Supplementary Information for:

Chiral Sugars Drive Enantioenrichment in Prebiotic Amino Acid Synthesis

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1. Experimental Procedures

General Experimental Details

All reactions were carried out in glassware that is not oven-dried; each reaction vial is capped under an atmosphere of air unless otherwise noted. NMR spectra were recorded at 298.0 °K on a Bruker DRX-500 at 500 MHz. $CDCl_3$ was used as an internal reference for ^1H NMR ($\delta = 7.26$) and ^{13}C NMR ($\delta = 77.16$) spectra collected in $CDCl_3$. CD_3OD was used as an internal reference for ^1H NMR ($\delta = 3.31$) and ^{13}C NMR ($\delta = 49.00$) spectra collected in CD_3OD. DMSO-d_6 was used as an internal reference for ^1H NMR ($\delta = 2.50$) and ^{13}C NMR ($\delta = 39.52$) spectra collected in DMSO-d_6. *t*-BuOH was used as an internal reference for ^1H NMR ($\delta = 1.24$) and ^{13}C NMR ($\delta = 30.29$) spectra collected in D_2O. Preparative chromatography was conducted with Analtech Uniplate thin-layer chromatography preparatory plates (UV 254, 20 × 20 cm, 1000 micron). 30 mm PTFE 0.2 μm and 13 mm PTFE 0.45 μm syringe filters were used for filtration of preparatory TLC and HPLC assay samples respectively. Chiral HPLC assays were conducted on an Agilent 1100 Series Liquid Chromatograph using a Chiralcel OZ-3 column (particle size: 3 μm; dimensions: 4.6 × 250 mm; Lot No. OZ30CE-PL009) and a Lux Amylose-1 column (particle size 5 μm; dimensions: 4.6 × 250 mm; S/No. H15-086884). Absolute mass information was collected on an Agilent ESI-TOF (LC/MSD TOF) by the Scripps Center for Mass Spectrometry. All starting materials, additional reagents, solvents, and deuterated solvents for NMR spectra were used without further purification.

Chemicals

Starting Materials. Phenylacetaldehyde, acetaldehyde, L-lyxose, D-xylose, L-xylose, D-erythrose, and D-talose were purchased from Alfa Aesar. D-phenylalanine methyl ester hydrochloride (D-Phe-OMe•HCl), L-phenylalanine methyl ester hydrochloride (L-Phe-OMe•HCl), D-tryptophan methyl ester hydrochloride (D-Trp-OMe•HCl), D-alanine methyl ester hydrochloride (D-Ala-OMe•HCl), tryptophol, and D-threose were purchased from Combi-Blocks. L-tryptophan methyl ester hydrochloride (L-Trp-OMe•HCl) and L-alanine methyl ester hydrochloride (L-Ala-OMe•HCl) were purchased from Ox-Chem. D-Lyxose was purchased from Acros. D-Arabinose and L-arabinose were purchased from Calbiochem. L-Ribose was purchased from TCI. D-Allose was purchased from Chem-Impex. D-Gulose was purchased from Toronto Research Chemicals. D-Ribose, 2-deoxy-D-ribose, D-mannose, D-galactose, and D-glucose were purchased from Sigma-Aldrich.

Additional Reagents. Ammonium chloride (NH_4Cl), sodium hydroxide (NaOH), benzoyl chloride (BzCl), triethylamine (NEt_3), and zinc (II) iodide (ZnI_2) were purchased from Acros. 7 N ammonia in methanol was purchased from Sigma-Aldrich. 2-Iodoxybenzoic acid (IBX) and trimethylsilyl cyanide (TMSCN) were purchased from Matrix Scientific. Potassium cyanide (KCN) was purchased from Alfa Aesar. Magnesium Sulfate ($MgSO_4$) was purchased from EMD.

Solvents. Ammonium hydroxide (NH_4OH) was purchased from Electron Microscopy Sciences. Purifications were conducted with ethyl acetate (EtOAc) and dichloromethane (CH_2Cl_2) purchased from Macron, HPLC grade methanol (CH_3OH) purchased from VWR, and hexanes purchased from Fisher. Aqueous reaction solutions for studies of aminonitriles with sugars were prepared with HPLC grade water purchased from VWR. *tert*-Butanol (*t*-BuOH) was purchased from Sigma-Aldrich. Chiral assays were conducted with HPLC grade hexanes and HPLC grade *iso*-propanol (*i*-PrOH) that were purchased from Fisher.

Deuterated Solvents for NMR Spectra. Chloroform ($CDCl_3$), methanol (CD_3OD), dimethyl-sulfoxide (DMSO-d_6), and water (D_2O) were purchased from Cambridge Isotope Laboratories.

General Reaction Procedure for Sugar-Mediated Reaction of AM-I to AM-II

All reactions were carried out according to this general procedure unless otherwise noted. To a 1 dram vial with a stirbar was added AM-**I** (0.250 mmol) and sugar (0.500 mmol). When the sugar is a solid, the sugar was massed on weigh paper and then added to AM-**I** in the 1 dram vial. When the sugar is a liquid, the sugar was massed in the 1 dram vial and AM-**I** was massed on weigh paper and added right before addition of water as solvent.

Reaction progress was initiated with the addition of 0.25 M NaOH in H_2O (1.000 mL) via micropipette and the reaction was stirred at room temperature for a given period of time. The solution of 0.25 M NaOH in H_2O was prepared in a 50 mL volumetric flask with NaOH (500.3 mg, 12.51 mmol) and H_2O. Temperature was measured via thermometer in an independent 1 dram vial containing H_2O open to air. The recorded temperature ranged between 22 and 24 °C.

In order to assess enantiomeric enrichment of AM-**II** at a given period of time, a derivatization protocol was developed to halt reaction progress, convert AM-**II** to Bz-AM-**II**, and isolate purified Bz-AM-**II**. At the time for a given enantiomeric enrichment measurement, the entire reaction vessel was treated with the following protocol: *i*-PrOH (1.000 mL) was added, followed immediately by benzoyl chloride (52 μL, 0.45 mmol) and triethylamine (55 μL, 0.40 mmol). The stirred solution was transferred to a 20 mL scintillation vial, which contained *i*-PrOH (3.0 mL) and solid $MgSO_4$. The 1 dram vial was washed with *i*-PrOH (1.0 mL) and CH_2Cl_2 (2.0 mL). The resulting solution was agitated, treated with an additional portion of solid $MgSO_4$ to ensure removal of water, agitated again, filtered (rinsing with CH_2Cl_2), and concentrated under reduced pressure to give the crude reaction mixture. *i*-PrOH (0.5 mL) and CH_2Cl_2 (0.5 mL) were added and the mixture was sonicated to ensure solvation. The solution was purified by preparatory TLC (Bz-Ala-**II**: 10% MeOH/CH_2Cl_2; Bz-Phe-**II**: 4% MeOH/CH_2Cl_2 run twice; Bz-Trp-**II**: 10% MeOH/CH_2Cl_2). The Bz-AM-**II** was recovered after analysis of the plate by UV (254 nm), removal of the silica pertaining to the Bz-AM-**II** UV band into a 20 mL scintillation vial, addition of methanol (8.0 mL), sonication, filtration, and concentration under reduced pressure. Chiral HPLC samples were filtered before analysis.

Reaction Procedures for Table 1, Table 2, and Table S.2. Independent AM-**I** reactions with D-ribose, D-lyxose, D-xylose, D-arabinose, and D-deoxyribose in Table 1 were conducted according to the general procedure. Bz-Ala-**II** e.e. data with D-ribose and D-lyxose independently are both averages of two trials. Bz-Phe-**II** e.e. data with D-ribose is an average of three trials. Isolated yields for reactions in Table 1 are included in Table S.1.

D-ribose/ D-lyxose mixture reactions were conducted according to the general procedure with the following modification: To a 1 dram vial with a stirbar was added AM-**I** (0.250 mmol), D-ribose (0.250 mmol), and D-lyxose (0.250 mmol).

D-ribose/D-lyxose/D-xylose/D-arabinose mixture reactions were conducted according to the general procedure with the following modification: To a 1 dram vial with a stirbar was added

AM-**I** (0.250 mmol), D-ribose (0.250 mmol), D-lyxose (0.250 mmol), D-xylose (0.250 mmol), and D-arabinose (0.250 mmol).

Reactions of Phe-**I** with L-aldopentoses and with C4 and C6 aldose sugars were carried out according to the general procedure and results are included in Tables 2 and S.2 respectively.

Reaction Procedures for Figure 1 Data. Reactions were conducted according to the general procedure with Phe-**I** and D-ribose. Independent reactions were conducted for each entry with *i*-PrOH (1.0 mL) and CH_2Cl_2 (1.0 mL) were added and the crude reaction mixture was sonicated to ensure solvation. A portion (100. μL) was removed for analysis via HPLC to assess conversion and the remainder was purified by preparatory TLC (4% MeOH/CH_2Cl_2; run twice). When both Bz-Phe-**I** and Bz-Phe-**II** are present, reaction conversion is calculated as the integrated peak values of Bz-Phe-**II**$_{R+S}$/(Bz-Phe-**I** $_{R+S}$ +Bz-Phe-**II** $_{R+S}$) and is uncalibrated. Experimental data is summarized in Figure 1. The kinetic model used in Figure 2 is summarized in Figures S.33-S.34.

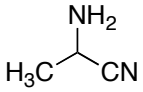
Reaction Procedures for Table 3 Data. Reactions were conducted according to the general procedure with Phe-**I** and D-ribose. Entries were halted at t = 24 h. Results are given in Table 3.

Reaction Procedures for Table 4 Data. Reactions were conducted according to the general procedure with Phe-**I** and D-ribose. Independent reactions were conducted for each entry at room temperature and at 37 °C in an oil bath. The solvent for Entries 1 and 2 is HPLC grade H_2O. The solvent for Entries 3 and 4 is a solution of 1.0 x 10^{-4} M NaOH in H_2O. This solution was prepared as follows: 0.25 M NaOH (1.0 mL) was added to a 25 mL volumetric flask and filled with H_2O, generating a solution of 1.0 x 10^{-2} M NaOH. 1.0 x 10^{-2} M NaOH (250. μL) was added to a 25 mL volumetric flask and filled with H_2O, generating a solution of 1.0 x 10^{-4} M NaOH in H_2O. Results are given in Table 4.

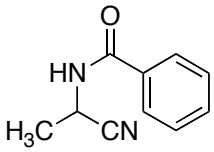
Procedures for NMR Studies in Figures S.35-S.40. To an NMR spectroscopy tube was added Phe-**I** (36.5 mg, 0.250 mmol) and D-ribose (75.1 mg, 0.500 mmol). Reaction progress was initiated with the addition of 0.25 M NaOH in D_2O (1.000 mL) via micropipette. The solution of 0.25 M NaOH in D_2O was prepared in a 10 mL volumetric flask. NaOH (100.1 mg, 2.503 mmol) was massed in the volumetric flask followed by the addition of D_2O (4.0 mL). *tert*-Butanol (47.8 μL, 0.500 mmol) was added to the volumetric flask, which was then filled to the line with D_2O in order to generate a solution of 0.25 M NaOH and 0.05 M *t*-BuOH in D_2O. The reaction was sonicated for 3 min to assist in mixing and inverted several times. The reaction was monitored via NMR spectroscopy. Averaged time points for spectra are included. Reactions were set up with an identical protocol to record experiments at the same time points. Results are given in Figures S.35-S.40.

2. Synthesis, Spectroscopic Characterization, and Chiral Assays of Compounds

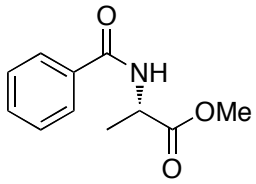
Reactions are not optimized for yield, but for providing sufficient quantities of material for the desired uses associated with each compound. ^{1}H NMR spectra, ^{13}C NMR spectra, and chiral HPLC data are included in Figures S.1-S.24. In the main text, aminonitrile or amino amide compounds denoted with (L) or (D) correspond to the stereogenic center found in the L- or D-amino acid. A designation of L corresponds to the *S* stereogenic center and a designation of D corresponds to the *R* stereogenic center for the compounds studied.



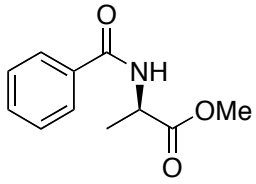
2-aminopropanenitrile (Ala-I).[1] To a round bottom flask with stirbar was added TMSCN (4.68 mL, 37.4 mmol) and acetaldehyde (1.68 mL, 29.9 mmol). The mixture was stirred vigorously and cooled to 0 °C via ice bath. ZnI_2 (95.7 mg, 0.300 mmol) was added. The solution was stirred for 10 min at 0 °C, warmed to room temperature, and stirred for 15 min. 7 N NH_3 in MeOH (23.1 mL) was added and the reaction was stirred at 40 °C for 3 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (19:1 CH_2Cl_2/*i*-PrOH) to give the product as a yellow oil (1.4741 g, 21.032 mmol, 70% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.78 (q, *J* = 7.0 Hz, 1H), 1.64 (brs, 2H), 1.48 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 122.9, 38.6, 21.7; HRMS (ESI-TOF, CH_3OH) *m* / *z* calcd for $C_3H_6N_2$ $(M+H)^+$ 71.0604, found 71.0604.



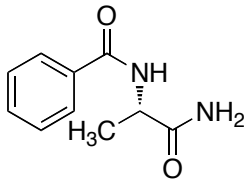
***N*-(1-cyanoethyl)benzamide (Bz-Ala-I).** To a 20 mL scintillation vial was added 2-aminopropanenitrile (21.2 mg, 0.302 mmol) and CH_2Cl_2 (0.60 mL). Benzoyl chloride (38.7 μL, 0.333 mmol) and triethylamine (50.5 μL, 0.362 mmol) were added. The reaction mixture was stirred for 1 h, concentrated under reduced pressure, and purified by column chromatography (19:1 CH_2Cl_2/CH_3OH) and to give the product as a white solid (21.3 mg, 0.122 mmol, 40% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.5 Hz, 2H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 6.74 (d, *J* = 7.5 Hz, 1H), 5.14 (quint, *J* = 7.0 Hz, 1H), 1.65 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 132.8, 132.5, 128.9, 127.3, 119.5, 36.5, 19.6; HRMS (ESI-TOF, CH_3OH) *m* / *z* calcd for $C_{10}H_{10}N_2O$ $(M+H)^+$ 175.0866, found 175.0867; Chiral HPLC (Lux Amylose-1, 5% *i*-PrOH in hexanes, 1.0 mL/min, UV detection at 254 nm t_1 = 15.4 min, t_2 = 17.7 min).



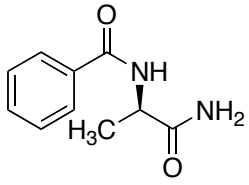
(*S*)-methyl 2-benzamidopropanoate (*S*-Bz-Ala-OMe). To an oven-dried round-bottom flask with a stirbar was added L-Ala-OMe•HCl (1.0005 g, 7.1679 mmol). CH_2Cl_2 (28 mL) was added and the mixture was stirred at room temperature. Triethylamine (2.20 mL, 15.8 mmol) was added, precipitating the ammonium salt, and the solution was stirred for 5 min. The reaction mixture was cooled to 0 °C via ice bath and benzoyl chloride (0.91 mL, 7.9 mmol) was added dropwise. The solution was stirred at 0 °C for 30 min, warmed to room temperature, and stirred overnight. H_2O (15 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 30 mL). The organic layers were combined, dried ($MgSO_4$), filtered, concentrated under reduced pressure, and purified by column chromatography (1:1 hexanes/EtOAc) to give the product as a clear oil (1.0616 g, 5.1228 mmol, 71% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80-7.78 (m, 2H), 7.50-7.47 (m, 1H), 7.43-7.40 (m, 2H), 6.83 (d, J = 6.0 Hz, 1H), 4.79 (quint, J = 7.0 Hz, 1H), 3.77 (s, 3H), 1.50 (d, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 166.9, 134.0, 131.8, 128.6, 127.1, 52.6, 48.6, 18.7; HRMS (ESI-TOF, CH_3OH) m / z calcd for $C_{11}H_{13}NO_3$ $(M+H)^+$ 208.0968, found 208.0970.



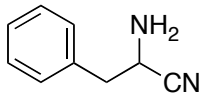
(*R*)-methyl 2-benzamidopropanoate (*R*-Bz-Ala-OMe). To an oven-dried round-bottom flask with a stirbar was added D-Ala-OMe•HCl (1.0005 g, 7.1679 mmol). CH_2Cl_2 (28 mL) was added and the mixture was stirred at room temperature. Triethylamine (2.20 mL, 15.8 mmol) was added, precipitating the ammonium salt, and the solution was stirred for 5 min. The reaction mixture was cooled to 0 °C via ice bath and benzoyl chloride (0.91 mL, 7.9 mmol) was added dropwise. The solution was stirred at 0 °C for 30 min, warmed to room temperature, and stirred overnight. H_2O (15 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 30 mL). The organic layers were combined, dried ($MgSO_4$), filtered, concentrated under reduced pressure, and purified by column chromatography (1:1 hexanes/EtOAc) to give the product as a clear oil (1.4216 g, 6.8600 mmol, 96% yield); ^{1}H and ^{13}C NMR spectral data matched the reported data for the *S*-enantiomer.



(*S*)-*N*-(1-amino-1-oxopropan-2-yl)benzamide (*S*-Bz-Ala-II). To a round bottom flask with a stirbar was added (*S*)-methyl 2-benzamidopropanoate (987.9 mg, 4.767 mmol). 7 N NH_3 in MeOH (2.38 mL) was added and the reaction was stirred at room temperature for 24 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (9:1 CH_2Cl_2/CH_3OH) to give the product as a white solid (201.0 mg, 1.046 mmol, 22% yield); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.39 (d, J = 7.5 Hz, 1H), 7.89 (d, J = 7.5 Hz, 2H), 7.46 (t, J = 7.5 Hz, 2H), 7.36 (brs, 1H), 6.98 (brs, 1H), 4.42 (quint, J = 7.0 Hz, 1H), 1.33 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.4, 165.9, 134.2, 131.2, 128.1, 127.4, 48.7, 18.0; HRMS (ESI-TOF, CH_3OH) m / z calcd for $C_{10}H_{12}N_2O_2$ $(M+H)^+$ 193.0971, found 193.0971; Chiral HPLC (Chiralcel OZ-3, 20% *i*-PrOH in hexanes, 1.0 mL/min, UV detection at 254 nm, t_S = 11.9 min, t_R = 18.3 min) 99% e.e.

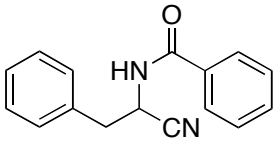


(*R*)-*N*-(1-amino-1-oxopropan-2-yl)benzamide (*R*-Bz-Ala-II). To a round bottom flask with a stirbar was added (*S*)-methyl 2-benzamidopropanoate (1.3485 g, 6.5073 mmol). 7 N NH_3 in MeOH (3.25 mL) was added and the reaction was stirred at room temperature for 24 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (9:1 CH_2Cl_2/CH_3OH) to give the product as a white solid (251.4 mg, 1.308 mmol, 22% yield); ^{1}H and ^{13}C NMR spectral data matched the reported data for the *S*-enantiomer. Chiral HPLC (Chiralcel OZ-3, 20% *i*-PrOH in hexanes, 1.0 mL/min, UV detection at 254 nm, t_S = 12.4 min, t_R = 17.4 min) 99% e.e.

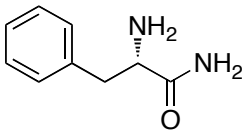


2-amino-3-phenylpropanenitrile (Phe-I).[2] To a round-bottom flask with a stirbar was added KCN (6.8365 g, 104.98 mmol) and NH_4Cl (9.0140 g, 168.51 mmol). NH_4OH (92 mL) was added and the solution was stirred 10 min at room temperature. Phenylacetaldehyde (10.0 mL, 85.5 mmol; in 40. mL *i*-PrOH) was added dropwise over 20 min. The solution was stirred at room temperature for 16 h. The reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the crude reaction mixture as a yellow oil. The mixture was purified by column chromatography (1:1 hexanes/EtOAc) to afford the product as a yellow oil that solidified in the freezer to give a yellow solid (5.0383 g, 34.464 mmol, 40% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.35 (m,

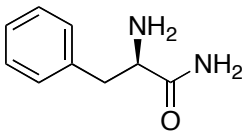
2H), 7.33-7.29 (m, 3H), 3.94 (t, J = 6.5 Hz, 1H), 3.03 (dd, J = 6.5, 2.0 Hz, 2H), 1.61 (brs, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.0, 129.7, 129.0, 127.8, 121.6, 44.7, 41.3; HRMS (ESI-TOF, CH_3OH) m / z calcd for $C_9H_{10}N_2$ $(M+H)^+$ 147.0917, found 147.0915.



***N*-(1-cyano-2-phenylethyl)benzamide (Bz-Phe-I).** To a round-bottom flask with a stirbar was added 2-2-amino-3-phenylpropanenitrile (100.0 mg, 0.6840 mmol). CH_2Cl_2 (3 mL) and *i*-PrOH (3 mL) were added, followed by benzoyl chloride (116 μL, 0.999 mmol) and triethylamine (139 μL, 0.997 mmol). The solution was stirred 10 min and then concentrated under reduced pressure. The reaction mixture was purified via trituration (CH_2Cl_2) to give the product as a white solid (127.1 mg, 0.5078 mmol, 74% yield); ^{1}H NMR (500 MHz, CD_3OD) δ 7.77 (d, J = 7.5 Hz, 2H), 7.55 (t, J = 7.5 Hz, 1H), 7.46 (t, J = 7.5 Hz, 2H), 7.35-7.31 (m, 4H), 7.29-7.25 (m, 1H), 5.20 (t, J = 8.0 Hz, 1H), 3.25 (ddd, J = 21.5, 14.0, 8.0 Hz, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 169.6, 136.6, 134.4, 133.3, 130.5, 129.7, 129.6, 128.5, 128.5, 119.5, 43.8, 39.4; HRMS (ESI-TOF, CH_3OH) m / z calcd for $C_{16}H_{14}N_2O$ $(M+H)^+$ 251.1179, found 251.1182; Chiral HPLC (Chiralcel OZ-3, 20% *i*-PrOH in hexanes, 1.0 mL/min, UV detection at 254 nm t_1 = 6.6 min, t_2 = 7.4 min); (Chiralcel OZ-3, 5% *i*-PrOH in hexanes, 1.0 mL/min, UV detection at 254 nm, t_1 = 20.7 min, t_2 = 25.3 min).

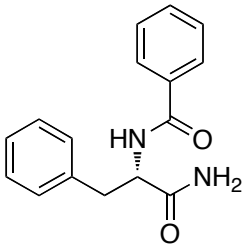


(*S*)-2-amino-3-phenylpropanamide (*S*-Phe-II). To an oven-dried round-bottom flask with a stirbar was added L-Phe-OMe•HCl (1.0140 g, 4.7014 mmol). 7 N NH_3 in MeOH (18 mL) was added and the reaction was stirred at 50 °C for 3 d. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (9:1 CH_2Cl_2/CH_3OH) to give the product as a white solid (274.6 mg, 1.672 mmol, 36% yield); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.30-7.27 (m, 3H), 7.22-7.17 (m, 3H), 6.94 (s, 1H), 3.33 (dd, J = 8.5, 5.0 Hz, 1H), 2.91 (dd, J = 13.5, 5.0 Hz, 1H), 2.59 (dd, J = 13.5, 8.5 Hz, 1H), 1.62 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 176.6, 138.9, 129.3, 128.0, 126.0, 56.2, 41.2; HRMS (ESI-TOF, CH_3OH) m / z calcd for $C_9H_{12}N_2O$ $(M+H)^+$ 165.1022, found 165.1023.

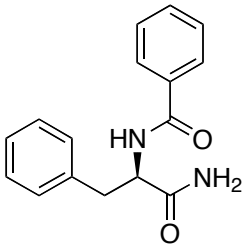


(*R*)-2-amino-3-phenylpropanamide (*R*-Phe-II). To an oven-dried round-bottom flask with a stirbar was added D-Phe-OMe•HCl (1.0022 g, 4.6467 mmol). 7 N NH_3 in MeOH (18 mL) was added and the reaction was stirred at 50 °C for 3 d. The reaction mixture was concentrated under

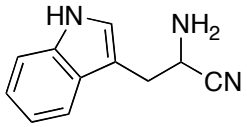
reduced pressure and purified by column chromatography (9:1 CH_2Cl_2/CH_3OH) to give the product as a white solid (297.3 mg, 1.811 mmol, 39% yield); ^1H and ^{13}C NMR spectral data matched the reported data for the *S*-enantiomer.



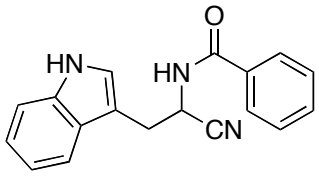
(*S*)-*N*-(1-amino-1-oxo-3-phenylpropan-2-yl)benzamide (*S*-Bz-Phe-II). To a 1 dram vial with a stirbar was added (*S*)-2-amino-3-phenylpropanamide (18.3 mg, 0.111 mmol). CH_3OH (0.500 mL) was added, followed by benzoyl chloride (19 μL, 0.16 mmol) and triethylamine (23 μL, 0.17 mmol). The solution was stirred 10 min and then concentrated under reduced pressure. The reaction mixture was purified by column chromatography (9:1 CH_2Cl_2/CH_3OH) to give the product as a white solid (20.1 mg, 0.0749 mmol, 67% yield); ^1H NMR (500 MHz, CD_3OD) δ 7.72-7.71 (m, 2H), 7.51 (t, J = 7.5 Hz, 1H), 7.42 (t, J = 7.5 Hz, 2H), 7.31-7.25 (m, 4H), 7.19 (d, J = 7.0 Hz, 1H), 4.84 (t, 1H), 3.27 (dd, J = 14.0, 6.0 Hz, 1H), 3.05 (dd, J = 14.0, 9.0 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 176.3, 170.1, 138.7, 135.3, 132.8, 130.3, 129.5, 129.4, 128.4, 127.8, 56.3, 38.9; HRMS (ESI-TOF, CH_3OH) m / z calcd for $C_{16}H_{16}N_2O_2$ $(M+H)^+$ 269.1284, found 269.1283; Chiral HPLC (Chiralcel OZ-3, 20% *i*-PrOH in hexanes, 1.0 mL/min, UV detection at 254 nm, t_S = 14.2 min) >99% e.e.



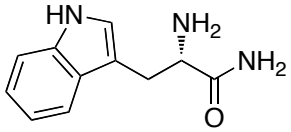
(*R*)-*N*-(1-amino-1-oxo-3-phenylpropan-2-yl)benzamide (*R*-Bz-Phe-II). To a 1 dram vial with a stirbar was added (*R*)-2-amino-3-phenylpropanamide (19.0 mg, 0.116 mmol). CH_3OH (0.500 mL) was added, followed by benzoyl chloride (20. μL, 0.17 mmol) and triethylamine (24 μL, 0.17 mmol). The solution was stirred 10 min and then concentrated under reduced pressure. The reaction mixture was purified by column chromatography (9:1 CH_2Cl_2/CH_3OH) to give the product as a white solid (18.3 mg, 0.0682 mmol, 59% yield); ^1H and ^{13}C NMR spectral data matched the reported data for the *S*-enantiomer; Chiral HPLC (Chiralcel OZ-3, 20% *i*-PrOH in hexanes, 1.0 mL/min, UV detection at 254 nm, t_S = 14.6 min, t_R = 42.7 min) 98% e.e.



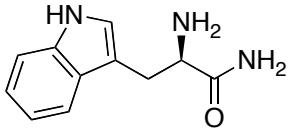
2-amino-3-(1*H*-indol-3-yl)propanenitrile (Trp-I).[1,3] To an oven-dried round-bottom flask with a stirbar was added tryptophol (5.0179 g, 31.128 mmol) and 2-iodoxybenzoic acid (9.5550 g, 34.123 mmol). DMSO (125 mL) was added and the reaction was stirred at room temperature for 2 h. The reaction mixture was filtered, and H_2O (240 mL) was added. The solution was extracted with Et_2O (3 × 300. mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the unpurified aldehyde 2-(1*H*-indol-3-yl)acetaldehyde as an oil. The oil was immediately carried on to the next step. To the oil in a round-bottom flask with a stirbar was added TMSCN (4.85 mL, 38.8 mmol). ZnI_2 (509.0 mg, 1.595 mmol) was then added and the reaction mixture was stirred at room temperature for 20 min. 7 N NH_3 in MeOH (23.3 mL) was added and the flask was transferred to an oil bath at 40 °C and stirred for 8 h. The solution was concentrated under reduced pressure to afford a dark brown oil. The reaction mixture was purified via trituration (CH_2Cl_2) to afford the desired product as a tan solid (1.0431 g, 5.6314 mmol, 18% yield). ^{1}H NMR (500 MHz, CD_3OD) δ 7.59 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 7.22 (s, 1H), 7.11 (t, *J* = 7.0 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 4.04 (t, *J* = 7.0 Hz, 1H), 3.27 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 138.1, 128.6, 125.0, 123.1, 122.6, 120.0, 119.2, 112.4, 109.8, 45.7, 32.2; HRMS (ESI-TOF, CH_3OH) *m* / *z* calcd for $C_{11}H_{11}N_3$ $(M+H)^+$ 186.1026, found 186.1026.



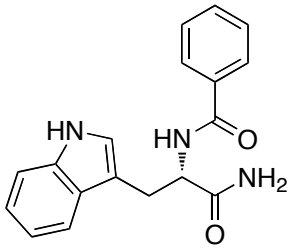
***N*-(1-cyano-2-(1*H*-indol-3-yl)ethyl)benzamide (Bz-Trp-I).** To a 1 dram vial with a stirbar was added 2-amino-3-(1*H*-indol-3-yl)propanenitrile (29.8 mg, 0.161 mmol). CH_3OH (1.0 mL) was added, followed by benzoyl chloride (28 μL, 0.24 mmol) and triethylamine (34 μL, 0.24 mmol). The solution was stirred 10 min and then concentrated under reduced pressure. The reaction mixture was purified by column chromatography (19:1 CH_2Cl_2/CH_3OH) to give the product as an off-white solid (30.6 mg, 0.106 mmol, 66% yield). ^{1}H NMR (500 MHz, CD_3OD) δ 7.78-7.77 (m, 2H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.24 (s, 1H), 7.11 (t, *J* = 7.0 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 5.27 (t, *J* = 7.5 Hz, 1H), 3.42 (dddd, *J* = 14.5, 14.5, 14.5, 8.0 Hz, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 169.7, 138.1, 134.5, 133.2, 129.6, 128.5, 128.5, 125.0, 122.7, 120.1, 120.0, 119.1, 112.5, 109.5, 43.7, 29.9; HRMS (ESI-TOF, CH_3OH) *m* / *z* calcd for $C_{18}H_{15}N_3O$ $(M+H)^+$ 290.1288, found 290.1290; Chiral HPLC (Chiralcel OZ-3, 20% i-PrOH in hexanes, 1.0 mL/min, UV detection at 254 nm, t_1 = 10.4 min, t_2 = 11.8 min).



(*S*)-2-amino-3-(1*H*-indol-3-yl)propanamide (*S*-Trp-II). To an oven-dried round-bottom flask with a stirbar was added L-Trp-OMe•HCl (1.0047 g, 3.9444 mmol). 7 N NH_3 in MeOH (12 mL) was added and the reaction was stirred at 50 °C for 3 d. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (1:1 CH_2Cl_2/CH_3OH) to give the desired product as a yellow oil (254.3 mg, 1.251 mmol, 32% yield); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.83 (s, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.34-7.32 (m, 2H), 7.16 (d, J = 2.5 Hz, 1H), 7.06 (t, J = 8.0 Hz, 1H), 6.97 (t, J = 8.0 Hz, 1H), 6.94 (brs, 1H), 3.40 (dd, J = 8.5, 5.0 Hz, 1H), 3.06 (dd, J = 14.0, 4.5 Hz, 1H), 2.72 (dd, J = 14.0, 8.0 Hz, 1H), 1.66 (brs, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 177.1, 136.2, 127.4, 123.6, 120.8, 118.5, 118.2, 111.3, 110.9, 55.3, 31.2; HRMS (ESI-TOF, CH_3OH) m / z calcd for $C_{11}H_{13}N_3O$ $(M+H)^+$ 204.1131, found 204.1131.

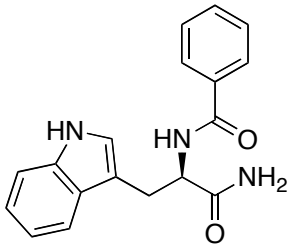


(*R*)-2-amino-3-(1*H*-indol-3-yl)propanamide (*R*-Trp-II). To an oven-dried round-bottom flask with a stirbar was added D-Trp-OMe•HCl (1.0002 g, 3.9268 mmol). 7 N NH_3 in MeOH (12 mL) was added and the reaction was stirred at 50 °C for 3 d. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (1:1 CH_2Cl_2/CH_3OH) to give the desired product as a yellow oil (267.1 mg, 1.314 mmol, 33% yield); ^{1}H and ^{13}C NMR spectral data matched the reported data for the *S*-enantiomer.



(*S*)-*N*-(1-amino-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)benzamide (*S*-Bz-Trp-II). To a 1 dram vial with a stirbar was added (*S*)-2-amino-3-(1*H*-indol-3-yl)propanamide (17.7 mg, 0.0871 mmol). CH_3OH (0.500 mL) was added, followed by benzoyl chloride (15 μL, 0.13 mmol) and triethylamine (18 μL, 0.13 mmol). The solution was stirred 10 min and then concentrated under reduced pressure. The reaction mixture was purified by column chromatography (9:1 CH_2Cl_2/CH_3OH) to give the product as a solid (15.1 mg, 0.0491 mmol, 56% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (brs, 1H), 7.80 (d, J = 7.5 Hz, 1H), 7.71 (d, J = 7.0 Hz, 2H), 7.49 (t, J = 7.5 Hz, 1H), 7.40-7.36 (m, 3H), 7.21 (t, J = 7.0 Hz, 1H), 7.15-7.13 (m, 2H), 7.05 (d, J = 7.0 Hz, 1H), 5.92 (brs, 1H), 5.56 (brs, 1H), 4.99 (ddd, J = 7.5, 7.5, 5.5 Hz, 1H), 3.48 (dd, J = 14.5, 5.0 Hz, 1H), 3.26 (dd, J = 14.5, 8.0 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 173.7, 167.4, 136.4, 133.7, 132.0, 128.7, 127.5, 127.2, 123.4, 122.6, 120.1, 119.1, 111.5, 110.8, 41.1, 28.4;

HRMS (ESI-TOF, CH_3OH) *m* / *z* calcd for $C_{18}H_{17}N_3O_2$ $(M+H)^+$ 308.1393, found 308.1396; Chiral HPLC (Chiralcel OZ-3, 20% *i*-PrOH in hexanes, 1.0 mL/min, UV detection at 254 nm, t_S = 24.3 min, t_R = 32.7 min) 98% e.e.



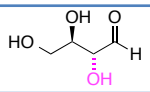
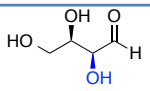
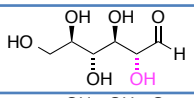
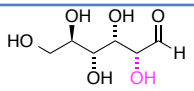
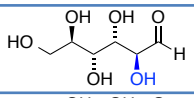
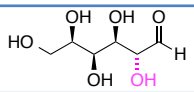
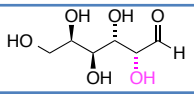
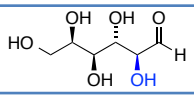
(*R*)-*N*-(1-amino-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)benzamide (*R*-Bz-Trp-II). To a 1 dram vial with a stirbar was added (*R*)-2-amino-3-(1*H*-indol-3-yl)propanamide (12.5 mg, 0.0615 mmol). CH_3OH (0.500 mL) was added, followed by benzoyl chloride (11 μL, 0.095 mmol) and triethylamine (13 μL, 0.093 mmol). The solution was stirred 10 min and then concentrated under reduced pressure. The reaction mixture was purified by column chromatography (9:1 CH_2Cl_2/CH_3OH) to give the product as a solid (11.3 mg, 0.0368 mmol, 60% yield). ^1H and ^{13}C NMR spectral data matched the reported data for the *S*-enantiomer. Chiral HPLC (Chiralcel OZ-3, 20% *i*-PrOH in hexanes, 1.0 mL/min, UV detection at 254 nm, t_S = 25.2 min, t_R = 31.2 min) 99% e.e.

3. Tables S.1 – S.2

Table S.1. Isolated yields for reactions in Table 1

Entry	AM-**I**	Sugar	Isolated Yield (%)
1	Ala-**I**	D-ribose	12
2	Ala-**I**	D-lyxose	13
3	Ala-**I**	D-xylose	9
4	Ala-**I**	D-arabinose	11
5	Ala-**I**	D-deoxyribose	13
6	Ala-**I**	D-ribose/D-lyxose	6
7	Ala-**I**	D-ribose/D-lyxose/D-xylose/D-arabinose	7
8	Phe-**I**	D-ribose	12
9	Phe-**I**	D-lyxose	14
10	Phe-**I**	D-xylose	13
11	Phe-**I**	D-arabinose	17
12	Phe-**I**	D-deoxyribose	12
13	Phe-**I**	D-ribose/D-lyxose	10
14	Phe-**I**	D-ribose/D-lyxose/D-xylose/D-arabinose	9
15	Trp-**I**	D-ribose	23
16	Trp-**I**	D-lyxose	20
17	Trp-**I**	D-xylose	22
18	Trp-**I**	D-arabinose	28
19	Trp-**I**	D-deoxyribose	17
20	Trp-**I**	D-ribose/D-lyxose	17
21	Trp-**I**	D-ribose/D-lyxose/D-xylose/D-arabinose	17
22	Phe-**I**	L-ribose	9
23	Phe-**I**	L-lyxose	14
24	Phe-**I**	L-xylose	14
25	Phe-**I**	L-arabinose	16
26	Phe-**I**	control (no sugar)	12

Table S.2. Reaction of Table 1 with Phe-I and C4 and C6 aldose sugars (7 d)

Sugar	Phe-**II** ee (%)	Isolated Yield (%)
D-erythrose 	3 (D)	14
D-threose 	4 (L)	16
D-allose 	19 (D)	17
D-glucose 	6 (D)	16
D-mannose 	52 (L)	13
D-gulose 	28 (D)	13
D-galactose 	26 (D)	17
D-talose 	72 (L)	13

4. NMR Spectra and Chiral HPLC Assays of Compounds

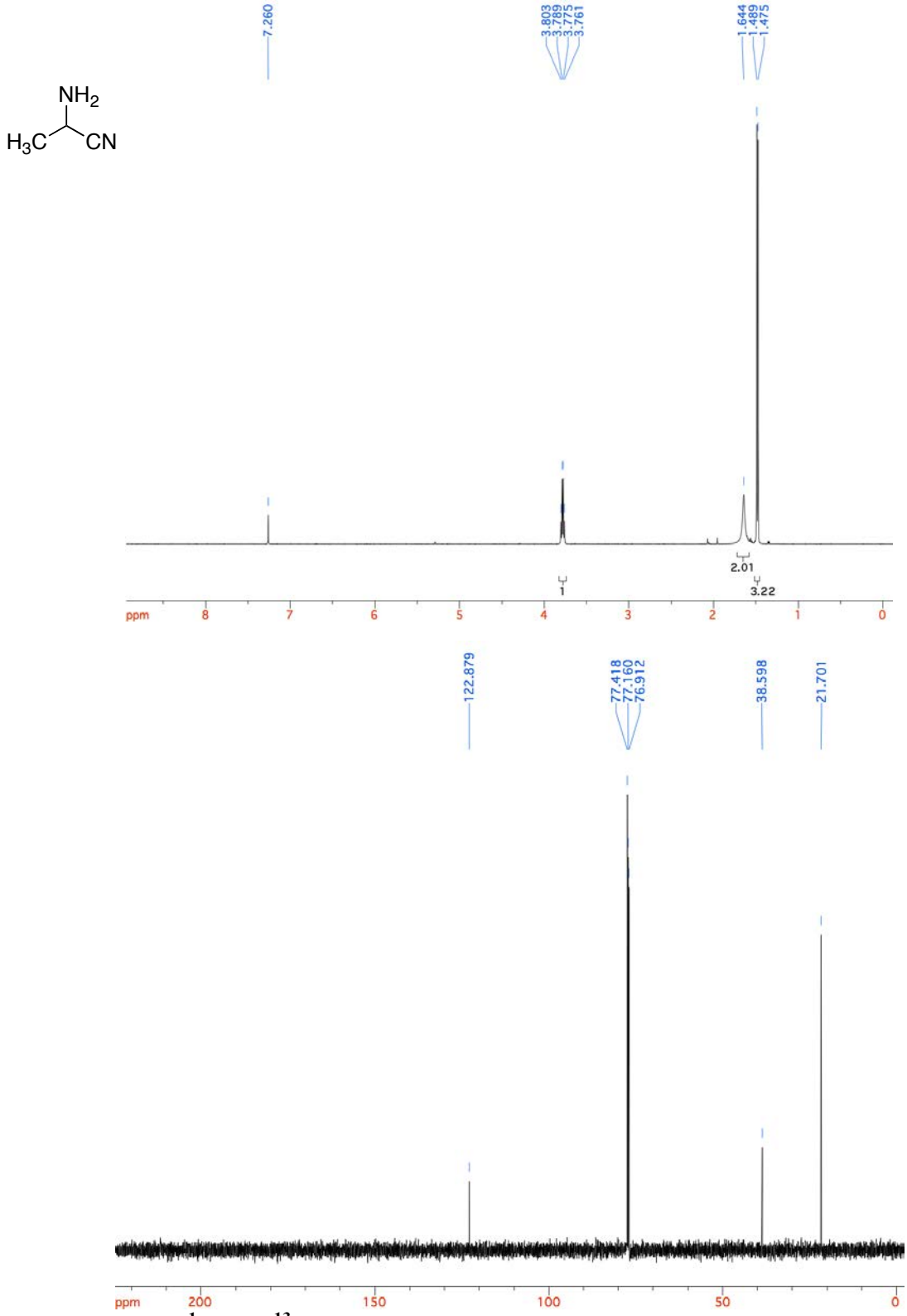


Figure S.1. Ala-I ^{1}H and ^{13}C NMR Spectra

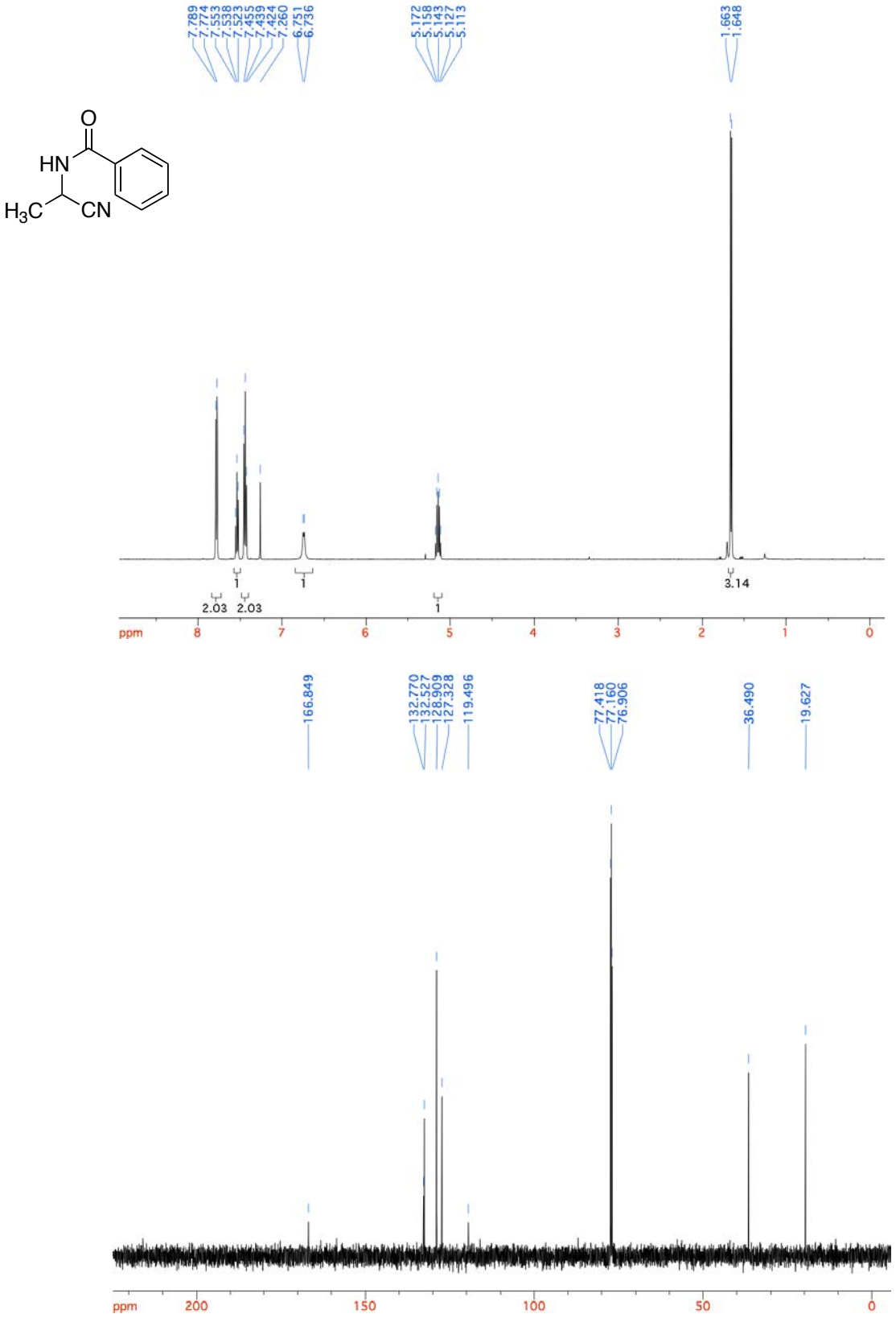


Figure S.2. Bz-Ala-I ^{1}H and ^{13}C NMR Spectra

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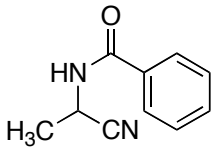


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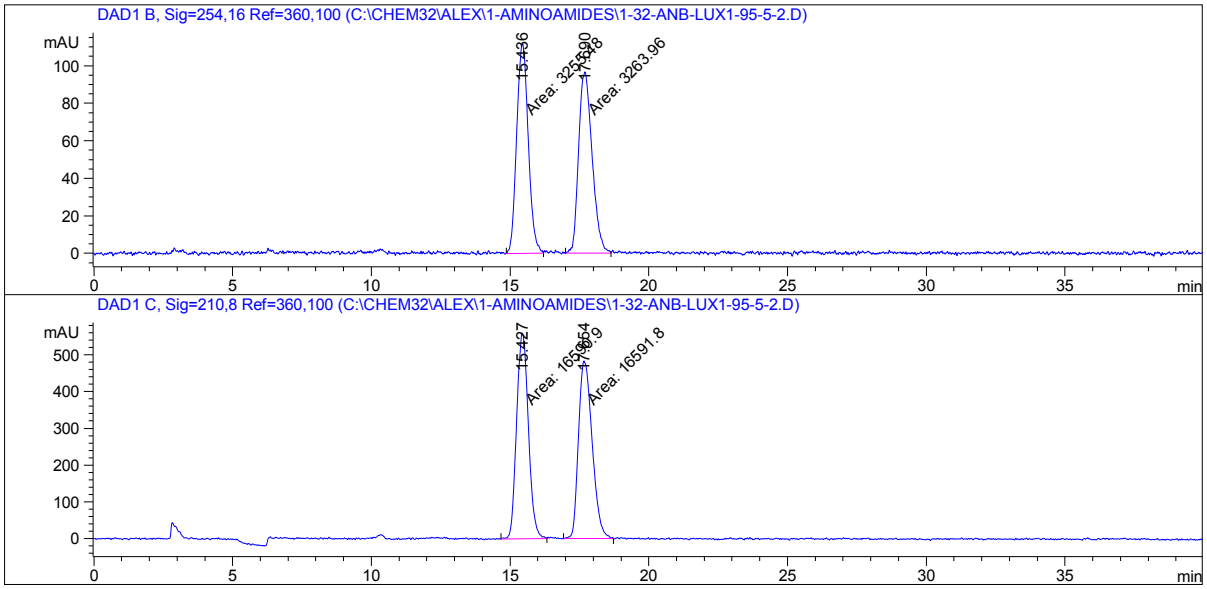


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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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Peak RetTime Type  Width     Area      Height     Area
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Figure S.3. Bz-Ala I Chiral HPLC Assay

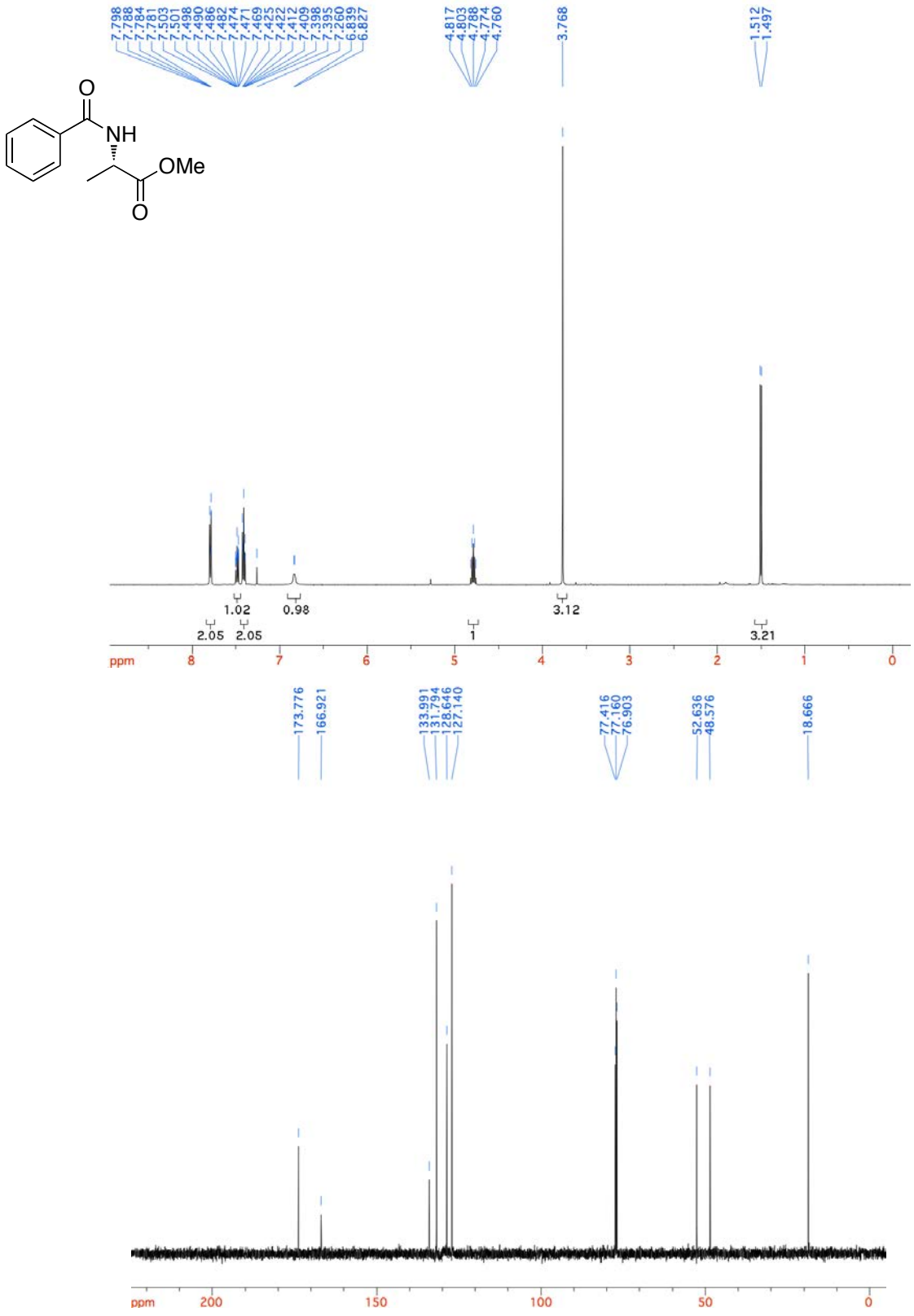


Figure S.4. *S*-Bz-Ala-OMe ^{1}H and ^{13}C NMR Spectra

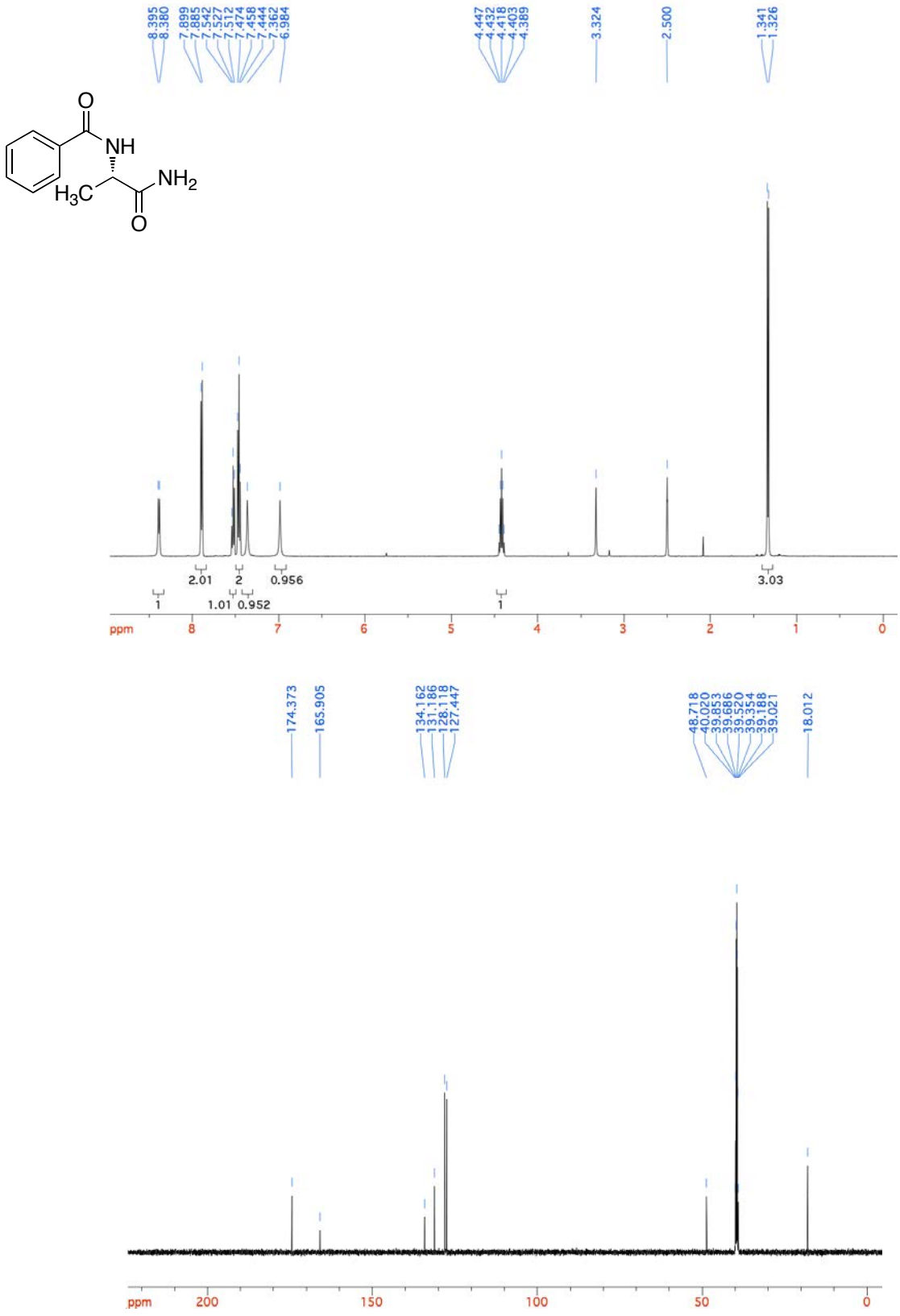
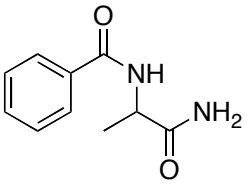
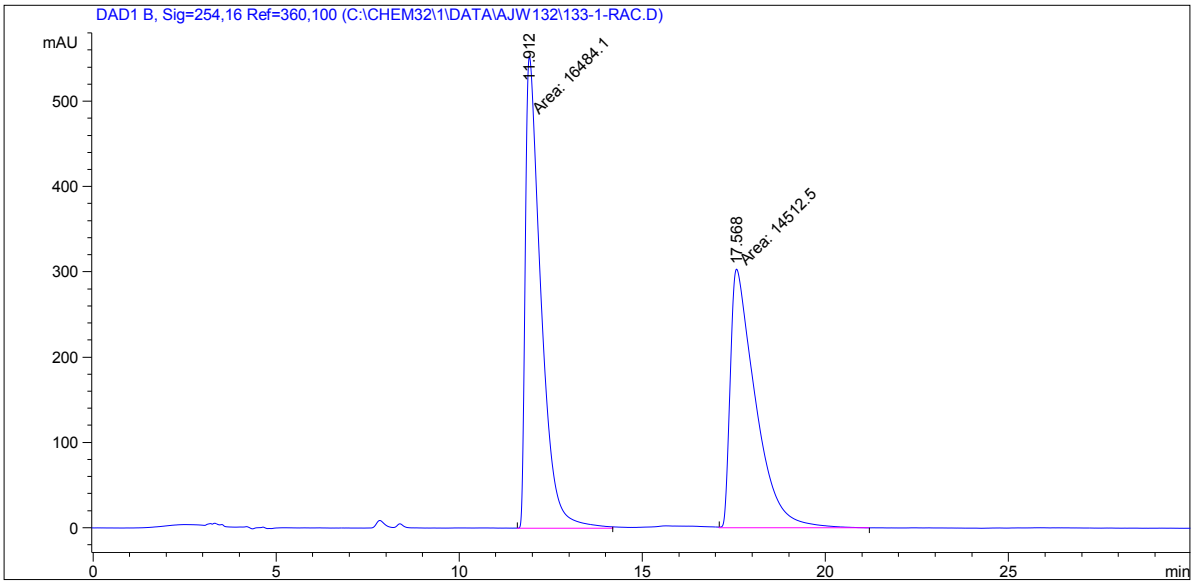


Figure S.5. *S*-Bz-Ala-II ^{1}H and ^{13}C NMR Spectra

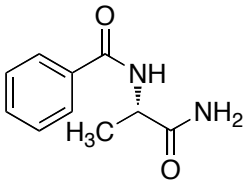



```
Data File C:\CHEM32\1\DATA\AJW132\133-1-RAC.D
Sample Name: 133-1-rac

    ======================================================================
    Acq. Operator   : Alex                          Seq. Line :   5
    Acq. Instrument : LC-MS                        Location : Vial 28
    Injection Date  : 11/16/2016 1:51:50 PM             Inj :   1
                                                  Inj Volume : 10 µl
    Acq. Method     : C:\CHEM32\1\METHODS\COL1_HI_80_20_50MIN.M
    Last changed    : 11/16/2016 1:50:49 PM by Alex
                      (modified after loading)
    Analysis Method : C:\CHEM32\1\METHODS\COL1_HI_80_20_50MIN.M
    Last changed    : 11/16/2016 3:39:08 PM by Alex
                      (modified after loading)
```

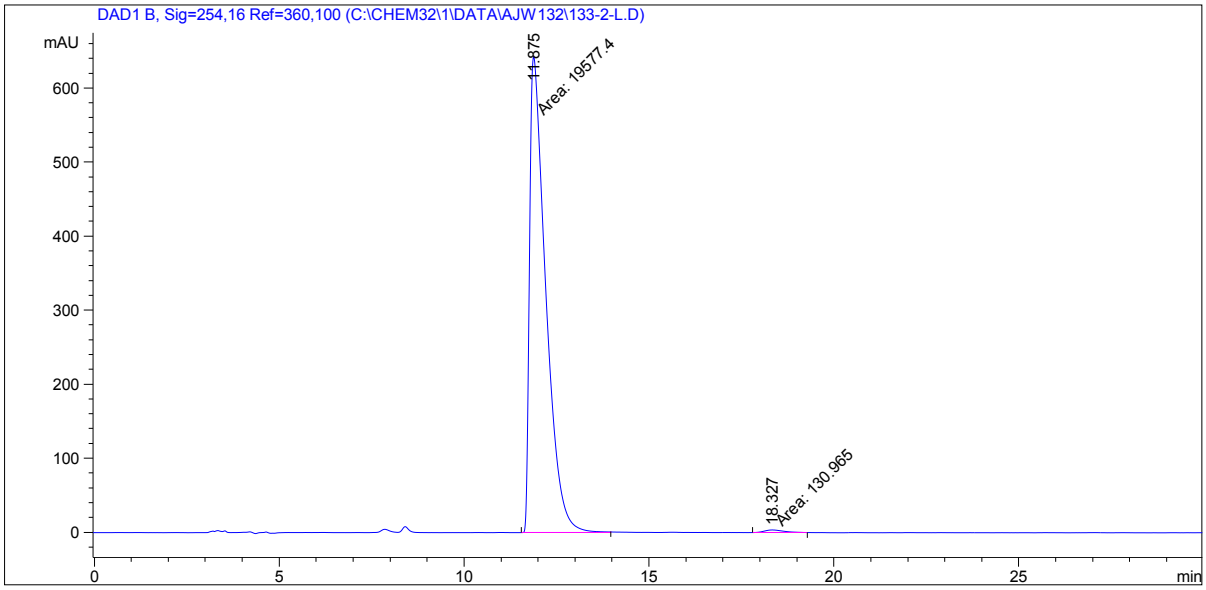



```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 B, Sig=254,16 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  11.912 MM    0.4966 1.64841e4   553.17792  53.1805
       2  17.568 MM    0.7974 1.45125e4   303.34500  46.8195

    Totals :                  3.09966e4   856.52292

LC-MS 11/16/2016 3:40:03 PM Alex                          Page   1 of 2
```

Figure S.6. Mixture of *S*-Bz-Ala-II and *R*-Bz-Ala-II Chiral HPLC Assay
The solution was prepared by mixing enantiopure compounds to create a scalemic sample to test enantiomeric peak separation.



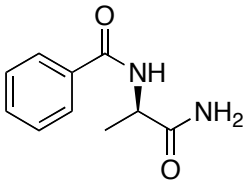

```
Data File C:\CHEM32\1\DATA\AJW132\133-2-L.D
Sample Name: 133-2-L

    ======================================================================
    Acq. Operator    : Alex                              Seq. Line :   6
    Acq. Instrument : LC-MS                               Location : Vial 29
    Injection Date  : 11/16/2016 2:23:06 PM                   Inj :   1
                                                        Inj Volume : 10 µl
    Acq. Method     : C:\CHEM32\1\METHODS\COL1_HI_80_20_50MIN.M
    Last changed    : 11/16/2016 2:22:05 PM by Alex
                      (modified after loading)
    Analysis Method : C:\CHEM32\1\METHODS\COL1_HI_80_20_50MIN.M
    Last changed    : 11/16/2016 3:40:04 PM by Alex
                      (modified after loading)
```



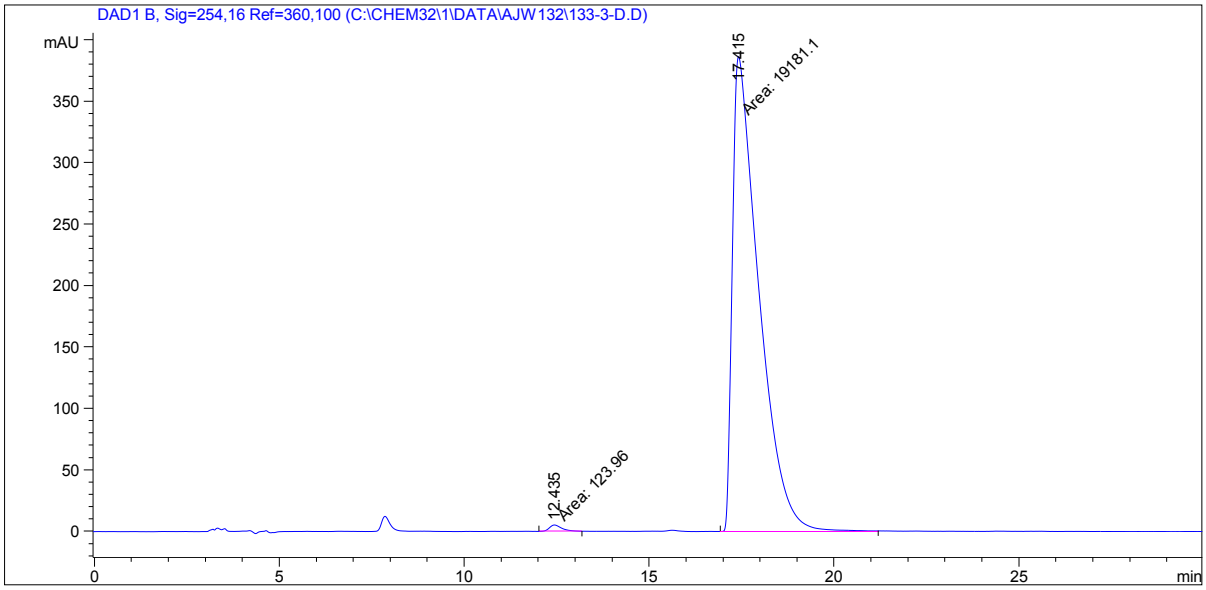

```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 B, Sig=254,16 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  11.875 MM    0.5074 1.95774e4   643.04706  99.3355
       2  18.327 MM    0.6138  130.96460    3.55627   0.6645

    Totals :                  1.97083e4   646.60333

LC-MS 11/16/2016 3:41:11 PM Alex                              Page   1 of 2
```

Figure S.7. *S*-Bz-Ala-II Chiral HPLC Assay

Data File C:\CHEM32\1\DATA\AJW132\133-3-D.D
Sample Name: 133-3-D




```
==========================================================================
Acq. Operator   : Alex                          Seq. Line :   7
Acq. Instrument : LC-MS                         Location : Vial 30
Injection Date  : 11/16/2016 2:54:24 PM             Inj :   1
                                               Inj Volume : 10 µl
Acq. Method     : C:\CHEM32\1\METHODS\COL1_HI_80_20_50MIN.M
Last changed    : 11/16/2016 2:53:22 PM by Alex
                  (modified after loading)
Analysis Method : C:\CHEM32\1\METHODS\COL1_HI_80_20_50MIN.M
Last changed    : 11/16/2016 3:41:12 PM by Alex
                  (modified after loading)
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=254,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  12.435 MM    0.3974  123.96037    5.19855   0.6421
   2  17.415 MM    0.8273 1.91811e4   386.41077  99.3579

Totals :                  1.93050e4   391.60932
```


Figure S.8. *R*-Bz-Ala-II Chiral HPLC Assay

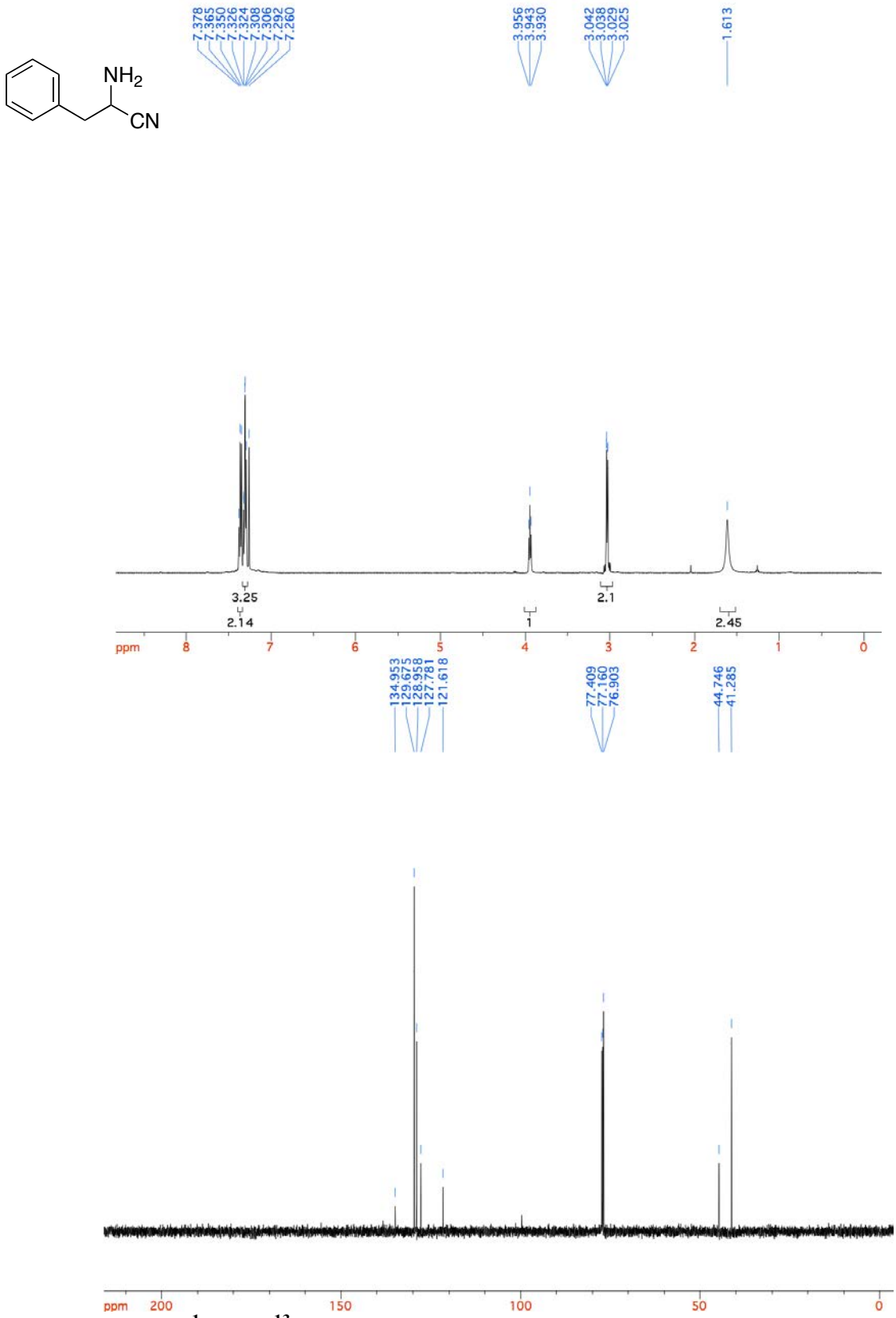


Figure S.9. Phe-I ^{1}H and ^{13}C NMR Spectra

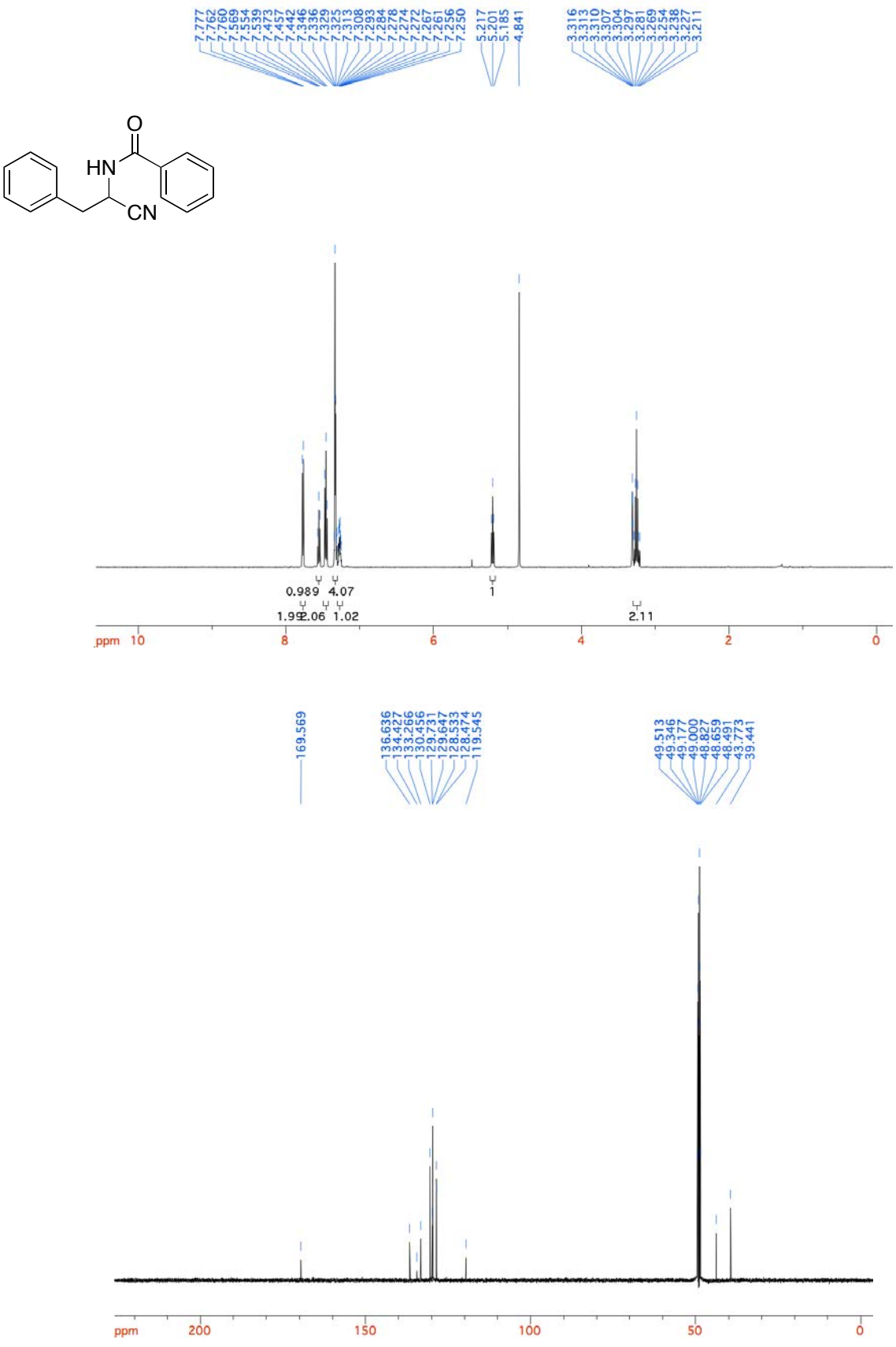
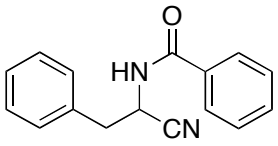
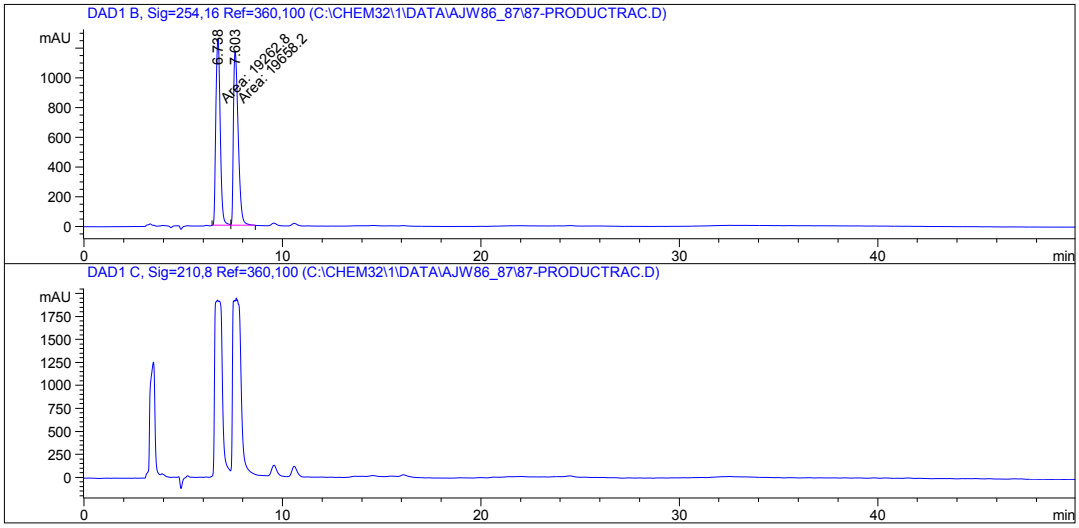


Figure S.10. Bz-Phe-I ^{1}H and ^{13}C NMR Spectra

```
Data File C:\CHEM32\1\DATA\AJW86_87\87-PRODUCTRAC.D
Sample Name: 87-productrac

======================================================================
Acq. Operator   : Alex                          Seq. Line :   4
Acq. Instrument : LC-MS                        Location : Vial 37
Injection Date  : 8/2/2016 12:01:33 PM              Inj :   1
                                               Inj Volume : 10 µl
Acq. Method     : C:\CHEM32\1\METHODS\COL1_HI_80_20_50MIN.M
Last changed    : 8/2/2016 12:00:40 PM by Alex
                  (modified after loading)
Analysis Method : C:\CHEM32\1\METHODS\COL1_HI_80_20_50MIN.M
Last changed    : 11/3/2016 11:42:28 AM by Neil
                  (modified after loading)
```






```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=254,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   6.738 MF    0.2552 1.92628e4  1257.93103  49.4920
   2   7.603 FM    0.2795 1.96582e4  1172.07300  50.5080

Totals :                  3.89210e4  2430.00403

LC-MS 11/3/2016 11:50:46 AM Neil                          Page   1 of 2
```

Figure S.11. Bz-Phe I Chiral HPLC Assay

AM-**I** conversion in crude reaction mixtures was assessed for the time-course analysis of Phe-**I** with D-ribose because this assay allows integration of both Bz-Phe-**I** and total Bz-Phe-**II** in a single chromatogram. All HPLC assays in this section were collected at wavelengths of 254 and 210 nm. Integration of peaks for calculating enantiomeric excess was conducted at 254 nm.

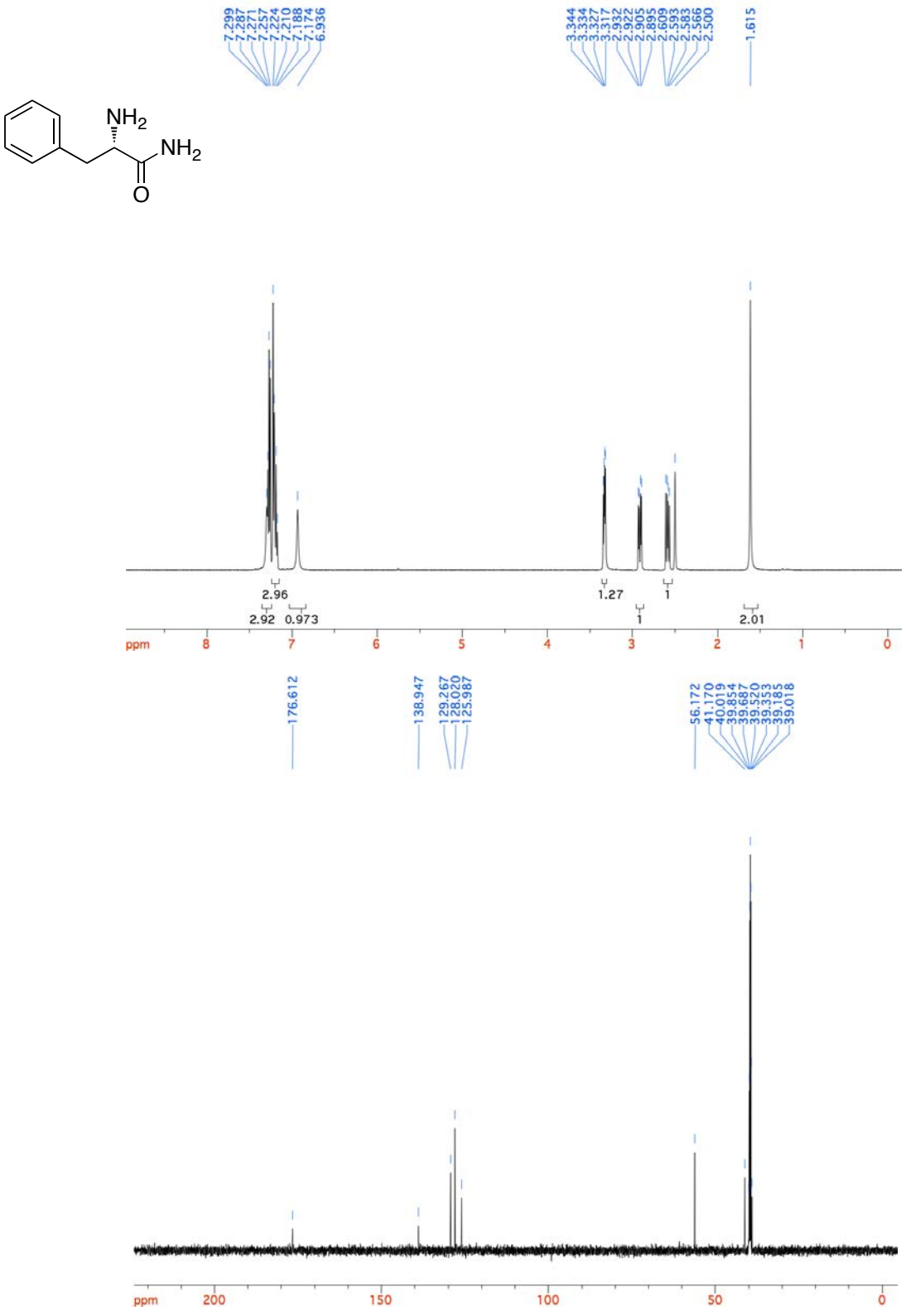


Figure S.12. *S*-Phe-II ^{1}H and ^{13}C NMR Spectra

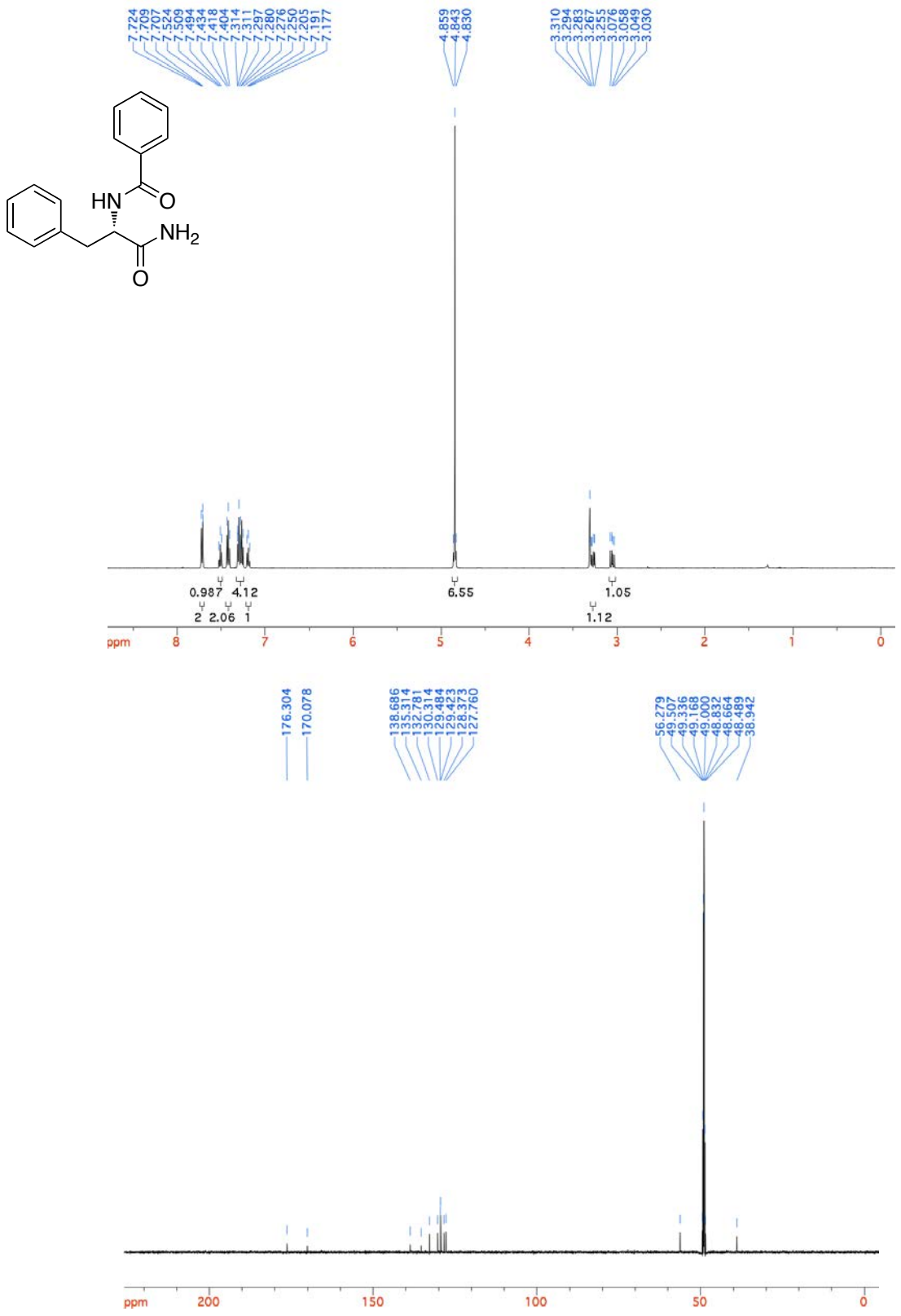
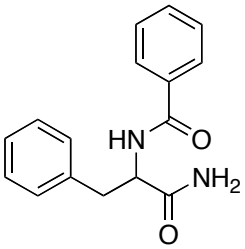
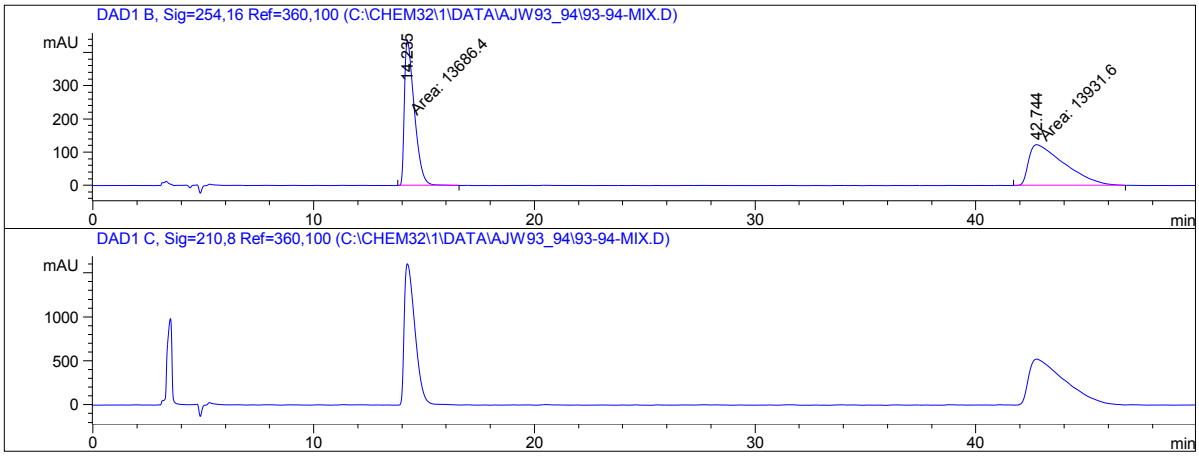


Figure S.13. *S*-Bz-Phe-II ^{1}H and ^{13}C NMR Spectra

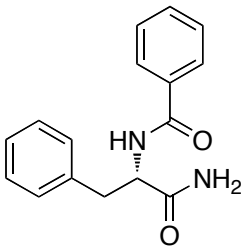



```
Data File C:\CHEM32\1\DATA\AJW93_94\93-94-MIX.D
Sample Name: 93-94-mix
    ======================================================================
    Acq. Operator    : Alex                              Seq. Line :   1
    Acq. Instrument  : LC-MS                              Location : Vial 52
    Injection Date   : 8/5/2016 11:30:26 AM                  Inj :   1
                                                        Inj Volume : 10 µl
    Acq. Method      : C:\CHEM32\1\METHODS\COL1_HI_80_20_50MIN.M
    Last changed     : 8/5/2016 11:29:35 AM by Alex
                       (modified after loading)
    Analysis Method  : C:\CHEM32\1\METHODS\COL1_OZ3_IODINATION2.M
    Last changed     : 8/11/2016 1:15:02 PM by Mower
                       (modified after loading)
    ======================================================================
```

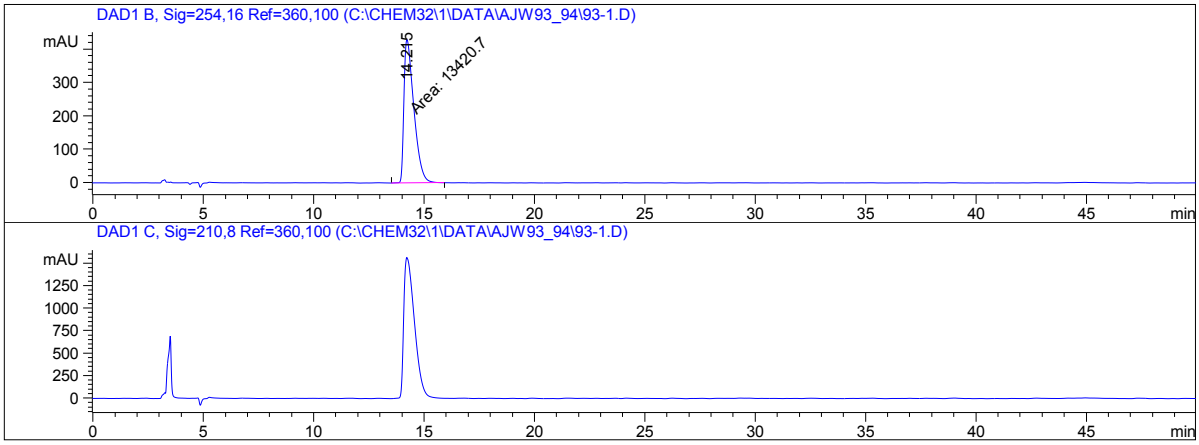



```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 B, Sig=254,16 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  14.235 MM    0.5224 1.36864e4   436.61710  49.5562
       2  42.744 MM    1.8867 1.39316e4   123.06785  50.4438

    Totals :                  2.76180e4   559.68494

LC-MS 8/11/2016 1:16:51 PM Mower                          Page   1 of 2
```

Figure S.14. Mixture of *S*-Bz-Phe-II and *R*-Bz-Phe-II Chiral HPLC Assay
The solution was prepared by mixing enantiopure compounds to create a scalemic sample to test enantiomeric peak separation.



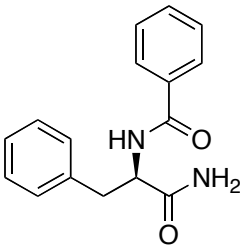

```
Data File C:\CHEM32\1\DATA\AJW93_94\93-1.D
Sample Name: 93-1
    ======================================================================
    Acq. Operator    : Alex                          Seq. Line :   2
    Acq. Instrument : LC-MS                          Location : Vial 53
    Injection Date  : 8/5/2016 12:21:41 PM              Inj :   1
                                                    Inj Volume : 10 µl
    Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
    Acq. Method     : C:\CHEM32\1\METHODS\COL1_HI_80_20_50MIN.M
    Last changed    : 8/5/2016 12:20:56 PM by Alex
                      (modified after loading)
    Analysis Method : C:\CHEM32\1\METHODS\COL1_OZ3_IODINATION2.M
    Last changed    : 8/11/2016 1:16:52 PM by Mower
                      (modified after loading)
    ======================================================================
```



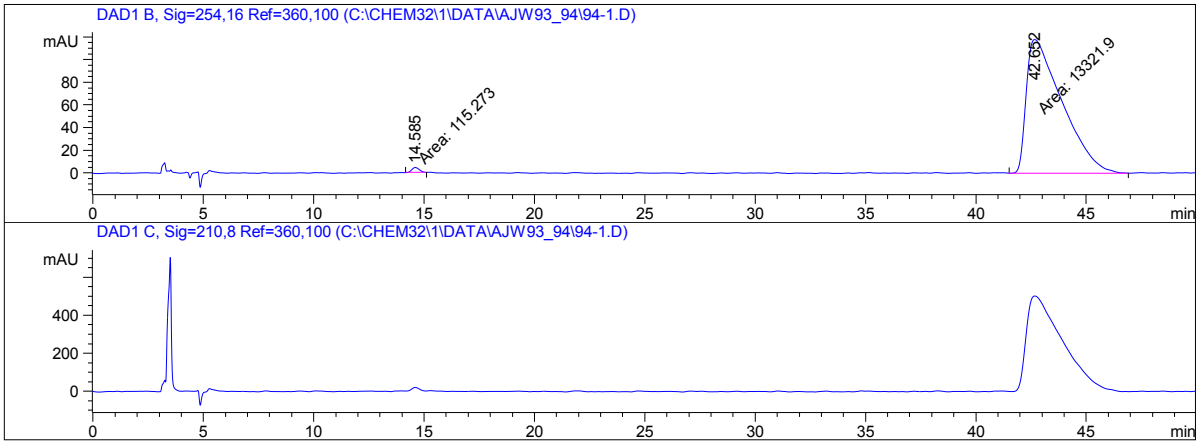

```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 B, Sig=254,16 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  14.215 MM    0.5208 1.34207e4   429.47223 100.0000

    Totals :                  1.34207e4   429.47223
```


Figure S.15. *S*-Bz-Phe-II Chiral HPLC Assay

Data File C:\CHEM32\1\DATA\AJW93_94\94-1.D
Sample Name: 94-1




```
    ========================================================================
    Acq. Operator   : Alex                          Seq. Line :   3
    Acq. Instrument : LC-MS                          Location : Vial 54
    Injection Date  : 8/5/2016 1:12:53 PM                Inj :   1
                                                   Inj Volume : 10 µl
    Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
    Acq. Method     : C:\CHEM32\1\METHODS\COL1_HI_80_20_50MIN.M
    Last changed    : 8/5/2016 1:12:09 PM by Alex
                      (modified after loading)
    Analysis Method : C:\CHEM32\1\METHODS\COL1_OZ3_IODINATION2.M
    Last changed    : 8/11/2016 1:17:44 PM by Mower
                      (modified after loading)
    ========================================================================
```




```
    ========================================================================
                            Area Percent Report
    ========================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 B, Sig=254,16 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  14.585 MM    0.4162  115.27266    4.61607   0.8579
       2  42.652 MM    1.8807 1.33219e4   118.06036  99.1421

    Totals :                  1.34371e4   122.67643
```


Figure S.16. *R*-Bz-Phe-II Chiral HPLC Assay

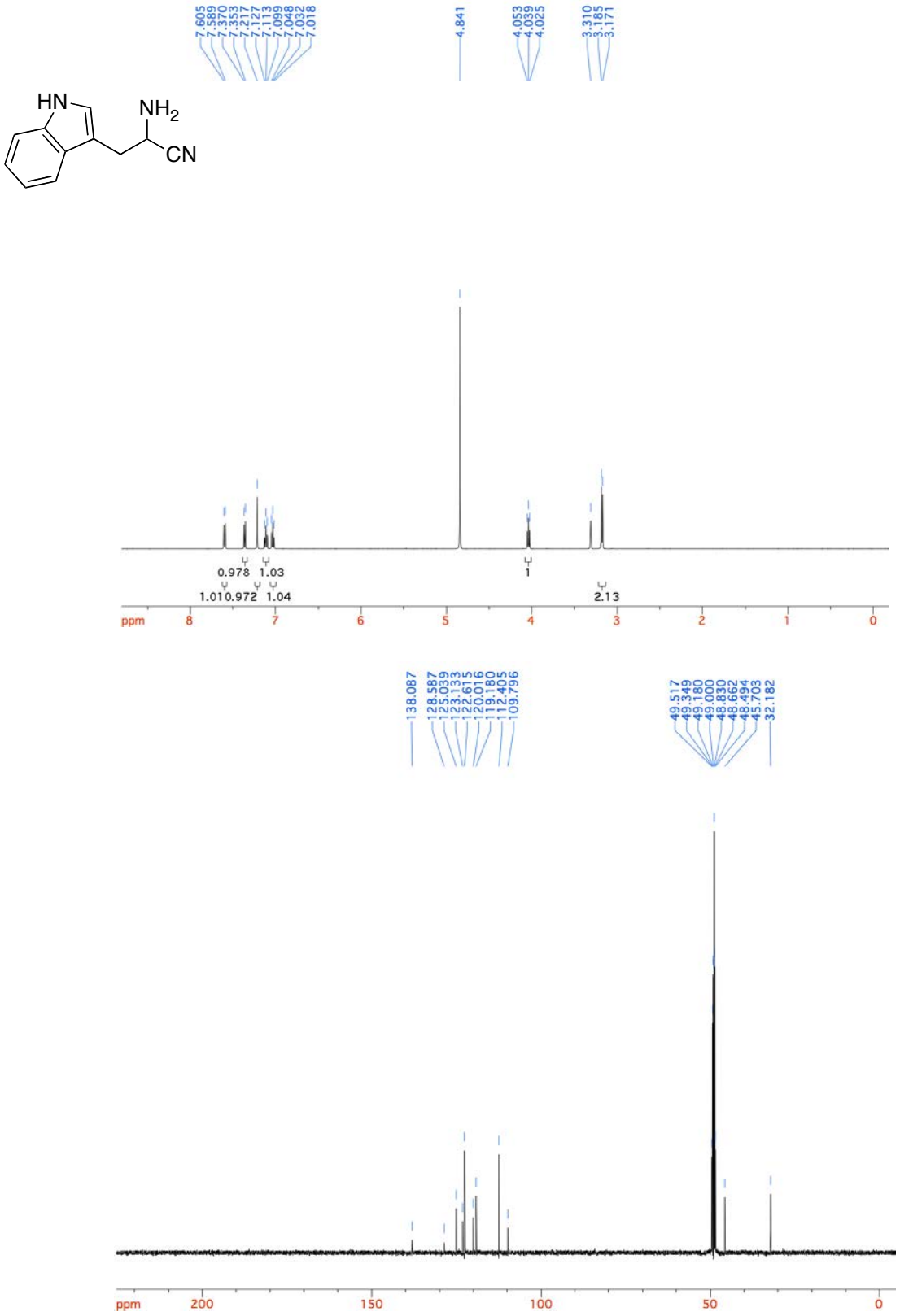


Figure S.17. Trp-I ^{1}H and ^{13}C NMR Spectra

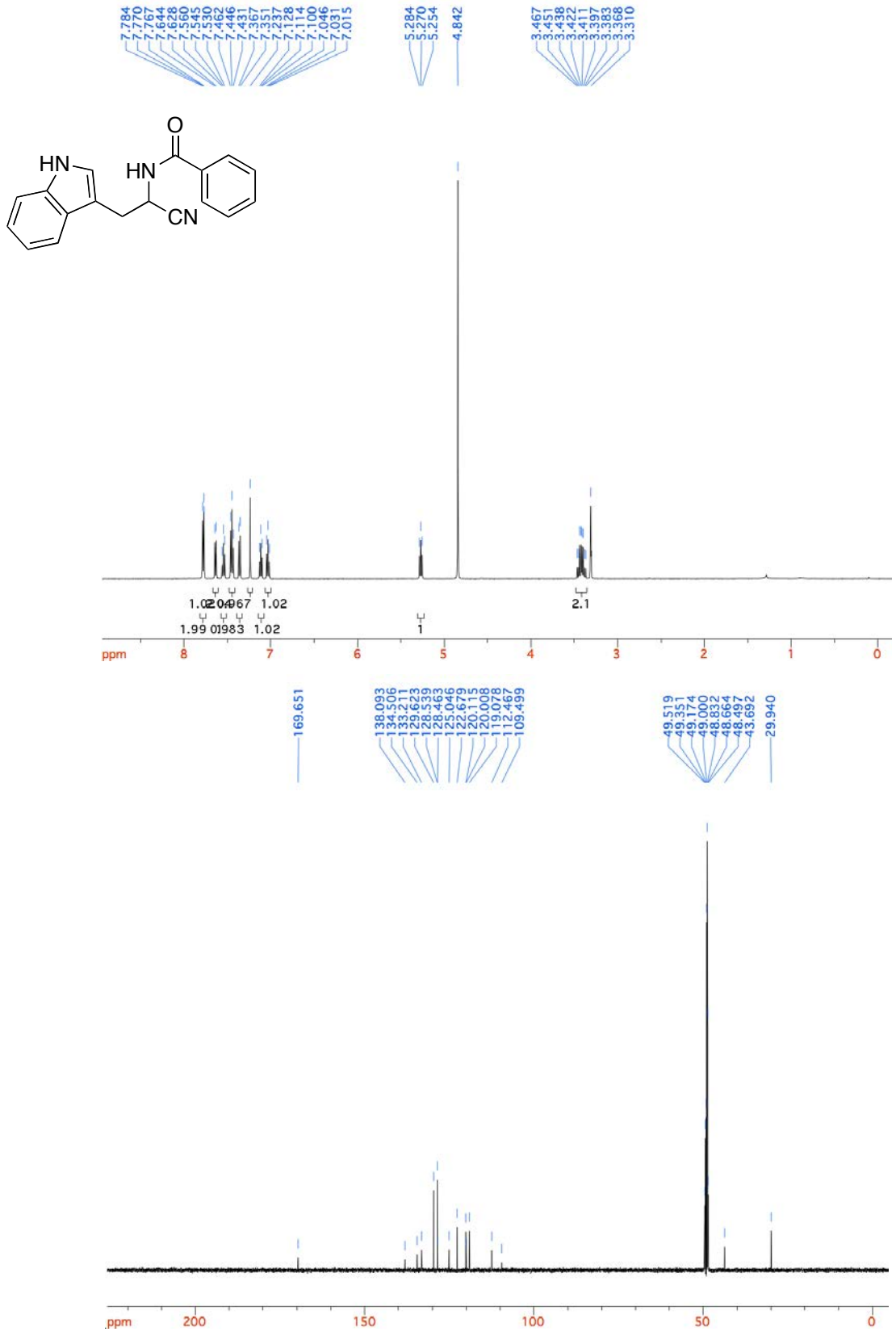
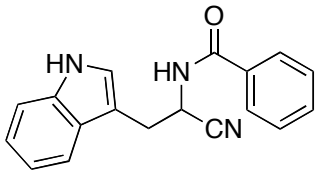
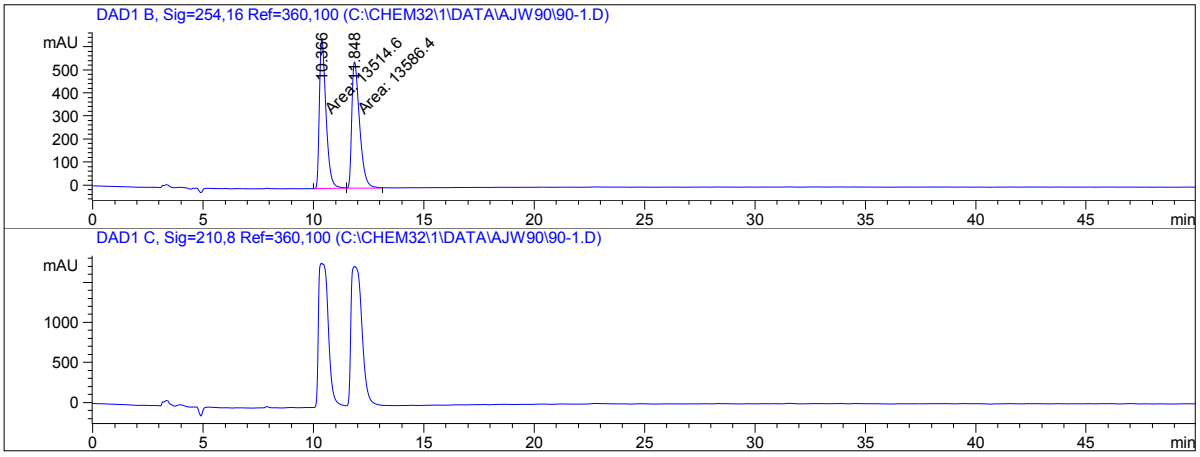


Figure S.18. Bz-Trp-I ^{1}H and ^{13}C NMR Spectr

Data File C:\CHEM32\1\DATA\AJW90\90-1.D
Sample Name: 90-1




```
==========================================================================
Acq. Operator   : Alex                          Seq. Line :   1
Acq. Instrument : LC-MS                         Location : Vial 51
Injection Date  : 8/5/2016 10:18:27 AM               Inj :   1
                                               Inj Volume : 10 µl
Acq. Method     : C:\CHEM32\1\METHODS\COL1_HI_80_20_50MIN.M
Last changed    : 8/5/2016 10:17:39 AM by Alex
                  (modified after loading)
Analysis Method : C:\CHEM32\1\METHODS\COL1_OZ3_IODINATION2.M
Last changed    : 8/5/2016 5:27:30 PM by Mower
                  (modified after loading)
==========================================================================
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=254,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.366 MF    0.3494 1.35146e4   644.64246  49.8675
   2  11.848 FM    0.4127 1.35864e4   548.69904  50.1325

Totals :                  2.71010e4  1193.34149
```


Figure S.19. Bz-Trp-I Chiral HPLC Assay

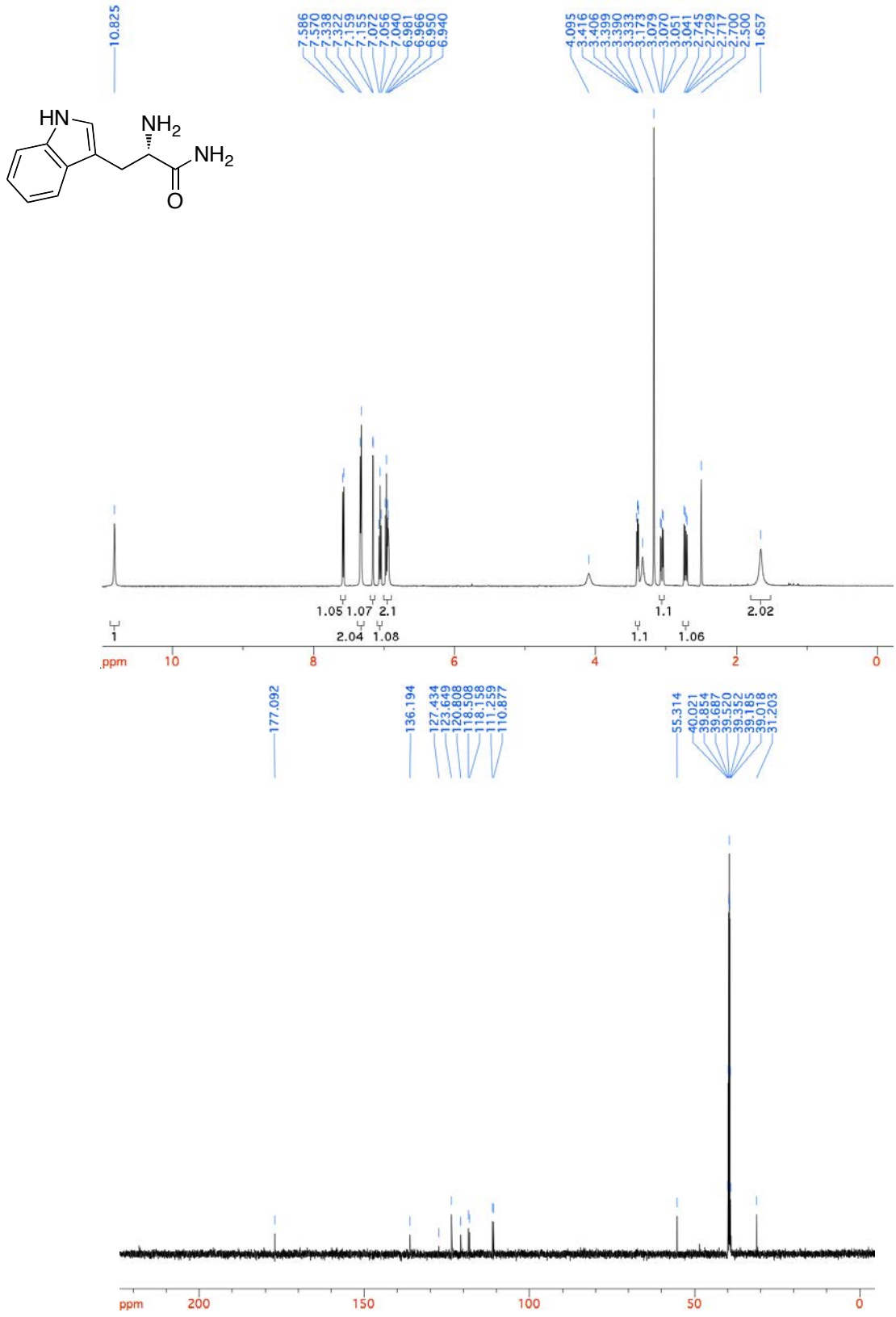


Figure S.20. *S*-Trp-II ^{1}H and ^{13}C NMR Spectra

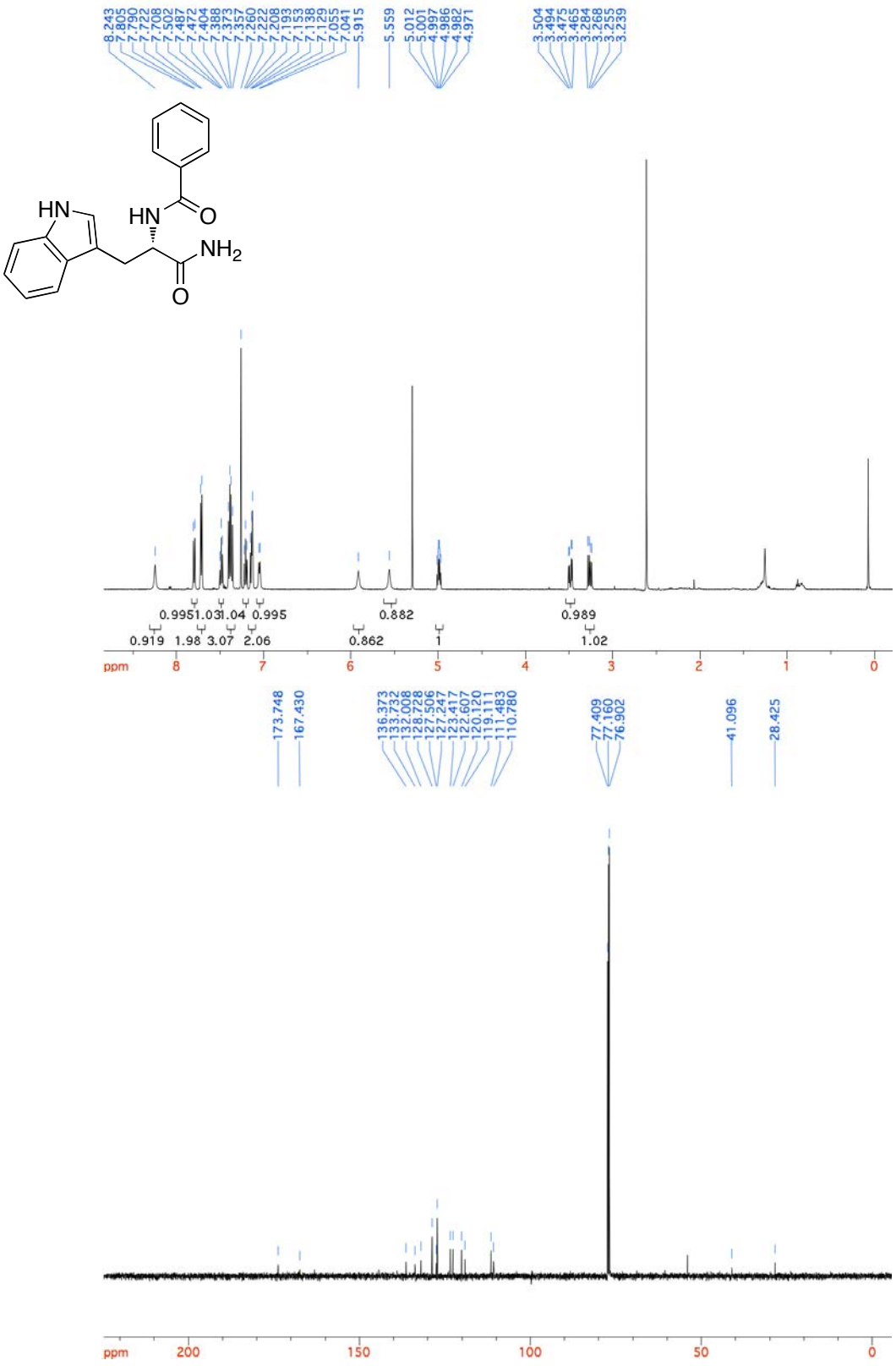
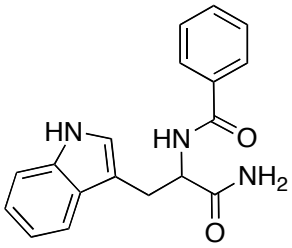
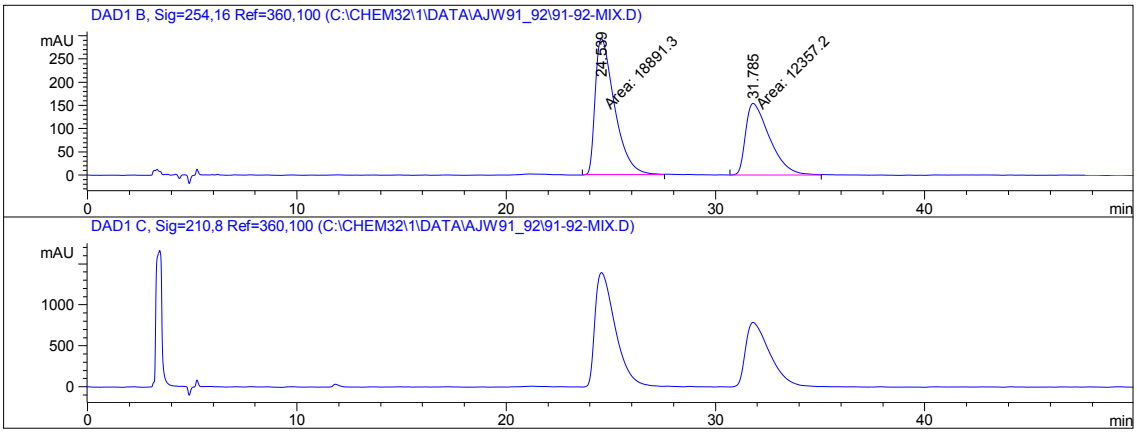


Figure S.21. *S*-Bz-Trp-II ^{1}H and ^{13}C NMR Spectra

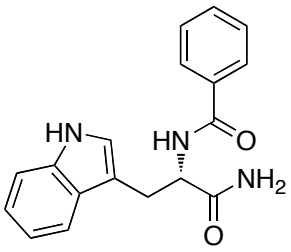
```
Data File C:\CHEM32\1\DATA\AJW91_92\91-92-MIX.D
Sample Name: 91-92-mix
    ======================================================================
    Acq. Operator   : Alex                          Seq. Line :   1
    Acq. Instrument : LC-MS                        Location : Vial 55
    Injection Date  : 8/5/2016 2:18:03 PM              Inj :   1
                                                  Inj Volume : 10 µl
    Acq. Method     : C:\CHEM32\1\METHODS\COL1_HI_80_20_50MIN.M
    Last changed    : 8/5/2016 2:17:15 PM by Alex
                      (modified after loading)
    Analysis Method : C:\CHEM32\1\METHODS\COL1_OZ3_IODINATION2.M
    Last changed    : 8/11/2016 1:11:15 PM by Mower
                      (modified after loading)
    ======================================================================
```



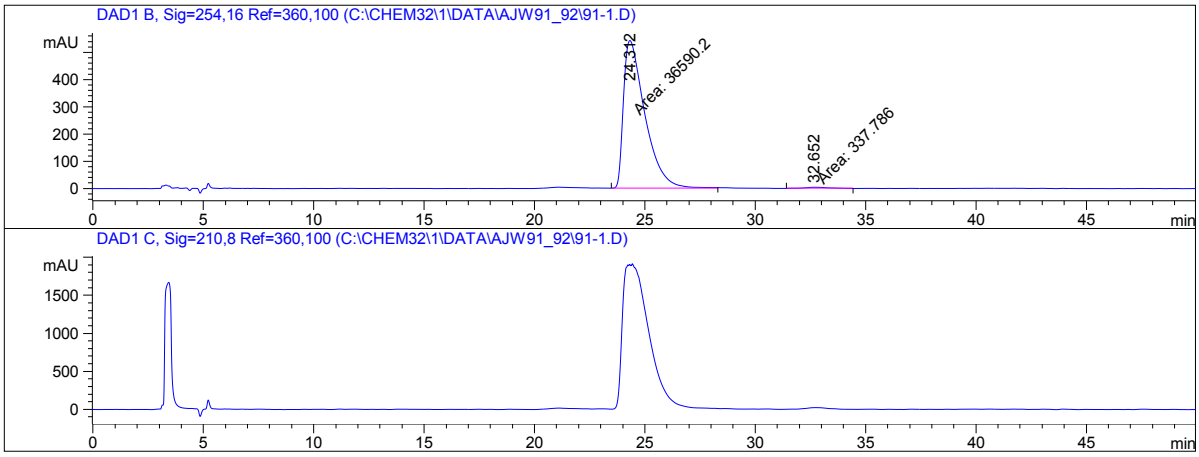



```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 B, Sig=254,16 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  24.539 MM    1.0735 1.88913e4   293.29895  60.4551
       2  31.785 MM    1.3331 1.23572e4   154.49130  39.5449

    Totals :                  3.12485e4   447.79025
```


Figure S.22. Mixture of *S*-Bz-Trp-II and *R*-Bz-Trp-II Chiral HPLC Assay
The solution was prepared by mixing enantiopure compounds to create a scalemic sample to test enantiomeric peak separation.



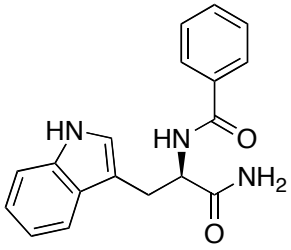

```
Data File C:\CHEM32\1\DATA\AJW91_92\91-1.D
Sample Name: 91-1
    ======================================================================
    Acq. Operator   : Alex                          Seq. Line :   2
    Acq. Instrument : LC-MS                         Location : Vial 56
    Injection Date  : 8/5/2016 3:09:22 PM               Inj :   1
                                                   Inj Volume : 10 µl
    Acq. Method     : C:\CHEM32\1\METHODS\COL1_HI_80_20_50MIN.M
    Last changed    : 8/5/2016 3:08:33 PM by Alex
                      (modified after loading)
    Analysis Method : C:\CHEM32\1\METHODS\COL1_OZ3_IODINATION2.M
    Last changed    : 8/11/2016 1:12:32 PM by Mower
                      (modified after loading)
    ======================================================================
```



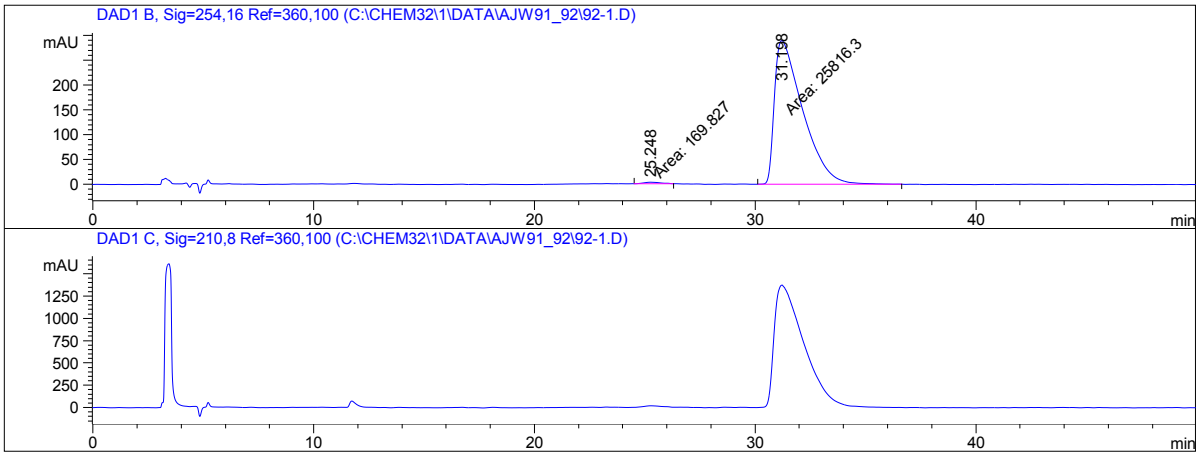

```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 B, Sig=254,16 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  24.312 MM    1.1238 3.65902e4   542.66974  99.0853
       2  32.652 MM    1.2923  337.78650    4.35647   0.9147

    Totals :                  3.69280e4   547.02621
```


Figure S.23. *S*-Bz-Trp-II Chiral HPLC Assay

Data File C:\CHEM32\1\DATA\AJW91_92\92-1.D
Sample Name: 92-1




```
    ======================================================================
    Acq. Operator   : Alex                          Seq. Line :   3
    Acq. Instrument : LC-MS                         Location : Vial 57
    Injection Date  : 8/5/2016 4:00:40 PM              Inj :   1
                                                   Inj Volume : 10 µl
    Acq. Method     : C:\CHEM32\1\METHODS\COL1_HI_80_20_50MIN.M
    Last changed    : 8/5/2016 3:59:52 PM by Alex
                      (modified after loading)
    Analysis Method : C:\CHEM32\1\METHODS\COL1_OZ3_IODINATION2.M
    Last changed    : 8/11/2016 1:13:49 PM by Mower
                      (modified after loading)
    ======================================================================
```

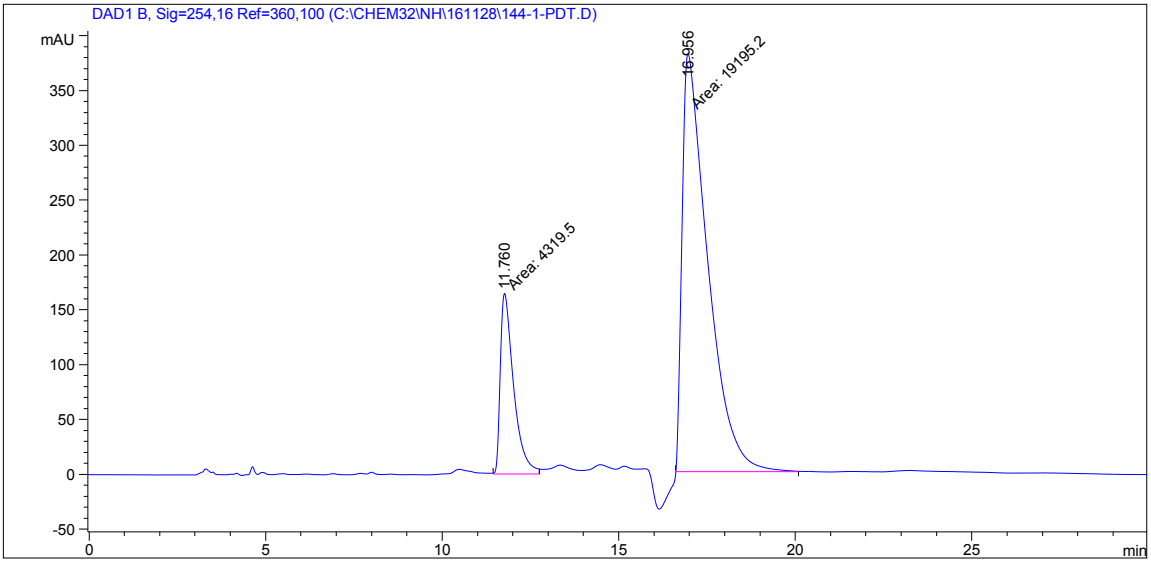



```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 B, Sig=254,16 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  25.248 MM    0.9111  169.82707    3.10671   0.6535
       2  31.198 MM    1.4859 2.58163e4   289.56207  99.3465

    Totals :                  2.59862e4   292.66878
```


Figure S.24.*R*-Bz-Trp-II Chiral HPLC Assay

5. HPLC Assays from Reactions with Ala-I, Phe-I, and Trp-I

```
Data File C:\CHEM32\NH\161128\144-1-PDT.D
Sample Name: 144-1-pdt

    ======================================================================
    Acq. Operator    : Neil                              Seq. Line :  14
    Acq. Instrument : LC-MS                               Location : Vial 11
    Injection Date   : 11/28/2016 6:35:43 PM                   Inj :   1
                                                        Inj Volume : 10 µl
    Acq. Method      : C:\CHEM32\1\METHODS\COL1_HI_80_20_30MIN.M
    Last changed     : 11/28/2016 6:34:45 PM by Neil
                       (modified after loading)
    Analysis Method : C:\CHEM32\1\METHODS\COL1_HI_80_20_30MIN.M
    Last changed     : 11/28/2016 3:36:41 PM by Alex
                       (modified after loading)
```

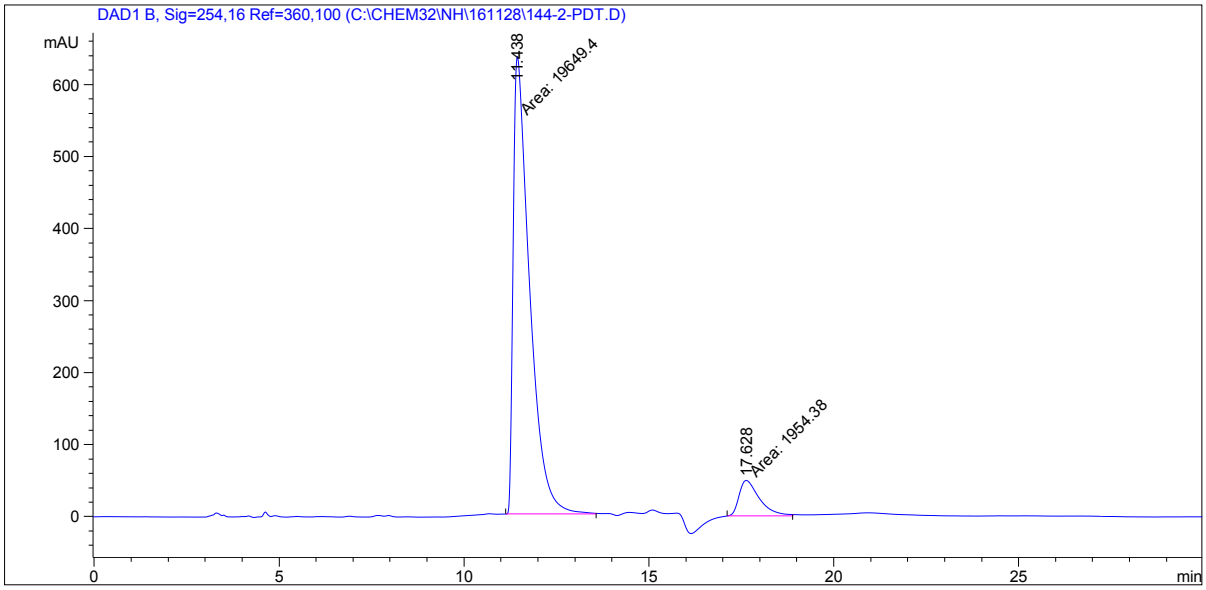



```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 B, Sig=254,16 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  11.760 MM    0.4374 4319.49951  164.59904  18.3694
       2  16.956 MM    0.8393 1.91952e4   381.15628  81.6306

    Totals :                  2.35147e4   545.75533

LC-MS 11/29/2016 7:21:25 AM Alex                                  Page   1 of 2
```

Figure S.25. D-Ribose with Ala-I – Bz-Ala-II Chiral HPLC Assay

Data File C:\CHEM32\NH\161128\144-2-PDT.D
Sample Name: 144-2-pdt

```
    ======================================================================
    Acq. Operator   : Neil                          Seq. Line :  15
    Acq. Instrument : LC-MS                          Location : Vial 12
    Injection Date  : 11/28/2016 7:06:57 PM               Inj :   1
                                                   Inj Volume : 10 µl
    Acq. Method     : C:\CHEM32\1\METHODS\COL1_HI_80_20_30MIN.M
    Last changed    : 11/28/2016 7:06:01 PM by Neil
                      (modified after loading)
    Analysis Method : C:\CHEM32\1\METHODS\COL1_HI_80_20_30MIN.M
    Last changed    : 11/29/2016 7:21:26 AM by Alex
                      (modified after loading)
```

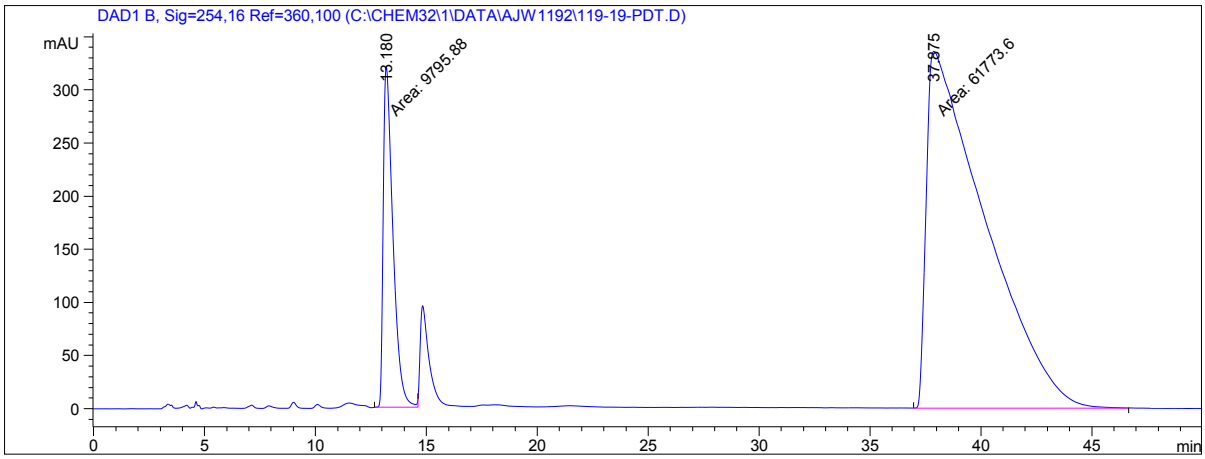



```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 B, Sig=254,16 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  11.438 MM    0.5154 1.96494e4   635.44440  90.9536
       2  17.628 MM    0.6534 1954.37512   49.85096   9.0464

    Totals :                  2.16038e4   685.29535
```


Figure S.26. D-Lyxose with Ala-I – Bz-Ala-II Chiral HPLC Assay

Data File C:\CHEM32\1\DATA\AJW1192\119-19-PDT.D
Sample Name: 119-19-pdt

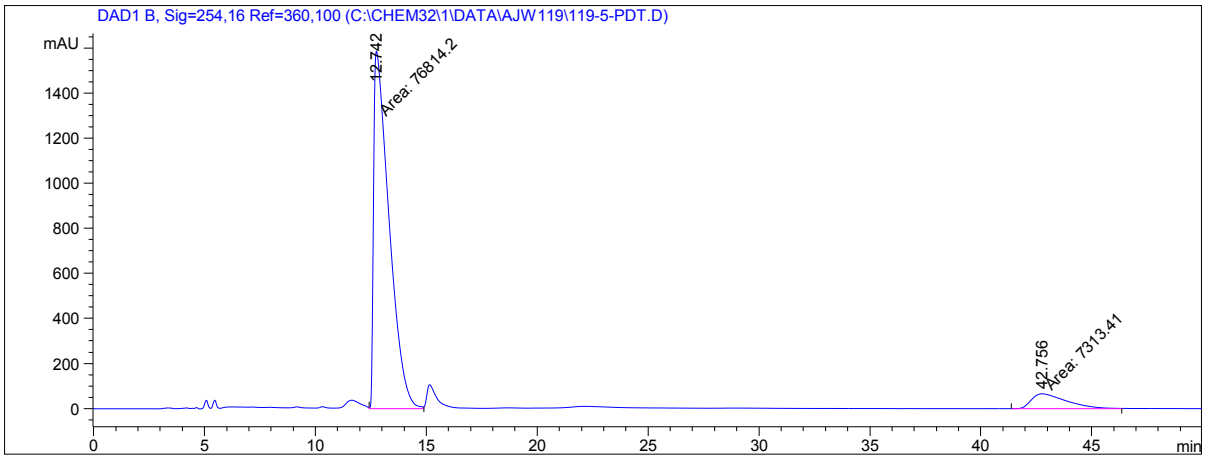
```
    ========================================================================
    Acq. Operator   : Alex                          Seq. Line :  17
    Acq. Instrument : LC-MS                          Location : Vial 28
    Injection Date  : 10/20/2016 2:34:27 AM               Inj :   1
                                                   Inj Volume : 10 µl
    Acq. Method     : C:\CHEM32\1\METHODS\COL1_HI_80_20_50MIN.M
    Last changed    : 10/20/2016 2:33:01 AM by Alex
                      (modified after loading)
    Analysis Method : C:\CHEM32\1\METHODS\COL1_OZ3_IODINATION2.M
    Last changed    : 10/20/2016 7:59:29 AM by Neil
                      (modified after loading)
    ========================================================================
```




```
    ========================================================================
                              Area Percent Report
    ========================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 B, Sig=254,16 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  13.180 MM    0.5087 9795.88379  320.95276  13.6872
       2  37.875 MM    3.0656 6.17736e4   335.84094  86.3128

    Totals :                  7.15695e4   656.79370


    ========================================================================
                              Summed Peaks Report
```


Figure S.27. D-Ribose with Phe-I – Bz-Phe-II Chiral HPLC Assay

```
Data File C:\CHEM32\1\DATA\AJW119\119-5-PDT.D
Sample Name: 119-5-pdt
    ======================================================================
    Acq. Operator   : Alex                          Seq. Line :  14
    Acq. Instrument : LC-MS                        Location : Vial 25
    Injection Date  : 10/8/2016 1:53:19 AM             Inj :   1
                                                  Inj Volume : 10 µl
    Acq. Method     : C:\CHEM32\1\METHODS\COL1_HI_80_20_50MIN.M
    Last changed    : 10/8/2016 1:52:27 AM by Alex
                      (modified after loading)
    Analysis Method : C:\CHEM32\1\METHODS\COL1_OZ3_IODINATION2.M
    Last changed    : 10/10/2016 5:38:03 PM by Neil
                      (modified after loading)
    ======================================================================
```

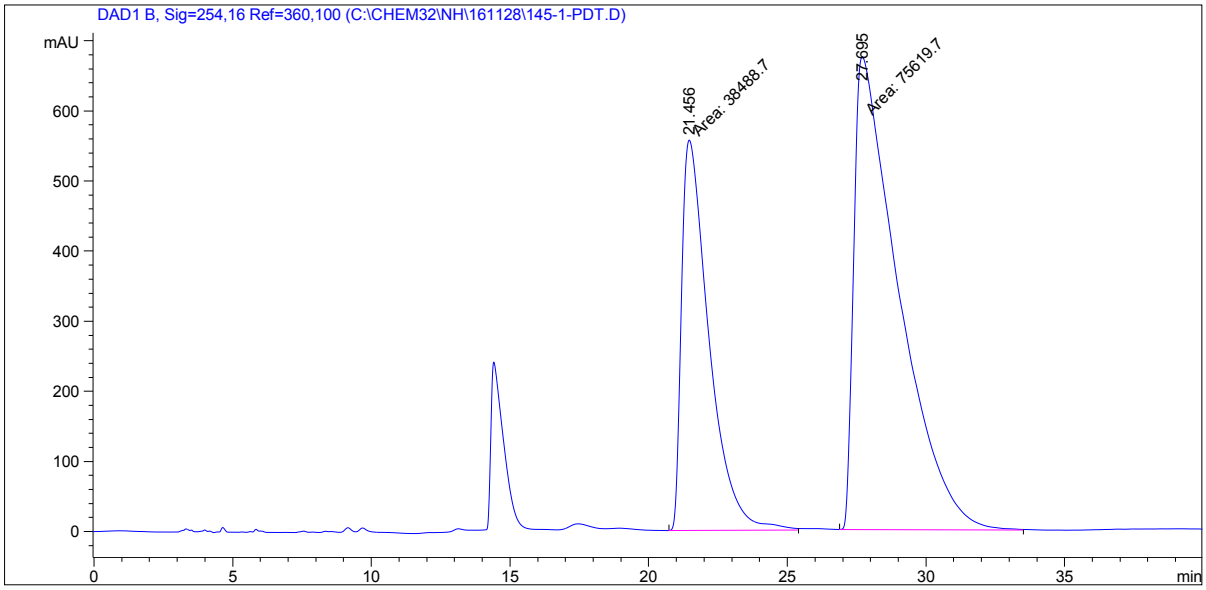



```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 B, Sig=254,16 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  12.742 MM    0.8072 7.68142e4  1585.94531  91.3068
       2  42.756 MM    1.8429 7313.40625   66.14054   8.6932

    Totals :                  8.41276e4  1652.08585


    ======================================================================
                            Summed Peaks Report
```


Figure S.28. D-Lyxose with Phe-I – Bz-Phe-II Chiral HPLC Assay

Data File C:\CHEM32\NH\161128\145-1-PDT.D
Sample Name: 145-1-pdt

```
    ======================================================================
    Acq. Operator    : Neil                          Seq. Line :  19
    Acq. Instrument : LC-MS                           Location : Vial 16
    Injection Date  : 11/28/2016 9:12:07 PM               Inj :   1
                                                    Inj Volume : 10 µl
    Acq. Method     : C:\CHEM32\1\METHODS\COL1_HI_80_20_40MIN.M
    Last changed    : 11/28/2016 9:11:07 PM by Neil
                      (modified after loading)
    Analysis Method : C:\CHEM32\1\METHODS\COL1_HI_80_20_30MIN.M
    Last changed    : 11/29/2016 7:25:48 AM by Alex
                      (modified after loading)
```

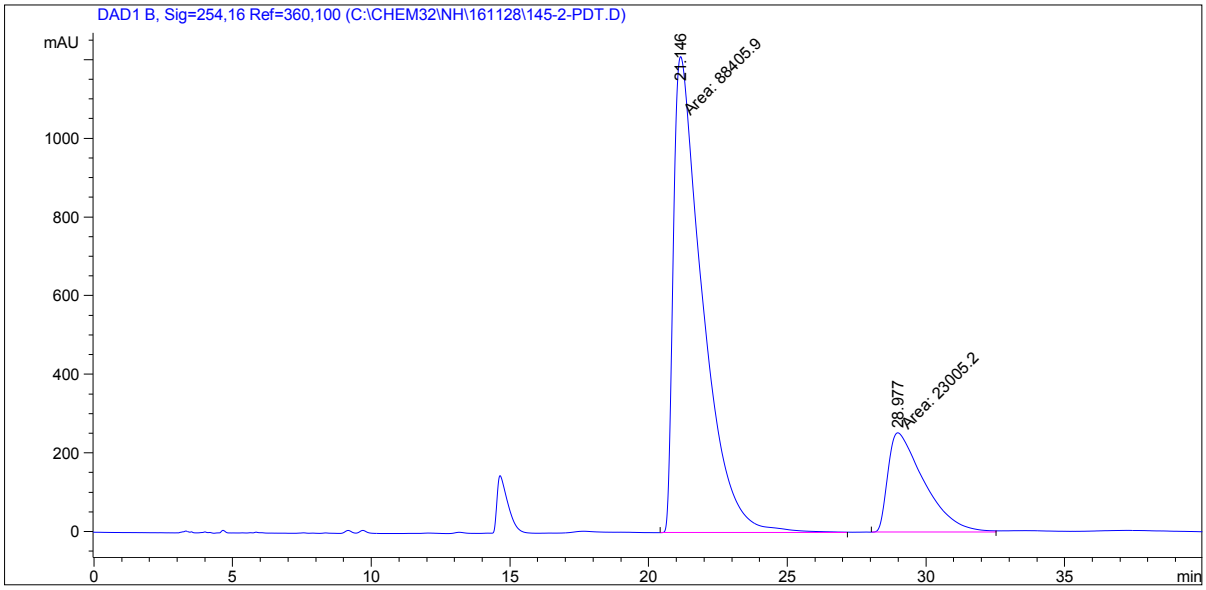



```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 B, Sig=254,16 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  21.456 MM    1.1511 3.84887e4   557.26892  33.7299
       2  27.695 MM    1.8672 7.56197e4   674.97705  66.2701

    Totals :                  1.14108e5  1232.24597
```


Figure S.29. D-Ribose with Trp-I – Bz-Trp-II Chiral HPLC Assay

Data File C:\CHEM32\NH\161128\145-2-PDT.D
Sample Name: 145-2-pdt

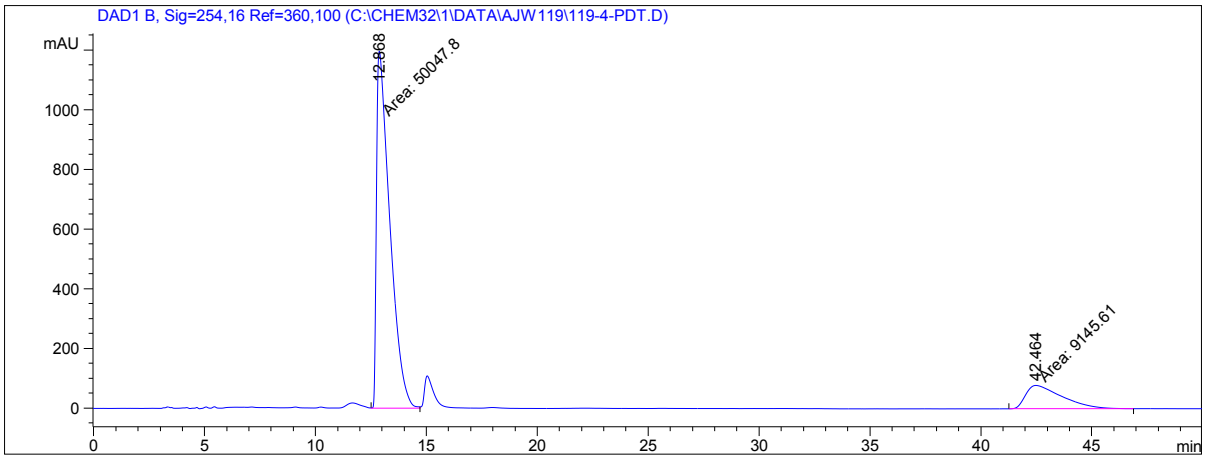
```
    ======================================================================
    Acq. Operator    : Neil                              Seq. Line :  20
    Acq. Instrument : LC-MS                               Location : Vial 17
    Injection Date  : 11/28/2016 9:53:26 PM                    Inj :   1
                                                        Inj Volume : 10 µl
    Acq. Method     : C:\CHEM32\1\METHODS\COL1_HI_80_20_40MIN.M
    Last changed    : 11/28/2016 9:52:25 PM by Neil
                      (modified after loading)
    Analysis Method : C:\CHEM32\1\METHODS\COL1_HI_80_20_30MIN.M
    Last changed    : 11/29/2016 7:27:19 AM by Alex
                      (modified after loading)
```




```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 B, Sig=254,16 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  21.146 MM    1.2172 8.84059e4  1210.54565  79.3510
       2  28.977 MM    1.5161 2.30052e4   252.90536  20.6490

    Totals :                  1.11411e5  1463.45102
```


Figure S.30. D-Lyxose with Trp-I – Bz-Trp-II Chiral HPLC Assay

```
Data File C:\CHEM32\1\DATA\AJW119\119-4-PDT.D
Sample Name: 119-4-pdt
    ========================================================================
    Acq. Operator   : Alex                          Seq. Line :  13
    Acq. Instrument : LC-MS                        Location : Vial 24
    Injection Date  : 10/8/2016 1:02:04 AM             Inj :   1
                                                  Inj Volume : 10 µl
    Acq. Method     : C:\CHEM32\1\METHODS\COL1_HI_80_20_50MIN.M
    Last changed    : 10/8/2016 1:01:11 AM by Alex
                      (modified after loading)
    Analysis Method : C:\CHEM32\1\METHODS\COL1_OZ3_IODINATION2.M
    Last changed    : 10/10/2016 5:35:44 PM by Neil
                      (modified after loading)
    ========================================================================
```

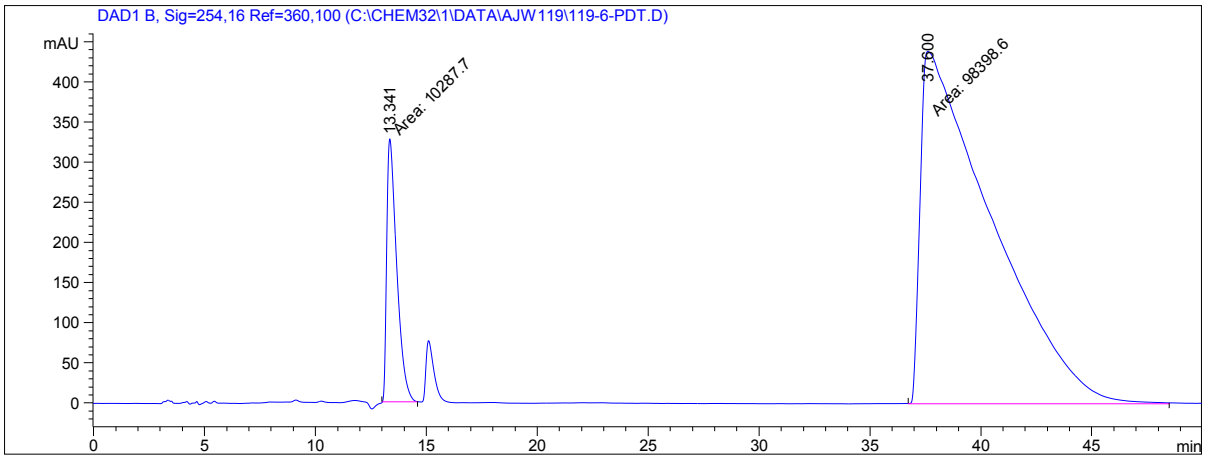



```
    ========================================================================
                            Area Percent Report
    ========================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 B, Sig=254,16 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]    [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  12.868 MM    0.6971 5.00478e4  1196.56458  84.5496
       2  42.464 MM    1.9331 9145.61328   78.85239  15.4504

    Totals :                  5.91934e4  1275.41696


    ========================================================================
                            Summed Peaks Report

LC-MS 10/10/2016 5:36:46 PM Neil                                  Page   1 of 2
```

Figure S.31. L-Ribose with Phe-I – Bz-Phe-II Chiral HPLC Assay

Data File C:\CHEM32\1\DATA\AJW119\119-6-PDT.D
Sample Name: 119-6-pdt

```
    ========================================================================
    Acq. Operator    : Alex                          Seq. Line :  15
    Acq. Instrument : LC-MS                           Location : Vial 26
    Injection Date  : 10/8/2016 2:44:35 AM                Inj :   1
                                                    Inj Volume : 10 µl
    Acq. Method     : C:\CHEM32\1\METHODS\COL1_HI_80_20_50MIN.M
    Last changed    : 10/8/2016 2:43:43 AM by Alex
                      (modified after loading)
    Analysis Method : C:\CHEM32\1\METHODS\COL1_OZ3_IODINATION2.M
    Last changed    : 10/10/2016 5:40:50 PM by Neil
                      (modified after loading)
    ========================================================================
```




```
    ========================================================================
                            Area Percent Report
    ========================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 B, Sig=254,16 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  13.341 MM    0.5236 1.02877e4   327.46478   9.4655
       2  37.600 MM    3.7342 9.83986e4   439.17657  90.5345

    Totals :                  1.08686e5   766.64136


    ========================================================================
                            Summed Peaks Report
```


Figure S.32. L-Lyxose with Phe-I – Bz-Phe-II Chiral HPLC Assay

6. Kinetic Modeling

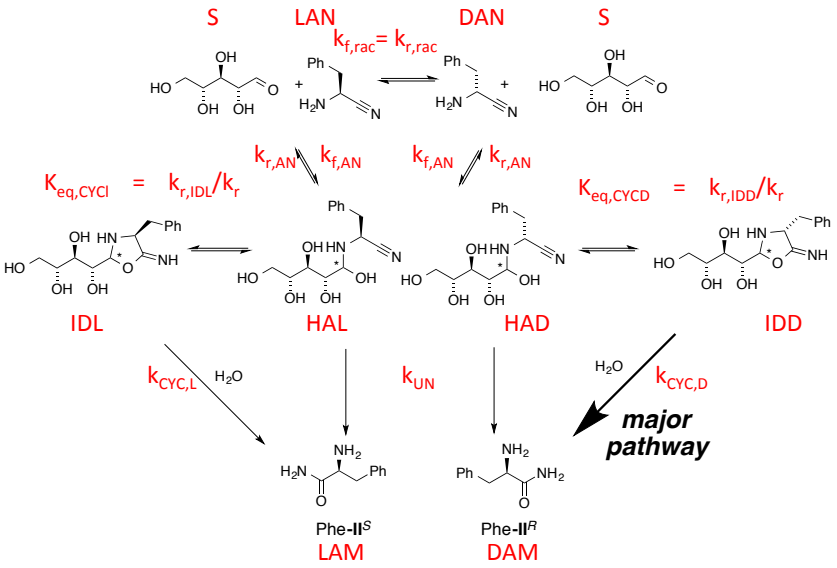


Figure S.33. Reaction network of Figure 2. The reaction network of Figure 2 in the manuscript is described by a set of elementary reactions given below. These equations are fit to the temporal experimental data for enantiomeric excess and conversion shown in Figure 1 using the CoPaSi program with the Levenberg-Marquardt method and an iteration limit = 2000 and tolerance = $1x10^6$. The parameter designations used in the program are given in the scheme.

# ▲	Name	Reaction	Rate Law
1	reaction_1	LAN + S = HAL	Mass action (reversible)
2	reaction_2	DAN + S = HAD	Mass action (reversible)
3	reaction_3	LAN = DAN	Mass action (reversible)
4	reaction_4	HAL = IDL	Mass action (reversible)
5	reaction_5	HAD = IDD	Mass action (reversible)
6	reaction_6	HAL -> LAM + S	Mass action (irreversible)
7	reaction_7	HAD -> DAM + S	Mass action (irreversible)
8	reaction_8	IDL -> LAM + S	Mass action (irreversible)
9	reaction_9	IDD -> DAM + S	Mass action (irreversible)

Rate constants returned in the simulation:
Rxn 1, Rxn 2: $k_{f,AN} = 2.41$ e-03 $M^{-1}hr^{-1}$; $k_{r,AN} = 9.34$ e-03 hr^{-1};
Rxn 3: $k_{f,rac} = k_{r,rac} = 1$ e+02 hr^{-1}
Rxn 4: $k_{f,IDL} = 7$ e-02 hr^{-1}; $k_r = 1.03$ e-02 hr^{-1};
Rxn 5: $k_{f,IDD} = 6$ e-01 hr^{-1}; $k_r = 1.03$ e-02 hr^{-1};
Rxn 6, Rxn 7: $k_{UN} = 2.03$ e-03 hr^{-1};
Rxn 8: $k_{CYC,D} = 2.79$ e-03 hr^{-1};
Rxn 9: $k_{CYC,L} = 5.66$ e-06 hr^{-1}

$K_{eq,CYC,L} = 6.74$ kcal/mol
$K_{eq,CYC,D} = 58.8$ kcal/mol
$\Delta\Delta G = 2.15$ kcal/mol

Figure S.34. Elementary reaction steps and rate constants returned by the model

7. Preliminary NMR Spectroscopy Studies

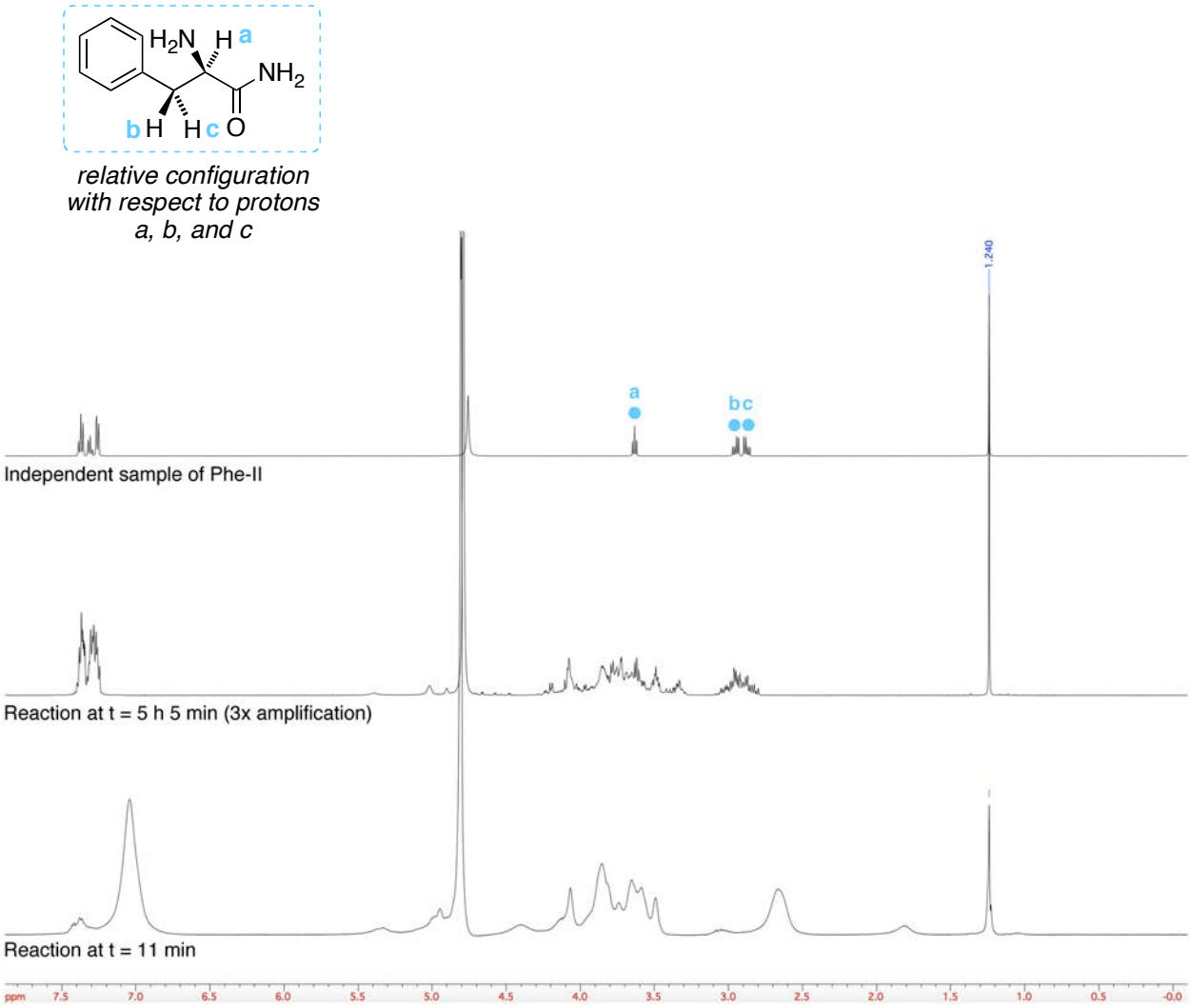


Figure S.35. ^{1}H NMR spectra of reaction at t = 11 min and t = 5 h 5 min compared to Phe-**II**. Comparison of ^{1}H NMR spectra of the reaction at t = 11 min with t = 5 h 5 min did not immediately provide useful information. The reaction spectra at t = 5 h 5 min shows protons in the appropriate region of the diastereotopic protons **b** and **c** present on Phe-**II**.

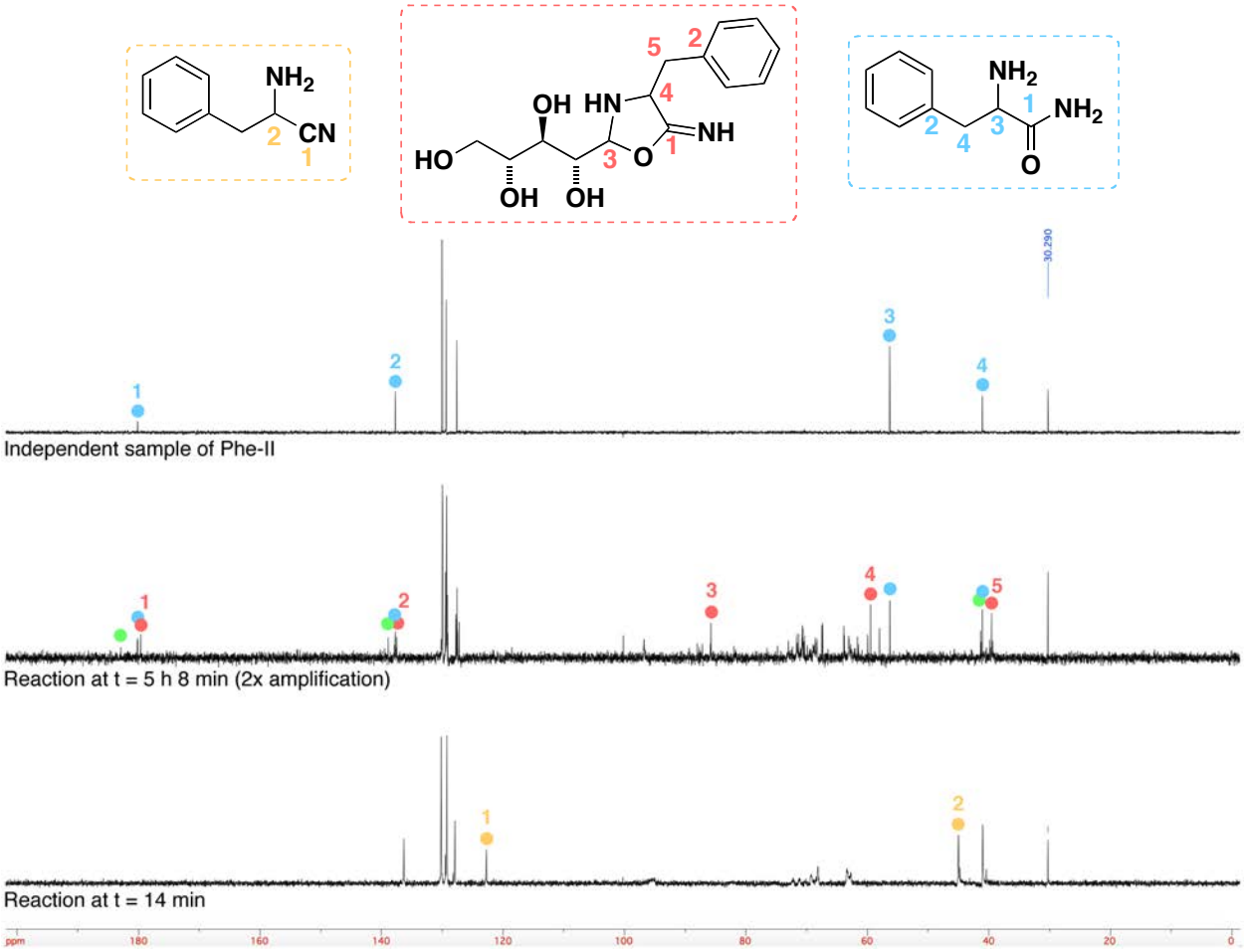


Figure S.36. ^{13}C NMR spectra of reaction at t = 14 min and t = 5 h 8 min compared to Phe-**II** showing consumption of Phe-**I**. Apparent formation of two distinct species containing carbons with similar chemical shifts as carbon 1 and carbon 2 of Phe-**II** is noted by the green and red dots respectively. The red species contains the carbon scaffold of **Phe-I** as shown, but it also appears to have a covalently bound carbon that falls at the appropriate chemical shift for what is labeled as carbon 3 on hypothesized intermediate **CYC**. HMBC correlations were utilized to determine carbons present on the green species and the red species (Figs. S.37, S.38).

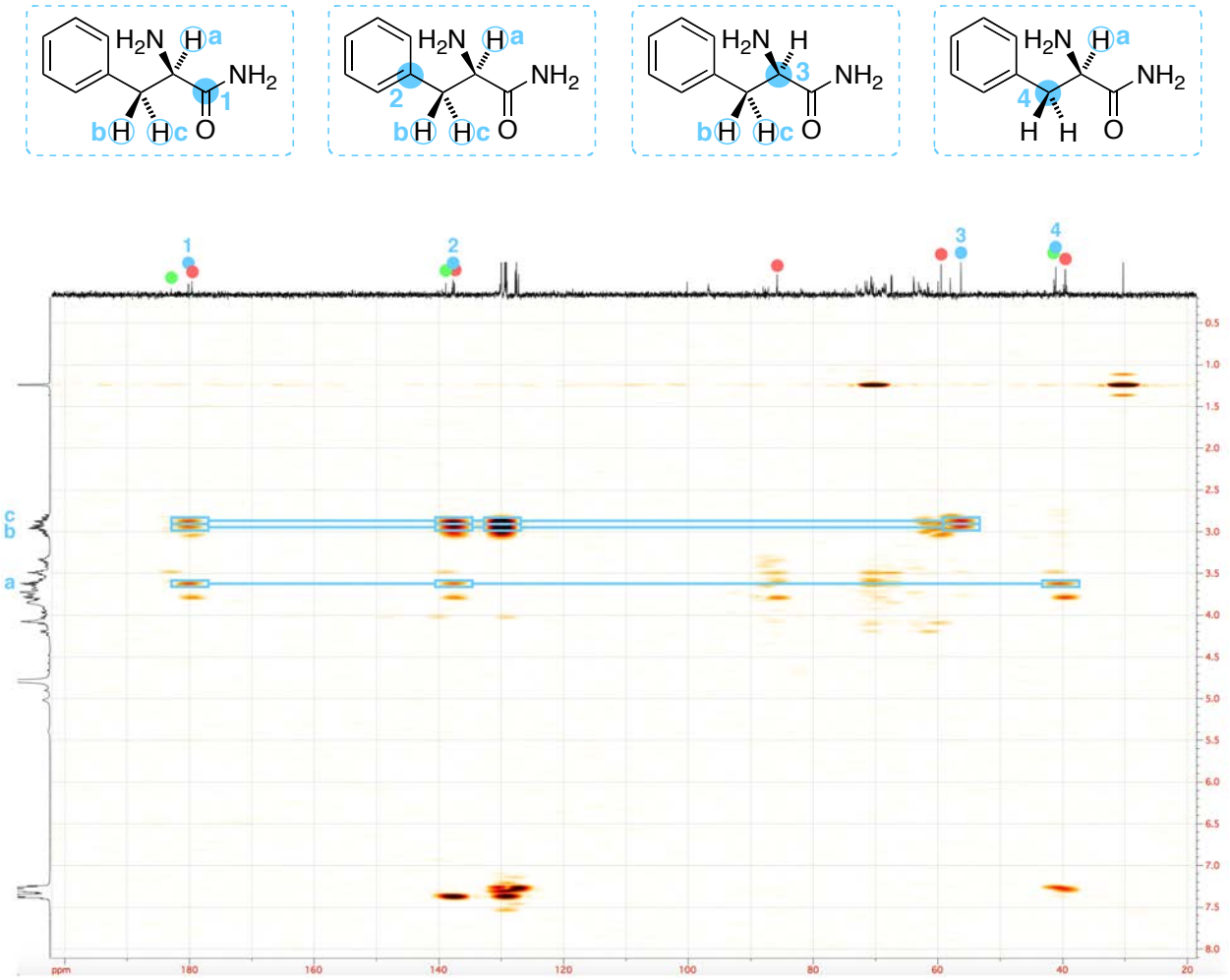


Figure S.37. HMBC of the reaction at t = 5 h 26 min. Correlations for carbons 1-4 with protons **a-c** of the product Phe-**II** are shown in blue boxes. Lines are drawn between boxes for clarity. Carbonyl carbon 1 shows correlation with protons **a**, **b**, and **c**. Carbon 2 similarly shows correlation with protons **a**, **b**, and **c**. Carbon 3 shows correlations to protons **b** and **c** on the adjacent methylene. Carbon 4 shows correlations to proton **a** on the adjacent carbon.

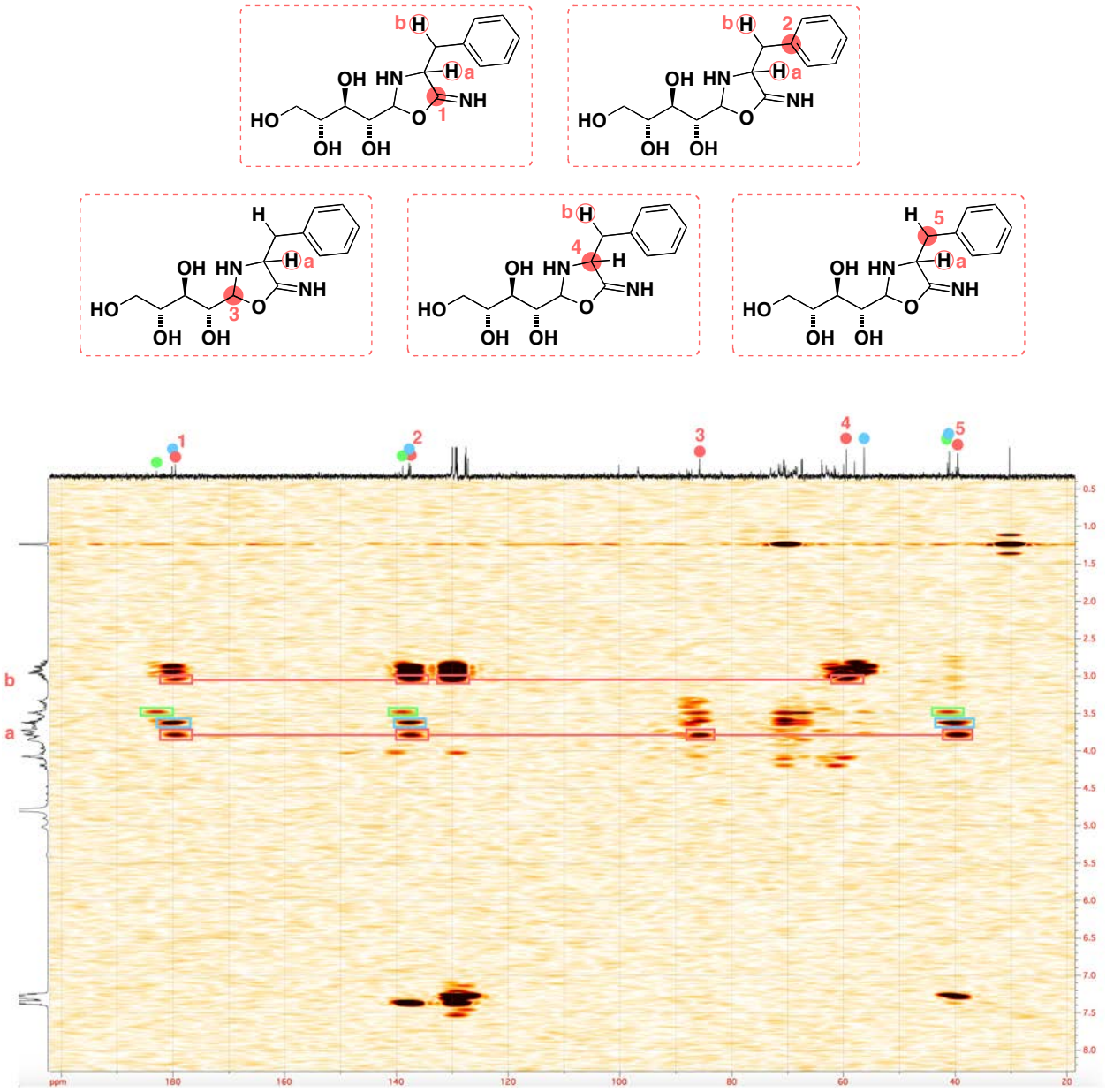


Figure S.38. HMBC of the reaction at t = 5 h 26 min. Correlations for carbons 1-5 with protons **a** and **b** of the red species are shown in red boxes. Both carbon 1 and carbon 2 show correlations with protons **a** and **b**. Carbon 4 shows correlation with proton **b** and carbon 5 shows correlation with proton **a**. All of these patterns match the carbon framework of Phe-**II**, which indicates that the core structure is present on the red species. Carbon 3 shows correlation with proton **a**. This indicates connection of the carbon framework of Phe-**II** to another molecule. The chemical shift of carbon 3 is also consistent with the proposed structure (N and O bound to 3).

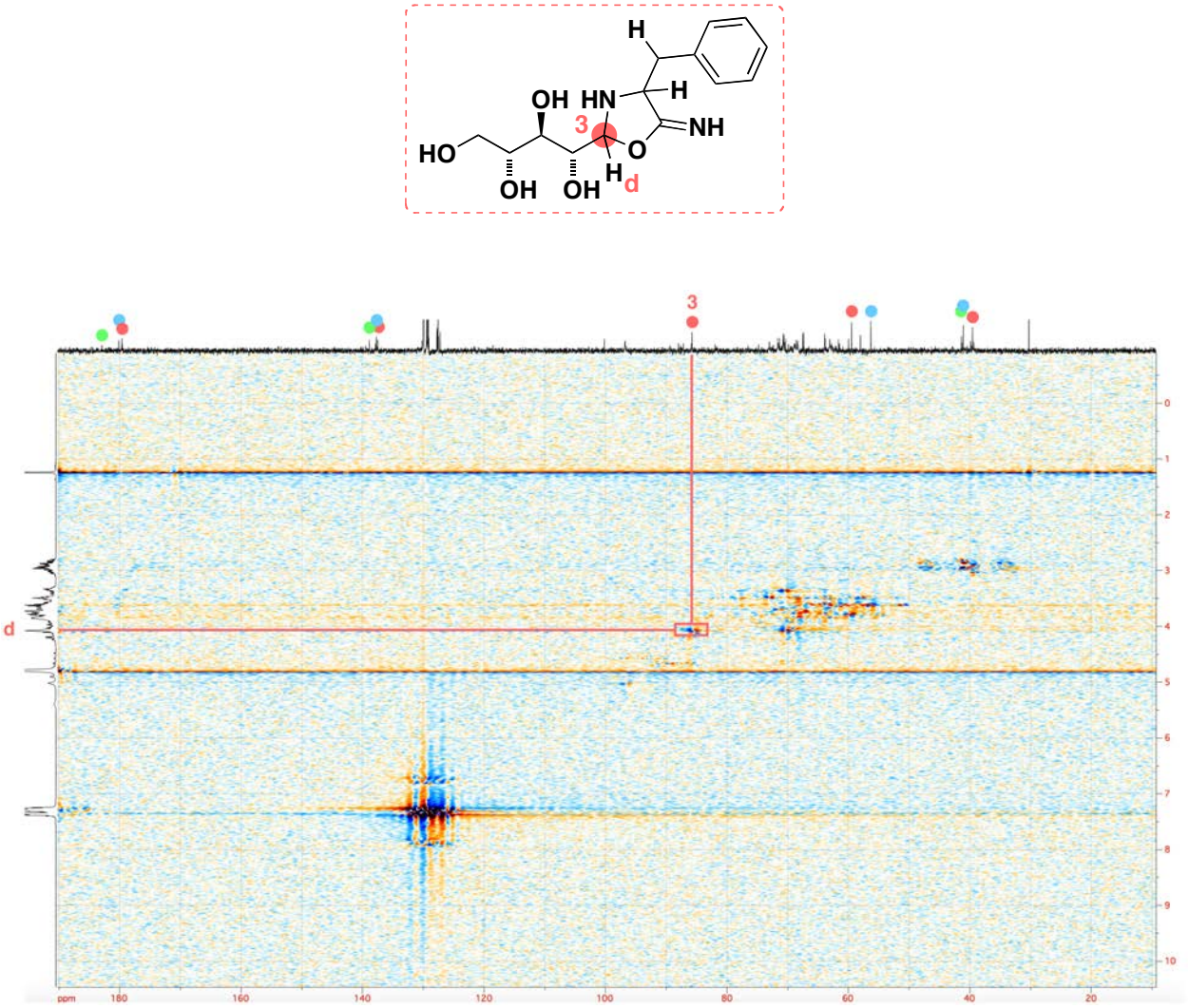


Figure S.39. HSQC of the reaction mixture at 5 h 23 min. Correlations for carbons 3 with proton **d** of the red species is shown in a red box. Lines are drawn between the box for clarity.

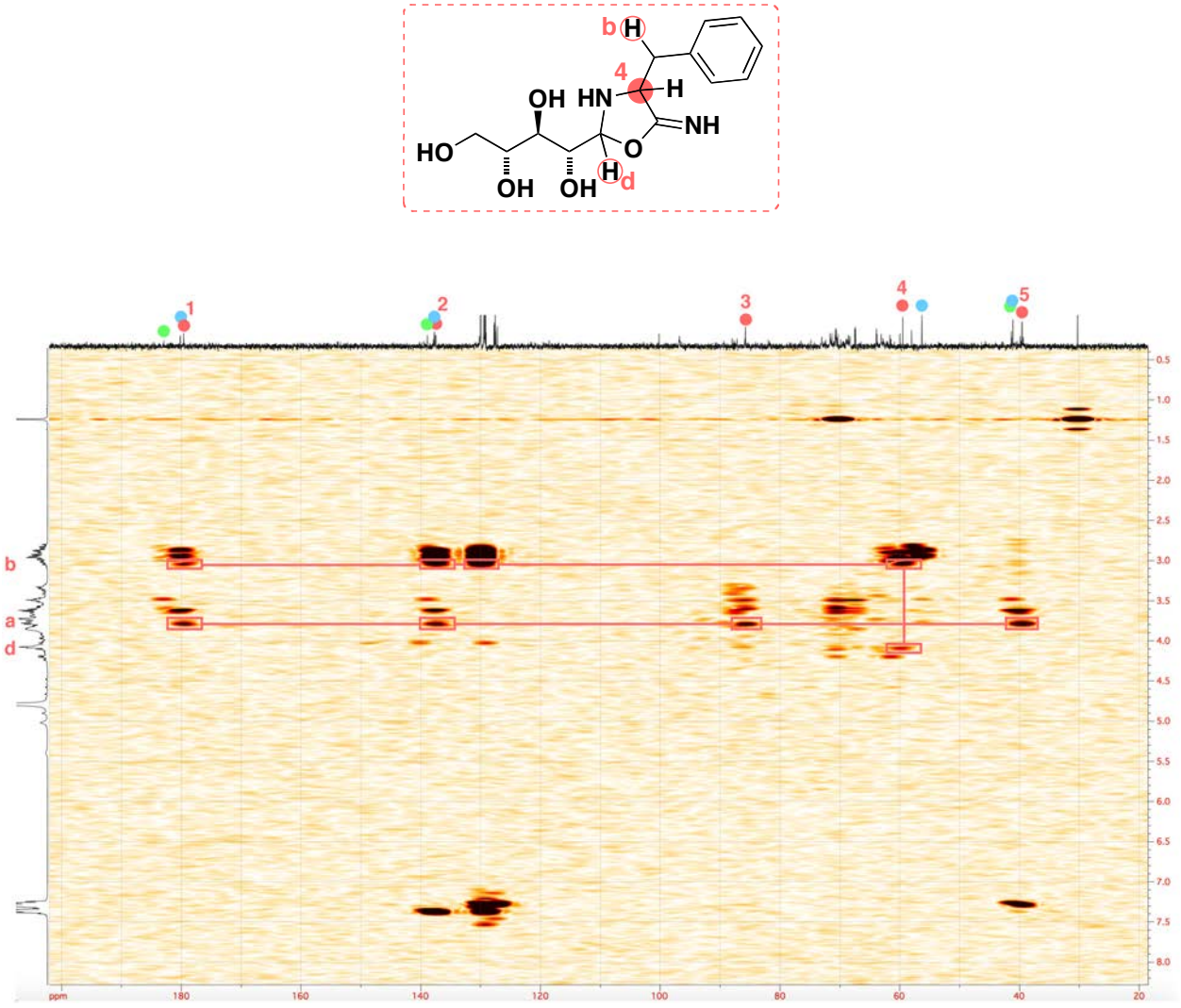


Figure S.40. HMBC of the reaction at t = 5 h 26 min. Correlations for carbons 1-5 with protons **a**, **b**, and **d** of the red species are shown in red boxes. Updated correlations for carbon 4 with protons **b** and **d** of the red species are also shown. Carbon 4 shows correlations with proton **b** and proton **d**, providing additional evidence of a covalent linkage between the carbon framework contained in Phe-**II** and a carbon (carbon 3). Lines are drawn between boxes for clarity.

8. Computational Procedures and Results

Procedures for Computational Calculations in Table 5 and Figure 3

There are four families of hemiaminal intermediates **III** and cyclic intermediates **IV** (Scheme S.1) defined by the configurations of the stereocenters. The following designations are used:

- ***RR*** family: *R*-amino nitrile and *R*-carbon atom bearing hydroxy-group in hemiaminal motif.
- ***RS*** family: *R*-amino nitrile and *S*-carbon atom bearing hydroxy-group in hemiaminal motif.
- ***SR*** family: *S*-amino nitrile and *R*-carbon atom bearing hydroxy-group in hemiaminal motif.
- ***SS*** family: *S*-amino nitrile and *S*-carbon atom bearing hydroxy-group in hemiaminal motif.

Computational analysis was performed for phenylalanine aminonitrile and D-ribose. We characterized conformational landscapes of four families of hemiaminal intermediates **III** and corresponding cyclic intermediates **IV**, and performed a transition state search for the intramolecular cyclization of the deprotonated hemiaminals **ADD** (Figure 2).

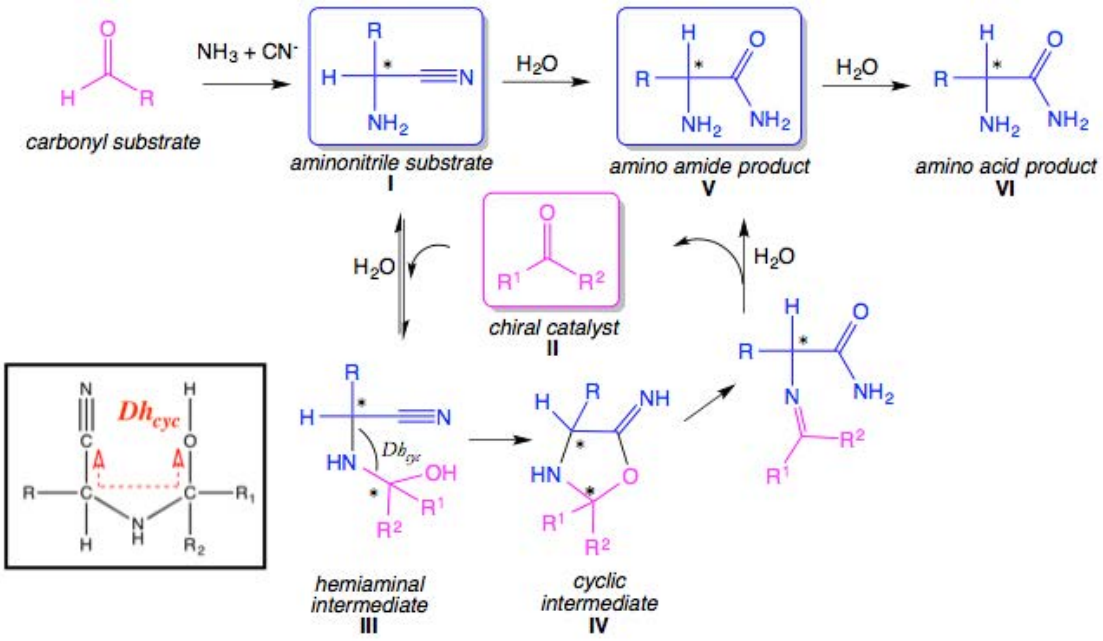
The first stage of the conformational analysis included Monte Carlo sampling using classical force-fields and implicit solvent models of water as implemented in BOSS and MAESTRO software.[5-8] Specifically, we used Optimized Potentials for Liquid Simulations - All Atom (OPLS-AA) force-field[9,10] in combination with Generalized Born/Surface Area (GB/SA) implicit solvent model for water.[11] Atomic charges for the classical force-field runs were obtained from AM1 semiempirical calculations.[12]

The second stage of the conformational analysis included refinement of the sampled conformational landscapes using density functional theory (DFT) as implemented in Gaussian 09 software.[13] Geometries were re-optimized at M062X/6-31+G* level of theory. M062X[14] is a global hybrid density functional that ensures adequate treatment of non-covalent interactions, such as hydrogen bonding and cation-pi interactions, that are expected to contribute to the stabilization of hemiaminals formed from phenylalanine aminonitrile and sugars. We used Self-Consistent Reaction Field (SCRF) continuum model of water implemented as Solvation Model based on Density (SMD).[15] Convergence of optimization to the local minima was confirmed via normal mode analysis. We used the same level of theory and standard methods of transition state optimization implemented in Gaussian 09[13,16,17] followed by normal mode analysis to identify and validate transition states of intramolecular cyclization of the deprotonated hemiaminals **ADD**.

Conformational sampling of the torsional degrees of freedom in hemiaminal intermediate **III** was performed with BOSS software; refined structures were used to generate transition states and cyclic intermediates **IV**. MAESTRO software has a capability for mixed torsional/low-mode sampling suitable for ring conformations and was used to sample conformational landscape of cyclic intermediate **IV**; refined structures were used to generate transitions states and hemiaminal intermediates **III**. Structural motifs associated with low-energy conformers in the samples were used to manually generate ~10 conformers that were added to the sample. Overall, we characterized 330 conformers of the neutral hemiaminal intermediate **III**, 220 anionic transition states for the intramolecular cyclization of **ADD** (Figure 2), and 211 cyclic intermediates **IV**.

Results from the computational studies are included in Figures S.41-S.48.

Scheme S.1. Strecker amino acid synthesis directed by chiral carbonyl catalyst. Hemiaminal intermediate **III** is a protonated counterpart of hemiaminals **ADD** (Figure 2). Stereocenters are labeled with stars. The inset shows definition of the dihedral angle $\boldsymbol{Dh_{cyc}}$ between C-CN and C-OH bonds involved in hemiaminal cyclization; $\boldsymbol{Dh_{cyc}}$ serves as a measure of geometric favorability of the reaction.



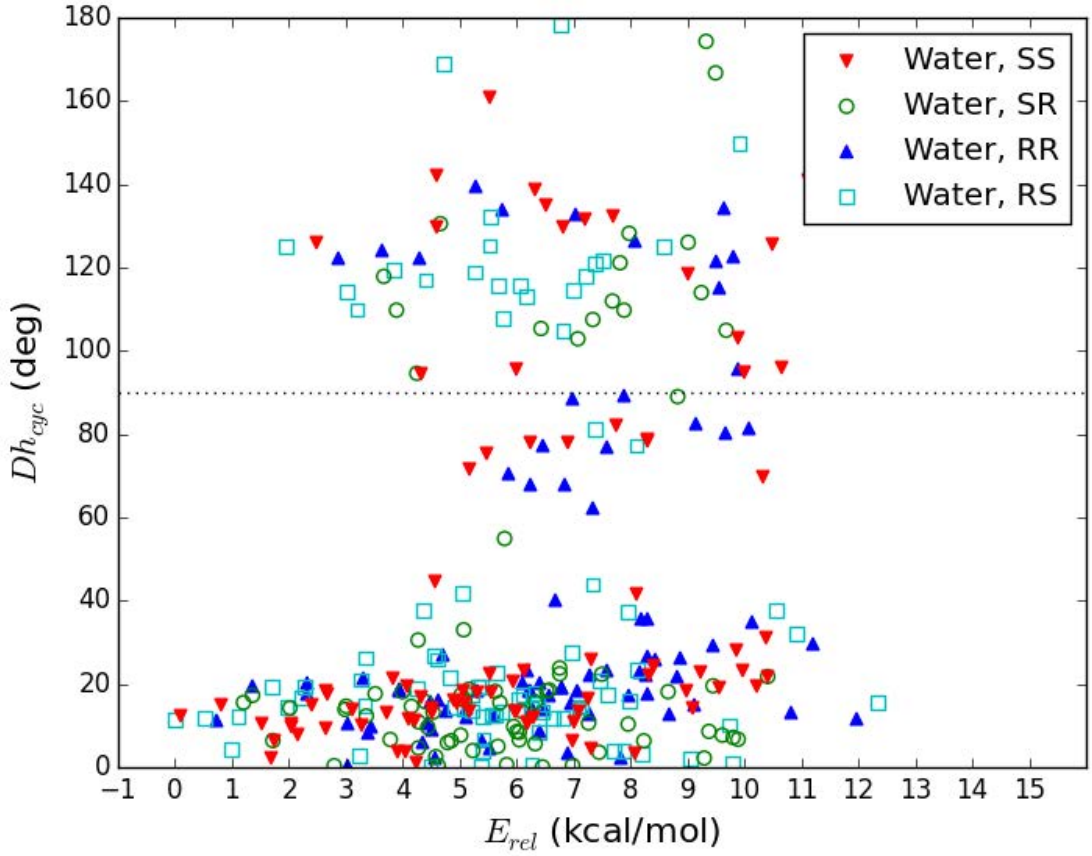
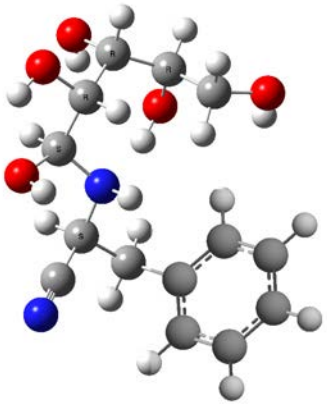
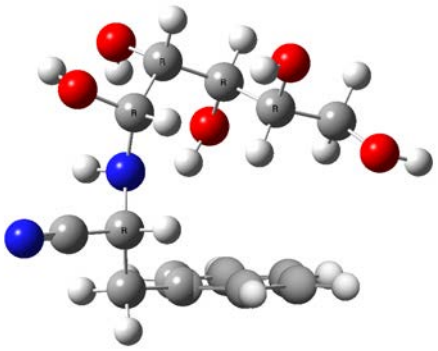


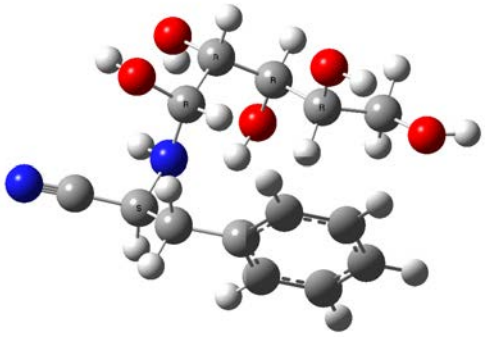
Figure S.41. Results of the conformational analysis for hemiaminal intermediate **III** in water. Dihedral angle $\boldsymbol{Dh_{cyc}}$ is plotted against relative energies $\boldsymbol{E_{rel}}$. Zero corresponds to the energy of the most stable conformation in ***RS*** family. Conformers with $\boldsymbol{Dh_{cyc}}$ exceeding 90 deg have unfavorable arrangement of nitrile and hydroxyl groups within hemiaminal motif and cannot undergo intramolecular cyclization. They are considered non-reactive in the intramolecular cyclization leading to the indirect hydration of aminonitrile.



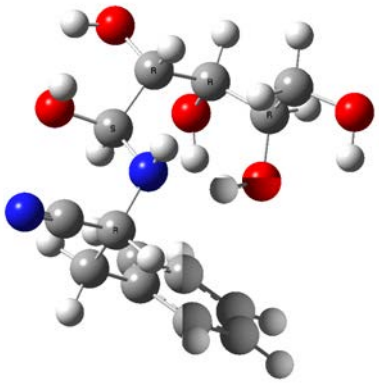
SS E_{rel} = 0.1 kcal/mol



RR E_{rel} = 0.7 kcal/mol



SR E_{rel} = 1.2 kcal/mol



RS E_{rel} = 0.0 kcal/mol

Figure S.42. The most stable conformations in each of four families of hemiaminal intermediate **III** and their relative potential energies.

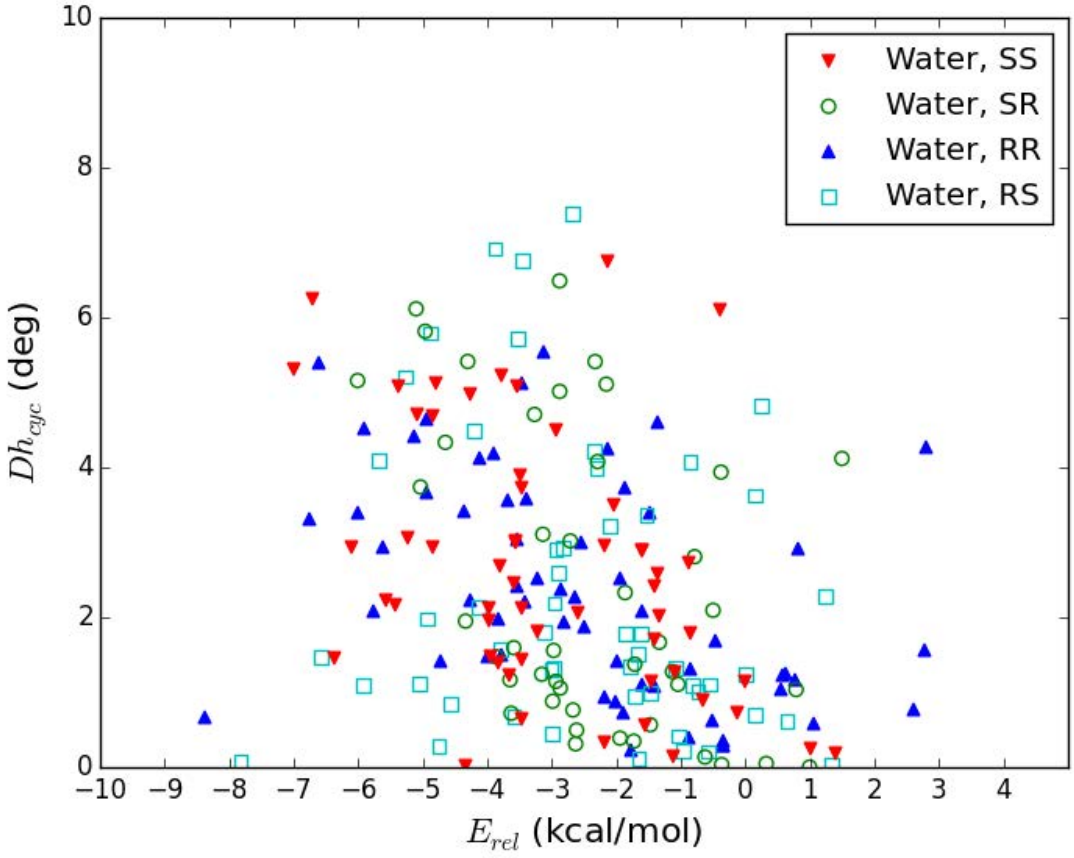
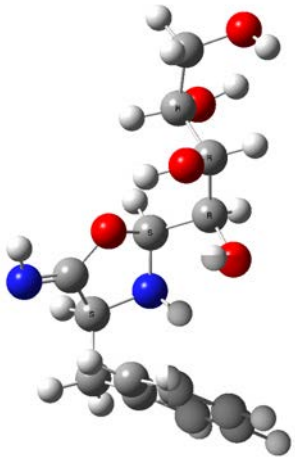
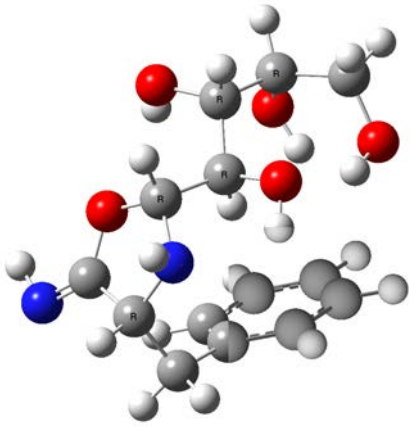


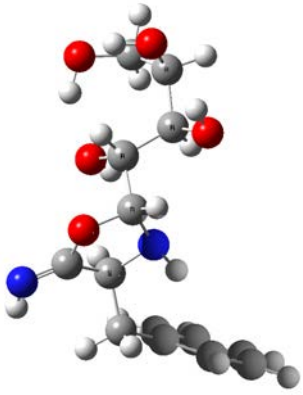
Figure S.43. Results of the conformational analysis for cyclic intermediate **IV** in water. Dihedral angle $\boldsymbol{Dh_{cyc}}$ is plotted against relative energies $\boldsymbol{E_{rel}}$. Zero corresponds to the energy of the most stable conformation of hemiaminal intermediate **III** in ***RS*** family (see Figure S.41). In cyclic intermediates $\boldsymbol{Dh_{cyc}}$ characterizes conformation of the formed ring.



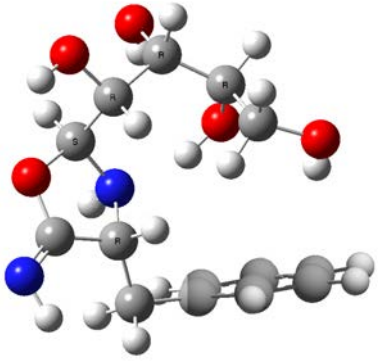
SS E_{rel} = -7.0 kcal/mol



RR E_{rel} = -8.4 kcal/mol



SR E_{rel} = -6.0 kcal/mol



RS E_{rel} = -7.8 kcal/mol

Figure S.44. The most stable conformations in each of four families of cyclic intermediate **IV** and their relative potential energies.

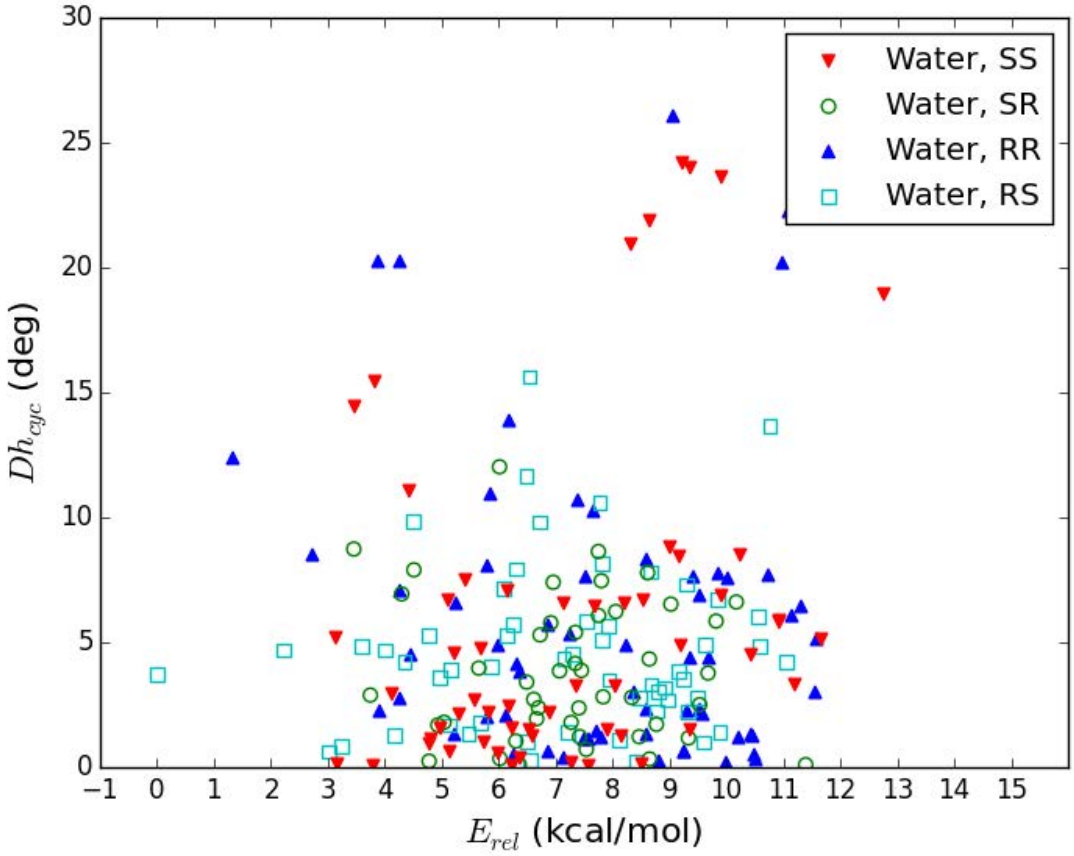
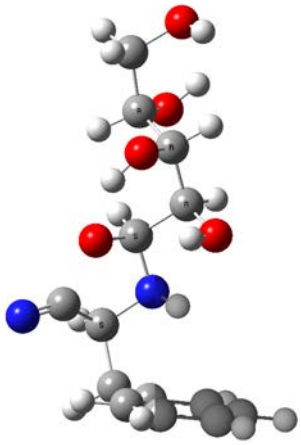
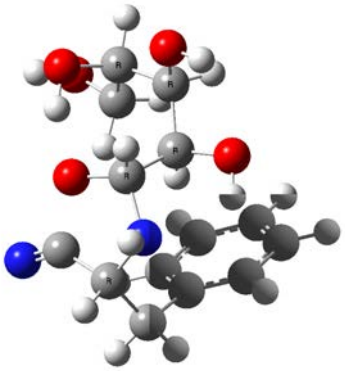


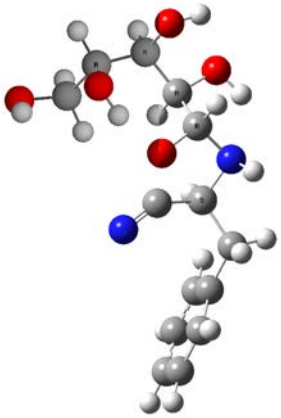
Figure S.45. Results of the transition state search for the intramolecular cyclization of deprotonated hemiaminal intermediate **ADD**. Dihedral angle $\boldsymbol{Dh_{cyc}}$ is plotted against relative energies $\boldsymbol{E_{rel}}$ of transition states. Zero corresponds to the energy of the lowest transition state in ***RS*** family. In transition states of the intramolecular cyclization $\boldsymbol{Dh_{cyc}}$ characterizes conformation of the forming ring.



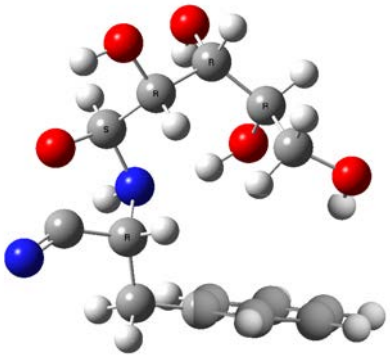
SS E_{rel} = 3.1 kcal/mol



RR E_{rel} = 1.3 kcal/mol



SR E_{rel} = 3.5 kcal/mol



RS E_{rel} = 0.0 kcal/mol

Figure S.46. The lowest transition states for intramolecular cyclization of deprotonated hemiaminal intermediate **ADD** and their relative potential energies. The relative energies are not directly comparable with relative energies in Figures S.42 and S.44 because of different stoichiometry of anionic transition states and neutral intermediates **III** and **IV**.

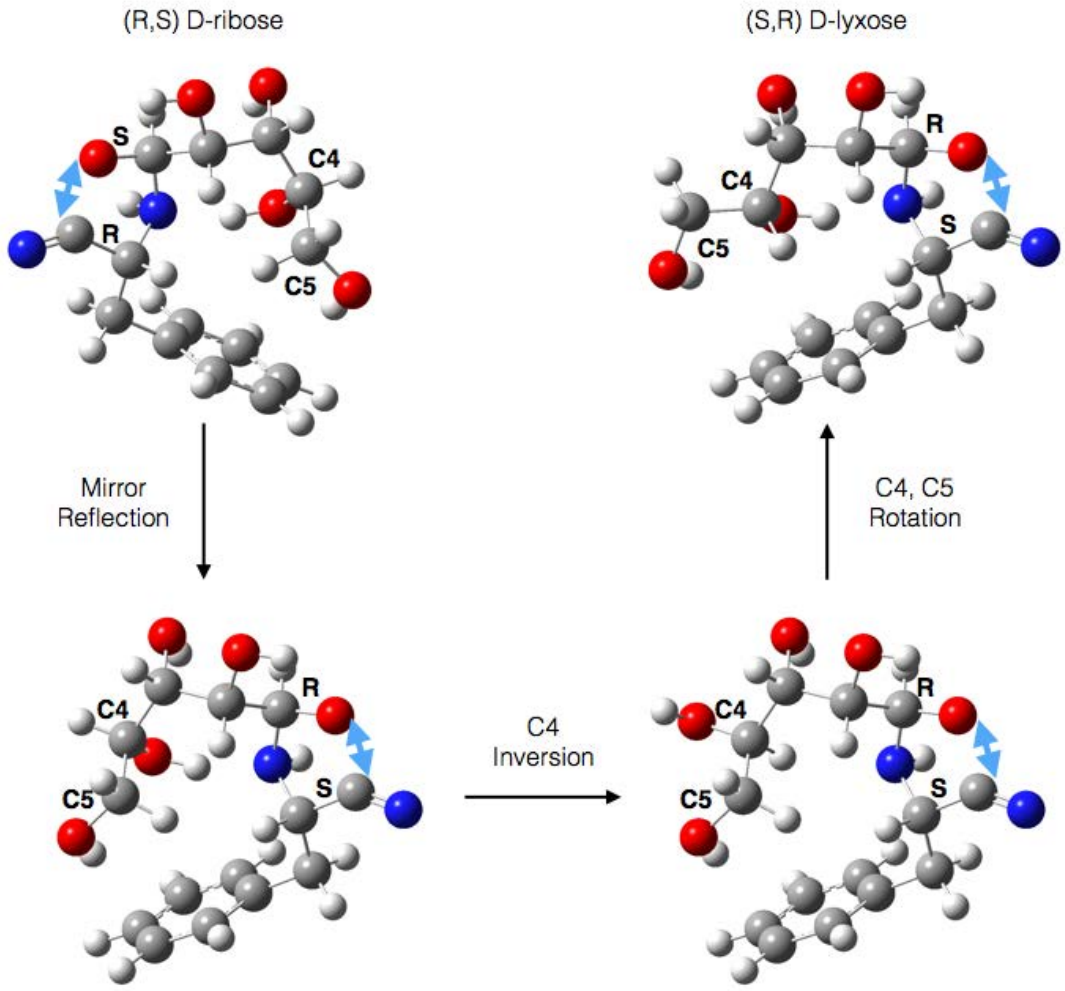


Figure S.47. Symmetry operations demonstrating the pseudo-enantiomeric character of the transition states for cyclization of (*R*,*S*) D-ribose and (*S*,*R*) D-lyxose with **Phe-I**, starting from the lowest transition state of the ribose **ADD^{R}** anionic hemiaminal. Light blue arrow shows O-C distance for attack of carbonyl oxygen on nitrile carbon. These operations connect ground state conformations of (*R*,*S*) D-ribose and (*S*,*R*) D-lyxose with **Phe-I** as well as transition states. Conformational adjustment of hydroxyls at C4 and/or C5 via rotations at the last stage ensures recovery of the pattern of intramolecular interactions at these centers comparable to D-ribose counterpart.

Family (D-ribose)	$\Delta G^{\ddagger}$ (kcal/mol)	Family (D-lyxose)	$\Delta G^{\ddagger}$ (kcal/mol)
SS	3.2	*RR*	4.5
SR	3.9	*RS*	4.8
RR	3.9	*SS*	3.9
RS	1.1	*SR*	3.2

Figure S.48. The lowest ***free energy barriers*** for intramolecular cyclization of **ADD** anionic hemiaminal for D-ribose and D-lyxose. Barriers for D-lyxose are obtained from D-ribose data using pseudoenantiomeric relationships described above: (*S*,*S*) D-ribose maps onto (*R*,*R*) D-lyxose, (*S*,*R*) D-ribose to (*S*,*R*) D-lyxose, (*R*,*R*) D-ribose to (*S*,*S*) D-lyxose, and (*S*,*R*) D-ribose to (*R*,*S*) D-lyxose. The barriers are computed as differences between free energies of isolated deprotonated transition state (Figure S.46) and water molecule and isolated protonated hemiaminal intermediate **III** (Figure S.42) and hydroxyl anion. The source of free energies is thermochemical module of Gaussian 09 software.

9. References

Synthesis

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