, 1453, 1350, 1271, 1102, 700 cm^{-1} ; LRMS (APCI) calcd for $C_{31}H_{39}N_2O_2$ ($M + H$) $^+$: 471.3, found 471.3; Anal. calcd for $C_{31}H_{38}N_2O_2$: C, 79.11; H, 8.14; N, 5.95, found C, 78.97; H, 8.20; N, 5.62.

(2R,3R,6S)-1-[(E)-[(1S)-1-[(benzyloxy)methyl]-2-methylpropyl]imino](phenyl)methyl]-2-

methyl-6-phenylpiperidin-3-ol (13e). Dimethylzinc (0.32 mL of a 2.0 M solution in toluene, 0.64 mmol) was added to an Argon flushed dry flask, which then was cooled to $-78\text{ }^{\circ}\text{C}$. In a separate flask, the tetrahydropyridine derivative **12a** (28 mg, 0.063 mmol) was dissolved in 0.42 mL THF and the solution was cooled down to $-78\text{ }^{\circ}\text{C}$. A $-78\text{ }^{\circ}\text{C}$ solution of dimethyldioxirane (1.3 mL of a 0.052 M solution in acetone, 0.070 mmol) was added rapidly using a syringe and the mixture stirred at $-78\text{ }^{\circ}\text{C}$ for 6 minutes. The $-78\text{ }^{\circ}\text{C}$ precooled dimethylzinc solution was transferred to the epoxide via canula. The flask and canula were rinsed with 1.0 mL of THF ($-78\text{ }^{\circ}\text{C}$ transfer) and the solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 3.5 hours. The reaction was quenched by addition of saturated ammonium chloride (2 mL) and the mixture was warmed to room temperature. Zinc salts were dissolved upon addition of ammonium hydroxide 28% (4 mL) and the aqueous phase was extracted three times with ethyl ether. The organic phase was dried with potassium carbonate, filtered and concentrated under reduced pressure. Flash chromatography of the oily residue (gradient 10-50% EtOAc/hexane containing 1% NEt_3) afforded 27 mg of **13e** (91%) as a colorless oil.

(2R,3R,6S)-1-[(E)-[(1S)-1-[(benzyloxy)methyl]-2-methylpropyl]imino](phenyl)methyl]-2-ethyl-

6-phenylpiperidin-3-ol (13f). Diethylzinc (0.17 mL, 210 mg, 1.7 mmol) was added to an Argon flushed dry flask, 1.7 mL of THF was added and the solution was cooled to $-78\text{ }^{\circ}\text{C}$. In a separate flask, the tetrahydropyridine derivative **12a** (147 mg, 0.336 mmol) was dissolved in 2.2 mL THF and the solution was cooled to $-78\text{ }^{\circ}\text{C}$. A $-78\text{ }^{\circ}\text{C}$ solution of dimethyldioxirane⁶ (4.0 mL of a 0.093 M solution in acetone, 0.37 mmol) was added rapidly using a syringe and the mixture stirred at $-78\text{ }^{\circ}\text{C}$ for 10 minutes. The $-78\text{ }^{\circ}\text{C}$ precooled diethylzinc solution was transferred to the epoxide via canula. The flask and canula were rinsed with 1.0 mL of THF ($-78\text{ }^{\circ}\text{C}$ transfer) and the solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 3 hours. The reaction was quenched by addition of saturated ammonium chloride (10 mL) and the mixture was warmed to room temperature. Zinc salts were dissolved upon addition of ammonium hydroxide 28% (20 mL) and the aqueous phase was extracted three times with ethyl ether. The organic phase was dried with potassium carbonate, filtered and concentrated under reduced pressure. Flash chromatography of the oily residue (gradient 10-50% EtOAc/hexane containing 1% NEt_3) afforded 121 mg of **13f** (75%) as a colorless oil. R_f 0.21 (EtOAc); $[\alpha]_D^{20} = -275$ (c 1.33, C_6H_6); ^1H NMR (C_6D_6 , 400 MHz) δ 7.75-45 (br s + d, $J = 7.0\text{ Hz}$, 5H), 7.28 (m, 4H), 7.17 (t, $J = 7.4\text{ Hz}$, 3H), 7.05 (t, $J = 7.3\text{ Hz}$, 1H), 7.02 (t, $J = 7.2\text{ Hz}$, 2H), 6.93 (t, $J = 7.3\text{ Hz}$, 1H), 4.56 (d, $J = 11.8\text{ Hz}$, 1H), 4.46 (d, $J = 11.7\text{ Hz}$, 2H), 3.84 (br s, 1H), 3.66 (t, $J = 8.9\text{ Hz}$, 1H), 3.56 (dd, $J = 9.0$, 3.8 Hz, 1H), 3.43 (dt, $J = 9.5$, 3.9 Hz, 1H), 2.95 (ddd, $J = 8.5$, 6.4, 2.1 Hz, 1H), 2.74 (dq, $J = 13.9$, 7.7 Hz, 1H), 2.35 (m, 1H), 2.08 (dq, $J = 13.9$, 6.9 Hz, 1H), 1.98 (dq, $J = 13.1$, 3.6 Hz, 1H), 1.77-

1.68 (m, 2H), 1.62 (dsp, $J = 4.9, 6.8$ Hz, 1H), 1.10 (t, $J = 7.4$ Hz, 3H), 0.90 (d, $J = 6.8$ Hz, 3H), 0.70 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (C_6D_6 , 100 MHz) δ 165.4, 141.2, 139.9, 135.5, 129.4, 129.0 (2), 128.9 (3), 128.7 (2), 128.5 (3), 128.0, 127.4 (2), 127.0, 74.4, 74.2, 69.8, 65.1, 61.2, 59.3, 32.1, 30.9, 23.4, 22.4, 20.1, 18.7, 12.7; FTIR (neat) 3500-3000, 3184, 3061, 1613, 1595, 1107 cm^{-1} ; LRMS (APCI) calcd for $\text{C}_{32}\text{H}_{41}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}^+$): 485.3, found 485.3; Anal. calcd for $\text{C}_{32}\text{H}_{40}\text{N}_2\text{O}_2$: C, 79.30; H, 8.32; N, 5.78, found C, 79.30; H, 8.38; N, 5.43.

(2R,3R,6R)-2-ethyl-1-[(E)-[(1S)-1-(methoxymethyl)-2-methylpropyl]imino}(phenyl)methyl]-6-methylpiperidin-3-ol (13g). Diethylzinc (0.12 mL, 0.14 g, 1.2 mmol) was added to an Argon flushed dry flask, 1.2 mL of THF was added and the solution was cooled to -78°C . In a separate flask, the tetrahydropyridine derivative **12b** (69 mg, 0.23 mmol) was dissolved in 1.5 mL THF and the solution was cooled to -78°C . A -78°C solution of dimethyldioxirane⁶ (5.3 mL of a 0.048 M solution in acetone, 0.25 mmol) was added rapidly using a syringe and the mixture stirred at -78°C for 10 minutes. The -78°C precooled diethylzinc solution was transferred to the epoxide via canula. The flask and canula were rinsed with 1.0 mL of THF (-78°C transfer) and the solution was stirred at -78°C for 2.5 hours. The reaction was quenched by addition of saturated ammonium chloride (4 mL) and the mixture was warmed to room temperature. Zinc salts were dissolved upon addition of ammonium hydroxide 28% (8 mL) and the aqueous phase was extracted three times with ethyl ether. The organic phase was dried with potassium carbonate, filtered and concentrated under reduced pressure. Flash chromatography of the oily residue (gradient 10-50% EtOAc/hexane containing 1% NEt_3) afforded 45 mg of **13g** (57%) as a colorless oil. R_f 0.05 (90 % EtOAc/hexane); $[\alpha]_D^{20} = -3.31$ (c 0.54, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz) δ 7.80-7.30 (br s, 1H), 7.37 (s, 5H), 3.84 (dt, $J = 2.9, 4.9$ Hz, 1H), 3.54 (dd, $J = 9.7, 4.9$ Hz, 1H), 3.39 (dd, $J = 9.1, 7.7$ Hz, 1H), 3.38 (s, 3H), 3.28 (sx, $J = 6.1$ Hz, 1H), 3.19 (dt, $J = 7.6, 4.8$ Hz, 1H), 3.09 (ddd, $J = 8.8, 6.2, 2.9$ Hz, 1H), 2.37 (dq, $J = 14.0, 7.5$ Hz, 1H), 2.05-1.80 (m, 3H), 1.68-1.53 (m, 2H), 1.11-1.02 (m and t, $J = 7.4$ Hz, 4H), 0.96 (d, $J = 6.8$ Hz, 3H), 0.78 (d, $J = 6.8$ Hz, 3H), 0.66 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 165.1, 135.0, 129.5 (2), 129.1, 128.3 (2), 76.0, 69.8, 63.8, 59.5, 58.9, 52.4, 31.2, 30.2, 26.0, 21.6, 19.6, 18.0, 17.9, 12.3; FTIR (neat) 3600-2800, 3061, 2961, 2929, 2873, 1610, 1595, 1446, 1322, 1115, 1071, 781, 706 cm^{-1} ; LRMS (APCI) calcd for $\text{C}_{21}\text{H}_{35}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}^+$): 347.3, found 347.2; Anal. calcd for $\text{C}_{21}\text{H}_{34}\text{N}_2\text{O}_2$: C, 72.79; H, 9.89; N, 8.08, found C, 72.80; H, 9.80; N, 8.14.

(2R,3R,6R)-6-ethyl-1-[(E)-[(1S)-1-(methoxymethyl)-2-methylpropyl]imino}(phenyl)methyl]-2-methylpiperidin-3-ol (13h). Dimethylzinc (1.5 mL of a 2.0 M solution in toluene, 3.1 mmol) was added to an Argon flushed dry flask, which was cooled to -78°C . In a separate flask, the tetrahydropyridine derivative **12c** (96 mg, 0.31 mmol) was dissolved in 2.1 mL THF and the solution was cooled to -78°C . A -78°C solution of dimethyldioxirane⁶ (5.6 mL of a 0.060 M solution

in acetone, 0.34 mmol) was added rapidly using a syringe and the mixture stirred at $-78\text{ }^{\circ}\text{C}$ for 13 minutes. The $-78\text{ }^{\circ}\text{C}$ precooled dimethylzinc solution was transferred to the epoxide via canula. The flask and canula were rinsed with 1.0 mL of THF ($-78\text{ }^{\circ}\text{C}$ transfer) and the solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 10 hours. The reaction was quenched by addition of saturated ammonium chloride (5 mL) and the mixture was warmed to room temperature. Zinc salts were dissolved upon addition of ammonium hydroxide 28% (10 mL) and the aqueous phase was extracted three times with ethyl ether. The organic phase was dried with potassium carbonate, filtered and concentrated under reduced pressure. Flash chromatography of the oily residue (gradient 10-50% EtOAc/hexane containing 1% NEt_3) afforded 79 mg of **13h** (75%) as a colorless oil. R_f 0.13 (75 % EtOAc/hexane); $[\alpha]_D^{20} = -287$ (c 1.26, C_6H_6); ^1H NMR (C_6D_6 , 400 MHz) δ 7.80-7.30 (br s, 1H), 7.43 (br d, $J = 5.3$ Hz, 2H), 7.21 (t, $J = 7.3$ Hz, 2H), 7.15 (t, $J = 7.1$ Hz, 1H), 3.93 (br m, 1H), 3.55 (d, $J = 6.7$ Hz, 1H), 3.54 (d, $J = 5.6$ Hz, 1H), 3.42 (dt, $J = 7.0, 5.1$ Hz, 1H), 3.34 (s, 3H), 3.23 (qd, $J = 7.0, 2.1$ Hz, 1H), 3.16 (dddd, $J = 9.4, 7.4, 5.5, 3.1$ Hz, 1H), 2.18 (tdd, $J = 13.0, 5.5, 4.1$ Hz, 1H), 2.00 (dq, $J = 13.8, 4.0$ Hz, 1H), 1.86 (d, $J = 7.1$ Hz, 3H), 1.77 (tt, $J = 13.1, 4.3$ Hz, 1H), 1.72 (dsp, $J = 5.1, 6.8$ Hz, 1H), 1.56 (ddq, $J = 14.2, 8.7, 7.4$ Hz, 1H), 1.10-0.98 (m, 2H), 0.99 (d, $J = 6.8$ Hz, 3H), 0.77 (d, $J = 6.8$ Hz, 3H), 0.64 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (C_6D_6 , 75 MHz) δ 165.4, 136.0, 130.3, 129.2, 128.7 (2), 128.4, 76.6, 70.5, 65.0, 59.5, 58.2, 53.1, 32.2, 30.7, 23.6, 23.5, 20.1, 18.7, 17.4, 11.5; FTIR (neat) 3600-2400, 3580, 3060, 2962, 1613, 1596, 1321, 1113, 707 cm^{-1} ; LRMS (APCI) calcd for $\text{C}_{21}\text{H}_{35}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$: 347.3, found 347.3; Anal. calcd for $\text{C}_{21}\text{H}_{34}\text{N}_2\text{O}_2$: C, 72.79; H, 9.89; N, 8.08, found C, 72.62; H, 10.16; N, 8.17.

(2R,3R,6R)-2,6-diethyl-1-[(E)-{(1S)-1-(methoxymethyl)-2-methylpropyl}imino}(phenyl)methyl]piperidin-3-ol (13i). Diethylzinc (0.28 mL, 2.8 mmol) was added to an Argon flushed dry flask, 2.8 mL of THF was added and the solution was cooled to $-78\text{ }^{\circ}\text{C}$. In a separate flask, the tetrahydropyridine derivative **12c** (87 mg, 0.28 mmol) was dissolved in 1.9 mL THF and the solution was cooled to $-78\text{ }^{\circ}\text{C}$. A $-78\text{ }^{\circ}\text{C}$ solution of dimethyldioxirane⁶ (5.1 mL of a 0.060 M solution in acetone, 0.31 mmol) was added rapidly using a syringe and the mixture stirred at $-78\text{ }^{\circ}\text{C}$ for 14 minutes. The $-78\text{ }^{\circ}\text{C}$ precooled diethylzinc solution was transferred to the epoxide via canula. The flask and canula were rinsed with 1.0 mL of THF ($-78\text{ }^{\circ}\text{C}$ transfer) and the solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 2.5 hours. The reaction was quenched by addition of saturated ammonium chloride (5 mL) and the mixture was warmed to room temperature. Zinc salts were dissolved upon addition of ammonium hydroxide 28% (10 mL) and the aqueous phase was extracted three times with ethyl ether. The organic phase was dried with potassium carbonate, filtered and concentrated under reduced pressure. Flash chromatography of the oily residue (gradient 10-50% EtOAc/hexane containing 1% NEt_3) afforded 60 mg of **13i** (60%) as a colorless oil. R_f 0.14 (75 % EtOAc/hexane); $[\alpha]_D^{20} = -298$ (c 1.79, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz) δ 7.60 (d, $J = 5.9$ Hz, 1H), 7.37 (s, 5H), 3.83 (m, 1H), 3.54 (dd, $J = 9.3, 5.1$ Hz, 1H), 3.38 (dd, $J = 9.4, 7.5$ Hz, 1H), 3.37 (s, 3H), 3.15 (dt, $J = 7.3, 5.0$ Hz, 1H), 3.08 (m, 1H), 3.03 (ddd, $J = 8.6, 6.1, 2.4$ Hz, 1H), 2.46 (ddq, $J = 14.0, 8.7, 7.4$ Hz, 1H), 1.98 (dq, $J = 14.0, 7.4, 6.2$ Hz, 1H), 1.90 (m, 1H), 1.85 (tt, $J = 11.8, 4.0$ Hz, 1H), 1.73-1.61 (m, 3H), 1.22 (dqn, $J = 13.8, 7.4$ Hz, 1H), 1.14 (ddt, $J = 13.2, 5.7, 3.9$ Hz, 1H), 1.07 (t, $J = 7.4$ Hz, 3H), 0.81 (d, $J = 6.8$ Hz, 3H), 0.68 (d, $J = 6.8$ Hz, 3H), 0.64 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 165.3, 135.0, 129.5 (2), 128.9, 128.2 (2), 75.9, 69.6, 64.0, 59.4, 59.3, 57.9, 31.1, 30.1, 23.8, 23.5, 22.3, 19.7, 17.8, 12.5, 11.0; FTIR (neat) 3600-2400, 3058, 2962, 1611,

1595, 1463, 1344, 1115, 707 cm^{-1} ; LRMS (APCI) calcd for $\text{C}_{22}\text{H}_{37}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}^+$): 361.3, found 361.3; Anal. calcd for $\text{C}_{22}\text{H}_{36}\text{N}_2\text{O}_2$: C, 73.29; H, 10.06; N, 7.77, found C, 73.22; H, 10.31; N, 7.58.

(2R,3R,6S)-1-[(E)-{[(1S)-1-[(methoxy)methyl]-2-methylpropyl]imino}(phenyl)methyl]-2-ethyl-6-(2-furyl)piperidin-3-ol (13j). Diethylzinc (0.088 mL, 0.10 g, 0.86 mmol) was added to an Argon flushed dry flask, 0.9 mL of THF was added and the solution was cooled to $-78\text{ }^{\circ}\text{C}$. In a separate flask, the tetrahydropyridine derivative **12d** (60 mg, 0.17 mmol) was dissolved in 1.1 mL THF and the solution was cooled to $-78\text{ }^{\circ}\text{C}$. A $-78\text{ }^{\circ}\text{C}$ solution of dimethyldioxirane⁶ (2.6 mL of a 0.068 M solution in acetone, 0.18 mmol) was added rapidly using a syringe and the mixture stirred at $-78\text{ }^{\circ}\text{C}$ for 10 minutes. The $-78\text{ }^{\circ}\text{C}$ precooled diethylzinc solution was transferred to the epoxide via canula. The flask and canula were rinsed with 1.0 mL of THF ($-78\text{ }^{\circ}\text{C}$ transfer) and the solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 3 hours. The reaction was quenched by addition of saturated ammonium chloride (3 mL) and the mixture was warmed to room temperature. Zinc salts were dissolved upon addition of ammonium hydroxide 28% (6 mL) and the aqueous phase was extracted three times with ethyl ether. The organic phase was dried with potassium carbonate, filtered and concentrated under reduced pressure. Flash chromatography of the oily residue (gradient 10-50% EtOAc/hexane containing 1% NEt_3) afforded 44 mg of **13j** (65%) as a colorless oil. R_f 0.14 (EtOAc); $[\alpha]_{\text{D}}^{20} = -261$ (c 3.72, C_6H_6); ^1H NMR (CDCl_3 , 300 MHz) δ 7.66 (d, 5.7 Hz, 1H), 7.54 (d, $J = 7.9$ Hz, 1H), 7.53 (d, 7.4 Hz, 1H), 7.42-7.34 (m, 3H), 7.32 (dt, $J = 1.8, 0.9$ Hz, 1H), 6.29 (dd, $J = 3.2, 1.8$ Hz, 1H), 6.15 (ddd, $J = 3.2, 1.3, 0.9$ Hz, 1H), 4.33 (br d, $J = 4.6$ Hz, 1H), 3.81 (br s, 1H), 3.58 (dd, $J = 9.3, 4.8$ Hz, 1H), 3.44 (dd, $J = 9.3, 7.7$ Hz, 1H), 3.40 (s, 3H), 3.28 (dt, $J = 7.7, 4.7$ Hz, 1H), 3.06 (ddd, $J = 8.4, 6.2, 1.9$ Hz, 1H), 2.49 (ddq, $J = 13.9, 8.7, 7.4$ Hz, 1H), 2.12 (m, 1H), 1.93 (dq, $J = 14.0, 7.4, 6.3$ Hz, 1H), 1.90-1.80 (m, 3H), 1.66 (dsp, $J = 4.7, 6.8$ Hz, 1H), 1.01 (t, $J = 7.4$ Hz, 3H), 0.81 (d, $J = 6.8$ Hz, 3H), 0.70 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 164.1, 154.4, 141.8, 134.1, 129.6 (2), 129.4, 128.4 (2), 110.4, 107.3, 75.8, 69.4, 64.1, 61.1, 59.5, 55.3, 31.3, 30.8, 22.5, 21.6, 19.6, 18.1, 12.2; FTIR (neat) 3600-3000, 3114, 3061, 1615, 1596, 1446, 1357, 1114 cm^{-1} ; LRMS (APCI) calcd for $\text{C}_{24}\text{H}_{35}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}^+$): 399.3, found 399.2; Anal. calcd for $\text{C}_{24}\text{H}_{34}\text{N}_2\text{O}_3$: C, 72.32; H, 8.60; N, 7.03, found C, 72.14; H, 8.83; N, 6.95.

(2R,3R,6S)-1-[(E)-{[(1S)-1-(methoxymethyl)-2-methylpropyl]imino}(phenyl)methyl]-2-methyl-6-phenylpiperidin-3-ol (13k). Dimethylzinc (1.10 mL of a 2.0 M solution in toluene, 2.2 mmol) was added to an Argon flushed dry flask, which was cooled to $-78\text{ }^{\circ}\text{C}$. In a separate flask, the tetrahydropyridine derivative **12e** (79 mg, 0.22 mmol) was dissolved in 1.5 mL THF and the solution was cooled to $-78\text{ }^{\circ}\text{C}$. A $-78\text{ }^{\circ}\text{C}$ solution of dimethyldioxirane⁶ (3.0 mL of a 0.079 M solution in acetone, 0.24 mmol) was added rapidly using a syringe and the mixture stirred at $-78\text{ }^{\circ}\text{C}$ for 8 minutes. The $-78\text{ }^{\circ}\text{C}$ precooled dimethylzinc solution was transferred to the epoxide via canula. The

flask and canula were rinsed with 1.0 mL of THF (-78 °C transfer) and the solution was stirred at -78 °C for 3.5 hours. The reaction was quenched by addition of saturated ammonium chloride (5 mL) and the mixture was warmed to room temperature. Zinc salts were dissolved upon addition of ammonium hydroxide 28% (10 mL) and the aqueous phase was extracted three times with ethyl ether. The organic phase was dried with potassium carbonate, filtered and concentrated under reduced pressure. Flash chromatography of the oily residue (gradient 10-50% EtOAc/hexane containing 1% NEt₃) afforded 80 mg of **13k** (92%) as a colorless oil. *R*_f 0.12 (EtOAc); [α]_D²⁰ = -367 (c 1.29, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ 7.80-7.50 (br s, 1H), 7.47 (d, *J* = 6.7 Hz, 2H), 7.40-7.30 (m, 7H), 7.21 (t, *J* = 7.2 Hz, 1H), 4.41 (br t, *J* = 3.9 Hz, 1H), 3.70 (br s, 1H), 3.55 (dd, *J* = 9.3, 3.8 Hz, 1H), 3.46-3.38 (m, 1H), 3.41 (s, 3H), 3.30 (q, *J* = 6.6 Hz, 1H), 3.20 (dt, *J* = 7.6, 4.9 Hz, 1H), 2.26 (ddt, *J* = 14.2, 11.0, 5.5 Hz, 1H), 1.97 (dq, *J* = 14.1, 3.8 Hz, 1H), 1.88-1.78 (m, 2H), 1.72 (dsp, *J* = 5.5, 6.8 Hz, 1H), 1.66 (d, *J* = 7.1 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.75 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 164.8, 140.6, 134.6, 129.2 (2), 128.7 (2), 128.5 (3), 126.7 (2), 126.6, 75.8, 70.3, 64.3, 59.5, 58.7, 53.9, 31.3, 30.0, 21.5, 19.8, 18.1, 16.5; FTIR (neat) 3600-3000, 3083, 3061, 3028, 2933, 2870, 1615, 1597, 1446, 1350, 1271, 1114, 1072, 973, 701 cm⁻¹; LRMS (APCI) calcd for C₂₅H₃₅N₂O₂ (M + H)⁺: 395.3, found 395.2; Anal. calcd for C₂₅H₃₄N₂O₂: C, 76.10; H, 8.69; N, 7.10, found C, 76.36; H, 9.06; N, 6.90.

(2R,3R,6S)-1-[(E)-{[(1S)-1-(methoxymethyl)-2-methylpropyl]imino}(phenyl)methyl]-2,6-diphenylpiperidin-3-ol (13i).

Anhydrous zinc bromide (132 mg, 0.59 mmol) was dissolved in 3.0 mL THF and phenylmagnesium bromide (0.19 mL of a 3.0 M solution in ether, 0.57 mmol) was added at room temperature. The resulting white suspension was stirred for 1 hour and cooled to -78 °C. In a separate flask, the tetrahydropyridine derivative **12e** (41 mg, 0.11 mmol) was dissolved in 0.7 mL THF and the solution was cooled to -78 °C. A -78 °C solution of dimethyldioxirane⁶ (1.6 mL of a 0.079 M solution in acetone, 0.12 mmol) was added rapidly using a syringe and the mixture stirred at -78 °C for 9 minutes. The previously prepared phenylzinc bromide at -78 °C was transferred to the enamine epoxide at -78 °C via canula and the suspension was stirred at -78 °C for 3 hours. The reaction was quenched by addition of saturated ammonium chloride (2 mL) and the mixture was warmed to room temperature. Zinc salts were dissolved upon addition of ammonium hydroxide 28% (4 mL) and the aqueous phase was extracted three times with ethyl ether. The organic phase was dried with potassium carbonate, filtered and concentrated under reduced pressure. Flash chromatography of the oily residue (gradient 10-50% EtOAc/hexane containing 1% NEt₃) afforded 47 mg of **13i** (91%) as a colorless oil. *R*_f 0.25 (75 % EtOAc/hexane); [α]_D²⁰ = -448 (c 2.59, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ 8.24 (br s, 1H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 7.2 Hz, 2H), 7.45-7.32 (m, 7H), 7.23 (t, *J* = 7.0 Hz, 1H), 7.19 (t, *J* = 6.9 Hz, 1H), 4.62 (br dd, *J* = 4.4, 2.4 Hz, 1H), 4.46 (br m, 1H), 4.23 (br s, 1H), 3.42 (dd, *J* = 9.3, 4.6 Hz, 1H), 3.39 (s, 3H), 3.29 (t, *J* = 8.6 Hz, 1H), 2.97 (dt, *J* = 7.9, 4.6 Hz, 1H), 2.43 (tt, *J* = 14.0, 4.4 Hz, 1H), 2.18 (dtd, *J* = 14.0, 3.4, 2.4 Hz, 1H), 2.05 (dq, *J* = 14.0, 3.3 Hz, 1H), 1.93 (tt, *J* = 13.7, 3.6 Hz, 1H), 1.08 (dsp, *J* = 4.6, 6.9 Hz, 1H), 0.11 (d, *J* = 6.9 Hz, 3H), 0.10 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 163.3, 140.4, 140.0, 134.3, 129.2, 128.9 (3), 128.4 (5), 127.0 (2), 126.9 (3), 126.5, 75.5, 66.5, 64.5, 59.4, 59.2, 58.3, 30.6, 30.3, 20.5, 18.9, 17.2; FTIR (neat) 3600-2400, 3089, 3061, 3033, 2924, 1621, 1597, 1450, 1300, 1114, 993, 700 cm⁻¹; LRMS (APCI) calcd

for $C_{30}H_{37}N_2O_2$ ($M + H$)⁺: 457.3, found 457.3. Anal. calcd for $C_{30}H_{36}N_2O_2$: C, 78.91; H, 7.95; N, 6.13, found C, 79.16; H, 7.99; N, 5.73.

(2*R*,3*R*,6*S*)-1-[(*E*)-{[(1*S*)-1-(methoxymethyl)-2-methylpropyl]imino}(phenyl)methyl]-6-phenyl-2-vinylpiperidin-3-ol (13m). Anhydrous zinc bromide (135 mg, 0.60 mmol) was dissolved in 3.0 mL THF and vinylmagnesium bromide (1.4 mL of a 0.42 M solution in THF, 0.58 mmol) was added at room temperature. The resulting solution was stirred for 1 hour and the flask was cooled to -78 °C. In a separate flask, the tetrahydropyridine derivative **12e** (42 mg, 0.12 mmol) was dissolved in 0.8 mL THF and the solution was cooled to -78 °C. A -78 °C solution of dimethyldioxirane⁶ (1.6 mL of a 0.079 M solution in acetone, 0.13 mmol) was added rapidly using a syringe and the mixture stirred at -78 °C for 10 minutes. The previously prepared vinylzinc bromide -78 °C was added and the suspension was stirred at -78 °C for 3 hours. The reaction was quenched by addition of saturated ammonium chloride (2 mL) and the mixture was warmed to room temperature. Zinc salts were dissolved upon addition of ammonium hydroxide 28% (4 mL) and the aqueous phase was extracted three times with ethyl ether. The organic phase was dried with potassium carbonate, filtered and concentrated under reduced pressure. Flash chromatography of the oily residue (gradient 10-50% EtOAc/hexane containing 1% NEt₃) afforded 41 mg of **13m** (89%) as a colorless oil. R_f 0.17 (EtOAc); $[\alpha]_D^{20} = -350$ (c 1.79, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ 7.60 (br s, 1H), 7.46 (br s + d, $J = 8.1$ Hz, 4H), 7.40-7.30 (m, 5H), 7.22 (t, $J = 7.5$ Hz, 1H), 6.50 (ddd, $J = 17.5$, 10.6, 5.4 Hz, 1H), 5.33 (d, $J = 17.6$ Hz, 1H), 5.20 (d, $J = 10.6$ Hz, 1H), 4.45 (br s, 1H), 3.96 (br s, 1H), 3.71 (dd, $J = 5.2$, 1.7 Hz, 1H), 3.50 (dd, $J = 9.3$, 4.9 Hz, 1H), 3.39 (s, 3H), 3.37 (t, $J = 9.0$ Hz, 1H), 3.16 (dt, $J = 7.6$, 4.8 Hz, 1H), 2.29 (tt, $J = 13.7$, 4.5 Hz, 1H), 2.05 (dq, $J = 14.1$, 3.3 Hz, 1H), 1.88 (dq, $J = 14.0$, 3.7 Hz, 1H), 1.76 (tt, $J = 13.6$, 3.7 Hz, 1H), 1.67 (dsp, $J = 4.8$, 6.7 Hz, 1H), 0.84 (d, $J = 6.8$ Hz, 3H), 0.72 (d, $J = 6.9$ Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 164.1, 140.2, 137.3, 134.2, 129.2, 128.8 (3), 128.5 (2), 126.8 (3), 126.7, 115.4, 75.7, 68.2, 64.2, 59.5, 59.4, 58.0, 31.2, 29.9, 21.4, 19.8, 17.8; FTIR (neat) 3600-3000, 3584, 3061, 3028, 2927, 2871, 1621, 1597, 1446, 1299, 1114, 1072, 701 cm⁻¹; LRMS (APCI) calcd for $C_{26}H_{35}N_2O_2$ ($M + H$)⁺: 407.3, found 407.3. Anal. calcd. for $C_{26}H_{34}N_2O_2$: C, 76.81; H, 8.43; N, 6.89, found C, 76.82; H, 8.41; N, 6.65.

***N*-[[(1*E*)-[(2*R*)-2-[12-(benzyloxy)dodecyl]pyridin-1(2*H*)-yl](phenyl)methylene]-*N*[(1*S*)-1-(methoxymethyl)-2-methylpropyl]amine (17).** The amide **15** (221 mg, 1.00 mmol) was dissolved in 5 mL of dichloromethane. Pyridine (0.24 mL, 0.24 g, 3.0 mmol) was added and the mixture was cooled to -40 °C. Triflic anhydride (0.20 mL, 0.34 g, 1.2 mmol) was added dropwise, the mixture was warmed to room temperature and stirred for 3 hours. In a separate flask, 12-benzyloxy-1-

iodododecane⁷ (1.04 g, 2.60 mmol) was diluted with 5 mL of diethyl ether and charged in a syringe. *t*-BuLi (3.1 mL of a 1.6 M in pentane, 5.0 mmol) was charged in a separate flask and cooled to -78 °C. The solution of the alkyl iodide was then added dropwise *t*-BuLi over 10 minutes, then stirred for an additional 30 minutes. Anhydrous magnesium bromide diethyl etherate (670 mg, 2.60 mmol) was added rapidly as a solid in one portion via septum to the organolithium reagent. The suspension was warmed to room temperature and stirred for 5 minutes, affording a pale brown solution, which was charged in a syringe. The pyridinium salt was cooled to -78 °C and the freshly prepared 12-benzyloxidodecyl magnesium bromide (**16**) (containing 1 equivalent of lithium bromide and 2 equivalents of lithium iodide) was added over a period of 45 minutes with a syringe pump. The mixture was stirred at -78 to -70 °C for 12 hours, followed by addition of a saturated solution of sodium bicarbonate. The mixture was allowed to warm to room temperature, transferred in an separatory funnel and the aqueous phase extracted three times with ether. The combined organic phases were dried with magnesium sulfate, filtered and concentrated under reduced pressure. Flash chromatography of the oily residue (gradient 0-5% EtOAc/hexane) afforded 559 mg of **17** (80%) as a pale yellow oil. *R*_f 0.29 (10% EtOAc/hexane); [α]_D²⁰ = -462 (c 6.70, C₆H₆); ¹H NMR (CD₃COCD₃, 400 MHz) δ 7.50-7.40 (m, 4H), 7.37-7.30 (m, 4H), 7.28-7.24 (m, 1H), 7.10 (br d, *J* = 6.0, Hz, 1H), 5.89 (br s + dd, *J* = 9.3, 5.3 Hz, 2H), 5.56 (dd, *J* = 9.3, 5.9 Hz, 1H), 5.40 (br s, 1H), 4.85 (t, *J* = 5.9 Hz, 1H), 4.49 (s, 2H), 3.47 (t, *J* = 6.5 Hz, 2H), 3.45 (dd, *J* = 9.6, 5.1 Hz, 1H), 3.32 (dd, *J* = 8.9, 7.2 Hz, 1H), 3.24 (s, 3H), 3.00 (dt, *J* = 7.2, 4.9 Hz, 1H), 1.80-1.55 (m, 5H), 1.50-1.25 (m, 18H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.72 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (CD₃COCD₃, 75 MHz) δ 158.1, 140.1, 134.1, 129.9 (2), 129.6, 129.5, 129.4 (2), 129.0 (2), 128.2 (2), 128.1, 122.8, 121.0, 102.1, 76.5, 73.2, 71.0, 64.2, 59.1, 52.4, 33.5, 31.5, 30.6, 30.5, 30.4 (5), 30.3, 27.1, 25.2, 20.5, 17.9; FTIR (neat) 3040, 1634, 1600, 1568, 1455, 1336, 1267, 1114, 700 cm⁻¹; HRMS (FAB) calcd for C₃₇H₅₅N₂O₂ (M + H)⁺: 559.4264, found 559.4261.

***N*[(1*E*)-[(2*R*)-2-[12-(benzyloxy)dodecyl]-3,4-dihydropyridin-1(2*H*)-yl](phenyl)methylene]-*N*[(1*S*)-1-(methoxymethyl)-2-methylpropyl]amine (**18**).** The dihydropyridine derivative **17** (113 mg, 0.202 mmol) was dissolved in 2.5 mL of toluene. The palladium catalyst (4.8 mg of 10 wt. % Pd/C, 0.045 mmol Pd) was added and the mixture purged three times with hydrogen atmosphere. The mixture was stirred for 2 hours at room temperature under hydrogen atmosphere (1.0 bar), then filtered through Celite®, rinsed with CH₂Cl₂ and concentrated under reduced pressure. Flash chromatography of the oily residue (gradient 0-25% EtOAc/hexanes) afforded 80 mg of **18** (71%) as a colorless oil. *R*_f 0.23 (25 % EtOAc/hexanes); [α]_D²⁰ = -96.5 (c 3.36, CH₃COCH₃); ¹H NMR (CD₃COCD₃, 400 MHz) δ 7.42 (t, *J* = 6.9 Hz, 2H), 7.37 (t, *J* = 7.0 Hz, 1H), 7.34-7.68 (m, 4H), 7.23 (m, 2H), 7.09 (br d, *J* = 5.2 Hz, 1H), 5.95 (br s, 1H), 4.80 (br s, 1H), 4.46 (s, 2H), 4.37 (br s, 1H), 3.44 (t, *J* = 6.5 Hz, 2H), 3.35 (dd, *J* = 9.0, 5.8 Hz, 1H), 3.20 (t, *J* = 7.8 Hz, 1H), 3.17 (s, 3H), 2.90 (q, *J* = 5.0 Hz, 1H), 2.11 (br t, *J* = 12.7 Hz, 1H), 1.90 (dt, *J* = 16.6, 4.8 Hz, 2H), 1.78-1.63 (m, 3H), 1.58 (qn, *J* = 7.4 Hz, 2H), 1.50-1.30 (m, 19H), 0.85 (d, *J* = 6.7 Hz, 3H), 0.70 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (CD₃COCD₃, 100 MHz) δ 157.8, 140.2, 134.8, 129.7, 129.5, 129.2 (3), 129.0 (2), 128.3 (3),

(7) Prepared from in two steps from commercial 1,12-dodecanol by mono-benylation followed by iodination of the remaining alcohol according to the following procedure: Anan, H.; Seki, N.; Noshiro, O.; Honda, K.; Yasumuro, K.; Ozasa, T.; Fusetani, N. *Tetrahedron* **1996**, 52, 10849-10860.

128.1, 100.7, 76.7, 73.2, 71.0, 63.7, 59.0, 49.8, 31.4, 30.6, 30.5 (6), 30.4, 30.3, 27.1, 26.7, 24.7, 20.6, 19.0, 17.9; FTIR (neat) 3064, 3029, 1615, 1598, 1345, 1115, 700 cm^{-1} ; HRMS (FAB) calcd for $\text{C}_{37}\text{H}_{57}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}^+$): 561.4420, found 561.4417; Anal. calcd for $\text{C}_{37}\text{H}_{56}\text{N}_2\text{O}_2$: C, 79.24; H, 10.06; N, 4.99, found C, 79.33; H, 9.86; N, 4.96.

(2R,3R,6R)-6-[12-(benzyloxy)dodecyl]-1-[(E)-{[(1S)-1-(methoxymethyl)-2-methylpropyl]imino}(phenyl)methyl]-2-methylpiperidin-3-ol (19). Dimethylzinc (0.45 mL of a 2.0 M solution in toluene, 0.90 mmol) was added to an Argon flushed dry flask, which was cooled to -78°C . In a separate flask, the tetrahydropyridine derivative **18** (50 mg, 0.090 mmol) was dissolved in 0.6 mL THF and the solution was cooled to -78°C . A -78°C solution of dimethyldioxirane⁶ (1.6 mL of a 0.063 M solution in acetone, 0.099 mmol) was added rapidly using a syringe and the mixture stirred at -78°C for 4 minutes. The -78°C precooled dimethylzinc solution was transferred to the epoxide via canula. The flask and canula were rinsed with 1.0 mL of THF (-78°C transfer) and the solution was stirred at -78°C for 15 hours. The reaction was quenched by addition of a saturated solution of ammonium chloride (3 mL) and the mixture was warmed to room temperature. Zinc salts were dissolved upon addition of ammonium hydroxide 28% (6 mL) and the aqueous phase was extracted three times with ethyl ether. The organic phase was dried with potassium carbonate, filtered and concentrated under reduced pressure. Flash chromatography of the oily residue (gradient 10-50% EtOAc/hexane containing 1% NEt_3) afforded 39 mg of **19** (73%) as a colorless oil. R_f 0.07 (EtOAc); $[\alpha]_D^{20} = -252$ (c 1.53, C_6H_6); ^1H NMR (C_6D_6 , 400 MHz) δ 7.48 (br s, 3H), 7.34 (d, $J = 7.4$ Hz, 2H), 7.20 (t, $J = 7.1$ Hz, 2H), 7.16-7.05 (m, 4H), 4.37 (s, 2H), 3.88 (br s, 1H), 3.47 (t, $J = 9.0$ Hz, 1H), 3.44 (dd, $J = 9.0, 4.3$ Hz, 1H), 3.36 (t + m, $J = 6.4$ Hz, 3H), 3.28-3.18 (m, 2H), 3.26 (s, 3H), 2.13 (tt, $J = 13.4, 5.0$ Hz, 1H), 1.95 (dq, $J = 13.8, 4.0$ Hz, 1H), 1.80 (d, $J = 7.1$ Hz, 3H), 1.74 (tt, $J = 13.4, 3.6$ Hz, 1H), 1.68-1.50 (m, 2H), 1.64 (t, $J = 6.6$ Hz, 2H), 1.50-0.90 (m, 20H), 0.91 (d, $J = 6.8$ Hz, 3H), 0.68 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (C_6D_6 , 100 MHz) δ 165.4, 139.9, 136.1, 129.2, 128.9 (2), 128.7 (4), 128.1 (2), 127.9, 76.6, 73.3, 70.9, 70.5, 64.9, 59.5, 56.7, 53.2, 32.2, 30.8, 30.7 (2), 30.5, 30.4 (5), 30.3, 30.2, 27.1, 23.6, 20.1, 18.7, 17.4; FTIR (neat) 3581, 3550-3000, 3061, 3030, 2927, 2854, 1612, 1595, 1455, 1324, 1114, 1073, 707 cm^{-1} ; HRMS (FAB) calcd for $\text{C}_{38}\text{H}_{61}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}^+$): 593.4682, found 593.4673. Anal. calcd for $\text{C}_{38}\text{H}_{60}\text{N}_2\text{O}_3$: C, 76.98; H, 10.20; N, 4.72, found C, 77.17; H, 10.46; N, 4.74.

(2R,3R,6R)-6-[12-(hydroxy)dodecyl]-2-methylpiperidin-3-ol, (+)-Julifloridine (1). The piperidine derivative **19** (72 mg, 0.12 mmol) was dissolved in 3.6 mL THF and 2.5 mL of absolute ethanol (2.00 g, 42.5 mmol). The solution was cooled to -78°C , a dry ice-acetone condenser was added to the flask and ammonia (ca 20 mL) was condensed. Freshly cut lithium wire (255 mg, 0.425 mmol) was added upon stirring, the afforded black solution was stirred for 25 minutes at -78°C .

°C until it became colorless. More lithium wire (188 mg, 31.3 mmol) was added, the mixture was warmed to -33 °C and stirred under reflux of ammonia for 3 hours. Solid ammonium chloride was added until the black color disappeared and then the mixture was warmed to room temperature under a water bath. Stirring was continued until evolution of ammonia ceased, then water was added (10 mL). The mixture was transferred in separatory funnel and the aqueous phase extracted with ether (4X), the combined organic phase dried over potassium carbonate, filtered and concentrated under reduced pressure. The oily residue was purified by flash chromatography (gradient 2.5:2.5:95 to 10:10:80 AcOH/MeOH/CH₂Cl₂) and the fractions containing **1** (*R_f* 0.23 (10:10:80 AcOH/MeOH/CH₂Cl₂)) were collected in an Erlenmeyer flask. The flask was cooled to 0 °C with an ice bath and 10 M NaOH was added until the pH shown to be basic (>10). Extraction with CH₂Cl₂ (3X20 mL), drying with K₂CO₃, filtration and evaporation of the solvent afforded 30 mg (83%) of **1** as a white solid. *R_f* 0.23 (10:10:80 AcOH/MeOH/CH₂Cl₂); Mp: 82-83 °C, lit.⁸ 82-83 °C, lit.⁹ 85-87.5 °C; $[\alpha]_D^{20} = +7.3$ (c 0.23, MeOH), lit.^{9,10} +18 (c 0.84, MeOH); ¹H NMR (CDCl₃, 400 MHz) δ 3.64 (m + t, *J* = 6.6 Hz, 3H), 3.11 (dq, *J* = 6.3, 2.8 Hz, 1H), 2.82 (qn, *J* = 5.8 Hz, 1H), 2.20-1.90 (br s, 3H), 1.86 (ddt, *J* = 13.5, 8.9, 4.5 Hz, 1H), 1.76-1.44 (m, 5H), 1.40-1.20 (m, 20H), 1.08 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 69.5, 63.3, 50.3, 49.8, 33.1, 33.0, 29.9, 29.8 (6), 29.6, 28.0, 26.9, 25.9, 16.3; FTIR (neat) 3581, 3600-3000, 2924, 2853, 1740, 1464, 1370, 1060 cm⁻¹; LRMS (APCI) calcd for C₁₈H₃₈NO₂ (*M* + *H*)⁺: 300.3, Found 300.3.

benzyl (2R,3R,6R)-6-(12-[(tert-butyl(dimethyl)silyl]oxy)dodecyl)-3-hydroxy-2-methylpiperidine-1-carboxylate (20**).**

Julifloridine **1** (13 mg, 0.043 mmol) was dissolved in 1.0 mL CH₂Cl₂ and 1.0 mL of pyridine. DMAP (5.0 mg, 0.040 mmol) and *t*-butyldimethylsilylchloride (50 mg, 0.33 mmol) were added and the solution was stirred for 5h. 2.0 M NaOH (5 mL) was then added and the aqueous phase extracted with CH₂Cl₂ (3X5 mL). The combined organic phase was dried over potassium carbonate, filtered and concentrated under reduced pressure. CH₂Cl₂ (1.0 mL), 2.0 M NaOH (1.0 mL) and benzylchloroformate (50 µL, 60 mg, 0.35 mmol) were added and the biphasic solution was stirred for 16 hours. The mixture was transferred in a separatory funnel and the aqueous phase extracted with CH₂Cl₂ (3X5 mL), the combined organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. Flash chromatography of the oily residue (gradient 5-50% AcOEt/hexane) afforded 17 mg (72%) of **20** as a colorless oil. *R_f* 0.33 (25% AcOEt/hexane); $[\alpha]_D^{20} = -16$ (c 0.60, CHCl₃); ¹H NMR (CDCl₃, 1 drop of D₂O added, 400 MHz) δ 7.40-7.28 (m, 5H), 5.16 (d, *J* = 12.4 Hz, 1H), 5.11 (d, *J* = 12.3 Hz, 1H), 4.00 (td, *J* = 7.4, 4.0 Hz, 1H), 3.92 (qd, *J* = 6.7, 4.2 Hz, 1H), 3.87 (m, 1H), 3.61 (t, *J* = 6.6 Hz, 2H), 2.03-1.80 (m, 3H), 1.72-1.63 (m, 1H), 1.60-1.48 (m, 4H), 1.43-1.34 (m, 1H), 1.32 (d, *J* = 6.8 Hz, 3H), 1.32-1.20 (m, 17H), 0.90 (s, 9H), 0.06 (s, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 156.7, 137.0, 128.7 (2), 128.1 (3), 68.3, 67.1, 63.6, 52.9, 52.1, 34.0, 33.1, 29.8 (6), 29.7, 27.2, 26.2 (3), 26.0, 25.5, 23.2, 18.6, 14.9, -5.0 (2); FTIR (neat) 3600-3000, 2925, 2853, 1692, 1674, 1456, 1411, 1317, 1061, 1025, 697 cm⁻¹; LRMS (APCI) calcd for C₃₂H₅₈NO₄Si (*M* + *H*)⁺: 548.4, found 548.4.

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(10) Due to considerable difference in the optical rotation measured and the one published in ref. 8, we ascertained the optical purity of our synthetic julifloridine with the one prepared by the previous authors. This was done by derivatization to the Mosher ester of the secondary alcohol, as shown by the preparation of **21** from **20**, which is prepared from **1**. The absolute configuration of our synthetic julifloridine was proved as well (see p. S20-S21).

benzyl (2R,3R,6R)-6-(12-[[tert-butyl(dimethyl)silyl]oxy]dodecyl)-2-methyl-3-[[[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]oxy]piperidine-1-carboxylate (21**).** Alcohol **20** (3.5 mg, 6.4 μ mol), (R)-(+)- α -methoxy- α -(trifluoromethyl)phenylacetic acid (7.4 mg, 31.8 μ mol) and *N,N*-dimethyl-4-aminopyridine (DMAP, 1.1 mg, 9.0 μ mol) were dissolved in 0.2 mL CH_2Cl_2 and the solution was cooled to 0 $^\circ\text{C}$ with an ice bath. Dicyclohexylcarbodiimide (6.5 mg, 36 μ mol) was added and the white suspension was stirred for 1h at 0 $^\circ\text{C}$ then 16h at room temperature.¹¹ After completion of the reaction (TLC), the mixture was cooled to 0 $^\circ\text{C}$, a solution of saturated sodium bicarbonate (5 mL) was added and the mixture was transferred in a separatory funnel with CH_2Cl_2 (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3X5 mL), the combined organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was filtered with a short pad of silica using 25% AcOEt/hex to remove polar impurities. The afforded crude was analysed by ^{19}F NMR to be 99.3:0.7 d.r. ^{19}F NMR (25% TFA/ CDCl_3 , 94.1 MHz) δ -70.84 (**21**), -70.94 (diastereoisomer (2S,3S,6S) of **21**). Analytically pure sample was obtained after aqueous work-up as above and flash chromatography (gradient 0-25% AcOEt/hexane), which afforded 2.8 mg (57%) of **21** as a colorless oil. R_f 0.31 (10% AcOEt/hexane); $[\alpha]_D^{20} = 9.5$ (c 0.23, C_6H_6); ^1H NMR (C_6D_6 , 400 MHz) δ 7.68 (d, $J = 7.4$ Hz, 2H), 7.27 (d, $J = 7.4$ Hz, 2H), 7.15-6.95 (m, 6H), 5.19 (td, $J = 7.5, 4.2$ Hz, 1H), 5.16 (d, $J = 12.2$ Hz, 1H), 5.09 (d, $J = 12.2$ Hz, 1H), 4.16 (qd, $J = 6.7, 4.4$ Hz, 1H), 3.80 (m, 1H), 3.59 (t, $J = 6.3$ Hz, 1H), 3.39 (s, 3H), 1.82-1.28 (m, 26H), 1.25 (d, $J = 6.6$ Hz, 3H), 1.09 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (C_6D_6 , 100 MHz) δ 166.3, 155.8, 137.9, 133.2, 130.1 (2), 130-120 (9), 85.3, 73.0, 67.4, 63.7, 55.8, 52.5, 50.5, 34.2, 33.7, 30.5 (5), 30.3 (2), 27.7, 26.7, 26.5 (3), 23.4, 22.5, 18.9, 16.3, -4.8 (2); FTIR (neat) 3063, 3031, 2928, 2855, 1749, 1707, 1700, 1256, 1169, 1103, 1025 cm^{-1} ; LRMS (APCI) calcd for $\text{C}_{42}\text{H}_{64}\text{F}_3\text{NO}_6\text{Si}$ ($\text{M} + \text{H}$) $^+$: 764.5, found 764.4.

The reaction was also executed with racemic α -methoxy- α -(trifluoromethyl)phenylacetic acid to identify the ^{19}F absorption of both diastereoisomers. The Mosher ester **21** was then shown to be 99.3:0.7 d.r., thus the synthetic julifloridine **1** was 98.6 e.e. The preparation of the diastereoisomer **21** of the Mosher ester proves the absolute configuration of **1**.¹²

(11) Modification of a known procedure for the coupling of oxazolidinones and thiazolidinethiones with carboxylic acids: Andrade, C. K. Z.; Rocha, R. O.; Vercillo, O. E.; Silva, W. A.; Matos, R. A. F. *Synlett* **2003**, 2351-2352.

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^1H , ^{13}C and ^{19}F spectra of selected compounds