Experimental Section

General Methods. Melting points were uncorrected. Column chromatography was conducted on Silica gel 60 (Merck), and preparative thin-layer chromatography was carried out using Wakogel B-5F. Dichloromethane and acetonitrile were distilled from P_2O_5 and then CaH_2 and dried over MS4A. Toluene was distilled and dried over MS4A. THF and ether were distilled over sodium/benzophenone. 1,2-Dimethoxyethane (DME) and 1,2-dichloroethane were distilled over calcium hydride, and dried over MS4A. Methanol was distilled over magnesium, and dried over MS3A. $Sn(OTf)_2$[41], $Sc(OTf)_3$[42], and $Hf(OTf)_4$[43] were prepared according to reported procedures. Commercially available $Cu(OTf)_2$ (TCI) was used without further purification. $SnCl_4$, BF_3•OEt_2, and TMSOTf were distilled before use. All silyl enol ethers and ketene silyl acetals were prepared according to the modified House procedure.[44] The ketene silyl acetals of dimethyl malonate[32] and ethyl benzoylacetate[35] were prepared according to reported procedures. All chemical compounds were purified on the basis of standard procedures.

Typical Procedure for $Sc(OTf)_3$-Catalyzed Substitution: A typical experimental procedure is described in the reaction of **4d** with the silyl enolate of methyl isobutyrate: To a suspension of Sc(OTf)3 (0.05 mmol, 10 mol%) in dichloromethane (1 mL) was added a mixture of **4d** (0.5 mmol) and the silyl enolate (0.85 mmol) in dichloromethane (1.5 mL). The mixture was stirred at 0 °C for 1 h. Saturated aqueous sodium hydrogen carbonate was then added to quench the reaction, and the aqueous layer was extracted with dichloromethane. After a usual work-up, the product was isolated by silica gel column chromatography to afford *trans*-methyl 2-(3'-(*p*-methoxybenzoyl)-*N*-benzyloxycarbonylpiperidin-2'-yl)-2-methylpropionate (**13d**) in 94% yield (*trans*/*cis* = >99/1, determined by ^{1}H NMR analysis). Pale yellow oil; IR (neat) 1703 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.28 (s, 1.5H), 1.31 (s, 1.5H), 1.38 (s, 1.5H), 1.42 (s, 1.5H), 1.52 (m, 1H), 1.76-1.96 (m, 3H), 3.03 (m, 1H), 3.68 (s, 3H), 3.85 (s, 1.5H), 3.86 (s, 1.5H), 4.13 (d, 1H, *J* = 13.7 Hz), 4.24 (d, 1H, *J* = 12.8Hz), 4.43 (s, 0.5H), 4.50 (s, 0.5H), 4.90 (d, 0.5H, *J* = 12.5 Hz), 4.96 (d, 0.5H, *J* =

12.5 Hz), 5.04 (d, 0.5H, J = 12.5 Hz), 5.16 (d, 0.5H, J = 12.5 Hz), 5.31 (s, 0.5H), 5.38 (s, 0.5H), 6.77 (m, 2H), 7.07-7.19 (m, 9H), 7.27 (m, 2H), 7.80 (m, 2H); ^{1}H NMR (DMSO-d_6), rotamers, δ 1.29 (s, 3H), 1.37 (s, 1.5H), 1.38 (s, 1.5H), 1.51 (m, 1H), 1.79-1.90 (m, 3H), 2.96-3.13 (m, 1H), 3.69 (s, 3H), 3.90 (s, 3H), 4.20 (d, 1H, J = 11.9 Hz), 4.50 (d, 1H, J = 5.7 Hz), 5.03 (s, 1H), 5.14 (d, 0.5 H, J = 12.9 Hz), 5.24 (d, 0.5H, J = 12.9 Hz), 5.35 (d, 1H, J = 12.6 Hz), 7.04-7.45 (m, 7H), 7.85-7.92 (m, 2H); ^{1}H NMR (DMSO-d_6, 90 °C) δ 1.25 (s, 3H), 1.31 (s, 3H), 1.50 (m, 1H), 1.71-1.83 (m, 3H), 3.01 (m, 1H), 3.63 (s, 3H), 3.84 (s, 3H), 4.15 (d, 1H, J = 13.9 Hz), 4.49 (s, 1H), 4.87 (s, 2H), 5.30 (s, 1H), 6.98 (d, 2H, J = 8.8 Hz), 7.26 (br, 5H), 7.81 (d, 2H, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$), rotamers, δ 19.5, 19.9, 23.2, 23.6, 25.2, 25.4, 25.6, 40.2, 40.5, 40.8, 41.3, 45.68, 45.72, 52.13, 52.17, 55.37, 55.40, 61.7, 61.8, 67.2, 67.3, 67.6, 113.5, 113.6, 122.6, 122.7, 127.47, 127.54, 127.72, 127.84, 128.3, 128.4, 131.5, 131.6, 136.3, 137.6, 156.6, 156.7, 163.3, 163.4, 165.1, 176.8, 177.0; ^{13}C NMR (DMSO-d_6), rotamers, δ 19.1, 19.5, 22.9, 23.3, 24.9, 25.0, 45.27, 45.31, 52.1, 55.5, 60.9, 66.3, 66.5, 67.3, 113.97, 114.03, 121.9, 126.96, 127.03, 127.6, 127.7, 128.2, 128.4, 131.2, 136.5, 137.1, 155.6, 156.1, 163.16, 163.24, 164.3, 164.4, 175.98, 176.05; ^{13}C NMR (DMSO-d_6, 90 °C) δ 18.8, 22.8, 24.4, 24.7, 45.2, 51.5, 54.2, 55.1, 60.7, 66.1, 67.2, 113.6, 122.0, 126.7, 127.2, 127.8, 130.7, 136.4, 155.6, 162.9, 164.0, 175.5; HRMS(ESI) calcd for $C_{26}H_{32}NO_7$ 470.2179, found $(M+H)^+$ 470.2149; Anal. Calcd for $C_{26}H_{31}NO_7$: C, 66.51; H, 6.65; N, 2.98; Found: C, 66.46; H, 6.80; N, 3.00.

2-(*N*-Benzyloxycarbonylpiperidin-2-yl)acetophenone (5): Mp 78-79 °C; IR (KBr) 1684 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.30-1.80 (m, 6H), 2.96 (m, 1H), 3.10-3.40 (m, 2H), 4.11 (m, 1H), 4.91 (m, 1H), 5.09 (m, 2H), 7.26-7.56 (m, 8H), 7.94 (m, 2H); ^{13}C NMR ($CDCl_3$), rotamers, δ 18.7, 25.2, 27.8, 39.2, 39.9, 48.3, 67.1, 127.8, 127.9, 128.2, 128.4, 128.6, 133.1, 136.6, 136.7, 155.3, 198.3; HRMS(ESI) calcd for $C_{21}H_{24}NO_3$ 338.1756, found $(M+H)^+$ 338.1748; Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.69; H, 7.02; N, 4.14.

2-(*N*-Benzyloxycarbonylpiperidin-2-yl)pinacolone (6): Mp 58 °C; IR (KBr 1698 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.11 (s, 9H), 1.26-1.69 (m, 6H), 2.54 (dd,

1H, J = 16.3, 4.6 Hz), 2.76-2.91 (m, 1H), 2.93 (dd, 1H, J = 16.3, 9.3 Hz), 4.08 (d, 1H, J = 13.7 Hz), 4.78 (m, 1H), 5.09 (d, 1H, J = 12.6 Hz), 7.26-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$), rotamers, δ 18.8, 25.2, 26.1, 27.7, 36.6, 40.0, 44.4, 47.4, 66.9, 127.7, 127.8, 128.4, 136.8, 155.2, 213.2; HRMS(ESI) calcd for $C_{19}H_{28}NO_3$ 318.2069, found $(M+H)^+$ 318.2064; Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.84; H, 8.65; N, 4.36.

2-(*N*-Benzyloxycarbonylpiperidin-2-yl)propiophenone (7): (diastereomer ratio = 90/10, determined by ^{1}H NMR) Colorless oil; IR (neat) 1691 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.08-1.25 (m, 3H), 1.39-1.67 (m, 6H), 2.77-2.86 (m, 1H), 4.04-4.28 (m, 2H), 4.61-4.85 (m, 1H), 4.97-5.25 (m, 2H), 7.26-7.60 (m, 8H), 7.87-7.99 (m, 2H); ^{1}H NMR (DMSO-d_6), rotamers, δ 0.87-0.88 (m, 2.7 H), 1.08 (d, 0.3H, J = 6.6 Hz), 1.16-1.77 (m, 6H), 2.75-3.01 (m, 1H), 3.97 (m, 1H), 4.18-4.55 (m, 2H), 4.84 (s, 0.2H), 5.01 (d, 0.9H, J = 14.3 Hz), 5.07 (d, 0.9H, J = 14.3 Hz), 7.24-7.30 (m, 5H), 7.30-7.63 (m, 3H), 7.90 (m, 0.2H), 8.03 (m, 1.8H); ^{1}H NMR (DMSO-d_6, 60 °C) δ 0.90 (d, 2.7H, J = 7.0 Hz), 1.01 (d, 0.3H, J = 6.8 Hz), 1.16-1.77 (m, 6H), 2.90 (m, 1H), 3.62 (d, 0.1H, J = 13.2 Hz), 3.62 (d, 0.1H, J = 13.2 Hz), 3.94 (d, 0.1H, J = 12.6 Hz), 4.13-4.23 (m, 1H), 4.35 (m, 0.1H), 4.55 (m, 0.9H), 4.82 (d, 0.1H, J = 13.0 Hz), 4.87 (d, 0.1H, J = 12.8 Hz), 5.05 (s, 1.8H), 7.22-7.36 (m, 5H), 7.38-7.61 (m, 3H), 7.86 (m, 0.2H), 7.99 (m, 1.8H); ^{13}C NMR ($CDCl_3$), rotamers, δ 14.8, 15.3, 19.1, 19.4, 24.9, 25.2, 25.4, 27.0, 27.5, 39.0, 39.2, 39.5, 40.0, 52.9, 54.2, 67.0, 125.9, 127.7, 127.8, 127.9, 128.1, 128.3, 128.4, 128.5, 128.7, 128.8, 132.8, 133.1, 133.3, 136.6, 136.8, 137.2, 155.0, 155.8, 202.4, 202.7; ^{13}C NMR (DMSO-d_6, 60 °C) δ 14.8, 18.5, 24.8, 25.2, 26.9, 38.1, 38.3, 52.5, 66.0, 127.0, 127.1, 127.3, 127.5, 127.6, 127.9, 128.0, 128.1, 128.4, 128.6, 132.6, 133.2, 136.2, 136.9, 154.8, 202.7; HRMS(ESI) calcd for $C_{22}H_{26}NO_3$ 352.1912, found $(M+H)^+$ 352.1954; Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 74.91; H, 7.28; N, 3.92.

Methyl 2-(*N*-Benzyloxycarbonylpiperidin-2-yl)-2-methylpropionate (8): Colorless oil; IR (neat) 1727, 1696 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.22 (s, 3H), 1.24 (s, 3H), 1.39-1.78 (m, 6H), 2.90-2.97 (m, 1H), 3.64 (s, 3H), 4.08 (m, 1H), 4.34

(m, 1H), 5.14 (s, 2H), 7.27-7.36 (m, 5H); ^{13}C NMR ($CDCl_3$), rotamers, δ 19.2, 22.3, 23.4, 24.5, 40.1, 47.2, 51.8, 67.1, 127.7, 127.8, 128.4, 136.8, 156.8, 177.3; HRMS(ESI) calcd for $C_{18}H_{25}NO_4$ 320.1862, found $(M+H)^+$ 320.1902; Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.78; H, 7.82; N, 4.47.

***tert*-Butyl (*N*-Benzyloxycarbonylpiperidin-2-yl)thioacetate (9):** Pale yellow oil; IR (neat) 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.21-1.64 (m, 6H), 1.43 (s, 9H), 2.68 (dd, 1H, J = 13.8, 8.0 Hz), 2.86 (t, 1H, J = 12.6 Hz), 4.08 (m, 1H), 4.80 (m, 1H), 5.09 (d, 1H, J = 12.5 Hz), 5.15 (d, 1H, J = 12.5 Hz), 7.26-7.37 (m, 5H); ^{13}C NMR ($CDCl_3$), rotamers, δ 18.7, 25.1, 27.9, 29.6, 39.5, 44.5, 48.1, 48.7, 66.9, 127.6, 127.7, 128.3, 136.8, 155.1, 197.5; HRMS(ESI) calcd for $C_{19}H_{28}NO_3S$ 350.1790, found $(M+H)^+$ 350.1792; Anal. Calcd for $C_{19}H_{27}NO_3S$: C, 65.30; H, 7.79; N, 4.01. Found: C, 65.30; H, 7.84; N, 4.06.

Dimethyl (*N*-Benzyloxycarbonylpiperidin-2'-yl)malonate (10): Colorless oil; IR (neat) 1739, 1699 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.26-1.80 (m, 6H), 2.88 (m, 1H), 3.51 (s, 1H), 3.75 (s, 3H), 3.86-4.12 (m, 2H), 5.05-5.17 (m, 3H), 7.26-7.37 (m, 5H); ^{13}C NMR ($CDCl_3$), rotamers, δ 18.9, 24.9, 26.9, 27.2, 39.7, 40.0, 41.0, 50.4, 50.7, 51.1, 52.36, 52.45, 52.54, 127.8, 128.1, 128.3, 136.6, 155.1, 166.8, 167.5, 167.7; HRMS(ESI) calcd for $C_{18}H_{23}NO_6Na$ 372.1424, found $(M+Na)^+$ 372.1400.

2-(3-Benzyloxy-*N*-benzyloxycarbonylpiperidin-2-yl)acetophenone (11a): (*cis*/*trans* = 71/29, determined by HPLC analysis using YMC-pack (hexane/AcOEt, 9:1, flow rate 1.2 mL/min, t_R = 55 min (*cis*), 65 min (*trans*)) Colorless oil; IR (neat) 1698 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.48-1.95 (m, 4H), 2.92-3.56 (m, 4H), 4.05-4.18 (m, 1H), 4.46-4.68 (m, 2H), 4.89-5.34 (m, 3H), 7.05-7.61 (m, 13H), 7.89 (m, 2H); ^{13}C NMR ($CDCl_3$), rotamers, δ 23.7, 24.1, 24.3, 25.6, 34.4, 38.5, 51.1, 67.06, 67.14, 70.7, 75.4, 127.3, 127.5, 127.6, 127.7, 127.8, 128.2, 128.3, 128.5, 128.7, 132.8, 133.3, 136.5, 137.0, 138.1, 138.6, 155.2, 155.8, 198.2; HRMS(ESI) calcd for $C_{28}H_{29}NO_4Na$ 466.1995, found $(M+Na)^+$ 466.1995; Anal. Calcd for $C_{28}H_{29}NO_4$: C, 75.82; H, 6.59; N, 3.16. Found: C, 75.61; H, 6.57; N, 3.15.

2-(3-Acetoxy-*N*-benzyloxycarbonylpiperidin-2-yl)acetophenone (11b): (*cis/trans* = 17/83 , determined by ^{1}H NMR) Colorless oil; IR (neat) 1736, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.64-2.03 (m, 7H), 2.92-3.26 (m, 2.83 H), 3.47 (dd, 0.17H, *J* = 15.1, 6.7 Hz), 4.10-4.16 (m, 1H), 4.92-5.25 (m, 4H), 7.26-7.57 (m, 8H), 7.90-7.93 (m, 2H); ^{13}C NMR ($CDCl_3$), rotamers, δ 19.2, 19.5, 21.0, 22.8, 23.6, 38.4, 51.8, 67.1, 67.3, 69.2, 127.7, 127.9, 128.2, 128.4, 128.6, 128.7, 133.4, 136.3, 155.6, 170.2, 196.7; HRMS(ESI) calcd for $C_{23}H_{26}NO_5$ 396.1811, found $(M+H)^+$ 396.1820; Anal. Calcd for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37; N, 3.54. Found: C, 69.64; H, 6.58; N, 3.53.

2-(3-Benzoyloxy-*N*-benzyloxycarbonylpiperidin-2-yl)acetophenone (11c): (*cis/trans* = 16/84, determined by ^{1}H NMR) Pale yellow oil; IR (neat) 1720, 1661 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.56-2.05 (m, 4H), 3.07-3.38 (m, 2.84H), 3.57 (dd, 0.16H, *J* = 14.9, 6.1 Hz), 4.25 (m, 1H), 4.89-5.37 (m, 4H), 7.01-7.56 (m, 11H), 7.89-7.96 (m, 4H); ^{13}C NMR ($CDCl_3$), rotamers, δ 19.8, 23.8, 25.0, 35.6, 38.4, 50.8, 52.0, 67.1, 67.4, 69.8, 70.8, 127.5, 127.7, 127.8, 128.2, 128.4, 128.6, 128.7, 129.60, 129.64, 129.8, 130.2, 133.0, 133.10, 133.12, 133.4, 136.3, 155.2, 155.7, 165.49, 196.6, 197.1; MS (EI) *m/z* 457 (M^+); Anal. Calcd for $C_{28}H_{27}NO_5$: C, 73.51; H, 5.95; N, 3.06. Found: C, 73.52; H, 6.12; N, 3.28.

2-[*N*-Benzyloxycarbonyl-3-(*p*-methoxybenzoyloxy)piperidin-2-yl]acetophenone (11d): (*cis/trans* = 17/83, determined by ^{1}H NMR) Pale yellow oil; IR (neat) 1703 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.57 (m, 3H), 1.81-2.10 (m, 3H), 3.06-3.36 (m, 2.83H), 3.56 (dd, 0.17H, *J* = 14.9, 5.8 Hz), 3.84 (s, 3H), 4.25 (m, 1H), 4.83-5.34 (m, 5H), 6.76-6.87 (m, 2H), 7.02-7.53 (m, 8H), 7.85-7.91 (m, 4H); ^{13}C NMR ($CDCl_3$), rotamers, δ 14.1, 19.7, 21.0, 23.8, 25.0, 35.6, 38.3, 39.0, 50.9, 52.0, 55.4, 60.3, 67.0, 67.3, 69.4, 70.4, 113.5, 122.1, 122.5, 127.4, 127.6, 127.8, 128.2, 128.4, 128.5, 128.7, 131.6, 133.0, 133.3, 136.2, 155.1, 155.6, 163.3, 163.4, 164.9, 165.2, 196.6; HRMS(ESI) calcd for $C_{29}H_{30}NO_6$ 488.2073, found $(M+H)^+$ 488.2073; Anal. Calcd for $C_{29}H_{29}NO_6$: C, 71.44; H, 6.00; N, 2.87. Found: C, 71.50; H, 6.22; N, 2.85.

2-(3'-Acetoxy-*N*-benzyloxycarbonylpiperidin-2'-yl)pinacolone (12b): (*cis/trans* = 27/73, determined by ^{1}H NMR, and the ratio agreed with the ratio determined by HPLC analysis using YMC-pack (hexane/AcOEt, 9:1, flow late 1.2 mL/min, t_R = 48 min (*cis*), 65 min (*trans*)) Colorless oil; IR (neat) 1737, 1701 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.11-1.12 (m, 9H), 1.45-2.10 (m, 7H), 2.50 (dd, 0.27H, *J* =16.6, 6.1 Hz), 2.72-3.04 (m, 2.73H), 4.08-4.17 (m, 1H), 4.81-5.30 (m, 4H), 7.27-7.36 (m, 5H); ^{13}C NMR ($CDCl_3$), rotamers, δ 19.4, 21.1, 23.5, 23.6, 24.8, 26.0, 26.2, 33.1, 35.9, 38.9, 39.1, 44.3, 44.4, 49.1, 51.1, 67.0, 67.2, 69.1, 69.7, 127.6, 127.7, 127.8, 128.4, 136.6, 136.8, 155.0, 155.6, 169.5, 170.1, 211.6; HRMS(ESI) calcd for $C_{21}H_{30}NO_5$ 376.2124, found $(M+H)^+$ 376.2123; Anal. Calcd for $C_{21}H_{29}NO_5$: C, 67.18; H, 7.79; N, 3.73. Found: C, 66.85; H, 7.77; N, 3.77.

2-[*N*-Benzyloxycarbonyl-3-(*p*-methoxybenzoyloxy)piperidin-2-yl]pinacolone (12d): (*cis/trans* = 26/74, determined by HPLC analysis using YMC-pack (hexane/AcOEt, 9:1, flow rate 1.2 mL/min, t_R = 56 min (*cis*), 86 min (*trans*)) Pale yellow oil; IR (neat) 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 0.93-0.98 (m, 9H), 1.10-1.89 (m, 4H), 2.55-2.79 (m, 3H), 3.69 (s, 3H), 3.95-4.07 (m, 1H), 4.82-5.04 (m, 4H), 6.68-6.76 (m, 2H), 7.06-7.23 (m, 5H), 7.74-7.77 (m, 2H); ^{13}C NMR ($CDCl_3$), rotamers, δ 19.7, 23.5, 23.7, 25.0, 26.0, 26.1, 32.7, 35.8, 38.9, 39.2, 44.4, 51.4, 55.3, 60.4, 64.1, 67.0, 67.2, 69.4, 70.4, 74.6, 107.5, 108.2, 113.49, 113.51, 122.3, 122.6, 127.5, 127.7, 127.8, 127.9, 128.27, 128.33, 129.3, 131.51, 131.57, 136.6, 155.2, 155.7, 163.2, 163.4, 165.0, 165.1, 211.4; HRMS(ESI) calcd for $C_{27}H_{34}NO_6$ 468.2386, found $(M+H)^+$ 468.2395; Anal. Calcd for $C_{27}H_{33}NO_6$: C, 69.36; H, 7.11; N, 3.00. Found: C, 69.19; H, 7.23; N, 3.00.

***trans*-Methyl 2-(3-benzyloxy-*N*-benzyloxycarbonylpiperidin-2-yl)-2-methylpropionate (13a):** Colorless oil; IR (neat) 1726, 1696 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.21-1.41 (m, 7H), 1.52-1.66 (m, 1H), 1.76-2.03 (m, 2H), 2.87-3.04 (m, 1H), 3.60 (s, 3H), 3.69 (s, 1H), 4.13 (d, 0.5H, *J* = 14.3Hz), 4.27 (d, 0.5H, *J* = 15.4Hz), 4.40-4.69 (m, 3H), 5.16 (m, 2H), 7.25-7.33 (m, 10H); ^{1}H NMR (DMSO-d_6), rotamers, δ 1.07-1.11 (m, 6H), 1.27 (br, 1H), 1.44-1.74 (m, 3H), 2.74-2.92 (m, 1H), 3.47 (s,

3H), 3.53 (d, 1H, J = 13.9 Hz), 3.97 (t, 1H, J = 16.2 Hz), 4.32-4.47 (m, 3H), 4.95-5.06 (m, 2H), 7.14-7.25 (m, 10H); ^{1}H NMR (DMSO-d_6, 60 °C) δ 1.16 (s, 6H), 1.31-1.35 (m, 1H), 1.50-1.96 (m, 3H), 2.90 (s, 1H), 3.45 (s, 3H), 3.61 (s, 1H), 4.02 (s, 1H), 4.38-4.49 (m, 3H), 5.08 (s, 2H), 7.23-7.30 (m, 10H); ^{13}C NMR ($CDCl_3$), rotamers, δ 19.2, 19.6, 23.0, 23.1, 25.5, 25.6, 25.8, 40.5, 40.6, 45.7, 45.8, 51.90, 51.94, 60.1, 60.4, 67.15, 67.22, 69.95, 70.03, 71.26, 71.60, 127.29, 127.35, 127.56, 127.59, 127.74, 128.2, 128.3, 136.7, 137.0, 138.5, 156.8, 157.0, 177.0, 177.2; ^{13}C NMR (DMSO-d_6), rotamers, δ 18.8, 19.2, 22.8, 23.0, 24.9, 25.0, 25.2, 45.2, 45.3, 51.9, 52.0, 59.9, 60.1, 66.3, 66.5, 69.2, 69.3, 71.0, 127.2, 127.3, 127.5, 127.7, 128.2, 128.3, 128.4, 136.8, 137.1, 138.45, 138.52, 155.9, 156.3, 176.2, 176.3; ^{13}C NMR (DMSO-d_6, 60 °C) δ 18.6, 18.9, 22.7, 24.7, 24.9, 45.2, 51.5, 60.0, 66.2, 69.1, 71.1, 126.96, 126.98, 127.1, 127.4, 127.9, 128.0, 136.8, 138.3, 155.9, 176.0; HRMS(ESI) calcd for $C_{25}H_{32}NO_5$ 426.2280, found $(M+H)^+$ 426.2313; Anal. Calcd for $C_{25}H_{31}NO_5$: C, 70.57; H, 7.34; N, 3.29. Found: C, 70.29; H, 7.41; N, 3.28.

***trans*-Methyl 2-(3-acetoxy-*N*-benzyloxycarbonylpiperidin-2-yl)-2-methylpropionate (13b):** Colorless oil; IR (neat) 1732, 1698 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.01-1.38 (m, 7H), 1.56-1.71 (m, 3H), 1.80 (s, 1.5H), 1.91 (s, 1.5H), 2.88 (m, 1H), 3.60 (s, 3H), 4.06 (d, 0.5H, J = 12.8 Hz), 4.19 (d, 0.5H, J = 12.8 Hz), 4.19 (d, 0.5H, J = 13.4 Hz), 4.29 (s, 0.5H), 4.35 (s, 0.5H), 4.99-5.20 (m, 3H), 7.27-7.30 (m, 5H); ^{1}H NMR (DMSO-d_6), rotamers, δ 1.16 (s, 3H), 1.22 (s, 1.5H), 1.24 (s, 1.5H), 1.32-1.67 (m, 4H), 1.85 (s, 1.5H), 1.90 (s, 1.5H), 2.80-2.98 (m, 1H), 3.54 (s, 3H), 4.05 (t, 1H, J = 14.6 Hz), 4.29 (d, 1H, J = 9.8 Hz), 5.00-5.18 (m, 3H), 7.30-7.39 (m, 5H); ^{1}H NMR (DMSO-d_6, 90 °C) δ 1.20 (s, 3H), 1.25 (s, 3H), 1.46 (m, 1H), 1.63-1.69 (m, 3H), 1.88 (s, 3H), 2.93 (m, 1H), 3.61 (s, 3H), 4.06 (d, 1H, J = 13.4 Hz), 4.34 (s, 1H), 5.05-5.12 (m, 3H), 7.33-7.36 (m, 5H); ^{13}C NMR ($CDCl_3$), rotamers, δ 19.3, 19.6, 21.0, 21.2, 23.2, 23.4, 25.1, 25.2, 25.3, 25.5, 40.1, 40.4, 45.8, 52.07, 52.14, 61.3, 61.45, 67.18, 67.23, 67.4, 127.6, 127.9, 128.40, 128.44, 136.6, 136.9, 155.4, 156.7, 170.1, 176.7, 177.0; ^{13}C NMR (DMSO-d_6), rotamers, δ 18.9, 19.2, 20.7, 20.9, 22.9, 23.1, 24.7, 24.8, 45.3, 52.1, 60.6, 60.7, 66.5, 66.76, 66.83, 127.3, 127.8, 128.4, 136.9,

137.0, 155.6, 156.2, 169.5, 176.0; ^{13}C NMR (DMSO-d_6, 90 °C) δ 18.6, 19.1, 20.2, 22.7, 24.3, 24.5, 45.2, 51.4, 60.5, 66.2, 66.7, 126.8, 127.3, 127.9, 136.7, 155.6, 168.9, 175.5; HRMS(ESI) calcd for $C_{20}H_{28}NO_6$ 378.1916, found $(M+H)^+$ 378.1940; Anal. Calcd for $C_{20}H_{27}NO_6$: C, 63.64; H, 7.21; N, 3.71. Found: C, 63.49; H, 7.25; N, 3.68.

***tert*-Butyl (3-acetoxy-*N*-benzyloxycarbonylpiperidin-2-yl)thioacetate (14b):** (*cis*/*trans* = 31/69, determined by HPLC analysis using YMC-pack (hexane/AcOEt, 9:1, flow rate 1.2 mL/min, t_R = 26 min (*cis*), 30 min (*trans*)) Pale yellow oil; IR (neat) 1739, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.42-1.64 (m, 10H), 1.71-2.09 (m, 6H), 2 .61-2.91 (m, 3H), 4.11 (s, 1H), 4.84 (m, 1H), 5.01-5.22 (m, 2H), 7.27-7.36 (m, 5H); ^{13}C NMR ($CDCl_3$), rotamers, δ 19.43, 20.94, 21.1, 23.6, 24.7, 29.57, 29.63, 40.6, 43.6, 48.3, 48.6, 50.5, 52.2, 67.0, 67.3, 68.8, 69.8, 127.6, 127.7, 127.8, 128.4, 136.5, 136.8, 155.0, 155.5, 169.6, 170.1, 196.0, 196.8; HRMS(ESI) calcd for $C_{21}H_{29}NONa_5S$ 430.1664, found $(M+Na)^+$ 430.1644; Anal. Calcd for $C_{21}H_{29}NO_5S$: C, 61.89; H, 7.17; N, 3.44. Found: C, 61.72; H, 7.18; N, 3.43.

***tert*-Butyl [*N*-benzyloxycarbonyl-3-(*p*-methoxybenzoyl)piperidin-2-yl]thioacetate (14d):** (*cis*/*trans* = 33/67, determined by HPLC analysis using YMC-pack (hexane/AcOEt, 9:1, flow late 1.2 mL/min, t_R = 51 min (*cis*), 62 min (*trans*)) Pale yellow oil; IR (neat) 1720, 1700, 1674 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.39-1.45 (m, 9H), 1.53-2.04 (m, 4H), 3.86 (s, 3H), 4.15 (m, 1H), 5.00-5.19 (m, 4H), 6.84-6.92 (m, 2H), 7.20-7.37 (m, 5H), 7.88-7.96 (m, 2H); ^{13}C NMR ($CDCl_3$), rotamers, δ 14.2, 19.7, 21.1, 23.8, 24.9, 29.6, 38.8, 40.8, 43.6, 48.4, 48.6, 50.9, 52.6, 55.4, 60.4, 67.1, 67.4, 69.1, 70.1, 113.6, 122.3, 127.5, 127.7, 127.8, 127.9, 128.3, 128.4, 131.7, 131.8, 136.6, 163.4, 163.5, 164.9, 165.1, 196.0, 196.7; MS (EI) *m/z* 499 (M^+); Anal. Calcd for $C_{27}H_{33}NO_6S$: C, 64.91; H, 6.66; N, 2.80. Found: C, 64.76; H, 6.75; N, 2.77.

Dimethyl 2-(3-acetoxy-*N*-benzyloxycarbonylpiperidin-2-yl)malonate (15b): (*cis*/*trans* = <10/>90, determined by ^{1}H NMR (120 °C)) Colorless oil; IR (neat) 1740, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.26-1.99 (m, 7H), 2.76-2.96 (m, 1H), 3.40-3.54 (m, 3H), 3.73-4.23 (m, 5H), 4.90-5.42 (m, 4H), 7.27-7.45 (m, 5H); ^{1}H NMR (DMSO-d_6), rotamers, δ 1.03-1.57 (m, 3H), 1.72-1.99 (m, 4H), 2.63-2.93 (m, 1H),

3.37 (s, 1.5H), 3.40 (s, 1H), 3.58 (s, 3H), 3.58-3.86 (m, 1H), 3.86-4.17 (m, 1H), 4.74 (m, 1.8H), 4.89-5.07 (m, 2.2H), 7.18-7.28 (m, 5H); ^{1}H NMR (DMSO-d_6, 120 °C), rotamers, δ 1.32-1.36 (m, 1H), 1.49-1.68 (m, 2H), 1.79-2.00 (m, 4H), 2.72-2.90 (m, 1H), 3.41 (s, 0.3H), 3.44 (s, 2.7H), 3.61 (s, 3H), 3.75-4.00 (m, 2H), 4.78-4.82 (m, 1.8H), 4.96 (d, 1H, J = 12.7 Hz), 5.03 (d, 1H, J = 12.7 Hz), 5.13 (dd, 0.2H, J = 10.7, 5.4 Hz), 7.19-7.25 (m, 5H); ^{13}C NMR ($CDCl_3$), rotamers, δ 19.0, 19.4, 20.7, 20.9, 23.4, 23.6, 23.7, 24.8, 24.9, 39.1, 39.6, 49.9, 50.1, 51.2, 52.3, 52.4, 52.5, 52.6, 52.9, 53.6, 53.9, 67.2, 67.4, 69.1, 69.3, 127.8, 127.9, 128.3, 136.4, 136.6, 136.7, 155.0, 155.6, 166.3, 166.7, 167.2, 169.0, 169.7; ^{13}C NMR (DMSO-d_6), rotamers, δ 18.8, 19.2, 20.6, 20.7, 22.8, 23.2, 24.0, 50.0, 50.3, 51.6, 52.0, 52.3, 52.4, 52.5, 52.6, 52.7, 53.2, 53.6, 66.3, 66.4, 66.6, 67.4, 68.7, 69.1, 127.3, 127.5, 127.8, 128.3, 136.7, 136.9, 154.9, 155.0, 166.6, 167.0, 167.2, 168.9, 169.2; ^{13}C NMR (DMSO-d_6, 120 °C), rotamers, δ 18.3, 19.8, 22.6, 23.8, 49.0, 50.3, 51.5, 51.6, 51.8, 53.2, 66.0, 66.2, 67.1, 68.5, 126.7, 126.8, 127.08, 127.11, 127.7, 136.2, 136.4, 154.0, 154.5, 165.8, 166.0, 166.3, 166.4, 168.0, 168.3; HRMS(ESI) calcd for $C_{20}H_{25}NO_8Na$ 430.1478, found $(M+Na)^+$ 430.1503.

Ethyl 2-[*N*-benzyloxycarbonyl-3-(*p*-methoxybenzoyl)piperidin-2-yl]benzoylacetate (16d): Colorless oil; IR (neat) 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 0.94-1.06 (m, 1.7H), 1.18-1.29 (m, 1.3H), 1.54 (t, 1H, J = 12.3 Hz), 1.77-2.05 (m, 3H), 2.75-2.93 (m, 0.3H), 3.13-3.27 (m, 0.7H), 3.79-4.37 (m, 6H), 4.77-5.33 (m, 4H), 5.50-5.66 (m, 1H), 6.81-6.87 (m, 2H), 7.19-7.64 (m, 8H), 7.87-8.10 (m, 4H); ^{13}C NMR ($CDCl_3$), rotamers δ 13.5, 13.7, 13.8, 14.2, 19.4, 19.8, 24.0, 39.3, 39.8, 54.1, 54.2, 54.3, 54.47, 54.50, 55.4, 62.0, 62.2, 67.0, 67.3, 67.9, 68.0, 68.4, 113.5, 122.4, 127.5, 127.6, 127.7, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 128.9, 131.6, 131.8, 133.6, 133.9, 134.1, 135.7, 135.9, 136.3, 156.1, 163.3, 164.7, 166.4, 166.7, 167.1, 190.4, 191.2; HRMS(ESI) calcd for $C_{32}H_{33}NO_8Na$ 582.2104, found $(M+Na)^+$ 582.2076.

Ethyl [*N*-benzyloxycarbonyl-3-(*p*-methoxybenzoyl)piperidin-2-yl]acetate (17d): (*cis*/*trans* = 39/61, determined by HPLC analysis using YMC-pack

(hexane/AcOEt, 9:1, flow rate 1.2 mL/min, t_R = 105 min (*cis*), 148 min (*trans*)) Colorless oil; IR (neat) 1726, 1704 cm^{-1}; ^1H NMR ($CDCl_3$), rotamers, δ 1.00-1.25 (m, 3H), 1.55-2.01 (m, 5H), 2.30-2.56 (m, 3H), 3.86 (s, 3H), 3.89-4.24 (m, 3H), 4.98-5.15 (m, 4H), 6.85-6.92 (m, 2H), 7.19-7.37 (m, 5H), 7.89-7.95 (m, 2H); ^{13}C NMR ($CDCl_3$), rotamers δ 13.9, 14.0, 19.7, 23.8, 24.7, 31.9, 34.6, 50.6, 52.0, 53.0, 55.4, 60.7, 60.9, 67.1, 67.4, 69.2, 70.0, 113.6, 122.1, 122.5, 127.5, 127.7, 127.8, 127.9, 128.3, 128.4, 131.6, 131.7, 136.5, 155.8, 163.4, 163.5, 164.9, 165.2, 169.9, 170.7; HRMS(ESI) calcd for $C_{25}H_{29}NO_7N$a 478.1842, found $(M+Na)^+$ 478.1802; Anal. Calcd for $C_{25}H_{29}NO_7$: C, 65.92; H, 6.42; N, 3.08. Found: C, 65.62; H, 6.38; N, 3.11.

***trans*-Ethyl (*p*-methoxybenzoyl)-*N*-benzyloxycarbonylpiperidin-2-yl)acetate (*trans*-17d):** A mixture of **16d** (0.206 mmol) and LiOH (0.288 mmol) in THF (1 mL) was stirred under reflux for 2 h. The reaction mixture was cooled to room temperature, and a saturated aqueous NH_4Cl solution and ethyl acetate were added. The aqueous layer was extracted with ethyl acetate (twice). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by silica gel chromatography to afford ***trans*-17d** in 72% yield. It was found based on HPLC analysis that no *cis* derivative was present. Colorless oil; IR (neat) 1723, 1703 cm^{-1}; ^1H NMR ($CDCl_3$), rotamers, δ 1.17-1.26 (m, 3H), 1.53 (m, 1H), 1.85-2.01 (m, 3H), 2.59-2.74 (m, 2H), 2.99 (m, 1H), 3.85 (s, 3H), 3.99-4.23 (m, 2.5H), 4.98-5.07 (m, 3.5H), 6.86 (d, 2H, J = 8.7 Hz), 7.90 (d, 2H, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$), rotamers δ 14.0, 19.7, 23.7, 34.6, 38.7, 52.0, 55.4, 60.9, 67.0, 69.1, 113.6, 122.4, 127.5, 127.7, 128.3, 128.6, 131.6, 136.4, 155.7, 163.3, 165.1, 169.8; HRMS(ESI) calcd for $C_{25}H_{30}NO_7$ 456.2022, found $(M+H)^+$ 456.2007.

***N*-Benzyloxycarbonyl-2-hydroxypiperidine (21):**[6c] To a solution of *N*-benzyloxycarbonyl piperidone (**20**) (2.54 mmol) in dry THF (4 ml) was added a solution of $LiEt_3BH$ in THF (1M, 4 mL) at –78 °C. The reaction mixture was stirred for 1 h at the same temperature, and the reaction was quenched with water (1 mL) and warmed to room temperature. To the mixture were added a saturated aqueous $NaHCO_3$ solution (10 mL) and then 30% aq. H_2O_2 solution (2 mL). After stirring for

1 h, the mixture was extracted with ethyl acetate (twice). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified by silica gel chromatography to afford **21** in 89% yield as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.44-1.90 (m, 7H), 3.18 (td, 1H, J = 12.6, 3.0 Hz), 3.89 (d, 1H, J = 11.7 Hz), 5.15 (s, 2H), 5.79 (m, 1H), 7.32-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 17.6, 24.7, 30.5, 39.4, 67.2, 75.0, 125.6, 127.9, 128.1, 136.4, 160.2.

***N*-Benzyloxycarbonyl-2-methoxypiperidine (3):** (Table 1, entry 2) A solution of *p*-toluenesulfonic acid pyridinium salt (0.04 mmol) and **21** (0.4 mmol) in MeOH (2 mL) was stirred for 17 h at room temperature. The solvent was evaporated *in vacuo* and the residue was partitioned between ethyl acetate and a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified by silica gel chromatography to afford **3** in 64% yield as a colorless oil (Table 1, entry 4). A solution of $Sc(OTf)_3$ (0.04 mmol) and **21** (4.0 mmmol) in a mixture of CH_2Cl_2 (5 ml) and MeOH (2.5 mL) was stirred for 3 h at room temperature. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution and the mixture was extracted with CH_2Cl_2 (twice). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified by silica gel chromatography to afford **3** in 95% yield as a colorless oil. IR (neat) 1702 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.25-2.03 (m, 6H), 2.98 (q, 1H, J = 14.7 Hz), 3.18 (s, 1.5 H), 3.25 (s, 1.5 H), 3.98 (t, 1H, J = 14.7 Hz), 5.16 (m, 2H), 5.34 (s, 0.5H), 5.43 (s, 0.5H), 7.26-7.60 (m, 5H); ^{13}C NMR ($CDCl_3$), rotamers, δ 18.4, 24.97, 25.1, 30.0, 30.3, 38.7, 39.0, 54.3, 55.6, 67.0, 67.2, 82.0, 17.8, 128.0, 128.5, 136.6, 154.1; MS (EI) *m/z* 249 (M^+); Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.39; H, 7.75; N, 5.65.

5-Amino-*N*-benzyloxycarbonylpentanol (23):[25] To a solution of 5-aminopentanol (**22**, 0.184 mol) and $NaHCO_3$ (0.550 mol) in water (100 mL) was added a solution of benzyloxycarbonyl chloride (0.248 mol) in THF (100 mL) at 0 °C.

The reaction mixture was warmed to room temperature and then vigorously stirred for 12 h at the same temperature. The mixture was extracted with ethyl acetate (twice). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was triturated with n-hexane. The resulting powder was collected by filtration, washed with ether (3 times) and dried under reduced pressure to afford **23** in 97% yield. This material was used without further purification. Mp 42 °C; IR (KBr) 3332, 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36-1.64 (m, 7H), 3.20 (q, 2H, J = 6.5 Hz), 3.63 (s, 2H), 4.78 (s, 1H), 5.09 (s, 2H), 7.26-7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.9, 29.8, 32.2, 40.9, 62.7, 66.6, 128.1, 128.2, 128.5, 136.6, 154.4; HRMS(ESI) calcd for $C_{13}H_{20}NO_3$ 238.1443, found $(M+H)^+$ 238.1437.

***N*-Benzyloxycarbonyl-1, 2, 3, 4-tetrahydropyridine (24):** To a solution of oxalyl chloride (44.2 mmol) in CH_2Cl_2 (60 mL) was added dimethylsulfoxide (6.5 mL, 91.5 mmol) at –78 °C, and the mixture was stirred for 2 min. A solution of **23** (35.5 mmol) in CH_2Cl_2 (50 mL) was added dropwise over 20 min below –60 °C, and the reaction mixture was stirred at –78 °C for 1 h. The reaction was quenched with triethylamine (188 mmol) at the same temperature. The mixture was warmed to 0 °C for 1 h and an aqueous 3N HCl solution was added. The suspension was warmed to room temperature and stirred vigorously for 15 h at the same temperature. The mixture was extracted with CH_2Cl_2 (twice). The combined organic layers were washed with water, a saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residure was purified by silica gel chromatography to afford **24** in 94% yield as a colorless oil. IR (neat) 1705, 1655 cm^{-1}; ^1H NMR ($CDCl_3$), rotamers, δ 1.81-1.87 (m, 2H), 2.01-2.07 (m, 2H), 3.63 (t, 2H, J =5.5 Hz), 4.85 (dt, 0.5H, J = 8.4, 4.0 Hz), 4.96 (dt, 0.5H, J = 8.4, 3.8 Hz), 5.18 (s, 2H), 6.79 (d, 0.5 H, J = 8.4 Hz), 6.88 (d, 0.5 H, J = 8.4 Hz), 7.31-7.63 (m, 5H); ^{13}C NMR ($CDCl_3$), rotamers, δ 19.7, 21.2, 21.4, 21.6, 42.2, 42.4, 67.3, 67.4, 106.4, 106.7, 124.9, 125.4, 128.0, 128.1, 128.5, 136.4, 151.8; HRMS(ESI) calcd for $C_{13}H_{16}NO_2$ 218.1181, found $(M+H)^+$ 218.1156.

***N*-Benzyloxycarbonyl-3-hydroxy-2-methoxypiperidine (25):** To a solution of

24 (1.17 mmol) in MeOH (4 mL) *m*-chloroperbenzoic acid (1.38 mmol) was added portionwise at 0 °C, and the mixture was stirred for 1 h at the same temperature. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution, and the mixture was extracted with CH_2Cl_2 (3 times). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified by silica gel chromatography to afford **25** in 72% yield as a colorless oil (a mixture of diastereomers). IR (neat) 3453, 1702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23-1.90 (m, 4H), 2.43 (br, 1H), 2.77-2.96 (m, 1H), 3.20-3.43 (m, 3H), 3.55 (m, 1H), 3.84-3.95 (m, 1H), 5.08-5.29 (m, 2H), 5.32-5.44 (m, 1H), 7.27-7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.8, 23.8, 24.1, 25.6, 28.0, 37.5, 37.9, 38.7, 55.0, 66.1, 67.3, 67.5, 69.0, 69.2, 84.2, 84.4, 85.3, 127.8, 128.1, 128.2, 128.50, 128.55, 136.2, 136.4, 155.3, 155.7; HRMS(ESI) calcd for $C_{14}H_{19}NO_4Na$ 288.1212, found $(M+Na)^+$ 288.1205; Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.32; N, 5.28. Found: C, 63.29; H, 7.18; N, 5.28.

***N*-Benzyloxycarbonyl-2,3-dihydroxypiperidine (26):** Osmylation using microencapsulated OsO_4 (Table 2, entry 1). To a solution of **24** (10.4 mmol) and *N*-methylmorpholine (50% aqueous solution, ca. 16 mmol) in a mixture of acetonitrile (12 mL), acetone (12 mL) and water (12 mL) was added microencapsulated osmium tetraoxide[29] (0.42 mmol/g, 0.52 mmol) at room temperature. The reaction mixture was stirred for 24 h at the same temperature. The catalyst was filtered off and washed with acetonitrile (5 times). The filtrate was evaporated *in vacuo*. The residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (twice). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified by silica gel chromatography to afford **26** in 79 % (*cis*/*trans* = 100/0) yield as a colorless oil. **26** (*cis*)**:** IR (neat) 3419, 1682 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39-1.83 (m, 4H), 2.71 (s, 1H), 3.03 (dt, 1H, J = 12.9, 2.7 Hz), 3.58 (m, 1H), 3.83 (d, 1H, J = 11.6 Hz), 5.13 (s, 2H), 5.73 (d, 1H, J = 3.3 Hz), 7.26-7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.5, 26.8, 38.2, 67.6, 69.0, 76.5, 128.0, 128.2, 128.6, 136.2, 155.9; HRMS(ESI)

calcd for $C_{13}H_{17}NO_4Na$ 274.1056, found $(M+Na)^+$ 274.1041; Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.85; H, 7.07; N, 5.54. Osmylation of **24** by a standard method (Table 2, entry 2). To a solution of **24** (29.9 mmol), methanesulfonyl amide (2.31 mmol), potassium carbonate (91.3 mmol) and potassium ferricyanide (III) (90.2 mmol) in a mixture of water (225 mL) and *tert*-butanol (225 mmol) was added potassium osmate dihydrate (0.510 mmol) at room temperature. The reaction mixture was stirred for 24 h and the reaction was quenched with an aqueous solution of sodium thiosulfate (10.1 mmol). The mixture was extracted with ethyl acetate (3 times). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified by silica gel chromatography to afford **26** in 73 % yield as a mixture of diastereomers (*cis*/*trans* = 80/20). The diastereomer ratio was determined by ^1H NMR. **26** (*cis*/*trans* = 80/20): ^1H NMR ($CDCl_3$) δ 1.39-1.88 (m, 4H), 2.99-3.21 (m, 2H), 3.53-3.63 (m, 1H), 3.79-3.89 (m, 1H), 5.10 (s, 2H), 5.59 (d, 0.2 H, J = 2.4 Hz), 5.71 (d, 0.8 H, J = 3.3 Hz), 7.26-7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.6, 23.4, 24.8, 26.5, 27.3, 38.0, 38.8, 66.9, 67.4, 69.0, 76.4, 77.2, 78.0, 127.77, 127.8, 128.03, 128.08, 128.4, 128.5, 136.1, 155.9.

3-Benzyloxy-*N*-benzyloxycarbonyl-2-methoxypiperidine (27): To a suspension of NaH (60% dispersion in mineral oil, 12.0 mmol) in dry THF (10 mL) was added a mixture of 18-crown-6 (0.57 mmol) and **25** (11.4 mmol) in dry THF (10 mL) at room temperature. The mixture was stirred for 30 min at the same temperature and then cooled to 0 °C. Benzyl bromide (17.1 mmol) was added at the same temperature, and the reaction mixture was then stirred for 10 h at room temperature. The reaction was quenched with water, and the mixture was extracted with ethyl acetate (twice). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified by silica gel chromatography to afford **27-major** (more polar) and **27-minor** (less polar) in 50% and 37% yields as a colorless oil, respectively. These compounds were used as a mixture of diasereomers in the further transformation. **27-major:** IR (neat)

1702 cm^{-1}; ^1H NMR ($CDCl_3$), rotamers, δ 1.46-1.87 (m, 4H), 2.83-2.96 (m, 1H), 3.22-3.33 (m, 3H) 3.37-3.42 (m, 1H), 3.82-3.93 (m, 1H), 4.51-4.68 (m, 2H), 5.07-5.20 (m, 2H), 5.35-5.58 (m, 1H), 7.25-7.35 (m, 10H); ^{13}C NMR ($CDCl_3$), rotamers, δ 23.8, 24.2, 24.4, 24.7, 37.7, 38.0, 54.8, 55.2, 67.2, 67.3, 70.5, 70.7, 76.0, 76.2, 82.3, 82.8, 127.6, 127.7, 127.8, 127.9, 128.1, 128.3, 128.5, 136.4, 138.2, 138.3, 155.1, 155.6; HRMS(ESI) calcd for $C_{21}H_{25}NO_4$ 355.1784, found $(M+Na)^+$ 378.1659; Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.91; H, 7.07; N, 3.96. **27-minor:** IR (neat) 1701 cm^{-1}; ^1H NMR ($CDCl_3$), rotamers, δ 1.26-1.92 (m, 4H), 2.91-3.02 (m, 1H), 3.93-3.29 (m, 3H) 3.54-3.59 (m, 1H), 3.93-4.06 (m, 1H), 4.48-4.68 (m, 2H), 5.11-5.18 (m, 2H), 5.34-5.52 (m, 1H), 7.10-7.35 (m, 10H); ^{13}C NMR ($CDCl_3$), rotamers, δ 19.2, 19.4, 23.6, 23.9, 38.2, 38.6, 54.5, 54.9, 67.1, 70.5, 70.8, 72.8, 73.0, 82.4, 82.9, 127.2, 127.4, 127.5, 127.6, 127.8, 127.9, 128.3, 128.4, 136.6, 136.7, 138.4, 156.0, 156.4; HRMS(ESI) calcd for $C_{21}H_{25}NO_4Na$ 378.1682, found $(M+Na)^+$ 378.1659; Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.91; H, 7.07; N, 3.96.

3-Benzyloxy-*N*-benzyloxycarbonyl-2-hydroxypiperidine (28): To a solution of **27** (a mixture of diastereomers, 10.0 mmol) in a mixture of acetonitrile (80 mL) and water (20 mL) was added $Sc(OTf)_3$ (0.50 mmol) at room temperature. The reaction mixture was stirred for 24 h at the same temperature, and the reaction was quenched with saturated aqueous $NaHCO_3$ solution. The mixture was extracted with ethyl acetate (twice). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified by silica gel chromatography to afford **28** in 72 % yield as colorless oil (a mixture of diastereomers). IR (neat) 1701 cm^{-1}; ^1H NMR ($CDCl_3$), rotamers, δ 1.42-1.47 (m, 1H), 1.70-1.91 (m, 4H), 3.09-3.18 (m, 1H), 3.42-3.61 (m, 1H) 3.54-3.59 (m, 1H), 3.87-3.91 (m, 1H), 4.53-4.61(m, 2H), 5.10-5.17(m, 2H), 5.78-5.89 (m, 1H), 7.25-7.36 (m, 10H); ^{13}C NMR ($CDCl_3$), rotamers, δ 19.0, 22.9, 23.9, 38.8, 67.3, 67.4, 70.5, 70.7, 73.5, 75.9, 76.7, 127.4, 127.5, 127.7, 127.8, 128.0, 128.1, 128.3, 128.5, 136.3, 136.4, 137.8, 138.4; HRMS(ESI) calcd for $C_{20}H_{23}NO_4Na$ 364.1525, found

$(M+Na)^+$ 364.1564; Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.30; H, 6.86; N, 4.14.

2-Acetoxy-3-benzyloxy-*N*-benzyloxycarbonylpiperidine (4a): To a solution of **28** (1.00 mmol) and 4-*N*,*N*-dimethylaminopyridine (0.10 mmol) in triethylamine (5 mL) was added acetic anhydride (4.0 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3 h at the same temperature. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution at 0 °C. The mixture was extracted with ethyl acetate (twice). The combined organic layers were washed with water (5 times), saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified by silica gel chromatography to afford **4a** in 83% yield as a colorless oil (a mixture of diastereomers). IR (neat) 1745, 1700 cm^{-1}; ^1H NMR ($CDCl_3$), rotamers, δ 1.48-1.87 (m, 4H), 2.07 (s, 3H), 2.96-3.02 (m, 1H), 3.43-3.48 (m, 1H), 3.90-3.93 (m, 1H), 4.47-4.50 (m, 2H), 5.12-5.21 (m, 2H), 4.71-4.74 (m, 1H), 7.25-7.36 (m, 10H); ^{13}C NMR ($CDCl_3$), rotamers, δ 20.8, 23.2, 25.1, 39.2, 67.3, 67.6, 70.3, 70.8, 74.7, 74.8, 127.4, 127.5, 127.6, 127.7, 127.9, 128.0, 128.2, 128.4, 136.0, 137.8, 154.8, 159.3; HRMS(ESI) calcd for $C_{22}H_{25}NO_5Na$ 406.1631, found $(M+Na)^+$ 406.1669; Anal. Calcd for $C_{21}H_{25}NO_4$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.86; H, 6.59; N, 3.63.

2,3-Diacetoxy-*N*-benzyloxycarbonylpiperidine (4b): To a solution of **26** (*cis/trans* = 100/0, 1.75 mmol) and 4-*N*,*N*-dimethylaminopyridine (0.18 mmol) in triethylamine (1.5 mL) was added acetic anhydride (10.6 mmol) at room temperature. The reaction mixture was stirred for 3 h at the same temperature. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution at 0 °C. The mixture was extracted with ethyl acetate (twice). The combined organic layers were washed with water (5 times), saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified by silica gel chromatography to afford **4b** quantitatively as a colorless oil (*cis/trans* =95/5). The diastereomer ratio was determined by ^1H NMR. IR (neat) 1744, 1714, 1701 cm^{-1}; ^1H NMR ($CDCl_3$), rotamers, δ 1.60-1.87 (m, 4H), 2.01 (s, 3H), 2.07 (s, 3H), 3.01 (t, 1H,

J = 11.6 Hz), 3.96 (d, 1H, *J* = 9.3 Hz), 4.88 (m, 1H), 5.11 (d, 1H, *J* = 12.5 Hz), 5.21 (d, 1H, *J* = 12.5 Hz), 6.69 (d, 0.05H, *J* = 2.6 Hz), 6.99 (d, 0.95H, *J* = 3.3 Hz), 7.26-7.37 (m, 5H); ^{13}C NMR ($CDCl_3$), rotamers, δ 20.78, 20.84, 23.0, 39.2, 67.8, 69.4, 75.4, 128.0, 128.1, 128.5, 136.0, 154.8, 169.2, 170.0; HRMS(ESI) calcd for $C_{17}H_{21}NO_6Na$ 358.1267, found $(M+Na)^+$ 358.1231; Anal. Calcd for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.31; N, 4.18. Found: C, 60.83; H, 6.34; N, 4.15.

Similarly, **(3*S*)-4b** (*cis/trans* =57/43) was obtained from **(3*S*)-26** (*cis/trans* =56/44). **(3*S*)-4b** (*cis/trans* =57/43): $[\alpha]_D^{25}$ +6.1 (c = 0.97, $CHCl_3$); ^{1}H NMR ($CDCl_3$), rotamers, δ 1.56-2.09 (m, 10H), 2.96-3.05 (m, 1H), 3.94-4.08 (m, 1H), 4.84-4.91 (m, 1H), 5.09-5.23 (m, 2H), 6.69 (d, 0.43H, *J* = 2.6 Hz), 6.99 (d, 0.57H, *J* = 3.3 Hz), 7.26-7.37 (m, 5H).

***N*-Benzyloxycarbonyl-2,3-dibenzoyloxypiperidine (29):** To a solution of **26** (1.19 mmol) and 4-*N*,*N*-dimethylaminopyridine (0.12 mmol) in triethylamine (4 mL) was added benzoic anhydride (2.98 mmol) at room temperature. The reaction mixture was stirred for 20 h at the same temperature. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution at 0 °C. The mixture was extracted with ethyl acetate (twice). The combined organic layers were washed with water (5 times), a saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified by silica gel chromatography to afford **29** in 82% yield as a colorless oil. IR (neat) 1735, 1715, 1701 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.80-2.13 (m, 4H), 3.21 (t, 1H, *J* = 13.1 Hz), 4.12 (m, 1H), 5.15-5.24 (m, 3H), 7.26-7.62 (m, 1H), 7.87 (d, 2H, *J* = 7.7 Hz), 8.06 (d, 2H, *J* = 7.7 Hz); ^{13}C NMR ($CDCl_3$), rotamers, δ 23.1, 24.4, 39.5, 68.0, 70.6, 76.3, 76.4, 128.0, 18.1, 128.3, 128.5, 129.7, 129.8, 130.0, 133.0, 133.3, 136.0, 154.8, 164.6, 165.5; HRMS(ESI) calcd for $C_{27}H_{25}NO_6Na$ 482.1580, found $(M+Na)^+$ 482.1617; Anal. Calcd for $C_{27}H_{25}NO_6$: C, 70.58; H, 5.48; N, 3.05. Found: C, 70.46; H, 5.70; N, 2.97.

3-Benzoyloxy-*N*-benzyloxycarbonyl-2-hydroxypiperidine (30): Method A. A solution of **29** (0.352 mmol) in a mixture of THF (0.6 mL), water (0.6 mL) and acetic acid (1.8 mL) was stirred for 12 h at room temperature. The reaction was

carefully quenched with saturated aqueous $NaHCO_3$ solution at 0 °C, and the mixture was extracted with ethyl acetate (3 times). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (5 times), water and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified by silica gel chromatography to afford **30** quantitatively as a colorless oil (a mixture of diastereomers). **Method B.** To a suspension of **29** (0.12 mmol) in a mixture of acetonitrile (0.8 mL) and water (0.2 mL) was added $Sc(OTf)_3$ (0.012 mmol) at room temperature. The reaction mixture was stirred for 24 h at the same temperature and the reaction was quenched with a saturated aqueous $NaHCO_3$ solution. The mixture was extracted with ethyl acetate (twice). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified by silica gel chromatography to afford **30** quantitatively as a colorless oil (*cis/trans* = 30/70). The diastereomer ratio was determined by ^1H NMR. **30** (*cis/trans* = 30/70)**:** IR (neat) 3444, 1716, 1683 cm^{-1}; ^1H NMR ($CDCl_3$), rotamers, δ 1.50-2.11 (m, 5H), 3.24 (m, 1H), 4.00 (m, 1H), 5.08-5.18 (m, 3H), 5.84 (s, 0.7H), 5.99 (s, 0.3H), 7.26-7.56 (m, 8H), 7.98 (d, 1.4H, J = 7.7 Hz), 8.06 (d, 0.6H, J = 7.7 Hz); ^{13}C NMR ($CDCl_3$), rotamers, δ 19.5, 22.9, 23.0, 23.4, 67.3, 67.6, 69.4, 72.0, 74.9, 75.5, 127.7, 128.0, 128.2, 128.37, 128.43, 128.5, 128.7, 129.65, 129.71, 129.9, 130.0, 133.09, 133.14, 136.1, 136.2, 150.0, 165.6, 165.6; HRMS(ESI) calcd for $C_{20}H_{21}NO_5Na$ 378.1318, found $(M+Na)^+$ 378.1345; Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.62; H, 6.14; N, 3.93.

2-Acetoxy-3-benzoyloxy-*N*-benzyloxycarbonylpiperidine (4c): To a solution of **30** (0.505 mmol) and 4-*N*,*N*-dimethylaminopyridine (0.06 mmol) in triethylamine (0.7 mL) was added acetic anhydride (2.64 mmol) at room temperature. The reaction mixture was stirred for 1.5 h at the same temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ solution at 0 ° C. The mixture was extracted with ethyl acetate (twice). The combined organic layers were washed with water (5 times), saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified by silica gel chromatography to

afford **4c** in 85% yield as a colorless oil (mixture of diastereomers *cis/trans* = 30/70). The diastereomer ratio was determined by ^{1}H NMR. **4c** (*cis/trans* = 30/70)**:** IR (neat) 1748, 1738, 1716, 1701 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.58-2.25 (m, 7H), 3.02-3.13 (m, 1H), 4.00-4.15 (m, 1H), 5.07-5.28 (m, 3H), 6.85 (d, 0.7H, *J* = 2.6 Hz), 7.16-7.59 (m, 8.3H), 7.93-7.97 (m, 2H); ^{13}C NMR ($CDCl_3$), rotamers, δ 19.2, 20.8, 23.0, 23.4, 24.0, 39.2, 67.3, 67.5, 67.8, 70.4, 75.5, 76.3, 127.6, 128.0, 128.1, 128.3, 128.36, 128.43, 129.5, 129.7, 129.8, 133.07, 133.14, 136.0, 136.1, 154.7, 155.2, 165.1, 165.4, 168.6, 169.0; HRMS(ESI) calcd for $C_{22}H_{23}NO_6Na$ 420.1423, found $(M+Na)^+$ 420.1410; Anal. Calcd for $C_{27}H_{25}NO_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.31; H, 5.92; N, 3.51.

***N*-Benzyloxycarbonyl-2-hydroxy-3-(*p*-methoxybenzoyl)oxypiperidine (31):** To a solution of **26** (4.89 mmol) and 4-*N*,*N*-dimethylaminopyridine (0.49 mmol) in a mixture of triethylamine (15 mL) and CH_2Cl_2 (10 mL) was added *p*-methoxybenzoic anhydride[30] (14.6 mmol) at room temperature, and the reaction mixture was stirred for 24 h at the same temperature. The reaction was quenched with water at the same temperature. The mixture was extracted with ethyl acetate (twice). The combined organic layers were washed with water (5 times), a saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was dissolved in a mixture of THF (5 mL), water (5 mL) and acetic acid (15 mL), and was stirred for 24 h at room temperature. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution at 0 °C. The mixture was extracted with ethyl acetate (3 times). The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution (5 times), water and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified by silica gel chromatography to afford **31** in 84% yield as a colorless oil (*cis/trans* = 33/67). The diastereomer ratio was determined by ^{1}H NMR. IR (neat) 1715, 1700, 1683 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.53-2.09 (m, 4H), 3.17-3.29 (m, 1H), 3.80-3.99 (m, 4H), 4.95-5.14 (m, 3H), 5.82 (s, 0.67 H), 5.97 (s, 0.33 H), 6.88 (d, 2H, *J* = 8.7 Hz), 7.00-7.33 (m, 5H), 7.92 (d, 1.3 H, *J* = 8.7 Hz), 8.00 (d, 0.7 H, *J* = 8.7 Hz); ^{13}CNMR ($CDCl_3$), rotamers, δ

19.5, 22.9, 23.2, 23.4, 38.1, 38.5, 55.2, 55.37, 55.39, 67.2, 67.5, 69.1, 71.6, 75.0, 75.5, 77.2, 113.57, 113.59, 122.2, 122.4, 127.6, 128.0, 128.1, 128.4, 128.5, 131.7, 131.8, 136.1, 136.2, 155.5, 163.4, 163.5, 165.27, 165.34; HRMS(ESI) calcd for $C_{21}H_{23}NO_6Na$ 408.1423, found $(M+Na)^+$ 408.1448; Anal. Calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.15; H, 6.22; N, 3.58.

2-Acetoxy-*N*-benzyloxycarbonyl-3-(*p*-methoxybenzoyl)oxypiperidine (4d): To a solution of **31** (3.45 mmol) and 4-*N*,*N*-dimethylaminopyridine (0.35 mmol) in triethylamine (5 mL) was added acetic anhydride (10.6 mmol) at room temperature. The reaction mixture was stirred for 2.5 h at the same temperature. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution at 0 °C. The mixture was extracted with ethyl acetate (twice). The combined organic layers were washed with water (5 times), a saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified by silica gel chromatography to afford **4d** in 95% yield as a white solid. Mp 108-110 °C; IR (KBr) 1748, 1707 cm^{-1}; ^1H NMR ($CDCl_3$), rotamers, δ 1.61-2.17 (m, 7H), 3.06 (m, 1H), 3.85 (m, 1H), 4.13 (m, 1H), 5.03-5.30 (m, 3H), 6.84-6.91 (m, 3H), 7.15-7.37 (m, 5H), 7.89-7.92 (m, 2H); ^{13}C NMR ($CDCl_3$), rotamers, δ 19.2, 20.8, 23.5, 24.1, 55.40, 55.43, 64.9, 65.0, 67.0, 67.5, 67.8, 70.1, 75.6, 113.6, 122.1, 122.2, 127.6, 127.9, 18.0, 128.1, 128.4, 128.5, 131.6, 131.7, 131.8, 136.0, 136.2, 155.1, 155.2, 163.48, 163.53, 164.8, 165.1, 168.6, 169.0; HRMS(ESI) calcd for $C_{23}H_{25}NO_7Na$ 450.1529, found $(M+Na)^+$ 450.1524; Anal. Calcd for $C_{23}H_{25}NO_7$: C, 64.63; H, 5.90; N, 3.28. Found: C, 64.46; H, 5.84; N, 3.26.

2-(*N*-Benzyloxycarbonyl-3-hydroxypiperidin-2-yl)acetophenone (32): A solution of **11b** (major/minor = 76/24, 1.78 mmol) and MeONa (2.41 mmol) in MeOH (7 mL) was stirred for 4 h at room temperature. The solvent was evaporated *in vacuo*. The residue was partitioned between ethyl acetate and a saturated aqueous NH_4Cl solution. The aqueous layer was extracted with ethyl acetate (twice). The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The resulting

crude product was purified by silica gel chromatography to afford **32-major** (more polar) and **32-minor** (less polar) as colorless oils in 66% and 26% yields, respectively (a mixture of diastereomers). The configuration of **32-major** was determined as *trans* by X-ray crystallography of its 2-naphthoate derivative. **32-major (*trans*):** IR (neat) 1683 cm^{-1}; ^1H NMR ($CDCl_3$), rotamers, δ 1.46 (d, 1H, *J* = 12.7 Hz), 1.71-2.04 (m, 3H), 2.23 (s, 1H), 2.97 (t, 1H, *J* = 12.1 Hz), 3.19 (d, 2H, *J* = 7.3 Hz), 3.90 (s, 1H), 4.13 (t, 1H, *J* = 6.2 Hz), 4.86 (s, 1H), 5.04 (d, 1H, *J* = 12.4 Hz), 5.10 (d, 1H, *J* = 12.4 Hz), 7.26-7.41 (m, 7H), 7.53-7.58 (m, 1H), 7.91 (m, 2H); ^{13}C NMR ($CDCl_3$), rotamers, δ 18.8, 25.7, 38.7, 39.6, 54.6, 66.6, 67.3, 127.8, 127.9, 128.2, 128.4, 128.7, 133.4, 136.3, 136.5, 156.2, 197.5; MS (EI) *m/z* 353 (M^+); Anal. Calcd for $C_{21}H_{23}NO_4 \cdot 0.5H_2O$: C, 69.60; H, 6.67; N, 3.86. Found: C, 69.95; H, 6.50; N, 3.96. **32-minor (*cis*):** IR (neat) 1688 cm^{-1}; ^1H NMR ($CDCl_3$), rotamers, δ 1.32-1.91 (m, 4H), 2.85 (t, 1H, *J* = 11.7 Hz), 2.90 (s, 1H), 2.99 (dd, 1H, *J* = 15.6, 6.0 Hz), 3.82 (s, 1H), 4.03 (d, 1H, *J* = 13.0 Hz), 4.80-5.20 (m, 3H9, 7.12-7.63 (m, 8H), 7.92 (m, 2H); ^{13}C NMR ($CDCl_3$), rotamers, δ 23.6, 27.2, 34.9, 38.7, 52.5, 67.2, 68.2, 127.7, 127.8, 128.2, 128.3, 128.4, 133.1, 136.3, 136.6, 155.2, 199.6; MS (EI) *m/z* 353 (M^+); Anal. Calcd for $C_{21}H_{23}NO_4 \cdot 0.5H_2O$: C, 69.60; H, 6.67; N, 3.86. Found: C, 69.78; H, 6.48; N, 3.86.

***trans*-2-[*N*-Benzyloxycarbonyl-3-(2-naphthoyloxy)piperidin-2-yl]acetophenone (33):** To a solution of **32-major** (0.342 mmol), 2-naphthoic acid (0.350 mmol), triethylamine (0.820 mmol) and 4-*N*,*N*-dimethylaminopyridine (0.035 mmol) in CH_2Cl_2 (5 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrogen chloride (0.417 mmol) at room temperature. The reaction mixture was stirred for 24 h, and the reaction was quenched with an aqueous 1M hydrogen chloride solution. The mixture was extracted with CH_2Cl_2 (twice). The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by silica gel chromatography to afford **33** in 44% yield as a syrup, and the starting material (**32-major**) was recovered (50%, 88% conversion). X-ray quality single

crystals were obtained by crystallization from ether/n-hexane in 86% yield as colorless plates. The configuration was determined as *trans* by X-ray crystallography. Mp 88-89 °C; IR (KBr) 1708, 1688 cm^{-1}; ^1H NMR ($CDCl_3$), rotamers, δ 1.26-1.12 (m, 4H), 3.10 (t, 1H, J = 11.0 Hz), 3.26-3.38 (m, 2H), 4.29 (s, 1H), 4.87-5.25 (m, 4H), 7.00-7.97 (m, 16H), 8.50 (s, 1H); ^{13}C NMR ($CDCl_3$), rotamers, δ 19.8, 23.8, 38.4, 51.9, 67.1, 69.9, 125.1, 126.5, 127.4, 127.7, 128.1, 128.2, 128.7, 129.4, 131.1, 132.3, 133.3, 135.5, 136.2, 155.7, 165.6, 196.5; HRMS(ESI) calcd for $C_{32}H_{30}NO_5$ 508.2124, found $(M+H)^+$ 508.2111; Anal. Calcd for $C_{32}H_{29}NO_5$: C, 75.72; H, 5.76; N, 2.76. Found: C, 75.45; H, 5.92; N, 2.78.

***trans*-2-(3-Benzyloxy-*N*-benzyloxycarbonylpiperidin-2-yl)acetophenone (*trans*-11a):** To a solution of **32-major** (0.250 mmol) and benzyl trichloroacetoimidate (1.00 mmol) in ether (2 mL) was added a solution of trifluoromethanesulfonic acid in ether (0.17 M, 0.1 mL) at room temperature. After the reaction mixture was stirred for 20 h at the same temperature, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution. The mixture was extracted with ethyl acetate (twice). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. After silica gel chromatography of the residue, ***trans*-11a** was obtained in 38% yield as a colorless oil (2% of epimerization was observed by HPLC analysis. However, ***cis*-11a** was not observed by ^1H NMR analysis). The starting material (**32-major**) was recovered without epimerization (58%, 90% conversion). ***trans*-11a:** IR (neat) 1690 cm^{-1}; ^1H NMR ($CDCl_3$), rotamers, δ 1.48- 2.05 (m, 4H), 2.95-3.38 (m, 3H), 3.54 (s, 1H), 4.24 (br, 1H), 4.45-5.19 (m, 5H), 7.01-7.59 (m, 13H), 7.80-7.96 (m, 2H); ^{13}C NMR ($CDCl_3$), rotamers, δ 19.5, 19.8, 23.8, 24.4, 38.4, 38.9, 39.1, 39.7, 50.2, 51.9, 67.1, 67.5, 69.7, 70.2, 73.0, 76.6, 127.3, 127.5, 127.7, 127.8, 128.1, 128.2, 128.3, 128.4, 128.7, 129.6, 130.1, 133.0, 133.4, 136.3, 136.4, 136.7, 138.6, 141.1, 155.7, 155.9, 196.6, 197.5; HRMS(ESI) calcd for $C_{28}H_{30}NO_4$ 444.2175, found $(M+H)^+$ 444.2207

***trans*-2-(3-Acetoxy-*N*-benzyloxycarbonylpiperidin-2-yl)acetophenone (*trans*-11b):** A solution of **32-major** (0.203 mmol), triethylamine (0.494 mmol), 4-

N,*N*-dimethylaminopyridine (0.0221 mmol) and acetic anhydride (0.353 mmol) in CH_2Cl_2 (5mL) was stirred for 4 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford ***trans*-11b** in 89 % yield as a colorless oil. IR (neat) 1734, 1695 cm^{-1}; ^1H NMR ($CDCl_3$), rotamers, δ 1.45 (m, 1H), 1.73-1.99 (m, 6H), 2.92 (s, 1H), 3.12-3.20 (m, 2H), 4.11 (s, 1H), 4.83-5.03 (m, 4H), 7.12-7.49 (m, 8H), 7.84 (m, 2H); ^{13}C NMR ($CDCl_3$), rotamers, δ 19.5, 21.0, 13.6, 38.4, 39.0, 51.7, 67.0, 69.1, 127.6, 127.8, 128.2, 128.4, 128.6, 133.3, 136.2, 155.6, 170.2, 196.6; HRMS(ESI) calcd for $C_{23}H_{26}NO_5$ 396.1810, found $(M+H)^+$ 396.1835.

***cis*-2-(3-Acetoxy-*N*-benzyloxycarbonylpiperidin-2-yl)acetophenone (*cis*-11b):** Similarly, ***cis*-11b** was obtained from **32-minor** in 54% yield as colorless oil. IR (neat) 1739, 1697 cm^{-1}; ^1H NMR ($CDCl_3$), rotamers, δ 1.58-2.01 (m, 7H), 2.97 (m, 2H), 3.48 (dd, 1H, J = 15.2, 6.6 Hz), 4.07 (s, 1H), 4.92-5.09 (m, 3H), 5.24 (q, 1H, J = 6.3 Hz), 7.26-7.58 (m, 8H), 7.91 (m, 2H); ^{13}C NMR ($CDCl_3$), rotamers, δ 21.0, 23.6, 24.8, 35.4, 38.8, 50.3, 67.3, 70.1, 127.8, 127.9, 128.1, 128.4, 128.6, 133.1, 136.4, 136.7, 155.1, 169.6, 197.2; HRMS(ESI) calcd for $C_{23}H_{26}NO_5$ 396.1811, found $(M+H)^+$ 396.1790.

***trans*-Methyl 1-(3-benzyloxypiperidin-2-yl)-1-methylpropionate (34a): 13a** (0.428 mmol) was dissolved in MeOH (5 mL), and hydrogenated (10% Pd-C, 1atm) for 2.5 days at room temperature. After purification by silica gel chromatography, **34a** was obtained in 85% yield as a colorless oil. IR (neat) 3363, 1731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16-1.41 (m, 9H), 1.72-1.76 (m, 1H), 2.28 (m, 1H), 2.95 (d, 1H, J = 9.6 Hz), 3.05 (m, 1H), 3.16 (dt, 1H, J = 9.6, 4.0 Hz), 3.31 (s, 3H), 4.30 (d, 1H, J = 10.8 Hz), 4.50 (d, 1H, J = 10.8 Hz), 7.24-7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.2, 24.6, 26.2, 30.2, 43.6, 46.9, 51.3, 66.2, 70.5, 77.4, 127.4, 128.0, 128.4, 138.1, 177.7; HRMS(ESI) calcd for $C_{17}H_{26}NO_3$ 292.1912, found $(M+H)^+$ 292.1913.

***trans*-Methyl 1-(*N*-benzyloxycarbonyl-3-hydroxypiperidin-2-yl)-1-methylpropionate (35):** A solution of **13b** (0.130 mmol) and NaOMe (0.259 mmol) in MeOH (1.5 mL) was stirred for 10 h at room temperature. The reaction was

quenched with an aqueous 1N HCl solution (0.27 mL) and the solvent was evaporated *in vacuo*. The residue was purified by silica gel chromatography to afford **35** in 97% yield as a pale yellow oil (a single diastereomer). IR (neat) 1726, 1676 cm^{-1}; ^1H NMR ($CDCl_3$), rotamers, δ 1.14-1.60 (m, 7H), 1.63-1.86 (m, 3H), 2.43 (br, 1H), 2.84 (t, 0.5H, J = 12.3 Hz), 2.92 (t, 0.5H, J = 13.1 Hz), 3.58 (s, 3H), 3.95-4.04 (m, 1.5 H), 4.16 (d, 0.5 H, J = 12.3 Hz), 4.31 (d, 1 H, J = 14.3 Hz), 4.99-5.14 (m, 2H), 7.20-7.28 (m, 5H); ^1H NMR (DMSO-d_6), rotamers, δ 1.14-1.30 (m, 7H), 1.53-1.70 (m, 3H), 2.81 (t, 0.5 H, J = 12.8 Hz), 2.90 (t, 0.5 H, J = 13.4 Hz), 3.56 (s, 3H), 3.84 (d, 1H, J = 9.4 Hz), 4.00 (t, 1H, J = 16.3 Hz), 4.19 (d, 1H, J = 10.8 Hz), 4.81 (d, 1H, J = 11.9 Hz), 5.07-5.13 (m, 2H), 7.34 (m, 5H); ^1H NMR (DMSO-d_6, 90 °C) δ 1.17 (s, 3H), 1.21 (s, 3H), 1.26-1.42 (m, 1H), 1.55-1.81 (m, 3H), 2.88 (t, 1H, J = 11.3 Hz), 3.58 (s, 3H), 3.87 (s, 1H), 4.01 (d, 1H, J = 13.6Hz), 4.24 (s, 1H), 4.51 (s, 1H), 5.09 (s, 2H), 7.28-7.61 (m, 5H); ^{13}C NMR ($CDCl_3$), rotamers, δ 18.6, 19.0, 22.9, 25.5, 25.7, 27.3, 27.6, 40.3, 40.6, 45.8, 52.0, 64.2, 64.4, 64.6, 64.9, 67.3, 127.6, 127.7, 127.8, 128.4, 136.7, 156.9, 157.2, 177.2; ^{13}C NMR (DMSO-d_6), rotamers, δ 18.4, 18.8, 22.8, 23.1, 25.1, 25.3, 27.45, 27.54, 45.26, 45.35, 51.8, 62.7, 62.8, 64.0, 66.2, 66.4, 127.3, 127.4, 127.7, 128.3, 128.4, 136.9, 137.2, 156.1, 156.3, 176.5; ^{13}C NMR (DMSO-d_6, 90 °C) δ 18.2, 22.6, 24.6, 27.3, 45.2, 51.1, 62.8, 63.9, 65.9, 126.9, 127.2, 127.8, 136.7, 155.9, 175.9; HRMS(ESI) calcd for $C_{18}H_{26}NO_5$ 336.1811, found $(M+H)^+$ 336.1811.

Similarly, **13d** (0.319 mmol) was treated with NaOMe (0.555 mmol) in THF-MeOH (2/1, 15 mL) for 6 h under reflux. After the usual work-up and purification by silica gel chromatography, **35** and **36** were obtained in 59% and 21% yields, respectively.

Lactone 36: To a suspension of NaH (60% dispersion in mineral oil, 0.51 mmol) in dry THF (2 mL) was added a solution of 18-crown-6 (0.04 mmol) and **35** (0.43 mmol) in dry THF (5 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 24 h at the same temperature. The reaction was quenched with a saturated aqueous NH_4Cl solution. The mixture was extracted with ethyl acetate (twice). The combined organic layers were washed with water and brine,

dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified by silica gel chromatography to afford **36** in 77% yield as a single diastereomer. Colorless needles; Mp 115 °C; IR (KBr) 1777, 1717 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (s, 3H), 1.57 (s, 3H), 1.59-1.92 (m, 2H), 2.29-2.36 (m, 1H), 3.09 (d, 1H, J = 10.4 Hz), 3.16 (ddd, 1H, J = 13.5, 9.8, 3.7 Hz), 3.98 (dt, 1H, J = 13.5, 4.9 Hz), 4.09 (ddd, 1H, J = 11.0, 10.4, 4.8 Hz), 5.12 (s, 2H), 7.32-7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 17.3, 22.0, 25.1, 26.9, 45.5, 45.8, 67.5, 69.1, 75.7, 128.26, 128.32, 128.6, 136.0, 155.5, 180.2; MS (EI) *m/z* 303; Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.34; H, 7.16; N, 4.57.

***trans*-Methyl 1-(3-benzyloxypiperidin-2-yl)-1-methylpropionate (34d). 13d** (0.328 mmol) was dissolved in MeOH (3 mL), and hydrogenated (10% Pd-C, 1atm) for 5 days at room temperature. After purification by silica gel chromatography, **34d** was obtained in 88% yield as a pale yellow oil (a single diastereomer). IR (neat) 1726, 1649 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (s, 3H), 1.13 (s, 3H), 1.41-1.51 (m, 3H), 1.66-1.69 (m, 1H), 2.08-2.11 (m, 1H), 2.54 (td, 1H, J = 12.2, 2.9 Hz), 3.03 (dt, 1H, J = 12.7, 2.0 Hz), 3.15 (d, 2H, J = 10.0 Hz), 3.34 (s, 3H), 3.78 (s, 3H), 4.83 (dt, 1H, J = 10.0, 4.8 Hz), 6.82-6.86 (m, 2H), 7.85-7.89 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 19.6, 23.9, 26.4, 31.4, 44.7, 46.6, 51.8, 55.4, 64.7, 72.0, 113.5, 122.6, 131.7, 163.4, 165.1, 177.6; HRMS(ESI) calcd for $C_{18}H_{26}NO_5$ 336.1811, found $(M+H)^+$ 336.1839.

***trans*-Dimethyl 2-(3-benzyloxypiperidin-2-yl)malonate (37). 15b** (0.196 mmol) was dissolved in 25% HBr/AcOH (3 mL) at 0 °C, and the reaction mixture was stirred for 1.5 h at room temperature. To the solution was added piperidine (2 mL), and the resulting mixture was basified with a saturated aqueous $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by silica gel chromatography to afford the desired compound (**37**) in <67% yield as a pale yellow oil. A little contamination was not separated by this procedure. IR (neat) 1739 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28-1.73 (m, 4H), 2.04 (s, 3H), 2.15-2.25 (m, 1H), 2.54 (td, 1H, J = 12.3, 2.9 Hz), 3.01 (dq, 1H, J = 12.8, 2.0

Hz), 3.21 (dd, 1H, J = 10.0, 4.1 Hz), 3.68 (d, 0.8H, J = 5.0 Hz), 3.70 (s, 0.2H), 3.75 (s, 3H), 3.77 (s, 3H), 4.66 (ddd, 1H, J = 10.1, 10.0, 4.5 Hz); ^{13}C NMR ($CDCl_3$) δ 21.0, 25.8, 30.6, 45.9, 52.1, 52.4, 52.6, 59.9, 71.7, 168.3, 168.9, 169.9; MS (APCI) *m/z* 273 (M^+).

***O*-Benzyl-*N*-benzyloxycarbonylfebrifugines (18a):** *In situ*-prepared silyl enolate method (Table 9, entry 1). To a suspension of **19**[6e] (0.220 mmol) and diisopropylethylamine (0.451 mmol) in CH_2Cl_2 (0.3 mL) was added a solution of trimethylsilyl triflate (0.435 mmol) in CH_2Cl_2 (0.5 ml) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 1 h and cooled again to 0 °C. To this mixture were added $Sc(OTf)_3$ (0.029 mmol) and then a solution of **4a** (0.145 mmo) in CH_2Cl_2 (0.3 mL). The mixture was warmed to room temperature and stirred for 14 h. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution and the mixture was extracted with CH_2Cl_2 (twice). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. After purification by silica gel chromatography, ***trans*-18a** (more polar) and ***cis*-18a** (less polar) were obtained in 33% and 38% yields, respectively. ***trans*-18a:** Pale yellow oil; IR (neat) 1730, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.40 (d, 1H, J = 10.5 Hz), 1.60-1.66 (m, 1H), 1.86-1.93 (m, 2H), 2.74-2.95 (m, 3H), 3.50 (s, 1H), 4.05 (br, 1H), 4.50-5.25 (m, 7H), 7.24-7.31 (m, 10H), 7.46-7.49 (m, 1H), 7.70-7.90 (m, 4H), 8.24-8.26 (m, 1H); ^{13}C NMR ($CDCl_3$), rotamers, δ 19.3, 24.1, 39.4, 40.7, 50.5, 50.6, 53.8, 67.2, 70.3, 73.5, 121.7, 126.5, 127.2, 127.4, 127.5, 127.6, 127.9, 128.2, 128.4, 134.3, 136.4, 138.2, 146.4, 148.1, 160.8, 200.0; HRMS(ESI) calcd for $C_{31}H_{32}N_3O_5$ 526.2342, found $(M+H)^+$ 526.2324. ***cis*-18a:** Pale yellow oil; IR (neat) 1732, 1684 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.25-1.92 (m, 7H), 2.78-2.89 (m, 2H), 3.51 (m, 1H), 4.24 (m, 1H), 4.51-4.66 (m, 2H), 5.07-5.86 (m 3H) 7.25-7.81 (m, 14H), 8.25-8.28 (m, 1H); ^{13}C NMR ($CDCl_3$), rotamers, δ 23.8, 25.2, 36.7, 38.8, 50.9, 53.7, 67.6, 71.1, 75.4, 121.9, 126.7, 127.6, 127.7, 127.9, 128.1, 128.5, 128.7, 134.4, 136.4, 137.9, 146.8, 146.9, 148.2, 200.9; HRMS(ESI) calcd for $C_{31}H_{32}N_3O_5$ 526.2342, found

$(M+H)^+$ 526.2391; Anal. Calcd for $C_{28}H_{29}NO_4$: C, 70.84; H, 5.94; N, 7.99. Found: C, 70.56; H, 6.25; N, 7.68.

***O*-Acetyl-*N*-benzyloxycarbonylfebrifugines (18b): *In situ* prepared tin(II) enolate method (Table 9, entry 7).** To a suspension of tin (II) triflate (0.367 mmol) and **19**[6e] (0.184 mmol) in CH_2Cl_2 (0.5 mL) was added a solution of diisopropylethylamine (0.377 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 1 h and then heated to reflux. To the refluxing solution were added $Sc(OTf)_3$ (0.018 mmol) and then a solution of **4b** (0.092 mmol) in CH_2Cl_2 (0.3 mL). The mixture was heated under reflux for 30 min and cooled to room temperature. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution and the mixture was extracted with CH_2Cl_2 (twice). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. After silica gel chromatography of the residue, ***trans*-18b** (more polar) and ***cis*-18b** (less polar) were obtained in 55% and 14% yields, respectively. ***trans*-18b:** Colorless powder; Mp 179-181 °C (n-hexane/AcOEt); IR (KBr) 1733, 1680 cm^{-1}; ^1H NMR ($CDCl_3$), rotamers, δ 1.25-2.10 (m, 8H), 2.85-2.98 (m, 3H), 4.09 (br, 2H), 4.70-4.98 (m, 2H), 5.16 (m, 2H), 7.26-7.80 (m, 9H), 8.26-8.28 (m, 1H); ^{13}C NMR ($CDCl_3$), rotamers, δ 21.1, 23.6, 25.2, 34.4, 39.1, 45.2, 53.6, 67.6, 69.1, 121.8, 126.8, 127.3, 127.6, 127.8, 128.0, 128.1, 128.5, 132.4, 133.8, 134.5, 136.1, 136.3, 170.4, 199.4; HRMS(ESI) calcd for $C_{26}H_{28}N_3O_6$ 478.1978, found $(M+H)^+$ 478.1983; Anal. Calcd for $C_{26}H_{27}N_3O_6$: C, 65.40; H, 5.70; N, 8.80. Found: C, 65.43; H, 5.79; N, 8.84. ***cis*-18b:** Colorless oil; IR (neat) 1738, 1684 cm^{-1}; ^1H NMR ($CDCl_3$), rotamers, δ 1.21-2.07 (m, 7H), 2.81-2.96 (m, 2.75H), 3.46 (s, 0.75 H), 3.68-3.72 (m, 0.25H), 3.96 (br, 1H), 4.61-5.70 (m, 5.25H), 7.28-7.33 (m, 5H), 7.48-7.97 (m, 4H), 8.25-8.27 (m, 1H); ^{13}C NMR ($CDCl_3$), rotamers, δ 18.3, 19.2, 20.9, 22.7, 23.1, 23.4, 24.5, 37.1, 38.7, 50.1, 50.6, 53.7, 58.2, 67.1, 67.4, 67.7, 68.0, 69.8, 75.2, 121.7, 126.6, 127.2, 127.5, 127.6, 127.8, 128.0, 128.1, 128.4, 128.5, 134.4, 136.1, 136.4, 146.6, 148.2, 160.9, 169.7, 200.5; HRMS(ESI) calcd for $C_{26}H_{28}N_3O_6$ 478.1978, found $(M+H)^+$ 478.1993.

(3*S*) *-trans*-18b was prepared according to the same method. **(3*S*) *-trans* -18b:** $[\alpha]_D^{25}$ –51.3 (c = 0.80, $CHCl_3$).

(*S*)-2-Benzyloxy-5-hydroxy-*N*-methoxy-*N*-methylpentanamide (39): To a solution of *N,O*-dimethylhyldroxyamine hydrogen chloride (0.42 mmol) in CH_2Cl_2 (1.5 mL) was added a solution of trimethylaluminum in n-hexane (0.98 M, 0.42 mL) at –15 °C. The mixture was warmed to room temperature, stirred for 1 h and then cooled to –15 °C. To the reaction mixture was added a solution of **38**[5,37] (0.14 mmol) in CH_2Cl_2 (1.5 ml) at –15 °C. The reaction mixture was warmed to room temperature and stirred for 24 h. To the resulting mixture was added a 15% aqueous potassium sodium tartrate solution. After being stirred for 1 h, the mixture was filtered through a celite pad. The filtrate was extracted with CH_2Cl_2 (twice). The combined organic layers were dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was dissolved in a mixture of aqueous 1N hydrogen chloride solution and THF (1/5, 3 mL) and the solution was stirred for 5 h at room temperature. After neutralization, the mixture was extracted with CH_2Cl_2 (twice). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by silica gel chromatography to afford **39** in 65% yield (2 steps) as a colorless oil. IR (neat) 3749, 1651 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.62-1.95 (m, 5H), 3.22 (s, 3H), 3.58 (s, 3H), 3.60-3.77 (m, 2H), 4.32 (s, 1H), 4.37 (d, 1H, *J* = 8.8 Hz), 4.71 (d, 1H, *J* = 8.8 Hz), 7.23-7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.8, 28.8, 32.3, 49.8, 61.3, 62.3, 71.5, 75.1, 127.9, 128.1, 137.5.

(*S*)-2-Benzyloxy-5-hydroxy-*N*-methoxy-*N*-methylpentanamide (40): Method A. To a solution of **39** (0.117 mmol), triphenylphosphine (0.467 mmol) and diphenylphosphoryl azide (0.233 mmol) in dry THF (0.8 mL) was successively added a solution of DEAD (0.467 mmol) in dry THF (0.3 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h at the same temperature. The solvent was evaporated *in vacuo*. The residue was purified by silica gel chromatography to afford the corresponding azide. This azide was dissolved in EtOH (5 mL) and treated with few drops of aqueous 1N HCl solution. Catalytic

hydrogenation was then performed (10% Pd-C, 10 atm) for 3 h. The catalyst was filtered off, and the solvent was evaporated *in vacuo*. The resulting residue was dissolved in a mixture of THF-water (2/1, 15 mL). To this solution were added $NaHCO_3$ (0.584 mmol) and then benzyloxycarbonyl chloride (0.467 mmol). The mixture was stirred for 1 h at 0 °C and extracted with CH_2Cl_2 (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by silica gel chromatography to afford **40** in 42 % yield (3 steps) as a colorless oil. **Method B.** To a solution of **41**[40] (0.78 mmol), *N*,*O*-dimethylhyldroxyamine hydrogen chloride (0.83 mmol) and triethylamine (0.82 mmol) in CH_2Cl_2 (2 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrogen chloride (0.94 mmol) at room temperature. The mixture was stirred for 3 h at the same temperature and the reaction was quenched with water. The mixture was extracted with CH_2Cl_2 (3 times). The combined organic layers were washed with an aqueous 1N HCl solution, water and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by silica gel chromatography to afford **40** in 89% yield as a colorless oil. $[\alpha]_D^{25}$ -29.8 (c = 0.76, $CHCl_3$); IR (neat) 3338, 1712, 1656 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19-1.79 (m, 4H), 3.24 (s, 3H), 3.69 (s, 3H), 3.71-4.92 (s, 2H), 5.08 (s, 2H), 7.23-7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.6, 31.6, 32.4, 40.6, 61.3, 66.6, 68.2, 128.1, 128.5, 136.6, 156.4, 174.6; HRMS(ESI) calcd for $C_{15}H_{22}N_2O_5Na$ 333.1427, found $(M+Na)^+$ 333.1438; Anal. Calcd for $C_{15}H_{22}N_2O$: C, 58.05; H, 7.15; N, 9.03. Found: C, 57.76; H, 7.11; N, 8.93.

(3*S*)-*N*-Benzyloxycarbonyl-2,3-dihydroxypiperidine ((3*S*)-26): To a solution of **40** (0.493 mmol) in dry ether (2 mL) was added $LiAlH_4$ (1.77 mmol) at 0 °C. The reaction mixture was stirred for 1.5 h at the same temperature and the reaction was quenched with water. The mixture was filtered through a Celite pad, and the filtrate was extracted with ethyl acetate (twice). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by silica gel chromatography to afford **(3*S*)-26** in 91% yield as a

colorless oil (a mixture of diastereomers). Diastereomer ratio was determined by ^{1}H NMR, and it was found that the ratio depended on work-up procedures. The ratio of *cis/trans* = 56/44 was obtained by this work-up procedure, and the ratio of *cis/trans* = 34/66 was obtained when the reaction was quenched by an aqueous potassium sodium tartrate solution. **(3*S*)-26** (*cis/trans* = 56/44)**:** Colorless oil; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.38-1.95 (m, 4H), 2.94-3.40 (m, 2H), 3.51-3.88 (m, 2H), 5.02-5.14 (m, 2H), 5.58 (d, 0.44H, J = 2.4 Hz), 5.71 (d, 0.56H, J = 3.3 Hz), 7.26-7.37 (m, 5H).

Febrifugine (1): (3*S*)-*trans*-18b (0.052 mmol) was dissolved in 25% HBr/AcOH (3 mL) at 0 °C, and the reaction mixture was stirred for 30 min at the same temperature. To this solution was added piperidine (2 mL), and the resulting mixture was basified with a saturated aqueous $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was dissolved in MeOH (5 mL). To the solution was added NaOMe (0.065 mmol) and the reaction mixture was stirred for 1 h at room temperature. The mixture was partitioned between water and CH_2Cl_2, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. After purification by silica gel chromatography, **1** was obtained in 25% yield (2 steps). This material was identified with the authentic sample previously synthesized in our laboratory.[5]

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Experimental

Data Collection

A colorless platelet crystal of $C_{32}H_{29}O_5N$ having approximate dimensions of 0.10 x 0.10 x 0.10 mm was mounted on a glass fiber. All measurements were made on a Rigaku RAXIS-RAPID Imaging Plate diffractometer with graphite monochromated Mo-Kα radiation.

Indexing was performed from 2 oscillations which were exposed for 1.7 minutes. The camera radius was 127.40 mm. Readout was performed in the 0.100 mm pixel mode.

Cell constants and an orientation matrix for data collection corresponded to a primitive triclinic cell with dimensions:

a = 10.3133(3) $\AA$	α = 101.164(3)°
b = 17.3740(6) $\AA$	β = 106.457(3)°
c = 7.9204(4) $\AA$	γ = 89.030(4)
V = 1334.23(10) $\AA^3$	

For Z = 2 and F.W. = 507.58, the calculated density is 1.26 g/cm^3. Based on a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be:

$P\bar{1}$ (#2)

The data were collected at a temperature of 23 ± 1°C to a maximum 2θ value of 54.9°. A total of 44 images, corresponding to 220.0 ° oscillation angles, were collected with 2 different goniometer settings. Exposure time was 1.00 minutes per degree. The camera radius was 127.40 mm. Readout was performed in the 0.100 mm pixel mode. Data were processed by the PROCESS-AUTO program package.

Data Reduction

Of the 7179 reflections which were collected, 5672 were unique (R_{int} = 0.027); equivalent reflections were merged.

The linear absorption coefficient, μ, for Mo-Kα radiation is 0.9 cm^{-1}. A symmetry-related absorption correction using the program ABSCOR[1] was applied which resulted in transmission factors ranging from 0.88 to 0.99. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement

The structure was solved by direct methods[2] and expanded using Fourier techniques[3]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. The final cycle of full-matrix least-squares refinement[4] was based on 5668 observed reflections (I > -10.00σ(I)) and 459 variable parameters

and converged (largest parameter shift was 0.43 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma(Fo^2 - Fc^2)/\Sigma Fo^2 = 0.081$$

$$R_w = \sqrt{\Sigma w(Fo^2 - Fc^2)^2/\Sigma w(Fo^2)^2} = 0.148$$

$$R1 = \Sigma||Fo| - |Fc||/\Sigma|Fo| = 0.059 \quad for \;\; I > 2.0\sigma(I) \;\; data$$

The standard deviation of an observation of unit weight[5] was 1.41. The weighting scheme was based on counting statistics and included a factor (p = 0.050) to downweight the intense reflections. Plots of $\Sigma w(Fo^2 - Fc^2)^2$ versus Fo^2, reflection order in data collection, sin θ/λ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.35 and -0.33 $e^-/\AA^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[6] . Anomalous dispersion effects were included in Fcalc[7]; the values for Δf' and Δf" were those of Creagh and McAuley[8]. The values for the mass attenuation coefficients are those of Creagh and Hubbel[9]. All calculations were performed using the teXsan[10] crystallographic software package of Molecular Structure Corporation.

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(4) Least-Squares:

Function minimized: $\Sigma w(Fo^2 - Fc^2)^2$

where w = $\frac{1}{\sigma^2(Fo^2)} = [\sigma_c^2(Fo^2) + (p(Max(Fo^2, 0) + 2Fc^2)/3)^2]^{-1}$

$\sigma_c(Fo^2)$ = e.s.d. based on counting statistics

p = p-factor

(5) Standard deviation of an observation of unit weight:

$$\sqrt{\Sigma w(|Fo| - |Fc|)^2/(No - Nv)}$$

where: No = number of observations

Nv = number of variables

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