Supporting Information

Design, Synthesis, And Binding Affinities Of Pyrrolinone-Based Somatostatin Mimetics.

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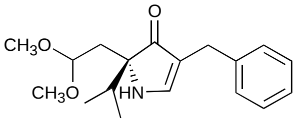
Experimental Section

Materials and Methods.

Reactions were carried out in oven or flame-dried glassware under an argon atmosphere, unless otherwise noted. All solvents were reagent grade. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were freshly distilled from sodium / benzophenone under argon. Reactions were magnetically stirred and monitored by thin layer chromotography (TLC) with 0.25 mm E. Merck pre-coated silica gel plates. Progress of the imine forming reactions can be monitored by NMR (C_6D_6). Flash chromatography was performed with silica gel 60 (particle size 0.040 – 0.062 mm) supplied by Silicycle and Sorbent Technologies. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. All melting points were obtained on a Thomas-Hoover apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer Model 283B spectrophotometer or a Jasco Model FT/IR-480 Plus spectrometer. Proton and carbon-13 NMR spectra were recorded on a Bruker AMX-500 spectrometer. Chemical shifts are reported relative to chloroform (δ 7.26), methylene chloride (δ 5.32), methanol (δ 3.31), or benzene (δ 7.15) for ^{1}H-NMR and chloroform (δ 77.0), methylene chloride (δ 53.8), methanol (δ 49.15), or benzene (δ 128.0) for ^{13}C NMR. Optical rotations were measured on a Perkin-Elmer model 241 polarimeter. High resolution mass spectra were measured at the University of Pennsylvania Mass Spectrometry Service Center on either a VG Micromass 70/70 H or VG ZAB-E spectrometer. Microanalyses were performed at the University of Pennsylvania.

Molecular Modeling Calculations were performed on a Silicon Graphics Iris 4D/440 VGX (Unix operating system). Minimization and Monte Carlo calculations were performed using the Batchmin accessory of MacroModel [Version 6.0 (Iris)]. The low energy conformation of **2** for overlay with L-363,301 was determined through a 20,000 step Monte Carlo conformational search using the MM2*[1] force field and the GB/SA solvation continuum ($CHCl_3$).[2]

Preparation of SRIF Mimetics 1-3



(–)-**5**

Monpyrrolinone (–)-**5.** A solution of (+)-**A** (3.86 g, 17.6 mmol) in benzene (176 mL) was treated with hydrocinnamaldehyde (2.64 mL, 19.26 mmol). Condensation was effected with concentration *in vacuo* followed by azeotropic dehydration with toluene (5 x 50 mL). The resultant oil was subjected to high vacuum for 1 h. After

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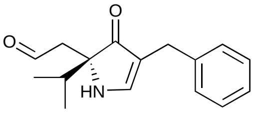
(1) (a) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still W. C. *J. Comput. Chem.* **1990,** *4*, 440-467. (b) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127-8134.

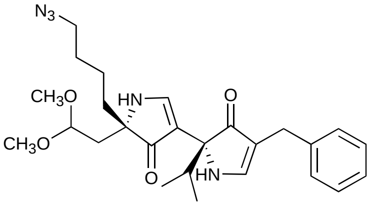
(2) Hasel, W.; Hendrickson, T. F.; Still, W. C. *Tetrahedron Comput. Method* **1988**, *1*, 103.

addition of THF (176 mL), 0.5 M KHMDS in toluene (140.8 mL, 70.41 mmol) was added dropwise rapidly at room temperature. The reaction mixture was stirred for another 15 min and quenched with 10% aqueous $NaHSO_4$ (100 mL). The layers were separated and the organic layer was then washed with saturated aqueous $NaHCO_3$ and brine (100 mL each), dried over anhydrous $MgSO_4$, concentrated *in vacuo*, and purified by flash chromatography using ethyl acetate-hexanes (50:50) as eluent to give (–)-**5** (4.50 g, 84% yield) as a pale yellow oil: $[\alpha]_D^{23}$ –100.00 (*c* 0.33, $CHCl_3$); IR ($CHCl_3$) 3431 (m), 3018 (s), 1758 (w), 1660 (s), 1586 (s), 1453 (m), 1422 (w), 1216 (s), 1120 (m), 1063 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (s, 1 H), 7.30-7.18 (m, 5 H), 5.28 (s, 1 H), 4.29 (apparent t, *J* = 5.5 Hz, 1 H), 3.47 (d, *J* = 15.7 Hz, 1 H), 3.43 (d, *J* = 15.7 Hz, 1 H), 3.27 (s, 3 H), 3.21 (s, 3 H), 2.08 (dd, *J* = 5.5, 14.4 Hz, 1 H), 1.91 (app sept., *J* = 6.8 Hz, 1 H), 1.89 (dd, *J* = 5.5, 14.4 Hz, 1 H), 0.89 (d, *J* = 6.8 Hz, 3 H), 0.88 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.4, 161.9, 141.0, 128.6, 128.4, 125.9, 115.0, 102.3, 70.0, 53.7, 53.4, 37.8, 33.8, 28.5, 17.0, 16.0; high resolution mass spectrum (ES, Na) *m/z* 326.1744 [$(M+Na)^+$; calcd for $C_{18}H_{25}NO_3Na$: 326.1732].



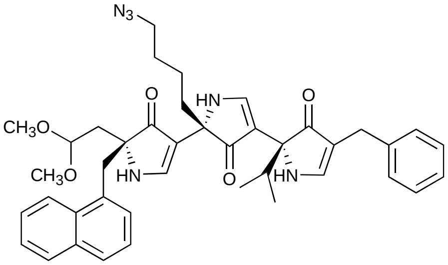
(–)-**S1**

Monpyrrolinone Aldehyde (–)-**S1.** To a solution of (–)-**5** (1.82 g, 6.00 mmol) in THF and H_2O (3:1, 60 mL) was added *p*-toluenesulfonic acid (2.40 g, 12.62 mmol). The mixture ws stirred under argon at 40°C for 5 h. The reaction was allowed to cool to room temperature and quenched by addition of saturated aqueous $NaHCO_3$ (20 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 20 mL), and the combined organic layers were washed with brine (40 mL). The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography using methanol-methylene chloride (3:97) as eluant to afford monopyrrolinone aldehyde (–)-**S1**, (1.46 g, 95% yield) as a pale yellow oil: $[\alpha]_D^{23}$ –12.55 (*c* 0.51, $CHCl_3$); IR ($CHCl_3$) 3444 (m), 3019, (s), 2970 (w), 1721 (s), 1662 (s), 1585 (s), 1494 (w), 1220 (s), 1143 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.48 (dd, *J* = 1.2, 3.6 Hz, 1 H), 7.60 (d, *J* = 3.7 Hz, 1 H), 7.26-7.16 (m, 5 H), 5.40 (s, 1 H), 3.48 (d, *J* = 15.6 Hz, 1 H), 3.45 (d, *J* = 15.6 Hz, 1 H), 2.75 (dd, *J* = 3.6, 15.4 Hz, 1 H), 2.71 (dd, *J* = 1.1, 15.4 Hz, 1 H), 2.07 (app sept., *J* = 6.8 Hz, 1 H), 0.91 (d, *J* = 6.8 Hz, 3 H), 0.82 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.1, 199.6, 161.7, 140.4, 128.5, 128.5, 126.1, 114.8, 70.1, 48.1, 33.9, 28.3, 17.0, 16.1; high resolution mass spectrum (ES, Na) *m/z* 258.1497 [$(M+H)^+$, calcd for $C_{16}H_{20}NO_2$: 258.1494].



(+)-**6**

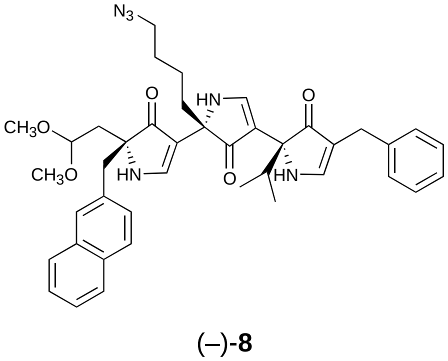
Bispyrrolinone (+)-**6.** To a solution of (–)-**B** (1.10 g, 4.01 mmol) in benzene (40 mL) was added (–)-**S1** (1.14 g, 4.43 mmol), and the solution was heated to 60°C for 2 h. The solution was concentrated *in vacuo*, followed by azeotropic dehydration with toluene (5 x 50 mL). The resultant oil was subjected to high vacuum for 1 h and then was dissolved in THF (40 mL). 0.5 M KHMDS in toluene (40.1 mL, 20.05 mmol) was added dropwise rapidly at room temperature. The reaction mixture was stirred for another 15 min, and quenched with 10% aqueous $NaHSO_4$ (100 mL). The organic layer was then washed with saturated aqueous $NaHCO_3$ and brine (100 mL each), dried over anhydrous $MgSO_4$, concentrated *in vacuo*, and purified by flash chromatography using ethyl acetate-hexanes (60:40-80:20) as eluent to give (+)-**6** (1.50 g, 79% yield) as a pale yellow foam: $[\alpha]_D^{23}$ +104.4 (*c* 0.525, $CHCl_3$); IR ($CHCl_3$) 3440 (w), 3010 (s), 2100 (s), 1730 (m), 1645 (s), 1580 (s), 1440 (m), 1205 (s), 1040 (s), 710 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.40 (d, *J* = 4.1 Hz, 1 H), 7.22 (m, 2 H), 7.13 (m, 3 H), 7.06 (s, 1 H), 6.06 (d, *J* = 3.5 Hz, 1 H), 4.37 (dd, *J* = 3.8, 7.6 Hz, 1 H), 3.45 (d, *J* = 15.6 Hz, 1 H), 3.38 (d, *J* = 15.7 Hz, 1 H), 3.24 (s 3 H), 3.20 (m, 2 H), 3.19 (s, 3 H), 2.01 (app sept, *J* = 6.8 Hz, 1 H), 1.82 (dd, *J* = 3.8, 14.4 Hz, 1 H), 1.68 (m, 3 H), 1.54 (m, 2 H), 1.26 (m, 1 H), 1.19 (m, 1 H), 1.19 (m, 1 H), 0.91 (d, *J* = 6.9 Hz, 3 H), 0.76 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.6, 203.1, 163.6, 162.2, 140.8, 128.4, 128.3, 125.8, 113.3, 109.2, 101.9, 70.9, 68.6, 54.2, 52.9, 51.2, 39.3, 37.8, 34.1, 29.0, 28.4, 20.6, 17.4, 16.4; high resolution mass spectrum (ESI, positive ion) *m/z* 504.2599 $[(M+Na)^+$, calcd for $C_{26}H_{35}N_5O_4Na$: 504.2587]



(–)-**7**

Trispyrrolinone (–)-**7.** To a solution of (+)-**6** (420 mg, 0.873 mmol) in THF (13 mL) was added freshly prepared, argon sparged aqueous 4 N HCl (4.4 mL) dropwise over 1 min. The reaction was heated at 50°C for 1 h. The reaction was quenched by pouring directly into sat. aqueous $NaHCO_3$ (20 mL). The aqueous layer was then extracted with ethyl acetate (3 x 10 mL). The organic layer was washed with sat. aqueous $NaHCO_3$ (20 mL), brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo* to provide the resulting aldehyde **6A** as a yellow oil.

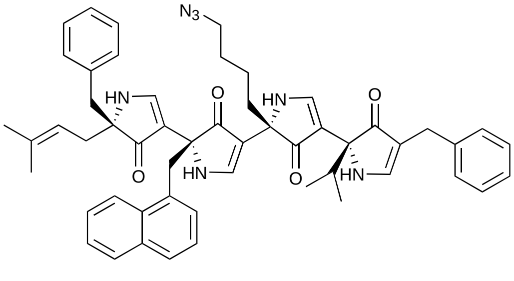
Amino ester (–)-**Cα** (249 mg, 0.786 mmol) was added to a solution of aldehyde **6A** (taken on directly from the previous reaction) in benzene (10 mL). The solution was concentrated *in vacuo*, and condensation was effected by azeotropic removal of water with toluene (30 x 10 mL). The resultant oil was dissolved in THF (20 mL) and added to a precooled (0°C) solution of 18-crown-6 (2.42 g, 9.17 mmol) in THF (15 mL) and 0.5 M KHMDS in toluene (17.5 mL, 8.73 mmol). The reaction was allowed to warm to room temp. After 5 h the reaction was quenched by addition of 10% aqueous $NaHSO_4$ (30 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 20 mL), and the combined organic layers were washed with sat. $NaHCO_3$ (30 mL), brine (30 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The resultant yellow oil was purified by flash chromatography using ethyl acetate : methylene chloride (35:65-50:50) as the eluent, to provide (–)-**7** (229.2 mg, 37% yield) as a yellow foam: : $[\alpha]^{23}_{D}$ –61.2 (*c* 0.15, $CHCl_3$); IR (neat) 3313 (s, br), 3058 (w), 2935 (s), 2098 (s), 1643 (s), 1569 (s), 1450 (m), 1261 (m), 1164 (s), 1056 (m), 960 (w), 783 (m), 736 (m) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 8.25 (d, *J* = 4.1 Hz, 1 H), 8.08 (d, *J* = 8.6 Hz, 1 H), 7.64 (d, *J* = 7.8 Hz, 1 H), 7.56 (d, *J* = 7.8 Hz, 1 H), 7.53 (d, *J* = 4.1 Hz, 1 H), 7.35 (ddd, 1.1, 6.7, 8.9 Hz, 1 H), 7.27 (ddd, *J* = 1.1, 6.7, 8.2 Hz, 1 H), 7.23-7.20 (m, 2 H), 7.18 (d, *J* = 7.8 Hz, 1 H), 7.16 (br s, 2 H), 7.12 (s, 2 H), 7.11 (s, br, 1 H), 7.04-7.00 (m, 2 H), 6.92 (d, *J* = 3.3 Hz, 1 H), 5.15 (d, *J* = 4.1 Hz, 1 H), 4.13 (dd, *J* = 4.4, 7.1 Hz, 1 H), 3.47 (d, *J* = 15.3 Hz, 1 H), 3.39 (d, *J* = 13.8 Hz, 1 H), 3.29 (d, *J* = 15.3 Hz, 1 H), 3.17 (d, *J* = 13.8 Hz, 1 H), 2.95 (s, 3 H), 2.94 (s, 3 H), 2.58 (ddd, *J* = 1.9, 7.0, 7.1 Hz, 1 H), 2.12 (app sept, *J* = 6.7 Hz, 1 H), 1.93 (dd, *J* = 7.1, 14.1 Hz, 1 H), 1.89 (dd, *J* = 4.5, 14.5 Hz, 1 H), 1.25 (ddd, *J* = 4.1, 11.9, 13.4 Hz, 1 H), 1.15 (ddd, *J* = 5.2, 11.5, 12.7 Hz, 1 H), 1.10 (m, 2 H), 1.02 (d, *J* = 6.7 Hz, 3 H), 1.0-0.92 (m, 1 H), 0.91 (d, *J* = 6.7 Hz, 3 H), 0.85-0.76 (m, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 203.3, 202.3, 202.1, 162.8, 162.7, 159.4, 141.5, 134.2, 133.3, 132.0, 129.0, 128.8, 128.7, 128.5, 128.3, 127.9, 126.0, 125.7, 125.1, 124.9, 113.9, 109.5, 108.3, 102.1, 70.7, 69.0, 67.8, 53.9, 52.7, 50.9, 39.2, 38.5, 38.0, 37.4, 28.92, 28.88, 20.7, 17.6, 16.7; high resolution mass spectrum (ESI, positive ion) *m/z* 725.3399 [$(M+Na)^+$, calcd for $C_{41}H_{46}N_6O_5Na$: 725.3427].



(–)-**8**

Trispyrrolinone (–)-**8.** To a solution of (+)-**6** (289 mg, 0.60 mmol) in THF (9 mL) was added freshly prepared, argon sparged aqueous 4 N HCl (3 mL) dropwise over 1 min. The reaction was heated at 45°C for 2.5 h. The reaction was quenched by pouring directly into sat. aqueous $NaHCO_3$ (20 mL). The aqueous layer was then extracted with ethyl acetate (3 x 10 mL). The organic layer was washed with brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo* to provide the resulting aldehyde **6A** as a yellow oil.

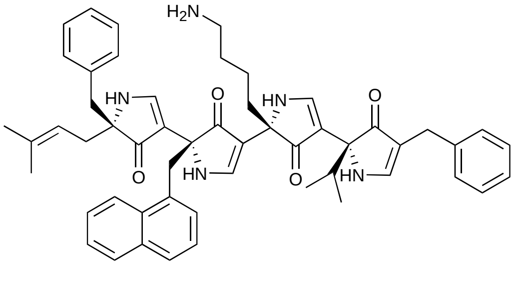
Amino ester (–)-**Cβ** (190 mg, 0.60 mmol) was added to a solution of aldehyde **6A** (taken on directly from the previous reaction) in benzene (20 mL). The solution was concentrated *in vacuo*, and condensation was effected by azeotropic removal of water with benzene (10 x 20 mL). The resultant oil was dissolved in THF (9 mL) and added to a precooled (0°C) solution of 18-crown-6 (1.22 g, 4.63 mmol) in THF (9 mL) and 0.5 M KHMDS in toluene (9.0 mL, 4.50 mmol). The reaction was stirred at 0°C for 2 h before the addition of additional 0.5 M KHMDS in toluene (9 mL, 4.5 mmol) followed by warming to room temp. After an additional 15 min, 10% aqueous $NaHSO_4$ (20 mL) was added, and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 20 mL), and the combined organic layers were washed with sat. $NaHCO_3$ (30 mL), brine (30 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The resultant yellow oil was purified by flash chromatography using neutral alumina (activity II) using ethyl acetate : methylene chloride (50:50-100:0) as the eluent, to provide (–)-**8** (149.8 mg, 35% yield) as a yellow foam: $[\alpha]_D^{23}$ –56.08 (*c* 0.79, $CHCl_3$); IR (neat) 3307 (m, br), 2928 (m), 2095 (s), 1640 (s), 1573 (s), 1452 (m), 1364 (w), 1252 (w), 1159 (m), 1053 (w), 955 (w), 700 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, *J* = 4.1 Hz, 1 H), 7.85 (d, *J* = 4.1 Hz, 1 H), 7.78 (m, 2 H), 7.69 (d, *J* = 8.2 Hz, 1 H), 7.61 (s, 1 H), 7.59 (d, *J* = 3.7 Hz, 1 H), 7.46 (m, 3 H), 7.30 (d, *J* = 4.0 Hz, 1 H), 7.30-7.22 (m, 3 H), 7.19-7.15 (m, 3 H), 7.05 (d, *J* = 3.3 Hz, 1 H), 6.40 (d, *J* = 3.3 Hz, 1 H), 4.48 (dd, *J* = 3.7, 7.8 Hz, 1 H), 3.46 (d, *J* = 15.6 Hz, 1 H), 3.33 (d, *J* = 15.6 Hz, 1 H), 3.29 (s, 3 H), 3.25 (s, 3 H), 3.15 (d, *J* = 13.0 Hz, 1 H), 3.09 (d, *J* = 13.0 Hz, 1 H), 2.77 (m, 2 H), 2.07 (dd, *J* = 4.1, 14.5 Hz, 1 H), 1.99 (app sept, *J* = 6.7 Hz, 1 H), 1.91 (dd, *J* = 7.4, 14.5 Hz, 1 H), 1.20-1.11 (m, 1 H), 1.08-0.93 (m, 2 H), 0.93-0.83 (m, 1 H), 0.88 (d, *J* = 6.7 Hz, 3 H), 0.76 (d, *J* = 6.7 Hz, 3 H), 0.73-0.63 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.4, 202.0, 201.8, 163.1, 162.5, 159.8, 140.7, 133.0, 132.3, 132.1, 128.8, 128.4, 128.4, 128.3, 128.3, 127.5, 127.5, 127.1, 126.0, 125.8, 113.2, 109.4, 108.0, 102.1, 70.7, 69.1, 67.6, 54.6, 53.0, 50.5, 41.0, 38.9, 379, 37.3, 28.3, 28.2, 20.0, 17.2, 16.3; high resolution mass spectrum (ESI, positive ion) *m/z* 725.3423 [$(M+Na)^+$, calcd for $C_{41}H_{46}N_6O_5Na$: 725.3427]



(–)-**S2**

Tetrapyrrolinone Azide (–)-**S2.** A solution of (–)-**7** (117.2 mg, 0.167 mmol) in THF (2.5 mL) was added dropwise to freshly prepared, argon sparged aqueous 4 N HCl (0.8 mL) over 1 min. The reaction was heated at 45°C for 2 h. The reaction was quenched by pouring directly into sat. aqueous $NaHCO_3$ (5 mL). The aqueous layer was then extracted with ethyl acetate (3 x 10 mL). The organic layer was washed with brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo* to provide the resulting aldehyde **7A** as a yellow oil.

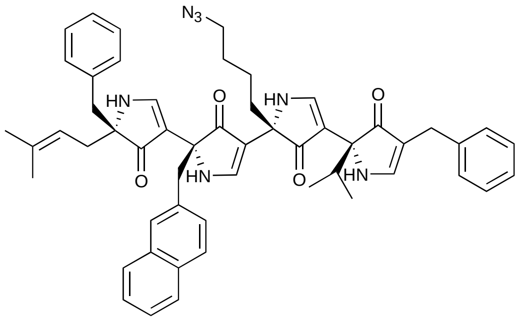
Amino ester (–)-**D** (34 mg, 0.139 mmol) was added to a solution of aldehyde **7A** (taken on directly from the previous reaction) in benzene (10 mL) and stirred at room temp. for 30 min. The solution was concentrated *in vacuo*, and condensation was effected by azeotropic removal of water with toluene (7 x 10 mL) and subjected to high vacuum overnight. The resultant oil was dissolved in THF (5 mL) and added to solution of 18-crown-6 (0.441 g, 1.67 mmol) in THF (5 mL) and 0.5 M KHMDS in toluene (3.34 mL, 1.67 mmol). After 4.5 h the reaction was quenched by addition of 10% aqueous $NaHSO_4$ (10 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 20 mL), and the combined organic layers were washed with sat. $NaHCO_3$ (30 mL), brine (30 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The resultant yellow foam was purified by flash chromatography using methanol : methylene chloride (2:98-5:95) as the eluent, to provide the tetrapyrrolinone azide **(–)-S2** (41.6 mg, 29% yield) as a yellow foam: $[\alpha]^{23}_{D}$ –22.69 (*c* 0.26, $CHCl_3$); IR (neat) 3282 (s, br), 2932 (m), 2095 (s), 1634 (s), 1565 (s), 1454 (m), 1159 (s), 938 (w), 837 (w), 783 (m), 700 (m) cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 8.29 (d, *J* = 4.1 Hz, 1 H), 8.25 (d, *J* = 8.9 Hz, 1 H), 8.00 (d, *J* = 4.1 Hz, 1 H), 7.82 (d, *J* = 8.2 Hz, 1 H), 7.73 (d, *J* = 8.2 Hz, 1 H), 7.62 (d, *J* = 4.1 Hz, 1 H), 7.60 (d, *J* = 3.0 Hz, 1 H), 7.57 (ddd, 1.1, 6.7, 7.8 Hz, 1 H), 7.48 (dd, *J* = 7.4, 7.4 Hz, 1 H), 7.31 (dd, *J* = 7.4, 7.4 Hz, 1 H), 7.27-7.17 (m, 10 H), 7.14-7.08 (m, 4 H), 6.04 (s, br, 1 H), 4.92 (app t, *J* = 7.1 Hz, 1 H), 3.46 (d, *J* = 14.1 Hz, 1 H), 3.39 (d, *J* = 15.6 Hz, 1 H), 3.23 (d, *J* = 15.6 Hz, 1 H), 3.10 (d, *J* = 7.1 Hz, 1 H), 3.08 (d, *J* = 7.1 Hz, 1 H), 2.94 (d, *J* = 14.1 Hz, 1 H), 2.88 (d, *J* = 15.6 Hz, 1 H), 2.85 (d, *J* = 13.7 Hz, 1 H), 2.30 (m 2 H), 1.93 (app sept, *J* = 6.7 Hz, 1 H), 1.54 (s, 3 H), 1.51 (s, 3 H), 1.38-1.22 (m, 3 H), 1.05-0.95 (m, 2 H), 0.86 (d, *J* = 6.7 Hz, 3 H), 0.84-0.74 (m, 1 H), 0.72 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 203.8, 203.3, 202.0, 201.2, 163.8, 162.1, 160.3, 160.1, 141.3, 136.5, 135.7, 133.9, 133.4, 132.0, 130.5, 128.8, 128.7, 128.6, 128.6, 128.3, 127.8, 127.2, 126.1, 125.6, 125.2, 125.1, 117.1, 113.0, 112.9, 109.5, 108.6, 108.1, 71.6, 70.9, 68.5, 67.8, 51.4, 41.4, 39.8, 38.3, 37.7, 34.8, 29.0, 28.7, 26.0, 20.6, 18.2, 17.5, 16.5; high resolution mass spectrum (ESI, positive ion) *m/z* 876.4276 [$(M+Na)^+$, calcd for $C_{53}H_{55}N_7O_4Na$: 876.4213]



(–)-**1**

Tetrapyrrolinone SRIF Mimetic (–)-**1.** To a solution of azide (–)-**S2** (41.6 mg, 0.0487 mmol) in THF (1 mL), was added PPh_3 (64 mg, 0.244 mmol) followed by H_2O (50 µL). The resulting solution was heated at 60°C for 2 h, then concentrated *in vacuo*, and purified by flash chromatography using methanol : methylene chloride (5:95-

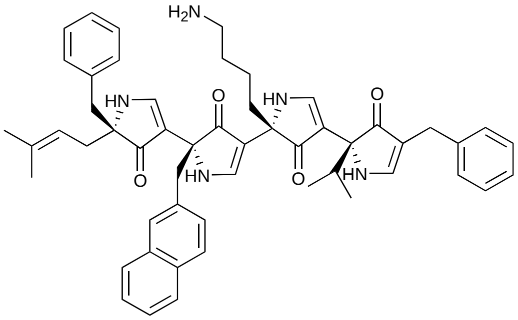
50:50) as eluent, to provide (–)-**1** (24.5 mg, 61% yield) as a colorless foam: $[\alpha]^{23}_{D}$ –28.33 (*c* 0.3, CH_2Cl_2); IR (neat) 3296 (s, br), 2929 (m), 1634 (s), 1574 (s), 1494 (w), 1362 (w), 1160 (s), 942(w), 839 (w), 783 (m) cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 8.26 (d, *J* = 3.2 Hz, 1 H), 8.23 (d, *J* = 8.5 Hz, 1 H), 7.95 (d, *J* = 4.1 Hz, 1 H), 7.80 (d, *J* = 7.6 Hz, 1 H), 7.70 (d, *J* = 8.1 Hz, 1 H), 7.58-7.54 (m, 3 H), 7.45 (ddd, *J* = 0.8, 7.9, 7.9 Hz, 1 H), 7.29-7.24 (m, 3 H), 7.23-7.16 (m, 6 H), 7.13-7.09 (m, 4 H), 7.04 (d, *J* = 3.6 Hz, 1 H), 5.69 (s, br, 1 H), 4.89 (m, 1 H), 3.46 (d, *J* = 13.9 Hz, 1 H), 3.38 (d, *J* = 15.6 Hz, 1 H), 3.21 (d, *J* = 15.6 Hz, 1 H), 2.90 (d, *J* = 13.9 Hz, 1 H), 2.86 (d, *J* = 13.7 Hz, 1 H), 2.82 (d, *J* = 13.7 Hz, 1 H), 2.47 (t, *J* = 6.7 Hz, 1 H), 2.28-2.26 (m, 1 H), 1.89 (app sept, *J* = 6.7 Hz, 1 H), 1.53 (s, 3 H), 1.50 (s, 3 H), 1.50-1.30 (br, 2 H), 1.33-1.26 (m, 2 H), 1.2-1.14 (m, 2 H), 1.05-0.95 (m, 3 H), 0.83 (d, *J* = 6.9 Hz, 3 H), 0.78-0.75 (m, 1 H), 0.68 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 203.8, 203.3, 202.1, 201.3, 163.7, 162.0, 160.3, 160.1, 141.4, 136.5, 135.8, 133.9, 133.5, 132.0, 130.5, 128.8, 128.7, 128.6, 128.5, 128.3, 127.8, 127.2, 126.1, 126.0, 125.6, 125.2, 125.0, 117.1, 113.0, 109.7, 108.9, 108.0, 71.5, 70.9, 68.4, 68.1, 42.1, 41.4, 39.8, 38.3, 38.1, 34.7, 28.7, 28.7, 26.0, 20.7, 18.2, 17.5, 16.5; high resolution mass spectrum (ESI, positive ion) *m/z* 828.4483 $[(M+H)^+$, calcd for $C_{53}H_{58}N_5O_4$: 828.4489]



(+)-**S3**

Tetrapyrrolinone Azide (+)-**S3.** To a solution of (–)-**8** (134 mg, 0.191 mmol) in THF (3 mL) was added freshly prepared, argon sparged aqueous 4 N HCl (1 mL) dropwise over 1 min. The reaction was heated at 45°C for 4 h. The reaction was quenched by pouring directly into sat. aqueous $NaHCO_3$ (50 mL). The aqueous layer was then extracted with ethyl acetate (3 x 10 mL). The organic layer was washed brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo* to provide the resulting aldehyde **8A** as a yellow oil.

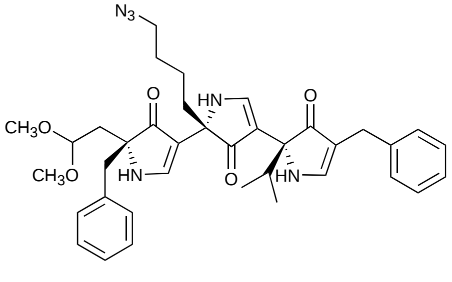
Amino ester (–)-**D** (45 mg, 0.191 mmol) was added to a solution of aldehyde **8A** (taken on directly from the previous reaction) in benzene (10 mL) and stirred at room temp. for 30 min. The solution was concentrated *in vacuo*, and condensation was effected by azeotropic removal of water with benzene (8 x 20 mL) and subjected to high vacuum for 30 min. The resultant oil was dissolved in THF (3 mL) and added to a precooled (0°C) solution of 18-crown-6 (0.5 g, 1.91 mmol) in THF (4 mL) and 0.5 M KHMDS in toluene (3.82 mL, 1.91 mmol). The reaction was allowed to warm to room temp. After 1 h additional KHMDS was added (3.81 mL, 1.91 mmol) followed 15 min later by the quenching the reaction 10% aqueous $NaHSO_4$ (10 mL). After separating the layers, the aqueous layer was extracted with ethyl acetate (3 x 20 mL), and the combined organic layers were washed with sat. $NaHCO_3$ (30 mL), brine (30 mL), dried over $MgSO_4$, and concentrated *in vacuo.* The resultant yellow foam was purified by flash chromatography on NEt_3 buffered silica gel using ethyl acetate : methylene chloride (50:50-100:0) as the eluent, to provide the tetrapyrrolinone azide (+)-**S3** (62.6 mg, 38% yield) as a pale yellow foam: $[\alpha]^{23}_{D}$ +13.89 (*c* 0.18, $CHCl_3$); IR (neat) 3286 (s, br), 2932 (m), 2094 (s), 1634 (s), 1563 (s), 1453 (s), 1365 (w), 1250 (w), 1158 (s), 938 (w), 842 (w), 746 (w), 700 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, *J* = 4.1 Hz, 1 H), 8.01 (d, *J* = 4.1 Hz, 1 H), 7.78 (d, J = 4.1 Hz, 1 H), 7.76-7.71 (m, 2 H), 7.64 (d, *J* = 8.2 Hz, 1 H), 7.55 (d, *J* = 3.4 Hz, 1 H), 7.50 (s, 1 H), 7.44-7.40 (m, 3 H), 7.25-7.14 (m, 10 H), 7.13-7.10 (m, 2 H), 7.06 (d, *J* = 3.7 Hz, 1 H), 5.63 (d, *J* = 4.5 Hz, 1 H), 4.95 (app t, *J* = 7.4 Hz, 1 H), 3.43 (d, *J* = 15.6 Hz, 1 H), 3.24 (d, *J* = 15.6 Hz, 1 H), 3.04 (d, *J* = 11.5 Hz, 1 H), 3.01 (d, *J* = 11.5 Hz, 1 H), 2.89 (d, *J* = 13.4 Hz, 1 H), 2.74-2.64 (m, 2 H), 2.61 (d, *J* = 13.4 Hz, 1 H), 2.32 (app d, 7.8 Hz, 2 H), 1.91 (app sept, *J* = 6.7 Hz, 1 H), 1.57 (s, 3 H), 1.55 (s, 3 H), 0.97-0.91 (m, 1 H), 0.90-0.84 (m, 2 H), 0.82 (d, *J* = 6.7 Hz, 3 H), 0.80-0.70 (m, 2 H), 0.69 (d, *J* = 6.7 Hz, 3 H), 0.60-0.54 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.0, 203.0, 201.7, 200.9, 163.6, 162.2, 160.3, 159.9, 140.6, 136.6, 134.9, 133.0, 132.4, 132.4, 130.4, 128.9, 128.7, 128.5, 128.3, 128.1, 127.6, 127.5, 127.1, 127.0, 126.0, 125.9, 125.7, 116.7, 113.3, 109.3, 108.8, 108.0, 71.4, 70.9, 68.1, 67.6, 50.6, 44.0, 41.2, 38.4, 37.5, 34.5, 28.4, 28.2, 25.9, 20.0, 18.3, 17.3, 16.3; high resolution mass spectrum (ESI, positive ion) *m/z* 876.4197 [$(M+Na)^+$, calcd for $C_{53}H_{55}N_7O_4Na$: 876.4213]



(+)-**2**

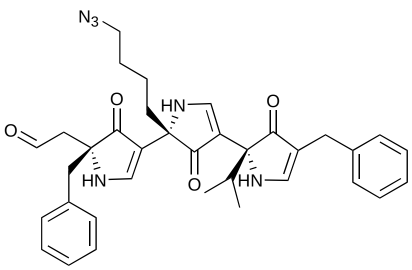
Tetrapyrrolinone SRIF Mimetic (+)-**2.** To a solution of azide (+)-**S3** (13 mg, 0.0152 mmol) in THF (0.3 mL), was added PPh_3 (20 mg, 0.0761 mmol) followed by H_2O (15 µL). The resulting solution was heated at 55°C for 3 h, then concentrated *in vacuo*. The resultant solid was dissolved in acetonitrile (5 mL) and washed with heptane (3 x 5 mL) to remove the excess PPh_3. The acetonitrile layer was concentrated *in vacuo* and purified by flash chromatography using methanol : methylene chloride (10:90-30:70) as eluent, to provide (+)-**2** (8.5 mg, 67% yield) as a tan foam: $[\alpha]^{23}_{D}$ +51.53 (*c* 0.59, CH_2Cl_2); IR (neat) 3298 (m, br), 2925 (m), 1635 (s), 1568 (m), 1452 (m), 1159 (s), 734 (w), 700 (m) cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 8.24 (d, *J* = 3.9 Hz, 1 H), 7.96 (d, *J* = 4.1 Hz, 1 H), 7.75 (m, 3 H), 7.66 (d, *J* = 8.4 Hz, 1 H), 7.58 (d, *J* = 3.7 Hz, 1 H), 7.42 (m, 2 H), 7.33 (d, *J* = 3.9 Hz, 1 H), 7.27-7.16 (m, 9 H), 7.11 (m, 2 H), 7.03 (d, *J* = 3.6 Hz, 1 H), 5.66 (d, *J* = 3.9 Hz, 1 H), 4.92 (t, *J* = 6.1 Hz, 1 H), 3.39 (d, *J* = 15.6 Hz, 1 H), 3.23 (d, *J* = 15.6 Hz, 1 H), 3.01 (dd, *J* = 12.7, 13.1 Hz, 2 H), 2.87 (d, *J* = 13.5 Hz, 1 H), 2.64 (d, *J* = 13.5 Hz, 1 H), 2.29 (d, 7.75 Hz, 2 H), 2.2 (m, 2 H), 1.88 (app sept, *J* = 6.7 Hz, 1 H), 1.54 (s, 3 H), 1.54 (s, 3 H), 1.50-1.20 (br, 2 H), 1.19 (m, 2 H), 0.92-0.70 (m, 4 H), 0.82 (d, *J* = 6.9 Hz, 3 H), 0.68 (d, *J* = 6.6

Hz, 3 H), 0.65-0.58 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.0, 203.0, 201.9, 200.9, 163.6, 162.0, 160.3, 159.9, 140.6, 136.6, 134.9, 133.0, 134.4, 132.3, 130.0, 128.9, 128.7, 128.5 128.3, 128.1, 127.7, 127.5, 127.1, 127.0, 125.8, 125.8, 125.5, 116.7, 113.3, 109.3, 109.0, 107.9, 71.4, 70.9, 68.0, 67.9, 44.0, 41.5, 41.2, 38.3, 37.9, 34.4, 33.3, 28.4, 25.9, 20.1, 18.2, 17.3, 16.3; high resolution mass spectrum (ESI, positive ion) *m/z* 828.4461 [(M+H)$^+$, calcd for $C_{53}H_{58}N_5O_4$: 828.4489]



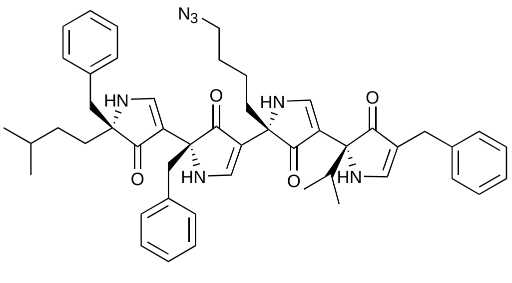
(–)-**9**

Trispyrrolinone (–)-**9.** A solution of bispyrrolinone aldehyde **6A** (769 mg, 1.766 mmol) and amino ester (–)-**C** (450 mg, 1.682 mmol) in benzene (20 mL) was stirred at 40 °C for 2 h, and then the solvent was evaporated *in vacuo*. The residue was azeotropically dehydrated with benzene (6x10 mL) and then stored for 1 h under high vacuum. The resulting crude imine was dissolved in THF (20 mL) and treated at room temperature with a 0.5 M solution of KHMDS in toluene (21.20 mL, 10.59 mmol). The reaction mixture was stirred for additional 20 min, then quenched with saturated aqueous NH_4Cl (5 mL) and diluted with EtOAc (50 mL). The organic layer was separated, washed with 10% aqueous $NaHSO_4$, 10% aqueous $NaHCO_3$, and brine (20 mL each), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography using ethyl acetate-hexanes (gradient from 1:1 to 4:1) as eluant to afford trispyrrolinone (–)-**9** as a colorless oil (210 mg, 19% yield). $[\alpha]^{23}_{D}$ –79.7 (*c* 0.36, $CHCl_3$); IR (neat) 3291 (s), 3064 (w), 2930 (s), 2872 (w), 2094 (m), 1636 (s), 1569 (s), 1453 (m), 1159 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, *J* = 4.0 Hz, 1 H), 7.86 (d, *J* = 4.0 Hz, 1 H), 7.59 (d, *J* = 3.7 Hz, 1 H), 7.10-7.30 (11 H), 7.01 (d, *J* = 4.0 Hz, 1 H), 5.99 (d, *J* = 4.0 Hz, 1 H), 4.40 (dd, *J* = 7.6, 3.8 Hz, 1 H), 3.44 (d, *J* = 15.7 Hz, 1 H), 3.32 (d, *J* = 15.7 Hz, 1 H), 3.26 (s, 3 H), 3.21 (s, 3 H), 3.13 (app t, *J* = 7.1 Hz, 2 H), 2.94 (d, *J* = 13.3 Hz, 1 H), 2.89 (d, *J* = 13.3 Hz, 1 H), 1.95-2.05 (2 H), 1.82 (dd, *J* = 14.5, 7.6 Hz, 1 H), 1.45-1.35 (3 H), 1.22 (m, 1 H), 1.08 (m, 1 H), 0.95 (m, 1 H), 0.89 (d, *J* = 6.9 Hz, 3 H), 0.75 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.6, 202.2, 201.9, 163.2, 162.6, 159.8, 140.8, 134.7, 130.2, 128.5, 128.3, 128.0, 127.0, 125.9, 113.5, 109.6, 108.3, 102.1, 70.8, 68.8, 67.8, 64.7, 53.1, 51.1, 40.9, 38.7, 38.0, 37.5, 28.7, 28.5, 20.4, 17.4, 16.4; high resolution mass spectrum (ESI positive ion) *m/z* 675.3289 [(M+Na)$^+$; calcd for $C_{37}H_{44}O_5N_6Na$: 675.3270].



(–)-**S4**

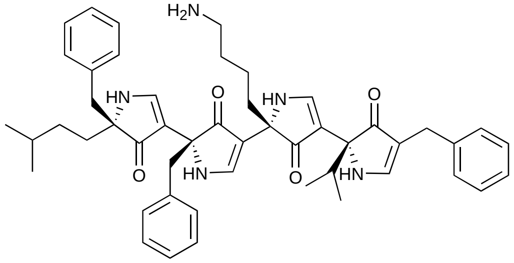
Trispyrrolinone (–)-**S4.** To a solution of dimethyl acetal (–)-**9** (200 mg, 0.307 mmol) in THF (23 mL) was added aqueous 4N HCl (7 mL), and the reaction mixture was stirred at room temperature for 8 h. EtOAc (40 mL) was added, followed by solid $NaHCO_3$ (2.5 g). The organic layer was separated and the aqueous phase was further extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with 10% aqueous $NaHCO_3$ and brine (10 mL each), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 2% methanol in dichloromethane as eluant to afford trispyrrolinone (–)-**S4** as a colorless oil (166 mg, 89% yield). $[\alpha]^{23}_{D}$ –69.8 (*c* 0.48, $CHCl_3$); IR (neat) 3298 (s), 3028 (w), 2926 (s), 2854 (m), 2095 (s), 1723 (s), 1644 (s), 1568 (s), 1495 (w), 1455 (m), 1160 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.66 (d, *J* = 1.5 Hz, 1 H), 8.39 (d, *J* = 4.1 Hz, 1 H), 7.85 (d, *J* = 4.1 Hz, 1 H), 7.61 (d, *J* = 3.7 Hz, 1 H), 7.26-7.10 (11 H), 6.98 (d, *J* = 3.6 Hz, 1 H), 6.31 (d, *J* = 4.0 Hz, 1 H), 3.46 (d, *J* = 15.7 Hz, 1 H), 3.36 (d, *J* = 15.7 Hz, 1 H), 3.14 (d, *J* = 7.0 Hz, 2 H), 3.10 (d, *J* = 13.4 Hz, 1 H), 2.96 (d, *J* = 13.4 Hz, 1 H), 2.96 (dd, *J* = 18.0, 1.5 Hz, 1 H), 2.54 (d, *J* = 18.0 Hz, 1 H), 1.99 (app sept, *J* = 6.7 Hz, 1 H), 1.48 (td, *J* = 13.0, 4.1 Hz, 1 H), 1.42 (quintet, *J* = 7.3 Hz, 2 H), 1.25 (td, *J* = 13.3, 4.7 Hz, 1 H), 1.23 (m, 1 H), 0.94 (m, 1 H), 0.90 (d, *J* = 6.9 Hz, 3 H), 0.75 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.6, 201.7, 201.1, 199.7, 163.3, 162.5, 160.9, 140.9, 134.1, 130.1, 128.5, 128.3, 128.2, 127.3, 125.9, 113.4, 108.9, 108.2, 70.7, 68.0, 67.5, 51.1, 48.1, 40.9, 38.0, 37.6, 28.7, 28.4, 20.4, 17.3, 16.4; high resolution mass spectrum (ESI positive ion) *m/z* 629.2858 [$(M+Na)^+$; calcd for $C_{33}H_{38}O_4N_6Na$: 629.2852].



(+)-**S5**

Tetrapyrrolinone (+)-**S5.** A solution of aldehyde (–)-**S4** (83 mg, 0.137 mmol) and aminoester (+)-**10** (31 mg, 0.124 mmol) in benzene (5 mL) was stirred at 40 °C for 2 h. The solvent was evaporated *in vacuo*. The residue was azeotropically dehydrated with benzene (7 x 1 mL) and then stored for 1 h under high vacuum. The resulting crude imine was dissolved in THF (10 mL) and treated at room temperature with a 0.5 M solution of

KHMDS in toluene (1.74 mL, 0.870 mmol). The reaction mixture was stirred for additional 15 min, then quenched with saturated aqueous NH_4Cl (1 mL) and diluted with EtOAc (20 mL). The organic layer was separated, washed with 10% aqueous $NaHSO_4$, 10% aqueous $NaHCO_3$, and brine (5 mL each), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 2% methanol in dichloromethane as eluant to afford tetrapyrrolinone (+)-**S5** as a white solid (38 mg, 38% yield). m.p. 204-205 °C, $[\alpha]^{23}_{D}$ +10.6 (*c* 0.44, $CHCl_3$); IR (neat) 3296 (s), 3062 (w), 3028 (w), 2955 (m), 2870 (w), 2095 (s), 1638 (s), 1568 (s), 1495 (w), 1454 (m), 1435 (m), 1158 (s) cm^{-1}; ^1H NMR (500 MHz, MeOH-d_4) δ 8.07 (s, 1 H), 7.78 (s, 1 H), 7.77 (s, 1 H), 7.56 (s, 1 H), 7.10-6.90 (15 H), 3.31 (d, *J* = 15.7 Hz, 1 H), 3.22 (d, *J* = 15.7 Hz, 1 H), 3.06 (t, *J* = 7.6 Hz, 2 H), 2.97 (d, *J* = 13.4 Hz, 1 H), 2.89 (d, *J* = 13.3 Hz, 1 H), 2.78 (d, *J* = 13.3 Hz, 1 H), 2.28 (d, *J* = 13.4 Hz, 1 H), 2.07 (app sept, *J* = 6.9 Hz, 1 H), 1.70-1.50 (3 H), 1.35-1.20 (3 H), 1.05-0.80 (5 H), 0.78 (d, *J* = 6.9 Hz, 3 H), 0.70 (d, *J* = 7.0 Hz, 3 H), 0.68 (d, *J* = 7.0 Hz, 3 H), 0.63 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.1, 203.1, 201.8, 200.9, 163.8, 162.3, 160.1, 160.1, 140.5, 134.9, 134.8, 130.6, 130.4, 130.0, 128.5, 128.3, 128.1, 127.7, 127.1, 125.9, 113.2, 108.8, 108.5, 108.0, 71.2, 71.0, 67.9, 67.7, 51.0, 44.0, 42.2, 38.3, 37.7, 33.8, 32.0, 28.7, 28.5, 28.1, 22.5, 22.3, 20.3, 17.3, 16.3; high resolution mass spectrum (ESI positive ion) *m/z* 828.4225 [$(M+Na)^+$; calcd for $C_{49}H_{55}O_4N_7Na$: 828.4213].

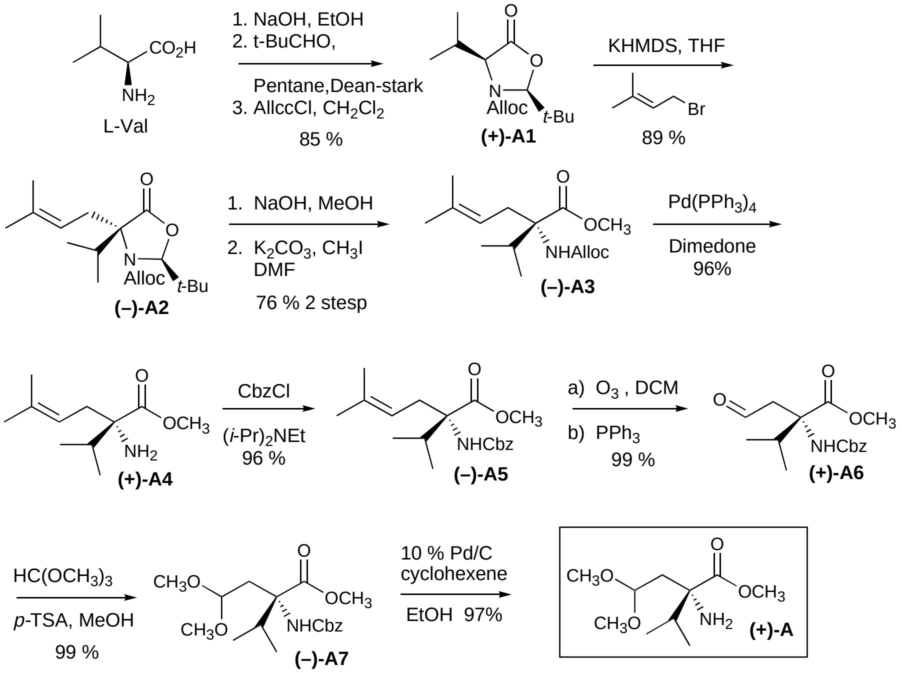


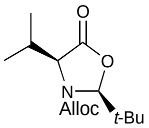
(+)-**3**

Tetrapyrrolinone (+)-**3.** To a solution of azide (+)-**S5** (38 mg, 0.047 mmol) in methanol (5 mL) was added 10% wt Pd on carbon (13 mg). The mixtured was briefly evacuated and opened to argon three times, then evacuated again and opened to hydrogen (1atm). After stirring at room temperature for 5 h, the reaction mixture was filtered through Celite, and concentrated *in vacuo*. The crude residue was subjected to preparative TLC (30% methanol in dichloromethane) to provide pure tetrapyrrolinone (+)-**3** as a white solid (21 mg, 57% yield). m.p. 173-174 °C, $[\alpha]^{23}_{D}$ +28.5 (*c* 0.26, MeOH); IR (neat) 3290 (s), 2956 (s), 2666 (m), 1635 (s), 1568 (s), 1455 (m), 1162 (m) cm^{-1}; ^1H NMR (500 MHz, MeOH-d_4) δ 7.99 (s, 1 H), 7.81 (s, 1 H), 7.77 (s, 1 H), 7.56 (s, 1 H), 7.10-6.90 (15 H), 3.31 (d, *J* = 15.7 Hz, 1 H), 3.23 (d, *J* = 15.7 Hz, 1 H), 3.00 (d, *J* = 13.4 Hz, 1 H), 2.89 (d, *J* = 13.3 Hz, 1 H), 2.78 (d, *J* = 13.3 Hz, 1 H), 2.57 (m, 2 H), 2.28 (d, *J* = 13.4 Hz, 1 H), 2.23 (app sept, *J* = 6.8 Hz, 1 H), 1.70-1.50 (3 H), 1.25-1.35 (3 H), 1.05 (m, 1 H), 1.00-0.65 (4 H), 0.77 (d, *J* = 6.8 Hz, 3 H), 0.70 (d, *J* = 6.7 Hz, 3 H), 0.69 (d, *J* = 6.7 Hz, 3 H), 0.62 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.9, 204.4, 202.2, 201.5, 166.7, 164.1, 163.0, 162.1, 142.4, 136.5, 136.4, 131.5, 131.2, 129.3, 129.2, 128.8, 128.6, 127.8, 127.7, 126.9, 111.8, 109.3, 109.0, 108.0, 73.3, 72.8, 69.6, 69.3, 43.7, 42.9, 40.6, 36.4, 35.7, 35.5, 33.0, 29.4, 29.3, 29.0, 23.0, 22.8, 21.1, 18.1, 16.5; high resolution mass spectrum (ESI positive ion) *m/z* 7804488 [$(M+H)^+$; calcd for $C_{49}H_{58}O_4N_5Na$: 780.4470].

Synthesis of Building Blocks

Amino Ester Building Block (+)-**A.**

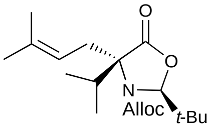




(+)-**A1**

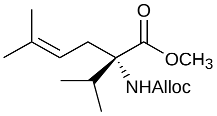
Oxazolidinone (+)-**A1.** To a mixture of L-valine (50.0 g, 427.0 mmol) in absolute ethanol (800 mL) was added a solution of NaOH (17.1 g, 380.0 mmol) in water (60 mL). The mixture was stirred at room temperature for 2 h over which time it became homogenous. The solution was concentrated *in vacuo* to give a solid mass, and *n*-pentane (1.2 L) was added followed by pivalaldehyde (69.5 mL, 640 mmol). The flask was fitted with a Dean-Stark trap, and the mixture was heated to gentle reflux at 45 °C for 72 h. The heat was then removed and the mixture was concentrated *in vacuo* to provide a white solid that was azeotropically dried with toluene (800 mL) and stored under high vacuum for 16 h.

A suspension of the dried salt in CH_2Cl_2 (1 L) was cooled to 0 °C, allyl chloroformate (67.9 mL, 640.0 mmol) was added, and the slurry mixture was stirred at 5 °C for 16 days. Water (600 mL) and a catalytic quantity of dimethylaminopyridine (DMAP) were then added to catalyze the hydrolysis of the excess chloroformate while the mixture was still cold. The biphasic system that resulted was warmed to room temperature and stirred for 16 h. The mixture was then extracted with EtOAc (2 x 600 mL), and the combined organic phases were washed with 10% aqueous $NaHSO_4$, saturated aqueous $NaHCO_3$, and brine (1 L each). The organic phase was then dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography using ethyl acetate-hexanes (10:90) as eluant to afford (+)-**A1** (98.1g, 85% yield) as a colorless oil: $[\alpha]_D^{23}$ +17.8° (*c* 1.34, $CHCl_3$); IR ($CHCl_3$) 3000 (s), 2960 (m), 2380 (m), 1780 (m), 1710 (s), 1370 (m), 1310 (m), 1035 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.98-5.90 (m, 1 H), 5.56 (s, 1 H), 5.39-5.28 (m, 2 H), 4.66 (d, *J* = 5.9 Hz, 2 H), 3.99 (d, *J* = 10.9 Hz, 1 H), 2.06-1.98 (m, 1 H), 1.27 (d, *J* = 6.6 Hz, 3 H), 1.09 (d, *J* = 6.6 Hz, 3 H), 1.00 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 156.5, 131.7, 119.0, 96.2, 67.2, 62.0, 36.6, 32.0, 25.0, 19.8, 19.5; high-resolution mass spectrum (CI, CH_4) *m/z* 270.1709 [(M + H)$^+$; calcd for $C_{14}H_{24}NO_4$: 270.1705]. Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.46; H, 8.61; N, 5.20. Found: C, 62.46; H, 8.94; N, 5.18.



(–)-**A2**

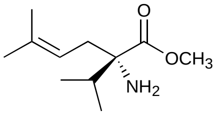
Prenyloxazolidinone (–)-**A2**. A solution of (+)-**A1** (46.5 g, 173.3 mmol) in THF (866 mL) was cooled to -78 °C, and 0.5 M KHMDS in toluene (416.0 mL, 208.0 mmol) was added via a dropping funnel at a rate that maintained an internal temperature no higher than -70 °C. The resulting yellow solution was stirred for 15 min, and then freshly distilled 1-bromo-3-methyl-2-butene (40.0 mL, 346.6 mmol) was added dropwise via syringe, again maintaining an internal temperature less than -70 °C. The solution was stirred for 45 min at -78 °C and was then quenched at -78 °C by pouring into 10% aqueous $NaHSO_4$ (500 mL). The resulting biphasic mixture was extracted with EtOAc (500 mL), and the organic phase was washed with saturated aqueous $NaHCO_3$ and brine (500 mL each), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The resulting yellow oil was purified by flash chromatography using ethyl acetate-hexanes (3:97) as eluant to afford (–)-**A2** (52.0 g, 89% yield) as a colorless oil: $[\alpha]_D^{23}$ –22.25° (*c* 1.29, $CHCl_3$); IR ($CHCl_3$) 3000 (s), 2980 (m), 2380 (m), 1770 (m), 1700 (m), 1420 (m), 1340 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.93-5.87 (m, 1 H), 5.47 (s, 1 H), 5.35-5.24 (m, 2 H), 4.75-4.71 (m, 1 H), 4,68-4.64 (m, 1 H), 4.47-4.43 (m, 1 H), 3.06 (dd, *J* = 6.0, 14.7 Hz, 1 H), 2.54 (dd, *J* = 6.0, 14.7 Hz, 1 H), 2.38-2.32 (m, 1 H), 1.67 (s, 3 H), 1.59 (s, 3 H), 1.17 (d, *J* = 3.8 Hz, 3 H), 1.16 (d, *J* = 3.8 Hz, 3 H), 1.00 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 155.1, 137.7, 131.9, 118.9, 116.3, 95.1, 70.1, 66.6, 37.7, 35.5, 30.0, 26.1, 25.9, 18.8, 18.5, 18.2; high-resolution mass spectrum (CI, CH_4) *m/z* 338.2335 [(M + H)$^+$; calcd for $C_{19}H_{32}NO_4$: 338.2331]. Anal. Calcd for $C_{19}H_{31}NO_4$: C, 67.69; H, 9.27; N, 4.16. Found: C, 67.50; H, 9.58; N, 4.16.



(–)-**A3**

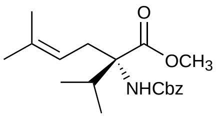
Alloc-protected Amino Ester (–)-**A3**. A heterogeneous mixture of oxazolidinone (–)-**A2** (29.5 g, 87.6 mmol) in MeOH and 3 N aqueous KOH (300 mL each) was heated at reflux for 16 h. The resulting homogenous solution was cooled to room temperature and was then concentrated *in vacuo*. The resultant mixture was acidified to pH 1 with 10% aqueous $NaHSO_4$ and then extracted with EtOAc (3 x 300mL). The combined organic phases were washed with H_2O and brine (500 mL each), dried over anhydrous $MgSO_4$, concentrated *in vacuo*, and placed under high vacuum for 8 h.

A solution of the crude residue in anhydrous DMF (120 mL) was treated with anhydrous K_2CO_3 (30 g), and cooled to 0 °C. Iodomethane (10.9 mL, 175.2 mmol) was added, and the mixture was stirred for 30 min and warmed to room temperature. The mixture was then diluted with Et_2O (800 mL) and was washed with water (4 x 100 mL), followed by brine (200 mL). The organic phase was then dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Flash chromatography using EtOAc-Hexanes (10:90) as eluant gave (–)-**A3** (18.0 g, 76% yield) as a colorless oil: $[\alpha]_D^{23}$ –30.78° (*c* 1.03, $CHCl_3$); IR ($CHCl_3$) 3000 (s), 2990 (m), 2390 (m), 1710 (m), 1500 (m), 1420 (m), 1210 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.95-5.87 (m, 1 H), 5.75 (s, 1 H), 5.31-5.27 (m, 1 H), 5.21-5.18 (m, 1 H), 4.92-4.89 (m, 1 H), 4.56-4.52 (m 2 H), 3.74 (s, 3 H), 3.11 (dd, *J* = 7.4, 14.6 Hz, 1 H), 2.65 (dd, *J* = 7.4, 14.6 Hz, 1 H), 2.49-2.47 (m, 1 H), 1.66 (s, 3 H), 1.59 (s, 3 H), 0.98 (d, *J* = 6.9 Hz, 3 H), 0.90 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 154.1, 135.1, 133.1, 118.4, 117.2, 67.4, 65.0, 52.2, 33.8, 31.0, 26.0, 17.9, 17.8, 17.8; high-resolution mass spectrum (CI, CH_4) *m/z* 284.1862 [$(M + H)^+$; calcd for $C_{15}H_{26}NO_4$: 284.1862]. Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.62; H, 8.90; N, 4.95. Found: C, 63.42; H, 8.73; N, 4.92.



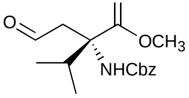
(+)-**A4**

Amine (+)-**A4.** To a solution of (–)-**A3** (33.7 g, 119.1 mmol) in THF (1.2 L) was added dimedone (83.50 g, 595.6 mmol) and $Pd(Ph_3P)_4$ (1.4 g, 1.2 mmol). The flask was wrapped with aluminum foil to exclude light, and the mixture was stirred for 16 h. The mixture was then diluted with ether (500 mL), and extracted with 1 N HCl (5 x 250 mL). The combined aqueous layers were made basic by addition of solid K_2CO_3, and additional base was added to facilitate extraction of the product. The resultant mixture was extracted with EtOAc (3 x 250 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine (500 mL each). The organic phase was then dried over anhydrous $MgSO_4$, concentrated *in vacuo*, Kugelrohr distillation provided (+)-**A4** (20.8 g, 93% yield) as a colorless oil: $[\alpha]^{23}_{D}$ +13.52° (*c* 1.58, $CHCl_3$); IR ($CHCl_3$) 3650 (w), 3600 (w), 3000 (s), 2950 (m), 2380 (m), 1720 (m), 1510 (m), 1420 (m), 1200 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.99-4.95 (m, 1 H), 3.68 (s, 3 H), 2.36 (dd, *J* = 8.4, 14.1 Hz, 1 H), 2.29 (dd, *J* = 8.4, 14.1 Hz, 1 H), 1.99 (app sept., *J* = 6.9 Hz, 1 H), 1.68 (s, 3 H), 1.60 (s, 3 H), 1.46 (s, 2 H), 0.93 (d, *J* = 6.8 Hz, 3 H), 0.82 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.7, 136.8, 119.6, 65.5, 52.7, 37.1, 36.3, 26.9, 18.9, 18.8, 17.1; high-resolution mass spectrum (CI, CH_4) *m/z* 198.1486 $[(M - H)^+$; calcd for $C_{11}H_{20}NO_2$: 198.1494].



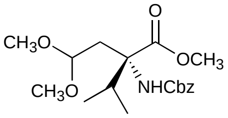
(–)-**A5**

Cbz Protected Amine (–)-**A5.** To a solution of (+)-**A4** (20.80 g, 104.3 mmol) in THF (522 mL) at 0 °C was added diisopropylethylamine (21.82 mL, 125.2 mmol) via a syringe. After 10 min, benzyl chloroformate (16.4 mL, 114.7 mmol) was added dropwise and the mixture was allowed to stir and warm to room temperature. The reaction mixture with diluted with ethyl acetate (100 mL) after 6 h and washed with 1 N HCl (500 mL), followed by saturated aqueous $NaHCO_3$ and brine (500 mL each). The organic phase was then dried over anhydrous $MgSO_4$, concentrated *in vacuo*, and purified by flash chromatography using ethyl acetate-hexanes (8:92) as eluant to give (–)-**A5** (33.40 g, 96% yield) as a colorless oil: $[\alpha]^{23}_{D}$ –19.89° (*c* 3.480, $CHCl_3$); IR ($CHCl_3$) 3010 (s), 2400 (m), 1730 (m), 1510 (m), 1420 (m), 1220 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.30 (m, 5 H), 5.97 (s, 1 H), 5.09 (d, *J* = 12.4 Hz, 1 H), 5.03 (d, *J* = 12.4 Hz, 1 H), 4.90-4.87 (m, 1 H), 3.73 (s, 3 H), 3.13 (dd, *J* = 7.3, 14.6 Hz, 1 H), 2.66 (dd, *J* = 7.3, 14.6 Hz, 1 H), 2.50-2.48 (m, 1 H), 1.64 (s, 3 H), 1.55 (s, 3 H), 0.98 (d, *J* = 6.9 Hz, 3 H), 0.91 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 154.5, 135.4, 128.7, 128.2, 128.1, 118.6, 67.7, 66.4, 52.5, 34.1, 31.3, 26.2, 18.1, 18.0; high-resolution mass spectrum (ES, Na) *m/z* 356.1822 $[(M + Na)^+$; calcd for $C_{19}H_{27}NO_4Na$: 356.1838]. Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.25; H, 8.42; N, 4.13.



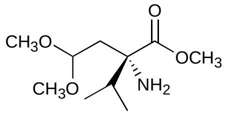
(+)-**A6**

Aldehyde (+)-**A6.** A solution of (–)-**A5** (1.66 g, 4.98 mmol) in CH_2Cl_2 (50 mL) was cooled to -78 °C and ozone was bubbled into the solution until a light blue color persisted. The solution was then purged with argon until the blue color dissipated. Ph_3P (1.44 g, 5.48 mmol) was then added. The resulting solution was stirred and warmed to room temperature under argon for 4 h. The solution was then concentrated *in vacuo* and purified by flash chromatography using ethyl acetate-hexanes (10:90) to ethyl acetate-hexanes (20:80) as eluants to yield (+)-**A6** (1.51 g, 99% yield) as a colorless oil: $[\alpha]_D^{23}$ +1.74° (*c* 4.71, $CHCl_3$); IR ($CHCl_3$) 3010 (s), 2400 (m), 1730 (s), 1510 (m), 1210 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.67 (s, 1 H), 7.36-7.30 (m, 5 H), 5.91 (s, 1 H), 5.07-5.00 (m, 2 H), 3.80 (d, *J* = 17.7 Hz, 1 H), 3.76 (s, 3 H), 3.07 (d, *J* = 17.7 Hz, 1 H), 2.37-2.33 (m, 1 H), 0.92 (d, *J* = 6.6 Hz, 3 H), 0.91 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.1, 171.8, 154.7, 136.3, 128.5, 128.0, 127.8, 66.5, 63.2, 52.6, 46.2, 34.5, 17.4, 17.2; high-resolution mass spectrum (CI, CH_4) *m/z* 308.1486 [(M + H)$^+$; calcd for $C_{16}H_{22}NO_5$: 308.1498]. Anal. Calcd for $C_{16}H_{21}NO_5$: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.99; H, 6.59; N, 10.32.



(–)-**A7**

Dimethyl acetal (–)-**A7.** To a solution of (+)-**A6** (16.7 g, 54.34 mmol) in MeOH (543 mL) was added trimethyl orthoformate (237.8 mL, 2.17 mol) and a catalytic quantity of *p*-TsOH. The solution was heated at reflux with stirring for 1.5 h, and was then diluted with Et_2O (500 mL). The mixture was washed with saturated aqueous $NaHCO_3$ and brine (300 mL each), and the organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Flash chromatography using ethyl acetate-hexanes (20:80) as eluant then afforded (–)-**A7** (19.00 g, 99% yield) as a colorless oil: $[\alpha]_D^{23}$ –13.24° (*c* 1.465, $CHCl_3$); IR ($CHCl_3$) 3408 (m), 3018 (s), 2954 (m), 1716 (s), 1499 (s), 1438 (m), 1357 (m), 1217 (s), 1248 (s), 1193 (m), 1065 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.25 (m, 5 H), 6.10 (s, 1 H), 5.12 (d, *J* = 12.4 Hz, 1 H), 5.03 (d, *J* = 12.4 Hz, 1 H), 4.15 (dd, *J* = 2.5, 8.5 Hz, 1 H), 3.72 (s, 3 H), 3.25 (s, 3 H), 3.23 (s, 3 H), 2.80 (dd, *J* = 2.5, 14.0 Hz, 1 H), 2.50 (app sept. *J* = 6.9 Hz, 1 H), 2.27 (dd, *J* = 8.5, 14.0 Hz, 1 H), 0.95 (d, *J* = 6.9 Hz, 3 H), 0.85 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 154.2, 136.9, 128.5, 128.1, 128.0, 103.8, 66.3, 64.6, 55.7, 54.2, 52.3, 36.3, 34.3, 17.6, 17.5; high-resolution mass spectrum (ES, Na) *m/z* 376.1739 [(M + Na)$^+$; calcd for $C_{18}H_{27}NO_6Na$: 376.1736]. Anal. Calcd for $C_{18}H_{27}NO_6$: C, 61.71; H, 7.70; N, 3.96. Found: C, 61.81; H, 7.75; N, 3.93.

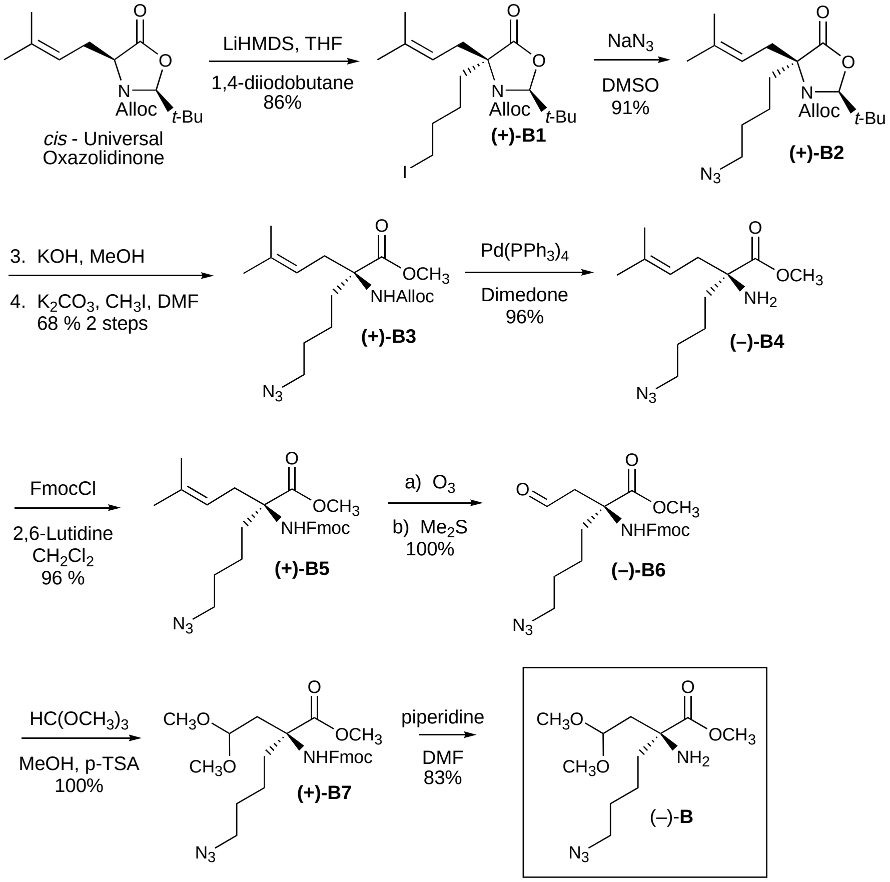


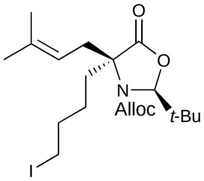
(+)-**A**

Amino Ester Building Block (+)-**A.** A mixture of (–)-**A7** (20.5 g, 58.0 mmol), 10% Pd/C (4.1 g), and freshly distilled cyclohexene (58.75 mL, 580 mmol) in absolute EtOH (232 mL) was heated at reflux for 2.5 h. The mixture was then filtered and concentrated *in vacuo*, purified by flash chromatography using methanol-dichloromathane (2:98) as eluant to give (+)-**A** (12.33 g, 97% yield) as a colorless oil: $[\alpha]_D^{23}$ +13.79° (*c* 1.16, $CHCl_3$); IR ($CHCl_3$) 3660 (w), 3600 (w), 3000 (s), 2980 (m), 2900 (w), 2380 (m), 1750 (m), 1530 (m), 1440 (m), 1220 (s), 1050 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.42 (app t, *J* = 5.6 Hz, 1 H), 3.70 (s, 3 H), 3.32 (s, 3 H), 3.29 (s, 3 H), 2.05 (dd, *J* = 5.6, 14.0 Hz, 1 H), 1.96 (app sept., *J* = 5.6 Hz, 1 H), 1.90 (dd, *J* = 5.6, 14.0 Hz, 1

H), 1.88 (br s, 2 H), 0.92 (d, *J* = 6.8 Hz, 3 H), 0.80 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.4, 103.0, 62.1, 53.6, 53.4, 51.9, 40.3, 36.2, 17.3, 16.1; high-resolution mass spectrum (CI, CH_4) *m/z* 220.1549 [(M + H)$^+$; calcd for $C_{10}H_{22}NO_4$: 220.1549].

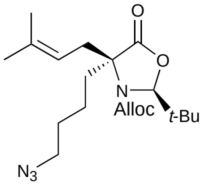
Amino Ester Building Block (–)-**B.**





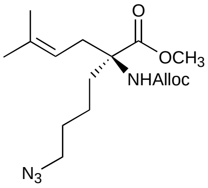
(+)-**B1**

Iodide (+)-**B1.** To a -78 °C solution of *cis*-Universal Oxazolidinone (22.0 g, 67.8 mmol) in THF (400 mL) was added 1.0 M LiHMDS in THF (74.6 mL, 74.6 mmol) followed by addition of 1,4-diiodobutane (34.7 g, 111.9 mmol) rapidly and in one portion. The resulting solution was stirred and warmed to 0 °C over 2 h, and was then quenched at 0 °C by addition of 10% aqueous $NaHSO_4$ (200 mL). The mixture was diluted with EtOAc (100 mL), washed with 10% aqueous $NaHSO_4$ (100 mL), then saturated aqueous $NaHCO_4$ and brine (100 mL each) The organic phase was then dried over anhydrous $MgSO_4$, concentrated *in vacuo*, and purified by flash chromatography using ethyl acetate-hexanes (1:19) as eluant to provide (+)-**B1** (27.7 g, 86% yield) as a colorless oil: $[\alpha]_D^{23}$ +10.8° (*c* 2.655, $CHCl_3$); IR ($CHCl_3$) 3005 (w), 2970 (w), 1790 (s), 1710 (s), 1390 (m), 1315 (m), 1190 (m), 1035 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.92 (m, 1 H), 5.50 (s, 1 H), 5.35 (d, *J* = 17.2 Hz, 1 H), 5.28 (m, 2 H), 4.65 (dd, *J* = 6.1, 12.6 Hz, 1 H), 4.60 (m, 1 H), 3.08 (m, 2 H), 2.75 (dd, *J* = 8.0, 14.3, 1 H), 2.64 (dd, *J* = 7.3, 14.6 Hz, 1 H), 2.30 (br s, 1 H), 1.74 (m, 3 H), 1.68 (s, 3 H), 1.60 (s, 3 H), 1.12 (m, 2 H), 0.96 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 135.4, 131.7, 119.6, 118.1, 95.2, 67.0, 66.7, 38.1, 36.1, 33.0, 25.9, 25.6, 24.5, 17.8, 5.5; high-resolution mass spectrum (CI, NH_3) *m/z* 495.1729 $[(M + NH_4)^+$, calcd for $C_{20}H_{36}IN_2O_4$: 495.1720]. Anal. Calcd for $C_{20}H_{32}INO_4$: C, 50.32; H, 6.76; N, 2.93. Found: C, 50.60; H, 6.84; N, 2.89.



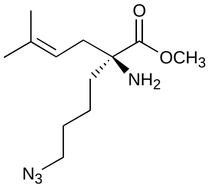
(+)-**B2**

Azide (+)-**B2.** To a solution of (+)-**B1** (27.7 g, 58.2 mmol) in DMSO (150 mL) was added NaN_3 (11.4 g, 174.6 mmol). The mixture was stirred for 1 h, and was then diluted with Et_2O (200 mL) and washed with water (2 x 100 mL), and brine (100 mL). The organic phase was dried over anhydrous $MgSO_4$, concentrated *in vacuo*, and purified by flash chromatography using ethyl acetate-hexanes (1:9) as eluant to yield (+)-**B2** (21.2 g, 91% yield) as a colorless oil: $[\alpha]_D^{23}$ +14.6 (*c* 2.145, $CHCl_3$); IR ($CHCl_3$) 3020 (w), 2980 (w), 2100 (s), 1790 (s), 1715 (s), 1390 (m), 1315 (m), 1190 (m), 1040 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.92 (m, 1 H), 5.49 (s, 1 H), 5.35 (d, *J* = 17.2 Hz, 1 H), 5.28 (m, 2 H), 4.64 (dd, *J* = 6.0, 12.7 Hz, 1 H), 4.58 (m, 1 H), 3.19 (m, 2 H), 2.76 (dd, *J* = 8.4, 14.4 Hz, 1 H), 2.64 (dd, *J* = 7.4, 14.6 Hz, 1 H), 2.32 (br s, 1 H), 1.73 (ddd, *J* = 4.8, 12.2, 13.9 Hz, 1 H), 1.69 (s, 3 H), 1.61 (s, 3 H), 1.51 (m, 2 H), 1.11 (m, 2 H), 0.96 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 135.4, 131.7, 119.5, 118.1, 95.2, 67.0, 66.7, 50.8, 38.1, 36.1, 28.4, 25.9, 25.6, 20.9, 17.8; high-resolution mass spectrum (CI, NH_3) *m/z* 410.2763 $[(M + NH_4)^+$, calcd for $C_{20}H_{36}N_5O_4$: 410.2767]. Anal. Calcd for $C_{20}H_{32}N_4O_4$: C, 61.20; H, 8.22; N, 14.27. Found: C, 61.37; H, 8.30; N, 13.97.



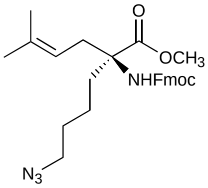
(+)-**B3**

Ester (+)-**B3.** A solution of (+)-**B2** (21.2 g, 52.9 mmol) in MeOH (200 mL) was treated with an aqueous solution of 3N KOH (200 mL) and the resulting mixture was heated at reflux for 2 h. The resultant homogenous solution was then cooled to room temperature and concentrated *in vacuo* to remove most of the MeOH. The resultant mixture was acidified with 10% $NaHSO_4$ to pH 1 and extracted with ethyl acetate (2 x 200 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude acid was then used without further purification. A 0 °C solution of the residue in DMF (100 mL) was treated with K_2CO_3 (20 g) and iodomethane (6.6 mL, 106 mmol) followed by warming to room temp. After 1 h the reaction was quenched with water (50 mL) and extracted with ether (2 x 100 mL). The combined extracts were washed with water (70 mL), brine (70 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification via flash chromatography (5-20% ethyl acetate:hexanes) then provided (+)-**B3** (12.0 g, 68% yield) as a colorless oil that was used without further purification: $[\alpha]_D^{23}$ +26.8° (*c* 1.17, $CHCl_3$); IR ($CHCl_3$) 3420 (m), 3005 (w), 2940 (m), 2100 (s), 1720 (s), 1505 (s), 1220 (s), 1070 (m), 905 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.88 (m, 1 H), 5.69 (s, 1 H), 5.28 (dq, *J* = 1.5, 17.2 Hz, 1 H), 5.18 (m, 1 H), 4.88 (apparent t, *J* = 7.5 Hz, 1 H), 4.51 (m, 2 H), 3.72 (s, 3 H), 3.21 (m, 2 H), 2.94 (dd, *J* = 7.2, 13.6 Hz, 1 H), 2.41 (dd, *J* = 7.5, 14.6 Hz, 1 H), 2.35 (m, 1 H), 1.80 (ddd, *J* = 4.8, 11.9, 13.6 Hz, 1 H), 1.64 (s, 3 H), 1.54 (s, 3 H), 1.53 (m, 2 H), 1.34 (m, 1 H), 1.07 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 153.9, 135.9, 132.9, 117.5, 65.1, 64.1, 52.7, 51.1, 34.5, 28.6, 25.9, 21.3, 17.8; high-resolution mass spectrum (CI, NH_3) *m/z* 339.2033 [$(M + H)^+$, calcd for $C_{16}H_{27}N_4O_4$: 339.2032].



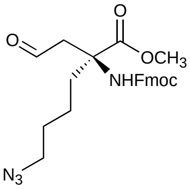
(–)-**B4**

Amine (–)-**B4** To a solution of (+)-**B3** (11.8 g, 35.1 mmol) in dried THF (200 mL) was added dimedone (19.7 g, 140.4 mmol) and $Pd(Ph_3P)_4$ (100 mg, 0.087 mmol). The flask was wrapped in foil to exclude light and the reaction was stirred at room temp for 16 h before diluting with ether (200 mL), and extracting with 1 N aq. HCl (5 x 100 mL). The combined aqueous layers were basified by addition of 3 N aq. KOH (500 mL) and extracted with ethyl acetate (3 x 200 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified via flash chromatography using ethyl acetate-hexanes (1:4 then 2:3) as eluant to provide (–)-**B4** (8.6 g, 96% yield) as a yellow oil: $[\alpha]^{23}_{D}$ –11.8° (*c* 0.96, $CHCl_3$); IR ($CHCl_3$) 3370 (w), 2960 (m), 2100 (s), 1730 (s), 1220 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.99 (app t, *J* = 7.6 Hz, 1 H), 3.69 (s, 3 H), 3.24 (t, *J* = 6.9 Hz, 2 H), 2.41 (dd, *J* = 6.7, 14.2 Hz, 1 H), 2.27 (dd, *J* = 8.6, 14.1 Hz, 1 H), 1.76 (ddd, *J* = 4.6, 12.4, 13.4 Hz, 1 H), 1.69 (s, 3 H), 1.66 (m, 2 H), 1.61 (s, 3 H), 1.55 (m, 3 H), 1.42 (m, 1 H), 1.18 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.3, 136.4, 117.9, 61.4, 52.1, 51.2, 39.4, 38.4, 29.1, 26.0, 21.3, 18.0; high-resolution mass spectrum (CI, NH_3) *m/z* 255.1827 [$(M + H)^+$, calcd for $C_{12}H_{23}N_4O_2$: 255.1821]. Anal. Calcd for $C_{12}H_{22}N_4O_2$: C, 56.67; H, 8.72; N, 22.03. Found: C, 56.66; H, 8.74; N, 21.81.



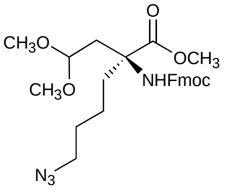
(+)-**B5**

Carbamate (+)-**B5.** To a solution of (–)-**B4** (5.48 g, 21.528 mmol) in CH_2Cl_2 (215 mL) was added 2,6-lutidine (3.54 mL, 30.4 mmol) and 9-fluorenylmethyl chloroformate (FmocCl, 6.68 g, 25.8 mmol). The solution was stirred for 16 h and was then washed with aqueous 1 N HCl and brine (200 mL each). The organic phase was then dried over anhydrous $MgSO_4$, concentrated *in vacuo,* and purified by flash chromatography using ethyl acetate-hexanes (3:17) as eluant to give (+)-**B5** (9.85 g, 96% yield) as a colorless oil: $[\alpha]^{23}_{D}$ +5.1 (*c* 1.11, $CHCl_3$); IR ($CHCl_3$) 3410 (m), 3010 (s), 2940 (s), 2090 (s), 1715 (s), 1495 (s), 1450 (s), 1330 (s), 1210 (s), 1080 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.6 Hz, 2 H), 7.58 (m, 2 H), 7.38 (t, *J* = 7.4 Hz, 2 H), 7.30 (td, *J* = 0.9, 7.4 Hz, 2 H), 5.77 (s, 1 H), 4.88 (m, 1 H), 4.38 (m, 1 H), 4.31 (m, 1 H), 4.21 (app t, *J* = 6.9 Hz, 1 H), 3.76 (s, 3 H), 3.22 (m, 2 H), 3.00 (dd, *J* = 7.3, 13.9 Hz, 1 H), 2.42 (m, 2 H), 1.65 (s, 3 H), 1.54 (br s, 5 H), 1.34 (m, 1 H), 1.08 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 154.0, 144.0, 143.9, 141.4, 134.0, 127.6, 127.0, 125.0, 120.0, 117.5, 66.2, 64.2, 52.7, 51.1, 47.3, 34.6, 34.5, 28.6, 23.9, 21.3, 17.8; high-resolution mass spectrum (ESI, positive ion) *m/z* 499.2324 [$(M + Na)^+$; calcd for $C_{27}H_{32}N_4O_4Na$: 499.2321]. Anal. Calcd for $C_{27}H_{32}N_4O_4$: C, 68.05; H, 6.77; N, 11.76. Found: C, 68.20; H, 6.94; N, 11.59.



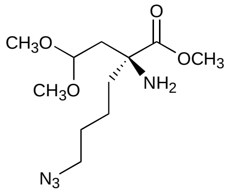
(–)-**B6**

Aldehyde (–)-**B6.** A -78 ^{o}C solution of (+)-**B5** (9.78 g, 20.52 mmol) in CH_2Cl_2 (200 mL) was saturated with ozone until a blue color persisted. The solution was then purged with argon until the blue color dissipated, and Me_2S (3.0 mL, 40.8 mmol) was added. The solution was stirred and warmed to room temperature under an argon atmosphere for 16 h. The solution was then concentrated in *vacuo* and the residue was purified by flash chromatography using ethyl acetate-hexanes (3:7) as eluant to yield (–)-**B6** (9.381 2 g, 100 % yield) as a colorless oil: $[\alpha]_{\mathrm{D}}^{23}$ –3.6 (*c* 1.39, $CHCl_3$); IR ($CHCl_3$) 3410 (w), 3010 (m), 2940 (m), 2090 (s), 1720 (s), 1495 (m), 1440 (m), 1215 (s), 1080 (m), 705 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.58 (s, 1 H), 7.74 (d, *J* = 7.5 Hz, 2 H), 7.55 (m, 2 H), 7.38 (t, *J* = 7.4 Hz, 2 H), 7.29 (m, 2 H), 5.99 (s, 1 H), 4.35 (d, *J* = 4.0 Hz, 2 H), 4.18 (app t, *J* = 6.5 Hz, 1 H), 3.77 (s, 3 H), 3.73 (m, 1 H), 3.20 (s, 2 H), 2.95 (d, *J* = 17.9 Hz, 1 H), 2.36 (m, 1 H), 1.63 (m, 1 H), 1.52 (m, 2 H), 1.30 (m, 1 H), 1.10 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.7, 172.7, 154.2, 143.7, 141.3, 127.7, 127.0, 125.0, 120.0, 66.4, 59.6, 53.1, 50.9, 49.0, 47.2, 35.1, 28.4, 20.6; high-resolution mass spectrum (ESI, positive ion) *m/z* 473.1811 [(M + Na)$^+$; calcd for $C_{24}H_{26}N_4O_5Na$: 473.1801].



(+)-**B7**

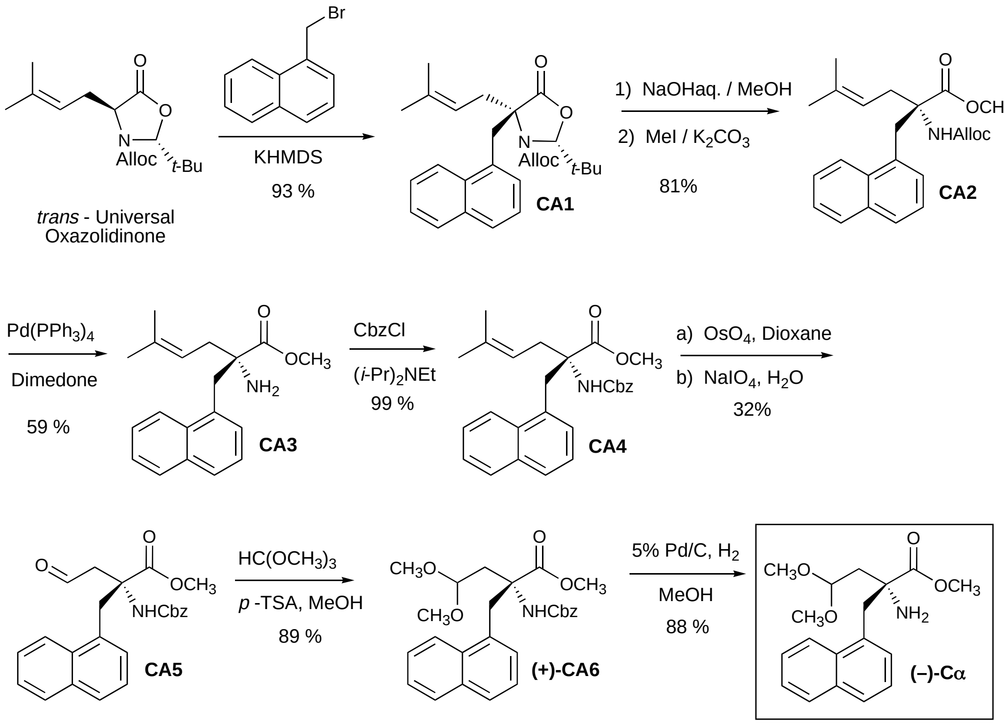
Acetal (+)-**B7.** To a solution of (–)-**B6** (9.2460 g, 20.523 mmol) in MeOH (100 mL) was added trimethyl orthoformate (100 mL) and *p*-TsOH (500 mg, 2.63 mmol). The solution was stirred for 2 h, and was then concentrated *in vacuo*. The residue was next diluted with ethyl acetate (300 mL), and washed with saturated aqueous $NaHCO_3$ and brine (200 mL each). The organic phase was next dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to afford (+)-**B7** (10.15 g, 100% yield) as a pale yellow oil that was used without further purification: $[\alpha]_{\mathrm{D}}^{23}$ +2.0 (*c* 1.60, $CHCl_3$); IR ($CHCl_3$) 3400 (w), 3010 (s), 2950 (m), 2090 (s), 1715 (s), 1495 (s), 1445 (s), 1205 (s), 1080 (s), 720 (s) cm^{-1} ; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d *J* = 7.5 Hz, 2 H), 7.59 (d *J* = 6.8 Hz, 2 H), 7.38 (t, *J* = 7.4 Hz, 2 H), 7.30 (td, *J* = 0.5, 7.4 Hz, 2 H), 6.01 (s, 1 H), 4.40 (m, 2 H), 4.25 (dd, *J* = 2.3, 7.6 Hz, 1 H), 4.21 (t, *J* = 6.8 Hz, 1 H), 3.74 (s, 3 H), 3.26 (s, 3 H), 3.24 (s, 3 H), 3.20 (m, 2 H), 2.65 (dd, *J* = 2.4, 14.1 Hz, 1 H), 2.33 (m, 1 H), 2.11 (dd, *J* = 8.1, 14.1 Hz, 1 H), 1.76 (m, 1 H), 1.52 (m, 2 H), 1.27 (m, 1 H), 1.03 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 154.0, 143.9, 141.4, 127.7, 127.0, 125.0, 120.0, 102.5, 66.1, 61.2, 55.0, 53.4, 52.7, 51.0, 47.3, 39.0, 34.9, 28.5, 20.8; high-resolution mass spectrum (ESI, positive ion) *m/z* 51 9.2214 [(M + Na)$^+$; calcd for $C_{26}H_{32}N_4NaO_6$: 519.2220].

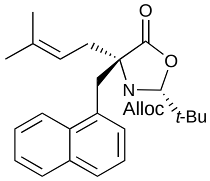


(–)-**B**

Amino Ester Building Block (–)-**B.** To a solution of (+)-**B7** (10.11 g, 20.4 mmol) in DMF (200 mL) was added piperidine (4.03 mL, 40.7 mmol). The solution was stirred for 30 min, and was then diluted with Et_2O (300 mL) and washed with water (2 x 300 mL). The organic phase was next dried over anhydrous $MgS0_4$, concentrated *in* vacuo, and purified by gradient flash chromatography using ethyl acetate-hexanes (1 :1) then methanol-methylene chloride (1:19) as the eluant to provide (–)-**B** (4.64 g, 83% yield) as a pale yellow oil: $[\alpha]_D^{23}$ –9.6 (*c* 0.72, $CHCl_3$); IR ($CHCl_3$) 3680 (w), 3380 (w), 3020 (s), 2960 (s), 2100 (s), 1730 (s), 1200 (s), 1120 (s), 1050 (s), 710 (s) cm^{-1} ; ^1H NMR (500 MHz, $CDCl_3$) δ 4.43 (t, *J* = 5.5 Hz, 1 H), 3.69 (s, 3 H), 3.29 (s, 3 H), 3.27 (s, 3 H), 3.23 (t, *J* = 6.9 Hz, 2 H), 2.09 (dd, *J* = 5.6, 14.1 Hz, 1 H), 1.89 (s, 2 H), 1.84 (dd, *J* = 5.4, 14.1 Hz, 1 H), 1.71 (ddd, *J* = 4.6, 12.4, 13.3 Hz, 1 H), 1.54 (m, 3 H), 1.42 (m, 1 H), 1.18 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ177.00, 102.5, 59.1, 53.5, 53.4, 52.1, 51.1, 42.2, 40.6, 28.9, 20.8; high-resolution mass spectrum (ESI, positive ion) *m/z* 275.1716 $[(M + H)^+$; calcd for $C_{11}H_{23}N_4O_4$: 275.1719]. Anal. Calcd for $C_{11}H_{22}N_40_4$: C, 48.16; H, 8.08; N, 20.42. Found: C, 47.80; H, 8.15; N, 20.23.

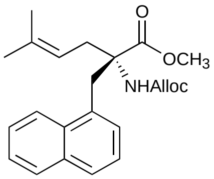
Amino Ester Building Block (–)-Cα





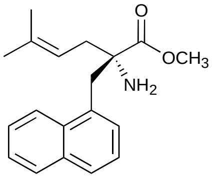
CA1

Oxazolidinone CA1. To a -78 °C solution of *trans*-Universal Oxazolidinone (20.0 g, 67.7 mmol) in THF (400 mL) was added LiHMDS 1.0 M THF solution (80 mL, 80 mmol) dropwise over 30 min. The resulting orange-brown suspension was stirred for 30 min and then 2-bromomethylnaphthalene (24.6 g, 111 mmol) was added. The mixture was stirred for 1 h at -78 °C and was gradually warmed to room temperature. The resulting suspension was poured into 10 % aqueous $NaHSO_4$ (200 mL). The mixture was extracted with Hexane-ethyl acetate 1:1 mixture (300 mL, 100mL x 2), and the combined extract was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography, using hexane-ethyl acetate (95:5) as eluant, gave 27.3 g (93 % yield) of **CA1** as a slightly yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (br, 1 H); 7.82 (d, *J* = 8.0 Hz, 1 H), 7.76 (d, *J* = 8.3 Hz, 1 H), 7.53-7.44 (m, 2 H), 7.38 (d, *J* = 7.5 Hz, 1 H), 7.26 (br, 1 H), 5.83 (br, 1 H), 5.46 (br, 1 H), 5.26 (br, 2 H), 4.54 (br, 3 H), 3.97 (br, 1 H), 3.64 (br, 1 H), 3.13 (br, 1 H), 2.99 ~ 3.03 (m, 1 H), 1.77 (s, 6 H), 0.83 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 135.9, 133.9, 132.4, 131.6, 128.5, 128.2, 127.8, 125.8, 125.7, 125.0, 124.2, 119.4, 118.7, 94.9, 66.4, 38.2, 36.3, 31.6, 26.0, 26.0, 25.9, 25.7, 22.6, 18.0.



CA2

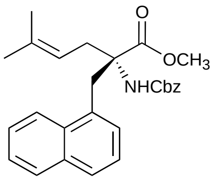
Alloc-Amino Ester CA2. To a solution of **CA1** (25.9 g, 59.6 mmol) in THF (125 mL) and MeOH (250 mL) was added 6 M aqueous KOH (125 mL). The resulting mixture was heated to reflux and stirred for 4 h. After cooling down the mixture was evaporated to remove most of the solvent. The resulting residue was acidified with conc. hydrochloric acid (ca. 60 mL) under ice bath, extracted with EtOAc (200 mL x 3), and the combined extract was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was dissolved in DMF (200 mL). To this solution was added K_2CO_3 (17 g, 122 mmol), followed by MeI (8mL, 129 mmol) under ice bath. The mixture was stirred overnight, and then diluted with ether (300 mL), and washed with water (300mL) The water layer was extracted with ether (100 mL x 2). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography, using hexane-ethyl acetate (95:5) as eluant, gave 17.6 g (81 % yield) of **CA2** as a slightly yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.8 Hz, 1 H), 7.83 (d, *J* = 7.1 Hz, 1 H), 7.74 (dm *J* = 8.1 Hz, 1 H), 7.47-7.41 (m, 2 H), 7.38 (t, *J* = 7.6 Hz, 1 H), 7.27 (d, *J* = 7.1 Hz, 1 H), 5.92 (m, 1 H), 5.60 (s, 1 H), 5.30 (d, *J* = 17.4 Hz, 1 H), 5.22 (d, *J* = 10.4 Hz, 1 H), 4.99 (t, *J* = 7.0 Hz, 1 H), 4.60 (m, 2 H), 4.07 (d, *J* = 14.4 Hz, 1 H), 3.68 (d, *J* = 14.4 Hz, 1 H), 3.58 (s, 3 H), 3.37 (dd, *J* = 6.9 14.3 Hz, 1 H), 2.78 (dd, *J* = 7.2, 14.5 Hz, 1 H), 1.70 (s, 3 H), 1.64 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 154.4, 135.8, 133.8, 133.0, 132.8, 132.7, 128.6, 128.1, 127.6, 125.6, 125.3, 125.1, 123.9, 117.7, 117.4, 65.2, 65.1, 52.3, 37.0, 34.4, 26.0, 17.9.



CA3

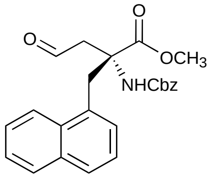
Amine CA3. To a solution of **CA2** (17.0 g, 46.4 mmol) in THF (350 mL) was added dimedone (26 g, 185 mmol), followed by $Pd(PPh_3)_4$ (500 mg, 0.43mmol). The resulting mixture was stirred overnight, then evaporated to remove most of THF. The residue was diluted with ether and filtered. The filtrate was extracted with 1N hydrochloric acid (100 mL x 10). The combined water layer was cooled by ice bath and basified with 6 N aqueous NaOH. The mixture was extracted with EtOAc (200 mL x 3), washed with brine, and dried over Na_2SO_4. Concentration *in vacuo* gave 8.1 g (59 % yield) of **CA3** as a yellow oil.; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J*= 8.4 Hz, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.75 (d, *J* = 8.0 Hz, 1 H), 7.50 (t, *J* = 8.2 Hz, 1 H), 7.45 (t, *J* = 8.1 Hz, 1 H), 7.39 (t, *J* = 8.0 Hz, 1 H), 7.35 (d, *J* = 8.2 Hz, 1 H), 5.10 (dd, *J* = 6.8, 8.4 Hz, 1 H), 3.58 (d, *J* = 13.9 Hz, 1 H), 3.56 (s, 3 H), 3.41 (d, *J* = 13.8 Hz, 1 H), 2.75 (dd, *J* = 6.7, 14.1 Hz, 1 H), 2.49 (dd, *J* = 8.4, 14.0 Hz, 1

H), 1.74 (s, 3 H), 1.69 (s, 3 H), 1.58 (br, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 136.4, 133.9, 133.0, 132.9, 128.6, 128.2, 127.6, 125.7, 125.4, 125.1, 124.5, 118.1, 63.1, 51.8, 41.7, 39.0, 16.0, 18.1.



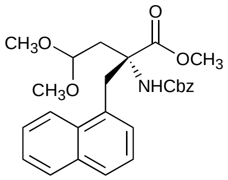
CA4

Cbz-Amino Ester CA4. To a solution of **CA3** (7.0 g, 23.5 mmol) in THF (140 mL) was added diisopropylethyl amine (15 mL, 86.1 mmol), followed by CbzCl (10 mL, 70.6 mmol).The resulting mixture was stirred overnight, then filtered to remove precipitation. The filtrate was diluted with ether, washed with 1N hydrochloric acid, sat. aqueous $NaHCO_3$, and brine. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography, using hexane-ethyl acetate (95:5) as eluant, gave 10.1 g (99 % yield) of **CA4** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.11 (d, *J* = 8.3 Hz, 1 H), 7.82 (d, *J* = 7.6 Hz, 1 H), 7.73 (d, *J* = 8.2 Hz, 1 H), 7.45-7.26 (m, 8 H), 7.20 (d, *J* = 7.0 Hz, 1 H), 5.63 (s, 1 H), 5.19 ~ 5.11 (m, 2 H), 4.98 (t, *J* = 7.1 Hz, 1 H), 4.07 (d, *J* = 14.3 Hz, 1 H), 3.69 (d, *J* = 14.3 Hz, 1 H), 3.59 (s, 3 H), 3.39 (dd, *J* = 7.1, 14.4 Hz, 1 H), 2.79 (dd, *J* = 7.2, 14.5 Hz, 1 H), 1.69 (s, 3 H), 1.62 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 154.5, 135.8, 133.8, 132.8, 132.6, 128.6, 128.4, 128.4, 128.1, 128.1, 127.7, 127.6, 125.6, 125.3, 125.1, 123.8, 117.6, 66.2, 65.3, 52.3, 37.0, 34.5, 25.9, 17.9.



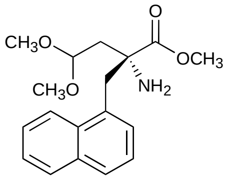
CA5

Aldehyde CA5. To a solution of **CA4** (26.5 g, 58.5 mmol) in 1,4-dioxane (400 mL) was added OsO_4 4 wt % aqueous solution (2mL, 0.31 mmol). The resulting mixture was stirred for 30 min. To this solution was added $NaIO_4$ (20.0 g, 93.5 mmol) aqueous solution (100 mL) portionwise. The mixture was stirred overnight and extracted with ether (300 mL, 100 mL x 2), and the combined extract was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography, using hexane-ethyl acetate (85:15) as eluant, gave 7.53 g (32 % yield) of **CA5** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.67 (s, 1 H); 7.96 (d, *J* = 8.2 Hz, 1 H), 7.82 (d, *J* = 7.5 Hz, 1 H), 7.74 (d, *J* = 8.2 Hz, 1 H), 7.45-7.27 (m, 8 H), 7.12 (d, *J* = 7.0 Hz, 1 H), 5.86 (s, 1 H), 5.18 (d, *J* = 12.3 Hz, 1 H), 5.02 (d, *J* = 12.3 Hz, 1 H), 4.13 (d, *J* = 17.6 Hz, 1 H), 3.90 (d, *J* = 14.2 Hz, 1 H), 3.62 (d, *J* = 14.1 Hz, 1 H), 3.50 (s, 3 H), 3.23 (d, *J* = 18.2 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5, 171.9, 154.7, 136.1, 133.8, 132.7, 131.1, 128.8, 128.6, 128.5, 128.2, 128.1, 126.0, 125.5, 125.1, 123.4, 66.6, 61.1, 52.7, 48.5, 37.9, 14.1.



(+)-**CA6**

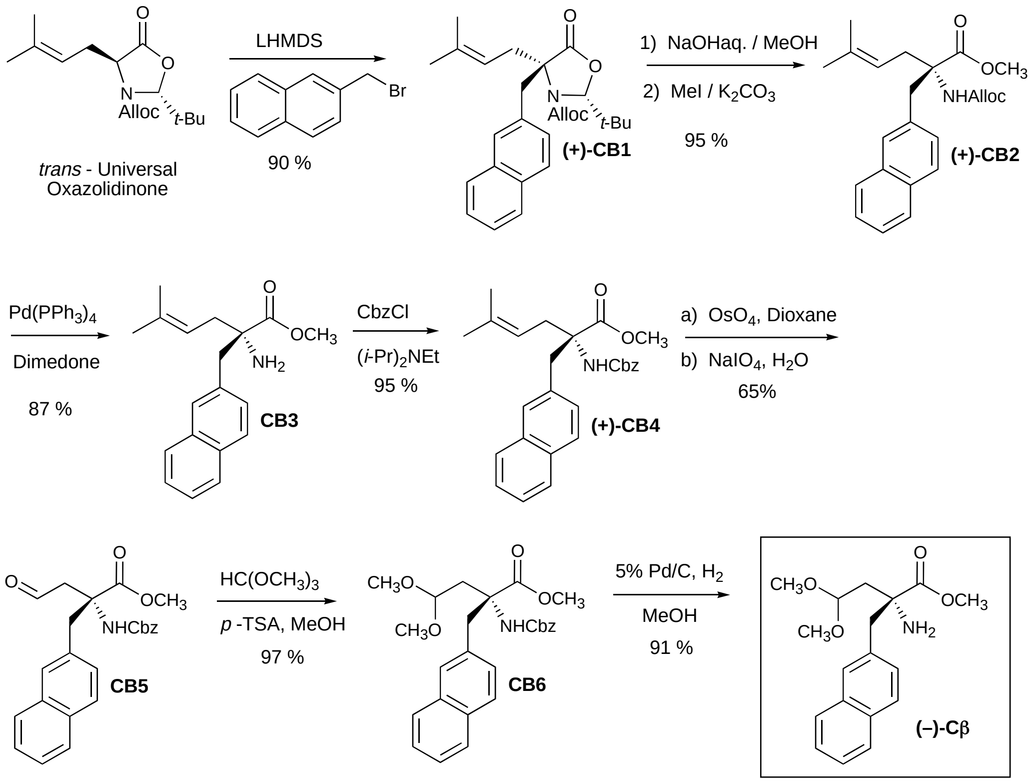
Acetal (+)-**CA6.** To a solution of **CA5** (0.82 g, 2.02 mmol) in MeOH (10 mL) and trimethyl orthoformate (3.0 mL) was added *p*-TsOH•H_2O (0.1 g, 0.58 mmol). The mixture was heated to reflux and stirred for 5 h. After cooling down the reaction mixture was poured into sat. aqueous $NaHCO_3$ and extracted with EtOAc (50 mL x 3), washed with brine, and dried over Na_2SO_4. Concentration *in vacuo* gave 0.81 g (89 %) of 79 as a colorless oil: $[\alpha]^{23}_{D}$ = +84.5° (*c* 1.09, $CHCl_3$); IR ($CHCl_3$) 3414 (w), 2951 (m), 2832 (w), 1720 (s), 1497 (s), 1454 (m), 1339 (m), 1306 (m), 1223 (m), 1126 (m), 1059 (s), 786 (m), 698 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.4 Hz, 1 H), 7.82 (d, *J* = 8.4 Hz, 1 H), 7.73 (d, *J* = 8.2 Hz, 1 H), 7.44-7.30 (m, 7 H), 7.28 (d, *J* = 7.9 Hz, 1 H), 7.16 (d, *J* = 7.1 Hz, 1 H), 5.88 (s, 1 H), 5.18 (d, *J* = 18.0 Hz, 1 H), 5.16 (d, *J* = 18.0 Hz, 1 H), 4.30 (dd, *J* = 3.3, 8.0 Hz, 1 H), 4.03 (d, *J* = 14.2 Hz, 1 H), 3.62 (d, *J* = 14.2 Hz, 1 H), 3.59 (s, 3 H), 3.24 (s, 3 H), 3.32 (s, 3 H), 3.02 (dd, *J* = 3.3, 14.1 Hz, 1 H), 2.48 (dd, *J* = 8.0, 14.1 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 154.5, 136.6, 133.7, 132.8, 132.0, 128.6, 128.4, 128.3, 128.2, 128.1, 127.7, 125.5, 125.3, 125.0, 123.8, 102.9, 66.3, 62.6, 55.1, 53.8, 52.2, 39.0, 37.2; high-resolution mass spectrum (ESI positive ion) m/z 474.1881 [(M+Na)$^+$, calcd for $C_{26}H_{29}N_1O_6Na$ 474.1893].

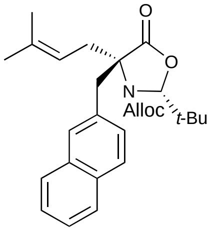


(–)-**Cα**

Amino Ester Building Block (–)-**Cα.** To a solution of (+)-**CA6** (0.79 g, 1.75 mmol) in MeOH (5 mL) was added 5 % Pd on Carbon (80 mg) suspended in *t*-BuOH (5 mL). The mixture was stirred under hydrogen atmosphere for 3 h, and filtered through celite bed. Concentration of filtrate *in vacuo* gave 0.49 g (88 % yield) of building block (–)-**Cα** as brown oil: $[\alpha]^{23}_{D}$ = –7.58 (*c* 1.13, CH_2Cl_2); IR (neat) 3386 (w, br), 3321 (w), 2943 (m), 2839 (w), 1732 (s), 1597 (m), 1446 (m), 1377 (w), 1196 (s), 1068 (s), 791 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.5 Hz, 1 H), 7.83 (d, *J* = 7.7 Hz, 1 H), 7.75 (d, *J* = 8.3 Hz, 1 H), 7.50 (t, *J* = 8.4 Hz, 1 H), 7.45 (t, *J* = 7.0 Hz, 1 H), 7.39 (t , *J* = 7.3 Hz, 1 H), 7.32 (d, *J* = 6.8 Hz, 1 H), 4.52 (t, *J* = 5.6 Hz, 1 H), 3.58 (s, 3 H), 3.51 (d, *J* = 13.9 Hz, 1 H), 3.43 (d, *J* = 13.9 Hz, 1 H), 3.33 (s, 3 H), 3.31 (s, 3 H), 2.45 (dd, *J* = 5.7, 14.0 Hz 1 H), 2.07 (dd, *J* = 5.6 14.0 Hz, 1 H), 1.99 (s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.7, 134.0, 133.0, 132.3, 128.6, 128.4, 127.8, 125.8, 125.5, 125.2, 124.4, 102.6, 60.9, 53.6, 53.3, 51.9, 42.6, 42.5; high resolution mass spectrum (ESI positive ion) *m/z* 340.1532, [(M + Na)$^+$; calcd for $C_{18}H_{23}NO_4Na$ 340.1525].

Amino Ester Building Block (–)-Cβ

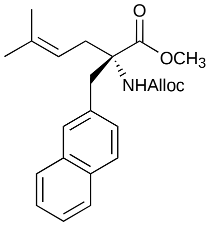




(+)-**CB1**

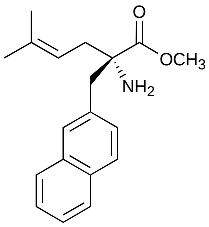
Oxazolidinone (+)-**CB1.** To a -78 °C solution of *trans*-Universal Oxazolidinone (20.0 g, 67.7 mmol) in THF (400 mL) was added LiHMDS 1.0 M THF solution (80 mL, 80 mmol) dropwise over 30 min. The resulting orange-brown suspension was stirred for 30 min and then 2-bromomethylnaphthalene (20 g, 90.5 mmol) was added. The mixture was stirred for 1 h at -78 °C and was gradually warmed to room temperature. The resulting suspension was poured into 10 % aqueous $NaHSO_4$ (200 mL). The mixture was extracted with hexane-ethyl acetate 1:1 mixture (300 mL, 100mL x 2), and the combined extract was washed with brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography, using hexane-ethyl acetate (95:5) as eluant, gave 26.4 g (90 % yield) of **(+)-CB1** as a colorless oil.: $[\alpha]_D^{23}$ = +44.5° (*c* 1.28, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.80-7.74 (m, 3 H); 7.55 (br, 1 H), 7.47 (m, 2 H), 7.44-7.23 (br, 1 H), 6.09 (br, 1 H), 5.91 (br, 1 H), 5.48 (br, 1 H), 5.32 (br, 1 H), 4.72, (br, 2 H), 4.61 (br, 1 H), 3.81 (br, 1 H), 3.25 (d, *J* = 14.0 Hz, 1 H), 2.71, (br, 1 H), 2.87 (dd, *J* = 7.2, 17.2 Hz, 1 H), 1.78 (s, 3 H), 1.74 (s, 3 H), 0.84 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

174.0; 154.0, 135.8, 133.3, 132.6, 131.7, 129.2, 128.2, 127.8, 127.6, 126.0, 125.8, 119.6, 118.4, 94.7, 68.7, 66.5, 39.9, 38.0, 36.2, 26.0, 25.7, 18.0.



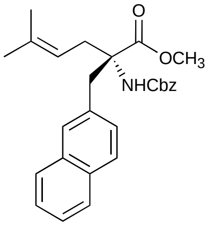
(+)-**CB2**

Alloc-Amino Ester (+)-**CB2.** To a solution of (+)-**CB1** (26.4 g, 60.6 mmol) in THF (125 mL) and MeOH (250 mL) was added 6 M aqueous KOH (125 mL). The resulting mixture was heated to reflux and stirred for 2.5 h. After cooling down the mixture was evaporated to remove most of the solvent. The resulting residue was acidified with conc. hydrochloric acid (ca. 60 mL) under ice bath, extracted with EtOAc (200 mL x 3), and the combined extract was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was dissolved in DMF (200 mL). To this solution was added K_2CO_3 (17 g, 122 mmol), followed by MeI (8mL, 129 mmol) under ice bath. The mixture was stirred overnight, and then dillued with ether (300 mL), and washed with water (300mL) The water layer was extracted with ether (100 mL x 2). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography, using hexane-ethyl acetate (95:5) as eluant, gave 22.0 g (95 % yield) of **(+)-CB2** as a pale yellow oil: $[\alpha]_D^{23}$ = +45.8° (*c* 1.56, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.81-7.72 (m, 3 H); 7.45 (m, 2 H), 7.53 (s, 1 H), 7.18 (dd, *J* = 1.6, 8.3 Hz, 1 H), 5.60 (s, 1 H), 5.98 (m, 1 H), 5.35 (d, *J* = 17.2 Hz, 1 H), 5.26 (d, *J* = 10.4 Hz, 1 H), 5.01 (t, *J* = 7.3 Hz, 1 H), 4.68 (dd, *J*= 5.5, 13.4 Hz, 1 H), 4.60 (dd, *J* = 5.2, 13.4 Hz, 1 H), 3.85 (d, *J* = 13.6 Hz, 1 H), 3.77 (s, 3 H), 3.34 (d, *J* = 13.6 Hz, 1 H), 3.21 (dd, *J* = 7.4, 14.4 Hz, 1 H), 2.66 (dd, *J* = 7.5, 14.5 Hz, 1 H), 1.72 (s, 3 H), 1.64 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 154.3, 135.9, 133.9, 133.3, 133.0, 132.4, 128.5, 127.8, 127.7, 127.6, 127.5, 127.5, 125.9, 125.5, 117.5, 65.3, 65.0, 52.4, 40.7, 34.6, 25.9, 17.9.



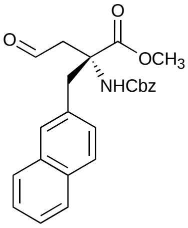
CB3

Amine CB3. To a solution of **(+)-CB2** (22.0 g, 57.7 mmol) in THF (350 mL) was added dimedone (20 g, 143 mmol), followed by $Pd(PPh_3)_4$ (600 mg, 0.52mmol). The resulting mixture was stirred overnight, then evaporated to remove most of the THF. The residue was diluted with ether and filtered. The filtrate was extracted with 1N hydrochloric acid (100 mL x 20) until the trace of product in organic layer disappeared. The combined water layer was cooled by ice bath and basified with 10 N aqueous NaOH. The mixture was extracted with EtOAc (200 mL x 3), washed with brine (100 mL), and dried over Na_2SO_4. Concentration *in vacuo* gave 15 g (87 % yield) of **CB3** as a white pink solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81-7.75 (m, 3 H), 7.45 (m, 2 H), 7.66 (s, 1 H), 7.28 (dd, *J* = 1.4, 8.3 Hz, 1 H), 5.11 (t, *J* = 8.0 Hz, 1 H), 3.70 (s, 3 H), 3.37 (d, *J* = 13.1 Hz, 1 H), 2.97 (d, *J* = 13.1 Hz, 1 H), 2.65 (dd, *J* = 7.5, 13.7 Hz, 1 H), 2.45 (dd, *J* = 8.6, 14.0 Hz, 1 H), 1.75 (s, 3 H), 1.69 (s, 3 H), 1.62 (br, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 136.3, 134.0, 133.3, 132.3, 128.6, 127.9, 127.8, 127.5, 127.5, 125.9, 125.5, 117.9, 62.6, 51.8, 46.0, 38.7, 26.0, 18.0.



CB4

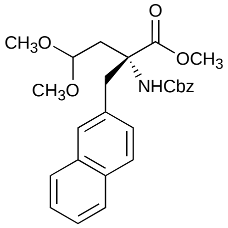
Cbz-Amino Ester CB4. To a solution of **CB3** (7.7 g, 25.9 mmol) in THF (150 mL) was added diisopropylethyl amine (11 mL, 63 mmol), followed by CbzCl (8 mL, 56.5 mmol). The resulting mixture was stirred for 2 h and then filtered. The filtrate was diluted with ether (100 mL), washed with 1N aq. HCl (50 mL), sat. aqueous $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was then dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography, using hexane-ethyl acetate (95:5) as eluant, gave 11.0 g (95 % yield) of **CB4** as a colorless oil.: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (m, 1 H), 7.66-7.61 (m, 2 H), 7.46-7.35 (m, 8 H), 7.09 (dd, *J* = 1.6, 6.7 Hz, 1 H), 5.60 (s, 1 H), 5.24 (d, *J* = 12.3 Hz, 1 H), 5.11 (d, *J* = 12.3 Hz, 1 H), 4.98 (t, *J* = 7.0 Hz, 1 H), 3.83 (d, *J* = 13.6 Hz, 1 H), 3.76 (s, 3 H), 3.32 (d, *J* = 13.6 Hz, 1 H), 3.21 (dd, *J* = 7.0, 14.2 Hz, 1 H), 2.64 (dd, *J* = 7.4, 14.4 Hz, 1 H), 1.69 (s, 3 H), 1.60 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 154.4, 136.3, 136.0, 133.9, 133.3, 132.4, 128.5, 128.4, 128.1, 128.1, 127.9, 127.8, 127.7, 127.5, 125.8, 125.5, 117.5, 66.2, 65.4, 52.5, 40.7, 34.6, 26.0, 17.9.



CB5

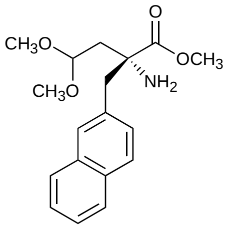
Aldehyde CB5. To a solution of **CB4** (10.0 g, 23.2 mmol) in 1,4-dioxane (150 mL) was added OsO_4 4 wt % aqueous solution (2 mL, 0.31 mmol). The resulting mixture was stirred for 30 min. To this solution was added $NaIO_4$ (10.5 g, 49.1 mmol) aqueous solution (60 mL) portionwise. The mixture was stirred overnight and extracted with ether (300 mL, 100 mL x 2), and the combined extract was washed with brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography, using hexane-ethyl acetate (85:15) as eluant, gave 6.14 g (65 % yield) of **CB5** as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.69 (s, 1 H), 7.80-7.78 (m, 1

H), 7.67 (d, *J* = 8.4 Hz, 1 H), 7.63-7.61 (m, 1 H), 7.46-7.26 (m, 8 H), 7.03 (dd, *J* = 1.7, 8.4 Hz, 1 H), 5.86 (s, 1 H), 5.26 (d, *J*= 12.3 Hz, 1 H), 5.02 (d, *J* = 12.3 Hz, 1 H), 3.97 (d, *J* = 18.0 Hz, 1 H), 3.78 (d, *J* = 13.4 Hz, 1 H), 3.74 (s, 3 H), 3.16 (d, *J* = 13.5 Hz, 1 H), 3.15 (d, *J* = 13.5 Hz, 1 H); ^{13}C NMR (125 MHz, $\mathrm{CDCl_3}$) δ 198.6, 171.9, 154.6, 136.3, 133.3, 132.5, 132.1, 128.7, 128.6, 128.2, 128.1, 127.9, 127.6, 127.6, 127.6, 126.0, 125.8, 66.5, 61.2, 52.9, 48.8, 41.6.



CB6

Acetal CB6. To a solution of **CB5** (6.14 g, 15.1 mmol) in MeOH (50 mL) and methyl orthoformate (10 mL) was added *p*-TsOH•$\mathrm{H_2O}$ (0.5 g, 2.9 mmol). The mixture was heated to reflux and stirred for 3 h. After cooling down the reaction mixture was evaporated to remove most of solvent and diluted with ether. The resulting mixture was washed with sat. aqueous $\mathrm{NaHCO_3}$ and dried over $\mathrm{Na_2SO_4}$. Concentration *in vacuo* gave 6.64 g (97 %) of **CB6** as a colorless oil: ^{1}H NMR (500 MHz, $\mathrm{CDCl_3}$) δ 7.79-7.76 (m, 1 H), 7.64 (d, *J* = 8.4 Hz, 1 H), 7.62-7.59 (m, 1 H), 7.44-7.26 (m, 8 H), 7.06 (dd, *J* = 1.6, 8.4 Hz, 1 H), 5.86 (s, 1 H), 5.29 (d, *J* = 12.3 Hz, 1 H), 5.12 (d, *J* = 12.3 Hz, 1 H), 4.35 (dd, *J* = 3.0, 8.1 Hz, 1 H), 3.77 (d, *J* = 13.8 Hz, 1 H), 3.76 (s, 3 H), 3.32 (s, 3 H), 3.27 (d, *J* = 13.5 Hz, 1 H), 3.26 (s, 3 H), 2.89 (dd, *J* = 3.0, 14.2 Hz, 1 H), 2.36 (dd, *J* = 8.2, 14.2 Hz, 1 H); ^{13}C NMR (125 MHz, $\mathrm{CDCl_3}$) δ 172.8, 154.4, 136.8, 133.3, 133.2, 132.4, 128.7, 128.5, 128.2, 128.1, 127.9, 125.7, 127.5, 125.8, 124.5, 102.6, 66.4, 62.6, 55.1, 53.6, 52.4, 41.2, 39.2, 31.5.

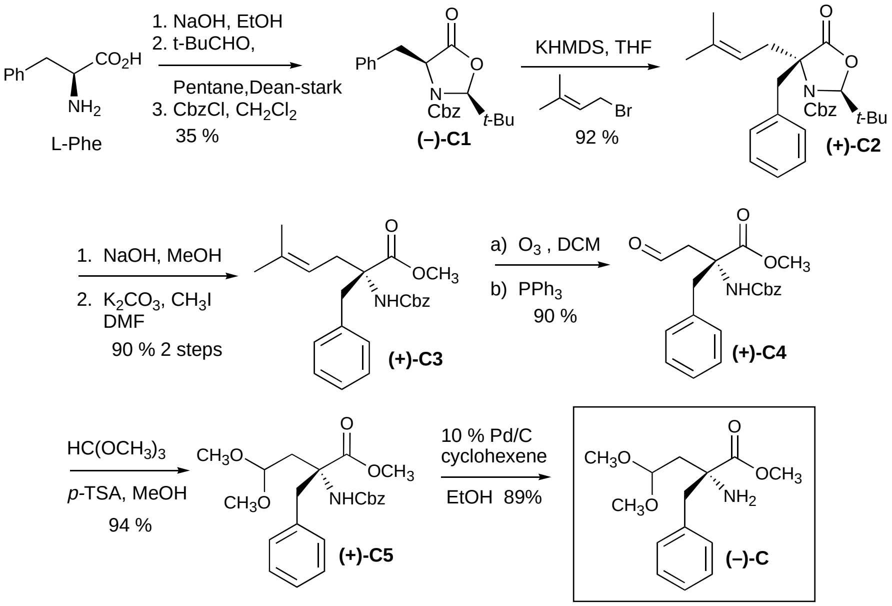


(–)-**Cβ**

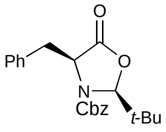
Amino Ester Building Block (–)-**Cβ.** To a solution of **CB6** (6.64 g, 14.7 mmol) in MeOH (120 mL) was added 5 % Pd on Carbon (200 mg) suspended in *t*-BuOH (5 mL). The mixture was stirred under hydrogen atmosphere for 3 h, and filtered through celite bed. Concentration of filtrate *in vacuo* gave 4.50 g (96 % yield) of building block (–)-**Cβ** as white-yellow solid: $[\alpha]^{23}_{D}$ –23.94 (*c* 0.85, $\mathrm{CH_2Cl_2}$); IR (neat) 3386 (w, br), 3321 (w), 3051 (w), 2943 (m), 2835 (w), 1736 (s), 1600 (m), 1442 (m), 1373 (w), 1196 (s), 1122 (s), 1061 (s), 964 9w), 902 (w), 860 (w), 821(m), 748 (m); ^{1}H NMR (500 MHz, $\mathrm{CDCl_3}$) δ 7.81-7.78 (m, 2 H), 7.63 (s, 1 H), 7.76 (d, J = 8.8 Hz, 1 H), 7.46 (m, 2 H), 7.25 (d, J = 8.4 Hz, 1 H), 4.51 (t, J = 5.5 Hz, 1 H), 3.71 (s, 3 H), 3.34 (s, 3 H), 3.31 (s, 3 H), 3.30

(d, J = 13.0 Hz, 1 H), 2.96 (d, J = 13.1 Hz, 1 H), 2.36 (dd, J = 5.6, 14.2 Hz, 1 H), 2.00 (dd, J = 5.4, 14.2 Hz, 1 H), 1.87 (br, 2 H),; ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5, 133.3, 132.5, 128.9, 128.2, 127.9, 127.6, 127.6, 127.5, 126.0, 125.6, 102.4, 60.2, 53.5, 53.4, 51.9, 47.1, 42.5; high resolution mass spectrum (ESI positive ion) *m/z* 340.1532, [$(M + Na)^+$; calcd for $C_{18}H_{23}NO_4Na$ 340.1525].

Building Block C (Phe)

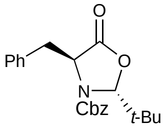


Oxazolidinone (–)-C1. A solution of NaOH (4.4 g, 110 mmol) in water (22 mL) was added to a mixture of L-phenylalanine (17.2 g, 104 mmol) in EtOH (230 mL). The mixture was stirred at room temperature for 1 h, and then it was concentrated *in vacuo* to provide a white solid. Pentane was added (300 mL), followed by pivalaldehyde (17 mL, 156 mmol). The flask was equipped with a Dean-Stark trap, and the reaction mixture was stirred at reflux for 72 h, when the collection of water had ceased. After cooling, the mixture was concentrated *in vacuo* to provide a white solid that was azeotropically dried with toluene (200 mL) and then stored under high vacuum overnight. The resulting dry imine was suspended in methylene chloride (270 mL) and treated with benzyl chloroformate at 0 °C. The reaction mixture was maintained at this temperature for 16 days, when water (100 mL) and DMAP (25 mg) were added and the resulting biphasic system was warmed to room temperature and stirred overnight. The mixture was extracted with EtOAc (500 mL) and the organic layer was washed with 10% aqueous $NaHSO_4$, saturated aqueous $NaHCO_3$, and brine (200 mL each), dried over Na_2SO_4, and concentrated *in vacuo.* The residue was purified by flash chromatography using ethyl acetate–hexanes (1:9) as eluant to afford a mixture of (–)-**C1** and its *trans* isomer (19 g, 50% yield) in a 2.5:1 diastereomeric ratio. Separation of the two isomers by preparative HPLC (Waters LC500), using 7% ethyl acetate in hexanes as eluant, provided the *cis* isomer (–)-**C1** as a colorless oil (13.3 g, 35%, d.r. > 20:1).

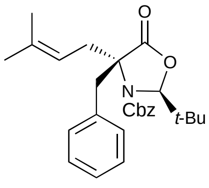


(–)-**C1**

***Cis* isomer** (–)-**C1.** $[\alpha]^{23}_{D}$ –10.7 (*c* 0.98, $CHCl_3$); IR (neat) 2961 (m), 1793 (s), 1722 (s), 1455 (w), 1392 (m), 1231 (m), 1035 (m), 697 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50-7.20 (10 H), 5.56 (s, 1 H), 5.14 (d, *J* = 11.9 Hz, 1 H), 4.93 (d, *J* = 11.8 Hz, 1 H), 4.48 (dd, *J* = 7.6, 5.6 Hz, 1 H), 3.21 (dd, *J* = 13.9. 7.6 Hz, 1 H), 3.12 (dd, *J* = 13.9, 5.5 Hz, 1 H), 1.00 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 155.9, 136.8, 135.2, 129.5, 128.7, 128.6, 128.5, 128.4, 126.9, 96.3, 68.3, 58.9, 39.3, 37.1, 24.9; high resolution mass spectrum (ESI positive ion) *m/z* 390.1684 $[(M+Na)^+$; calcd for $C_{22}H_{25}O_4NNa$: 390.1681].

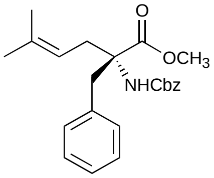


***Trans* isomer.** m.p. 66-68 °C, $[\alpha]^{23}_{D}$ +117.7 (*c* 1.02, $CHCl_3$); IR (neat) 2968 (m), 1796 (s), 1713 (s), 1455 (w), 1407 (s), 1357 (m), 1327 (m), 1228 (m), 1165 (m), 1123 (m), 1006 (m), 755 (m), 700 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45-7.35 (5 H), 7.25-7.10 (3 H), 7.01 (broad s, 2 H), 5.30 (d, *J* = 11.9 Hz, 1 H), 5.14 (broad s, 1 H), 5.06 (broad s, 1 H), 4.45 (m, 1 H), 3.80 (broad s, 1 H), 3.15 (dd, *J* = 14.2, 2.4 Hz, 1 H), 0.88 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 152.9, 135.2, 134.2, 129.8, 128.9, 128.7, 128.5, 128.1, 127.3, 95.0, 67.7, 58.4, 39.6, 34.4, 24.8; high resolution mass spectrum (ESI positive ion) *m/z* 390.1681 $[(M+Na)^+$; calcd for $C_{22}H_{25}O_4NNa$: 390.1681].



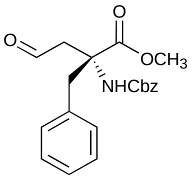
(+)-**C2**

Oxazolidinone (+)-**C2.** A solution of oxazolidinone (–)-**C1** (12.3 g, 33.4 mmol) in THF (125 mL) was treated dropwise with a 0.5 M solution of KHMDS in toluene (83.5 mL, 41.7 mmol) at –78 °C. After 20 min 1-bromo-3-methyl-butene (7.9 mL, 66.7 mmol) was added dropwise to the reaction mixture and stirring was continued at the same temperature for additional 45 min. The reaction was quenched with 10% aqueous $NaHSO_4$ (240 mL), followed by extraction with EtOAc (2 x 200 mL). The combined organic extracts were washed with 10% aqueous $NaHSO_4$, saturated aqueous $NaHCO_3$, and brine (170 mL each), dried over Na_2SO_4, and concentrated *in vacuo*. The product was purified by flash chromatography using 5% ethyl acetate in hexanes as eluant to afford oxazolidinone (+)-**C2** as a colorless oil (13.3 g, 92% yield). $[\alpha]_D^{23}$ +30.8 (*c* 0.74, $CHCl_3$); IR (neat) 3064 (w), 3032 (w), 2963 (m), 2932 (m), 1790 (s), 1716 (s), 1603 (w), 1496 (m), 1481 (m), 1455 (s), 1392 (s), 1324 (s), 1277 (s), 1213 (m), 1190 (s), 1129 (m), 1080 (w), 1043 (s), 1014 (s), 916 (w), 848 (w), 804 (w), 751 (m), 700 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50-7.30 (5 H), 7.19 (broad s, 5 H), 5.31 (d, *J* = 11.9 Hz, 1 H), 5.30 (broad s, 1 H), 5.11 (broad s, 1 H), 4.82 (broad t, *J* = 7.1 Hz, 1 H), 3.29 (broad s, 1 H), 3.28 (broad d, *J* = 0.7 Hz, 1 H), 2.93 (broad s, 1 H), 2.44 (m, 1 H), 1.65 (s, 3 H), 1.54 (s, 3 H), 0.53 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 156.0, 138.2, 135.9, 135.2, 131.0, 128.7, 128.6, 128.5, 128.2, 127.1, 115.5, 95.5, 69.3, 67.9, 42.1, 37.6, 36.9, 26.0, 25.0, 17.9; high resolution mass spectrum (ESI positive ion) *m/z* 458.2318 $[(M+Na)^+$; calcd for $C_{27}H_{33}NO_4Na$: 458.2307].



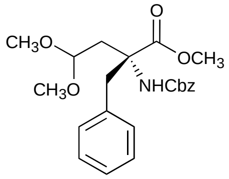
(+)-**C3**

Aminoester (+)-**C3.** A solution of oxazolidinone (+)-**C2** (13.5 g, 31 mmol) in methanol (150 mL) and aqueous 1N NaOH (150 mL) was stirred at reflux for 8 h. After cooling to room temperature the reaction mixture was concentrated in vacuo and the residue was acidified to pH 1 with aqueous 10% solution of $NaHSO_4$. The mixture was extracted with EtOAc (3x300 mL) and the combined organic extracts were washed with water and brine (250 L each), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was stored under high vacuum for 2 h, then dissolved in DMF (20 mL) and treated with iodomethane (4 mL, 62 mmol) at 0 °C. The reaction mixture was stirred at this temperature for 30 min, then at room temperature for additional 30 min. Water (30 mL) was added to the reaction followed by extraction with diethyl ether (2x300 mL). The combined organic extracts were washed with water (4x150mL), saturated aqueous $NaHCO_3$, and brine (150 mL each), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 8% ethyl acetate in hexanes as eluant to afford aminoester (+)-**C3** as a colorless oil (10.7 g, 90% yield). $[\alpha]_D^{23}$ +34.6 (*c* 1.47, $CHCl_3$); IR (neat) 3422 (m), 2951 (m), 1722 (s), 1498 (s), 1455 (m), 1343 (w), 1237 (m), 1075 (m), 1041 (m), 744 (w), 701 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50-7.30 (5 H), 7.20-7.10 (3 H), 7.00-6.90 (2 H), 5.60 (broad s, 1 H), 5.20 (d, *J* = 12.7 Hz, 1 H), 5.09 (d, *J* = 12.7 Hz, 1 H), 4.96 (t, *J* = 7.4 Hz, 1 H), 3.74 (s, 3 H), 3.66 (d, *J* = 13.6 Hz, 1 H), 3.17 (dd, *J* = 14.4, 7.4 Hz, 1 H), 3.14 (d, *J* = 13.6 Hz, 1 H), 2.59 (dd, *J* = 14.4, 7.4 Hz, 1 H), 1.68 (s, 3 H), 1.59 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 154.3, 136.8, 136.3, 135.9, 129.7, 128.4, 128.2, 128.1, 128.0, 126.8, 117.5, 66.2, 65.3, 52.4, 40.5, 34.5, 25.9, 17.9; high resolution mass spectrum (ESI positive ion) *m/z* 404.1835 $[(M+Na)^+$; calcd for $C_{23}H_{27}O_4NNa$: 404.1837].



(+)-**C4**

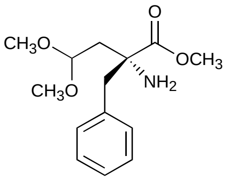
Aldehyde (+)-**C4.** Ozone was passed through a solution of alkene (+)-**C3** (10.6 g, 28 mmol) in dichloromethane (300 mL) at –78 °C until the blue color of the reaction mixture became persistent. Argon was then bubbled through the mixture until the blue color disappeared, when most of the excess ozone was removed. A solution of triphenyl phosphine (9.0 g, 34 mmol) in dichloromethane (70 mL) was added to the reaction mixture at –78 °C, and after warming to room temperature the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography using ethyl acetate-hexanes (1:4) as eluant to afford aldehyde (+)-**C4** as a white solid (8.9 g, 90% yield). m.p. 81-83 °C, $[\alpha]_D^{23}$ +96.2 (*c* 1.00, $CHCl_3$); IR (neat) 3419 (m), 3031 (w), 2953 (w), 1744 (s), 1724 (s), 1497 (s), 1455 (m), 1228 (s), 1078 (m), 1054 (m), 743 (w), 701 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.67 (broad s, 1 H), 7.45-7.35 (4 H), 7.25-7.10 (3 H), 6.95-6.85 (2 H), 5.83 (broad s, 1 H), 5.21 (d, *J* = 12.3 Hz, 1 H), 5.01 (d, *J* = 12.3 Hz, 1 H), 3.90 (d, *J* = 17.9 Hz, 1 H), 3.73 (s, 3 H), 3.60 (d, *J* = 13.4 Hz, 1 H), 3.10 (d, *J* = 17.9 Hz, 1 H), 2.98 (d, *J* = 13.4 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.6, 171.8, 154.5, 136.4, 134.5, 129.7, 128.5, 128.3, 128.1, 128.0, 127.3, 66.5, 61.0, 52.8, 48.7, 41.4; high resolution mass spectrum (ESI positive ion) *m/z* 378.1314 $[(M+Na)^+$; calcd for $C_{20}H_{21}NO_5Na$: 378.1317].



(+)-**C5**

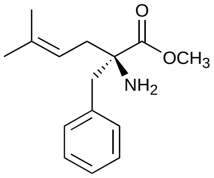
Acetal (+)-**C5.** To a solution of aldehyde (+)-**C4** (8.9 g, 25 mmol) in MeOH (22 mL) was added trimethyl orthoformate (22 mL, 200 mmol) and a catalytic amount of p-toluenesulfonic acid. The reaction mixture was stirred at reflux for 2 h. After cooling diethyl ether (300 mL) was added. The resulting organic solution was washed with saturated aqueous $NaHCO_3$ and brine (100 mL each), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography using ethyl acetate-hexane (1:9) to provide acetal (+)-**C5** as a colorless oil (9.4 g, 94% yield). $[\alpha]_D^{23}$ +69.8 (*c* 1.77, $CHCl_3$); IR (neat) 3417 (m), 3063 (w), 3031 (w), 2951 (m), 2833 (w), 1738 (s), 1722 (s), 1497 (s), 1454 (m), 1214 (s), 1074 (s), 745 (m), 701 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50-7.30 (5 H), 7.30-7.10 (3 H), 7.00-6.90 (2 H), 5.83 (broad s, 1 H), 5.09 (d, *J* = 12.3 Hz, 1 H), 4.31 (dd, *J* = 8.2, 3.0 Hz, 1 H), 3.73 (s, 3 H), 3.58 (d, *J* = 13.5 Hz, 1 H), 3.29 (s, 3 H), 3.25 (s, 3 H), 3.07 (d, *J* = 13.5 Hz, 1 H), 2.83 (dd, *J* = 14.2, 3.0 Hz, 1 H), 2.82 (d, *J* = 12.3 Hz, 1 H), 2.29 (dd, *J* = 14.2, 8.2

Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 154.3, 136.8, 135.6, 129.8, 128.5, 128.3, 128.1, 128.1, 126.9, 102.6, 66.3, 62.5, 55.0, 53.6, 52.4, 41. 0, 39.1; high resolution mass spectrum (ESI positive ion) *m/z* 424.1736 [(M+Na)$^+$; calcd for $C_{22}H_{27}O_6NNa$: 424.1736].



(–)-**C**

Aminoester (–)-**C.** A solution of Cbz-protected amine (+)-**C5** (2 g, 7.985 mmol) in ethanol (20 mL) was treated with 10% wt Pd on carbon (400 mg) and cyclohexene (5 mL, 50 mmol). The mixtured was stirred at reflux for 2.5 h. After cooling to room temperature the reaction mixture was filtered through Celite, and concentrated *in vacuo*. The crude residue was purified by flash-chromatography using ethyl acetate-hexanes (1:1) as eluant to provide aminoester (–)-**C** as a colorless oil (1.2 g, 89% yield). $[\alpha]_D^{23}$ –11.0 (*c* 0.74, $CHCl_3$); IR (neat) 3389 (m), 3323 (m), 3062 (m), 3029 (m), 2948 (s), 2832 (m), 1738 (s), 1603 (m), 1495 (w), 1454 (m), 1442 (m), 1195 (s), 1124 (s), 968 (m), 815 (w), 704 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.22 (3 H), 7.12 (d, *J* = 6.9 Hz, 2 H), 4.48 (t, *J* = 5.6 Hz, 1 H), 3.68 (s, 3 H), 3.32 (s, 3 H), 3.29 (s, 3 H), 3.13 (d, *J* = 13.1 Hz, 1 H), 2.77 (d, *J* = 13.1 Hz, 1 H), 2.29 (dd, *J* = 14.0, 5.8 Hz, 1 H), 1.91 (dd, *J* = 14.0, 5.4 Hz, 1 H), 1.71 (broad s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 135.8, 130.0, 128.3, 127.0, 102.4, 60.1, 53.4, 53.3, 51.9, 47.0, 42.5; high resolution mass spectrum (ESI positive ion) *m/z* 268.1552 [(M+H)$^+$; calcd for $C_{14}H_{22}O_4N$: 268.1548].



(–)-**D**

Amino Ester Building Block (–)-**D.**[3] $[\alpha]_D^{23}$ –2.6 (*c* 4.53, $CHCl_3$); IR ($CHCl_3$) 3360 (w), 2980 (m), 1735 (s), 1600 (m), 1500 (w), 1455 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.10 (m, 5 H), 5.07-5.03 (m, 1 H), 3.68 (s, 3 H), 3.18 (d, *J* = 13.1 Hz, 1 H), 2.79 (d, *J* = 13.2 Hz, 1 H), 2.60 (dd, *J* = 6.7, 14.1 Hz, 1 H), 2.48 (dd, *J* = 8.2, 14.1 Hz, 1 H), 1.73 (s, 3 H), 1.67 (s, 3 H), 1.53 (br s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.92, 136.50, 136.37, 129.84, 128.32, 126.86, 117.95, 62.57, 51.84, 45.92, 38.l73, 26.04, 18.05; high resolution mass spectrum (CI,

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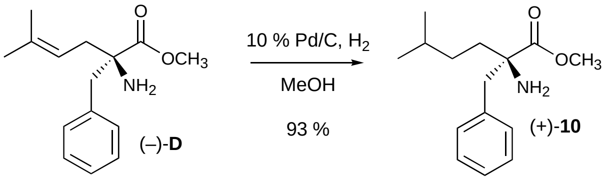
(3) Smith, A. B., III; Guzman, M. C.; Sprengeler, P. A.; Keenan, T. P.; Holcomb, R. C.; Wood, J. L.; Carroll, P. J.; Hirschmann, R. *J. Am. Chem. Soc*. **1994**, *116*, 9947-9962.

NH_3) *m/z* 248.1654 [(M+H)$^+$; calcd for $C_{15}H_{22}NO_2$: 248.1650]. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.89; H, 8.70; N, 5.65.



Aminoester (+)-**10.** To a solution of olefin (–)-**D** (110 mg, 0.445 mmol) in methanol (4 mL) was added 10% wt Pd on carbon (70 mg). The mixture was briefly evacuated and opened to argon three times, then evacuated again and opened to hydrogen (1atm). After stirring for 22 h at room temperature, the reaction mixture was filtered through Celite, and concentrated *in vacuo*. The crude residue was purified by flash-chromatography using ethyl acetate-hexanes (1:4) as eluant to provide amino ester (+)-**10** as a colorless oil (103 mg, 93% yield). $[\alpha]^{23}_{D}$ +31.3 (*c* 0 1.04, C_6H_6); IR (neat) 3382 (w), 3085 (m), 3029 (m), 2954 (s), 2927 (s), 2870 (m), 1737 (s), 1603 (m), 1495 (w), 1467 (m), 1454 (m), 1385 (m), 1367 (m), 1211 (s), 1192 (s), 1031 (m), 702 (m) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.40-7.15 (5 H), 3.40 (s, 3 H), 3.24 (d, *J* = 13.0 Hz, 1 H), 2.81 (d, *J* = 13.0 Hz, 1 H), 1.98 (td, *J* = 12.8, 4.3 Hz, 1 H), 1.64 (td, *J* = 12.8, 4.6 Hz, 1 H), 1.48 (thept., *J* = 6.7, 6.7 Hz, 1 H), 1.45 (broad s, 2 H), 1.19 (m, 1 H), 1.37 (m, 1 H), 0.93 (d, *J* = 6.7 Hz, 3 H) 0.92 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 176.8, 137.4, 130.4, 128.5, 127.0, 62.5, 51.2, 46.7, 38.7, 33.4, 28.6, 22.7, 22.6; high resolution mass spectrum (ESI positive ion) *m/z* 250.1801 [(M+H)$^+$; calcd for $C_{15}H_{24}NO_2$: 250.1807].