SUPPORTING INFORMATION

Substituted *N*-(Biphenyl-4'-yl)methyl (*R*)-2-Acetamido-3-methoxypropionamides: Potent Anticonvulsants That Affect Frequency (Use)-Dependence and Slow Inactivation of Sodium Channels

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SUPPORTING FIGURE LEGENDS

Supporting Figure S1. Effects of (*R*)-A compounds with a polar, aprotic substituent at the 4"-position on steady-state slow inactivation state of Na^+ currents in CAD cells. A. Voltage protocol for slow inactivation. Currents were evoked by 5 s prepulses between −120 mV and −20 mV and then fast-inactivated channels were allowed to recover for 150 ms at a hyperpolarized pulse to −120 mV. The fraction of channels available at 0 mV was analyzed. **B**-**D**. Summary of steady-state slow activation curves for CAD cells treated with DMSO (control) or various concentrations of the indicated compounds. **E**. Concentration versus $V_{1/2}$ response curve for effects on slow inactivation. To estimate the half-maximal value for induction of slow inactivation, dose-response curves were fit using the equation: Y = A1 + (A2-A1)/(1 + 10^((LOGx0-x)*p)), where Y is the measured response of the I_{Na}, A_2 and A_1 are the maximum and the minimum responses respectively of the I_{Na} obtained with a control sample, p is the slope parameter of the dose-response curve, x is the applied dose, and logX_0 is the center of the curve that is the concentration for half the I_{Na} response. The curves were well fitted with this dose-response function ($R^2 > 0.989$). Each point is the mean±SEM of 4–6 CAD cell recordings. The half-maximal values for slow inactivation for the indicated compounds are shown in the inset to the figure.

Supporting Figure S2. Effects of (*R*)-A compounds with a polar, aprotic substituent at the 4"-position on fast inactivation and steady-state activation states of Na^+ currents in CAD cells. A.

Voltage protocol for fast inactivation (*left*) and activation (*right*). **B.**-**D.** Representative Boltzmann fits for steady-state fast inactivation and activation for CAD cells treated with 0.1% DMSO (control) and 10 μM of the indicated compounds are shown. The $V_{1/2}$ and *k* of steady-state fast inactivation or activation were not different among any of the conditions tested ($p > 0.05$, one-way ANOVA). Data are from 3-6 cells per condition.

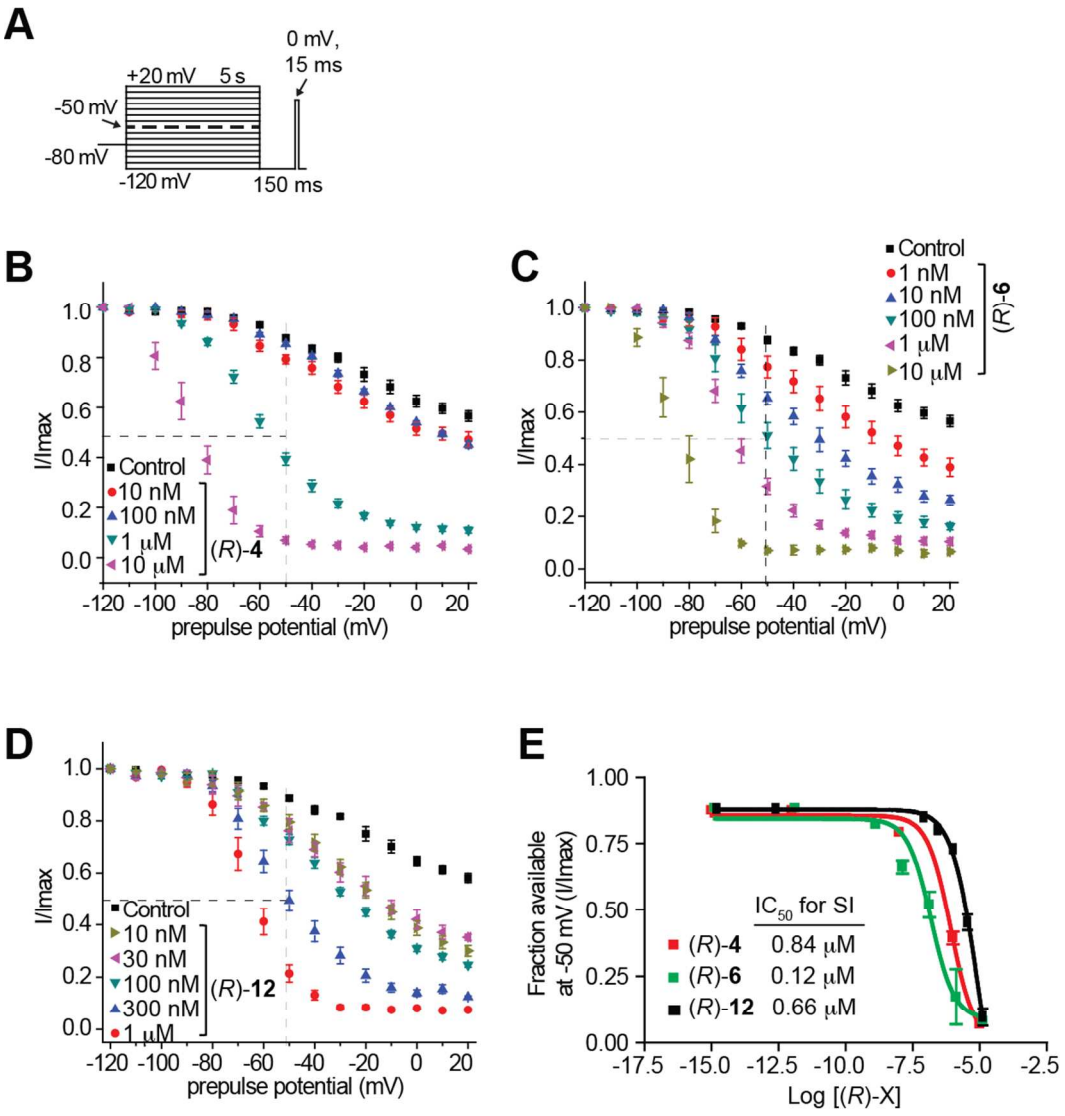
Supporting Figure S3. Effect on frequency (use)-dependent block by (*R*)-A compounds with a polar, aprotic substituent at the 4"-position on Na^+ currents in CAD cells. A. Summary of average frequency-dependent decrease in current amplitude over time (± SEM) produced by control (0.1% DMSO) or by the presence of 1 uM (*R*)-**4**, (*R*)-**6**, and (*R*)-**12**. **B.** Summary of the maximal decrement in current amplitude observed at the end of the 30-pulse train for control, or 1 μM (*R*)-**4**, (*R*)-**6**, and (*R*)-**12**. (*R*)-**4** and (*R*)-**6** caused a significant decrease in current amplitude compared with control (*, $p < 0.05$, one-way ANOVA with Dunnett's post-hoc test). Data are from 4–6 cells per condition.

Supporting Figure S4. Effects of (*R*)-A compounds with a polar, protic substituent at the 3"-position on steady-state slow inactivation state of Na^+ currents in embryonic cortical neurons. **A**. Voltage protocol for slow inactivation. Representative current traces from cortical neurons in the absence (control, 0.1% DMSO) or presence of 10 μM (*R*)-**15**. The black and colored traces represent the currents evoked at −100 and −50 mV, respectively (also highlighted in the voltage protocol as a dashed thick line). **B.**-**D.** Summary of steady-state slow activation curves for neurons treated with DMSO (control) or 10 μM (*R*)-**13**, (*R*)-**15**, or (*R*)-**16**. Significant drug-induced slow inactivation was evident at voltages more depolarizing that -80 mV in neurons

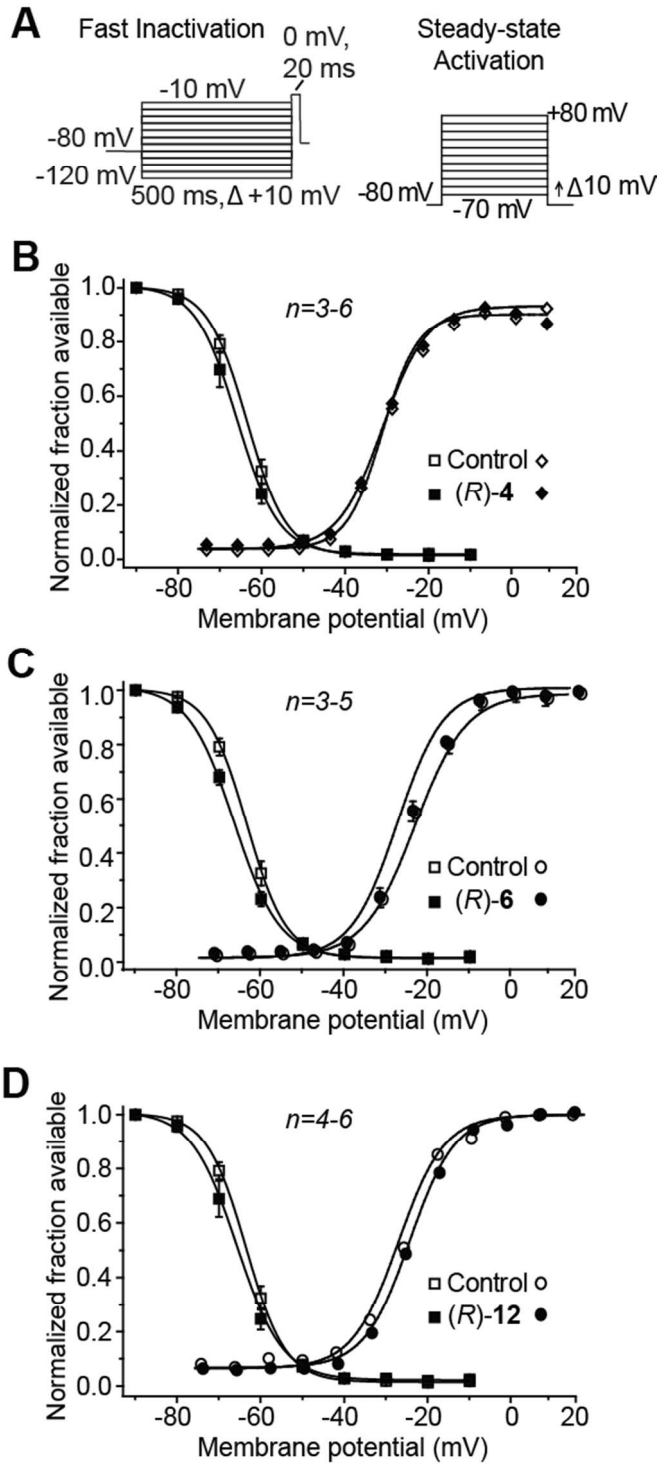
treated with (*R*)-**15**. **E**. Summary of the fraction of current available at −50 mV for neurons treated with DMSO (control) or 10 μM (*R*)-**13**, (*R*)-**15**, or (*R*)-**16**. Asterisk (*) indicates statistically significant difference in fraction of current available between control and (*R*)-**15** ($p < 0.05$, Student's t-test). Data are from 5 cells per condition.

Supporting Figure S5. Effect on frequency (use)-dependent block by (*R*)-A compounds with a polar, aprotic or a polar, protic substituent at the 3"-position on Na^+ currents in cortical neurons. Frequency (use)-dependence of block was examined by holding cells at the hyperpolarized potential of –70 mV and evoking currents at 10 Hz by 20-ms test pulses to –10 mV. **A.**-**B.** Summary of the maximal decrement in current amplitude observed at the end of the 30-pulse train for control, or the indicated compounds. None of the compounds tested caused a significant decrease in current amplitude compared with control ($p > 0.05$, one-way ANOVA with Dunnett's post-hoc test). Data are from 3–6 cells per condition.

Supporting Information, Figure S1



Supporting Information, Figure S2



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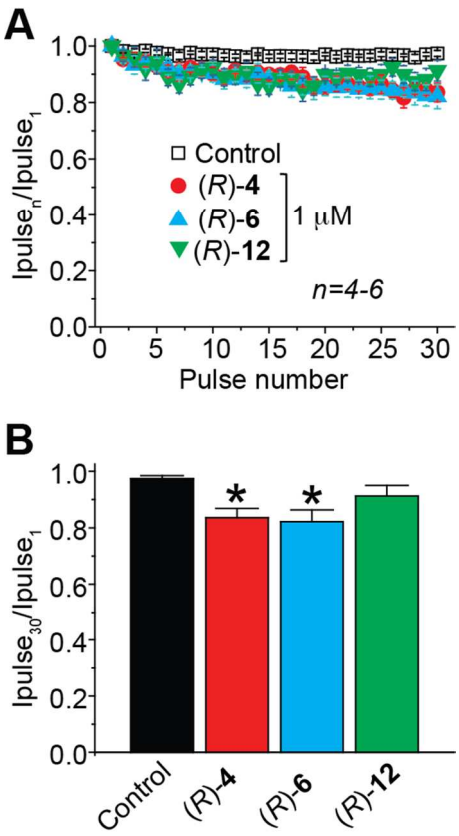

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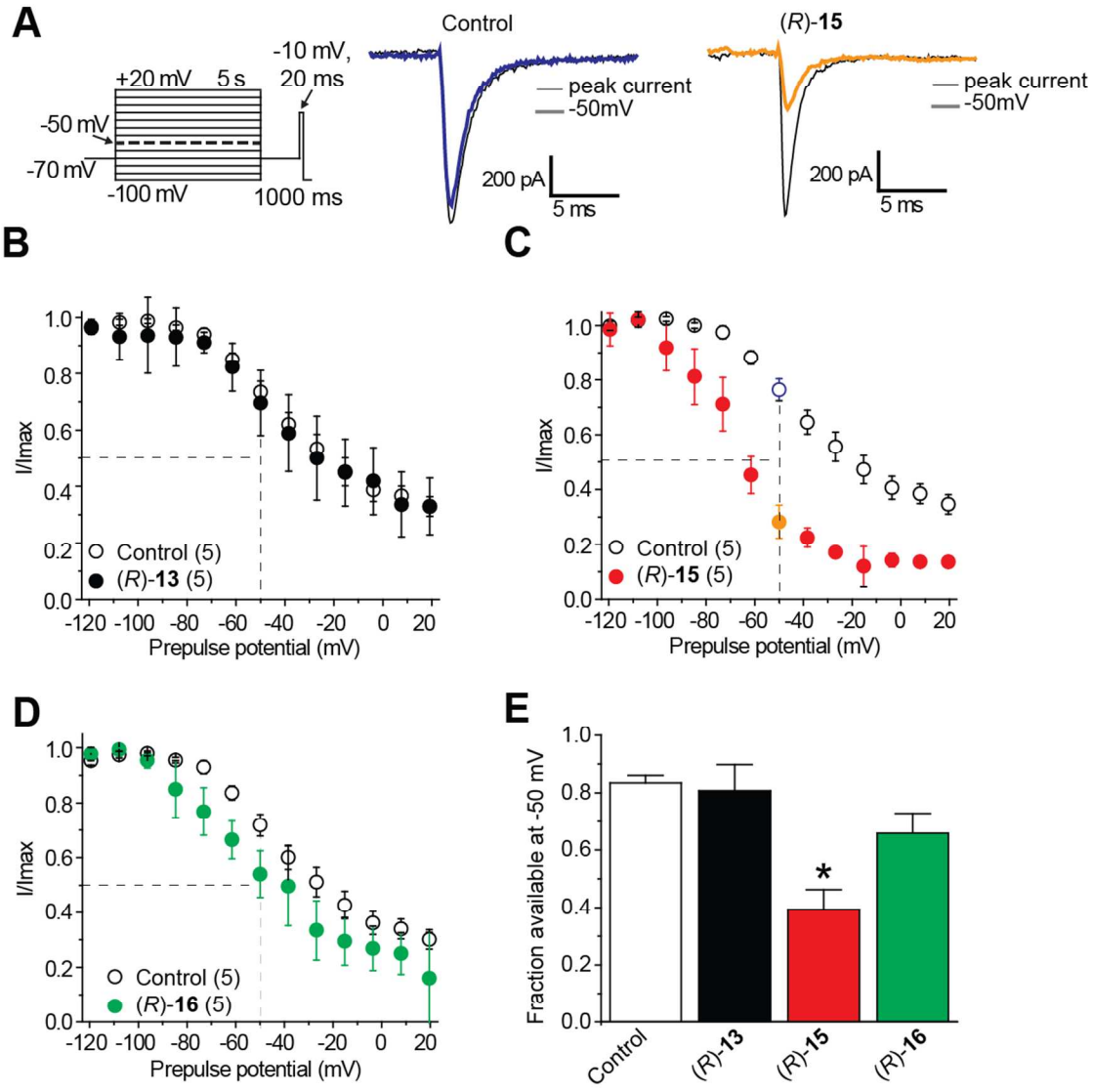

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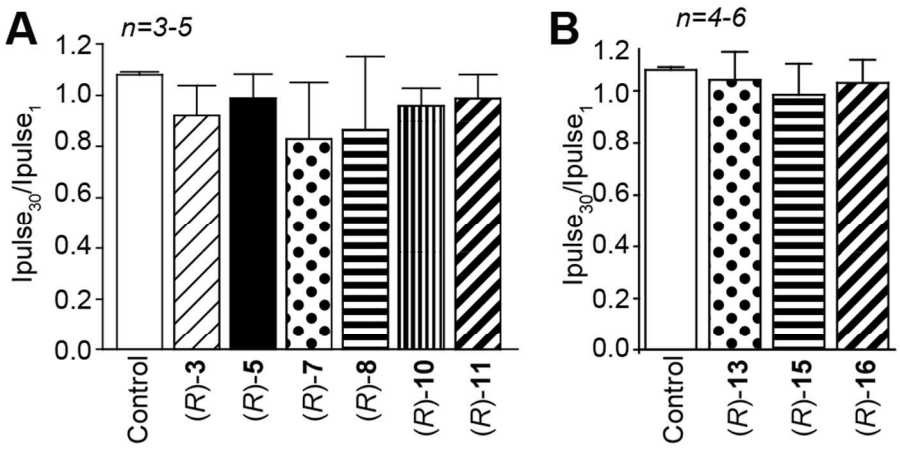


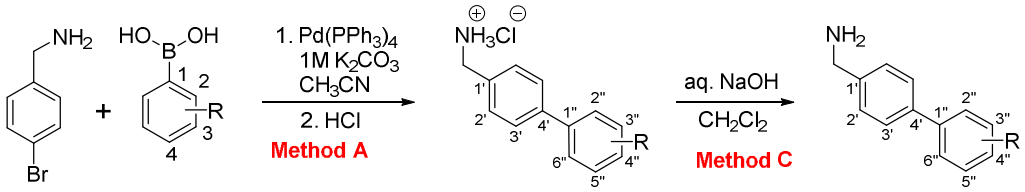
Table S1. Elemental Analyses for New Compounds

Cmpd	Molecular Formula	Calculated (%)	Found (%)
(*R*)-**4**	$C_{19}H_{21}FN_2O_3$	C, 66.26; H, 6.15; N, 8.13; F, 5.52	C, 65.97; H, 6.18; N, 8.11; F, 5.35
(*R*)-**5**	$C_{19}H_{21}ClN_2O_3$	C, 63.24; H, 5.87; N, 7.76; Cl, 9.83	C, 63.29; H, 6.01; N, 7.77; Cl, 9.71
(*R*)-**6**	$C_{19}H_{21}ClN_2O_3$	C, 63.24; H, 5.87; N, 7.76; Cl, 9.83	C, 63.00; H, 6.02; N, 7.69; Cl, 9.58
(*R*)-**7**	$C_{19}H_{21}BrN_2O_3$	C, 56.31; H, 5.22; N, 6.91; Br, 19.72	C, 56.58; H, 5.14; N, 6.90; Br, 19.45
(*R*)-**8**	$C_{19}H_{21}IN_2O_3$	C, 50.46; H, 4.68; N, 6.19; I, 28.06	C, 50.42; H, 4.64; N, 6.19; I, 27.76
(*R*)-**9**	$C_{20}H_{21}N_3O_3$	C, 68.36; H, 6.02; N, 11.96	C, 68.06; H, 6.04; N, 11.76
(*R*)-**10**	$C_{20}H_{21}F_3N_2O_3$	C, 60.91; H, 5.37; N, 7.10; F, 14.45	C, 61.02; H, 5.33; N, 7.17; F, 14.41
(*R*)-**11**	$C_{20}H_{21}F_3N_2O_4$	C, 58.53; H, 5.16; N, 6.83; F, 13.89	C, 58.56; H, 5.28; N, 6.80; F, 13.81
(*R*)-**12**	$C_{20}H_{21}F_3N_2O_4$	C, 58.53; H, 5.16; N, 6.83; F, 13.89	C, 58.50; H, 5.27; N, 6.82; F, 13.91
(*R*)-**14**	$C_{20}H_{24}N_2O_4$	C, 67.40; H, 6.79; N, 7.86	C, 67.32; H, 6.98; N, 7.74
(*R*)-**15**	$C_{20}H_{22}N_2O_5$	C, 64.45; H, 6.02; N, 7.52	C, 64.06; H, 6.09; N, 7.35
(*R*)-**46**	$C_{21}H_{25}FN_2O_4$	C, 64.93; H, 6.49; N, 7.21; F, 4.89	C, 64.71; H, 6.53; N, 7.22; F, 4.92
(*R*)-**47**	$C_{21}H_{25}ClN_2O_4$	C, 62.30; H, 6.22; N, 6.92; Cl, 8.76	C, 62.16; H, 6.32; N, 6.99; Cl, 8.61
(*R*)-**48**	$C_{21}H_{25}ClN_2O_4$	C, 62.30; H, 6.22; N, 6.92; Cl, 8.76	C, 62.03; H, 6.30; N, 6.84; Cl, 8.55
(*R*)-**53**	$C_{22}H_{25}F_3N_2O_5$	C, 58.15; H, 5.54; N, 6.16; F, 12.54	C, 57.99; H, 5.68; N, 6.11; F, 12.40
(*R*)-**54**	$C_{22}H_{25}F_3N_2O_5$	C, 58.15; H, 5.54; N, 6.16; F, 12.54	C, 58.09; H, 5.67; N, 6.25; F, 12.40
(*R*)-**56**	$C_{22}H_{27}FN_2O_4$	C, 65.66; H, 6.67; N, 6.96; F, 4.72	C, 65.58; H, 6.65; N, 6.84; F, 4.53
(*R*)-**57**	$C_{22}H_{27}ClN_2O_4$	C, 63.08; H, 6.50; N, 6.69; Cl, 8.46	C, 62.94; H, 6.67; N, 6.65; Cl, 8.24
(*R*)-**58**	$C_{22}H_{27}ClN_2O_4$	C, 63.08; H, 6.50; N, 6.69; Cl, 8.46	C, 62.88; H, 6.52; N, 6.68; Cl, 8.17
(*R*)-**63**	$C_{23}H_{27}F_3N_2O_5$	C, 58.97; H, 5.81; N, 5.98; F, 12.17	C, 59.05; H, 5.97; N, 5.92; F, 12.06
(*R*)-**64**	$C_{23}H_{27}F_3N_2O_5$	C, 58.97; H, 5.81; N, 5.98; F, 12.17	C, 58.92; H, 5.93; N, 5.95; F, 11.98
(*R*)-**68**	$C_{13}H_{17}NO_4$	C, 62.14; H, 6.82; N, 5.57	C, 62.27; H, 6.72; N, 5.77
(*R*)-**72**	$C_{23}H_{28}N_2O_5$	C, 66.97; H, 6.84; N, 6.79; O, 19.39	C, 67.59; H, 7.09; N, 6.57; O, 18.76

Table S2. High Resolution Mass Spectrometry (ESI^+)

Cmpd	Molecular Formula	Found	Calculated
(*R*)-**7**	$C_{19}H_{21}BrN_2O_3$	405.0814 $[M + H]^+$	405.0814
(*R*)-**8**	$C_{19}H_{21}IN_2O_3$	453.0675 $[M + H]^+$	453.0673
(*R*)-**9**	$C_{20}H_{21}N_3O_3$	352.1660 $[M + H]^+$	352.1661
(*R*)-**10**	$C_{20}H_{21}F_3N_2O_3$	395.1582 $[M + H]^+$	395.1583
(*R*)-**13**	$C_{21}H_{25}N_3O_3$	384.1924 $[M + H]^+$	384.1923
(*R*)-**15**	$C_{20}H_{22}N_2O_5$	371.1607 $[M + H]^+$	371.1607
(*R*)-**16**	$C_{19}H_{24}N_3ClO_3$	342.1817 $[M - Cl]^+$	342.1817
29·HCl	$C_{13}H_{13}ClFN$	202.1022 $[M - Cl]^+$	202.1032
34·HCl	$C_{14}H_{13}ClF_3NO$	268.0951 $[M - Cl]^+$	268.0949
35·HCl	$C_{14}H_{13}ClF_3NO$	268.0949 $[M - Cl]^+$	268.0949
36	$C_{15}H_{16}N_2O$	279.0937 $[M + K]^+$	279.0900
37·HCl	$C_{18}H_{24}ClNO$	292.1677 $[M + Na]^+$	292.1677
39·HCl	$C_{18}H_{23}ClN_2O_2$	321.1630 $[M - HCl + Na]^+$	321.1620
44·HCl	$C_{13}H_{13}ClN$	310.0093 $[M - Cl]^+$	310.0111
(*R*)-**49**	$C_{21}H_{25}BrN_2O_4$	449.1076 $[M + H]^+$	449.1074
(*R*)-**50**	$C_{21}H_{25}IN_2O_4$	497.0937 $[M + H]^+$	497.0935
(*R*)-**51**	$C_{23}H_{27}N_3O_4$	396.1924 $[M + H]^+$	396.1923
(*R*)-**52**	$C_{22}H_{25}F_3N_2O_4$	439.1874 $[M + H]^+$	439.1844
(*R*)-**55**	$C_{23}H_{29}N_3O_5$	450.2007 $[M + Na]^+$	450.2005
(*R*)-**59**	$C_{22}H_{27}BrN_2O_4$	463.1232 $[M + H]^+$	463.1234
(*R*)-**60**	$C_{22}H_{27}IN_2O_4$	511.1094 $[M + H]^+$	511.1097
(*R*)-**61**	$C_{23}H_{27}N_3O_4$	410.2084 $[M + H]^+$	410.2080
(*R*)-**62**	$C_{23}H_{27}F_3N_2O_4$	453.2033 $[M + H]^+$	453.2001
(*R*)-**65**	$C_{24}H_{31}N_3O_5$	442.2345 $[M + H]^+$	442.2342
(*R*)-**67**	$C_{12}H_{15}NO_4$	238.1078 $[M + H]^+$	238.1079
(*R*)-**71**	$C_{23}H_{30}N_2O_4$	399.2285 $[M + H]^+$	399.2284
(*R*)-**72**	$C_{23}H_{28}N_2O_5$	413.2079 $[M + H]^+$	413.2076
(*R*)-**73**	$C_{24}H_{32}N_2O_4$	413.2442 $[M + H]^+$	413.2440
(*R*)-**74**	$C_{24}H_{30}N_2O_5$	427.2237 $[M + H]^+$	427.2233
(*R*)-**75**	$C_{23}H_{31}N_3O_3$	574.1320 $[M + Cs]^+$	574.1318

Scheme 1. Preparation of (Biphenyl-4-yl)methylamines **29 - 39**



17

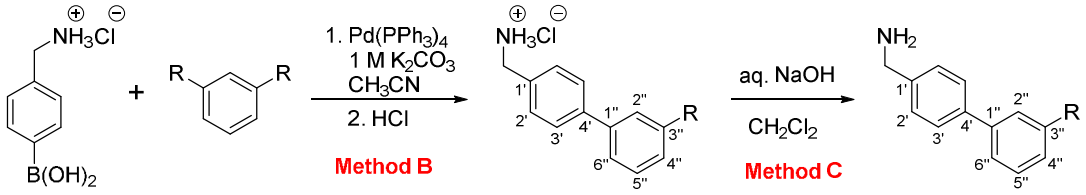
18; R = 4-F
19; R = 3-Cl
20; R = 4-Cl
21; R = 3-CN
22; R = 3-CF_3
23; R = 3-OCF_3
24; R = 4-OCF_3
25; R = 3-$N(H)C(O)CH_3$
26; R = 3-$CH_2OC(CH_3)_3$
27; R = 3-$CO_2C(CH_3)_3$
28; R = 3-$N(H)C(O)OC(CH_3)_3$

29·**HCl**; R = 4"-F
30·**HCl**; R = 3"-Cl
31·**HCl**; R = 4"-Cl

33·**HCl**; R = 3"-CF_3
34·**HCl**; R = 3"-OCF_3
35·**HCl**; R = 4"-OCF_3
36·**HCl**; R = 3"-$N(H)C(O)CH_3$
37·**HCl**; R = 3"-$CH_2OC(CH_3)_3$
38·**HCl**; R = 3"-$CO_2C(CH_3)_3$
39·**HCl**; R = 3"-$N(H)C(O)OC(CH_3)_3$

29; R = 4"-F
30; R = 3"-Cl
31; R = 4"-Cl
32; R = 3"-CN
33; R = 3"-CF_3
34; R = 3"-OCF_3
35; R = 4"-OCF_3
36; R = 3"-$N(H)C(O)CH_3$
37; R = 3"-$CH_2OC(CH_3)_3$
38; R = 3"-$CO_2C(CH_3)_3$
39; R = 3"-$N(H)C(O)OC(CH_3)_3$

Scheme 2. Preparation of (Biphenyl-4-yl)methylamines **43** and **44**



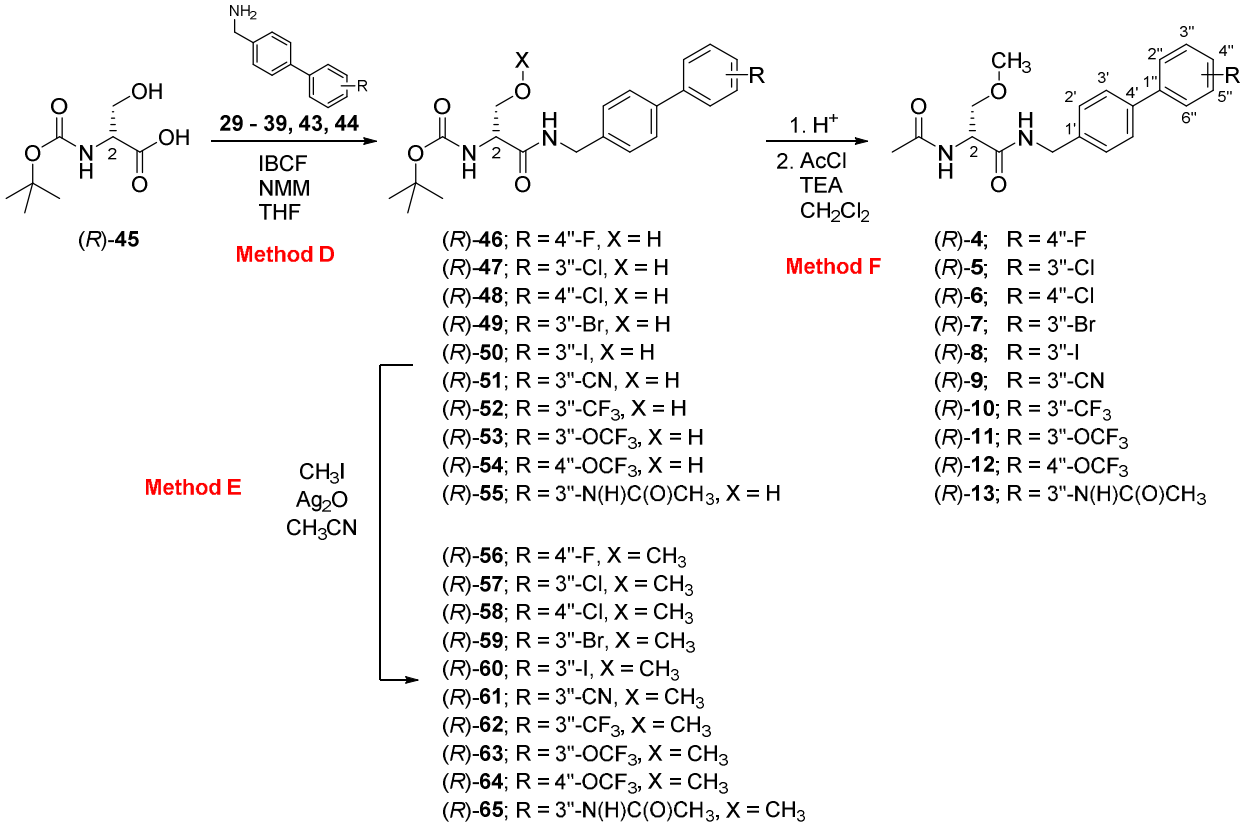
40

41; R = Br
42; R = I

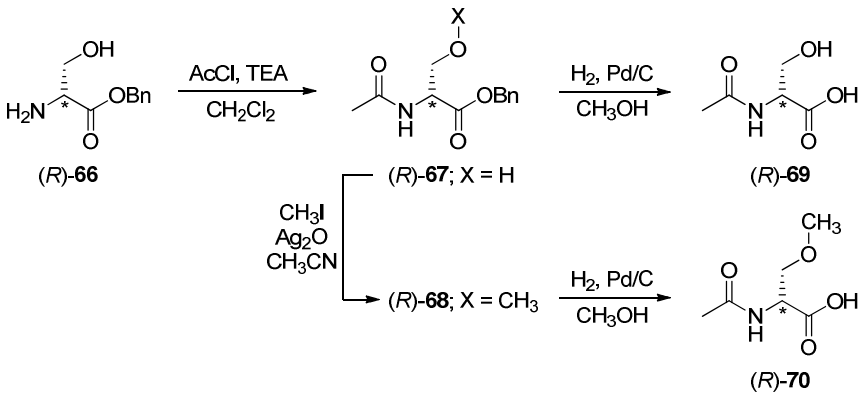
43·**HCl**; R = Br
44·**HCl**; R = I

43; R = Br
44; R = I

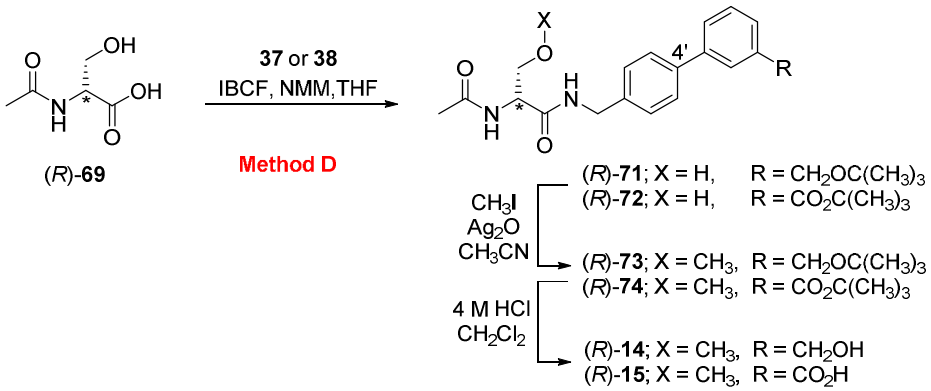
Scheme 3. Synthesis of Compounds (*R*)-**4** - (*R*)-**13**



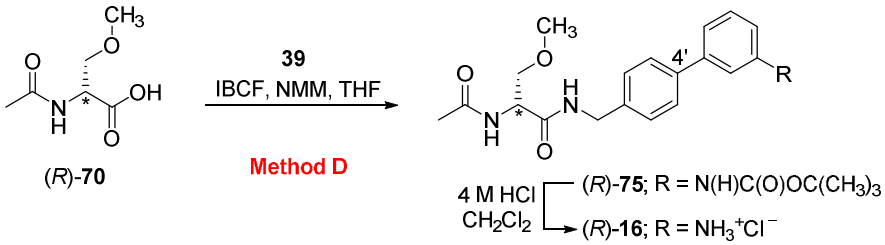
Scheme 4. Synthesis of (*R*)-**69** and (*R*)-**70**



Scheme 5. Synthesis of Compounds (*R*)-**14** and (*R*)-**15**



Scheme 6. Synthesis of Compound (*R*)-**16**



EXPERIMENTAL SECTION

General Methods. Melting points were determined in open capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra (IR) were run on an ATI Mattson Genesis FT-IR spectrometer. Absorption values are expressed in wavenumbers (cm^{-1}). Optical rotations were obtained on a Jasco P-1030 polarimeter at the sodium D line (589 nm) using a 1 dm path length cell. NMR spectra were obtained at 400 MHz (^{1}H) and 100 MHz (^{13}C) using TMS as an internal standard. Chemical shifts (δ) are reported in parts per million (ppm) from tetramethylsilane. Low-resolution mass spectra were obtained with a BioToF-II-Bruker Daltonics spectrometer by Dr. S. Habibi at the University of North Carolina Department of Chemistry. The high-resolution mass spectrum was performed on a Bruker Apex-Q 12 Telsa FTICR spectrometer by Dr. S. Habibi. Elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA). Reactions were monitored using thin-layer chromatography (TLC) plates (Aldrich, Cat # Z12272-6) and analyzed with 254 nm light and visualized with $KMnO_4$, Hanessian and ninhydrin stains. The reactions were purified by flash column chromatography using silica gel (Dynamic Adsorbents Inc., Cat # 02826-25). All chemicals and solvents were reagent grade and used as obtained from commercial sources without further purification. Yields reported are for purified products and were not optimized. Compounds were checked by TLC, ^{1}H and ^{13}C NMR, MS, and elemental analyses. The analytical results are within ±0.40% of the theoretical value. The TLC, NMR and the analytical data confirmed the purity of the products was ≥95%.

General Procedure for the Preparation of (Biphenyl-4-yl)methylamine and (Biphenyl-4-yl)methylamine Hydrochloride Derivatives 29 – 39 (Method A). To a dry CH_3CN solution (60 mL) of 4-bromobenzylamine (5.00 g, 26.9 mmol) was added the desired arylboronic acid (1-1.1

equiv). Then, a solution of 1 M K_2CO_3 (2.0 – 2.50 equiv) was added and the mixture was stirred and heated at reflux under Ar. After 15 min, tetrakis(triphenylphosphine)palladium(0)($Pd(PPh_3)_4$) (0.04 equiv) was added and stirred at reflux (12–16 h). The mixture was filtered and evaporated in vacuo. The resulting residue was dissolved in EtOAc (200 mL) and washed with H_2O (1× 200 mL) and brine (1× 200 mL). In the case of **32**, the organic layer was dried (Na_2SO_4) and the solvent removed in vacuo to provide the crude free amine. In the case of **29** – **31** and **33** – **39**, either 4 M HCl in dioxane (2 equiv) or aqueous concentrated HCl was added dropwise to the organic layer and stirred at room temperature (1 h), and the precipitate filtered and washed with hexanes to obtain the crude amine hydrochloride salt as a yellow solid.

General Procedure for the Preparation of (Biphenyl-4-yl)methylamine Hydrochloride Derivatives 43 and **44 (Method B).** Employing a procedure similar to Method A, and using *p*-aminomethylboronic acid (1.0 equiv), the 1,3-dihalobenzene (1.1 equiv), aqueous 1 M K_2CO_3 and $Pd(PPh_3)_4$ (0.05 equiv) in EtOH. For **43** and **44**, aqueous concentrated HCl was added to the organic layer and stirred at room temperature (1 h), and then the solvent was decanted from the pasty solid, washed, and then dried in vacuum to give the crude HCl salt as a yellow-orange solid.

General Procedure for the Preparation of Free (Biphenyl-4-yl)methylamine Derivatives 29 – 39, 43, and 44 (Method C). To a NaOH solution (pH 10, 200 mL) was added the 4-biphenylmethylamine hydrochloride derivative (2–5 g) and then the aqueous layer extracted with CH_2Cl_2 (3× 200 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was used without further purification.

General Procedure for the Mixed Anhydride Coupling Reaction (Method D). To a cooled THF or THF·DMSO (10:1) solution (–78 °C, dry ice acetone bath) of either (*R*)-*t*-Boc-D-serine ((*R*)-**45**) or (*R*)-2-acetamido-3-hydroxypropionic acid ((*R*)-**69**) or (*R*)-2-acetamido-3-methoxypropionic acid ((*R*)-**70**) ([C] ~ 0.1 – 0.8 M) were successively added *N*-methylmorpholine (NMM) (1.0–2.6 equiv), stirred for 2 min, isobutylchloroformate (IBCF) (0.8–1.3 equiv), stirred for 5 min, and then the desired benzylamine (0.7 –1.2 equiv). Upon addition the reaction mixture was allowed to warm to room temperature and further stirred (2–3 h). The salts were filtered through Celite® and rinsed with THF and the filtrate was concentrated in vacuo. The residue obtained was purified by column chromatography on SiO_2.

General Procedure for the Preparation of 2-*N*-(*tert.*-Butoxycarbonyl)amino-3-methoxypropionamide Derivatives (Method E). To a CH_3CN or CH_3CN ·DMF (10:1 – 20:1) solution of the (*R*)-*N*-(biphenyl-4-yl)methyl 2-*N*-(*tert.*-butoxycarbonyl)amino-3-hydroxypropionamide derivative ([C] ~0.05–0.5 M) was successively added Ag_2O (5 equiv) and MeI (10 equiv) at room temperature. The reaction mixture was maintained at room temperature (2–3 d) and filtered through Celite, and the solvent was evaporated in vacuo. The residue was purified by column chromatography on SiO_2.

General Procedure for the Deprotection and Acetylation of (*R*)-*N*-(Biphenyl-4-yl)methyl 2-*N*-(*tert.*-Butoxycarbonyl)amino-3-methoxypropionamide Derivatives (Method F). A CH_2Cl_2 solution (0.1–0.3 M) of the (*R*)-*N*-(biphenyl-4-yl)methyl 2-*N*-(*tert.*-butoxycarbonyl)amino-3-methoxypropionamide derivative was treated with 4 M HCl in dioxane (3–4 equiv) at room temperature (2–6 h). The reaction mixture was evaporated in vacuo. The resulting residue was

dissolved in CH_2Cl_2 (0.1–0.3 M) and then triethylamine (2–3 equiv) and acetyl chloride (1.0–1.2 equiv) were carefully added at 0 °C and the resulting solution was stirred at room temperature (2–4 h). The resulting solution was washed with an aqueous 10% citric acid solution followed by a saturated aqueous $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 and/or recrystallized with EtOAc/hexanes.

Preparation of (4”-Fluorobiphenyl-4’-yl)methylamine Hydrochloride (29·HCl). Using Method A, 4-bromobenzylamine (**17**) (5.00 g, 26.9 mmol), 4-fluorophenylboronic acid (**18**) (3.77 g, 26.9 mmol), aqueous 1 M K_2CO_3 (60 mL), and $Pd(PPh_3)_4$ (1.24 g, 1.1 mmol) gave crude **29·HCl** as a yellow solid (4.99 g, 78%): R_f = 0.00 (hexanes/EtOAc 1/2); mp 315-317 °C; ^{1}H NMR (DMSO-d_6) δ 4.06 (s, C**H**$_2$), 7.28–7.34 (m, 2 Ar**H**), 7.61–7.75 (m, 6 Ar**H**), 8.70 (s, N**H**$_3$Cl); ^{13}C NMR (DMSO-d_6) δ 41.7 (**C**H$_2$), 115.8 (d, J = 21.3 Hz, **C**$_{3''}$, **C**$_{5''}$), 126.7 (Ar**C**), 128.7 (d, J = 8.0 Hz, **C**$_{2''}$, **C**$_{6''}$), 129.6 (Ar**C**), 133.3 (Ar**C**), 136.0 (d, J = 3.7 Hz, **C**$_{1''}$), 139.1 (Ar**C**), 162.0 (d, J = 243.2 Hz, **C**$_{4''}$); HRMS (ESI$^+$) 202.1022 $[M - Cl]^+$ (calcd for $C_{13}H_{12}FNH^+$ 202.1032).

Preparation of (3”-Chlorobiphenyl-4’-yl)methylamine Hydrochloride (30·HCl). Using Method A, **17** (5.00 g, 26.9 mmol), 3-chlorophenylboronic acid (**19**) (4.21 g, 26.9 mmol), aqueous 1 M K_2CO_3 (60 mL), and $Pd(PPh_3)_4$ (1.24 g, 1.1 mmol) gave crude **30·HCl** as a yellow solid (4.37 g, 64%): R_f = 0.00 (hexanes/EtOAc 1/2); mp 285-287 °C; ^{1}H NMR (DMSO-d_6) δ 4.07 (s, C**H**$_2$), 7.43–7.76 (m, 8 Ar**H**), 8.75 (s, N**H**$_3$Cl); ^{13}C NMR (DMSO-d_6) δ 41.7 (**C**H$_2$), 125.4, 126.3, 126.9, 127.4, 129.7, 130.8, 133.8, 134.0, 138.5, 141.6 (Ar**C**); LRMS (ESI$^+$) 218.0 $[M - Cl]^+$ (calcd for $C_{13}H_{12}ClNH^+$ 218.0); HRMS (ESI$^+$) signal not detected.

Preparation of (4”-Chlorobiphenyl-4’-yl)methylamine Hydrochloride (31·HCl). Using Method A, **17** (5.00 g, 26.9 mmol), 4-chlorophenylboronic acid (**20**) (4.21 g, 26.9 mmol), aqueous 1 M K_2CO_3 (60 mL), and $Pd(PPh_3)_4$ (1.24 g, 1.1 mmol) gave crude **31·HCl** as a yellow solid (4.64 g, 68%): R_f = 0.00 (hexanes/EtOAc 1/2); mp 290-292 °C; ^{1}H NMR (DMSO-d_6) δ4.07 (s, C**H**$_2$), 7.52–7.73 (m, 8 Ar**H**), 8.77 (s, N**H**$_3$Cl); ^{13}C NMR (DMSO-d_6) δ41.7 (**C**H$_2$), 126.7, 128.4, 128.9, 129.7, 132.5, 133.7, 138.3, 138.7 (Ar**C**); LRMS (ESI$^+$) 218.0 $[M - Cl]^+$ (calcd for $C_{13}H_{12}ClNH^+$ 218.0); HRMS (ESI$^+$) signal not detected.

Preparation of (3”-Cyanobiphenyl-4’-yl)methylamine (32). Using Method A, **17** (5.76 g, 30.9 mmol), 3-cyanophenylboronic acid (**21**) (5.00 g, 34.0 mmol), aqueous 1 M K_2CO_3 (77.3 mL), and $Pd(PPh_3)_4$ (1.79 g, 1.5 mmol) gave the desired free amine **32** (7.06 g, 100%) as a colorless oil: R_f = 0.00 (hexanes/EtOAc 1/1); ^{1}H NMR ($CDCl_3$) δ3.92 (NC**H**$_2$), 7.32-7.83 (m, 8 Ar**H**); ^{13}C NMR ($CDCl_3$) δ46.1 (**C**H$_2$NH$_3$), 113.0 (Ar**C**), 119.0 (**C**N), 127.3, 128.0, 129.7, 130.6, 130.7, 131.5, 132.1, 137.5, 142.3 (9 Ar**C**); LRMS (ESI$^+$) 209.1 $[M + H]^+$ (calcd for $C_{14}H_{13}N_2^+$ 209.1); HRMS (ESI$^+$) signal not detected.

Preparation of (3’-(Trifluoromethyl)-4-biphenylmethammonium Chloride (33·HCl). Using Method A, **17** (2.45 g, 13.2 mmol), 3-trifluoromethylphenylboronic acid (**22**) (3.00 g, 15.8 mmol), aqueous 1 M K_2CO_3 (80 mL), and $Pd(PPh_3)_4$ (0.61 g, 0.50 mmol) gave **33·HCl** as a pale brownish solid (3.29 g, 87%): R_f = 0.00 (1:1 EtOAc/hexanes); mp 239–240 ^{o}C; ^{1}H NMR (DMSO-d_6) δ4.08 (q, J = 5.5 Hz, Ar-C**H**$_2$), 7.61–7.66 (d, J = 8.4 Hz, 2 Ar**H**), 7.69–7.77 (m, 2 Ar**H**), 7.82 (d, J = 8.4 Hz, 2 Ar**H**), 7.97–8.04 (m, 2 Ar**H**), 8.56 (br s, N**H**$_3$); ^{13}C NMR (DMSO-d_6) δ41.8 (**C**H$_2$), 123.0 (q,

J = 4.0 Hz), 124.2 (q, *J* = 272.0 Hz, **C**F_3), 124.3 (q, *J* = 4.0 Hz), 127.1, 129.7 (Ar**C**), 129.8 (q, *J* = 32.0 Hz), 130.1, 130.8, 134.1, 138.5, 140.5 (Ar**C**); HRMS (ESI^+): no signal detected.

Preparation of (3"-Trifluoromethoxybiphenyl-4'-yl)methylamine Hydrochloride (34·HCl). Using Method A, **17** (5.00 g, 26.9 mmol), 3-trifluoromethoxyphenylboronic acid (**23**) (5.54 g, 26.9 mmol), aqueous 1 M K_2CO_3 (60 mL), and $Pd(PPh_3)_4$ (1.24 g, 1.1 mmol) gave crude **34·HCl** as a yellow solid (6.11 g, 75%): R_f = 0.00 (hexanes/EtOAc 1/2); mp 285-287 °C; ^{1}H NMR (DMSO-d_6) δ4.09 (s, C**H**$_2$), 7.38–7.40 (m, 1 Ar**H**), 7.60–7.79 (m, 7 Ar**H**), 8.75 (s, N**H**$_3$Cl); ^{13}C NMR (DMSO-d_6) δ41.7 (**C**H_2), 119.2, 119.9 (Ar**C**), 120.1 (q, *J* = 254.9 Hz, O**C**F_3), 125.8, 126.9, 129.7, 130.9, 134.2, 138.3, 141.9, 149.0 (Ar**C**); HRMS (ESI^+) 268.0951 $[M - Cl]^+$ (calcd for $C_{14}H_{12}F_3NOH^+$ 268.0949).

Preparation of (4"-Trifluoromethoxybiphenyl-4'-yl)methylamine Hydrochloride (35·HCl). Using Method A, **17** (5.00 g, 26.9 mmol), 4-trifluoromethoxyphenylboronic acid (**24**) (5.54 g, 26.9 mmol), aqueous 1 M K_2CO_3 (60 mL), and $Pd(PPh_3)_4$ (1.24 g, 1.1 mmol) gave crude **35·HCl** as a yellow solid (5.94 g, 73%): R_f = 0.00 (hexanes/EtOAc 1/2); mp 305-308 °C; ^{1}H NMR (DMSO-d_6) δ4.06 (s, C**H**$_2$), 7.45 (d, *J* = 8.0 Hz, 2 Ar**H**), 7.63 (d, *J* = 8.0 Hz, 2 Ar**H**), 7.72 (d, *J* = 8.6 Hz, 2 Ar**H**), 7.81 (d, *J* = 8.6 Hz, 2 Ar**H**); ^{13}C NMR (DMSO-d_6) δ41.7 (**C**H_2), 120.1 (q, *J* = 254.9 Hz, O**C**F_3), 121.5, 126.9, 128.6, 129.7, 133.8, 138.6, 138.8, 148.0 (Ar**C**); HRMS (ESI^+) 268.0949 $[M - Cl]^+$ (calcd for $C_{14}H_{12}F_3NOH^+$ 268.0949).

Preparation of (3"-Acetamidobiphenyl-4'-yl)methylamine (36). Using Method A, **17** (4.72 g, 25.4 mmol), 3-acetylaminophenylboronic acid (**25**) (5.00 g, 27.9 mmol), aqueous 1 M K_2CO_3 (71 mL), and $Pd(PPh_3)_4$ (1.47 g, 1.3 mmol) gave the desired free amine **36** (6.00 g, 86%) as a colorless oil: R_f = 0.00 (hexanes/EtOAc 1/1); ^{1}H NMR ($CDCl_3$, CD_3OD)) δ2.11 (s, C(O)C**H**$_3$), 3.80

(NC**H**$_2$), 7.22-7.80 (m, 8 Ar**H**, N**H**C(O)); ^{13}C NMR ($CDCl_3$) δ24.3 (C(O)**C**H_3), 45.8 (**C**H_2NH_2), 118.7, 119.0, 122.8, 127.4, 127.9, 129.4, 132.2, 134.3, 138.9, 141.5 (10 Ar**C**), 169.5 (NH**C**(O)); LRMS (ESI$^+$) 279.1 $[M + K]^+$ (calcd for $C_{15}H_{16}N_2OK^+$ 279.1); HRMS (ESI$^+$) 279.0937 $[M + K]^+$ (calcd for $C_{15}H_{16}N_2OK^+$ 279.0900).

Preparation of (3'-*tert*-Butoxymethylbiphenyl-4-yl)methylamine Hydrochloride (37·HCl). Using Method A, **17** (1.01 g, 5.40 mmol), 3-*tert*-butoxymethylphenylboronic acid (**26**) (1.00 g, 4.50 mmol), aqueous 1 M K_2CO_3 (13.5 mL), and $Pd(PPh_3)_4$ (0.26 g, 0.23 mmol) gave **37·HCl** as awhite solid (0.97 g, 80%): R_f = 0.00 (EtOAc/hexanes 1/1); mp 190-191 °C; ^{1}H NMR ($CDCl_3$, MeOD) δ 1.33 (s, *t*-Bu), 4.13 (s, C**H**$_2$N), 4.52 (s, C**H**$_2$O), 7.35-7.50 (m, 3 Ar**H**), 7.51-7.57 (m, 3 Ar**H**), 7.65 (d, *J* = 8.0 Hz, 2 Ar**H**); ^{13}C NMR ($CDCl_3$, MeOD) δ27.4 (C(**C**H_3)), 43.0 (NH**C**H_2), 64.1 (**C**H_2O), 73.9 (**C**(CH_3)), 125.9, 126.1, 126.9, 127.6, 128.8, 129.3, 131.4, 140.0, 140.1, 141.9 (10 Ar**C**); LRMS (ESI$^+$) 270.2 $[M + H]^+$ (calcd for $C_{18}H_{24}NO^+$ 270.2); HRMS (ESI$^+$) 292.1677 $[M + Na]^+$ (calcd for $C_{18}H_{23}NONa^+$ 292.1677).

Preparation of (3'-*tert*-Butoxycarbonylbiphenyl-4-yl)methylamine Hydrochloride (38·HCl). Using Method A, **17** (0.76 g, 4.09 mmol), 3-*tert*-butoxycarbonylphenylboronic acid (**27**) (1.00 g, 4.50 mmol), aqueous 1 M K_2CO_3 (10.0 mL), and $Pd(PPh_3)_4$ (0.24 g, 0.22 mmol) gave **38·HCl** as a white solid (1.31 g, 70%): R_f = 0.00 (hexanes/EtOAc 1/1); mp 194-197 °C; ^{1}H NMR (CD_3OD) δ 1.61 (s, *t*-Bu), 3.91 (d, *J* = 6.0 Hz, C**H**$_2$N), 7.48 (d, *J* = 8.0 Hz, 2 Ar**H**), 7.46 (t, *J* = 8.0 Hz, 1 Ar**H**), 7.59 (d, *J* = 8.0 Hz, 2 Ar**H**), 7.73 (d, *J* = 7.8 Hz, Ar**H**), 7.96 (d, *J* = 7.8 Hz, Ar**H**), 8.22 (s, Ar**H**); ^{13}C NMR (CD_3OD) δ28.4 (C(**C**H_3)$_3$), 45.0 (**C**H_2), 81.3 (**C**(CH_3)$_3$), 127.5, 128.1, 128.4, 128.7, 128.9, 131.1,

132.7, 138.8, 139.6, 140.8 (10 Ar**C**), 165.8 (**C**(O)O); LRMS (ESI^+) 284.1 $[M - Cl]^+$ (calcd for $C_{18}H_{22}NO_2$ 284.2 HRMS (ESI^+) no signal detected.

Preparation of (3'-*N*-(*tert*-Butoxycarbonyl)aminobiphenyl-4-yl)methylamine Hydrochloride (39·HCl).[1] Using Method A, **17** (0.78 g, 4.20 mmol), 3-(*N*-*tert*-butoxycarbonylamino)phenylboronic acid (**28**) (1.00 g, 4.20 mmol), aqueous 1 M K_2CO_3 (15.0 mL), and $Pd(PPh_3)_4$ (0.19 g, 0.20 mmol) gave **39·HCl** as a yellow solid (0.79 g, 56%): R_f = 0.00 (hexanes/EtOAc 1/2); mp 242-244 °C; ^{1}H NMR (DMSO-d_6) δ1.49 (s, (C**H**$_3$)$_3$), 4.03–4.04 (br m, C**H**$_2$), 7.56–7.68 (m, 8 Ar**H**), 8.59 (s, N**H**$_3$Cl), 9.47 (s, N**H**); ^{13}C NMR (DMSO-d_6) δ28.1 ((**C**H$_3$)$_3$), 41.8 (**C**H$_2$), 79.1 (**C**(CH$_3$)$_3$), 118.4, 126.1, 126.8, 129.5, 132.6, 133.0, 139.3, 139.8 (Ar**C**), 155.2 (N**C**(O)O); HRMS (ESI^+) 321.1630 $[M - HCl + Na]^+$ (calcd for $C_{18}H_{22}N_2O_2Na^+$ 321.1620).

Preparation of 3'-Bromo-4-biphenylmethylamine Hydrochloride (43·HCl). Using Method B, 1,3-dibromobenzene (**41**) (4.15 g, 17.6 mmol), a solution of *p*-aminomethylboronic acid (**40**) (3.00 g, 16.0 mmol) in EtOH (5 mL), aqueous 1 M K_2CO_3 (75 mL), and $Pd(PPh_3)_4$ (0.54 g, 0.48 mmol) gave crude **43·HCl** as a yellow-orange solid (3.10 g, 65%): R_f = 0.00 (1:1 EtOAc/hexanes); mp 252–254 °C; ^{1}H NMR (DMSO-d_6) δ4.03 (s, C**H**$_2$), 7.38–7.45 (m, Ar**H**), 7.53–7.62 (m, 3 Ar**H**), 7.67–7.75 (m, 3 Ar**H**), 7.86 (t, J = 6.8 Hz, Ar**H**), 8.56 (br s, N**H**$_3$); ^{13}C NMR (DMSO-d_6) δ41.7 (**C**H$_2$), 122.4, 125.8, 126.9, 129.2, 129.6, 130.4, 131.1, 134.0, 138.5, 141.9 (Ar**C**); HRMS signal not detected.

Preparation of 3'-Iodo-4-biphenylmethylamine Hydrochloride (44·HCl). Using Method B, 1,3-diiodobenzene (**42**) (3.90 g, 11.7 mmol), a solution of **40** (2.00 g, 10.7 mmol) in EtOH (5 mL), aqueous 1 M K_2CO_3 (50 mL), and $Pd(PPh_3)_4$ (0.37 g, 0.32 mmol) gave crude **44·HCl** as a yellow-

orange paste (1.92 g, 52%): R_f = 0.00 (1:1 EtOAc/hexanes); ^{1}H NMR (DMSO-d_6) δ4.06 (s, C**H**$_2$), 7.49–7.66 (m, 3 Ar**H**), 7.69 (d, *J* = 8.2 Hz, 2 Ar**H**), 7.83 (d, *J* = 8.2 Hz, 2 Ar**H**), 7.93 (s, Ar**H**), 8.57 (br s, N**H**$_3$); ^{13}C NMR (DMSO-d_6) δ42.3 (**C**H$_2$), 96.1, 125.6, 126.5, 127.3, 127.5, 129.4, 130.0, 133.9, 140.5, 140.7 (Ar**C**); HRMS (ESI$^+$) 310.0093 [M]$^+$ (calcd for $C_{13}H_{13}ClIN$-Cl$^+$ 310.0111).

Preparation of (*R*)-*N*-(4"-Fluorobiphenyl-4'-yl)methyl 2-*N*-(*tert.*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-46). Using Method D, (*R*)-*t*-Boc-D-serine ((*R*)-**45**) (2.00 g, 9.8 mmol), NMM (1.61 mL, 14.6 mmol), IBCF (1.61 mL, 12.4 mmol), and amine **29** (2.36 g, 11.7 mmol, prepared by Method C from **29·HCl**) gave (*R*)-**46** as a white solid (3.40 g, 90%): R_f = 0.55 (hexanes/EtOAc 1/3); mp 140-141 °C; $[\alpha]^{26}_D$ +14.5° (*c* 1.1, $CHCl_3$); IR (nujol) 3145, 2917, 2852, 1658, 1531, 1458, 1378, 1303, 1238, 1169, 1008, 827, 648 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ1.42 (s, (C**H**$_3$)$_3$), 3.20-3.31 (br m, C**H**H'), 3.64–3.74 (br m, CH**H'**), 4.10–4.23 (br m, C**H**, O**H**), 4.39-4.54 (br m, C**H**$_2$N), 5.61–5.67 (br d, N**H**CH), 7.08–7.18 (m, 2 Ar**H**, N**H**CH$_2$), 7.29–7.32 (m, 2 Ar**H**), 7.46–7.52 (m, 4 Ar**H**); ^{13}C NMR (DMSO-d_6) δ28.2 ((**C**H$_3$)$_3$), 41.7 (N**C**H$_2$), 57.0 (OCH$_2$**C**H), 61.9 (O**C**H$_2$CH), 78.2 (**C**(CH$_3$)$_3$), 115.7 (d, *J* = 21.3 Hz, **C**$_{3''}$, **C**$_{5''}$), 126.4, 127.6 (Ar**C**), 128.5 (d, *J* = 8.1 Hz, **C**$_{2''}$, **C**$_{6''}$), 136.5 (d, *J* = 2.9 Hz, **C**$_{1''}$), 137.6, 138.7 (Ar**C**), 155.2 (N**C**(O)O), 161.8 (d, *J* = 242.5 Hz, **C**$_{4''}$), 170.5 (**C**(O)); LRMS (M + Na)$^+$(ESI$^+$) 411.2 [M + Na]$^+$ (calcd for $C_{21}H_{25}FN_2O_4$ Na$^+$ 411.2); Anal. Calcd. for $C_{21}H_{25}FN_2O_4$: C, 64.93; H, 6.49; F, 4.89; N, 7.21. Found: C, 64.71; H, 6.53; F, 4.92; N, 7.22.

Preparation of (*R*)-*N*-(3"-Chlorobiphenyl-4'-yl)methyl 2-*N*-(*tert.*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-47). Using Method D, (*R*)-**45** (3.00 g, 14.7 mmol), NMM (2.42 mL, 22.0 mmol), IBCF (2.42 mL, 18.6 mmol), and amine **30** (3.83 g, 17.6 mmol, prepared by Method C from **30·HCl**) gave (*R*)-**47** as a white solid (4.73 g, 80%): R_f = 0.55 (hexanes/EtOAc 1/3); mp

107-108 °C; $[\alpha]^{26}_{D}$ +13.5° (*c* 1.1, $CHCl_3$); IR (nujol) 3316, 2924, 2859, 1659, 1534, 1459, 1378, 1302, 1247, 1170, 1010, 872, 777, 656 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ1.41 (s, (C**H**$_3$)$_3$), 3.58-3.65 (br m, C**H**$_2$OH), 4.02–4.08 (br m, C**H**), 4.29–4.42 (br m, C**H**$_2$N), 4.85-4.90 (br m, O**H**), 6.68 (d, *J* = 8.0 Hz, N**H**CH), 7.36–7.50 (m, 4 Ar**H**), 7.61–7.70 (m, 4 Ar**H**), 8.37–8.41 (br m, N**H**CH$_2$); ^{13}C NMR (DMSO-d_6) δ28.2 ((**C**H$_3$)$_3$), 41.7 (N**C**H$_2$), 57.0 (OCH$_2$**C**H), 61.9 (O**C**H$_2$CH), 78.2 (**C**(CH$_3$)$_3$), 125.2, 126.3, 126.6, 127.1, 127.7, 130.7, 133.7, 137.0, 139.5, 142.1 (Ar**C**), 155.2 (N**C**(O)O), 170.5 (**C**(O)); LRMS (ESI$^+$) 405.2 $[M + H]^+$ (calcd for $C_{21}H_{25}ClN_2O_4H^+$ 405.2); Anal. Calcd. for $C_{21}H_{25}ClN_2O_4$: C, 62.30; H, 6.22; Cl, 8.76; N, 6.92. Found: C, 62.16; H, 6.32; Cl, 8.61; N, 6.99.

Preparation of (*R*)-*N*-(4”-Chlorobiphenyl-4’-yl)methyl 2-*N*-(*tert.*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-48). Using Method D, (*R*)-**45**, NMM (1.64 mL, 14.9 mmol), IBCF (1.64 mL, 12.7 mmol), and amine **31** (2.60 g, 12.0 mmol, prepared by Method C from **31·HCl**) gave (*R*)-**48** as a white solid (3.72 g, 93%): R_f = 0.55 (hexanes/EtOAc 1/3); mp 148-149 °C; $[\alpha]^{26}_{D}$ +13.4° (*c* 1.0, $CHCl_3$); IR (nujol) 3297, 2924, 2859, 1660, 1535, 1459, 1377, 1307, 1248, 1171, 1098, 1007, 805, 645 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ1.40 (s, (C**H**$_3$)$_3$), 3.57-3.63 (br m, C**H**$_2$OH), 4.00–4.05 (br m, C**H**), 4.27–4.40 (br m, C**H**$_2$N), 4.83-4.88 (br m, O**H**), 6.67 (d, *J* = 7.6 Hz, N**H**CH), 7.36 (d, *J* = 7.8 Hz, 2 Ar**H**), 7.43 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.59 (d, *J* = 7.8 Hz, 2 Ar**H**), 7.67 (d, *J* = 8.4 Hz, 2 Ar**H**), 8.34–8.38 (br m, N**H**CH$_2$); ^{13}C NMR (DMSO-d_6) δ28.2 ((**C**H$_3$)$_3$), 41.7 (N**C**H$_2$), 57.0 (OCH$_2$**C**H), 61.8 (O**C**H$_2$CH), 78.2 (**C**(CH$_3$)$_3$), 126.4, 127.7, 128.3, 128.8, 132.1, 137.2, 138.8, 139.1 (Ar**C**), 155.2 (N**C**(O)O), 170.5 (**C**(O)); LRMS (ESI$^+$) 405.2 $[M + H]^+$ (calcd for $C_{21}H_{25}ClN_2O_4H^+$ 405.2); Anal. Calcd. for $C_{21}H_{25}ClN_2O_4$: C, 62.30; H, 6.22; Cl, 8.76; N, 6.92. Found: C, 62.03; H, 6.30; Cl, 8.55; N, 6.84.

Preparation of (*R*)-*N*-(3"-Bromo-4-biphenylmethyl) 2-*N*-(*tert*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-49). Using Method D, (*R*)-**45** (2.40 g, 11.7 mmol), NMM (988 mg, 9.8 mmol), IBCF (1.33 g, 9.8 mmol), and **43** (2.56 g, 9.8 mmol, prepared by Method C from **43·HCl**) gave compound (*R*)-**49** as a white solid (2.51 g, 57%): R_f = 0.41 (1:20 MeOH/CH_2Cl_2); mp 116–117 °C; $[\alpha]^{23}_D$ +11.8° (c = 1.0, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ1.37 (s, (C**H**$_3$)$_3$C), 3.51–3.62 (m, CHC**H**$_2$), 3.93–4.04 (m, C**H**CH$_2$), 4.22–4.39 (m, NHC**H**$_2$), 4.82 (t, *J* = 5.7 Hz, O**H**), 6.63 (d, *J* = 7.8 Hz, N**H**CH), 7.32 (d, *J* = 8.2 Hz, 2 Ar**H**), 7.38 (t, *J* = 8.0 Hz, Ar**H**), 7.51 (d, *J* = 6.8 Hz, Ar**H**), 7.55–7.66 (m, 3 Ar**H**), 7.75–7.82 (m, Ar**H**), 8.33 (t, *J* = 6.0 Hz, N**H**CH$_2$); ^{13}C NMR (DMSO-d_6) δ28.2 ((**C**H$_3$)$_3$C), 41.7 (NH**C**H$_2$), 56.9 (**C**H), 61.8 (**C**H$_2$OH), 78.2 ((CH$_3$)$_3$**C**), 122.3, 125.6, 126.6, 127.6, 129.1, 130.0, 131.0, 136.9, 139.5, 142.4 (Ar**C**), 155.2 (NH**C**(O)), 170.5 (**C**(O)); LRMS (ESI$^+$) 449.1 [M + H]$^+$ (100%), 451.1 [M + 2 + H]$^+$ (100%); HRMS (ESI$^+$) 449.1076 [M + H]$^+$ (calcd for $C_{21}H_{25}{}^{79}BrN_2O_4H^+$ 449.1074).

Preparation of (*R*)-*N*-(3"-Iodo-4-biphenylmethyl) 2-*N*-(*tert*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-50). Using Method D, (*R*)-**45** (1.00 g, 4.9 mmol), NMM (448 mg, 4.4 mmol), IBCF (605 mg, 4.4 mmol), and **44** (1.37 g, 4.4 mmol, prepared by Method C from **44·HCl**) gave compound (*R*)-**45** as a white solid (900 mg, 41%): R_f = 0.46 (1:20 MeOH/CH_2Cl_2); mp 84-86 °C; $[\alpha]^{24}_D$ +10.2° (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ1.40 (s, (C**H**$_3$)$_3$C), 3.59–3.61 (m, CHC**H**$_2$), 3.98–4.04 (m C**H**CH$_2$), 4.27–4.39 (m, NHC**H**$_2$), 4.84–4.86 (m, O**H**), 6.66 (d, *J* = 7.8 Hz, N**H**CH), 7.25 (t, *J* = 7.8 Hz, Ar**H**), 7.35 (d, *J* = 8.2 Hz, 2 Ar**H**), 7.57–7.60 (m, 2 Ar**H**), 7.65–7.72 (m, 2 Ar**H**), 7.98 (s, Ar**H**), 8.34 – 8.37 (m, N**H**CH$_2$); ^{13}C NMR ($CDCl_3$) δ28.2 ((**C**H$_3$)$_3$C), 41.7 (NH**C**H$_2$), 57.0 (**C**H), 61.8 (**C**H$_2$OH), 78.2 ((CH$_3$)$_3$**C**), 95.5, 126.0, 126.6, 127.6, 131.0, 134.9, 135.9, 136.9, 139.3, 142.3

(Ar**C**), 155.2 (NH**C**(O)), 170.5 (**C**(O)); HRMS (ESI^+) 497.0937 $[M + H]^+$ (calcd for $C_{21}H_{25}IN_2O_4H^+$ 497.0935).

Preparation of (*R*)-(3"-Cyanobiphenyl-4'-yl)methyl 2-*N*-(*tert.*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-51). Using Method D, (*R*)-**45** (10.22 g, 50.8 mmol), NMM (13.7 g, 135.4 mmol), IBCF (6.94 g, 50.8 mmol), and amine **32** (7.06 g, 33.8 mmol) gave the desired product (*R*)-**51** (6.40 g, 48%) as a colorless oil: R_f = 0.32 (CH_2Cl_2/CH_3OH 19/1); $[\alpha]^{22.5}_D$ +12.3 **°** (c 1.0, CH_3OH); ^1H NMR ($CDCl_3$/CD_3OD) δ1.38 (s, (C**H$_3$**)$_3$C), 3.70-3.75 (br s, C**H**H'OH), 3.98-4.00 (m, CH**H'**OH), 4.23-4.27 (br s, C**H**), 4.42-4.46 (br s, NHC**H$_2$**), 5.83-5.89 (br s, N**H**CH), 7.31 (d, *J* = 8.0 Hz, 2 Ar**H**), 7.39-7.51 (m, 3 Ar**H**, N**H**C**H$_2$**), 7.56 (d, *J* = 8.0 Hz, Ar**H**), 7.71 (d, *J* = 8.0 Hz, 2 Ar**H**); ^{13}C NMR ($CDCl_3$/CD_3OD) δ28.4 (C(**C**H$_3$)$_3$), 43.0 (N**C**H$_2$), 55.6 (C**H**), 62.9 (O**C**H$_2$), 80.6 (**C**(CH$_3$)$_3$), 113.0 (Ar**C**), 119.0 (**C**N), 127.3, 128.7, 129.2, 130.4, 131.1, 131.4, 137.9, 138.1, 142.9 (9 Ar**C**), 156.3 ((CH$_3$)$_3$CN(H)**C**(O)O), 171.6 (**C**(O)); LRMS (ESI^+) 396.2 $[M + H]^+$ (calcd for $C_{22}H_{26}N_3O_4^+$ 396.2); HRMS (ESI^+) 396.1924 $[M + H]^+$ (calcd for $C_{22}H_{26}N_3O_4^+$ 396.1923).

Preparation of (*R*)-*N*-(3"-Trifluoromethyl)-4-biphenylmethyl 2-*N*-(*tert*-Butoxycarbonyl) amino-3-hydroxypropionamide ((*R*)-52). Using Method D, (*R*)-**45** (930 mg, 4.5 mmol), NMM (417 mg, 4.1 mmol), IBCF (563 mg, 4.1 mmol), and amine **33** (1.04 g, 4.1 mmol, prepared by Method C from **33·HCl**) gave compound (*R*)-**52** as a white solid (1.53 g, 77%): R_f = 0.58 (1:20 MeOH/CH_2Cl_2); mp 128–129 °C; $[\alpha]_D^{22}$ = +12.8° (c = 1.0, $CHCl_3$); ^1H NMR (DMSO-d_6) δ1.40 ((C**H$_3$**)$_3$C), 3.54–3.65 (m, CHC**H$_2$**), 3.96–4.07 (m, C**H**CH$_2$), 4.26–4.44 (m, NHC**H$_2$**), 4.86 (t, *J* = 5.7 Hz, O**H**), 6.67 (d, *J* = 8.2 Hz, N**H**CH), 7.39 (d, *J* = 8.2 Hz, 2 Ar**H**), 7.64–7.74 (m, 4 Ar**H**), 7.90–8.01 (m, 2 Ar**H**), 8.38 (t, *J* = 5.9 Hz, N**H**CH$_2$); ^{13}C NMR (DMSO-d_6) δ28.1 ((**C**H$_3$)$_3$C), 41.7 (NH**C**H$_2$), 57.0 (**C**H), 61.8 (**C**H$_2$OH), 78.2 ((CH$_3$)$_3$**C**), 122.9 (q, *J* = 4.0 Hz), 123.9 (q, *J* = 4.0 Hz), 124.2 (q, *J* = 272.0

Hz, **C**F_3), 126.7, 127.7 (Ar**C**), 129.7 (q, *J* = 32.0 Hz), 130.0, 130.7, 136.9, 139.6, 141.0 (Ar**C**), 155.2 (NH**C**(O)), 170.5 (**C**(O)); LRMS (ESI$^+$) 439.2 $[M + H]^+$ (calcd for $C_{22}H_{26}F_3N_2O_4^+$ 439.2); HRMS (ESI$^+$) 439.1874 $[M + H]^+$ (calcd for $C_{22}H_{26}F_3N_2O_4^+$ 439.1844).

Preparation of (*R*)-*N*-(3”-Trifluoromethoxybiphenyl-4’-yl)methyl 2-*N*-(*tert.*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-53). Using Method D, (*R*)-**45** (2.09 g, 10.2 mmol), NMM (1.68 mL, 15.3 mmol), IBCF (1.68 mL, 13.0 mmol), and amine **34** (3.27 g, 12.2 mmol, prepared by Method C from **34·HCl**) gave (*R*)-**53** as a white solid (3.79 g, 82%): R_f = 0.55 (hexanes/EtOAc 1/3); mp 96-97 °C; $[\alpha]^{26}_D$ +13.0° (*c* 1.1, $CHCl_3$); IR (nujol) 3176, 2949, 2850, 1689, 1657, 1530, 1458, 1374, 1294, 1159, 1085, 997, 788, 724 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ1.43 (s, (C**H**$_3$)$_3$), 3.08-3.22 (br m, C**H**H’), 3.66–3.74 (br m, CH**H’**), 4.12–4.22 (br m, C**H**, O**H**), 4.39-4.59 (br m, C**H**$_2$N), 5.60–5.65 (br d, N**H**CH), 7.12–7.54 (m, 8 Ar**H**, N**H**CH$_2$); ^{13}C NMR (DMSO-d_6) δ28.2 ((**C**H$_3$)$_3$), 41.7 (N**C**H$_2$), 57.0 (OCH$_2$**C**H), 61.9 (O**C**H$_2$CH), 78.2 (**C**(CH$_3$)$_3$), 119.1, 119.6 (Ar**C**), 120.1 (d, *J* = 254.9 Hz, O**C**F$_3$), 125.7, 126.7, 127.7, 130.8, 136.8, 139.7, 142.4, 149.0 (Ar**C**), 155.2 (N**C**(O)O), 170.5 (**C**(O)); LRMS (ESI$^+$) 477.1 $[M + Na]^+$ (calcd for $C_{22}H_{25}F_3N_2O_5Na^+$ 477.2); Anal. Calcd. for $C_{22}H_{25}F_3N_2O_5$: C, 58.15; H, 5.54; F, 12.54; N, 6.16. Found: C, 57.99; H, 5.68; F, 12.40; N, 6.11.

Preparation of (*R*)-*N*-(4”-Trifluoromethoxybiphenyl-4’-yl)methyl 2-*N*-(*tert.*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-54). Using Method D, (*R*)-**45** (1.03 g, 5.0 mmol), NMM (0.82 mL, 7.5 mmol), IBCF (0.82 mL, 7.5 mmol), and amine **35** (1.60 g, 6.0 mmol, prepared by Method C from **35·HCl**) gave (*R*)-**54** as a white solid (1.92 g, 83%): R_f = 0.55 (hexanes/EtOAc 1/3); mp 166-167 °C; $[\alpha]^{26}_D$ +13.3° (*c* 0.8, $CHCl_3$); IR (nujol) 3304, 2924, 2859, 1658, 1534, 1457, 1378, 1284, 1230, 1162, 1009, 835, 647 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ1.42 (s, (C**H**$_3$)$_3$), 3.30-3.40 (br m, C**H**H’), 3.64–3.74 (br m, CH**H’**), 4.11–4.22 (br m, C**H**, O**H**), 4.40-4.56 (br

m, C**H**$_2$N), 5.64–5.69 (br d, N**H**CH), 7.20–7.34 (m, 4 Ar**H**, N**H**CH$_2$), 7.47–7.56 (m, 4 Ar**H**); ^{13}C NMR (DMSO-d_6) δ28.2 ((**C**H$_3$)$_3$), 41.7 (N**C**H$_2$), 57.0 (OCH$_2$**C**H), 61.8 (O**C**H$_2$CH), 78.2 (**C**(CH$_3$)$_3$), 120.1 (d, *J* = 254.9 Hz, O**C**F$_3$), 121.4, 126.6, 127.7, 128.4, 137.1, 139.2, 139.3, 147.7 (Ar**C**), 155.2 (N**C**(O)O), 170.5 (**C**(O)); LRMS (ESI$^+$) 587.0 [M + Cs]$^+$ (calcd for $C_{22}H_{25}F_3N_2O_5Cs^+$ 587.1); Anal. Calcd. for $C_{22}H_{25}F_3N_2O_5$: C, 58.15; H, 5.54; F, 12.54; N, 6.16. Found: C, 58.09; H, 5.67; F, 12.40; N, 6.25.

Preparation of (*R*)-*N*-(3”-Acetylaminobiphenyl-4’-yl)methyl 2-*N*-(*tert.*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-55). Using Method D, *(R)*- **45** (7.54 g, 37.5 mmol),NMM (10.1 g, 99.9 mmol), IBCF (5.12 g, 37.5 mmol), and amine **36** (6.00 g, 25.0 mmol) gave the desired product (*R*)-**55** (4.00 g, 38%) as a colorless oil: R_f = 0.17 (CH_2Cl_2/CH_3OH 19/1); $[\alpha]^{22.5}_D$ +17.3 **°** (c 1.0, CH_3OH); ^{1}H NMR ($CDCl_3$) δ1.41 (s, (C**H$_3$**)$_3$C), 2.14 (s, C**H$_3$**CO), 3.65-3.57 (m, C**H**H’OH), 3.97-4.07 (m, CH**H’**OH), 4.17-4.24 (br s, C**H**), 4.24-4.46 (m, NHC**H$_2$**), 5.73-5.77 (br d, N**H**CH), 7.19 (m, 3 Ar**H**), 7.31 (t, *J* = 8.0 Hz, Ar**H**), 7.41 (d, *J* = 8.0 Hz, 2 Ar**H**), 7.47 (d, *J* = 8.0 Hz, Ar**H**), 7.62 (s, Ar**H**), 7.95 (br s, ArN**H**C(O)); ^{13}C NMR ($CDCl_3$) δ24.7 (**C**H$_3$CO), 28.4 (C(**C**H$_3$)$_3$), 43.3 (N**C**H$_2$), 55.4 (C**H**), 63.0 (O**C**H$_2$), 80.8 (**C**(CH$_3$)$_3$), 118.8, 119.2, 123.1, 127.5, 128.0, 129.6, 137.2, 138.6, 140.0, 141.6 (10 Ar**C**), 156.5 ((CH$_3$)$_3$CN(H)**C**(O)O), 169.1, 171.6 (2 **C**(O)); LRMS (ESI$^+$) 428.2 [M + H]$^+$ (calcd for $C_{23}H_{29}N_3O_5H^+$ 428.2); HRMS (ESI$^+$) 450.2007 [M + Na]$^+$ (calcd for $C_{23}H_{29}N_3O_5Na^+$ 450.2005).

Preparation of (*R*)-2-*N*-Acetamido-3-hydroxypropionate Benzyl Ester ((*R*)-67). To a suspension of D-serine benzyl ester hydrochloride ((*R*)-**66**) (5.00 g, 21.6 mmol) in CH_2Cl_2 (100 mL) was added triethylamine (4.59 g, 45.3 mmol) at −20 °C under Ar and stirred (10 min). To the resulting solution was added AcCl (1.52 g, 19.4 mmol) at −20 °C under Ar and then stirred (4 h). The reaction mixture was filtered and washed with aqueous 0.5 M HCl (2 × 100 mL) and brine (2

× 40 mL). The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by column choromatography (CH_2Cl_2/MeOH 19/1) to give the desired product (*R*)-**66** (6.07 g, 100%) as a white solid: R_f = 0.26 (CH_2Cl_2/MeOH 19/1); mp 78-79 °C; $[\alpha]^{25}_D$ – 20.6 **°** (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ1.96 (s, C**H$_3$**C(O)), 3.72-3.84 (m, **H**OC**H**H'), 3.90-3.97 (m, HOCH**H'**), 4.61-4.64 (m, C**H**), 5.14 (s, OC**H$_2$**Ph), 6.91 (d, *J* = 7.6 Hz, N**H**C(O)), 7.24-7.38 (m, 5 Ar**H**); ^{13}C NMR ($CDCl_3$) δ23.0 (**C**H$_3$C(O)), 55.0 (**C**H), 62.9 (HO**C**H$_2$), 67.5 (O**C**H$_2$Ph), 128.2, 128.6, 128.7, 135.3 (4 Ar**C**), 170.7 (CH**C**O(O)), 171.3 (CH$_3$**C**(O)); HRMS (ESI$^+$) 238.1078 [M + H]$^+$ (calcd for $C_{12}H_{16}NO_4^+$ 238.1079).

Preparation of (*R*)-2-*N*-Acetamido-3-methoxypropionate Benzyl Ester ((*R*)-68). To a solution of (*R*)-**67** (1.00 g, 4.2 mmol) in acetonitrile (50 mL) was added CH_3I (5.98 gm 42.2 mmol) and Ag_2O (4.88 g, 21.1 mmol) at room temperature under Ar and stirred (36 h). The reaction mixture was filtered through Celite and concentrated in vacuo. The residue was purified by SiO_2 column choromatography (EtOAc/hexanes 1/1) to give the desired product (*R*)-**68** (1.06 g, 100%) as a white solid: R_f = 0.23 (EtOAc/hexanes 1/1); mp 80-81 °C; $[\alpha]^{25}_D$ – 23.3 **°** (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ2.05 (s, C**H$_3$**C(O)), 3.29 (s, OC**H$_3$**), 3.62 (dd, *J* = 3.2, 9.2 Hz, OC**H**H'), 3.81 (dd, *J* = 3.2, 9.2 Hz, OCH**H'**), 4.76-4.80 (m, C**H**), 5.16 (½AB$_q$, *J* = 12.2 Hz, OC**H**H'Ph), 5.26 (½AB$_q$, *J* = 12.2 Hz, OCH**H'**Ph), 6.27-6.38 (br s, N**H**C(O)), 7.27-7.38 (m, 5 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of the product gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ23.4 (**C**H$_3$C(O)), 53.0 (**C**H), 59.4 (O**C**H$_3$), 67.5 (O**C**H$_2$Ph), 72.5 (CH$_3$O**C**H$_2$), 128.3, 128.6, 128.8, 135.6 (4 Ar**C**), 170.1 (CH**C**O(O)), 170.5 (CH$_3$**C**(O)); LRMS (ESI$^+$) 274.1 [M + H]$^+$ (calcd for $C_{13}H_{18}NO_4^+$ 274.1); Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.27; H, 6.72; N, 5.77.

Preparation of (*R*)-2-*N*-Acetamido-3-hydroxypropionic Acid ((*R*)-69). To a solution of *(R)*-2-*N*-acetamido-3-hydroxypropionate benzyl ester ((*R*)-**67**) (1.47 g, 10.0 mmol) in MeOH (150 mL) was added Pd on activated carbon (10% Pd/C, wet) (0.53 g, 0.5 mmol) at room temperature and stirred (1 h) under H_2. The reaction mixture was filtered through Celite and concentrated in vacuo. The resulting residue was further dried under high vacuum (15-24 h) and (*R*)-**69** was used without further purification: R_f = 0.00 (EtOAc); $[\alpha]^{25}_D$ – 26.0 **°** (c 1.0, MeOH).

Preparation of (*R*)-2-*N*-Acetamido-3-methoxypropionic Acid[2] ((*R*)-70). To a solution of *(R)*-2-*N*-acetamido-3-methoxypropionate benzyl ester ((*R*)-**68**) (0.25 g, 1.0 mmol) in MeOH (15 mL) was added Pd on activated carbon (10% Pd/C, wet) (53.2 mg, 0.05 mmol) at room temperature and stirred (30 min) under H_2. The reaction mixture was filtered through Celite and concentrated in vacuo. The resulting residue (*R*)-**70** was further dried under high vacuum (15 h) and used without further purification: R_f = 0.00 (EtOAc); $[\alpha]^{25}_D$ – 19.2 **°** (c 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 2.04 (s, C**H$_3$**C(O)), 3.33 (s, OC**H$_3$**), 3.58-3.65 (m, OC**H**H'), 3.75-3.85 (m, OCH**H'**), 4.63-4.76 (br s, C**H**), 6.75-6.95 (m, N**H**C(O), C(O)O**H**); ^{13}C NMR ($CDCl_3$) δ22.9 (**C**H$_3$C(O)), 52.9 (**C**H), 59.3 (O**C**H$_3$), 72.1 (CH_3O**C**H_2), 171.7 (CH_3**C**(O)), 172.4 (CH**C**O(O)H).

Preparation of (*R*)-*N*-(3"-*tert*-Butoxymethylbiphenyl-4'-yl)methyl 2-Acetamido-3-hydroxypropionamide ((*R*)-71). Using Method D, *(R)*-2-acetamido-3-hydroxypropionic acid ((*R*)-**69**) (1.70 g, 11.5 mmol), anhydrous THF/DMSO (150 mL/15 mL), NMM (1.17 g, 11.5 mmol), IBCF (1.26 g, 9.2 mmol), and amine **37** (2.07 g, 7.7 mmol, prepared by Method C from **37·HCl**) gave the desired product (*R*)-**70** (1.03 g, 34%) as a white solid: R_f = 0.11 (EtOAc/hexanes 1/1); mp 125-126 °C; $[\alpha]^{22.5}_D$ +9.6 **°** (c 1.0, CH_3OH); ^{1}H NMR ($CDCl_3$/CD_3OD) δ1.24 (s, (C**H$_3$**)$_3$C), 1.95 (s,

C**H$_3$**C(O)), 3.29-3.64 (m, C**H**H'OH), 3.81-3.87 (m, CH**H'**OH), 4.35-4.45 (m, C**H**, C**H$_2$**O, C**H$_2$**N), 7.23-7.45 (m, 5 Ar**H**), 7.46-7.52 (m, 3 Ar**H**); ^{13}C NMR ($CDCl_3/CD_3OD$) δ22.8 (**C**H$_3$C(O)), 27.7 (C(**C**H$_3$)$_3$), 43.1 (N**C**H$_2$), 54.8 (C**H**), 62.5 (O**C**H$_2$), 64.3 (Ar**C**H$_2$O), 73.9 (**C**(CH$_3$)$_3$), 126.0, 126.3, 126.7, 127.4, 127.9, 128.8, 139.8, 140.3, 140.5, 140.7 (10 Ar**C**), 170.9, 171.7 (2 **C**(O)NH); LRMS (ESI$^+$) 399.2 [M + H]$^+$ (calcd for $C_{23}H_{30}N_2O_4H^+$ 399.2); HRMS (ESI$^+$) 399.2285 [M + H]$^+$ (calcd for $C_{23}H_{30}N_2O_4H^+$ 399.2284).

Preparation of (*R*)-*N*-(3"-*tert*-Butoxycarbonylbiphenyl-4'-yl)methyl 2-Acetamido-3-hydroxypropionamide ((*R*)-72). Using Method D, (*R*)-**69** (1.20 g, 8.2 mmol), anhydrous THF/DMSO (90 mL/9 mL), NMM (1.24 g, 12.3 mmol), IBCF (1.12 g, 8.2 mmol), and amine **38** (2.32 g, 8.2 mmol, prepared by Method C from **38·HCl**) gave the desired product (*R*)-**72** (0.86 g, 50%) as a white solid: R_f = 0.12 (EtOAc/hexanes 1/1); mp 123-124 °C; $[\alpha]^{22.5}_D$ +10.7 ° (*c* 1.0, CH_3OH); ^{1}H NMR ($CDCl_3/CD_3OD$) δ1.62 (s, (C**H$_3$**)$_3$C), 2.05 (s, C**H$_3$**C(O)), 3.67-3.72 (m, C**H**H'OH), 3.94-3.99 (m, CH**H'**OH), 4.41-4.52 (m, C**H,** C**H$_2$**N), 7.29 (d, *J* = 7.8 Hz, 2 Ar**H**), 7.48 (m, Ar**H**), 7.58 (d, *J* = 7.8 Hz, 2 Ar**H**), 7.74 (d, *J* = 7.6 Hz, Ar**H**), 7.96 (d, *J* = 7.6 Hz, Ar**H**), 8.18 (s, Ar**H**); ^{13}C NMR ($CDCl_3/CD_3OD$) δ23.0 (**C**H$_3$C(O)), 28.3 (C(**C**H$_3$)$_3$), 43.2 (N**C**H$_2$), 54.6 (C**H**), 62.6 (O**C**H$_2$), 81.36 (**C**(CH$_3$)$_3$), 127.5, 128.1, 128.2, 128.4, 128.9, 131.1, 132.6, 137.4, 139.6, 141.9 (10 Ar**C**), 166.5 (Ar**C**(O)), 171.0, 171.5 (2 **C**(O)NH); LRMS (ESI$^+$) 413.2 [M + H]$^+$ (calcd for $C_{23}H_{28}N_2O_5H^+$ 413.2); HRMS (ESI$^+$) 413.2079 [M + H]$^+$ (calcd for $C_{23}H_{28}N_2O_5H^+$ 413.2076).

Preparation of (*R*)-*N*-(4"-Fluorobiphenyl-4'-yl)methyl 2-*N*-(*tert.*-Butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-56). Using Method E, (*R*)-**46** (3.50 g, 9.0 mmol), Ag_2O (10.45 g, 45.1 mmol), and CH_3I (5.63 mL, 90.2 mmol) gave (*R*)-**56** as a white solid (3.40 g, 94%): R_f = 0.40

(hexanes/EtOAc 1/1); mp 108-109 °C; $[\alpha]^{26}_{D}$ –19.7° (*c* 1.2, $CHCl_3$); IR (nujol) 3172, 2952, 2862, 1653, 1529, 1458, 1374, 1240, 1169, 1116, 1062, 818, 723, 611 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ1.41 (s, (C**H**$_3$)$_3$), 3.27 (s, OC**H**$_3$), 3.51-3.56 (br m, C**H**$_2$O), 4.21–4.26 (br m, C**H**), 4.30–4.41 (br m, C**H**$_2$N), 6.87 (d, *J* = 8.0 Hz, N**H**CH), 7.25–7.40 (m, 4 Ar**H**), 7.57–7.70 (m, 4 Ar**H**), 8.46–8.49 (br t, N**H**CH$_2$); ^{13}C NMR (DMSO-d_6) δ28.1 ((**C**H$_3$)$_3$), 41.8 (N**C**H$_2$), 54.4 (OCH$_2$**C**H), 58.1 (O**C**H$_3$), 72.0 (O**C**H$_2$CH), 78.2 (**C**(CH$_3$)$_3$), 115.6 (d, *J* = 21.2 Hz, **C**$_{3''}$, **C**$_{5''}$), 126.4 (Ar**C**), 127.6 (Ar**C**), 128.5 (d, *J* = 8.1 Hz, **C**$_{2''}$, **C**$_{6''}$), 136.4 (d, *J* = 2.9 Hz, **C**$_{1''}$), 137.6 (Ar**C**), 138.6 (Ar**C**), 155.2 (N**C**(O)O), 161.8 (d, *J* = 242.5 Hz, **C**$_{4''}$), 170.5 (**C**(O)); LRMS (ESI$^+$) 425.2 [M + Na]$^+$ (calcd for $C_{22}H_{27}FN_2O_4Na^+$ 425.2); Anal. Calcd. for $C_{22}H_{27}FN_2O_4$: C, 65.66; H, 6.67; F, 4.72; N, 6.96. Found: C, 65.58; H, 6.65; F, 4.53; N, 6.84.

Preparation of (*R*)-*N*-(3”-Chlorobiphenyl-4’-yl)methyl 2-*N*-(*tert.*-Butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-57). Using Method E, (*R*)-**47** (4.00 g, 9.9 mmol), Ag_2O (11.47 g, 49.5 mmol), and CH_3I (6.18 mL, 99.0 mmol) gave (*R*)-**57** as a sticky foam (4.00 g, 97%): R_f = 0.40 (hexanes/EtOAc 1/1); $[\alpha]^{26}_{D}$ –17.0° (*c* 1.1, $CHCl_3$); IR (nujol) 3162, 2923, 2857, 1659, 1459, 1375, 1247, 1164, 1109, 874, 771 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ1.40 (s, (C**H**$_3$)$_3$), 3.26 (s, OC**H**$_3$), 3.48-3.53 (br m, C**H**$_2$O), 4.16–4.22 (br m, C**H**), 4.27–4.39 (br m, C**H**$_2$N), 6.86 (d, *J* = 8.0 Hz, N**H**CH), 7.33–7.50 (m, 4 Ar**H**), 7.61–7.70 (m, 4 Ar**H**), 8.44–8.48 (br t, N**H**CH$_2$); ^{13}C NMR (DMSO-d_6) δ 28.1 ((**C**H$_3$)$_3$), 41.7 (N**C**H$_2$), 54.3 (OCH$_2$**C**H), 58.1 (O**C**H$_3$), 72.0 (O**C**H$_2$CH), 78.2 (**C**(CH$_3$)$_3$), 125.2, 126.2, 126.6, 127.1, 127.6, 130.7, 133.7, 137.0, 139.3, 142.1 (Ar**C**), 155.2 (N**C**(O)O), 170.1 (**C**(O)); LRMS (ESI$^+$) 419.2 [M + H]$^+$ (calcd for $C_{22}H_{27}ClN_2O_4H^+$ 419.2); Anal. Calcd. for $C_{22}H_{27}ClN_2O_4$: C, 63.08; H, 6.50; Cl, 8.46; N, 6.69. Found: C, 62.94; H, 6.67; Cl, 8.24; N, 6.65.

Preparation of (*R*)-*N*-(4"-Chlorobiphenyl-4'-yl)methyl 2-*N*-(*tert.*-Butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-58). Using Method E, (*R*)-**48** (3.60 g, 8.9 mmol), Ag_2O (10.32 g, 44.5 mmol), and CH_3I (5.56 mL, 89.1 mmol) gave (*R*)-**58** as a white solid (3.27 g, 88%): R_f = 0.40 (hexanes/EtOAc 1/1); mp 97-98 °C; $[\alpha]^{26}_D$ –19.3° (*c* 1.0, $CHCl_3$); IR (nujol) 3155, 2967, 2850, 1662, 1530, 1458, 1376, 1308, 1247, 1166, 1100, 1048, 806, 722 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.40 (s, (C**H**$_3$)$_3$), 3.26 (s, OC**H**$_3$), 3.47-3.53 (br m, C**H**$_2$O), 4.17–4.22 (br m, C**H**), 4.28–4.39 (br m, C**H**$_2$N), 6.87 (d, *J* = 8.0 Hz, N**H**CH), 7.34 (d, *J* = 7.2 Hz, 2 Ar**H**), 7.50 (d, *J* = 8.0 Hz, 2 Ar**H**), 7.60 (d, *J* = 7.2 Hz, 2 Ar**H**), 7.68 (d, *J* = 8.0 Hz, 2 Ar**H**), 8.44–8.47 (br t, N**H**CH$_2$); ^{13}C NMR (DMSO-d_6) δ28.1 ((**C**H$_3$)$_3$), 41.7 (N**C**H$_2$), 54.3 (OCH$_2$**C**H), 58.1 (O**C**H$_3$), 72.0 (O**C**H$_2$CH), 78.2 (**C**(CH$_3$)$_3$), 126.4, 127.6, 128.3, 128.8, 132.2, 137.2, 138.8, 139.0 (Ar**C**), 155.2 (N**C**(O)O), 170.0 (**C**(O)); LRMS (ESI^+) 419.2 $[M + H]^+$ (calcd for $C_{22}H_{27}ClN_2O_4H^+$ 419.2); Anal. Calcd. for $C_{22}H_{27}ClN_2O_4$: C, 63.08; H, 6.50; Cl, 8.46; N, 6.69. Found: C, 62.88; H, 6.52; Cl, 8.17; N, 6.68.

Preparation of (*R*)-*N*-(3"-Bromo-4-biphenylmethyl) 2-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-59). Using Method E, Ag_2O (4.30 g, 18.7 mmol), MeI (5.31 g, 37.4 mmol), and (*R*)-**49** (1.68 g, 3.7 mmol) gave compound (*R*)-**59** as a colorless sticky foam (1.32 g, 76%): R_f = 0.48 (1:20 MeOH/CH_2Cl_2); $[\alpha]^{24}_D$ –13.3° (c = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ1.44 (s, (C**H**$_3$)C), 3.38 (s, OC**H**$_3$), 3.52 (dd, *J* = 3.4, 9.1 Hz, C**H**H'OCH$_3$), 3.85 (dd, *J* = 3.7, 9.1 Hz, CH**H**'OCH$_3$), 4.23–4.35 (m, C**H**CH$_2$), 4.45–4.59 (m, NHC**H**$_2$), 5.37–5.49 (m, N**H**CH), 6.82–6.84 (m, N**H**CH$_2$), 7.28–7.34 (m, 3 Ar**H**), 7.41–7.55 (m, 4 Ar**H**), 7.69–7.70 (m, Ar**H**); ^{13}C NMR ($CDCl_3$) δ28.2 (C(**C**H$_3$)$_3$), 43.0 (NH**C**H$_2$), 54.1 (**C**H), 59.1 (O**C**H$_3$), 72.0 (**C**H$_2$O), 80.3 ((CH$_3$)$_3$**C**), 122.9, 125.6, 127.3, 127.9, 130.0, 130.2, 130.3, 137.8, 138.8, 142.8 (Ar**C**), 155.5 (NH**C**(O)), 170.4 (**C**(O)); LRMS (ESI^+)

463.1 $[M + H]^+$ (100%), 465.1 $[M + 2 + H]^+$ (100%); HRMS (ESI^+) 463.1232 $[M + H]^+$ (calcd for $C_{22}H_{27}{}^{79}BrN_2O_4H^+$ 463.1234).

Preparation of (*R*)-*N*-(3"-Iodo-4-biphenylmethyl) 2-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-60). Using Method E, Ag_2O (2.10 g, 9.0 mmol), MeI (2.57 g, 18.1 mmol), and (*R*)-**50** (900 mg, 1.8 mmol) gave compound (*R*)-**60** as a colorless sticky foam (674 mg, 73%): R_f = 0.62 (1:20 MeOH/CH_2Cl_2); $[\alpha]^{24}{}_D$ –12.9° (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ1.45 (s, (CH_3)$_3$C), 3.40 (s, OC**H**$_3$), 3.53 (dd, *J* = 3.6, 9.1 Hz, C**H**H'OCH_3), 3.87 (dd, *J* = 3.7, 9.1 Hz, CH**H**'OCH_3), 4.28–4.32 (m, C**H**CH_2), 4.47–4.60 (m, NHC**H**$_2$), 5.40– 5.44 (m, N**H**CH), 6.79 (t, *J* = 5.0 Hz, N**H**CH_2), 7.17 (t, *J* = 7.8 Hz, Ar**H**), 7.35 (d, *J* = 8.2 Hz, 2 Ar**H**), 7.44–7.60 (m, 3 Ar**H**), 7.65–7.71 (m, Ar**H**), 7.92 (s, Ar**H**); ^{13}C NMR ($CDCl_3$) δ28.3 (C(**C**H_3)$_3$), 43.1 (NH**C**H_2), 58.1 (**C**H), 59.1 (O**C**H_3), 72.0 (**C**H_2O), 78.6 ((CH_3)$_3$**C**), 94.8, 126.3, 127.3, 127.9, 130.4, 136.0, 136.2, 137.7, 138.8, 142.9 (Ar**C**), 155.3 (NH**C**(O)), 170.4 (**C**(O)); HRMS (ESI^+) 511.1094 $[M + H]^+$ (calcd for $C_{22}H_{27}IN_2O_4H^+$ 511.1097).

Preparation of (*R*)-*N*-(3"-Cyanobiphenyl-4'-yl)methyl 2-*N*-(*tert.*-Butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-61). Using Method E, (*R*)-**51** (6.40 g, 15.9 mmol), acetonitrile (300 mL), DMF (30 mL), Ag_2O (18.5 g, 79.5 mmol), and CH_3I (22.50 g, 159.3 mmol) were stirred (48 h). The reaction mixture was filtered through Celite and concentrated in vacuo. The residue was diluted in CH_2Cl_2 (200 mL) and washed with H_2O (2 × 200 mL) and saturated aqueous brine (2 × 100 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and then purified by SiO_2 column chromatography (CH_2Cl_2/CH_3OH 20/1) and further purified by recrystallization (EtOAc/hexanes) to give the desired product (*R*)-**61** (3.10 g, 48%) as a colorless oil: R_f = 0.50 (CH_2Cl_2/CH_3OH 20/1); $[\alpha]^{25}{}_D$ +16.9 ° (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ1.35 (s, (C**H$_3$**)$_3$CO), 3.27 (s,

OC**H$_3$**), 3.46-3.50 (m, C**H**H'OCH$_3$), 3.70-3.74 (m, CH**H'**OCH$_3$), 4.20-4.50 (m, C**H**, C**H**$_2$N), 5.59-5.65 (br s, N(**H**)CH), 7.17-7.30 (m, 2 Ar**H**, N(**H**)CH$_2$), 7.35-7.52 (m, 4 Ar**H**), 7.68-7.73 (m, 2 Ar**H**); ^{13}C NMR ($CDCl_3$) δ28.1 (C(**C**H$_3$)$_3$), 42.7 (N**C**H$_2$), 54.1 (**C**H), 58.9 (O**C**H$_3$), 72.2 (O**C**H$_2$), 80.2 (**C**(CH$_3$)$_3$), 112.7 (Ar**C**), 118.6 (**C**N), 127.0, 127.9, 128.6, 129.5, 130.5, 131.4, 137.5, 138.6, 141.7 (9 Ar**C**), 155.5 (NH**C**(O)O), 170.5, (**C**(O)CH); LRMS (ESI$^+$) 410.2 [M + H]$^+$ (calcd for $C_{23}H_{28}N_3O_4^+$ 410.2); HRMS (ESI$^+$) 410.2084 [M + H]$^+$ (calcd for $C_{23}H_{28}N_3O_4^+$ 410.2080).

Preparation of (*R*)-*N*-(3"-Trifluoromethyl)-4-biphenylmethyl 2-*N*-(*tert*-Butoxycarbonyl) amino-3-methoxypropionamide ((*R*)-62). Using Method E, Ag_2O (3.96 g, 17.1 mmol), MeI (4.85 g, 34.2 mmol), and (*R*)-**52** (1.50 g, 3.4 mmol) gave compound (*R*)-**62** as a colorless sticky foam (1.39 g, 90%): R_f = 0.72 (1:20 MeOH/CH_2Cl_2); $[\alpha]^{22}_D$ –30.9^o (c = 1.0, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ1.39 (s, (C**H**$_3$)$_3$C), 3.32 (s, OC**H**$_3$), 3.49–3.51 (m, CHC**H**$_2$), 4.15–4.25 (m, C**H**CH$_2$), 4.28–4.42 (m, NHC**H**$_2$), 6.86 (d, *J* = 8.2 Hz, N**H**CH), 7.38 (d, *J* = 8.2 Hz, 2 Ar**H**), 7.65–7.73 (m, 4 Ar**H**), 7.94 (s, Ar**H**), 7.97 (d, *J* = 6.7 Hz, Ar**H**), 8.48 (t, *J* = 6.1 Hz, N**H**CH$_2$); ^{13}C NMR (DMSO-d_6) δ28.1 (C(**C**H$_3$)$_3$), 41.7 (NH**C**H$_2$), 54.3 (O**C**H$_3$), 58.1 (**C**H), 72.0 (**C**H$_2$O), 78.2 ((CH$_3$)$_3$**C**), 122.9 (q, *J* = 4.0 Hz), 123.9 (q, *J* = 4.0 Hz), 124.2 (q, *J* = 272.0 Hz, **C**F$_3$), 126.8, 127.7 (Ar**C**), 129.7 (q, *J* = 32.0 Hz), 130.0, 130.6, 136.9, 139.5, 141.0 (Ar**C**), 155.2 (NH**C**(O)), 170.1 (**C**(O)); LRMS (ESI$^+$) 453.2 [M + H]$^+$ (calcd for $C_{23}H_{28}F_3N_2O_4^+$ 453.2); HRMS (ESI$^+$) 453.2033 [M + H]$^+$ (calcd for $C_{23}H_{28}F_3N_2O_4^+$ 453.2001).

Preparation of (*R*)-*N*-(3"-Trifluoromethoxybiphenyl-4'-yl)methyl 2-*N*-(*tert.*-Butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-63). Using Method E, (*R*)-**53** (2.54 g, 5.6 mmol), Ag_2O (6.48 g, 28.0 mmol), and CH_3I (3.50 mL, 55.9 mmol) gave (*R*)-**63** as a white solid (2.29 g, 88%): R_f = 0.40 (hexanes/EtOAc 1/1); mp 83-84 °C; $[\alpha]^{26}_D$ –16.5° (*c* 1.1, $CHCl_3$); IR (nujol) 3166, 2913, 2842, 1662, 1527, 1459, 1375, 1254, 1161, 1051, 952, 855, 782, 646 cm^{-1}; ^{1}H NMR

(DMSO-d_6) δ1.40 (s, (C**H**$_3$)$_3$), 3.27 (s, OC**H**$_3$), 3.51–3.53 (m, C**H**$_2$OCH$_3$), 4.19–4.24 (m, C**H**), 4.30-4.41 (m, C**H**$_2$N), 6.88 (d, *J* = 8.0 Hz, N**H**CH), 7.34–7.38 (m, 3 Ar**H**), 7.57–7.72 (m, 5 Ar**H**), 8.48 (t, *J* = 6.0 Hz, N**H**CH$_2$); ^{13}C NMR (DMSO-d_6) δ28.1 ((**C**H$_3$)$_3$), 41.7 (N**C**H$_2$), 54.3 (OCH$_2$**C**H), 58.1 (O**C**H$_3$), 72.0 (O**C**H$_2$CH), 78.2 (**C**(CH$_3$)$_3$), 119.1, 119.6 (Ar**C**), 120.1 (d, *J* = 254.9 Hz, O**C**F$_3$), 125.7, 126.7, 127.7, 130.8, 136.8, 139.5, 142.3, 149.0 (Ar**C**), 155.2 (N**C**(O)O), 170.1 (**C**(O)); LRMS (ESI$^+$) 491.1 [M + Na]$^+$ (calcd for $C_{23}H_{27}F_3N_2O_5Na^+$ 491.2); Anal. Calcd. for $C_{23}H_{27}F_3N_2O_5$: C, 58.97; H, 5.81; F, 12.17; N, 5.98. Found: C, 59.05; H, 5.97; F, 12.06; N, 5.92.

Preparation of (*R*)-*N*-(4”-Trifluoromethoxybiphenyl-4’-yl)methyl 2-*N*-(*tert.*-Butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-64). Using Method E, (*R*)-**54** (0.93 g, 2.1 mmol), Ag_2O (2.37 g, 10.2 mmol) and CH_3I (1.28 mL, 20.5 mmol) gave (*R*)-**64** as a white solid (0.88 g, 91%): R_f = 0.40 (hexanes/EtOAc 1/1); mp 131-132 °C; $[\alpha]^{26}_D$ –16.7° (*c* 0.9, $CHCl_3$); IR (nujol) 3332, 2924, 2858, 2657, 1532, 1458, 1378, 1260, 1151, 1047, 953, 839, 677 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ1.44 (s, (C**H**$_3$)$_3$), 3.39 (s, OC**H**$_3$), 3.52 (dd, *J* = 6.0, 9.2 Hz, C**H**H’OCH$_3$), 3.92 (dd, *J* = 4.0, 9.2 Hz, CH**H’**OCH$_3$), 4.25–4.32 (br m, C**H**), 4.48-4.58 (br m, C**H**$_2$N), 5.36–5.44 (br d, N**H**CH), 6.76–6.81 (m, N**H**CH$_2$), 7.28 (d, *J* = 8.0 Hz, 2 Ar**H**), 7.35 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.50–7.59 (m, 4 Ar**H**); ^{13}C NMR (DMSO-d_6) δ28.1 ((**C**H$_3$)$_3$), 41.7 (N**C**H$_2$), 54.3 (OCH$_2$**C**H), 58.1 (O**C**H$_3$), 72.0 (O**C**H$_2$CH), 78.2 (**C**(CH$_3$)$_3$), 120.1 (d, *J* = 254.9 Hz, O**C**F$_3$), 121.4, 126.6, 127.6, 128.4, 137.2, 139.1, 139.3, 147.7 (Ar**C**), 155.2 (N**C**(O)O), 170.1 (**C**(O)); LRMS (ESI$^+$) 601.1 [M + Cs]$^+$ (calcd for $C_{23}H_{27}F_3N_2O_5Cs^+$ 601.1); Anal. Calcd. for $C_{23}H_{27}F_3N_2O_5$: C, 58.97; H, 5.81; F, 12.17; N, 5.98. Found: C, 58.92; H, 5.93; F, 11.98; N, 5.95.

Preparation of (*R*)-*N*-(3"-Acetylaminobiphenyl-4'-yl)methyl 2-*N*-(*tert.*-Butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-65). Using Method E and the workup conditions for (*R*)-**61**, (*R*)-**55** (4.00 g, 9.36 mmol), acetonitrile (200 mL), DMF (10 mL), Ag_2O (10.80 g, 46.8 mmol), and CH_3I (13.28 g, 93.6 mmol) gave the desired product (*R*)-**65** (1.80 g, 44%) as a colorless oil: R_f = 0.28 (CH_2Cl_2/CH_3OH 20/1); $[\alpha]^{25}_D$ +21.9 **°** (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ1.43 (s, (C**H$_3$**)$_3$CO), 2.19 (s, C**H$_3$**CO), 3.38 (s, OC**H$_3$**), 3.48-3.54 (m, C**H**H'OCH$_3$), 3.80-3.87 (m, CH**H'**OCH$_3$), 4.23-4.29 (br s, C**H**), 4.47-4.54 (br s, C**H**$_2$N), 5.40-5.44 (br s, N(**H**)CH), 6.77-6.81 (br s, N(**H**)CH$_2$), 7.24-7.38 (m, 4 Ar**H**), 7.42-7.54 (m, 3 Ar**H**, ArN**H**C(O)), 7.71 (s, Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of the product gave only one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ24.9 (**C**H$_3$CO), 28.5 (C(**C**H$_3$)$_3$), 43.4 (N**C**H$_2$), 54.3 (**C**H), 59.3 (O**C**H$_3$), 72.3 (O**C**H$_2$), 118.7, 119.0, 123.2, 127.6, 128.1, 129.6, 137.5, 138.6, 140.1, 141.8, (10 Ar**C**), 155.8 (NH**C**(O)O), 168.6, 170.6 (2 **C**(O)), the *t*-butyl carbon resonance was not detected and is believed to be overlap with the nearby solvent resonance; LRMS (ESI$^+$) 442.2 [M + H]$^+$ (calcd for $C_{24}H_{32}N_3O_5^+$ 442.2); HRMS (ESI$^+$) 442.2345 [M + H]$^+$ (calcd for $C_{24}H_{32}N_3O_5^+$ 442.2342).

Preparation of (*R*)-*N*-(3"-*tert.*-Butoxymethylbiphenyl-4'-yl)methyl 2-Acetamido-3-methoxypropionamide ((*R*)-73). Using Method E and the workup conditions for (*R*)-**61**, (*R*)-**71** (1.03 g, 2.6 mmol), acetonitrile (30 mL), DMF (3 mL), Ag_2O (2.99 g, 12.9 mmol), CH_3I (3.67 g, 25.8 mmol) gave the desired product (*R*)-**73** (0.65 g, 61%) as a white solid: R_f = 0.31 (EtOAc/hexanes 1/1); mp 139-140 °C; $[\alpha]^{23}_D$ - 21.7 ° (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ1.31 (s, (C**H$_3$**)$_3$CO), 2.01 (C**H$_3$**C(O)), 3.37 (s, OC**H$_3$**), 3.46-3.51 (m, C**H**H'OCH$_3$), 3.76-3.80 (m, CH**H'**OCH$_3$), 4.45-4.55 (m, ArC**H$_2$**O, C**H**$_2$N), 4.60-4.64 (m, C**H**), 6.72-6.74 (br d, N(**H**)CH), 7.08-7.12 (br t, N(**H**)CH$_2$), 7.29-7.50 (m, 5 Ar**H**), 7.52-7.57 (m, 3 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to

a $CDCl_3$ solution of (*R*)-**73** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ23.3 (**C**H_3C(O)), 27.9 (C(**C**H_3)$_3$), 43.4 (N**C**H_2), 52.8 (**C**H), 59.3 (O**C**H_3), 64.3 (Ar**C**H_2O), 72.0 (O**C**H_2), 73.9 (**C**$(CH_3)_3$), 126.1, 126.3, 126.7, 127.6, 128.0, 128.9, 137.0, 140.6, 140.7, 140.8 (10 Ar**C**), 170.2, 170.7 (2 **C**(O)NH); LRMS (ESI^+) 413.2 $[M + H]^+$ (calcd for $C_{24}H_{32}N_2O_4H^+$ 413.2); HRMS (ESI^+) 413.2442 $[M + H]^+$ (calcd for $C_{24}H_{32}N_2O_4H^+$ 413.2440).

Preparation of (*R*)-*N*-(3"-*tert.*-Butoxycarbonylbiphenyl-4'-yl)methyl 2-Acetamido-3-methoxypropionamide ((*R*)-74). Using Method E and the workup conditions for (*R*)-**61**, *(R)*-**72** (0.90 g, 2.2 mmol), acetonitrile (50 mL), DMF (5 mL), Ag_2O (2.53 g, 10.9 mmol), and CH_3I (3.10 g, 21.8 mmol) gave the desired product (*R*)-**74** (0.31 g, 33%) as a white solid: R_f = 0.39 (EtOAc/hexanes 1/1); mp 166-168 °C; $[\alpha]^{22.5}_D$ +11.8 ° (c 1.0, CH_3OH); ^1H NMR ($CDCl_3$) δ1.61 (s, (C**H$_3$**)$_3$CO), 2.05 (s, C**H$_3$**C(O)), 3.39 (s, OC**H$_3$**), 3.45-3.50 (m, C**H**H'OCH_3), 3.80-3.84 (m, CH**H'**OCH_3), 4.51-4.54 (m, C**H**$_2$N), 4.55-4.61 (br s, C**H**), 6.54-6.58 (br s, N(**H**)CH), 6.91-6.95 (br s, N(**H**)CH_2), 7.35 (d, *J* = 7.8 Hz, 2 Ar**H**), 7.47-7.49 (br t, Ar**H**), 7.57-7.59 (d, *J* = 7.8 Hz, 2 Ar**H**), 7.72-7.74 (m, Ar**H**), 7.95-7.77 (m, Ar**H**), 8.19 (s, Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-**73** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ23.4 (**C**H_3C(O)), 28.4 (C(**C**H_3)$_3$), 43.5 (N**C**H_2), 52.8 (**C**H), 59.4 (O**C**H_3), 71.8 (O**C**H_2), 81.4 (**C**$(CH_3)_3$), 127.7, 128.2, 128.3, 128.5, 128.9, 131.2, 132.8, 137.5, 139.8, 141.0 (10 Ar**C**), 165.9 (Ar**C**(O)O), 170.3, 170.7 (2 **C**(O)NH); LRMS (ESI^+) 427.2 $[M +H]^+$ (calcd for $C_{24}H_{30}N_2O_5H^+$ 427.2); HRMS (ESI^+) 427.2237 $[M + H]^+$ (calcd for $C_{24}H_{30}N_2O_5H^+$ 427.2233).

Preparation of (*R*)-*N*-(3"-*tert.*-Butoxycarbonylaminobiphenyl-4'-yl)methyl 2-Acetamido-3-methoxypropionamide ((*R*)-75).[1] To a cooled THF solution (–78 °C, dry ice acetone bath) of (*R*)-

70[2] (0.18 g, 1.1 mmol) were successively added *N*-methylmorpholine (NMM) (0.18 mL, 1.6 mmol), stirred for 2 min, isobutylchloroformate (IBCF) (0.18 mL, 1.4 mmol), stirred for 5 min, and then **39** (0.39 g, 1.3 mmol, prepared by Method C from **39·HCl**). Upon addition the reaction mixture was allowed to warm to room temperature and further stirred (2–3 h). The salts were filtered and rinsed with THF and the filtrate was concentrated in vacuo. The residue obtained was purified by column chromatography on SiO_2 to give (*R*)-**75** as a white solid (0.34 g, 70%): R_f = 0.45 (MeOH/$CHCl_3$ 1/15); mp 187-188 °C; $[\alpha]^{26}_D$ –12.7° (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ1.53 (s, (C**H**$_3$)$_3$), 2.04 (s, C(O)C**H**$_3$), 3.40 (s, OC**H**$_3$), 3.45 (dd, *J* = 7.6, 9.2 Hz, C**H**H'OCH$_3$), 3.82 (dd, *J* = 4.0, 9.2 Hz, CH**H'**OCH$_3$), 4.45–4.58 (m, C**H**$_2$N, C**H**), 6.44 (d, *J* = 6.4, N**H**CH), 6.55 (s, N**H**-*t*Boc), 6.76–6.79 (br t, N**H**CH$_2$), 7.23 (d, *J* = 8.6 Hz, 2 Ar**H**), 7.42 (d, *J* = 8.6 Hz, 2 Ar**H**), 7.49–7.53 (m, 4 Ar**H**); ^{13}C NMR (DMSO-d_6) δ22.5 (C(O)**C**H$_3$), 28.1 ((**C**H$_3$)$_3$), 41.7 (N**C**H$_2$), 52.6 (O**C**H$_3$), 58.2 (OCH$_2$**C**H), 72.1 (O**C**H$_2$CH), 79.1 (**C**(CH$_3$)$_3$), 118.4, 125.9, 126.7, 127.5, 133.5, 137.9, 138.2, 138.9 (Ar**C**), 152.7 (N**C**(O)O), 169.5, 169.8 (2 **C**(O)); HRMS (ESI$^+$) 574.1320 [M + Cs]$^+$ (calcd for $C_{24}H_{31}N_3O_5Cs^+$ 574.1318).

Preparation of (*R*)-*N*-(4"-Fluorobiphenyl-4'-yl)methyl 2-Acetamido-3-methoxypropionamide ((*R*)-4). Using Method F, (*R*)-**56** (3.17 g, 7.9 mmol) and 4 M HCl (6.90 mL, 27.6 mmol), followed by Et_3N (2.42 mL, 17.3 mmol) and AcCl (0.61 mL, 8.7 mmol) gave (*R*)-**4** as a white solid (2.50 g, 92%): R_f = 0.40 (MeOH/CH_2Cl_2 1/20); mp 189-190 °C; $[\alpha]^{26}_D$ –17.8° (*c* 1.0, $CHCl_3$); IR (nujol) 3295, 2922, 2860, 1634, 1550, 1460, 1372, 1314, 1222, 1101, 916, 823, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.04 (s, C(O)C**H**$_3$), 3.40 (s, OC**H**$_3$), 3.44–3.48 (m, C**H**H'OCH$_3$), 3.83 (dd, *J* = 3.9, 9.0 Hz, CH**H'**OCH$_3$), 4.45–4.59 (m, C**H**$_2$N, C**H**), 6.43–5.46 (br d, N**H**CH), 6.81–6.85 (m, N**H**CH$_2$), 7.12 (t, *J* = 8.6 Hz, 2 Ar**H**), 7.32 (d, *J* = 7.6 Hz, 2 Ar**H**), 7.49–7.54 (m, 4 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to

a $CDCl_3$ solution of (*R*)-**4** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR (DMSO-d_6) δ22.6 (C(O)**C**H_3), 41.8 (N**C**H_2), 52.7 (OCH_2**C**H), 58.2 (O**C**H_3), 72.1 (O**C**H_2CH), 115.7 (d, *J* = 21.3 Hz, $\mathbf{C}_{3''}$, $\mathbf{C}_{5''}$), 126.5 (Ar**C**), 127.6 (Ar**C**), 128.5 (d, *J* = 8.0 Hz, $\mathbf{C}_{2''}$, $\mathbf{C}_{6''}$), 136.4 (d, *J* = 2.9 Hz, $\mathbf{C}_{1''}$), 137.6 (Ar**C**), 138.6 (Ar**C**), 161.8 (d, *J* = 242.4 Hz, $\mathbf{C}_{4''}$), 169.5, 169.8 (2 **C**(O)); LRMS (ESI^+) 367.1 $[M + Na]^+$ (calcd for $C_{19}H_{21}FN_2O_3Na^+$ 367.1); Anal. Calcd. for $C_{19}H_{21}FN_2O_3$: C, 66.26; H, 6.15; F, 5.52; N, 8.13. Found: C, 65.97; H, 6.18; F, 5.35; N, 8.11.

Preparation of (*R*)-*N*-(3”-Chlorobiphenyl-4’-yl)methyl 2-Acetamido-3-methoxypropionamide ((*R*)-5). Using Method F, (*R*)-**57** (4.00 g, 9.6 mmol) and 4 M HCl (8.36 mL, 33.4 mmol), followed by Et_3N (2.93 mL, 21.0 mmol) and AcCl (0.74 mL, 10.5 mmol) gave (*R*)-**5** as a white solid (2.85 g, 83%): R_f = 0.40 (MeOH/CH_2Cl_2 1/20); mp 172-173 °C; $[\alpha]^{26}_D$ −15.8° (*c* 1.1, $CHCl_3$); IR (nujol) 3286, 3071, 2950, 2879, 1637, 1549, 1458, 1383, 1307, 1247, 1132, 784, 717, 609 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ2.00 (s, C(O)C**H**$_3$), 3.37 (s, OC**H**$_3$), 3.49 (dd, *J* = 7.0, 9.0 Hz, C**H**H’OCH_3), 3.78 (dd, *J* = 4.0, 9.0 Hz, CH**H’**OCH_3), 4.43 (1/2**H**H’$_q$, *J* = 5.8, 15.0 Hz, C**H**H’Ar), 4.49 (1/2H**H’**$_q$, *J* = 5.8, 15.0 Hz, CH**H’**Ar), 4.62–4.67 (m, C**H**), 6.71 (d, *J* = 6.8 Hz, N**H**CH), 7.15–7.18 (m, N**H**CH_2), 7.30–7.52 (m, 8 Ar**H**), addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**5** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ23.3 (C(O)**C**H_3), 43.3 (N**C**H_2), 52.7 (OCH_2**C**H), 59.2 (O**C**H_3), 72.1 (O**C**H_2CH), 125.3, 127.3, 127.5, 128.1, 130.2, 134.8, 137.9, 139.1, 142.6 (Ar**C**), 170.3, 170.6 (2 **C**(O)), the remaining aromatic peak was not detected and is believed to overlap with the observed signals; LRMS (ESI^+) 383.1 $[M + Na]^+$ (calcd for $C_{19}H_{21}ClN_2O_3Na^+$ 383.1); Anal. Calcd. for $C_{19}H_{21}ClN_2O_3$: C, 63.24; H, 5.87; Cl, 9.83; N, 7.76. Found: C, 63.29; H, 6.01; Cl, 9.71; N, 7.77.

Preparation of (*R*)-*N*-(4”-Chlorobiphenyl-4’-yl)methyl 2-Acetamido-3-methoxypropionamide ((*R*)-6). Using Method F, (*R*)-**58** (2.80 g, 6.7 mmol) and 4 M HCl (6.70 mL, 26.7 mmol), followed by Et_3N (2.10 mL, 14.7 mmol) and AcCl (0.52 mL, 7.4 mmol) gave (*R*)-**6** as a white solid (1.83 g, 76%): R_f = 0.40 (MeOH/CH_2Cl_2 1/20); mp 215-216 °C; $[\alpha]^{26}_D$ −16.9° (*c* 1.1, $CHCl_3$); IR (nujol) 3288, 2926, 2858, 1634, 1544, 1459, 1375, 1311, 1198, 1102, 918, 811, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.03 (s, C(O)C**H**$_3$), 3.39 (s, OC**H**$_3$), 3.44–3.48 (m, C**H**H’OCH_3), 3.82 (dd, *J* = 4.0, 9.2 Hz, CH**H’**OCH_3), 4.45–4.61 (m, C**H**$_2$N, C**H**), 6.45–6.49 (br d, N**H**CH), 6.86–6.91(m, N**H**CH_2), 7.32 (d, *J* = 8.0 Hz, 2 Ar**H**), 7.39 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.48–7.52 (m, 4 Ar**H**), addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**6** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ23.4 (C(O)**C**H_3), 43.4 (N**C**H_2), 52.7 (OCH_2**C**H), 59.3 (O**C**H_3), 71.9 (O**C**H_2CH), 127.5, 128.2, 128.5, 129.2, 133.7, 137.5, 139.3, 139.4 (Ar**C**), 170.3, 170.5 (2 **C**(O)); LRMS (ESI^+) 361.2 $[M + H]^+$ (calcd for $C_{19}H_{21}ClN_2O_3H^+$ 361.2); Anal. Calcd. for $C_{19}H_{21}ClN_2O_3$: C, 63.24; H, 5.87; Cl, 9.83; N, 7.76. Found: C, 63.00; H, 6.02; Cl, 9.58; N, 7.69.

Preparation of (*R*)-*N*-(3”-Bromo-4-biphenylmethyl) 2-Acetamido-3-methoxypropionamide ((*R*)-7). Using Method F, 4 M HCl in dioxane (3.5 mL), (*R*)-**59**, (1.30 g, 2.8 mmol), Et_3N (862 mg, 8.5 mmol), and AcCl (268 mg, 3.4 mmol) gave compound (*R*)-**7** as a white solid (620 mg, 54%): R_f = 0.44 (1:20 MeOH/CH_2Cl_2); mp 171–173 °C; $[\alpha]^{26}_D$ –17.3° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ2.00 (s, (C**H**$_3$C(O)), 3.37 (s, OC**H**$_3$), 3.45–3.49 (m, C**H**H’OCH_3), 3.79 (dd, *J* = 4.0, 9.0 Hz, CH**H**’OCH_3), 4.40–4.55 (m, NHC**H**$_2$), 4.56–4.66 (m, C**H**CH_2), 6.60 (d, *J* = 6.4 Hz, N**H**CH), 6.98–7.08 (br s, N**H**CH_2), 7.24–7.35 (m, 3 Ar**H**), 7.39–7.56 (m, 4 Ar**H**), 7.68 (s, Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-**7** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ23.1 (C(O)**C**H_3), 43.1 (NH**C**H_2), 52.5

(**C**HCH$_2$), 59.1 (O**C**H$_3$), 71.8 (CH**C**H$_2$), 122.9, 125.6, 127.3, 127.9, 130.0, 130.2, 130.3, 137.6, 138.8, 142.7 (Ar**C**), 170.1, 170.3 (2 **C**(O)); LRMS (ESI$^+$) 405.0 [M + H]$^+$ (100%), 407.0 [M + 2 + H]$^+$ (100%); HRMS (ESI$^+$) 405.0814 [M + H]$^+$ (calcd for $C_{19}H_{21}{}^{79}BrN_2O_3H^+$ 405.0814). Anal. Calcd. for $C_{19}H_{21}BrN_2O_3$: C, 56.31; H, 5.22; Br, 19.72; N, 6.91. Found: C, 56.58; H, 5.14; Br, 19.45; N, 6.90.

Preparation of (*R*)-*N*-(3"-Iodo-4-biphenylmethyl) 2-Acetamido-3-methoxypropionamide ((*R*)-8). Using Method F, 4 M HCl in dioxane (2.0 mL), (*R*)-**60,** (670 mg, 1.3 mmol), Et$_3$N (515 mg, 3.9 mmol), and AcCl (123 mg, 1.6 mmol) gave compound (*R*)-**8** as a white solid (515 mg, 87%): R_f = 0.41 (1:20 MeOH/CH_2Cl_2); mp 161–163 ^{o}C; $[\alpha]^{26}_D$ –11.0^o (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ2.05 (s, C**H**$_3$C(O)), 3.41 (s, OC**H**$_3$), 3.43–3.50 (m, C**H**H'OCH$_3$), 3.84 (dd, *J* = 4.3, 9.3 Hz, CH**H'**OCH$_3$), 4.46–4.55 (m, NHC**H**$_2$), 4.57–4.60 (m, C**H**CH$_2$), 6.45 (d, *J* = 6.8 Hz, N**H**CH), 6.83 (t, *J* = 4.8 Hz, N**H**CH$_2$), 7.17 (t, *J* = 7.8 Hz, Ar**H**), 7.34 (d, *J* = 8.2 Hz, 2 Ar**H**), 7.48–7.55 (m, 3 Ar**H**), 7.68 (d, *J* = 7.8 Hz, Ar**H**), 7.92 (s, Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-**8** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ23.2 (C(O)**C**H$_3$), 43.2 (NH**C**H$_2$), 52.4 (**C**HCH$_2$), 59.1 (O**C**H$_3$), 71.6 (CH**C**H$_2$), 94.8, 126.3, 127.4, 127.9, 130.4, 136.0, 136.2, 137.6, 138.9, 142.9 (Ar**C**), 170.0, 170.3 (2 **C**(O)); HRMS (ESI$^+$) 453.0675 [M + H]$^+$ (calcd for $C_{19}H_{21}IN_2O_3H^+$ 453.0673). Anal. Calcd. for $C_{19}H_{21}IN_2O_3$: C, 50.46; H, 4.68; I, 28.06; N, 6.19. Found: C, 50.42; H, 4.64; I, 27.76; N, 6.19.

Preparation of (*R*)-*N*-(3"-Cyanobiphenyl-4'-yl)methyl 2-Acetamido-3-methoxypropionamide ((*R*)-9). Using Method F, (*R*)-**61** (3.10 g, 7.6 mmol) and 4 M HCl (9.5 mL, 38.0 mmol), followed by Et$_3$N (2.30 g, 22.7 mmol) and AcCl (0.71 g, 9.1 mmol) gave the desired product **(***R*)-**9** (2.00 g, 75%) as a white solid: R_f = 0.42 (CH_2Cl_2/CH_3OH 19/1); mp 122-123 °C; $[\alpha]^{24.5}_D$ -16.0 ° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ2.03 (s, C**H$_3$**C(O)), 3.40 (s, OC**H$_3$**), 3.47-3.52 (m, C**H**H'OCH$_3$), 3.79-3.84

(m, CH**H'**OCH_3), 4.48-4.54 (m, C**H**$_2$N), 4.59-4.63 (m, C**H**), 6.56-6.59 (br d, N**H**CH_2), 7.03-7.07 (br t, N**H**C(O)), 7.36 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.48-7.64 (m, 4 Ar**H**), 7.76-7.82 (m, 2 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-**9** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ23.4 (**C**H_3CO), 43.3 (N**C**H_2), 52.7 (**C**H), 59.3 (O**C**H_3), 71.9 (O**C**H_2), 113.2 (Ar**C**), 119.0 (**C**N), 127.5, 128.3, 129.8, 130.8, 130.9, 131.6, 138.2, 138.5, 142.9 (9 Ar**C**), 170.4, 170.6 (2 **C**(O)); LRMS (ESI$^+$) 352.2 $[M + H]^+$ (calcd for $C_{20}H_{22}N_3O_3^+$ 352.2); HRMS (ESI$^+$) 352.1660 $[M + H]^+$ (calcd for $C_{20}H_{22}N_3O_3^+$ 352.1661); Anal. Calcd. for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.96. Found: C, 68.06; H, 6.04; N, 11.76.

Preparation of (*R*)-*N*-(3"-Trifluoromethyl)-4-biphenylmethyl 2-Acetamido-3-methoxypropionamide ((*R*)-10). Using Method F, (*R*)**-62,** (1.34 g, 3.0 mmol), Et_3N (896 mg, 8.9 mmol), 4 M HCl in dioxane (3.0 mL, 12.0 mmol), and AcCl (348 g, 4.4 mmol) gave compound (*R*)**-10** as a white solid (1.02 g, 88%): R_f = 0.42 (1:20 MeOH/CH_2Cl_2); mp 161–162 ^{o}C; $[\alpha]^{24}_D$ – 13.7^o (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ2.03 (s, C**H**$_3$C(O)), 3.40 (s, OC**H**$_3$), 3.49 (dd, *J* = 4.3, 9.3 Hz, C**H**H'OCH_3), 3.81 (dd, *J* = 4.3, 9.3 Hz, C**H**H'OCH_3), 4.45–4.58 (m, NHC**H**$_2$) 4.61–4.64 (m, C**H**CH_2), 6.58 (d, *J* = 7.0 Hz, N**H**CH), 7.04 (t, *J* = 5.3 Hz, N**H**CH_2), 7.36 (d, *J* = 8.2 Hz, 2 Ar**H**), 7.51–7.62 (m, 4 Ar**H**), 7.73 (d, *J* = 7.4 Hz, Ar**H**), 7.80 (s, Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)**-10** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ23.1 (C(O)**C**H_3), 43.1 (NH**C**H_2), 52.5 (**C**HCH_2), 59.1 (O**C**H_3), 71.7 (CH**C**H_2), 123.7 (q, *J* = 4.0 Hz), 124.0 (q, *J* = 4.0 Hz), 124.1 (q, *J* = 272.0 Hz, **C**F_3), 127.4, 126.0, 129.2, 130.2 (Ar**C**), 131.2 (q, *J* = 32.0 Hz), 137.9, 138.9, 141.4 (Ar**C**), 170.1, 170.4 (2 **C**(O)); MS (ESI$^+$) 395.2 $[M + H]^+$ (calcd for $C_{20}H_{22}F_3N_2O_3^+$ 395.2); HRMS (ESI$^+$) 395.1583 $[M + H]^+$ (calcd for

$C_{20}H_{22}F_3N_2O_3^+$ 395.1582); Anal. Calcd. for $C_{20}H_{21}F_3N_2O_3$: C, 60.91; H, 5.37; F, 14.45; N, 7.10. Found: C, 61.02; H, 5.33; F, 14.41; N, 7.17.

Preparation of (*R*)-*N*-(3"-Trifluoromethoxybiphenyl-4'-yl)methyl 2-Acetamido-3-methoxypropionamide ((*R*)-11). Using Method F, (*R*)-**63** (2.14 g, 4.6 mmol) and 4 M HCl (4.00 mL, 16.0 mmol), followed by Et_3N (1.40 mL, 10.1 mmol) and AcCl (0.36 mL, 5.0 mmol) gave (*R*)-**11** as a white solid (1.69 g, 90%): R_f = 0.40 (MeOH/CH_2Cl_2 1/20); mp 139-140 °C; $[\alpha]^{26}_D$ –13.5° (*c* 1.3, $CHCl_3$); IR (nujol) 3274, 3071, 2951, 2857, 1639, 1557, 1458, 1378, 1291, 1153, 1048, 975, 785, 720, 604 cm^{-1}; ^1H NMR ($CDCl_3$) δ2.03 (s, C(O)C**H**$_3$), 3.40 (s, OC**H**$_3$), 3.47 (dd, *J* = 7.4, 9.2 Hz, C**H**H'OCH_3), 3.82 (dd, *J* = 4.0, 9.2 Hz, CH**H'**OCH_3), 4.46–4.61 (m, C**H**$_2$N, C**H**), 6.49 (d, *J* = 6.4 Hz, N**H**CH), 6.89–6.93 (m, N**H**CH_2), 7.18–7.21 (m, 1 Ar**H**), 7.33–7.54 (m, 7 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-**11** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR (DMSO-d_6) δ22.5 (C(O)**C**H_3), 41.7 (N**C**H_2), 52.7 (OCH_2**C**H), 58.2 (O**C**H_3), 72.1 (O**C**H_2CH), 119.1, 119.6 (Ar**C**), 120.1 (q, *J* = 254.9 Hz, O**C**F_3), 125.7, 126.7, 127.7, 130.8, 136.8, 139.5, 142.3, 149.0 (Ar**C**), 169.4, 169.8 (2 **C**(O)); LRMS (ESI^+) 433.1 $[M + Na]^+$ (calcd for $C_{20}H_{21}F_3N_2O_4Na^+$ 433.1); Anal. Calcd. for $C_{20}H_{21}F_3N_2O_4$: C, 58.53; H, 5.16; F, 13.89; N, 6.83. Found: C, 58.56; H, 5.28; F, 13.81; N, 6.80.

Preparation of (*R*)-*N*-(4"-Trifluoromethoxybiphenyl-4'-yl)methyl 2-Acetamido-3-methoxypropionamide ((*R*)-12). Using Method F, (*R*)-**64** (0.81 g, 1.7 mmol) and 4 M HCl (1.49 mL, 6.0 mmol), followed by Et_3N (0.53 mL, 3.8 mmol) and AcCl (0.13 mL, 1.9 mmol) gave (*R*)-**12** as a white solid (0.59 g, 84%): R_f = 0.40 (MeOH/CH_2Cl_2 1/20); mp 194-195 °C; $[\alpha]^{26}_D$ –14.3° (*c* 0.9, $CHCl_3$); IR (nujol) 3294, 3093, 2924, 2858, 1640, 1557, 1458, 1382, 1279, 1215, 1165, 814, 697, 612 cm^{-1}; ^1H NMR ($CDCl_3$) δ2.02 (s, C(O)C**H**$_3$), 3.39 (s, OC**H**$_3$), 3.48 (dd, *J* = 7.4, 9.2 Hz,

C**H**H'OCH_3), 3.81 (dd, *J* = 4.0, 9.2 Hz, CH**H'**OCH_3), 4.45–4.55 (m, C$\mathbf{H}_2$N), 4.58–4.63 (m, C**H**), 6.56 (d, *J* = 6.4 Hz, N**H**CH), 6.98–7.01 (m, N**H**CH_2), 7.27 (d, *J* = 8.0 Hz, 2 Ar**H**), 7.33 (d, *J* = 8.0 Hz, 2 Ar**H**), 7.49–7.58 (m, 4 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-**12** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR (DMSO-d_6) δ22.5 (C(O)**C**H_3), 41.7 (N**C**H_2), 52.7 (OCH_2**C**H), 58.2 (O**C**H_3), 72.1 (O**C**H_2CH), 120.1 (q, *J* = 254.9 Hz, O**C**F_3), 121.4, 126.6, 127.7, 128.4, 137.1, 139.1, 139.3, 147.7 (Ar**C**), 169.4, 169.8 (2 **C**(O)); LRMS (ESI$^+$) 433.1 $[M + Na]^+$ (calcd for $C_{20}H_{21}F_3N_2O_4Na^+$ 433.1); Anal. Calcd. for $C_{20}H_{21}F_3N_2O_4$: C, 58.53; H, 5.16; F, 13.89; N, 6.83. Found: C, 58.50; H, 5.27; F, 13.91; N, 6.82.

Preparation of (*R*)-*N*-(3"-Acetylaminobiphenyl-4'-yl)methyl 2-Acetamido-3-methoxypropionamide ((*R*)-13). Using Method F, (*R*)-**65** (1.80 g, 4.1 mmol) and 4 M HCl (3.1 mL, 12.4 mmol), followed by Et_3N (1.24 g, 12.2 mmol) and AcCl (0.38 g, 4.9 mmol) gave the desired product (*R*)-**13** (1.05 g, 71%) as a white powder: R_f = 0.20 (CH_2Cl_2/CH_3OH 19/1); mp 150-151 °C; $[\alpha]^{24.5}_D$ +11.1 ° (*c* 1.0, CH_3OH); ^{1}H NMR ($CDCl_3$/CD_3OD) δ2.04 (s, C$\mathbf{H_3}$C(O)), 2.16 (s, C$\mathbf{H_3}$C(O)), 3.47 (s, OC$\mathbf{H_3}$), 3.52-3.57 (m, C**H**H'OCH_3), 3.68-3.73 (m, CH**H'**OCH_3), 4.40-4.52 (m, C$\mathbf{H}_2$N), 4.54-4.60 (m, C**H**), 7.29-7.40 (m, 4 Ar**H**), 7.50-7.56 (m, 3 Ar**H**), 7.76 (s, Ar**H**); ^{13}C NMR ($CDCl_3$/CD_3OD) δ22.8, 23.9 (2 **C**H_3CO), 43.1 (N**C**H_2), 53.1 (**C**H), 59.1 (O**C**H_3), 72.0 (O**C**H_2), 118.6, 119.0, 122.8, 127.4, 127.9, 129.3, 137.1, 138.8, 140.3, 141.5, (10 Ar**C**), 170.4, 171.5 (2 **C**(O)), one carbonyl resonance was not detected and believed to be overlapped with an adjacent peak; LRMS (ESI$^+$) 384.2 $[M + H]^+$ (calcd for $C_{21}H_{26}N_3O_3^+$ 384.2); HRMS (ESI$^+$) 384.1924 $[M + H]^+$ (calcd for $C_{21}H_{26}N_3O_3^+$ 384.1923).

Preparation of (*R*)-*N*-(3"-Hydroxymethylbiphenyl-4'-yl)methyl 2-Acetamido-3-methoxypropionamide ((*R*)-14). To a solution of (*R*)-**73** (0.65 g, 1.6 mmol) in CH_2Cl_2 (16 mL) was added 4 M HCl in dioxane (1.5 mL, 6.0 mmol) and stirred at room temperature (4 h). The reaction mixture was evaporated in vacuo and recrystallized (CH_3OH/EtOAc/hexanes) to give the desired product (*R*)-**14** (0.51 g, 90%) as a white solid: R_f = 0.48 (CH_2Cl_2/CH_3OH 9/1); mp 152-153 °C; $[\alpha]^{22.5}_D$ +12.7 ° (*c* 1.0, CH_3OH); ^{1}H NMR ($CDCl_3$/CD_3OD) δ2.00 (s, C**H$_3$**C(O)), 3.34 (s, OC**H$_3$**), 3.45-3.49 (m, C**H**H'OCH_3), 3.67-3.72 (m, CH**H'**OCH_3), 4.42-4.46 (m, C**H$_2$**N), 4.51-4.55 (m, C**H**), 4.69 (s, C**H$_2$**OH), 7.27-7.31 (m, 3 Ar**H**), 7.35-7.41 (m, Ar**H**), 7.44-7.46 (m, Ar**H**), 7.50-7.54 (m, 3 Ar**H**); ^{13}C NMR ($CDCl_3$/CD_3OD) δ23.1 (**C**H_3C(O)), 43.3 (N**C**H_2), 52.9 (**C**H), 59.3 (O**C**H_3), 65.0 (Ar**C**H_2OH), 72.0 (CH_3O**C**H_2), 125.7, 126.1, 126.3, 127.5, 128.0, 129.1, 137.1, 140.4, 141.0, 141.8 (10 Ar**C**), 170.3, 171.2 (2 **C**(O)NH); LRMS (ESI^+) 357.1 $[M + H]^+$ (calcd for $C_{20}H_{24}N_2O_4H^+$ 357.2); Anal. Calcd. for $C_{20}H_{24}N_2O_4$: C, 67.40; H, 6.79; N, 7.86. Found: C, 67.32; H, 6.98; N, 7.74.

Preparation of (*R*)-*N*-(3"-Carboxybiphenyl-4'-yl)methyl 2-Acetamido-3-methoxypropionamide ((*R*)-15). Using the previous procedure, (*R*)-**74** (0.31 g, 0.7 mmol) and 4 M HCl (0.8 mL, 3.2 mmol) gave the desired product (*R*)-**15** (0.21 g, 82%) as a white solid: R_f = 0.56 (CH_2Cl_2/CH_3OH 9/1); mp 196-197 °C; $[\alpha]^{23}_D$ +9.6 ° (*c* 1.0, CH_3OH); ^{1}H NMR ($CDCl_3$/CD_3OD) δ1.99 (s, C**H$_3$**C(O)), 3.46-3.50 (m, C**H**H'OCH_3), 3.63-3.66 (m, CH**H'**OCH_3), 4.39 (dd, *J* = 5.8, 14.0 Hz, C**H**H'N), 4.46 (dd, *J* = 5.8, 14.0 Hz, CH**H'**N), 4.50-4.55 (br t, C**H**), 6.78-6.84 (m, N(**H**)CH_2), 7.16-7.21 (m, Ar**H**), 7.28-7.56 (m, N(**H**)C(O), 7 Ar**H**), the methoxy proton resonance was not detected and believed to be overlapped with the adjacent peak near δ 3.40; ^{13}C NMR ($CDCl_3$/CD_3OD) δ22.8 (**C**H_3C(O)), 43.1 (N**C**H_2), 52.9 (**C**H), 59.1 (O**C**H_3), 72.1 (O**C**H_2), 127.4, 128.0, 128.4, 128.8, 128.9, 131.0, 131.5, 137.5, 139.4, 141.0 (10 Ar**C**), 168.9 (Ar**C**(O)), 170.4, 171.5 (2 **C**(O)NH); LRMS (ESI^+) 371.2 [M +

H]$^+$ (calcd for $C_{20}H_{22}N_2O_5H^+$ 371.2); HRMS (ESI$^+$) 371.1607 [M + H]$^+$ (calcd for $C_{20}H_{22}N_2O_5H^+$ 371.1607); Anal. Calcd. for $C_{20}H_{22}N_2O_5 \cdot 0.13H_2O$: C, 64.45; H, 6.02; N, 7.52. Found: C, 64.06; H, 6.09; N, 7.35.

Preparation of (*R*)-*N*-(3"-Aminobiphenyl-4'-yl)methyl 2-Acetamido-3-methoxypropionamide Hydrochloride ((*R*)-16). Using the procedure for (*R*)-**14**, *(R)*-**75** (1.18 g, 3.59 mmol) and 4 M HCl (2.7 mL, 10.80 mmol) gave the desired product (*R*)-**16** (0.91 g, 90%) as a yellow solid: R_f = 0.00 (EtOAc/hexanes 1/1); mp 99-100 °C; $[\alpha]^{23.5}_D$ +10.4 **°** (*c* 1.0, CH_3OH); ^{1}H NMR ($CDCl_3/CD_3OD$) δ 1.99 (s, C**H**$_3$C(O)), 3.36 (s, OC**H**$_3$), 3.50 (dd, *J* = 4.0, 9.2 Hz, C**H**H'OCH_3), 3.78 (dd, *J* = 7.2, 9.2 Hz, CH**H'**OCH_3), 4.43 (dd, *J* = 5.8, 15.0 Hz, C**H**H'N), 4.48 (dd, *J* = 5.8, 15.0 Hz, CH**H'**N), 4.59-4.64 (m, C**H**), 6.63-6.67 (m, N(**H**)CH, 1 Ar**H**), 6.85 (m, 1 Ar**H**), 6.93-6.96 (m, 1 Ar**H**), 6.99-7.05 (br t, N(**H**)CH_2), 7.20 (t, *J* = 7.8 Hz, 1 Ar**H**), 7.26 (d, *J* = 6.0 Hz, 2 Ar**H**), 7.49 (dd, *J* = 1.6, 6.4 Hz, 2 Ar**H**); ^{13}C NMR (CD_3OD) δ22.6 (**C**H$_3$C(O)), 42.8 (N**C**H$_2$), 52.8 (**C**H), 58.3 (O**C**H$_3$), 72.1 (O**C**H$_2$), 121.2, 122.0 ,126.0, 126.6, 127.8, 130.4, 132.8, 137.2, 139.5, 141.4, (10 Ar**C**), 169.6, 169.9 (2 **C**(O)NH); LRMS (ESI$^+$) 364.2 [M + Na- HCl]$^+$ (calcd for $C_{19}H_{23}NaN_3O_3^+$ 364.2); HRMS (ESI$^+$) 342.1817 [M – Cl]$^+$ (calcd for $C_{19}H_{24}N_3O_3$ 342.1817).

Refererences

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2. Salome, C., Salome-Grosjean, E., Park, K. D., Morieux, P., Swendiman, R., DeMarco, E., Stables, J. P., and Kohn, H. Synthesis and anticonvulsant activities of (*R*)-*N*-(4'-

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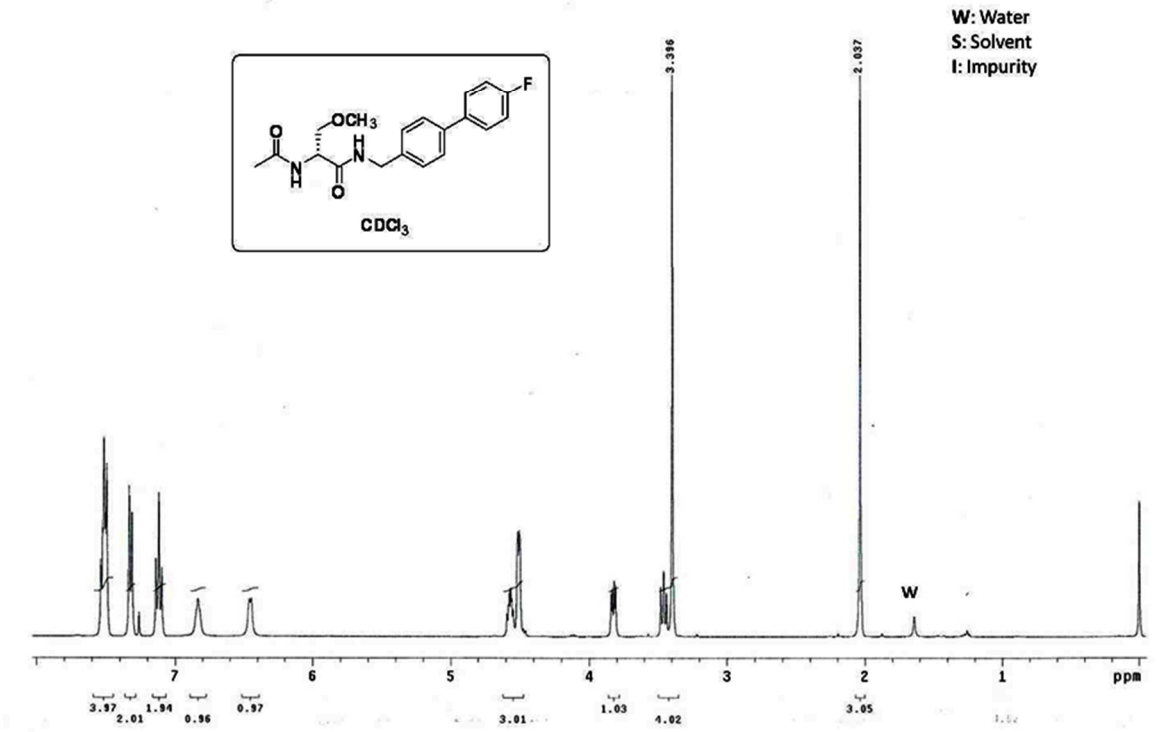
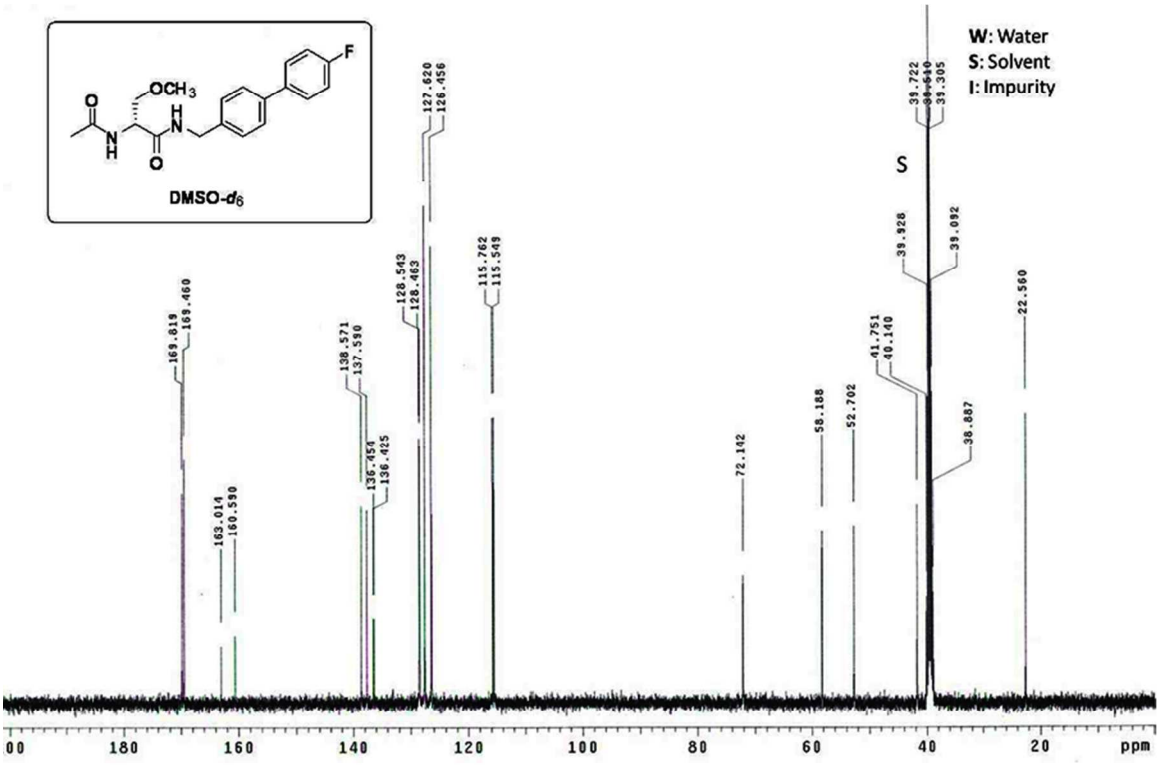
(*R*)-*N*-(4”-Fluorobiphenyl-4’-yl)methyl 2-Acetamido-3-methoxypropionamide ((*R*)-4)





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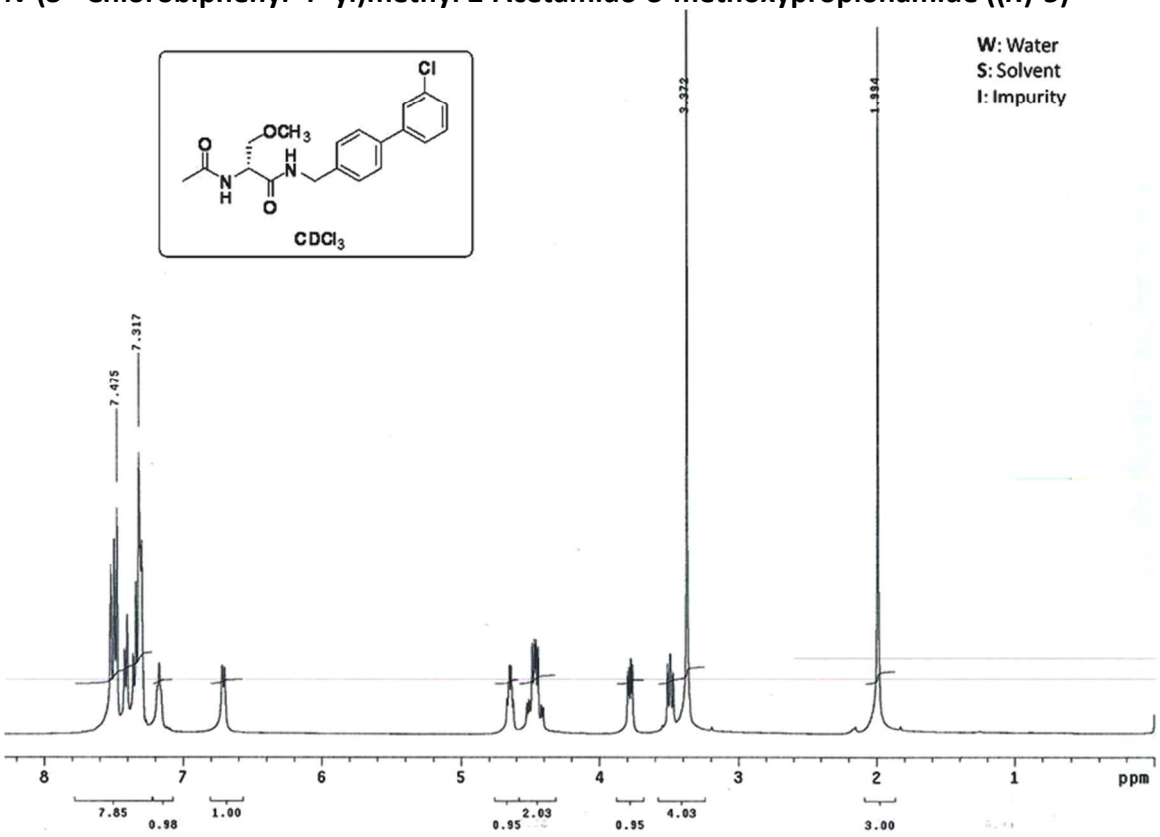

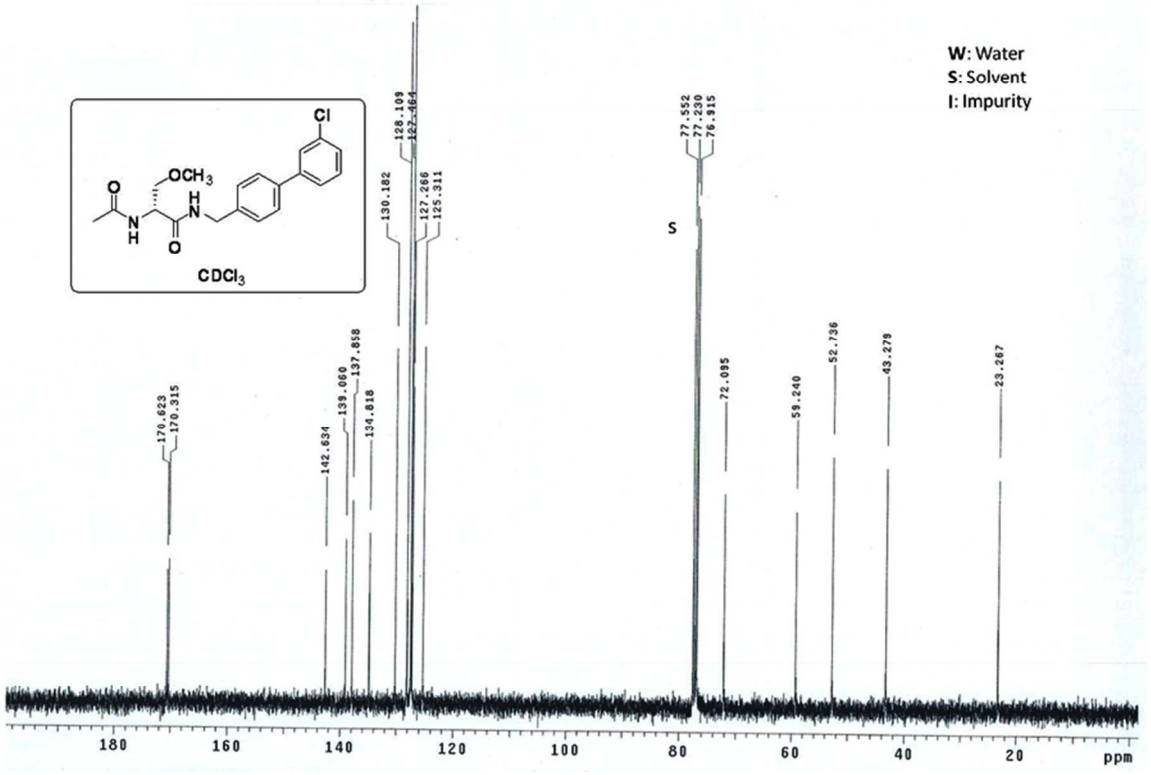

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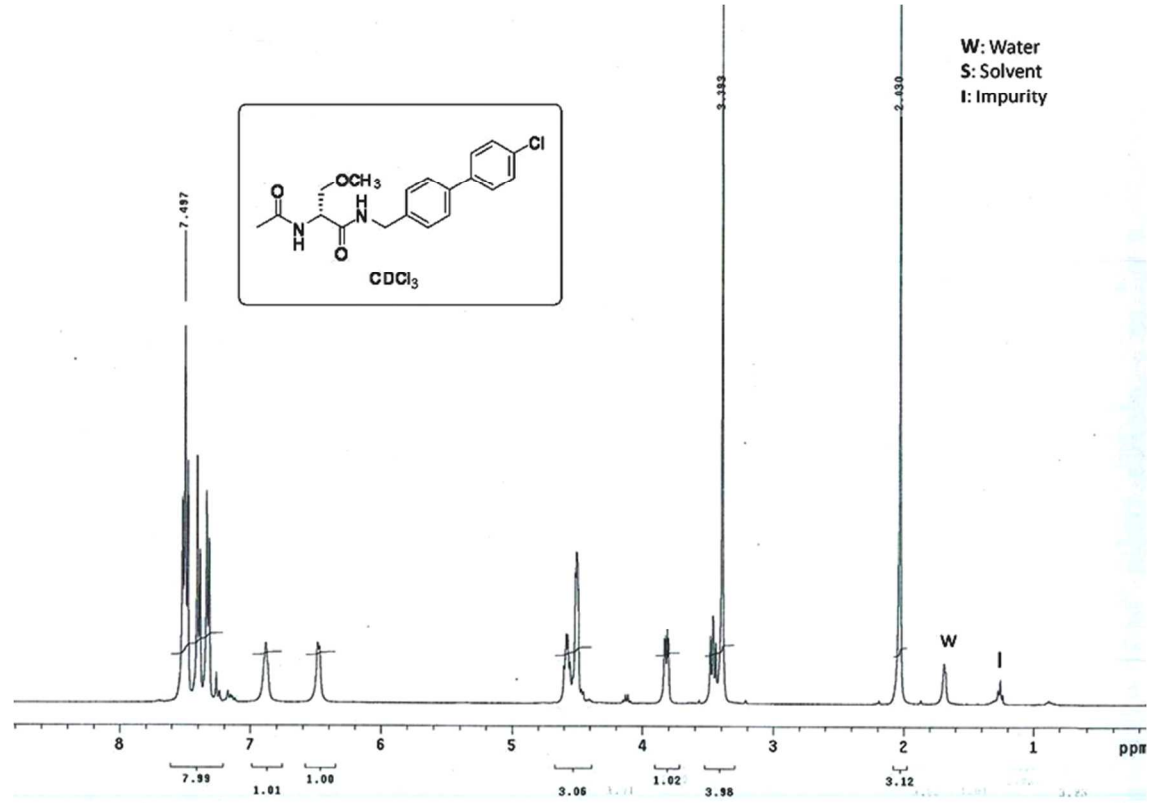

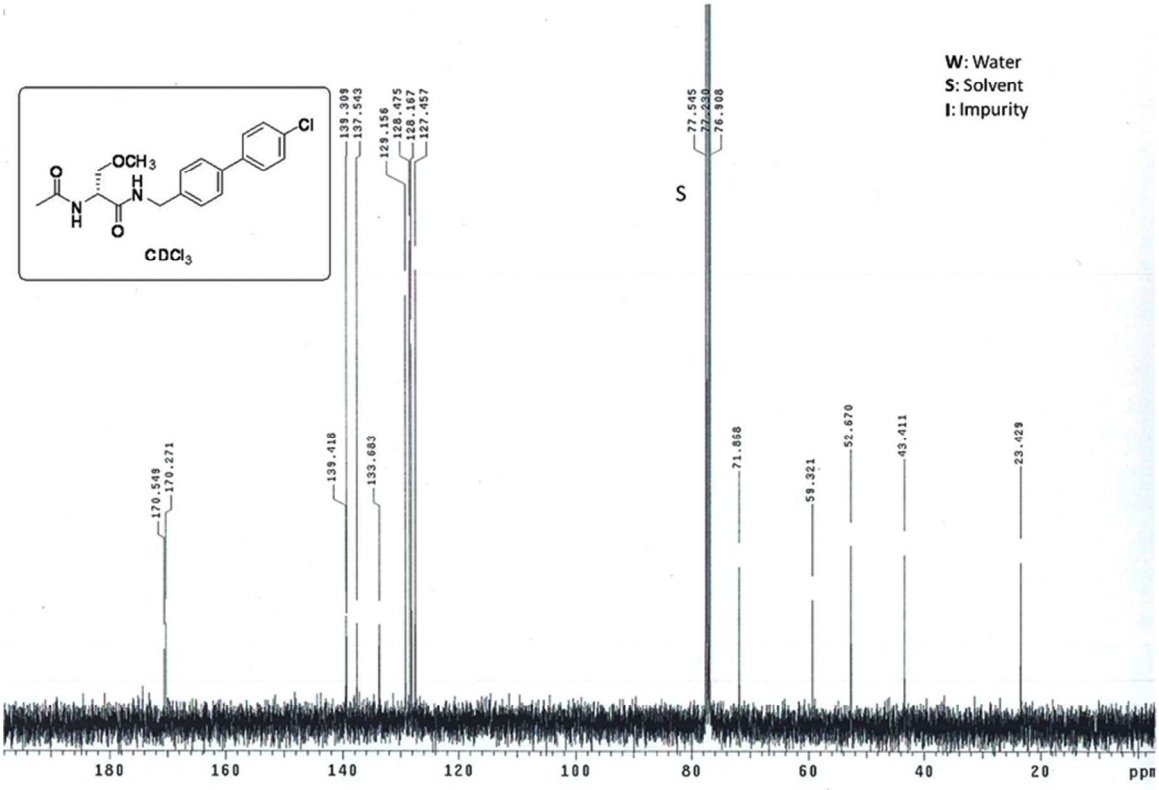

(*R*)-*N*-(3”-Bromo-4-biphenylmethyl) 2-Acetamido-3-methoxypropionamide ((*R*)-7)

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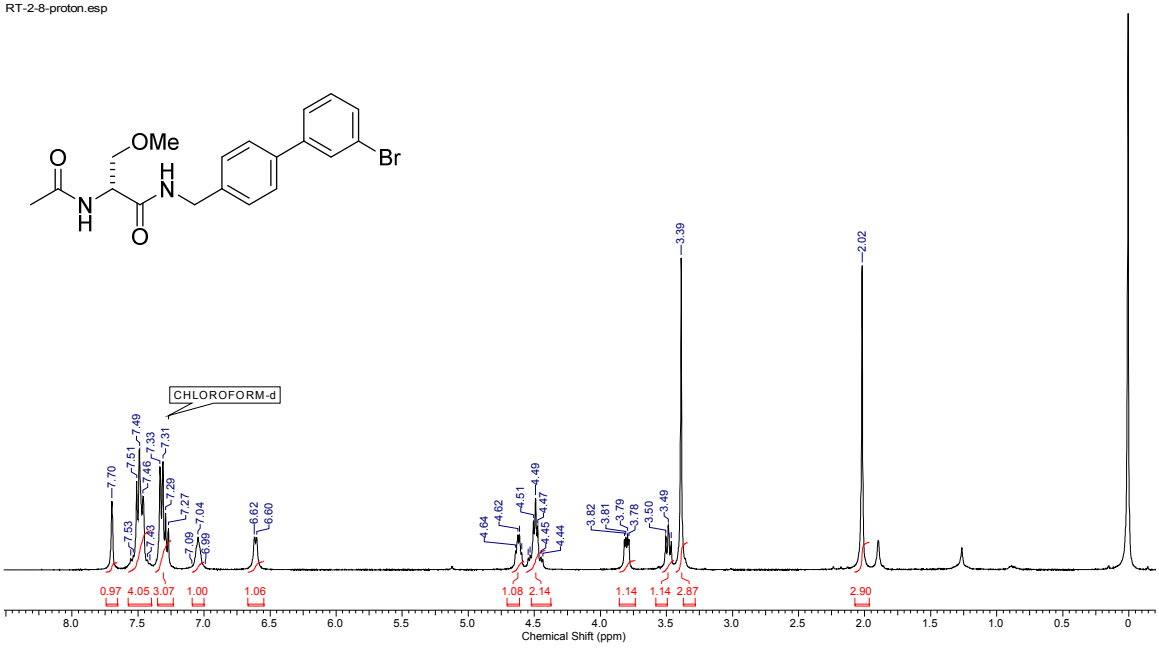
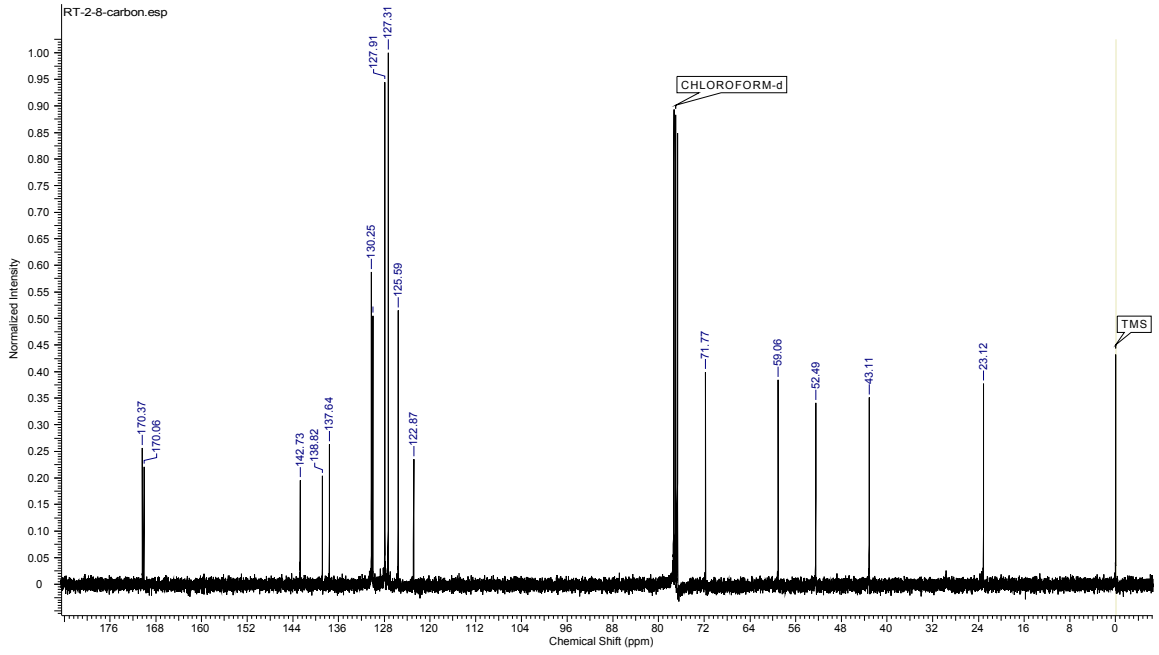
Spectrum Offset (Hz)	2403.7048	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6410.26	***Temperature (degree C)***	26.000

RT-2-8-proton.esp



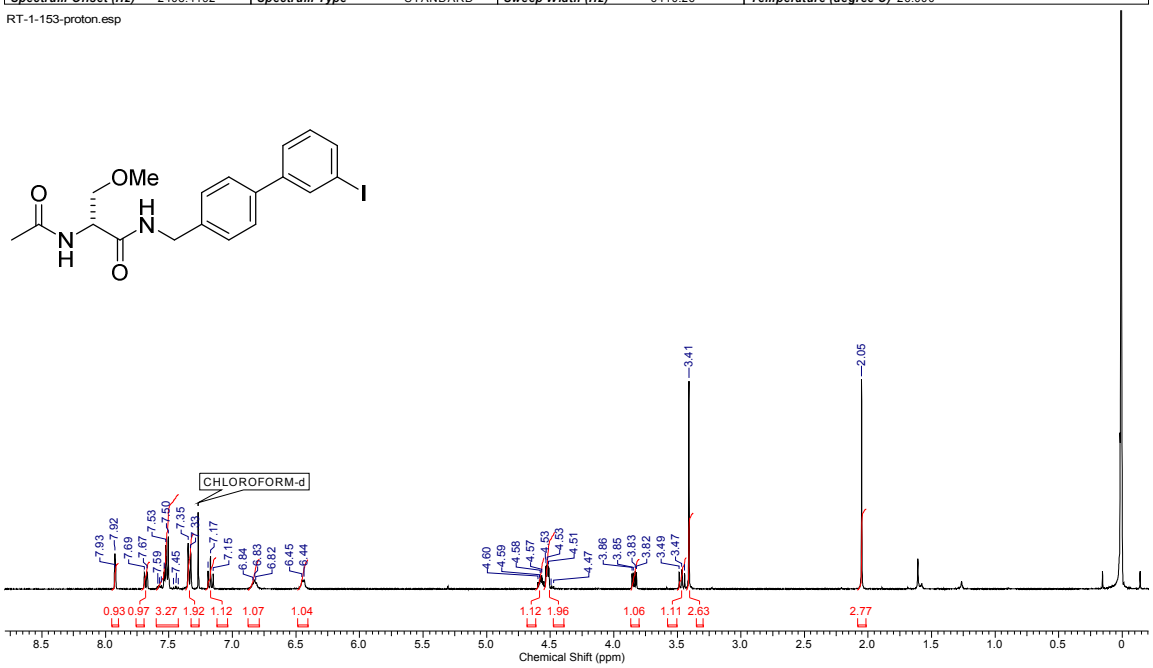
Acquisition Time (sec)	1.3107	***Comment***	RT-2-8	***Date***	May 9 2013	***Date Stamp***	May 9 2013
File Name	C:\Users\Robert\Documents\NMR Carbon\2_8_CARBON_001.fid\fid					***Frequency (MHz)***	100.52
Nucleus	13C	***Number of Transients***	1000	***Original Points Count***	32768	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	11053.0596	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	25000.00	***Temperature (degree C)***	26.000

RT-2-8-carbon.esp

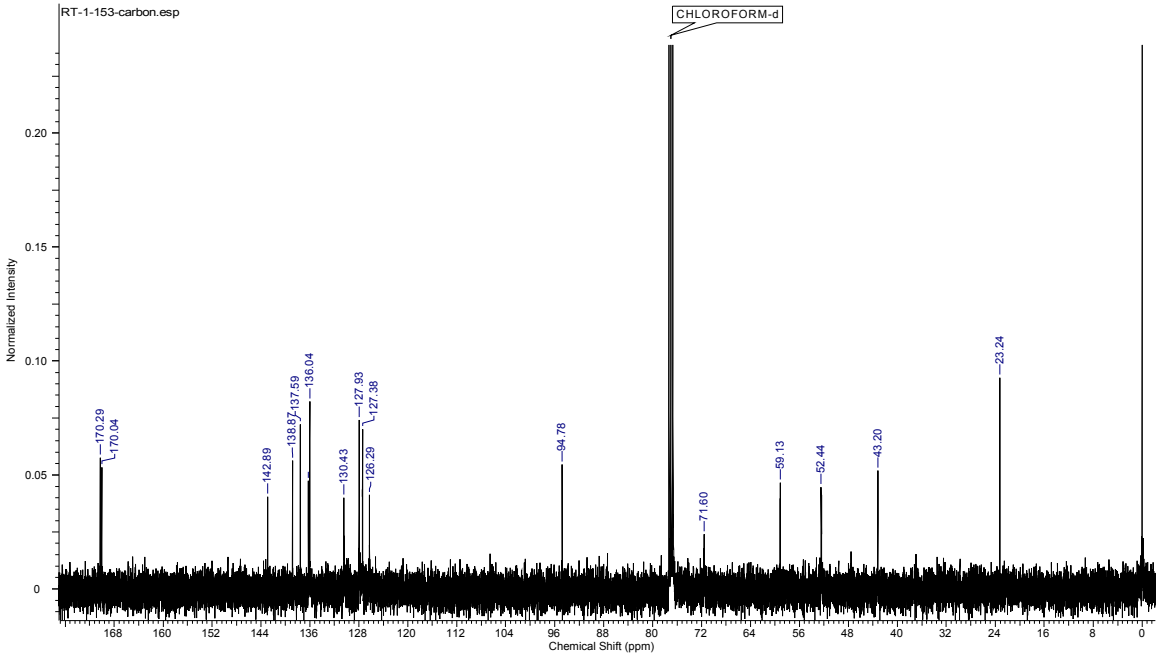


(*R*)-*N*-(3”-Iodo-4-biphenylmethyl) 2-Acetamido-3-methoxypropionamide ((*R*)-8)

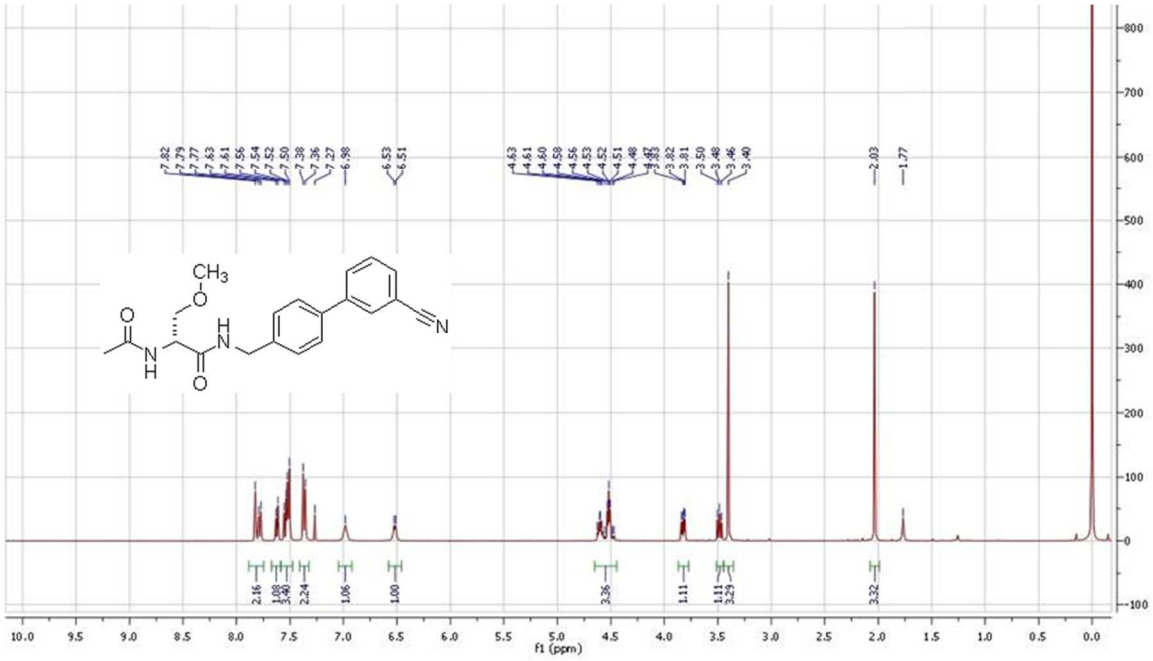
Acquisition Time (sec)	2.5559	***Comment***	RT-1-153	***Date***	Apr 1 2013	***Date Stamp***	Apr 1 2013
File Name	C:\Documents and Settings\rtorreg\My Documents\NMR Proton\1_153_PROTON_001.fid\fid					***Frequency (MHz)***	399.71
Nucleus	1H	***Number of Transients***	8	***Original Points Count***	16384	***Points Count***	16384
Pulse Sequence	s2pul	***Receiver Gain***	42.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2408.4192	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6410.26	***Temperature (degree C)***	26.000

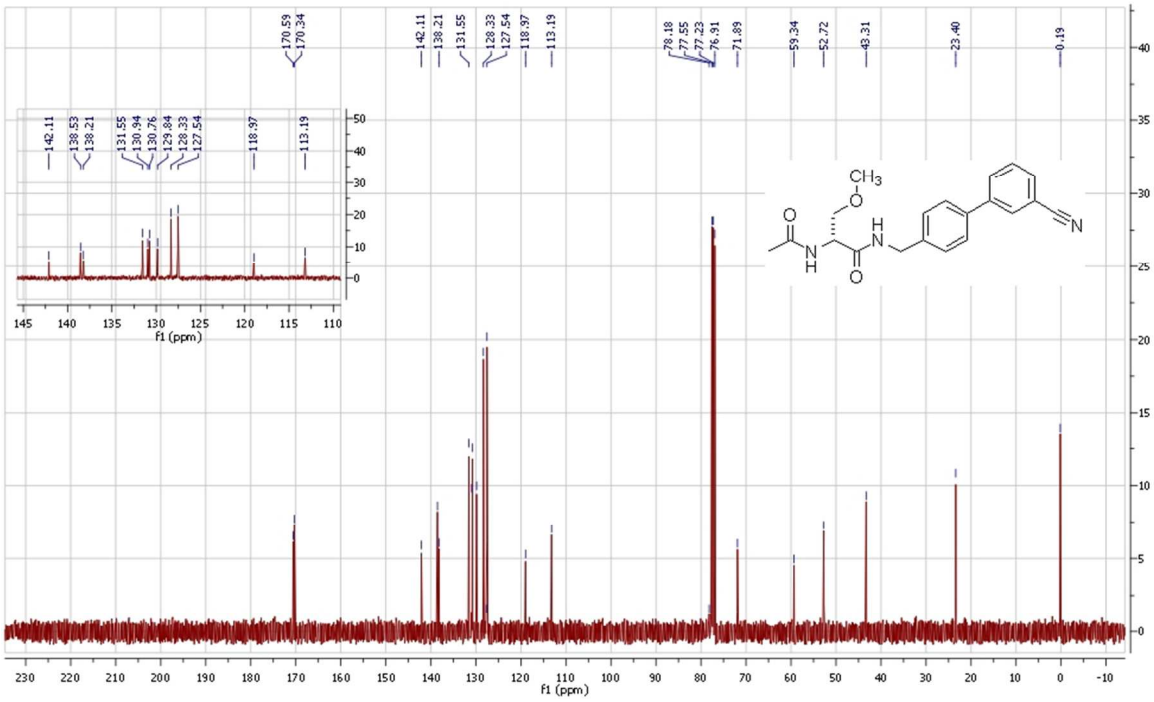


Acquisition Time (sec)	1.3107	***Comment***	RT-1-153	***Date***	Apr 1 2013	***Date Stamp***	Apr 1 2013
File Name	C:\Documents and Settings\rtorreg\My Documents\NMR Carbon\1_153_CARBON_001.fid\fid					***Frequency (MHz)***	100.52
Nucleus	13C	***Number of Transients***	2000	***Original Points Count***	32768	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	11058.4512	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	25000.00	***Temperature (degree C)***	26.000



(*R*)-*N*-(3”-Cyanobiphenyl-4’-yl)methyl 2-Acetamido-3-methoxypropionamide ((*R*)-9)

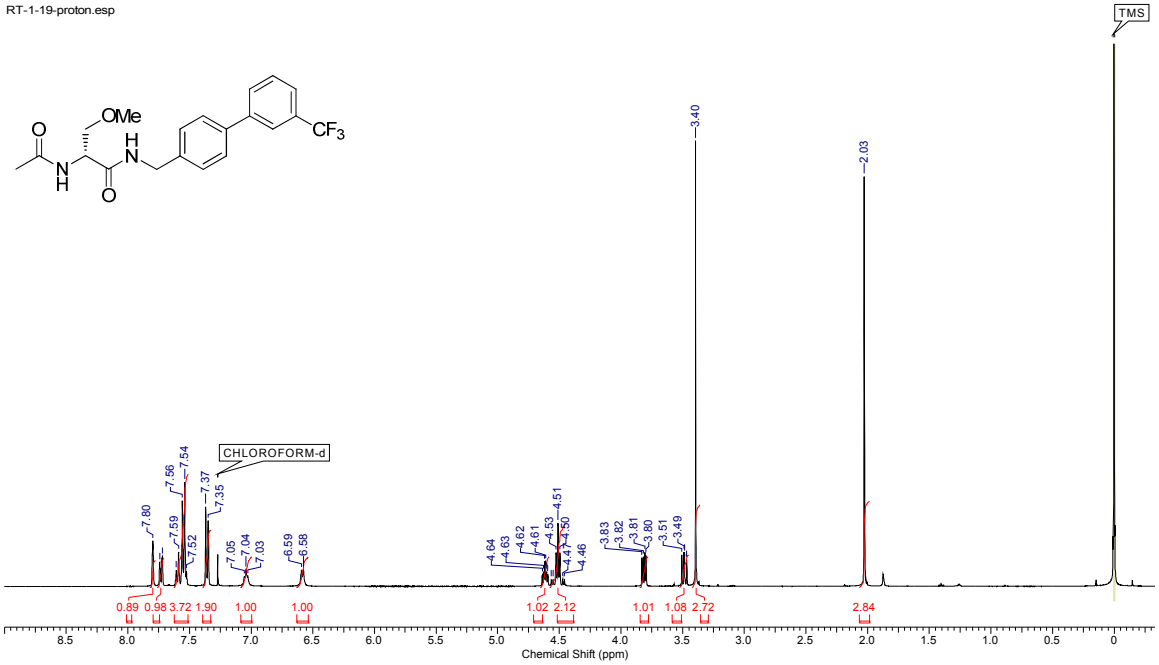




(*R*)-*N*-(3”-Trifluoromethyl)-4-biphenylmethyl 2-Acetamido-3-methoxypropionamide ((*R*)-10)

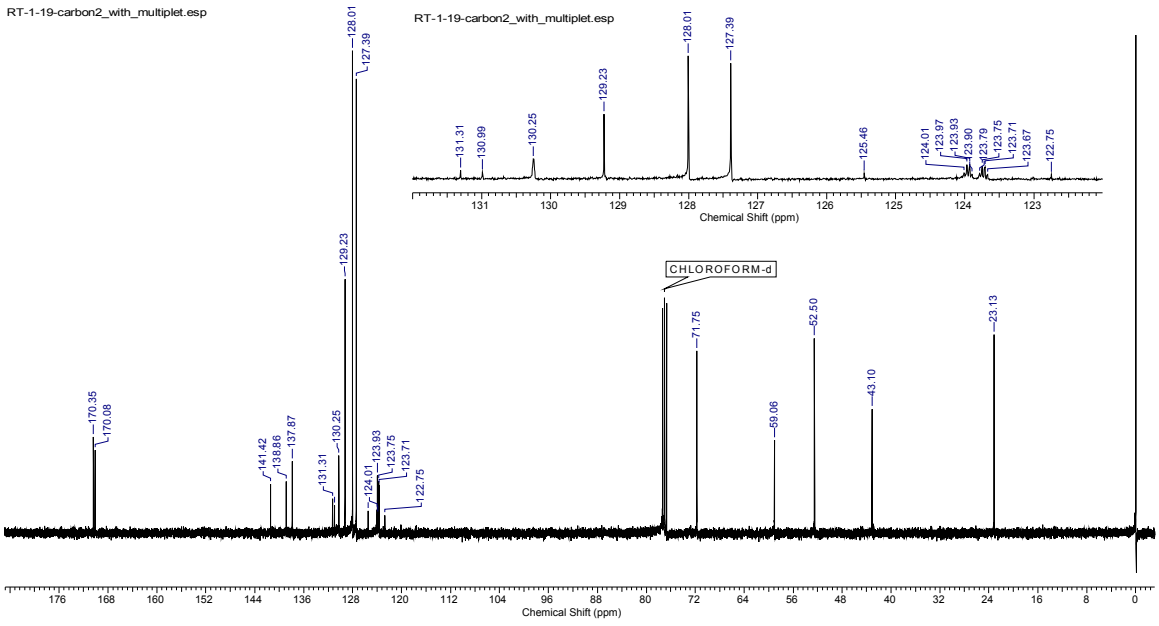
Acquisition Time (sec)	2.5559	***Date***	Nov 28 2012	***Date Stamp***	Nov 28 2012		
File Name	C:\Documents and Settings\rtorreg\My Documents\NMR Proton\1_19_PROTON_003.fid\fid					***Frequency (MHz)***	399.72
Nucleus	1H	***Number of Transients***	16	***Original Points Count***	16384	***Points Count***	16384
Pulse Sequence	s2pul	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2402.2251	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6410.26	***Temperature (degree C)***	26.000

RT-1-19-proton.esp

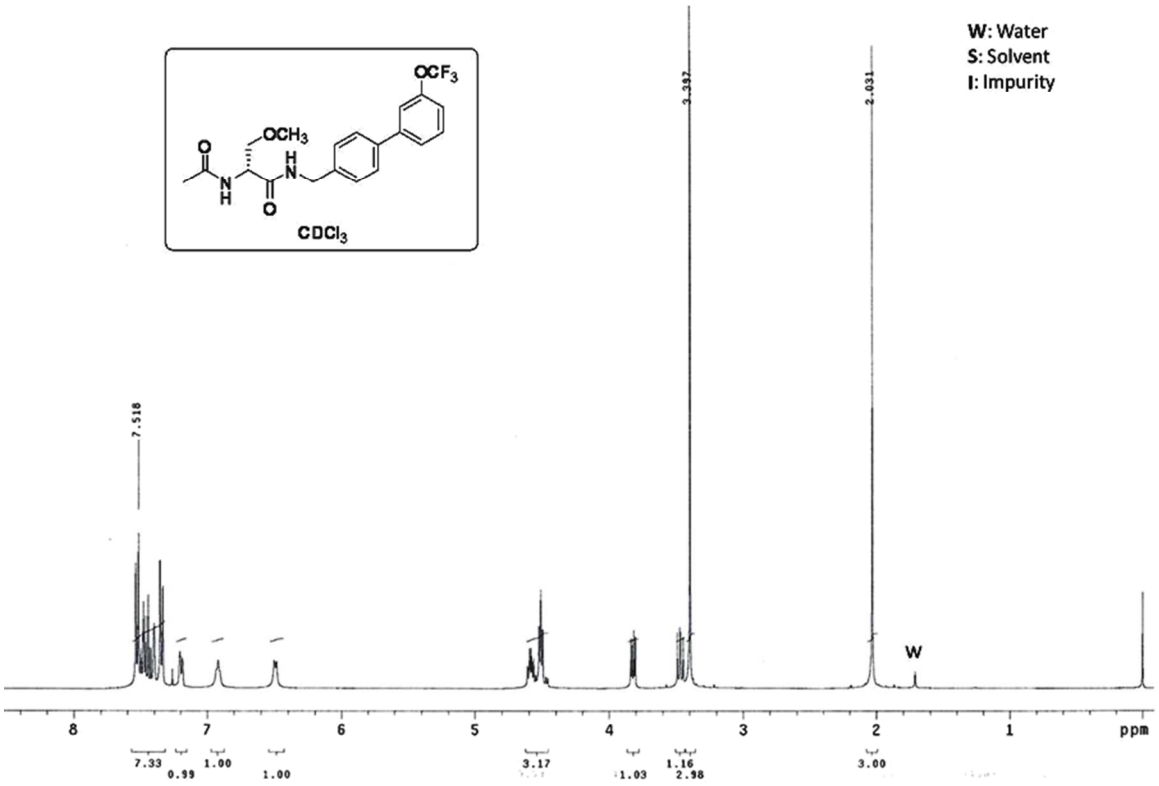


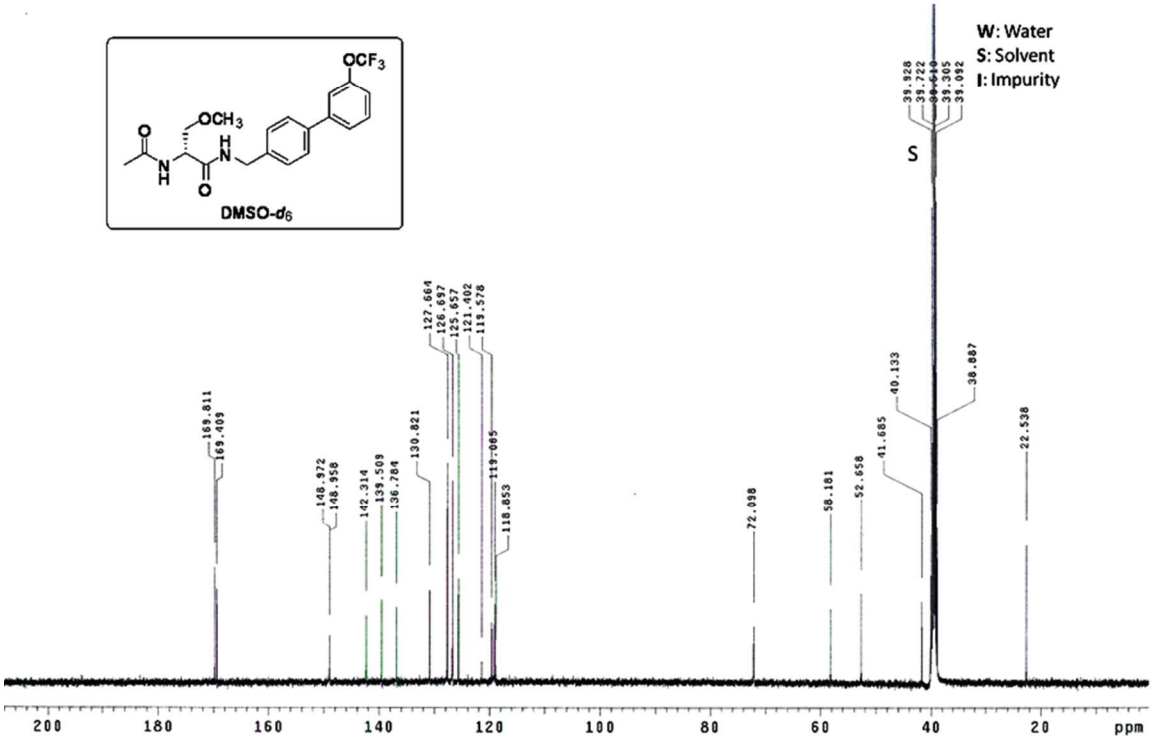
Acquisition Time (sec)	1.3107	***Date***	Nov 29 2012	***Date Stamp***	Nov 29 2012		
File Name	C:\Documents and Settings\rtorreg\My Documents\NMR Carbon\1_19_CARBON_002.fid\fid					***Frequency (MHz)***	100.52
Nucleus	13C	***Number of Transients***	1000	***Original Points Count***	32768	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	11054.0508	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	25000.00	***Temperature (degree C)***	26.000

RT-1-19-carbon2_with_multiplet.esp

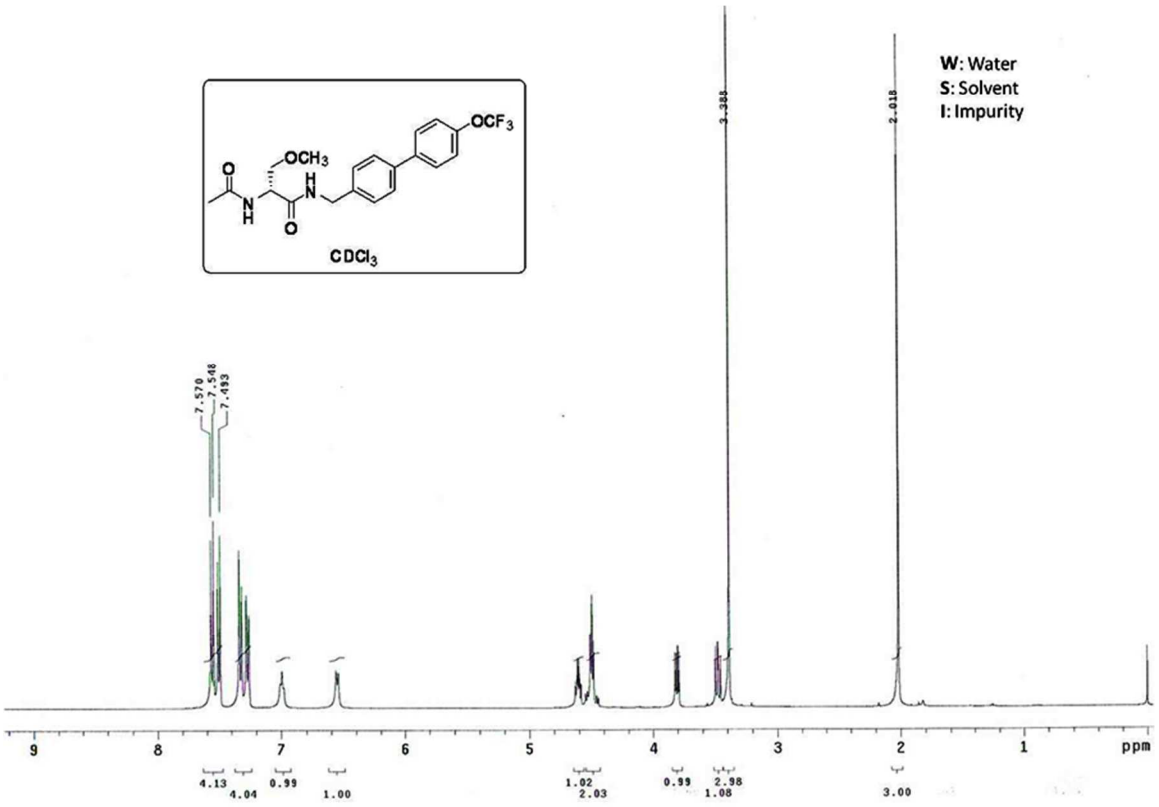


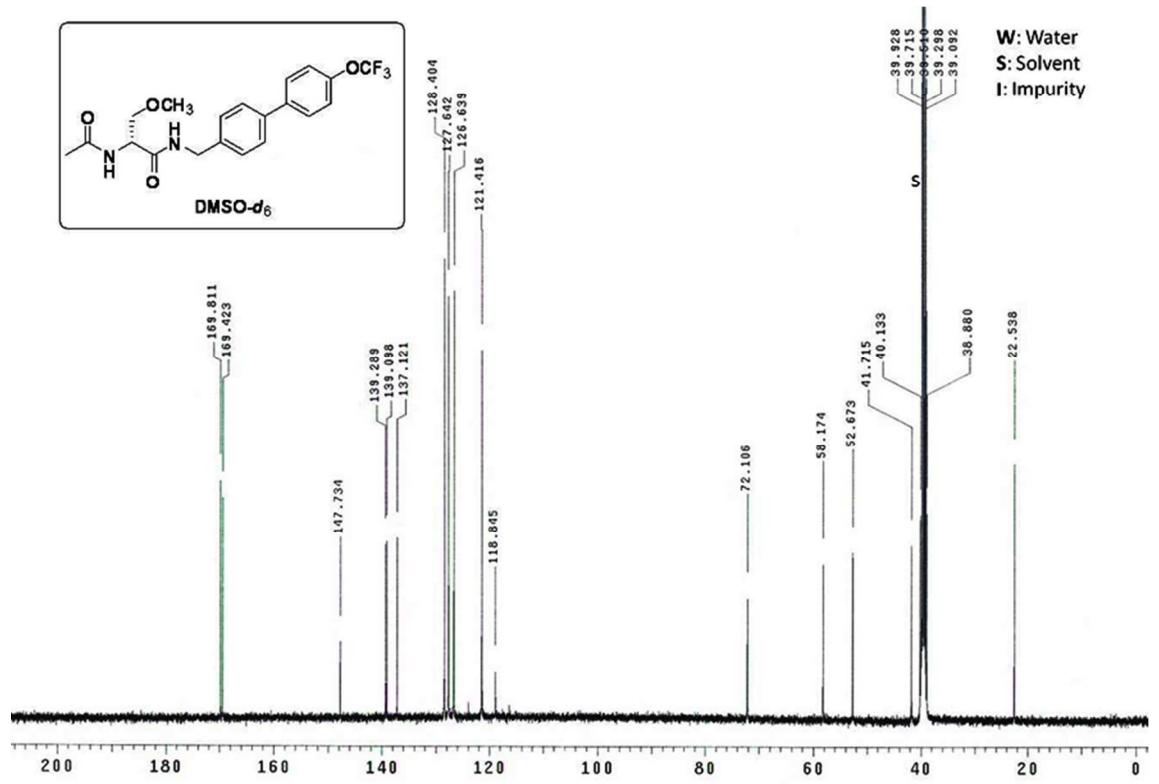
(*R*)-*N*-(3”-Trifluoromethoxybiphenyl-4’-yl)methyl 2-Acetamido-3-methoxypropionamide ((*R*)-11)



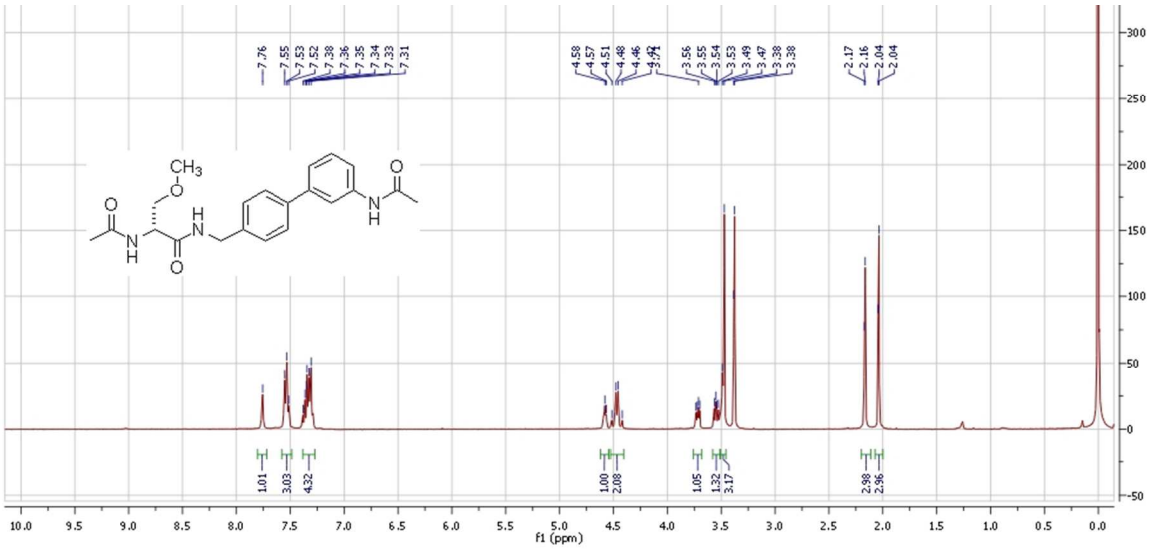


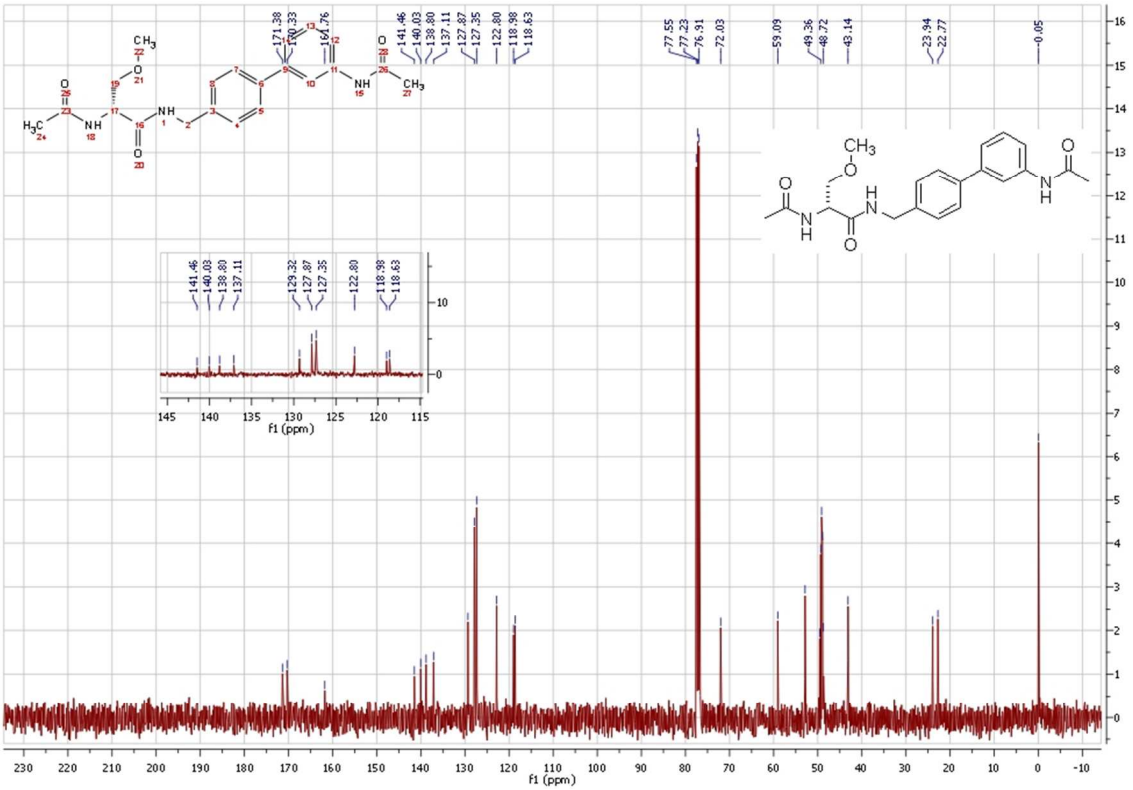
(*R*)-*N*-(4”-Trifluoromethoxybiphenyl-4’-yl)methyl 2-Acetamido-3-methoxypropionamide ((*R*)-12)



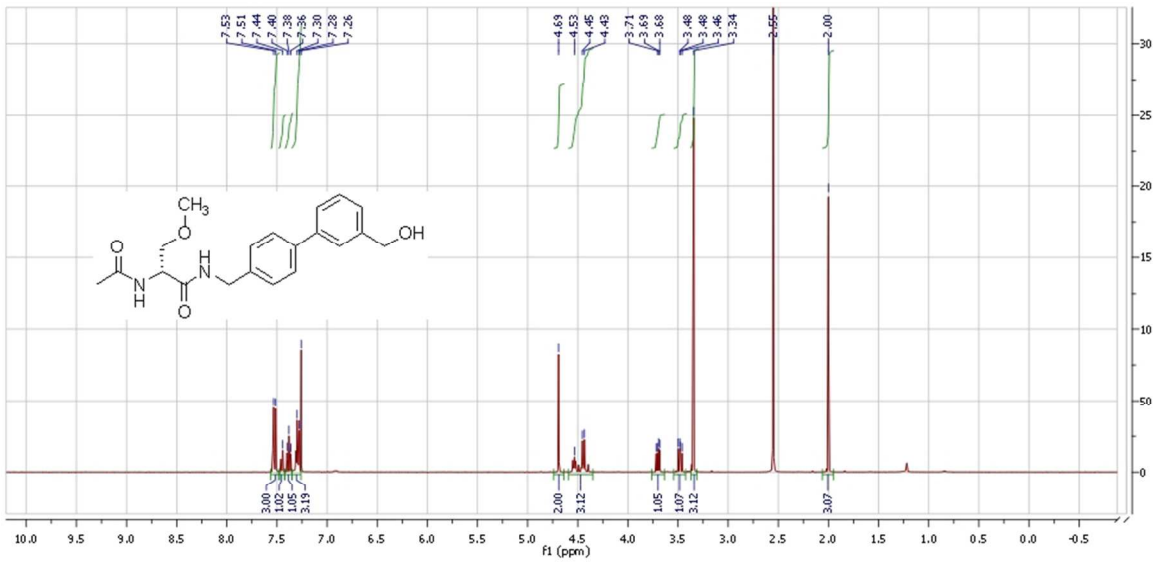


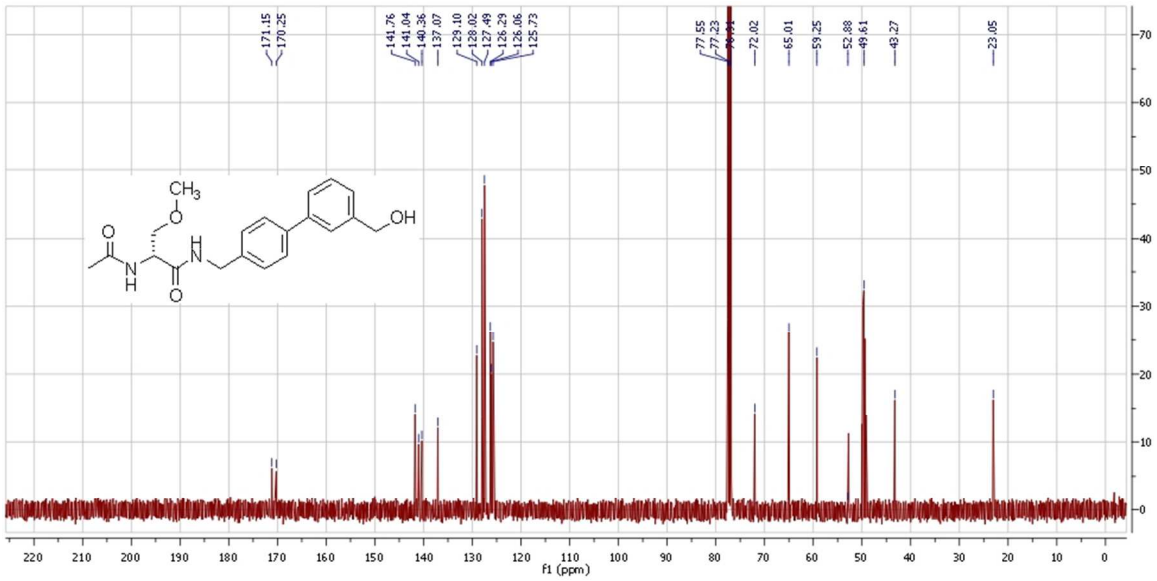
(*R*)-*N*-(3”-Acetylaminobiphenyl-4’-yl)methyl 2-Acetamido-3-methoxypropionamide ((*R*)-13)



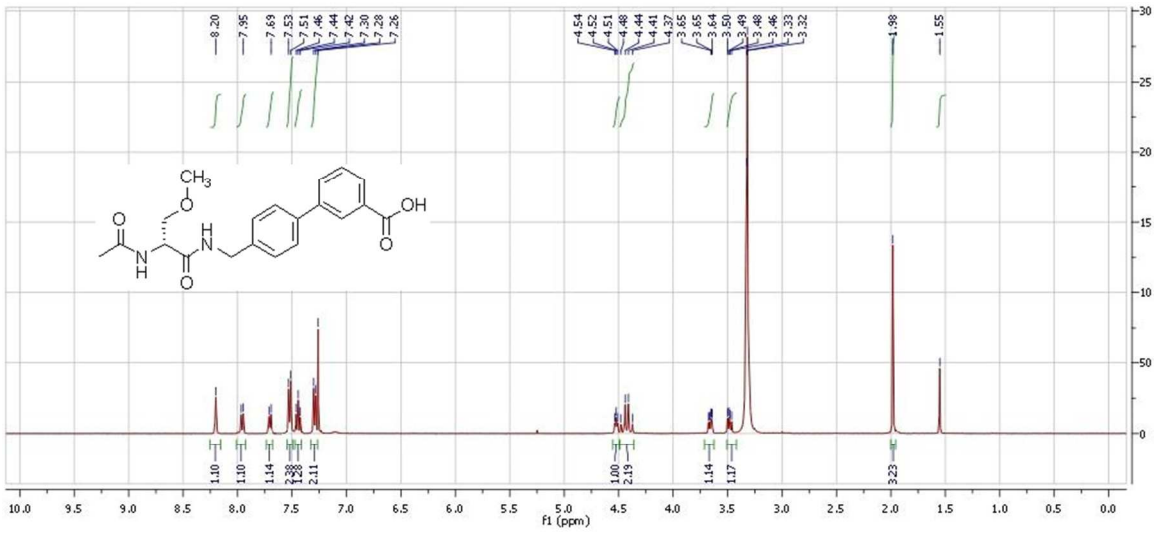


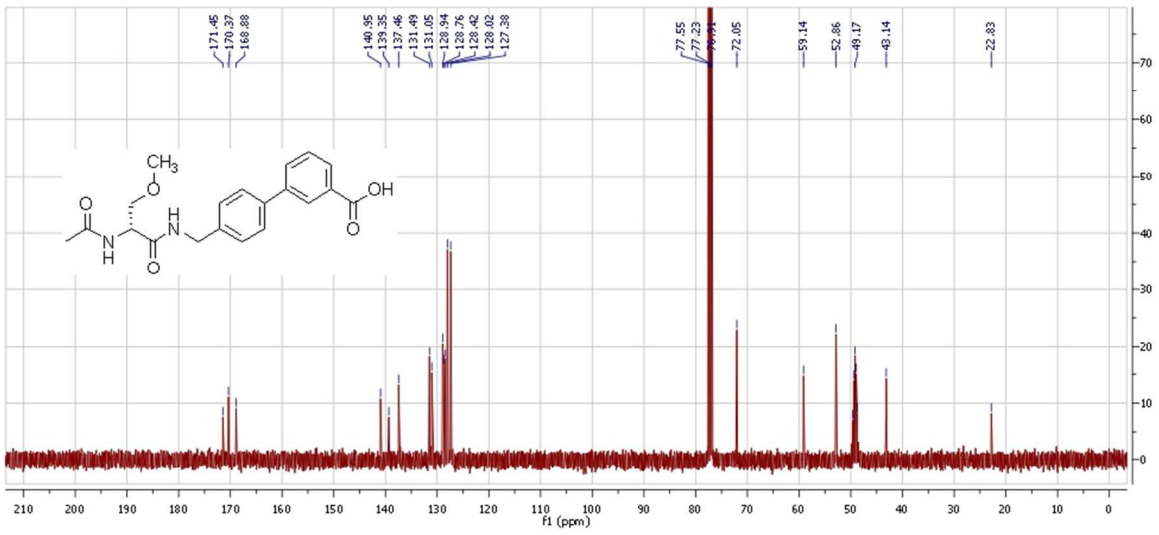
(*R*)-*N*-(3”-Hydroxymethylbiphenyl-4’-yl)methyl 2-Acetamido-3-methoxypropionamide ((*R*)-14)





(*R*)-*N*-(3”-Carboxybiphenyl-4’-yl)methyl 2-Acetamido-3-methoxypropionamide ((*R*)-15)





(*R*)-*N*-(3”-Aminobiphenyl-4’-yl)methyl 2-Acetamido-3-methoxypropionamide Hydrochloride ((*R*)-16)