

Supporting Information

Apparatus and Reagents. Melting points were determined on an Electrothermal apparatus and are uncorrected. Infrared spectra were recorded by using an ATI Mattson Genesis Series FT-IR instrument. IR data are given in cm^{-1} . Proton nuclear magnetic resonance (^1H NMR) and carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were obtained with a Bruker DPX-300, or a Bruker DPX-400, or a Varian Associates VXR-200, or a VXR-300 instrument by using deuteriochloroform solutions unless otherwise specified. Chemical shifts (δ) are reported in parts per million downfield from tetramethylsilane, and coupling constants (J values) are given in hertz. Elemental analyses were obtained from Quantitative Technologies Inc. (Whitehouse, New Jersey) or Robertson Microlit Laboratories, Inc. (Madison, New Jersey). Fast atom bombardment mass spectra (FAB-MS) were obtained from Washington University Resource for Biomedical and Bioorganic Mass Spectrometer at Washington University (St. Louis, Missouri). The positive ion peaks are given in m/z .

Precoated silica gel plates (Merck 60) were used for analytical thin-layer chromatography. E Merck silica gel (230-400 mesh) was employed for column chromatography. Tetrahydrofuran was distilled from benzophenone ketyl; dichloromethane, *N,N*-dimethylformamide, triethylamine, *N,N*-diisopropylamine, pyridine, *n*-hexane, and toluene were distilled from calcium hydride. Other reagents were obtained commercially and used as received unless otherwise specified. All reactions except those in aqueous solutions were run under a static argon atmosphere or under a slow stream of nitrogen.

Racemic 1-*N*-(*t*-Butoxycarbonyl)-1,2,5,6-tetrahydro-3-*R,S*-pyridinecarboxylic acid [(*R,S*)-7]. A solution of 16.32 g (63.92 mmol) of ethyl ester **6** in 160 mL of methanol was stirred with 19.2 mL of 5 *N* sodium hydroxide (96 mmol) at 15 °C for 30 min and at room temperature for 15 h. The reaction mixture was concentrated, and then dissolved in 150 mL of dichloromethane. The solution was washed with 50 mL of 2 *N* hydrochloric acid, and the aqueous layer was back extracted with dichloromethane (2 x 80 mL). The combined organic layer was washed with water (3 x 60 mL), dried over magnesium sulfate, and then concentrated to give 14.24 g (98%) of the carboxylic acid as

a white solid. A portion of the product was further purified by crystallization from 2:1 ethyl acetate / hexanes to give colorless crystals, mp 135–136 °C: IR (KBr) 3000, 2930, 1700, 1650, 1420, 1370, 1240, 1290, 1240, 1170; ¹H NMR (400 MHz) 7.22 (s, 1 H), 4.13 (s, 2 H), 3.51 (t, *J* = 5.7, 2 H), 2.35 (br d, *J* = 2.9, 2 H), 1.50 (s, *t*-butyl, 9 H); ¹³C NMR (100 MHz) 170.3, 154.8, 140.4, 127.9, 80.2, 42.3, 39.7, 38.6 (extra peak due to Boc rotamers), 28.4, 25.7. Anal. Calcd for C₁₁H₁₇NO₄: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.27; H, 7.49; N, 6.06.

A solution of 16.8 g (166 mmol) *N,N*-diisopropylamine in 220 mL of THF was stirred with *n*-BuLi (1.6 *M* solution in hexane, 100 mL) at –78 °C for 10 min and at –10 °C for 30 min, and then 22 mL of HMPA was added at –10 °C. The reaction mixture was cooled to –78 °C, and then a solution of 14.52 g (63.9 mmol) of the conjugated acid in 50 mL of THF was added by syringe over a period of 15 min. The reaction mixture gradually turned a bright yellow color, indicating the formation of dianion. The resulting solution was stirred at –78 °C for 2 h, and then was treated sequentially with 80 mL of saturated aqueous ammonium chloride and 100 mL of ethyl acetate. The aqueous layer was adjusted to pH 1.5–2 by adding 6*N* hydrochloric acid. The aqueous layer was further extracted with ethyl acetate (2 x 100 mL). The combined organic layer was washed with water (3 x 80 mL) and brine (80 mL), dried over magnesium sulfate, and then concentrated to give 13.80 g (95%) of the deconjugated carboxylic acid (**(R,S)**-**7**) as a white powder. A portion of the product was further purified by crystallization from 20:80 ethyl acetate / hexanes to give (**(R,S)**-**7**, mp 142–143 °C: IR (KBr) 3140, 2980, 1740, 1700, 1650, 1430, 1370, 1240, 1170; ¹H NMR (400 MHz) 5.94 (br m, 1 H), 5.89 (br m, 1 H), 4.02–3.85 (br m, 3 H), 3.59 (br m, 1 H), 3.28 (br s, 1 H), 1.47 (s, *t*-butyl, 9 H); ¹³C NMR (100 MHz) 177.1, 154.8, 126.9, 122.6, 80.3, 42.8, 42.3, 40.8, 28.3. Anal. Calcd for C₁₁H₁₇NO₄: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.31; H, 7.46; N, 6.05.

Resolved 1-*N*-(*t*-Butoxycarbonyl)-1,2,3,6-tetrahydro-3-*R*--pyridinecarboxylic acid [((R)**-**7**].** A mixture of 3.431 g (15.09 mmol) of racemic acid (**(R,S)**-**7**, 50 mL of ethyl acetate, and 1.829 g (1.95 mL, 15.09 mmol) of (*R*)-(+)- α -methylbenzylamine was stirred at 40 °C for 10 min to allow solids to dissolve. The mixture was then stirred at room temperature for 3 h, during which period the amine salt gradually precipitated. The salt was isolated by filtration, and the wet cake was rinsed with 20 mL of ethyl acetate. The

solid was further purified by trituration with 30 mL of ethyl acetate at room temperature for 3 h. The solid was isolated again by filtration, and the wet solid was washed with 20 mL of ethyl acetate. The solid was recrystallized from 30 mL of ethyl acetate by heating to 55 °C, then cooling to room temperature. The product was isolated as before, dried under reduced pressure for 1 h, and then was treated with 15 mL of 1 *N* hydrochloric acid. The mixture was extracted with dichloromethane (3 x 20 mL), and the combined organic layer was washed with water (2 x 20 mL). The organic solution was concentrated, and the residue was azeotropically dried with toluene (3 x 15 mL) to remove a trace amount of water, and then stirred with 20 mL of ethyl acetate at room temperature for 2 h. Filtration and drying under reduced pressure at room temperature gave 1.406 g (41%) of acid (**R**)-**7** as a white powder. The minimum enantiomeric excess was estimated at 85% by ¹H NMR analysis of a derivative (see below).

All mother liquor and wash solutions were combined and concentrated to a solid residue, which contained the enantiomerically enriched amine salt (**S**)-**7**. After salt breaking and isolation by the procedure described above, 1.750 g (51%) of acid (**S**)-**7** was isolated as a white powder. Acid (**S**)-**7** was quantitatively racemized (according to analysis of the derived amide) to (**R,S**)-**7** by using the LDA deconjugation procedure described previously.

1-*N*-(*t*-Butoxycarbonyl)-1,2,3,6-tetrahydro-3-*R*-pyridine-*N*-(1*S*-phenyl-1-ethyl)-carboxamide (8). The experimental procedure was the same as for **9** (below). From 170 mg of acid (**R**)-**7**, 225 mg of amide **8** was obtained after coupling with (*S*)-(-)- α -methylbenzylamine and purification. ¹H NMR analysis of a CD₃CN solution of **8** (the signal for H-2 at 3.3-3.5 ppm) indicated a diastereomeric ratio of approximately 12:1.

1-*N*-(*t*-Butoxycarbonyl)-3-*R*-piperidine-*N*-(1*S*-phenyl-1-ethyl)-carboxamide (9, from 8). A mixture of 33 mg (0.1 mmol) of **8**, 2 mL of ethanol, and 10 mg of 10% palladium on carbon catalyst was stirred under a hydrogen atmosphere at room temperature for 12 h. The catalyst was removed by filtration, and the filtrate was concentrated to give 30 mg of amide **9** as a colorless oil (see below). ¹H NMR analysis of a CD₃CN solution of **9** indicated a diastereomeric ratio of approximately 12:1.

1-*N*-(*t*-Butoxycarbonyl)-3-*R*-piperidine-*N*-(1*S*-phenyl-1-ethyl)-carboxamide (9, from 10). A solution of 615 mg (2.0 mmol) of ethyl (*R*)-nipecotate *L*-tartrate salt **10**

(Aldrich) in 3.0 mL of 12 *N* hydrochloric acid was heated at 60 °C for 24 h. The reaction mixture was concentrated under reduced pressure, and then the residue was azeotropically dried with toluene (5 x 5 mL) to remove traces of water and hydrochloric acid. The residue was dissolved in 20 mL of dichloromethane and treated with saturated aqueous Na₂HPO₄ until the aqueous layers pH reached 6.5–7.0. The aqueous layer was back extracted with 10 mL of dichloromethane. The combined organic layer was concentrated to an oil, which was dissolved in 10 mL of THF and 5 mL of water. The resulting solution was adjusted to pH 10 with 1 *N* NaOH, and then was treated with 480 mg (2.2 mmol) of di-*tert*-butyldicarbonate and was stirred at room temperature for 12 h. The reaction mixture was concentrated to remove the organic solvent. The aqueous solution was adjusted to pH 4.5 with saturated aqueous ammonium chloride, and then was extracted with ethyl acetate (2 x 15 mL). The combined organic extract was washed with water (2 x 10 mL) and brine (10 mL), dried over magnesium sulfate, and then concentrated to give 416 mg (91%) of the *N*-protected nipecotic acid as a colorless oil, which was directly used for the next coupling reaction without further purification.

A solution of 170 mg (0.75 mmol) of the *N*-protected nipecotic acid in 8 mL of acetonitrile and 2 mL of water was treated with 109 mg (116 µL, 0.9 mmol) of (*S*)-(-)- α -methylbenzylamine at room temperature. The resulting solution was treated with 12.2 mg (0.09 mmol) of 1-hydroxybenzotriazole and 173 mg (0.9 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, and then was stirred at room temperature for 5 h. The reaction mixture was concentrated and azeotropically dried with toluene (2 x 5 mL) to remove acetonitrile. The remaining aqueous mixture was mixed with 10 mL of ethyl acetate. The organic layer was washed with water (3 x 4 mL), dried over magnesium sulfate, and then concentrated to an oil, which was purified on a short silica gel column (1 inch in height) with 50:50:2 hexanes / ethyl acetate / methanol as the eluant to give 220 mg of amide **9** as colorless oil. ¹H NMR analysis of a CD₃CN solution of **9** prepared in this way indicated a diastereomeric ratio of >19:1, and matching the diastereomer as from the resolution of (*R*)-**7** (above).

(3*S*,4*S*,5*S*)-5-Bromo-1-*N*-(*t*-butoxycarbonyl)-hexahydro-{{[3,2-*c*]-4-keto-oxeto}-piperidine (12). A solution of 1.38 g (6.07 mmol) of deconjugated acid (*R*)-**7** in 15 mL of dichloromethane was treated with tetrabutylammonium hydroxide (6.1 mL, 1 *M*

solution in methanol, 6.1 mmol) at 0 °C for 10 min and at room temperature for 1 h. The reaction mixture was concentrated to oil, which was azeotropically dried with toluene (3 x 10 mL) to remove trace amounts of methanol. The carboxylate salt **11** thus obtained was dissolved in 15 mL of dichloromethane, and the resulting reaction mixture was treated with a solution of 1.02 g (6.4 mmol) of bromine in 5 mL of dichloromethane by addition over a period of 20 min at –78 °C. The resulting solution was stirred at –78 °C for 3 h and at –30 °C for 1 h. The reaction mixture was concentrated to oil, which was dissolved in 30 mL of ethyl acetate. The organic solution was washed with saturated sodium bicarbonate (2 x 10 mL), saturated brine (10 mL), dried over magnesium sulfate, and then concentrated to a residue, which was purified on a flash silica gel column with 80:20 hexanes / ethyl acetate as the eluant to give 1.32 g (71%) of the β -lactone **12** as a white solid, mp 114–115 °C: IR (KBr) 2980, 2930, 1840, 1700, 1460, 1400, 1370, 1260, 1160, 1120; ¹H NMR (400 MHz) 4.94 (br s, 1 H), 4.55 (br d, *J* = 23.8, 1 H), 4.14–3.97 (br m, 4 H), 3.71 (dd, *J* = 14.1, 5.1, 1 H), 1.48 (s, *t*-butyl, 9 H); ¹³C NMR (100 MHz) 168.7, 154.7, 81.0, 68.7 and 68.4 (rotamers), 49.6, 42.9 and 42.1 (rotamers), 42.8, 37.3 and 36.2 (rotamers), 28.3. Anal. Calcd for C₁₁H₁₆BrNO₄: C, 43.15; H, 5.27; N, 4.58; Br, 26.10. Found: C, 43.21; H, 5.16; N, 4.45; Br, 26.13.

(3*S*,4*S*,5*R*)-3-Bromo-1-*N*-(*t*-butoxycarbonyl)-4-hydroxy-5-(pivaloyloxymethyl)-piperidine (13). A solution of 950 mg (3.10 mmol) of bromo lactone **12** in 35 mL of diethyl ether was stirred with 203 mg (9.30 mmol) of lithium borohydride at 0 °C for 2 h and at room temperature for 12 h. The reaction mixture was then quenched with 10 mL of saturated aqueous ammonium chloride at 0 °C. The aqueous layer was extracted with diethyl ether (2 x 20 mL). The combined organic layer was washed with water (2 x 20 mL) followed by brine (20 mL). The organic layer was dried over magnesium sulfate, and then concentrated to oil, which was purified on a flash silica gel column with 50:50 hexanes / ethyl acetate as the eluant to give the 827 mg (86%) of the diol as a colorless solid. A larger sample of the diol (5.59 g) was crystallized from 9:1 ethyl acetate / hexanes to afford 5.13 g, mp 133–134 °C: IR (KBr) 3390, 2980, 2930, 1670, 1430, 1370, 1240, 1170, 1140; ¹H NMR (400 MHz, CD₃CN) 4.13–4.08 (m, 1 H), 4.02–3.97 (m, 1 H), 3.92–3.82 (br m, 1 H), 3.76–3.70 (m, 3 H), 3.64–3.58 (m, 1 H), 3.52–3.46 (m, 1 H), 3.30–3.01 (br m, 1 H), 2.83 (t, *J* = 5.0, 1 H),

2.29–2.21 (m, 1 H), 1.45 (s, *t*-butyl, 9 H); ^{13}C NMR (100 MHz, CD_3CN) 154.6, 79.3, 70.3, 60.8, 51.5, 45.9 (br), 40.4, 38.7 (br), 27.5. Anal. Calcd for $\text{C}_{11}\text{H}_{20}\text{BrNO}_4$: C, 42.59; H, 6.50; N, 4.52. Found: C, 42.68; H, 6.38; N, 4.38.

A solution of 200 mg (0.645 mmol) of the bromo diol and 10 mg (0.083 mmol) DMAP in 2.0 mL of dichloromethane and 2.0 mL of pyridine was treated with a first portion of pivaloyl chloride (78 mg, 0.645 mmol) at 0 °C for 5 h and at room temperature for 10 h. The reaction mixture was cooled back to 0 °C, and then a second portion of pivaloyl chloride (39 mg, 0.323 mmol) was added. The reaction required another 4–5 h at room temperature to complete, according to TLC analysis. The reaction mixture was cooled to 0 °C, and then treated with 5 mL of water and 10 mL of ethyl acetate. The organic layer was washed with water (3 x 5 mL) and brine (5 mL), dried over magnesium sulfate, and then concentrated to an oil, which was purified on a flash silica gel column with 70:30 hexanes / ethyl acetate as the eluant to give 242 mg (95%) of the mono-pivaloate **13** as a colorless solid, mp 94–95 °C: IR (KBr) 3440, 2970, 2930, 1730, 1700, 1670, 1480, 1460, 1430, 1280, 1160, 990; ^1H NMR (400 MHz) 4.33 (dd, $J = 11.2, 7.2$, 1 H), 4.07 (br s, 1 H), 3.89 (br, 3 H), 3.82–3.70 (br m, 2 H), 3.59–3.33 (br m, 1 H), 3.18–2.94 (br m, 1 H), 2.59 (br, 1 H), 1.47 (s, *t*-butyl, 9 H), 1.23 (s, pivaloyl, 9 H); ^{13}C NMR (100 MHz) 179.1 (br), 154.7, 80.3, 70.6 and 69.5 (rotamers), 62.3, 50.2, 46.0, 42.0 and 40.1 (rotamers), 38.9, 37.0 and 35.8 (rotamers), 28.3, 27.1. Anal. Calcd for $\text{C}_{17}\text{H}_{34}\text{BrNO}_4$: C, 48.11; H, 8.07; N, 3.30. Found: C, 48.98; H, 6.99; N, 3.51.

1-*N*-(*t*-Butoxycarbonyl)-4-*R*-hydroxy-3-*S*-(pivaloyloxymethyl)-1,4,3,6-tetrahydropyridine (14). A solution of 200 mg (0.507 mmol) of bromo alcohol **13** and 5 mg of 4-(*N,N*-dimethylamino)pyridine in 4.0 mL of THF and 0.6 mL of pyridine was treated with 0.4 mL (4.2 mmol) of acetic anhydride at 45 °C for 15 h. The reaction was quenched by adding 5 mL of water at room temperature. The reaction mixture was extracted with ethyl acetate (2x10 mL). The combined organic layer was washed with water (3 x 5 mL) and brine (5 mL), dried over magnesium sulfate, and then concentrated to an oil, which was purified on a flash silica gel column with 80:20 hexanes / ethyl acetate as the eluant to give 190 mg (86%) of the acetate as a colorless solid. A larger sample of the acetate (4.62 g) was crystallized from 19:1 ethyl acetate / hexanes to afford 4.32 g, mp 133–134 °C: mp 133–134 °C: IR (KBr) 2980, 1730, 1700, 1420, 1370,

1280, 1230, 1150; ^1H NMR (400 MHz) 5.13 (t, $J = 4.04$, 1 H), 4.11 (dd, $J = 7.67$, 4.41, 1 H), 4.08–3.92 (br, 2 H), 3.93 (t, $J = 9.43$, 1 H), 3.82–3.57 (br m, 2 H), 3.30–2.92 (br, 1 H), 2.87–2.62 (br, 1 H), 2.12 (s, 3 H), 1.48 (s, *t*-butyl, 9 H), 1.21 (s, pivaloyl, 9 H); ^{13}C NMR (100 MHz) 178.1, 169.5, 154.4, 80.4, 71.5 and 70.8 (rotamers), 61.4, 46.5 (br), 45.3 (br), 42.4 and 40.7 (rotamers), 38.8, 35.1 and 33.9 (rotamers), 28.3, 27.1, 20.7. Anal. Calcd for $\text{C}_{18}\text{H}_{30}\text{BrNO}_6$: C, 49.55; H, 6.93; N, 3.21. Found: C, 49.52; H, 6.78; N, 3.07.

A mixture of 300 mg (0.689 mmol) of the bromo acetate and 367 mg (2.41 mmol) of 1,8-diazabicyclo[5,4,0]undec-7-ene was azeotropically dried four times with 5 mL portions of toluene to remove trace amounts of moisture. The oily residue was dissolved in 5 mL of toluene, and the reaction mixture was heated at 80 °C for 18 h. The reaction mixture was cooled to room temperature, and was mixed with 15 mL of ethyl acetate and 5 mL of water. The aqueous layer was extracted with 10 mL of ethyl acetate. The combined organic layer was washed with half saturated brine (2 x 10 mL), dried over magnesium sulfate, and then concentrated to oil, which was purified on a short flash silica gel column (about 1 inch in height) with 90:8:2 hexanes / ethyl acetate / triethylamine as the eluant to give 225 mg (92%) of the unsaturated acetate as a colorless solid, mp 54–55.5 °C: IR (KBr) 2980, 1730, 1710, 1650, 1370, 1230, 1160; ^1H NMR (400 MHz) 7.13–6.96 (br m, 1 H), 5.22 (t, $J = 4.10$, 1 H), 5.20–5.00 (br m, 1 H), 4.20–4.11 (br m, 1 H), 4.10–4.00 (br m, 1 H), 4.10–3.87 (br m, 1 H), 3.21–3.01 (br m, 1 H), 2.35–2.26 (m, 1 H), 2.04 (s, 3 H), 1.50 (s, *t*-butyl, 9 H), 1.21 (s, pivaloyl, 9 H); ^{13}C NMR (100 MHz) 178.2, 170.3, 151.8 (br), 129.8 and 129.6 (rotamers), 102.0 and 101.5 (rotamers), 81.7, 63.9, 62.1, 40.1 and 39.0 (rotamers), 38.8, 36.1, 28.2, 27.1, 21.0. Anal. Calcd for $\text{C}_{18}\text{H}_{29}\text{NO}_6$: C, 60.83; H, 8.22; N, 3.94. Found: C, 60.70; H, 8.03; N, 3.82.

Guanidine hydrochloride (1.912 g, 20 mmol) was mixed with freshly made sodium ethoxide (1 M, 20 mL, 20 mmol) at 10 °C with stirring; solid sodium chloride precipitated simultaneously. The mixture was stirred at room temperature for 30 min, and then the solid was allowed to settle. A solution of 355 mg (1.0 mmol) of the unsaturated acetate in 0.7 mL of dichloromethane and 6.3 mL of ethanol was treated with the above freshly made guanidine supernatant (1 M, 1.05 mL, 1.05 mmol) at 10 °C for 30 min and at room temperature for 1.5 h. The reaction mixture was concentrated to an oil,

which was redissolved in 15 mL of ethyl acetate. The organic solution was washed with water (2 x 5 mL) and brine (5 mL), dried over sodium sulfate, and then concentrated to give 260 mg (83%) of the allylic alcohol **14** as a colorless oil. Since alcohol **14** is unstable, it was used for the next epoxidation reaction directly without further purification. For crude **14**: IR (KBr) 3440 (br), 2980, 2930, 1730, 1710, 1370, 1160, 1130 cm^{-1} ; ^1H NMR (200 MHz) no acetate singlet near 2.04 ppm.

(3S,4S,5S)-1-N-(*t*-Butoxycarbonyl)-4,5-*O*-isopropylidene-6-methoxy-3-(pivaloyloxymethyl)-piperidine (15). A mixture of 360 mg (1.15 mmol) of freshly made allylic alcohol **14**, 5.0 mL of methanol, 2.5 mL of dichloromethane, and 126 mg (1.50 mmol) of sodium bicarbonate was treated with *m*-chloroperoxybenzoic acid (pre-purified, 208 mg, 1.21 mmol) at 0 °C for 5 h. The reaction mixture was concentrated to a solid residue, which was mixed with ethyl acetate (15 mL), and then washed with saturated aqueous sodium bicarbonate (2 x 5 mL) and brine (5 mL), dried over magnesium sulfate, and concentrated to an oil, which was used for the next ketalization step without further purification. Five mL of 2,2-dimethoxypropane and a catalytic amount of toluenesulfonic acid was added, and the reaction mixture was stirred at room temperature for 15 h. The solution was concentrated to oil, which was redissolved in 15 mL of ethyl acetate. The organic solution was washed with saturated aqueous sodium bicarbonate (2 x 5 mL) and brine (5 mL), dried over magnesium sulfate, and then concentrated to an oil, which was purified on a flash silica gel column with 80:20 hexanes / ethyl acetate as the eluant to give 314 mg (68% overall from **14**) of the ketal **15** as a colorless oil: IR (KBr) 3400, 2980, 2940, 1730, 1700, 1400, 1380, 1370, 1160, 1090; ^1H NMR (400 MHz) 5.34 and 5.19 (two s, H-2, rotamers), 4.42–4.31 (m, 2 H), 4.18–4.01 (m, 2 H), 3.33 and 3.30 (two s, $-\text{OCH}_3$, rotamers), 3.29–3.13 (m, 2 H), 2.70–2.60 (m, 1 H), 1.49 (s, *t*-butyl, 9 H), 1.38 (s, 3 H), 1.32 (s, 3 H), 1.22 and 1.21 (two s, pivaloyl, rotamers); ^{13}C NMR (100 MHz) 178.2, 156.2 and 155.5 (rotamers), 109.4 and 109.3 (rotamers), 83.3 and 82.2 (rotamers), 80.5 and 80.2 (rotamers), 74.8 and 74.7 (rotamers), 70.6 and 70.5 (rotamers), 64.0 and 63.8 (rotamers), 55.4 and 55.2 (rotamers), 39.1, 38.8 and 38.6 (rotamers), 32.7 and 32.5 (rotamers), 28.3, 27.2, 26.1, 24.2; FAB-MS 402 ($\text{M}^+ + 1$).

(3*S*,4*S*,5*R*,6*S*)-6-Acetamido-1-*N*-(*t*-butoxycarbonyl)-4,5-isopropylidenedioxy-3-(pivaloyloxymethyl)-piperidine (16). A solution of 60 mg (0.149 mmol) ketal **15** in 2 mL of dichloromethane was treated with 0.2 mL (1.50 mmol) of azidotrimethylsilane and 0.06 mL (0.48 mmol) of boron trifluoride diethyl etherate at $-30\text{ }^{\circ}\text{C}$ for 3 h. The reaction was quenched by addition of 2 mL of saturated aqueous sodium bicarbonate at $-10\text{ }^{\circ}\text{C}$. The reaction mixture was then mixed with 15 mL of ethyl acetate. The organic layer was washed with water (2 x 5 mL) and brine (5 mL), dried over magnesium sulfate, and then concentrated to an oil, which was purified on a flash silica gel column with 90:10 hexanes / ethyl acetate as the eluant to give 47 mg (77%, single diastereomer) of the azide product as a colorless oil: IR (KBr) 2980, 2930, 2110, 1730, 1710, 1390, 1210, 1160; ^1H NMR (400 MHz) 5.93–5.80 (br m, 1 H), 4.39 (dd, $J = 7.55, 1.55$, 1 H), 4.26 (dd, $J = 7.58, 2.07$, 1 H), 4.21–4.10 (br m, 1 H), 4.09–3.98 (br m, 1 H), 3.56–3.37 (br m, 1 H), 3.13 (t, $J = 12.29$, 1 H), 2.58–2.45 (br m, 1 H), 1.51 (s, *t*-butyl, 9 H), 1.41 (s, 3 H), 1.32 (s, 3 H), 1.23 (s, pivaloyl, 9 H); ^{13}C NMR (100 MHz) 178.2, 154.5 (br), 109.4, 81.8 and 81.2 (rotamers), 74.6, 69.9, 69.4 and 68.6 (rotamers), 63.2, 38.8, 38.2, 34.1, 28.1, 27.2, 25.9, 24.0; FAB-MS 413 ($\text{M}^+ + 1$).

A mixture of 36 mg (0.087 mmol) of the azide, 1.0 mL of THF, 0.5 mL of acetic anhydride, and 7.2 mg of 10% palladium on carbon was stirred under a hydrogen atmosphere at $40\text{ }^{\circ}\text{C}$ for 20 h. The reaction mixture was filtered (PTFE, $0.45\text{ }\mu\text{M}$) to remove the solid catalyst. The filtrate was concentrated and the residue was azeotropically dried with toluene (3 x 2 mL) to give an oil, which was purified on a flash silica gel column with 50:50:2 hexanes / ethyl acetate / methanol to afford 35 mg (94%) of the acetamide **16** as a colorless oil: IR (KBr) 2980, 2930, 1730, 1700, 1650, 1380, 1160; ^1H NMR (400 MHz) δ 5.75–5.60 (br, 1 H), 4.57 (dd, $J = 6.98, 2.52$, 1 H), 4.40 (dd, $J = 7.07, 2.51$, 1 H), 4.18 (dd, $J = 11.13, 6.59$, 1 H), 4.06 (dd, $J = 11.10, 7.94$, 1 H), 3.52 (dd, $J = 12.21, 4.21$, 1 H), 3.04 (t, $J = 18.63$, 1 H), 2.27–2.18 (m, 1 H), 2.00 (s, 3 H), 1.46 (s, *t*-butyl, 9 H), 1.44 (s, 3 H), 1.32 (s, 3 H), 1.21 (s, pivaloyl, 9 H); ^{13}C NMR (100 MHz) 178.4, 169.4, 155.1, 108.8, 80.9, 74.4, 70.1, 63.2, 60.2, 38.8 (overlapped), 35.9, 28.3, 26.2, 24.2, 23.4; FAB-MS 429 ($\text{M}^+ + 1$).

(3*S*,4*S*,5*R*,6*S*)-6-Acetamido-1-*N*-(*t*-butoxycarbonyl)-4,5-isopropylidenedioxy-3-piperidinecarboxylic acid (17). A solution of 110 mg (0.257 mmol) of acetamide **16**

in 3 mL of methanol was treated with tetrabutylammonium hydroxide (1 *M* solution in methanol, 0.64 mL, 0.64 mmol) at 0 °C for 1 h and at room temperature for 16 h. The reaction was quenched by addition of 2 mL of saturated aqueous ammonium chloride at 0 °C. The resulting mixture was concentrated to wet residue, which was mixed with 15 mL of ethyl acetate. The organic layer was washed with water (2 x 5 mL) and brine (5 mL), dried over magnesium sulfate, and then concentrated to oil, which was purified on a flash silica gel column with 95:5 to 90:10 dichloromethane / methanol as the eluant to give 81 mg (91.5%) of the primary alcohol as a colorless oil: IR (KBr) 3300, 2980, 2940, 1700, 1680, 1660, 1540, 1390, 1170, 1070; ¹H NMR (400 MHz) 6.03–5.55 (br, 1 H), 5.73 (br s, 1 H), 4.65–4.56 (br m, 1 H), 4.52 (dd, *J* = 6.70, 2.27, 1 H), 3.78 (s, 1 H), 3.76 (s, 1 H), 3.51 (dd, *J* = 12.33, 3.89, 1 H), 3.16 (t, *J* = 12.51, 1 H), 2.34–2.19 (br s, 1 H), 2.11–1.99 (br m, 1 H), 1.98 (s, 3 H), 1.47 (s, *t*-butyl, 9 H), 1.45 (s, 3 H), 1.34 (s, 3 H); ¹³C NMR (100 MHz) 169.9, 155.5, 108.8, 80.8, 74.7, 70.6, 62.1, 59.6, 37.9 (br), 28.5, 28.1, 26.0, 24.1, 22.9; FAB-MS 351 (*M*⁺ + Li).

A solution of 75 mg (0.218 mmol) of the primary alcohol in 0.8 mL of DMF was treated with 328 mg (0.87 mmol) of pyridinium dichromate at room temperature for 24 h. The reaction was quenched by adding 2 mL of water. The mixture was extracted with ethyl acetate (3 x 10 mL), and the combined organic layer was washed with water (3 x 5 mL) and brine (5 mL), dried over magnesium sulfate, and then concentrated to oil, which was chromatographed with a gradient 95:10:0 to 90:10:1 dichloromethane / methanol / acetic acid as the eluant to give 59 mg (75.5%) of the piperidinecarboxylic acid as an amorphous solid: IR (KBr) 3300, 2980, 2930, 1700, 1660, 1540, 1380, 1170, 1070; ¹H NMR (300 MHz) 5.79 (d, *J* = 2.1 Hz, H-2), 4.79 (dd, *J* = 7.2, 3.0, H-4), 4.50 (d, *J* = 6.0 Hz, H-3), 3.61 (dd, *J* = 12.0, 4.8, H-6eq), 3.39 (t, *J* = 12.6, H-6ax), 3.09 (ddd, *J* = 12.6, 4.8, 3.0, H-5), 1.94 (s, NCOCH₃), 1.46 (s, *t*-butyl, 9 H), 1.38 (s, 3 H, isopropylidene), 1.32 (s, 3 H, isopropylidene); ¹³C NMR (100 MHz, CD₃OD) 172.0, 171.5, 155.6, 109.1, 80.9, 74.8, 70.7 and 70.6 (rotamers), 59.4, 40.6, 36.8, 27.4, 25.1, 23.08, 21.21 and 21.17 (rotamers); FAB-MS 365 (*M*⁺ + Li).

(+)-Siastatin B (1·HCl). A solution of 30 mg (0.84 mmol) of carboxylic acid **17** in 1.2 mL of TFA at 0 °C was stirred for 30 min. Water (0.2 mL) was added. The resulting reaction mixture was stirred at 0 °C for 20 min and at room temperature for 20

min. The reaction mixture was concentrated to a residue, which was azeotropically dried with toluene (3 x 2 mL), and then was dissolved in 1 mL of ethanol. The solution was treated with 0.1 mL of 12 *N* hydrochloric acid at 5 °C for 10 min and at room temperature for 10 min. The reaction mixture was concentrated to an oil, which was azeotropically dried with toluene (3 x 2 mL). The residue was treated with 0.5 mL of hexanes, and a solid gradually formed. The solid was collected, washed with diethyl ether (2 x 1 mL), and dried under vacuum to afford 21 mg (98.5%) of **1·HCl** as a white solid, mp 165-170 °C (dec); $[\alpha]^{25}_{\text{D}} +52^{\circ}$ ($c = 0.25$, H₂O), lit.* $[\alpha]^{22}_{\text{D}} +53^{\circ}$ ($c = 0.25$, H₂O); IR (KBr) 3330, 3040, 1720, 1670, 1540, 1370, 1310, 1110, 920; ¹H NMR (300 MHz, D₂O) 4.91 (d, $J = 10.2$, H-2), 4.43 (t, $J = 2.4$, H-4), 3.88 (dd, $J = 10.5$, 2.7, H-3), 3.38–3.31 (m, H-6ax and H-6eq), 3.02 (ddd, $J = 9.6$, 7.8, 2.4, H-5), 1.95 (s, NCOCH₃); ¹³C NMR (100 MHz, D₂O) δ 175.5, 172.5, 67.72, 67.68, 59.9, 42.6, 38.4, 21.8; FAB-MS 219 ($M^+ + 1$, as free base). The ¹H and ¹³C NMR spectra match the published values (see Table 1). *Nishimura, Y.; Wang, W.; Kudo, T.; Kondo, S. *Bull. Chem. Soc. Jpn.* **1992**, 65, 978-986.

(3*S*,4*S*,5*R*,6*S*)-1-*N*-(*t*-Butoxycarbonyl)-6-trifluoroacetamido-4,5-isopropylidenedioxy-3-(pivaloyloxymethyl)-piperidine (19). A mixture of 52 mg (0.126 mmol) of the azide **18** (from azidolysis of **15**), 2.0 mL of ethanol, and 8 mg of 10% palladium on carbon was stirred under an atmosphere of hydrogen gas at 40 °C for 20 h. The reaction mixture was filtered (PTFE, 0.45 μ M) to remove the solid catalyst. The filtrate was concentrated and azeotropically dried with toluene (3 x 2 mL) to give an oil, which was redissolved in 2.0 mL of dichloromethane. The solution was treated with 31 μ L (0.38 mmol) of pyridine and 21 μ L (0.151 mmol) of trifluoroacetic anhydride at –20 °C for 1 h. The reaction mixture was then concentrated to an oil, which was redissolved in 10 mL of ethyl acetate. The solution was washed with water (3 x 4 mL) and brine (4 mL), dried over magnesium sulfate, and then concentrated to an oily residue, which was purified on a flash silica gel column with 50:50:2 hexanes / ethyl acetate / methanol as the eluant to give 46 mg (76%) of the trifluoroacetamido product **19** as a colorless oil: ¹H NMR (300 MHz) 6.88–6.22 (br m, 1 H), 5.70 (br m, 1H), 4.54 (dd, $J = 6.9$, 3.0, 1 H), 4.44 (dd, $J = 6.9$, 2.1, 1 H), 4.17 (dd, $J = 11.1$, 6.6, 1 H), 4.07 (dd, $J = 11.1$, 7.8, 1 H), 3.58 (dd, $J = 12.6$, 3.6, 1 H), 3.03 (t, $J = 12.3$, 1 H), 2.24–2.10 (br m, 1 H), 1.46

(s, overlapped, *t*-butyl and acetonide CH₃, 12 H), 1.33 (s, acetonide CH₃, 3 H), 1.22 (s, pivaloyl, 9 H); ¹³C NMR (75 MHz) 178.5, 156.5 (q, *J* = 37.8), 155.0, 115.7 (q, *J* = 287.8), 109.4, 81.8, 74.4 (t, *J* = 71.2), 69.9 (t, *J* = 76.7), 63.3 (t, *J* = 32.7), 61.0 (t, *J* = 75.0), 39.1, 38.9, 35.7 (t, *J* = 72.4), 28.5 (q, *J* = 49.8), 26.2 (q, *J* = 43.23), 24.7, 24.0.

(3*S*,4*S*,5*R*,6*S*)-1-*N*-(*t*-Butoxycarbonyl)-3-(hydroxymethyl)-4,5-

(isopropylidenedioxy)-6-trifluoroacetamido-piperidine (20). A solution of 42 mg (0.087 mmol) of the pivaloate **19** in 1.5 mL of methanol was treated with 0.26 mL (0.26 mmol) of 1 *M* tetrabutylammonium hydroxide in methanol at room temperature for 20 h. The reaction was quenched by adding 1 mL of saturated aqueous ammonium chloride at 0 °C. The resulting mixture was concentrated to a wet solid, which was mixed with 10 mL of ethyl acetate. The organic layer was washed with water (2 x 3 mL) and brine (3 mL), dried over magnesium sulfate, and then concentrated to oil, which was purified on a flash silica gel column with 95:5 to 90:10 dichloromethane / methanol as the eluant to give 28.5 mg (82%) of the primary alcohol **20** as a colorless oil: ¹H NMR (300 MHz) 7.54 (d, *J* = 5.4, 1 H), 5.83 (d, *J* = 5.7, 1 H), 4.49 (s, 2 H), 3.75 (dd, *J* = 11.4, 6.0, 1 H), 3.65 (dd, *J* = 11.4, 6.9, 1 H), 3.53 (dd, *J* = 12.3, 3.9, 1 H), 3.07 (t, *J* = 12.3, 1 H), 2.19–2.05 (br m, 1 H), 1.42 (s, overlapped, *t*-butyl and acetonide CH₃, 12 H), 1.31 (s, acetonide CH₃); ¹³C NMR (75 MHz) 156.7 (q, *J* = 37.7), 155.4, 115.7 (q, *J* = 287.5), 109.4, 82.0, 74.5, 70.6, 62.2, 60.8, 38.7 and 38.3 (br, rotamers), 28.5, 26.2, 24.3. The ¹H NMR spectrum matches the published values (Satoh, T.; Nishimura, Y.; Kondo, S.; Takeuchi, T. *Carbohydr. Res.* **1996**, 286, 173-178).

(3*R*,4*S*,5*R*,6*R*)-3,4-Isopropylidenedioxy-6-trifluoroacetamido-3-

piperidinecarboxylic acid (21). The procedure was the same as that for preparation of **17**. Oxidation of 46 mg (0.115 mmol) of trifluoroacetamide **20** with PDC in DMF afforded 35.2 mg (74%) of the carboxylic acid **21** as a colorless oil: ¹H NMR (300 MHz, CD₃OD, contains some DMF) 5.80 (d, *J* = 2.1, 1 H), 4.24 (t, *J* = 3.0, 1 H), 4.53 (dd, *J* = 7.8, 2.1, 1 H), 3.65 (dd, *J* = 12.3, 4.8, 1 H), 3.71 (t, *J* = 12.9, 1 H), 3.09 (ddd, *J* = 12.6, 4.8, 3.2, 1 H), 1.46 (s, *t*-butyl, 9 H), 1.40 (s, 3 H), 1.34 (9s, 3H); ¹³C NMR (75 MHz) 158.8 (q, *J* = 38.6), 115.7 (q, *J* = 286.3), 68.7 (m), 67.5 (m), 61.4, 60.4 (t, *J* = 16.9), 41.0 (t, *J* = 19.2), 40.3. The ¹H NMR spectrum matches the reported values (Satoh, T.; Nishimura, Y.; Kondo, S.; Takeuchi, T. *Carbohydr. Res.* **1996**, 286, 173-178).

(3*R*,4*R*,5*S*,6*S*)-3,4-Dihydroxy-2-trifluoroacetamido-5-piperidinecarboxylic acid Hydrochloride (3). The procedure was the same as that for preparation of siastatin B (**1**). The cleavage of Boc and acetonide, and then HCl salt formation, starting with 19.5 mg (0.047 mmol) of trifluoroacetamide **21** afforded 14 mg (96%) of **3** as a colorless solid, mp 115-120 °C (dec): $[\alpha]_{\text{D}}^{25} +28^{\circ}$ (*c* 0.25, H₂O), lit.* $[\alpha]_{\text{D}}^{31} +27^{\circ}$ (*c* 0.22, H₂O); ¹H NMR (300 MHz, D₂O) 5.03 (d, *J* = 10.5, 1H), 4.46 (t, *J* = 2.4, 1 H), 4.00 (dd, *J* = 10.5, 2.7, 1 H), 3.46–3.34 (m, 2 H), 3.04 (ddd, *J* = 9.9, 7.5, 1.8, 1 H). The ¹H NMR spectrum matches the reported values (see Table 2). *Nishimura, Y.; Kudo, T.; Kondo, S.; Takeuchi, T. *J. Antibiot.* **1994**, *47*, 101-107.

Table 1. Siastatin B (**1** · HCl): ¹H and ¹³C NMR Data

Source of data	This work	Literature *
Solvent	D ₂ O	D ₂ O
¹ H NMR	Chemical shift, multiplicity, <i>J</i>	Chemical shift, multiplicity, <i>J</i>
H-2	4.91, d, <i>J</i> = 10.2 Hz	5.07, d, <i>J</i> = 11.0 Hz
H-4	4.43, t, <i>J</i> = 2.4 Hz	4.58, t, <i>J</i> = 3.0 Hz
H-3	3.88, dd, <i>J</i> = 10.5, 2.7 Hz	4.03, dd, <i>J</i> = 11.0, 3.0 Hz
H-6ax, H-6eq	3.38–3.31, m	3.55–3.45, m
H-5	3.02, ddd, <i>J</i> = 9.6, 7.8, 2.4 Hz	3.14, ddd, <i>J</i> = 10, 8.0, 3.0 Hz
CH ₃ CON-	1.95, s	2.11, s
Carbon	Chemical shift	Chemical shift
HNCO	175.5	176.27
CO ₂ H	172.5	173.57
C-4, C-3	67.7	68.56
C-2	59.9	60.74
C-5	42.6	43.58
C-6	38.4	39.35
CH ₃ CONH	21.8	22.58

* Nishimura, Y.; Wang, W.; Kudo, T.; Kondo, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 978-986

Table 2. ^1H NMR Data for **3**

Compound	This work	Literature *
Solvent	D ₂ O	D ₂ O
Proton	Chemical shift, multiplicity, and <i>J</i>	Chemical shift, multiplicity, and <i>J</i>
H-2	5.03, d, <i>J</i> = 10.5 Hz	5.01, d, <i>J</i> = 10.6 Hz
H-4	4.46, t, <i>J</i> = 2.4 Hz	4.42, t, <i>J</i> = 2.3 Hz
H-3	4.00, dd, <i>J</i> = 10.5, 2.7 Hz	3.96, dd, <i>J</i> = 10.6, 2.6 Hz
H-6ax, H-6eq	3.46–3.34, m	3.39–3.32, m
H-5	3.04, ddd, <i>J</i> = 9.9, 7.5, 1.8 Hz	2.92, ddd, <i>J</i> = 10, 8.0, 2.3 Hz

* Nishimura, Y.; Kudo, T.; Kondo, S.; Takeuchi, T. *J. Antibiot.* **1994**, *47*, 101-107

Ethyl 1 -*N*-(*t*-Butoxycarbonyl)-3-phenylmethyl-1,2,3,6-tetrahydropyridine-3-carboxylate (22). A solution of 1.444 g (14.27 mmol) of *N,N*-diisopropylamine and HMPA (5 mL) in THF (20 mL) was cooled to -78°C . *n*-BuLi (1.6 M solution in hexanes, 9.4 mL, 15.04 mmol) was added slowly to keep the internal temperature below -65°C . The reaction mixture was stirred at -78°C for 15 min. A solution of 3.47 g (13.59 mmol) ester **6** in 5 mL of THF was added to the LDA solution at -78°C over a period of 15 min. The resulting reaction mixture was stirred at -78°C for 20 min, and then benzyl bromide (2.44 g, 14.27 mmol) was added at -78°C . The reaction mixture was allowed to gradually warm to room temperature and was stirred for 15 h. The reaction was quenched with saturated aqueous ammonium chloride (40 mL) at 0°C . The aqueous layer was extracted with ethyl acetate (40 mL). The combined organic layer was washed with water (2x30 mL) and brine (30 mL), dried over magnesium sulfate, filtered, concentrated, and then chromatographed with 85:15 hexanes / ethyl acetate as the eluant to give the alkylated ester **22** (4.23 g, 90%) as a colorless oil: IR (KBr) 1720, 1690, 1410, 1210, 1150; ^1H NMR (300 MHz) 7.29–7.21 (m, 3 H), 7.16 (m, 2 H), 5.91 (br s, 1 H), 5.77 (br, 1 H), 4.10–3.94 (br dd, overlapped, $J = 14.3, 7.1$ Hz, 3 H), 3.83–3.76 (m, 2 H), 3.58 (d, $J = 13.2$, 1 H), 3.02 (d, $J = 13.3$, 1 H), 2.88 (d, $J = 13.3$, 1 H), 1.50 (s, 9 H), 1.14 (t, $J = 7.1$ Hz, 3 H); ^{13}C NMR (75 MHz) 173.2, 155.0, 136.5, 130.1, 128.6, 128.1, 126.8, 124.9, 80.0, 60.8, 49.2, 47.1, 43.3, 42.9, 28.5, 14.1. Anal. Calcd for $\text{C}_{20}\text{H}_{27}\text{NO}_4$: C, 69.54; H, 7.88; N, 4.05. Found: C, 69.36; H, 7.88; N, 4.06.

(3*S,4*S**,5*S**)-5-Bromo-1-*N*-(*t*-butoxycarbonyl)-3-phenylmethyl-[[3,2-*c*]-4-keto-oxeto]-piperidine (23).** A solution of 500 mg (1.45 mmol) of the alkylated ester **22** in 5 mL of methanol was treated with 1.45 mL of tetrabutylammonium hydroxide (1M solution in methanol, 1.45 mmol) at room temperature for 15 h. The reaction mixture was concentrated to an oil, which was azeotropically dried with toluene (2x5 mL), and then dissolved in 5 mL of dichloromethane. The solution was cooled to -78°C and then a solution of bromine (231 mg, 1.45 mmol) in 0.5 mL of dichloromethane was added over a 2 min period. The bromine color disappeared quickly. The reaction mixture was stirred at -78°C for 30 min and at -30°C for 30 min, and then was diluted with 10 mL of dichloromethane. The resulting organic solution was washed with 10 mL of saturated aqueous sodium bicarbonate followed by water (2x10 mL). The organic layer was dried

over magnesium sulfate, filtered, concentrated, and chromatographed with 85:15 hexanes / ethyl acetate as the eluant to give 437 mg (76%) of the bromolactone **23** as a colorless oil: IR (KBr) 1840, 1700, 1400, 1200, 1150; ^1H NMR (300 MHz) 7.38–7.23 (m, 5 H), 4.65 (br d, $J = 3.2$ Hz, 1 H), 4.60–4.52 (br m, 1 H), 4.31–4.08 (m, 2 H), 3.94–3.86 (dd, $J = 15.3, 7.4$ Hz, 1 H), 3.58 (dd, $J = 13.9, 9.3$, 1 H), 3.15 (dd, $J = 14, 3.3$, 1 H), 2.89 (dd, $J = 13.8, 11.6$, 1 H), 1.48 and 1.46 (two s, rotamers, Boc-*t*-butyl, 9 H); ^{13}C NMR (75 MHz, extra peaks due to Boc rotamers) 171.0, 170.9, 154.6, 154.4, 133.7, 130.1, 129.0, 127.8, 81.1, 81.0, 77.3, 71.6, 71.5, 61.8, 61.7, 43.9, 43.4, 43.1, 42.1, 41.9, 37.7, 37.4, 28.3. Anal. Calcd for $\text{C}_{18}\text{H}_{22}\text{NO}_4\text{Br}$: C, 54.56; H, 5.60; N, 3.53; Br, 20.16. Found: C, 54.58; H, 5.34; N, 3.27; Br, 20.33.

Benzyl 1-*N*-(*t*-Butoxycarbonyl)-4*R,5*S**-epoxy-3*S**-phenylmethyl-piperidine-3-carboxylate (24).** A solution of 1.17 g (10.81 mmol) of benzyl alcohol in THF (20 mL) was treated with *n*-BuLi (4.73 mL, 1.6 *M* solution in hexane, 7.57 mmol) at -40°C for 20 min and at 0°C 20 min. A solution of 2.86 g (7.21 mmol) of bromo β -lactone **23** in 10 mL of dry THF was added over 2 min while the temperature was kept below 0°C . The reaction mixture was allowed to gradually warm to room temperature and then was stirred room temperature for 12 h. The reaction was quenched by adding 15 mL of aqueous saturated ammonium chloride and 10 mL of ethyl acetate at 0°C . The aqueous layer was extracted with 10 mL of ethyl acetate. The combined organic layer was dried over magnesium sulfate, concentrated, and chromatographed with 85:15 hexanes / ethyl acetate as the eluant to give 2.14 g (70%) of the epoxy ester **24** as a colorless oil: IR (KBr) 1720, 1690, 1450, 1400, 1360, 1200, 1150; ^1H NMR (300 MHz) 7.34–7.10 (br m, 10 H), 5.07 (br, 2 H), 4.09–3.87 (br m, 2 H), 3.64–3.39 (br m, 3 H), 3.08–2.99 (br m, 3 H), 1.50 (s, 9 H); ^{13}C NMR (75 MHz) 172.1, 155.0, 135.4, 135.2, 130.0, 128.6, 128.4, 128.3, 127.1 (one Ph signal overlapped), 80.5, 66.8, 55.3, 50.9, 49.4, 41.8 and 41.7 (rotamers), 41.5 and 40.9 (rotamers), 38.5, 28.4; FAB-MS 424.2 ($\text{M}^+ + 1$).

Benzyl 1-*N*-(*t*-Butoxycarbonyl)-4*S-hydroxy-3*S**-phenylmethyl-5*S**-(phenylselenenyl)-piperidine-3-carboxylate (25).** A solution of 465 mg (1.49 mmol) of diphenyl diselenide in 5 mL of ethanol was treated with 113 mg (2.98 mmol) of sodium borohydride at 5°C for 20 min and at room temperature for 30 min. A solution of 1.05 g, (2.48 mmol) of epoxy ester **24** in 10 mL of ethanol was added via a syringe. The reaction

mixture was stirred at room temperature for 12 h, and then quenched by adding saturated aqueous ammonium chloride at 0 °C. The resulting mixture was concentrated, and the residue was mixed with 25 mL of ethyl acetate. The organic layer was washed with water (10 mL) and brine (10 mL), dried over magnesium sulfate, concentrated, and then chromatographed with 85:15 hexanes / ethyl acetate as the eluant to give 1.18 g (82%) of the phenylselenenyl product **25** as a colorless oil: IR (KBr) 1690, 1450, 1420, 1360, 1280, 1200, 1140; ¹H NMR (300 MHz) 7.56 (dd, *J* = 7.5, 1.4 Hz, 2 H), 7.38–7.17 (m, 13 H), 5.30–4.95 (br d, 2 H), 4.70–4.45 (br, 1 H), 4.32–4.02 (br, 1 H), 3.85 (d, *J* = 10.5, 1 H), 3.47 (br, 1 H), 3.32 (t, *J* = 10.5, 1 H), 3.14 (dd, *J* = 18.4, 13.6, 2 H), 2.61–2.46 (br m, 2 H), 1.28 (s, 9 H); ¹³C NMR (75 MHz) 175.1, 153.8, 135.9, 135.2, 134.9, 130.7, 129.1, 128.6, 128.4, 128.2, 127.1 (3 phenyl signals overlapped), 80.0, 75.0, 67.1, 53.4, 49.3(br), 48.5 (br), 44.5, 39.7, 28.2; FAB-MS 582 (*M*⁺ + 1).

Benzyl 1-*N*-(*t*-Butoxycarbonyl)-4*R-hydroxy-3*S**-phenylmethyl-1,2,3,4-tetrahydropyridine-3-carboxylate (26).** A solution of 11.2 g (19.3 mmol) of alcohol **25**, 122 mg (1 mmol) of DMAP, 22.9 g (290 mmol) of pyridine, 150 mL of THF, and 19.69 g (192.9 mmol) of acetic anhydride was stirred at 45 °C for 14 h. The reaction mixture was diluted with 200 mL of ethyl acetate and then acidified with 150 mL of 1 *N* hydrochloride acid at 0 °C. The aqueous layer pH was 2–3. The organic layer was washed with water (2x100 mL) followed by saturated aqueous sodium bicarbonate (2x100 mL) and brine (100 mL). The organic solution was then dried with magnesium sulfate and concentrated to oil, which was purified on a flash silica gel column with 85:15 hexanes / ethyl acetate as the eluant to give 12.0 g (100%) of the acetate product as a colorless oil: IR (KBr) 1740, 1690, 1420, 1220, 1150; ¹H NMR (300 MHz) 7.59 (m, 2 H), 7.38–7.23(m, 13 H), 5.35 (br d, *J* = 6.9, 1 H), 4.02 (br s, 2 H), 3.90–3.86 (br, 2 H), 3.66–3.41 (br, 3 H), 3.07 (dd, *J* = 20.9, 13.7, 2 H), 1.79 (br s, 3 H), 1.44 (s, 9 H); ¹³C NMR (75 MHz) 171.0, 170.1, 154.4, 135.5, 134.8, 134.7, 134.6, 134.4, 130.5, 129.3, 128.7, 128.6, 128.4, 128.0, 127.1, 80.4, 76.1, 66.7, 52.1, 47.6, 46.4 (br), 42.0, 39.4, 28.4, 20.7; FAB-MS 623 (*M*⁺).

A solution of 623 mg (1 mmol) selenoether acetate in 10 mL of THF and 0.25 mL (2 mmol) of *N,N*-diisopropylamine was treated with 1 mL (10 mmol) of 30% hydrogen peroxide at 0 °C, and resulting solution was stirred at 0 °C for 2 h and at room

temperature for 4 h. The reaction was quenched by adding 15 mL of ethyl acetate and 10 mL of saturated aqueous ammonium chloride. The organic layer was washed with 10 mL of water and then 10 mL of brine. The organic solution was dried over magnesium sulfate and concentrated to an oil, which was purified on an activated neutral aluminum oxide column with 85:15 hexanes / ethyl acetate as the eluant to give the product alkene (400 mg, 86%) as a white solid, mp 103–104 °C; IR (KBr) 2920, 1700, 1640, 1350, 1210, 1150; ¹H NMR (300 MHz) 7.31 (br, 4 H), 7.21–7.18 (m, 5 H), 6.94–6.91 (m, 2 H), 5.26–5.12 (m, 4 H), 4.19–3.85 (br, 1 H), 3.27 (br d, *J* = 13.0 Hz, 1 H), 2.94 (br d, *J* = 13.8, 1 H), 2.58 (d, *J* = 13.6, 1 H), 1.70 (s, 3 H), 1.54 (br s, 9 H); ¹³C NMR (75 MHz) 171.3, 169.8, 152.1, 135.4, 129.8, 129.4, 128.9, 128.7, 128.5, 128.4, 127.2, 99.9, 82.0, 76.1, 69.4, 66.5, 49.5, 39.1(br), 37.9, 28.2, 20.7. Anal. Calcd for C₂₇H₃₁NO₆: C, 69.66; H, 6.71; N, 3.01. Found: C, 69.93; H, 7.76; N, 2.93.

A solution of 2.5 g (5.37 mmol) of the unsaturated acetate in 25 mL of methanol containing 3.0 g (28.3 mmol) of sodium carbonate was stirred at room temperature for 24 h. After the reaction was complete the solid was removed by filtration. The filtrate was concentrated to an oil and dissolved in 50 mL of ethyl acetate. The organic solution was washed with 30 mL of saturated aqueous ammonium chloride, followed by 30 mL of water and 20 mL of brine. The organic solution was dried over magnesium sulfate, and concentrated to oil, which was purified on a flash silica gel column with 70:30 hexanes / ethyl acetate as the eluant to give 1.82 g (80%) of the unsaturated alcohol **26** as a colorless oil: IR (KBr) 3470, 2980, 1740, 1710, 1370, 1170; ¹H NMR (300 MHz) 7.22–7.38 (br m, 5 H), 7.06–7.22 (br m, 3 H), 6.88–6.98 (m, 2 H), 4.96–5.22 (br m, 3 H), 4.20 (t, *J* = 5.2, 1 H), 3.78–3.98 (br m, 1 H), 3.23–3.47 (br m, 1 H), 2.89 (d, *J* = 14.5, 1 H), 2.09–2.21 and 2.43–2.67 (br m, 2 H), 1.48 (s, 9 H); ¹³C NMR (75 MHz) 172.5, 152.5, 135.2, 135.1, 129.8, 128.6, 128.3, 128.0, 127.0, 103.6, 81.8, 67.0, 66.6, 52.0, 40.0, 38.1 (br), 28.2; FAB-MS 424 (*M*⁺ + 1).

Benzyl 1-*N*-(*t*-Butoxycarbonyl)-4*S,5*R**-isopropylidenedioxy-6*R**-methoxy-3*S**-phenylmethyl-piperidine-3-carboxylate (27).** Preparation of dimethyl dioxirane (DDO, 0.09 *M* solution in acetone): A 1000 mL three neck round bottom flask containing a mixture of 80 mL of water, 52 mL (0.708 mol) of acetone, 48 g of sodium bicarbonate, and a magnetic stirring bar, was equipped with a charged solids addition

funnel containing 100 g (0.164 mol) of potassium monoperoxy sulfate. A 100-mL receiving flask cooled with a dry ice / acetone bath was connected to the main reaction flask via a distillation unit. Under a slight vacuum (ca. 180 torr, water aspirator), the solid potassium monoperoxy sulfate was added in five portions at 3 min intervals, while vigorous stirring was maintained. The yellow dioxirane / acetone solution (40 mL, 0.09 *M*) was collected in the receiving flask.

Epoxidation reaction: A solution of 850 mg (2.00 mmol) of allylic alcohol **26** in 5 mL of dichloromethane was stirred with freshly made DDO (0.09 *M* solution in acetone, 33 mL, 3.00 mmol) at room temperature for 8 h. The reaction mixture was concentrated to an oil, which was dissolved in 8.5 mL of 2,2-dimethoxypropane. Toluenesulfonic acid (5 mg) was added to the solution, and the reaction mixture was stirred at room temperature for 24 h. The reaction was quenched with 10 mL of saturated aqueous sodium bicarbonate. The mixture was extracted with 20 mL of ethyl acetate. The organic layer was washed with water (2x10 mL) and brine (10 mL), dried over magnesium sulfate, and then concentrated to oil, which was purified on a flash silica gel column with 70:30 hexanes / ethyl acetate as the eluant to give 760 mg (74%) of the ketal **27** as a colorless solid, mp 120-121 °C; IR (KBr) 3140, 3030, 1740, 1700, 1400, 1170, 1080; ¹H NMR (400 MHz) 7.35–7.27 (m, 5 H), 7.20–7.16 (m, 3 H), 6.99 (m, 2 H), 5.25 (s, 1 H), 5.14 (s, 2 H), 4.55 (dd, *J* = 6.8, 1.6, 1 H), 4.54 (dd, *J* = 6.8, 1.0, 1 H), 3.65 (d, *J* = 13.5, 1 H), 3.55 (s, 3 H), 3.51 (d, *J* = 13.5, 1 H), 3.41 (d, *J* = 13.5, 1 H), 3.05 (d, *J* = 13.5, 1 H), 1.49 (s, 9 H), 1.36 (s, 3 H), 1.34 (s, 3 H); ¹³C NMR (100 MHz) 172.0, 156.1, 136.6, 135.8, 129.8, 128.4, 128.3, 128.3, 128.1, 126.8, 108.5, 83.2, 80.6, 76.2, 74.6, 66.3, 56.9, 52.1, 38.8, 37.8, 28.4, 26.2, 24.3. Anal. Calcd for C₂₉H₃₇NO₇: C, 68.08; H, 7.29; N, 2.74. Found: C, 68.33; H, 7.14; N, 2.67.

Benzyl 6*R-Azido-1-*N*-(*t*-butoxycarbonyl)-4*S**,5*R**-isopropylidenedioxy-3*S**-phenylmethyl-piperidine-3-carboxylate (28).** A solution of 65 mg (0.127 mmol) of ketal **27** in 2 mL of dichloromethane was stirred with 0.1 mL (0.75 mmol) of azidotrimethylsilane and 0.03 mL (0.24 mmol) of boron trifluoride diethyl etherate at –40 °C for 3 h. The reaction was quenched by adding 2 mL of saturated aqueous sodium bicarbonate. The reaction mixture was warmed to room temperature and diluted with 15 mL of ethyl acetate. The organic layer was washed with water (2x5 mL), dried over

magnesium sulfate, and concentrated to an oil, which was purified on a flash silica gel column with 80:20 hexanes / ethyl acetate as the eluant to give 57 mg (86%) of the azide **28** as a colorless solid, mp 118–119 °C: IR (KBr) 3140, 3030, 2110, 1740, 1700, 1400, 1260, 1220, 1160; ¹H NMR (400 MHz) 7.36–7.30 (m, 5 H), 7.25–7.17 (m, 3 H), 6.99 (m, 2 H), 5.84 (d, *J* = 1.4, 1 H), 5.17 (d, *J* = 12.3, 1 H), 5.13 (d, *J* = 12.3, 1 H), 4.52 (dd, *J* = 6.8, 1.9, 1 H), 4.46 (dd, *J* = 6.8, 1.8, 1 H), 3.60 (d, *J* = 13.4, 1 H), 3.43 (d, *J* = 13.7, 1 H), 3.29 (dd, *J* = 13.6, 0.9, 1 H), 3.13 (d, *J* = 13.7, 1 H), 1.52 (s, 9 H), 1.37 (s, 3 H), 1.33 (s, 3 H); ¹³C NMR (100 MHz) 171.4, 155.6, 135.9, 135.6, 129.6, 128.47, 128.43, 128.41, 128.2, 127.0, 108.7, 81.8, 75.72, 75.67, 69.5, 66.5, 52.8, 38.7, 38.0, 28.2, 26.1, 24.2. Anal. Calcd for C₂₈H₃₄N₄O₆: C, 64.35; H, 6.56; N, 10.72. Found: C, 64.50; H, 6.61; N, 10.64.

Benzyl 6*S-Acetamido-1-*N*-(*t*-butoxycarbonyl)-4*S**,5*R**-isopropylidenedioxy-3*S**-phenylmethyl-piperidine-3-carboxylate (**29**).** A solution of 25 mg (0.048 mmol) of azide **28** in 0.5 mL of THF and 0.5 mL of ethanol was mixed with Lindlar catalyst (6 mg). The reaction mixture was stirred under a hydrogen atmosphere at room temperature for 3 h. The crude product mixture was passed through a filter (PTFE, 0.45 μM) to remove the solid catalyst. The filtrate was concentrated and azeotropically dried with dry toluene (3x5 mL) to afford the crude intermediate amine as an oil. A solution of the amine, 1 mL of THF, 0.2 mL (2.47 mmol) of pyridine, and 0.15 mL (1.59 mmol) of acetic anhydride was stirred at room temperature for 12 h. The reaction mixture was diluted with 10 mL of ethyl acetate, and the resulting organic solution was washed with water (3x5 mL). The organic layer was concentrated and azeotropically dried with dry toluene (4x5 mL) to give oil, which was chromatographed with 50:50:2 hexanes / ethyl acetate / methanol as the eluant to give 21 mg (81%) of the acetamide **29** as a white solid, mp 90-91 °C; IR (KBr) 3310, 2980, 2940, 1740, 1700, 1660, 1380, 1250, 1200, 1170; ¹H NMR (400 MHz) 7.35–7.27 (m, 5 H), 7.23–7.19 (m, 3 H), 7.02–7.01 (m, 2 H), 6.24 (d, *J* = 3.6, 1 H), 5.47 (dd, *J* = 5.3, 3.5, 1 H), 5.13 (d, *J* = 12.3, 1 H), 5.05 (d, *J* = 12.3, 1 H), 4.83 (dd, *J* = 6.0, 3.5, 1 H), 4.53 (dd, *J* = 6.0, 1.2, 1 H), 3.84 (dd, *J* = 13.9, 1.2, 1 H), 3.41 (d, *J* = 13.9, 1 H), 3.16 (d, *J* = 13.8, 1 H), 2.88 (d, *J* = 13.8, 1 H), 2.05 (s, 3 H), 1.46 (s, 9 H), 1.40 (s, 3 H), 1.32 (s, 3 H); ¹³C NMR (100 MHz) 171.0, 169.8, 155.6, 135.6, 135.5, 129.5, 128.9, 128.3, 128.3, 128.3, 128.0, 127.0, 108.1, 81.3, 74.0, 66.3, 61.3, 52.3, 40.6,

38.5, 28.2, 26.5, 24.6, 23.7. Anal. Calcd for $C_{30}H_{38}N_2O_7$: C, 66.90; H, 7.11; N, 5.20. Found: C, 66.81; H, 6.90; N, 5.01.

6*S-Acetamido-4*S**,5*R**-dihydroxy-3*S**-phenylmethyl-piperidine-3-carboxylic Acid Hydrochloride (4).** A mixture of 50 mg (0.093 mmol) of the benzyl ester **29**, 1 mL of ethanol, and 12 mg of 10% Pd/C catalyst was stirred under a hydrogen atmosphere at room temperature for 4 h. The crude product mixture was passed through a filter (PTFE, 0.45 μ M) to remove the solid catalyst. The filtrate was concentrated to an oil, which was chromatographed with 95:5 dichloromethane / methanol as the eluant to give 36 mg (86%) of the carboxylic acid as a white solid, mp 138-139 °C; IR (KBr) 3340, 2980, 2940, 1700, 1670, 1380, 1260, 1220, 1160, 1040; 1H NMR (400 MHz) 7.28-7.25 (m, 3 H), 7.14 (m, 2 H), 6.40 (br s, 1 H), 5.44 (dd, $J = 5.1, 3.1, 1$ H), 4.90 (dd, $J = 6.0, 3.0, 1$ H), 4.53 (d, $J = 6.0, 1$ H), 3.72 (dd, $J = 13.9, 0.9, 1$ H), 3.42 (d, $J = 13.9, 1$ H), 3.18 (d, $J = 13.9, 1$ H), 2.92 (d, $J = 13.9, 1$ H), 2.03 (s, 3 H), 1.45 (s, 12H, Boc and one acetonide CH_3 overlapped), 1.36 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3:CD_3COCD_3 = 3:1$) 171.8, 170.2, 154.9, 135.4, 129.6, 127.5, 126.2, 107.3, 80.2, 75.7, 74.4, 60.3, 51.6, 39.0, 37.7, 27.6, 25.8, 23.9, 22.4. Anal. Calcd for $C_{23}H_{32}N_2O_7$: C, 61.59; H, 7.19; N, 6.25. Found: C, 61.49; H, 7.11; N, 6.02.

A solution of 100 mg (0.223 mol) of the carboxylic acid in 2 mL of dichloromethane was treated with 1 mL of trifluoroacetic acid at 5–10 °C, and then stirred at -10 °C for 30 min and at room temperature for 30 min. The reaction mixture was treated with 0.1 mL of water at room temperature. After 30 min, the solution was concentrated and azeotropically dried with toluene (5x2 mL) to give an oil, which was dissolved in 4 mL of ethanol. The solution was treated with hydrochloric acid (12 N, 0.1 mL) at 10 °C for 20 min. The mixture was concentrated to give 75 mg (97%) of **4** as a white solid, mp 142–144 °C (dec); IR (KBr) 3330, 3060, 1680, 1540, 1400, 1380, 1270, 1210, 1090; 1H NMR (400 MHz) 7.32–7.27 (m, 5 H), 5.18 (d, $J = 8.1, 1$ H), 4.25 (d, $J = 2.2, 1$ H), 4.15 (dd, $J = 8.2, 2.4, 1$ H), 3.43 (d, $J = 13.7, 1$ H), 3.25 (d, $J = 13.8, 1$ H), 3.14 (d, $J = 13.7, 1$ H), 3.07 (d, $J = 13.8, 1$ H), 2.12 (s, 3 H); ^{13}C NMR (100 MHz) 173.2, 172.9, 134.7, 129.7, 128.2, 127.0, 71.9, 66.3, 62.1, 50.9, 41.3, 37.2, 21.2. Anal. Calcd for $C_{15}H_{21}ClN_2O_5$: C, 52.26; H, 6.14; N, 8.13. Found: C, 52.38; H, 6.22; N, 8.00.