Supporting Information

Merging the Structural Motifs of Functionalized Amino Acids and α-Aminoamides: Compounds with Significant Anticonvulsant Activities

Christophe Salomé,[1] Elise Salomé-Grosjean,[1] James P. Stables,[2]

and Harold Kohn*,[1,3]

[1]Division of Medicinal Chemistry and Natural Products, UNC Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina 27599-7568, USA

[2]Epilepsy Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, 6001 Executive Boulevard, Suite 2106, Rockville, MD 20892

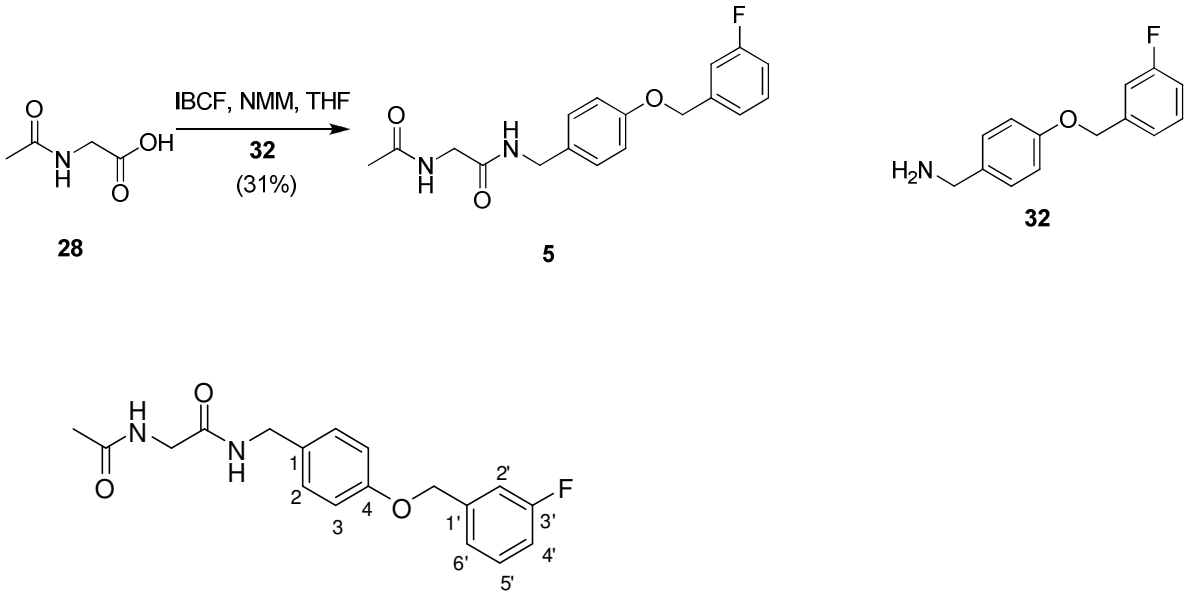
[3]Department of Chemistry, University of North Carolina, Chapel Hill, North Carolina 27599-3290, USA

Table of Contents

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 300 MHz or 400 MHz (^{1}H) and 75 MHz or 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 Drs. Matt Crowe and 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 Drs. Matt Crowe and S. Habibi. Microanalyses were performed by Atlantic Microlab, Inc. (Norcross, GA). Reactions were monitored by analytical thin-layer chromatography (TLC) plates (Aldrich, Cat # Z12272-6) and analyzed with 254 nm light. The reactions were purified by MPLC (CombiFlash Rf) with self-packed columns (silica gel from Dynamic Adsorbents Inc., Cat # 02826-25) or 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. THF was distilled from blue sodium benzophenone ketyl. 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%.

1. Preparation of *N*-4'-((3''-Fluoro)benzyloxy)benzyl 2-Acetamidoacetamide (5).

Reaction Overview



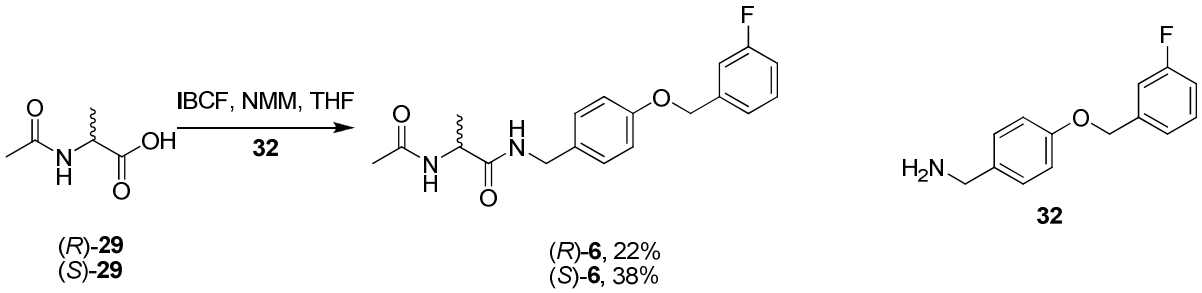
Preparation of *N*-4'-((3''-fluoro)benzyloxy)benzyl 2-Acetamidoacetamide (5).

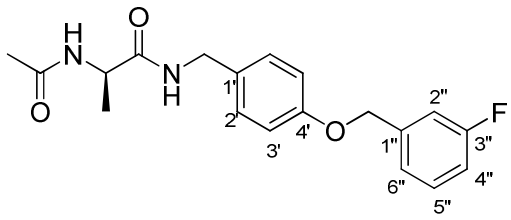
A THF solution (120 mL) of *N*-acetylglycine (**28**) (1.50 g, 12.8 mmol) was stirred and cooled at -78 °C under Ar and then 4-methylmorpholine (NMM) (1.7 mL, 15.4 mmol) was added dropwise. After 2 min of stirring at this temperature, isobutylchloroformate (IBCF) (2.0 mL, 15.4 mmol) was added dropwise leading to the precipitation of a white solid. The reaction was allowed to proceed for additional 2 min and 4-((3'-fluoro)benzyloxy)benzylamine (**32**) (3.26 g, 14.1 mmol) was added portionwise at -78 °C. The mixture was allowed to stir at room temperature (2 h), and then the white solid filtered and the organic layer concentrated in vacuo. The solid was purified by flash column chromatography on silica gel with Methanol/EtOAc (0/10 -> 5/5) as the eluant to obtain a white solid (1.30 g, 31%): R_f = 0.11 (EtOAc); mp 155-156 °C; IR (nujol) 3305, 3070, 2921, 2862, 1647, 1549, 1457, 1374, 1249, 1145, 1017, 933, 879, 825, 781, 724 cm^{-1};^{1}H NMR ($CDCl_3$) δ 2.03 (s, C(O)C**H$_3$**), 3.92 (d, J = 5.1 Hz, C**H$_2$**N), 4.38 (d, J = 5.7 Hz, NC**H$_2$**Ar), 5.05 (s, C**H$_2$**O), 6.24-6.35 (br m, 2 N**H**), 6.92 (m, 2 Ar**H**), 6.97-7.04 (m, 1 Ar**H**), 7.11-7.21 (m, 4 Ar**H**), 7.30-7.38 (m, 1 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 22.9 (C(O)**C**H$_3$), 43.0, 43.4 (2 **C**H$_2$), 69.2 (d, J = 1.7 Hz,

Ph**C**H_2O), 114.1 (d, *J* = 22.1 Hz, $\mathbf{C_{4'}}$ or $\mathbf{C_{2'}}$), 114.8 (d, *J* = 21.1 Hz, $\mathbf{C_{2'}}$ or $\mathbf{C_{4'}}$), 115.0 ($\mathbf{C_1}$), 122.6 (d, *J* = 2.9 Hz, $\mathbf{C_{6'}}$), 129.1 (Ar**C**), 130.1 (d, *J* = 8.5 Hz, $\mathbf{C_{5'}}$), 130.3 (Ar**C**), 139.5 (d, *J* = 7.4 Hz, $\mathbf{C_{1'}}$), 157.9 ($\mathbf{C_4}$), 163.0 (d, *J* = 244.7 Hz, $\mathbf{C_{3'}}$), 168.6, 170.7 (2 **C**(O)); MS (M+H^+)(ESI$^+$) 331.1 [M + H^+] (calcd for $C_{18}H_{19}FN_2O_3H^+$ 331.1); Anal. Calcd. for $C_{18}H_{19}FN_2O_3$·0.35 H_2O: C, 64.21; H, 5.90; F, 5.64; N, 8.32. Found: C, 63.83; H, 5.56; F, 5.49; N, 8.22.

2. Preparation of (*R*)-*N*-4'-((3''-Fluoro)benzyloxy)benzyl 2-Acetamidopropanamide ((*R*)-6) and (*S*)-*N*-4'-((3''-fluoro)benzyloxy)benzyl 2-Acetamidopropanamide ((*S*)-6).

Reaction Overview

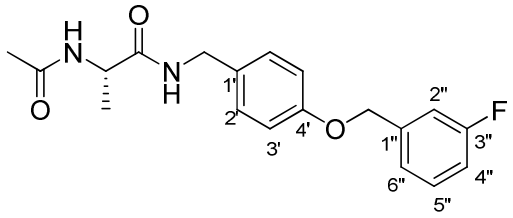




Preparation of (*R*)-*N*-4'-((3''-Fluoro)benzyloxy)benzyl 2-Acetamidopropanamide ((*R*)-6).

A THF solution (100 mL) of (*R*)-*N*-acetylalanine ((*R*)-**29**) (1.50 g, 11.4 mmol) was stirred and cooled at -78 °C under Ar and then 4-methylmorpholine (NMM) (1.5 mL, 13.7 mmol) was added dropwise. After 2 min of stirring at this temperature, isobutylchloroformate (IBCF) (1.8 mL, 13.7 mmol) was added dropwise leading to the precipitation of a white solid. The reaction was allowed to proceed for additional 2

min and 4-((3'-fluoro)benzyloxy)benzylamine (**32**) (2.90 g, 12.6 mmol) was added portionwise at -78 °C. The mixture was allowed to stir at room temperature (2 h), and then the white solid filtered and the organic layer concentrated in vacuo. The solid was recrystallized with EtOAc to obtain (*R*)-**6** as a white solid (905 mg, 22%): R_f = 0.16 (EtOAc); mp 158 °C; $[\alpha]^{26.2}_D$ +27.3° (*c* 1, $CHCl_3$); IR (nujol) 3284, 2937, 2862, 1629, 1546, 1457, 1375, 1242, 1151, 1020, 778, 722 cm^{-1};^{1}H NMR ($CDCl_3$) δ 1.37 (d, *J* = 6.9 Hz, C**H**$_3$), 1.94 (s, C(O)C**H**$_3$), 4.32 (d, *J* = 5.7 Hz, C**H**$_2$N), 4.46-4.56 (m, C**H**), 5.02 (s, C**H**$_2$O), 6.41 (d, *J* = 7.5 Hz, N**H**), 6.79-6.85 (br m, N**H**), 6.87-6.92 (m, 2 Ar**H**), 7.00 (td, *J* = 2.4, 8.4 Hz, 1 Ar**H**), 7.10-7.20 (m, 4 Ar**H**), 7.30-7.37 (m, 1 Ar**H**), addition of excess (*R*)-(-)-mandelic acid to a $CDCl_3$ solution of (*R*)-**6** gave only one signal for the acetyl methyl protons; ^{13}C NMR ($CDCl_3$) δ 18.5 (**C**H_3), 23.1 (C(O)**C**H_3), 43.0 (N**C**H_2), 48.8 (**C**H), 69.1 (d, *J* = 1.6 Hz, Ph**C**H_2O), 114.1 (d, *J* = 21.6 Hz, **C$_{4'}$** or **C$_{2'}$**), 114.8 (d, *J* = 21.0 Hz, **C$_{2'}$** or **C$_{4'}$**), 115.0 (**C$_1$**), 122.6 (d, *J* = 2.9 Hz, **C$_{6'}$**), 129.0 (Ar**C**), 130.1 (d, *J* = 8.5 Hz, **C$_{5'}$**), 130.5 (Ar**C**), 139.5 (d, *J* = 7.4 Hz, **C$_{1'}$**), 157.9 (**C$_4$**), 163.0 (d, *J* = 244.7 Hz, **C$_{3'}$**), 170.0, 172.2 (2 **C**(O)); MS (M+H$^+$)(ESI$^+$) 345.2 [M + H$^+$] (calcd for $C_{19}H_{21}FN_2O_3H^+$ 344.2); Anal. Calcd. for $C_{19}H_{21}FN_2O_3$: C, 66.26; H, 6.15 F, 5.44; N, 8.13;. Found: C, 65.98; H, 6.10 F, 5.41; N, 8.03.



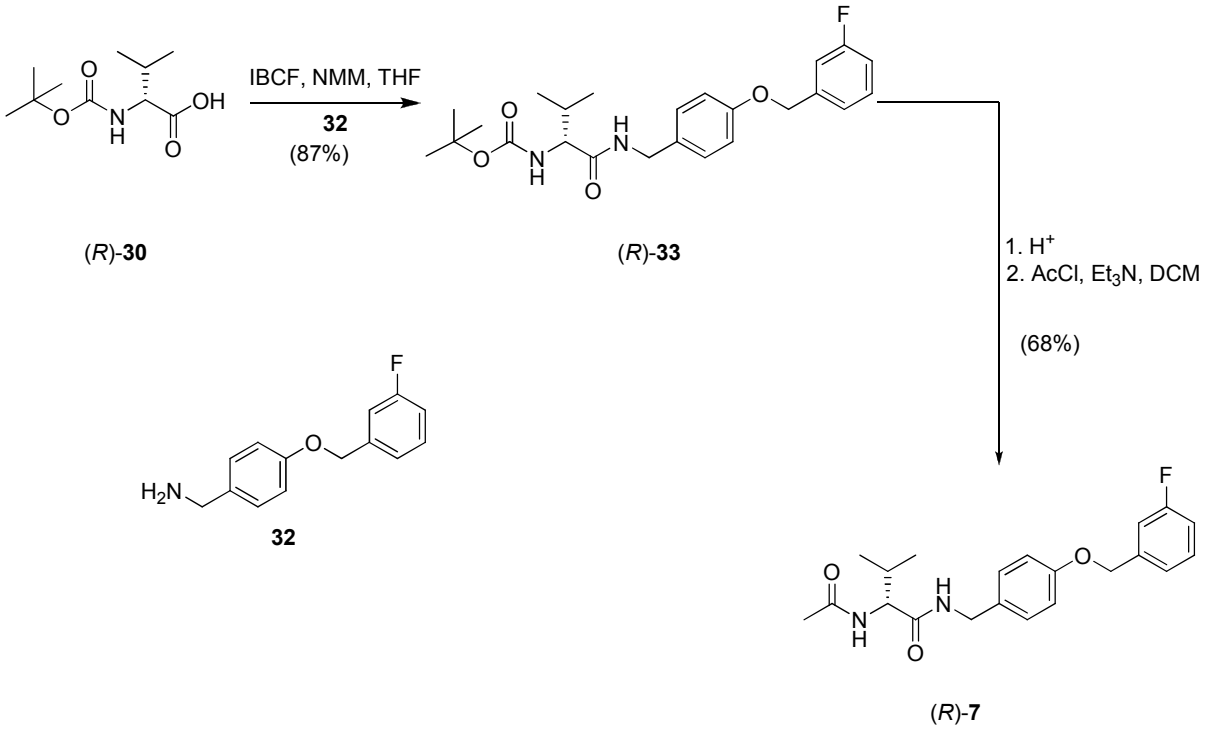
Preparation of (*S*)-*N*-4'-((3''-Fluoro)benzyloxy)benzyl 2-Acetamidopropanamide ((*S*)-6).

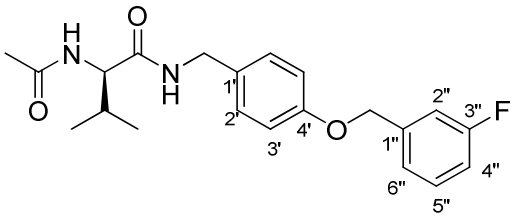
A THF solution (80 mL) of (*S*)-*N*-acetylalanine ((*S*)-**29**) (1.50 g, 11.4 mmol) was stirred and cooled at -78 °C under Ar and then 4-methylmorpholine (NMM) (1.5 mL, 13.7 mmol) was added dropwise. After 2 min of stirring at this temperature, isobutylchloroformate (IBCF) (1.8 mL, 13.7 mmol) was added dropwise leading to the precipitation of a white solid. The reaction was allowed to proceed for additional 2 min and 4-((3'-fluoro)benzyloxy)benzylamine (**32**) (2.90 g, 12.6 mmol) was added

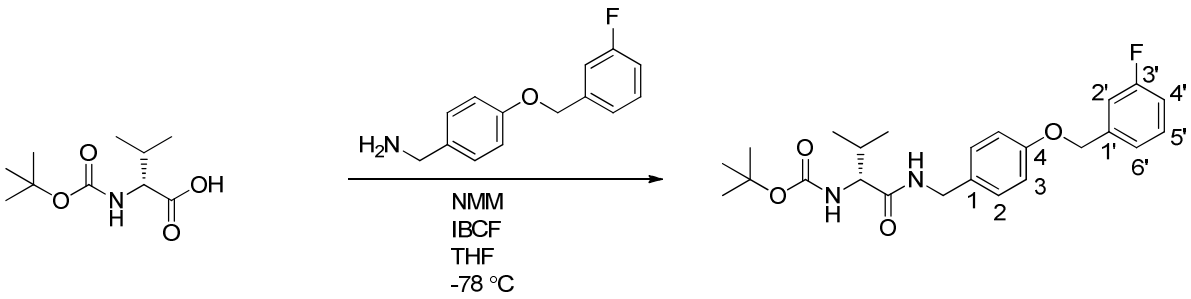
portionwise at -78 °C. The mixture was allowed to stir at room temperature (2 h), and then the white solid filtered and the organic layer concentrated in vacuo. The solid was recrystallized with EtOAc to obtain (*S*)-**6** as a white solid (1.50 g, 38%): R_f = 0.16 (EtOAc); mp 153-154 °C; $[\alpha]^{26.2}_D$ -28.1° (*c* 1, $CHCl_3$); IR (nujol) 3286, 2921, 2862, 1631, 1544, 1457, 1375, 1304, 1247, 1151, 1044, 778, 723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (d, *J* = 7.2 Hz, C**H**$_3$), 1.94 (s, C(O)C**H**$_3$), 4.32 (d, *J* = 5.7 Hz, C**H**$_2$N), 4.46-4.57 (m, C**H**), 5.02 (s, C**H**$_2$O), 6.38-6.46 (br d, N**H**), 6.78-6.85 (br m, N**H**), 6.89 (d, *J* = 8.4 Hz, 2 Ar**H**), 6.98-7.04 (m, 1 Ar**H**), 7.10-7.20 (m, 4 Ar**H**), 7.30-7.37 (m, 1 Ar**H**), addition of excess (*R*)-(-)-mandelic acid to a $CDCl_3$ solution of (*S*)-**6** gave only one signal for the acetyl methyl protons; ^{13}C NMR ($CDCl_3$) δ 18.4 (**C**H_3), 23.1 (C(O)**C**H_3), 43.0 (N**C**H_2), 48.8 (**C**H), 69.2 (d, *J* = 1.6 Hz, Ph**C**H_2O), 114.1 (d, *J* = 21.6 Hz, **C$_{4'}$** or **C$_{2'}$**), 114.8 (d, *J* = 21.0 Hz, **C$_{2'}$** or **C$_{4'}$**), 115.0 (**C$_1$**), 122.6 (d, *J* = 2.9 Hz, **C$_{6'}$**), 129.0 (Ar**C**), 130.1 (d, *J* = 8.0 Hz, **C$_{5'}$**), 130.5 (Ar**C**), 139.5 (d, *J* = 7.4 Hz, **C$_{1'}$**), 157.9 (**C$_4$**), 163.0 (d, *J* = 244.7 Hz, **C$_{3'}$**), 170.1, 172.1 (2 **C**(O)); MS ($M+H^+$)(ESI^+) 345.2 [M + H^+] (calcd for $C_{19}H_{21}FN_2O_3H^+$ 345.2); Anal. Calcd. for $C_{19}H_{21}FN_2O_3$: C, 66.26; H, 6.15; F, 5.44; N, 8.13. Found: C, 65.98; H, 6.11; F, 5.44; N, 8.05.

3. Preparation of (*R*)-*N*-4'-((3''-Fluoro)benzyloxy)benzyl 2-Acetamido-3-methylbutanamide ((*R*)-7).

Reaction Overview







(*R*)-*N*-4'-((3''-Fluoro)benzyloxy)benzyl 2-*N*'-(*t*-Butoxycarbonyl)amino-3-methylbutanamide ((*R*)-33).[1] Using (*R*)-2-*N*-(*t*-butoxycarbonyl)amino-3-methylbutanoic acid ((*R*-**30**) (3.07 g, 14.14 mmol), 4-methylmorpholine (2.02 mL, 18.38 mmol), isobutyl chloroformate (1.84 mL, 15.55 mmol), and (4-(3'-

[1] King, A.; Kohn, H., unpublished results

fluoro)benzyloxy)benzylamine (**32**) (3.43 g, 14.85 mmol) in anhydrous THF (15 mL) gave the crude product that was purified by flash column chromatography (SiO_2; 1-10% MeOH/CH_2Cl_2) to give the desired product (*R*)-**33** (5.29 g, 87%) as a pale yellow solid: R_f 0.21 (10% EtOAc/hexanes); mp 109-110 ºC; $[\alpha]^{25}_D$ + 4.3° (*c* 1.1, CH_2Cl_2); IR (nujol) 3298, 2947 (br), 1652, 1530, 1458, 1375, 1301, 1245, 1170, 1017, 879, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, *J* = 6.8 Hz, CH(C**H$_3$**)(CH$_3$)'), 0.95 (d, *J* = 6.8 Hz, CH(CH$_3$)(C**H$_3$**)'), 1.41 (s, C(C**H$_3$**)$_3$), 2.09-2.19 (m, C**H**(CH$_3$)$_2$), 3.86-3.92 (m, C**H**), 4.23-4.42 (m, NHC**H$_2$**Ph), 5.04 (s, OC**H$_2$**), 5.08-5.12 (br d, C(O)N**H**), 6.36 (t, *J* = 5.2 Hz, N**H**CH$_2$Ph), 6.88-6.93 (m, 2 Ar**H**), 6.98-7.03 (m, 1 Ar**H**), 7.12-7.22 (m, 4 Ar**H**), 7.31-7.36 (1 Ar**H**); ^{13}C NMR (300 MHz, $CDCl_3$) δ 18.1 (CH(**C**H$_3$)CH$_3$), 19.6 (CH(CH$_3$)**C**H$_3$), 28.5 (C(**C**H$_3$)$_3$), 30.9 (**C**H(CH$_3$)CH$_3$), 43.1 (NH**C**H$_2$Ph), 60.4 (**C**H), 69.4 (O**C**H$_2$), 80.1 (**C**(CH$_3$)$_3$), 114.4 (d, *J* = 21.9 Hz, **C$_4$'** or **C$_2$'**), 115.0 (d, *J* = 21.2 Hz, **C$_2$'** or **C$_4$'**), 115.2 (**C$_1$**), 122.9 (d, *J* = 2.6 Hz, **C$_6$'**), 129.3 (Ar**C**), 130.3 (d, *J* = 8.3 Hz, **C$_5$'**), 130.9 (Ar**C**), 139.8 (d, *J* = 7.1 Hz, **C$_1$'**), 156.1 (O**C**(O)N), 158.1 (**C$_4$**), 163.2 (d, *J* = 244.4 Hz, **C$_3$'**), 171.7 (**C**(O)N); HRMS (ESI) 453.2178 [M + Na^+] (calcd for $C_{24}H_{31}FN_2O_4Na$ 453.2166); Anal. Calcd for $C_{24}H_{31}FN_2O_4$: C, 66.96; H, 7.26; F, 4.41; N, 6.51. Found: C, 67.23; H, 7.22; F, 4.47; N, 6.28.

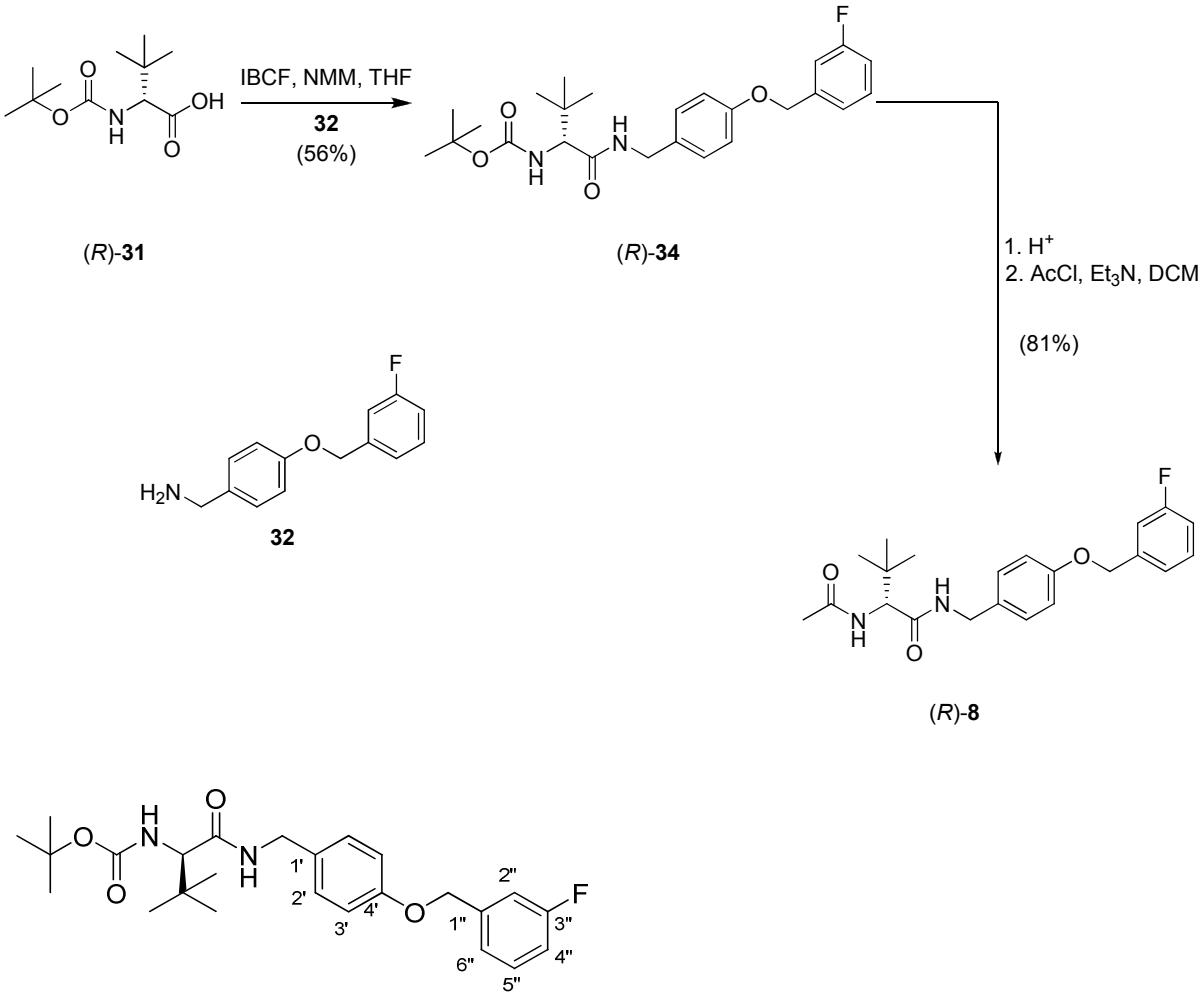
Preparation of (*R*)-*N*-4'-((3"-Fluoro)benzyloxy)benzyl 2-Acetamido-3-methylbutanamide ((*R*)-7).

Trifluoroacetic acid (2 mL) was added to a CH_2Cl_2 (10 mL) solution of solution (*R*)-*N*-4'-((3"-fluoro)benzyloxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methylbutanamide ((*R*)-**33**)(1.00 g, 2.3 mmol) at 0 °C and the solution was stirred at room temperature (16 h). The reaction solution was concentrated in vacuo, dried (30 min), and CH_2Cl_2 (20 mL) and a saturated aqueous Na_2CO_3 solution (20 mL) were added. The layers were separated and the aqueous layer was washed with CH_2Cl_2 (2 x 20 mL). The organic layers were combined and concentrated under vacuum.

The residue was dissolved in CH_2Cl_2 (20 mL) and Et_3N (0.49 mL, 3.5 mmol) and AcCl (200 μL, 2.8 mmol) were successively added at 0 °C. The mixture was stirred at room temperature (3 h), aqueous 10% citric acid (60 mL) was added, and the organic layer was separated. The aqueous layer was washed with CH_2Cl_2 (2 x 30 mL). All the organic layers were combined, washed with aqueous saturated $NaHCO_3$ (30 mL), and H_2O (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The solid was recrystallized with EtOAc to obtain (*R*)-*N*-4'-((3"-fluoro)benzyloxy)benzyl 2-acetamido-3-methylbutanamide ((*R*)-**7**) (585 mg, 68%) as a white solid: R_f = 0.26 (EtOAc); mp 199–200 °C; $[\alpha]^{25.2}_D$ +25.6° (*c* 0.5, MeOH); IR (nujol) 3292, 3215, 3136, 3066, 2917, 2862, 1651, 1457, 1376, 1166, 1073, 950, 728 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.81 (d, *J* = 3.0 Hz, (C**H**$_3$)$_2$), 0.83 (d, *J* = 3.0 Hz, (C**H**$_3$)$_2$), 1.87 (s, C**H**$_3$C(O)), 1.90–1.99 (m, C**H**(CH$_3$)$_2$), 4.12–4.43 (dd, *J* = 6.4, 8.8 Hz, C**H**), 4.19 (d, *J* = 5.8 Hz, C**H**$_2$NH), 5.11 (s, C**H**$_2$O), 6.95 (d, *J* = 8.4 Hz, 2 **H**$_3$), 7.11–7.19 (m, 3 Ar**H**), 7.24–7.28 (m, 2 Ar**H**), 7.39–7.46 (m, 1 Ar**H**), 7.87 (d, *J* = 8.8 Hz, N**H**C(O)CH$_3$), 8.38 (t, *J* = 5.8 Hz, N**H**), addition of excess (*R*)-(-)-mandelic acid to a $CDCl_3$ solution of (*R*)-**7** gave only one signal for the acetyl methyl protons; ^{13}C NMR (100 MHz, DMSO-d_6) δ 18.1, 19.1 (2 **C**H$_3$), 24.4 (**C**H$_3$C(O)), 30.2 (**C**H(CH$_3$)$_3$), 41.3 (N**C**H$_2$), 57.8 (**C**H), 68.2 (d, *J* = 2.0 Hz, **C**H$_2$O), 114.0 (d, *J* = 21.9 Hz, **C$_{2'}$** or **C$_{4'}$**), 114.4 (d, *J* = 20.6 Hz, **C$_{4'}$** or **C$_{2'}$**), 114.5 (**C$_3$**), 123.3 (d, *J* = 2.5 Hz, **C$_{6'}$**), 128.5 (**C$_2$**), 130.3 (d, *J* = 8.3 Hz, **C$_{5'}$**), 131.8 (**C$_1$**), 140.1 (d, *J* = 7.8 Hz, **C$_{1'}$**), 156.9 (**C$_4$**), 163.0 (d, *J* = 242.5 Hz, **C$_{3'}$**), 169.1 (N**C**(O)O), 170.9 (**C**(O)); HRMS (M+Na$^+$)(ESI$^+$) 395.1747 [M + Na$^+$] (calcd for $C_{21}H_{25}FN_2O_3Na^+$ 395.1747); Anal. Calcd. for $C_{21}H_{25}FN_2O_3$: C, 67.72; H, 6.77; F, 5.10; N, 7.52. Found: C, 67.95; H, 6.71; F, 5.18; N, 7.51.

4. Preparation of (*R*)-*N*-4'-((3"-Fluoro)benzyloxy)benzyl 2-Acetamido-3,3-dimethylbutanamide ((*R*)-8).

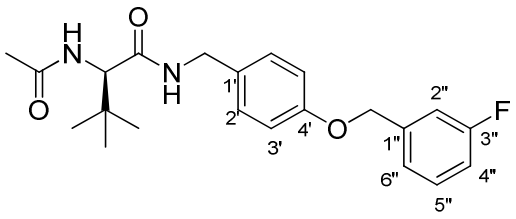
Reaction Overview



Preparation of (*R*)-*N*-4'-((3''-Fluoro)benzyloxy)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3,3-dimethylbutanamide ((*R*)-34).

A THF solution (120 mL) of (*R*)-2-*tert*-butoxycarbonylamino-3,3-dimethylbutyric acid ((*R*)-**31**) (3.25 g, 14.0 mmol) was stirred and cooled at -78 °C under Ar and then 4-methylmorpholine (NMM) (1.8 mL, 16.8 mmol) was added dropwise. After 2 min of stirring at this temperature, isobutylchloroformate (IBCF) (2.2 mL, 16.8 mmol) was added dropwise leading to the precipitation of a white solid. The reaction was allowed to proceed for additional 2 min and then (4-(3'-fluoro)benzyloxy)benzylamine (**32**) (3.90 g, 16.8 mmol) was added portionwise at -78 °C. The mixture was allowed to stir at room temperature (2 h), and then the white solid filtered and the organic layer concentrated in vacuo. The solid was purified by flash column chromatography on silica gel with EtOAc/hexanes (0/10 to 1/9) as the eluant to obtain (*R*)-*N*-4'-((3''-fluoro)benzyloxy)benzyl 2-*N*-(*tert*-

butoxycarbonyl)amino-3,3-dimethylbutanamide ((*R*)-**34**) as colorless sticky gum (1.50 g, 56%): R_f = 0.80 (EtOAc/hexanes 5/5); $[\alpha]^{25.6}_D$ +13.9° (*c* 1.7, $CHCl_3$); IR (nujol) 3292, 3215, 3136, 3066, 2917, 2862, 1651, 1457, 1376, 1166, 1073, 950, 728 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.99 (s, (C**H**$_3$)$_3$), 1.41 (s, (C**H**$_3$)$_3$C(O)), 3.80 (d, *J* = 9.6 Hz, C**H**), 4.29 (1/2 ABq, *J* = 5.2, 14.4 Hz, NC**H**H'), 4.40 (d, *J* = 6.0, 14.4 Hz, NCH**H'**), 5.04 (s, C**H**$_2$O), 5.28 (br d, *J* = 9.6 Hz, N**H**), 6.01–6.10 (br t, N**H**), 6.90 (d, *J* = 8.7 Hz, 2 **H**$_3$), 6.97–7.04 (m, 1 Ar**H**), 7.11–7.21 (m, 4 Ar**H**), 7.30–7.38 (m, 1 Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.6 ((**C**H$_3$)$_3$), 28.3 ((**C**H$_3$)$_3$), 34.5 (**C**(CH$_3$)$_3$), 42.9 (**C**H$_2$), 62.4 (**C**H), 69.2 (d, *J* = 1.9 Hz, Ar**C**H$_2$O), 79.7 (O**C**(CH$_3$)$_3$), 114.1 (d, *J* = 22.5 Hz, **C$_{4'}$** or **C$_{2'}$**), 114.8 (d, *J* = 21.2 Hz, **C$_{2'}$** or **C$_{4'}$**), 115.0 (**C$_1$**), 122.6 (d, *J* = 3.2 Hz, **C$_{6'}$**), 129.2 (Ar**C**), 130.1 (d, *J* = 8.4 Hz, **C$_{5'}$**), 130.6 (Ar**C**), 139.5 (d, *J* = 7.1 Hz, **C$_{1'}$**), 155.9 (**C$_4$**), 157.8 (**C**(O)O), 162.9 (d, *J* = 245.0 Hz, **C$_{3'}$**), 170.9 (**C**(O)); MS (M+Na^+)(ESI^+) 467.2322 [M + Na^+] (calcd for $C_{25}H_{33}FN_2O_4Na^+$ 467.2322); Anal. Calcd. for $C_{25}H_{33}FN_2O_4$: C, 67.55; H, 7.52; N, 6.30. Found: C, 67.25; H, 7.52; N, 6.09.



Preparation of (*R*)-*N*-4'-((3''-Fluoro)benzyloxy)benzyl 2-Acetamido-3,3-dimethylbutanamide ((*R*)-8).

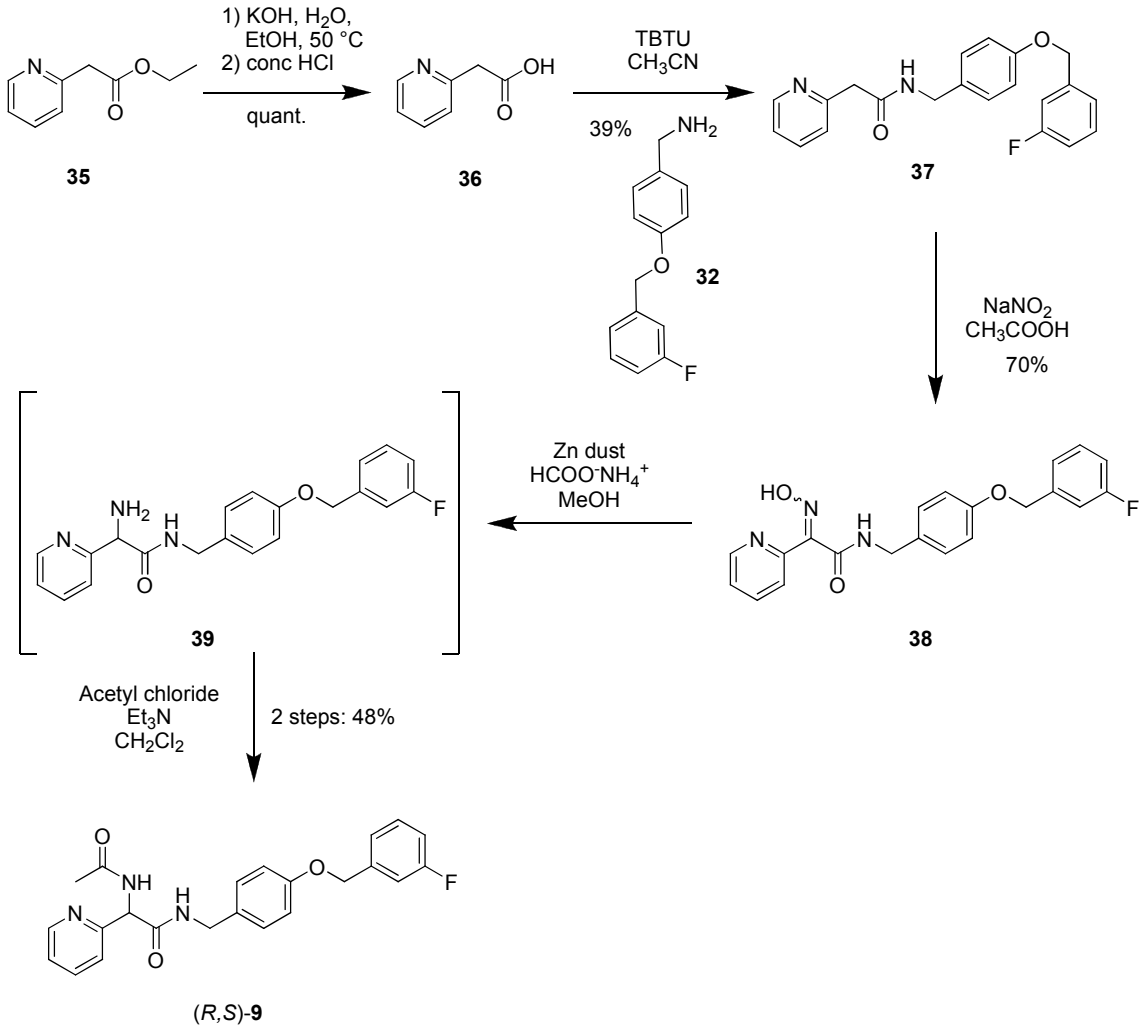
A saturated HCl solution in dioxane (1 mmol/2 mL, 15.8 mL) was added to (*R*)-*N*-4'-((3"-fluoro)benzyloxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3,3-dimethylbutanamide ((*R*)-**34**) (3.50 g, 7.9 mmol) at 0 °C and the solution was stirred at room temperature (16 h). The reaction solution was concentrated in vacuo and dried (30 min). The residue was purified by flash column chromatography on silica gel with EtOAc/MeOH (10/0 to 9/1) as the eluant to obtain (*R*)-*N*-4'-((3"-fluoro)benzyloxy)benzyl 2-amino-3,3-dimethylbutanamide as a beige solid (2.40 g, 89%): R_f = 0.20 (EtOAc); mp 66-67 °C; $[\alpha]^{25.6}_D$ +13.4° (*c* 1, $CHCl_3$); IR (nujol) 3136, 2950, 1638, 1538, 1457, 1375, 1242, 1177, 1132, 1031, 930, 781, 734, 680, 595 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (s, (C**H**$_3$)$_3$), 1.56 (s, N**H**$_2$), 3.12 (s, C**H**), 4.38 (d, *J*

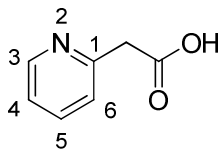
= 6.4 Hz, NC**H$_2$**), 5.05 (s, C**H$_2$**O), 6.90–7.03 (m, 3 Ar**H**, N**H**), 7.13–7.25 (m, 4 Ar**H**), 7.31–7.37 (m, 1 Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.7 ((**C**H$_3$)$_3$), 34.2 (**C**(CH$_3$)$_3$), 42.6 (**C**H$_2$), 64.4 (**C**H), 69.2 (d, *J* = 1.6 Hz, Ph**C**H$_2$O), 114.1 (d, *J* = 22.5 Hz, **C$_{4'}$** or **C$_{2'}$**), 114.8 (d, *J* = 20.9 Hz, **C$_{2'}$** or **C$_{4'}$**), 115.0 (**C$_1$**), 122.6 (d, *J* = 3.1 Hz, **C$_{6'}$**), 129.2 (Ar**C**), 130.1 (d, *J* = 7.7 Hz, **C$_{5'}$**), 131.2 (Ar**C**), 139.6 (d, *J* = 7.8 Hz, **C$_{1'}$**), 157.8 (**C$_4$**), 163.0 (d, *J* = 244.7 Hz, **C$_{3'}$**), 173.3 (**C**(O)); MS (M+H$^+$)(ESI$^+$) 345.1978 [M + H$^+$] (calcd for for $C_{20}H_{25}FN_2O_2H^+$ 345.1978); Anal. Calcd. for $C_{20}H_{25}FN_2O_2 \bullet H_2O$: C, 66.28; H, 7.58; F, 5.24; N, 7.73. Found: C, 66.28; H, 7.72; F, 5.40; N, 7.72.

(*R*)-*N*-4'-((3"-Fluoro)benzyloxy)benzyl 2-amino-3,3-dimethylbutanamide (1.20 g, 3.3 mmol) was dissolved in CH_2Cl_2 (40 mL) and Et_3N (0.93 mL, 6.6 mmol) and AcCl (0.34 mL, 4.8 mmol) were successively added at 0 °C. The mixture was stirred at room temperature (16 h), aqueous 10% citric acid (60 mL) was added, and then the organic layer was separated. The aqueous layer was washed with CH_2Cl_2 (2 x 30 mL). All of the organic layers were combined, washed with aqueous saturated $NaHCO_3$ (30 mL) and H_2O (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The solid was purified by flash column chromatography on silica gel with EtOAc/hexanes (8/2 to 10/0) as the eluant to obtain (*R*)-*N*-4'-((3"-fluoro)benzyloxy)benzyl 2-acetamido-3,3-dimethylbutanamide ((*R*)-**8**) as a white solid (1.03 g, 81%): R_f = 0.56 (EtOAc); mp 64-66 °C; $[\alpha]^{27.0}_D$ -15.6° (*c* 1, $CHCl_3$); IR (nujol) 3111, 2938, 2862, 1657, 1557, 1511, 1458, 1373, 1304, 1176, 1044, 930, 826, 768, 723, 680, 569 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, (C**H$_3$**)$_3$), 1.89 (s, C**H$_3$**C(O)), 4.42 (1/2 ABq, *J* = 5.2, 14.4 Hz, NC**H**H'), 4.34–4.40 (m, C**H**, NCH**H'**), 5.02 (s, C**H$_2$**O), 6.41 (br d, *J* = 8.8 Hz, N**H**C(O)CH$_3$), 6.88 (d, *J* = 8.8 Hz, 2 **H$_3$**), 6.85–6.96 (br m, N**H**), 7.00 (t, *J* = 8.4 Hz, 1 Ar**H**), 7.11–7.18 (m, 4 Ar**H**), 7.30-7.36 (m, 1 Ar**H**), addition of excess (*R*)-(-)-mandelic acid to a $CDCl_3$ solution of (*R*)-**8** gave only one signal for the acetyl methyl protons; ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2 (**C**H$_3$C(O)), 26.6 ((**C**H$_3$)$_3$), 34.8 (**C**(CH$_3$)$_3$), 43.0 (N**C**H$_2$), 60.5 (**C**H), 69.1 (d, *J* = 2.3 Hz, **C**H$_2$O), 114.1 (d, *J* = 21.7 Hz, **C$_{4'}$** or **C$_{2'}$**), 114.8 (d, *J* = 20.9 Hz, **C$_{2'}$** or **C$_{4'}$**), 115.0 (**C$_1$**), 122.6 (d, *J* = 3.1 Hz, **C$_{6'}$**), 129.2 (**C$_2$**), 130.1 (d, *J* = 8.5 Hz, **C$_{5'}$**), 130.4 (**C$_1$**), 139.5 (d, *J* = 7.8 Hz, **C$_{1'}$**), 157.8 (**C$_4$**), 162.9 (d, *J* = 244.7 Hz, **C$_{3'}$**), 170.0, 170.5 (2 **C**(O)); HRMS (M+Na$^+$)(ESI$^+$) 409.1903 [M + Na$^+$] (calcd for $C_{22}H_{27}FN_2O_3Na^+$ 409.1903); Anal. Calcd. for $C_{22}H_{27}FN_2O_3$: C, 68.37; H, 7.04; F, 4.92; N, 7.25. Found: C, 68.31; H, 7.20; F, 5.08; N, 7.25.

5. Preparation of *N*-4'-((3''-Fluoro)benzyloxy)benzyl 2-Acetamido-2-(pyridin-2-yl)acetamide ((*R*)-9).

Reaction Overview

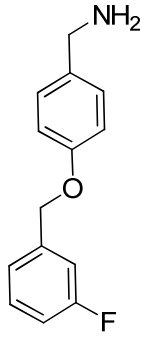




Preparation of 2-(Pyridin-2-yl)acetic Acid[2] (36).

[2] Baruah. P.; Kohn, H., unpublished results

To an EtOH solution (40 mL) of ethyl 2-(pyridin-2-yl)acetate (5.00 g, 30.27 mmol, 1 equiv) was added an aqueous solution (13 mL) of KOH (2.04 g, 36.32 mmol, 1.2 equiv). The resulting solution was stirred at 50 ºC (2 h). The solution was concentrated to one third of the original volume and then washed with Et_2O (3 x 20 mL). The aqueous layer was neutralized with aqueous concentrated HCl (3.0 mL), and then concentrated in vacuo. The crude 2-(pyridin-2-yl)acetic acid (**36**) (4.15 g) was used without further purification for the next step: R_f = 0.06 (EtOAc); ^{1}H NMR (DMSO-d_6) δ 3.93 (s, C**H$_2$**), 7.54 (dd, J = 1.8, 5.4 Hz, **H$_4$**), 7.60 (d, J = 7.9 Hz, **H$_6$**), 8.06 (dt, J = 1.8, 7.9 Hz, **H$_5$**), 8.64 (d, J = 5.4 Hz, **H$_3$**).



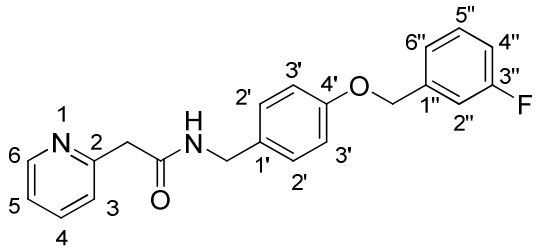
Preparation of 4-((3'-Fluoro)benzyloxy)phenylmethanamine[2] (32)[3].

A mixture of 4-cyanophenol (11.91 g, 100.0 mmol), K_2CO_3 (55.20 g, 400.0 mmol), and 3-(fluoro)benzylbromide (22.68 g, 120.0 mmol) were heated in acetone (400 mL) at reflux (5 h). The volatiles were evaporated and the residue was diluted in CH_2Cl_2 (300 mL), and then washed with H_2O (500 mL), dried ($MgSO_4$), and concentrated in vacuo to give white needles (19.81 g, 87%): R_f = 0.45 (hexanes/EtOAc 9/1); mp 104-105 °C; ^{1}H NMR ($CDCl_3$) δ 5.11 (s, C**H$_2$**O), 6.98–7.20 (m, 5 Ar**H**), 7.33–7.41 (m, 1 Ar**H**), 7.59 (d, J = 8.7 Hz, 2 Ar**H**); HRMS (M+Na$^+$)(ESI$^+$) 250.0641 [M + Na$^+$] (calcd for $C_{14}H_{10}NONa^+$ 250.0641).

To a $LiAlH_4$ (5.02 g, 132.0 mmol) suspension in THF (400 mL) was added dropwise a THF (30 mL) solution of 4-((3'-fluoro)benzyloxy)benzonitrile (10.00 g, 44.0 mmol) at 0

[3] Nakamoto, Kazutaka; Tsukada, Itaru; Tanaka, Keigo; Matsukura, Masayuki; Haneda, Toru; Inoue, Satoshi; Ueda, Norihiro; Abe, Shinya; Hata, Katsura; Watanabe, Naoaki, WO 2005033079 (2005).

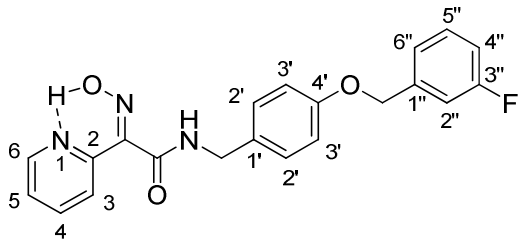
°C. The mixture was stirred at room temperature (16 h) and H_2O (4 mL) was added dropwise at 0 °C followed by an aqueous NaOH solution (2 mL, 15% w/w), and then H_2O (4 mL). The mixture was stirred at room temperature (2 h), and the precipitate filtered and washed with CH_2Cl_2. The filtrate was concentrated in vacuo to obtain a white solid (8.82 g, 86%): R_f = 0.00 (hexanes/EtOAc 9/1); mp 44–45 ºC; ^{1}H NMR ($CDCl_3$) δ 1.61 (br s, N**H**$_2$), 3.79 (s, C**H**$_2$NH$_2$), 5.04 (s, C**H**$_2$O), 6.90–7.04 (m, 3 Ar**H**) 7.13–7.37 (m, 5 Ar**H**); HRMS (M-NH_2^+)(ESI$^+$) 215.088 [M – NH_2^+] (calcd for $C_{14}H_{12}O^+$ 215.087).

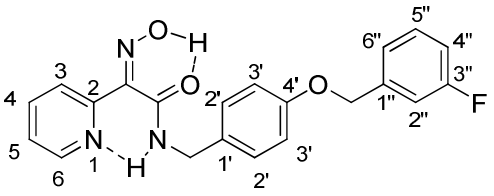


Preparation of *N*-4'-((3''-Fluoro)benzyloxy)benzyl 2-(Pyridin-2-yl)acetamide (37).

To a CH_3CN solution (20 mL) of 2-(pyridin-2-yl)acetic acid (**36**) (1.48 g, 10.81 mmol, 1 equiv) at 0 ºC was added 4-((3'-fluoro)benzyloxy)phenylmethanamine (**32**) (2.50 g, 10.81 mmol, 1 equiv). Upon addition of DMF (5 mL) the contents of the reaction went into solution, and then TBTU (4.16 g, 12.97 mmol, 1.2 equiv) was added at 0 ºC. The reaction mixture was stirred at room temperature under Ar (16 h). The reaction mixture was concentrated in vacuo. EtOAc (50 mL) was added, and the organic layer was successively washed with H_2O (5 x 50 mL), brine (2 x 50 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash liquid chromatography on silica gel with EtOAc/hexanes (5/5 to 10/0) as the eluent. The white solid was recrystallized with EtOH to obtain *N*-4'-((3''-fluoro)benzyloxy)benzyl 2-(pyridin-2-yl)acetamide (**37**) as a white solid (1.48 g, 39%): R_f = 0.43 (EtOAc); mp 127–129 ºC; IR (nujol mull) 3464, 3404, 3338, 3157, 3125, 2850, 1636, 1555, 1456, 1375, 1255, 1146, 1109, 1027, 933, 882, 775, 687, 635, 574, 498, 406 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.79 (s, C**H**$_2$C(O)), 4.40 (d, *J* = 5.7 Hz, C**H**$_2$N), 5.04 (s, C**H**$_2$O), 6.89 (d, *J* = 8.7 Hz, 2 Ar**H**), 7.01 (dt, *J* = 2.3, 8.7 Hz, 1 Ar**H**), 7.13–7.38 (m, 7 Ar**H**), 7.58–7.68 (br s, N**H**), 7.69 (dt, *J* = 1.6, 7.7 Hz, **H$_5$**), 8.51 (d, *J* = 4.2 Hz, **H$_3$**); ^{13}C NMR ($CDCl_3$) δ 42.9 (**C**H$_2$),

45.2 (**C**H_2), 69.2 (d, *J* = 1.7 Hz, **C**H_2O), 114.1 (d, *J* = 21.6 Hz, **C$_{2"}$** or **C$_{4"}$**), 114.8 (d, *J* = 20.5 Hz, **C$_{4"}$** or **C$_{2"}$**), 114.9 (**C$_{3'}$**), 122.0 (**C$_4$** or **C$_6$**), 122.6 (d, *J* = 2.9 Hz, **C$_{6"}$**), 124.1 (**C$_6$** or **C$_4$**), 128.9 (**C$_{2'}$**), 130.1 (d, *J* = 8.6 Hz, **C$_{5"}$**), 131.0 (**C$_{1'}$**), 137.1 (**C$_5$**), 139.6 (d, *J* = 7.4 Hz, **C$_{1"}$**), 149.1 (**C$_3$**), 155.6 (**C$_{4'}$** or **C$_1$**), 157.7 (**C$_1$** or **C$_{4'}$**), 163.0 (d, *J* = 224.7, **C$_{3"}$**), 169.1 (**C**(O)); M_r (+ESI) 373.13 $[M+Na]^+$ (calcd for $C_{21}H_{19}FN_2O_2Na^+$ 373.13 $[M+Na]^+$); Anal. Calcd for $C_{21}H_{19}FN_2O_2$: C, 71.98; H, 5.47; F, 5.42; N, 8.00. Found: C, 72.12; H, 5.36; F, 5.29; N, 7.98.





Preparation of *N*-4'-((3''-Fluoro)benzyloxy)benzyl 2-(Hydroxyimino)-2-(pyridin-2-yl)acetamide (38).

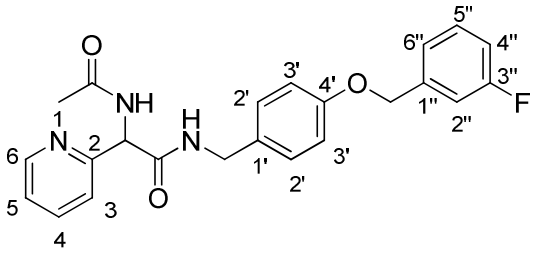
To a stirred glacial acetic acid solution (16 mL) of *N*-4'-((3''-fluoro)benzyloxy)benzyl 2-(pyridin-2-yl)acetamide (**37**) (2.40 g, 6.85 mmol, 1 equiv) maintained at 0 ºC was added portionwise an aqueous solution (5 mL) of $NaNO_2$ (490 mg, 7.05 mmol, 1.03 equiv). The reaction mixture was stirred at room temperature under Ar (16 h) and then H_2O was added and the reaction stirred at room temperature (1 h). The reaction mixture was extracted with CH_2Cl_2 (2 x 100 mL). The organic layers were combined and washed sequentially with an aqueous saturated $NaHCO_3$ solution (2 x 100 mL) and brine (2 x 100 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash liquid chromatography on silica gel with EtOAc/hexanes (2/8 to 5/5) as the eluent to obtain two different isomers of *N*-4'-((3''-fluoro)benzyloxy)benzyl-2-(hydroxyimino)-2-(pyridin-2-yl)acetamide (**38**) as a white solid (1.81 g, 70%, approximative ratio 1/1).

Data for the mixture (A and B): R_f = 0.60, 0.82 (EtOAc); mp 146–148 ºC; IR (nujol mull) 3417, 3323, 3275, 3179, 3137, 3091, 2958, 2896, 1622, 1577, 1457, 1374, 1233, 1178, 1088, 1026, 959, 876, 828, 777, 731, 622, 440, 401 cm^{-1}; ^1H NMR

($CDCl_3$) δ 4.52 (d, *J* = 6.0 Hz, C**H**$_2$N, A or B), 4.58 (d, *J* = 6.0 Hz, C**H**$_2$N**,** B or A), 5.06 (s, C**H**$_2$O**,** A and B), 6.91–7.05 (m, 3 Ar**H,** A and B), 7.14–7.20 (m, 2 Ar**H,** A and B), 7.27–7.38 (m, 3.5 Ar**H,** A and B), 7.38–7.47 (br s, N**H,** A or B), 7.48–7.53 (m, Ar**H,** A or B), 7.78 (dt, *J* = 1.7, 7.9 Hz, Ar**H**, A or B), 7.97 (dt, *J* = 1.9, 8.0 Hz, Ar**H,** B or A), 8.09–8.12 (m, Ar**H**, A or B), 8.42–8.44 (m, Ar**H**, A or B), 8.51–8.53 (m, Ar**H**, B or A), 8.60–8.63 (m, Ar**H**, B or A), 11.45–11.53 (br s, N**H**); ^{13}C NMR ($CDCl_3$) δ 42.2 (**C**H_2, A or B), 42.9 (**C**H_2, B or A), 69.2 (d, *J* = 0.9 Hz, **C**H_2O, A and B), 114.2 (d, *J* = 16.3 Hz, **C$_2$**" or **C$_4$**", A and B), 114.8 (d, *J* = 15.9 Hz, **C$_4$**" or **C$_2$**", A or B), 114.8 (d, *J* = 15.9 Hz, **C$_4$**" or **C$_2$**", B or A), 122.7 (d, *J* = 2.4 Hz, **C$_6$**", A and B), 130.1 (d, *J* = 6.2 Hz, **C$_5$**", A or B), 130.2 (d, *J* = 5.8 Hz, **C$_5$**", B or A), 139.5 (d, *J* = 5.8 Hz, **C$_1$**", A or B), 139.6 (d, *J* = 5.3 Hz, **C$_1$**", B or A), 115.1, 115.1, 122.1, 123.7, 125.2, 125.5, 129.0, 129.2, 129.7, 130.5, 137.6, 138.5, 142.4, 143.0, 144.8, 146.6 (Ar**C**, A and B), 149.9, 152.9 (**C**(NOH, A and B), 157.9, 158.0, 161.8, 163.2 (Ar**C**, A and B), 164.2, 164.6 (**C**(O), A and B); M_r (+ESI) 380.19 $[M+H]^+$ (calcd for $C_{21}H_{18}FN_3O_3H^+$ 380.14 $[M+H]^+$); Anal. Calcd for $C_{21}H_{18}FN_3O_3$: C, 66.48; H, 4.78; F, 5.01; N, 11.08. Found: C, 66.21; H, 4.81; F, 4.89; N, 10.95.

Data for top spot: R_f = 0.82 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 4.51 (d, *J* = 6.3 Hz, C**H**$_2$N), 5.06 (s, C**H**$_2$O), 6. 93 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.01 (dt, *J* = 2.1, 8.4 Hz, 1 Ar**H**), 7.12–7.39 (m, 5 Ar**H**), 7.39–7.46 (br s, N**H**), 7.50 (ddd, *J* = 1.2, 5.1, 7.7 Hz, 1 Ar**H**), 7.97 (dt, *J* = 1.8, 8.1 Hz, 1 Ar**H**), 8.51–8.54 (m, 1 Ar**H**), 8.59–8.63 (m, 1 Ar**H**).

Data for bottom spot: R_f = 0.60 (EtOAc); mp 167–168 ºC; IR (nujol mull) 2919, 2858, 2728, 1622, 1575, 1458, 1375, 1235, 1152, 1041, 960, 828, 726 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.58 (d, *J* = 5.7 Hz, C**H**$_2$N), 5.06 (s, C**H**$_2$O), 6.94–7.39 (m, 9 Ar**H**), 7.78 (dt, *J* = 1.8, 7.9 Hz, 1 Ar**H**), 8.09–8.12 (m, 1 Ar**H**), 8.42–8.44 (m, 1 Ar**H**) , 11.40–11.52 (br s, N**H**); Anal. Calcd for $C_{21}H_{18}FN_3O_3$: C, 66.48; H, 4.78; F, 5.01; N, 11.08. Found: C, 66.26; H, 4.70; F, 4.97; N, 11.06.



Preparation of *N*-4'-((3''-Fluoro)benzyloxy)benzyl 2-Acetamido-2-(pyridin-2-yl)acetamide (9)

To a solution of *N*-4'-((3''-fluoro)benzyloxy)benzyl 2-(hydroxyimino)-2-(pyridin-2-yl)acetamide (**38**) (1.81 g, 4.77 mmol, 1 equiv) in MeOH (95 mL) was added ammonium formate (1.21 g, 19.08 mmol, 4 equiv) as a solid and then the reaction mixture was stirred at room temperature (5 min). Zn dust (Sigma-Aldrich < 10 micron, 1.20 g, 19.08 mmol, 4 equiv) was added and the reaction heated at reflux (6 h), and then maintained at room temperature (16 h). The reaction mixture was filtered through Celite®. The filtrate was concentrated and the residue was dissolved in CH_2Cl_2 (100 mL). The CH_2Cl_2 layer was washed with brine (2 x 100 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude *N*-4'-((3''-fluoro)benzyloxy)benzyl 2-amino-2-(pyridin-2-yl)acetamide crude material **39** was used without further purification for the next step: R_f = 0.00 (EtOAc).

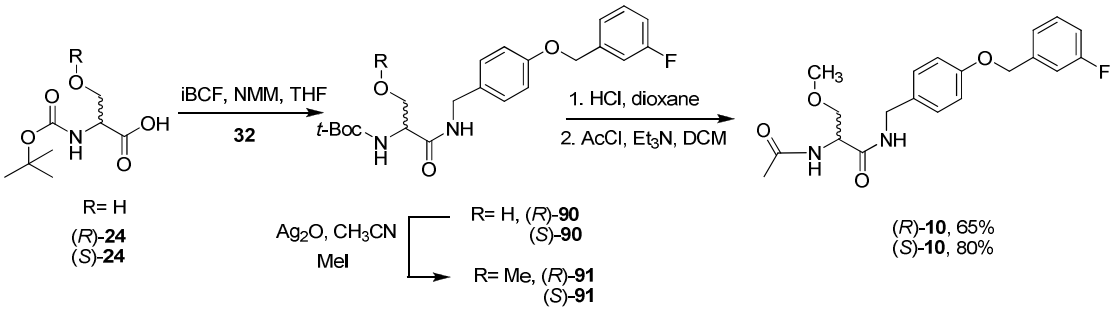
N-4'-((3''-Fluoro)benzyloxy)benzyl 2-amino-2-(pyridin-2-yl)acetamide (**39**) (4.77 mmol, 1 equiv) was dissolved in CH_2Cl_2 (100 mL) and then triethylamine (0.8 mL, 5.72 mmol, 1.2 equiv) and acetyl chloride (0.4 mL, 5.72 mmol, 1.2 equiv) were carefully added at 0 °C and the resulting solution was stirred at room temperature (2 h). An aqueous saturated $NaHCO_3$ solution (100 mL) was added and the organic layer was extracted with CH_2Cl_2 (3 x 100 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo. TLC (EtOAc) analysis showed the presence of two major products at R_f 0.47 and 0.80. The residue was purified by chromatography on silica gel with EtOAc/hexanes (7/3 to 10/0) as the eluent. Two major fractions were collected.

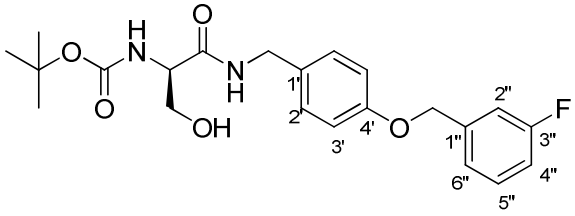
Fractions corresponding to the the second spot were combined, concentrated in vacuo, and recrystallized with EtOAc to obtain *N*-4'-((3''-fluoro)benzyloxy)benzyl 2-

acetamido-2-(pyridin-2-yl)acetamide (**9**) as a white solid (935 mg, 48%): R_f = 0.47 (EtOAc); mp 154–155 ºC; IR (nujol mull) 3150, 2977, 2888, 1874, 1635, 1542, 1456, 1373, 1249, 1139, 1056, 992, 926, 824, 749, 690, 622, 548, 507, 443 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.14 (s, C(O)C**H**$_3$), 4.29–4.41 (m, C**H**$_2$N), 5.03 (s, C**H**$_2$O), 5.56 (d, *J* = 6.0 Hz, C**H**), 6.87 (d, *J* = 9.0 Hz, 2 Ar**H**), 6.98–7.43 (m, 8 Ar**H**, 2 N**H**), 7.70 (dt, *J* = 1.6, 7.8 Hz, 1 Ar**H**), 8.50–8.52 (m, 1 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 23.2 (C(O)**C**H$_3$), 43.2 (**C**H$_2$N), 58.0 (**C**H), 69.2 (d, *J* = 2.3 Hz, **C**H$_2$O), 114.2 (d, *J* = 22.5 Hz, **C$_{2"}$** or **C$_{4"}$**), 114.8 (d, *J* = 21.0 Hz, **C$_{4"}$** or **C$_{2"}$**), 115.0 (**C$_{3'}$**), 121.0 (**C$_4$** or **C$_6$**), 122.7 (d, *J* = 3.1 Hz, **C$_{6"}$**), 123.0 (**C$_6$** or **C$_4$**), 128.8 (**C$_{2'}$**), 130.1 (d, *J* = 7.7 Hz, **C$_{5"}$**), 130.4 (**C$_{1'}$**), 137.2 (**C$_5$**), 139.6 (d, *J* = 6.9 Hz, **C$_{1"}$**), 148.9 (**C$_3$**), 155.9 (**C$_{4'}$** or **C$_1$**), 157.9 (**C$_1$** or **C$_{4'}$**), 163.0 (d, *J* = 244.7 Hz, **C$_{3"}$**), 168.5, 170.3 (2 **C**(O)); M_r (+ESI) 540.05 $[M+Cs]^+$ (calcd for $C_{23}H_{22}FN_3O_3Cs^+$ 540.07 $[M+Cs]^+$); Anal. Calcd for $C_{23}H_{22}FN_3O_3$: C, 67.80; H, 5.44; F, 4.66; N, 10.31. Found: C, 67.56; H, 5.38; F, 4.58; N, 10.24.

6. Preparation of (*R*)-*N*-4'-((3''-Fluoro)benzyloxy)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-10) and (*S*)-*N*-4'-((3''-Fluoro)benzyloxy)benzyl 2-Acetamido-3-methoxypropionamide ((*S*)-10).

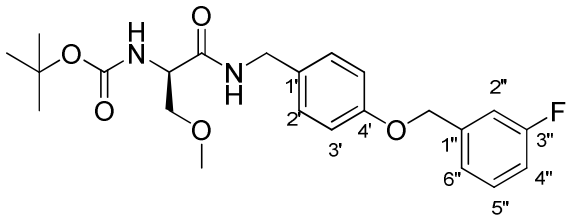
Reaction Overview





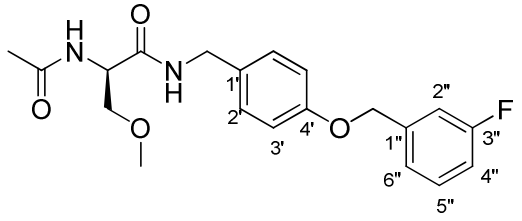
Preparation of (*R*)-*N*-4'-((3''-Fluoro)benzyloxy)benzyl 2-*N*-(*tert.*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-90)

A THF solution (75 mL) of *(R)-t*-Boc-serine ((*R*)-**24**) (4.00 g, 19.5 mmol) was stirred and cooled at -78 °C under Ar and then 4-methylmorpholine (NMM) (2.6 mL, 23.4 mmol) was added dropwise. After 2 min of stirring at this temperature, isobutylchloroformate (IBCF) (3.0 mL, 23.4 mmol) was added dropwise leading to the precipitation of a white solid, and the reaction was allowed to proceed for additional 2 min and then 4-((3'-fluoro)benzyloxy)benzylamine (**32**) (5.40 g, 23.4 mmol) was added portionwise at -78 °C. The mixture was allowed to stir at room temperature (2 h), and the white solid filtered and the organic layer concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (50/50 to 80/20) as the eluant to obtain (*R)-N*-4'-((3''-fluoro)benzyloxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-**90**) as a white solid (5.40 g, 66%): R_f = 0.33 (hexanes/EtOAc 5/5); mp 88-89 °C; $[\alpha]^{25.8}_D$ +25.8° (*c* 1, $CHCl_3$); IR (nujol) 3319, 2966, 1659, 1527, 1456 1376, 1304, 1242, 1166, 1007, 864, 775, 673 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, (CH_3)$_3$), 3.21-3.33 (br m, C**H**H'), 3.59–3.72 (br m, CH**H'**), 4.04–4.20 (br m, C**H**, O**H**), 4.24-4.48 (br m, CH_2N), 5.03 (s, CH_2O), 5.56–5.66 (br d, N**H**), 6.86–6.92 (m, 2 Ar**H**), 6.94–6.99 (m, 1 Ar**H**, N**H**), 7.10–7.21 (m, 4 Ar**H**), 7.30–7.38 (m, 1 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 28.2 ((CH_3)$_3$), 42.8 (NCH_2), 55.2 (OCH_2CH), 62.8 (OCH_2CH), 69.1 (CH_2O), 80.5 ($C(CH_3)_3$), 114.1 (d, *J* = 22.0 Hz, **C$_{4'}$** or **C$_{2'}$**), 114.6 (d, *J* = 21.0 Hz, **C$_{2'}$** or **C$_{4'}$**), 114.9 (**C$_1$**), 122.6 (d, *J* = 2.9 Hz, **C$_{6'}$**), 128.8 (Ar**C**), 130.1 (d, *J* = 8.2 Hz, **C$_{5'}$**), 130.3 (Ar**C**), 139.5 (d, *J* = 7.2 Hz, **C$_{1'}$**), 156.1 (N**C**(O)O), 157.8 (**C$_4$**), 162.9 (d, *J* = 244.7 Hz, **C$_{3'}$**), 171.1 (**C**(O)); HRMS (M+H$^+$)(ESI$^+$) 419.1983 [M + H$^+$] (calcd for $C_{22}H_{27}FN_2O_5H^+$ 419.1982); Anal. Calcd. for $C_{22}H_{27}FN_2O_5$: C, 63.14; H, 6.50; F, 4.54; N, 6.69. Found: C, 63.12; H, 6.55; F, 4.38; N, 6.65.



Preparation of (*R*)-*N*-4'-((3''-Fluoro)benzyloxy)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-91)

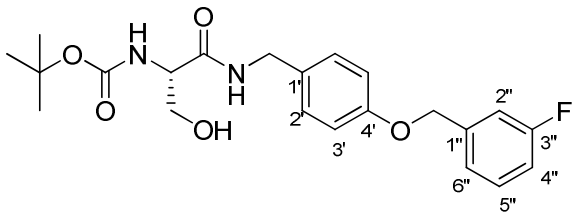
Ag_2O (13.90 g, 60.0 mmol) was added to a CH_3CN solution (300 mL) of (*R*)-*N*-4'-((3''-fluoro)benzyloxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-**90**) (5.00 g, 12.0 mmol) and CH_3I (7.45 mL, 119.6 mmol) at room temperature under Ar. The reaction mixture was stirred at room temperature (3 d), filtered, and the filtrate concentrated in vacuo to obtain a white solid (5.10 g, 98%): R_f = 0.29 (1/1 EtOAc/hexanes); mp 68-70 °C; $[\alpha]^{24.3}_D$ -16.6° (*c* 1, $CHCl_3$); IR (nujol) 3308, 2951, 2857, 1648, 1523, 1457, 1376, 1317, 1168, 1088, 1046, 916, 862, 778, 677 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (s, (CH_3)$_3$), 3.36 (s, OC**H$_3$**), 3.49 (dd, *J* = 6.3, 9.3 Hz, C**H**H'), 3.83 (dd, *J* = 3.9, 9.3 Hz, CH**H'**), 4.18–4.31 (br m, C**H**CH_2), 4.36–4.44 (br m, C**H$_2$**N), 5.05 (s, OC**H$_2$**), 5.36–5.48 (br m, OC(O)N**H**), 6.64–6.72 (br t, CH_2N**H**), 6.91 (d, *J* = 8.1 Hz, 2 Ar**H**), 6.97–7.04 (m, 1 Ar**H**), 7.11–7.24 (m, 4 Ar**H**), 7.30–7.38 (m, 1 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 28.2 (**C**H_3)$_3$), 42.8 (N**C**H_2), 53.6 (OCH_2**C**H), 59.0 (O**C**H_3), 69.1 (**C**H_2O), 72.0 (O**C**H_2CH), 80.2 (**C**$(CH_3)_3$), 114.1 (d, *J* = 22.0 Hz, **C$_4$'** or **C$_2$'**), 114.6 (d, *J* = 21.0 Hz, **C$_2$'** or **C$_4$'**), 114.9 (**C$_1$**), 122.6 (d, *J* = 2.9 Hz, **C$_6$'**), 128.8 (Ar**C**), 130.0 (d, *J* = 8.2 Hz, **C$_5$'**), 130.7 (Ar**C**), 139.5 (d, *J* = 7.3 Hz, **C$_1$'**), 155.0 (N**C**(O)O), 157.8 (**C$_4$**), 162.9 (d, *J* = 244.8 Hz, **C$_3$'**), 170.1 (**C**(O)); HRMS (M+H^+)(ESI$^+$) 433.2139 [M + H^+] (calcd for $C_{23}H_{29}FN_2O_5H^+$ 433.2139); Anal. Calcd. for $C_{23}H_{29}FN_2O_5$: C, 63.87; H, 6.76; F, 4.39; N, 6.48. Found: C, 63.57; H, 6.75; F, 4.13; N, 6.39.



Preparation of (*R*)-*N*-4'-((3''-Fluoro)benzyloxy)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-10)

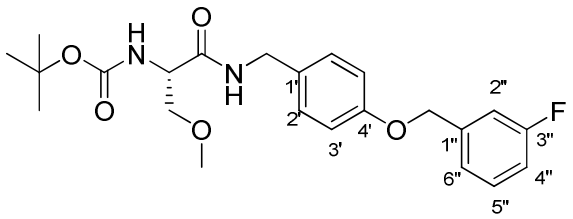
A saturated HCl solution in dioxane (1 mmol/2 mL, 21.75 mL) was added to (*R*)-*N*-4'-((3''-fluoro)benzyloxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-**91**) (4.70 g, 10.9 mmol) at 0 °C and the solution was stirred at room temperature (4 h). The reaction solution was concentrated in vacuo and dried (30 min): ^{1}H NMR ($CDCl_3$) δ 3.23 (s, OC**H$_3$**), 3.80–4.00 (br m, C**H$_2$**), 4.14 (d, J = 11.0 Hz, C**H**H'), 4.40 (d, J = 11.0 Hz, CH**H'**), 4.58–4.35 (m, NC(**H**)CO), 4.87 (s, OC**H$_2$**), 6.79 (d, J = 8.1 Hz, 2 Ar**H**), 6.95 (t, J = 8.4 Hz, 1 Ar**H**), 7.01–7.20 (m, 4 Ar**H**), 7.22–7.30 (m, 1 Ar**H**), 8.11–8.28 (br s, N**H$_3$**), 8.55–8.61 (br s, N**H**C(O)); HRMS (M+H$^+$)(ESI$^+$) 333.1615 [M + H$^+$] (calcd for $C_{18}H_{21}FN_2O_3H^+$ 333.1614).

The residue was dissolved in CH_2Cl_2 (40 mL) and Et_3N (4.47 mL, 32.6 mmol) and AcCl (1.16 mL, 16.30 mmol) were successively added at 0 °C. The mixture was stirred at room temperature (2 h), aqueous 10% citric acid (60 mL) was added and then the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). All of the organic layers were combined, washed with aqueous saturated $NaHCO_3$ (30 mL) and H_2O (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The solid was recrystallized with EtOAc to obtain (*R*)-*N*-4'-((3''-fluoro)benzyloxy)benzyl 2-acetamido-3-methoxypropionamide ((*R*)-**10**) (2.60 g, 65%) as a white solid: R_f = 0.29 (7/3 hexanes/EtOAc); mp 152 °C; $[\alpha]^{24.5}_D$ -18.9° (*c* 1, $CHCl_3$); IR (nujol) 3284, 1633, 1552, 1457, 1376, 1305, 1247, 1137, 1050, 978, 722 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.03 (s, C**H$_3$**CO), 3.37 (s, OC**H$_3$**), 3.43 (dd, J = 7.2, 9.0 Hz, C**H**H'), 3.79 (dd, J = 3.9, 9.0 Hz, CH**H'**), 4.40 (d, J = 5.7 Hz, C**H$_2$**N), 4.49–4.55 (m, NC(**H**)CO), 5.05 (s, C**H$_2$**O), 6.43 (br d, J = 7.2 Hz, N**H**C(O)CH_3), 6.64–6.83 (br m, CH_2N**H**), 6.89–7.05 (m, 3 Ar**H**), 7.10–7.22 (m, 4 Ar**H**), 7.31-7.38 (m, 1 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 ($CDCl_3$) δ 23.1 (**C**H_3C(O)), 43.0 (N**C**H_2), 52.4 (OCH_2**C**H), 59.0 (O**C**H_3), 69.1 (**C**H_2O), 71.7 (O**C**H_2CH), 114.1 (d, J = 21.9 Hz, **C$_{4'}$** or **C$_{2'}$**), 114.8 (d, J = 21.1 Hz, **C$_{2'}$** or **C$_{4'}$**), 115.0 (**C$_1$**), 122.6 (d, J = 2.9 Hz, **C$_{6'}$**), 128.8 (Ar**C**), 130.1 (d, J = 8.2 Hz, **C$_{5'}$**), 130.5 (Ar**C**), 139.5 (d, J = 7.3 Hz, **C$_{1'}$**), 157.8 (**C$_4$**), 162.9 (d, J = 244.8 Hz, **C$_{3'}$**), 169.8, 170.3 (2 **C**(O)); HRMS (M+H$^+$)(ESI$^+$) 375.1720 [M + H$^+$] (calcd for $C_{20}H_{23}FN_2O_4H^+$ 375.1720); Anal. Calcd. for $C_{20}H_{23}FN_2O_4$: C, 64.16; H, 6.19; F, 5.07; N, 7.48. Found: C, 64.14; H, 6.15; F, 5.05; N, 7.37.



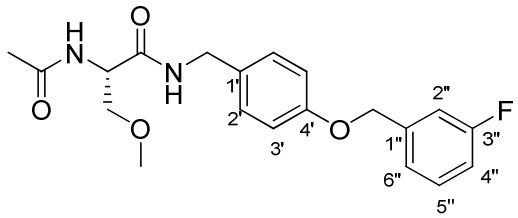
Preparation of (*S*)-*N*-4'-((3''-Fluoro)benzyloxy)benzyl 2-*N*-(*tert.*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*S*)-90)

A THF solution (75 mL) of (*S*)-*t*-Boc-serine ((*S*)-**24**) (4.00 g, 19.5 mmol) was stirred and cooled at -78 °C under Ar and then 4-methylmorpholine (NMM) (2.6 mL, 23.4 mmol) was added dropwise. After 2 min of stirring at this temperature, isobutylchloroformate (IBCF) (3.0 mL, 23.4 mmol) was added dropwise leading to the precipitation of a white solid. The reaction was allowed to proceed for additional 2 min and 4-((3'-fluoro)benzyloxy)benzylamine (**32**) (5.40 g, 23.4 mmol) was added portionwise at -78 °C. The mixture was allowed to stir at room temperature (2 h), and then the white solid filtered and the organic layer concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (50/50 to 80/20) as the eluant to obtain (*S*)-*N*-4'-((3''-fluoro)benzyloxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide ((*S*)-**90**) as a white solid (5.10 g, 60%): R_f = 0.33 (hexanes/EtOAc 5/5); mp 88-89 °C; $[\alpha]^{25.8}_D$ -24.0° (*c* 1, $CHCl_3$); IR (nujol) 3322, 2944, 2858, 1659, 1525, 1457 1375, 1304, 1243, 1166, 1008, 868, 775, 725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, ($C\mathbf{H_3}$)$_3$), 3.21–3.39 (br m, C**H**H'), 3.59–3.74 (br m, CH**H'**), 4.04–4.20 (br m, C**H**, O**H**), 4.24–4.47 (br m, $C\mathbf{H_2}N$), 5.03 (s, $C\mathbf{H_2}O$), 5.63 (d, *J* = 6.6 Hz, N**H**), 6.87-6.93 (d, *J* = 9.0 Hz, 2 Ar**H**), 6.94–7.09 (m, 1 Ar**H**, N**H**), 7.10–7.21 (m, 4 Ar**H**), 7.30–7.38 (m, 1 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 28.2 (($\mathbf{C}H_3$)$_3$), 42.8 ($N\mathbf{C}H_2$), 54.9 ($OCH_2\mathbf{C}H$), 62.8 ($O\mathbf{C}H_2CH$), 69.1 (d, *J* = 1.6 Hz, $Ph\mathbf{C}H_2O$), 80.6 ($\mathbf{C}(CH_3)_3$), 114.1 (d, *J* = 22.2 Hz, $\mathbf{C_4}$' or $\mathbf{C_2}$'), 114.8 (d, *J* = 21.0 Hz, $\mathbf{C_2}$' or $\mathbf{C_4}$'), 115.0 ($\mathbf{C_1}$), 122.6 (d, *J* = 2.9 Hz, $\mathbf{C_6}$'), 128.9 (Ar**C**), 130.1 (d, *J* = 8.0 Hz, $\mathbf{C_5}$'), 130.3 (Ar**C**), 139.5 (d, *J* = 7.4 Hz, $\mathbf{C_1}$'), 156.2 (N**C**(O)O), 157.9 ($\mathbf{C_4}$), 162.9 (d, *J* = 244.7 Hz, $\mathbf{C_3}$'), 171.2 (**C**(O)); HRMS (M+H$^+$)(ESI$^+$) 419.1983 [M + H$^+$] (calcd for $C_{22}H_{27}FN_2O_5H^+$ 419.1982); Anal. Calcd. for $C_{22}H_{27}FN_2O_5$: C, 63.14; H, 6.50; F, 4.54; N, 6.69. Found: C, 63.31; H, 6.53; F, 4.45; N, 6.77.



Preparation of (*S*)-*N*-4'-((3''-Fluoro)benzyloxy)benzyl 2-*N*-(*tert.*-Butoxycarbonyl)amino-3-methoxypropionamide ((*S*)-91)

Ag_2O (13.65 g, 58.6 mmol) was added to a CH_3CN solution (300 mL) of (*S*)-*N*-4'-((3''-fluoro)benzyloxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide ((*S*)-**90**) (4.90 g, 11.7 mmol) and CH_3I (7.3 mL, 117.0 mmol) at room temperature under Ar. The reaction mixture was stirred at room temperature in the dark (3 d), filtered, and the filtrate concentrated in vacuo to obtain a white solid (4.90 g, 98%): R_f = 0.29 (1/1 EtOAc/hexanes); mp 70-71 °C; $[\alpha]^{24.3}_D$ +16.8° (*c* 1, $CHCl_3$); IR (nujol) 3412, 3170, 3120, 1648, 1522, 1457, 1375, 1246, 1167, 1088, 1048, 918, 861, 778, 677 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (s, (CH_3)$_3$), 3.35 (s, OC**H**$_3$), 3.49 (dd, *J* = 6.3, 9.3 Hz, C**H**H'), 3.83 (dd, *J* = 3.9, 9.3 Hz, CH**H'**), 4.18–4.31 (br m, C**H**CH_2), 4.36–4.44 (br m, C**H**$_2$N), 5.05 (s, OC**H**$_2$), 5.36–5.48 (br m, OC(O)N**H**), 6.63–6.74 (br t, CH_2N**H**), 6.91 (d, *J* = 8.7 Hz, 2 Ar**H**), 6.97–7.04 (m, 1 Ar**H**), 7.11–7.23 (m, 4 Ar**H**), 7.30–7.38 (m, 1 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 28.2 ((CH_3)$_3$), 42.8 (N**C**H_2), 54.0 (OCH_2**C**H), 59.0 (O**C**H_3), 69.1 (d, *J* = 1.7 Hz, Ph**C**H_2O), 72.0 (O**C**H_2CH), 80.2 (**C**$(CH_3)_3$), 114.1 (d, *J* = 21.7 Hz, **C$_{4'}$** or **C$_{2'}$**), 114.7 (d, *J* = 21.1 Hz, **C$_{2'}$** or **C$_{4'}$**), 114.9 (**C$_1$**), 122.6 (d, *J* = 2.9 Hz, **C$_{6'}$**), 128.8 (Ar**C**), 130.1 (d, *J* = 8.5 Hz, **C$_{5'}$**), 130.6 (Ar**C**), 139.5 (d, *J* = 6.8 Hz, **C$_{1'}$**), 155.5 (N**C**(O)O), 157.8 (**C$_4$**), 162.9 (d, *J* = 244.7 Hz, **C$_{3'}$**), 170.1 (**C**(O)); HRMS (M+H$^+$)(ESI$^+$) 433.2139 [M + H$^+$] (calcd for $C_{23}H_{29}FN_2O_5H^+$ 433.2139); Anal. Calcd. for $C_{23}H_{29}FN_2O_5$: C, 63.87; H, 6.76; F, 4.39; N, 6.48. Found: C, 63.75; H, 6.82; F, 4.22; N, 6.51.



Preparation of (*S*)-*N*-4'-((3''-Fluoro)benzyloxy)benzyl 2-Acetamido- 3-methoxypropionamide ((*S*)-10)

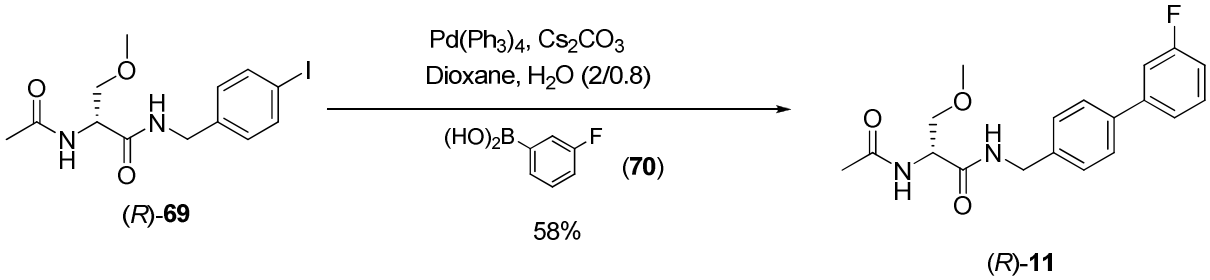
A saturated HCl solution in dioxane (1 mmol/2 mL, 20.8 mL) was added to (*S*)-*N*-4'-((3''-fluoro)benzyloxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide ((*S*)-**91**) (4.50 g, 10.4 mmol) at 0 °C and the solution was stirred at room temperature (4 h). The reaction solution was concentrated in vacuo and dried (30 min): ^{1}H NMR (DMSO-d_6) δ 3.29 (s, OC**H$_3$**), 3.71 (d, *J* = 4.8 Hz, C**H$_2$**), 3.94–4.06 (br m, C**H**), 4.27 (d, *J* = 5.4 Hz, NC**H$_2$**), 5.13 (s, OC**H$_2$**), 6.97 (d, *J* = 8.1 Hz, 2 Ar**H**), 7.10–7.32 (m, 5 Ar**H**), 7.40–7.47 (m, 1 Ar**H**), 8.31-8.42 (br s, N**H$_3$**), 9.05–9.13 (br t, N**H**C(O)).

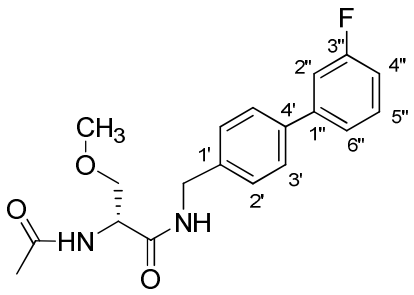
The residue was dissolved in CH_2Cl_2 (40 mL) and Et_3N (4.3 mL, 31.2 mmol) and AcCl (1.1 mL, 15.6 mmol) were successively added at 0 °C. The mixture was stirred at room temperature (2 h), aqueous 10% citric acid (60 mL) was added and then the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). All of the organic layers were combined, washed with aqueous saturated $NaHCO_3$ (30 mL) and H_2O (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The solid was recrystallized with EtOAc to obtain (*S*)-*N*-4'-((3''-fluoro)benzyloxy)benzyl 2-acetamido-3-methoxypropionamide ((*S*)-**10**) (3.10 g, 80%) as a white solid: R_f = 0.29 (7/3 hexanes/EtOAc); mp 149-150 °C; $[\alpha]^{24.5}_D$ +18.8° (*c* 1, $CHCl_3$); IR (nujol) 3281, 2946, 2890, 1634, 1553, 1457, 1376, 1304, 1246, 1135, 1050, 953, 720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.02 (s, C**H$_3$**CO), 3.36 (s, OC**H$_3$**), 3.43 (dd, *J* = 7.5, 9.1 Hz, C**H**H'), 3.79 (dd, *J* = 4.2, 9.1 Hz, CH**H'**), 4.40 (d, *J* = 5.7 Hz, C**H$_2$**N), 4.50–4.55 (m, NC(**H**)CO), 5.05 (s, C**H$_2$**O), 6.47 (br d, *J* = 6.0 Hz, N**H**C(O)CH_3), 6.70–6.79 (br m, CH_2N**H**), 6.90–7.05 (m, 3 Ar**H**), 7.10–7.22 (m, 4 Ar**H**), 7.31–7.38 (m, 1 Ar**H**), addition of excess (*R*)-(-)-mandelic acid to a $CDCl_3$ solution of ((*S*)-**10**) gave only one signal for the acetyl methyl and one signal for the ether methyl protons and addition of excess (*R*)-(-)-mandelic acid to a $CDCl_3$ solution of ((*S*)-**10**) and ((*R*)-**10**) (2/1) gave two signals for the acetyl methyl (δ 2.00 and 2.02) and two signals for the ether methyl protons in an ~ 2/1 proportion (δ 3.30 and 3.34); ^{13}C NMR ($CDCl_3$) δ 23.1 (**C**H_3C(O)), 42.9 (N**C**H_2), 52.4 (OCH_2**C**H), 59.0 (O**C**H_3), 69.1 (d, *J* = 2.3 Hz, **C**H_2O), 71.8 (O**C**H_2CH), 114.1 (d, *J* = 22.2 Hz, **C$_{4'}$** or **C$_{2'}$**), 114.8 (d, *J* = 21.1 Hz, **C$_{2'}$** or **C$_{4'}$**),

114.9 (**C$_1$**), 122.6 (d, *J* = 2.9 Hz, **C$_{6'}$**), 128.8 (Ar**C**), 130.1 (d, *J* = 8.0 Hz, **C$_{5'}$**), 130.5 (Ar**C**), 139.5 (d, *J* = 6.9 Hz, **C$_{1'}$**), 157.8 (**C$_4$**), 162.9 (d, *J* = 244.7 Hz, **C$_{3'}$**), 169.8, 170.3 (2 **C**(O)); HRMS (M+H$^+$)(ESI$^+$) 375.1720 [M + H$^+$] (calcd for $C_{20}H_{23}FN_2O_4H^+$ 375.1720); Anal. Calcd. for $C_{20}H_{23}FN_2O_4$: C, 64.16; H, 6.19; F, 5.07; N, 7.48. Found: C, 64.33; H, 6.23; F, 5.01; N, 7.50.

7. Preparation of (*R*)-*N*-(3''-Fluorobiphenyl-4-yl)methyl 2-Acetamido-3-methoxypropionamide ((*R*)-11).

Reaction Overview





Preparation of (*R*)-*N*-(3''-Fluorobiphenyl-4-yl)methyl 2-Acetamido-3-methoxypropionamide ((*R*)-11).

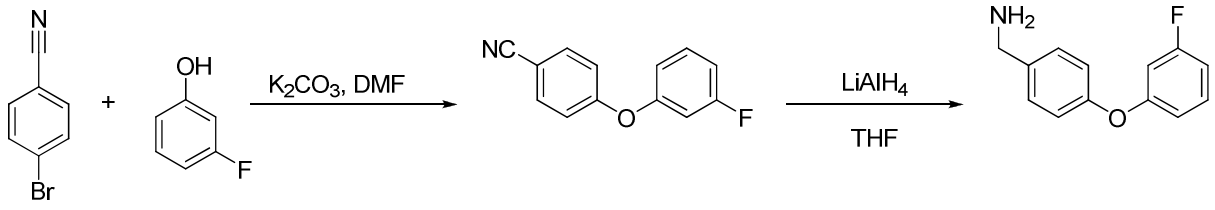
To a flame-dried Schlenck tube, under Ar, containing a dioxane (22.5 mL) solution of (*R*)-*N*-4'-(iodo)benzyl 2-acetamido-3-methoxypropionamide[4] ((*R*)-**69**) (1.50 g, 4.0 mmol), palladiumtetrakis(triphenylphosphine) (464 mg, 0.402), and 3-fluorophenylboronic acid (**70**) (670 mg, 4.80 mmol) was added an aqueous solution (9 mL) of Cs_2CO_3 (2.60 g, 8.0 mmol). The mixture was stirred at reflux (16 h). Then

[4] Salome, C.; Salome-Grosjean, E.; Park, K.D. ; Morieux, P. ; Swendiman, R. ; DeMarco, E. ; Stables, J.P. ; Kohn, H. *J. Med. Chem.* **2010**, *53*, 1288–1305.

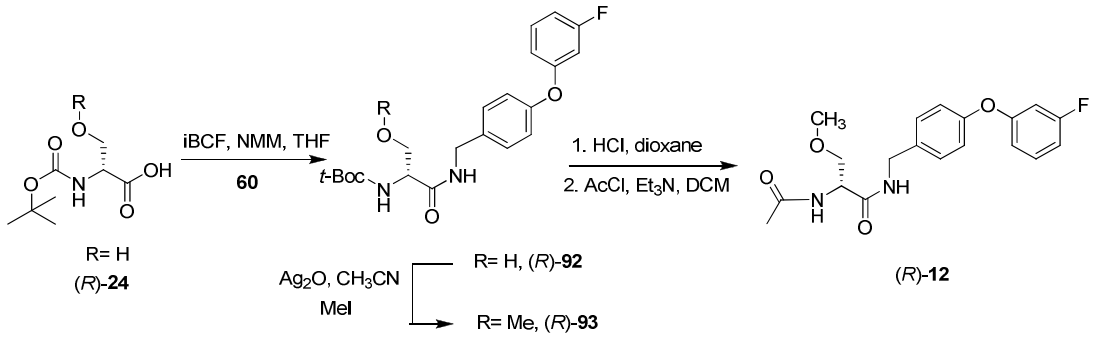
MeOH and silica gel were added, and the volatiles were concentrated in vacuo. The residue was purified by flash chromatography on silica gel with EtOAc/MeOH (10/0 to 9/1) as the eluant to obtain (*R*)-*N*-(3'-fluorobiphenyl-4-yl)methyl 2-acetamido-3-methoxypropionamide ((*R*)-**11**) (0.95 g, 60%) as a yellowish solid. To remove traces of palladium impurities, the solid was treated with 6.00 g of resin scavenger (SPM32, PhosPhonics) in CH_2Cl_2. The mixture was stirred at room temperature (2 h), filtered, and the filtrate evaporated under vacuum to obtain 800 mg (58%) of (*R*)-*N*-(3''-fluorobiphenyl-4-yl)methyl 2-acetamido-3-methoxypropionamide ((*R*)-**11**) as a white solid: R_f = 0.22 (EtOAc); mp 170-172 °C; $[\alpha]^{25.3}_D$ = –8.1° (c 0.5, $CHCl_3$); IR (nujol mull) 3288, 2922, 2857, 1642, 1549, 1457, 1376, 1299, 1254, 1190, 1108, 1048, 875, 784, 723, 604 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.03 (s, C**H**$_3$C(O)), 3.39 (s, OC**H**$_3$), 3.47 (d, *J* = 7.5, 9.3 Hz, C**H**H'O), 3.81 (d, *J* = 3.9, 9.3 Hz, CH**H'**O), 4.45–4.55 (m, C**H**$_2$N), 4.56–4.63 (m, NC(**H**)CO), 6.53 (br d, *J* = 6.6 Hz, N**H**C(O)CH_3), 6.93–7.07 (m, CH_2N**H**, Ar**H**), 7.23–7.51 (m, 5 Ar**H**), 7.53 (d, *J* = 8.1 Hz, 2 Ar**H**), addition of excess (*R*)-(-)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(3''-fluorobiphenyl-4-yl)methyl 2-acetamido-3-methoxypropionamide ((*R*)-**11**) gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR (DMSO-d_6) δ 23.2 (**C**H_3C(O)), 43.2 (**C**H_2N), 52.4 (**C**HCH_2), 59.1 (O**C**H_3), 71.7 (**C**H_2OCH_3), 113.8 (d, *J* = 18.8 Hz, **C**$_{2'}$ or **C**$_{4'}$), 114.1 (d, *J* = 17.7 Hz, **C**$_{4'}$ or **C**$_{2'}$), 122.6 (d, *J* = 2.8 Hz, **C**$_{6'}$), 127.3, 127.9 (**C**$_2$, **C**$_3$), 130.2 (d, *J* = 8.5 Hz, **C**$_{1'}$ or **C**$_{5'}$), 137.6 (**C**$_1$), 139.1 (d, *J* = 2.3 Hz, **C**$_4$), 142.9 (d, *J* = 8.0 Hz, **C**$_{5'}$ or **C**$_{1'}$), 163.2 (d, *J* = 244.2 Hz, **C**$_{3'}$), 170.1, 170.3 (2 **C**(O)); HRMS (M+Cs^+)(ESI^+) 477.0591 [M + Cs^+] (calcd for $C_{19}H_{21}FN_2O_3Cs^+$ 477.0587); Anal. Calcd. for $C_{19}H_{21}FN_2O_3$: C, 66.26; H, 6.15; F, 5.52; N, 8.13. Found: C, 66.05; H, 6.13; F, 5.32; N, 8.04.

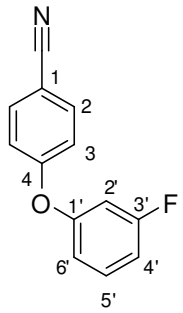
8. Preparation of (*R*)-*N*-4'-((3''-Fluoro)phenoxy)benzyl 2-*N*-Acetamido-3-methoxypropionamide ((*R*)-12).

Reaction Overview



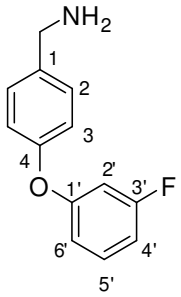
52 **54** **57** **60**



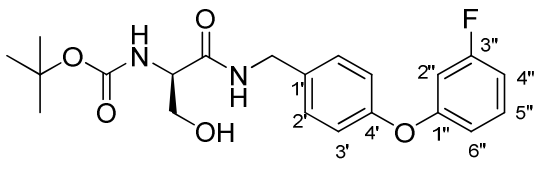


Preparation of 4-((3'-Fluoro)phenoxy)benzonitrile (57). A DMF (83 mL) solution of K_2CO_3 (12.60 g, 91.3 mmol), 4-bromobenzonitrile (**52**) (15.00 g, 83.0 mmol) and 3-fluorophenol (**54**) (8.2 mL, 91.3 mmol) was stirred at reflux (24 h). DMF was removed by distillation and the residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (0/10 to 5/95) as the eluent to obtain 4-((3'-fluoro)phenoxy)benzonitrile (**57**) as a white solid (9.81 g, 56%): R_f = 0.54 (EtOAc/hexanes 5/95); mp 67–69 °C; IR (nujol) 3073, 2961, 2912, 2862, 2219, 1593, 1461, 1376, 1265, 1225, 1163, 1119, 954, 869, 830, 788, 677, 543 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.79 (dt, *J* = 2.1, 9.9 Hz, 1 Ar**H**), 6.84–6.98 (m, 2 Ar**H**), 7.05 (d, *J* = 9.0 Hz, 2 $\mathbf{H_3}$), 7.32–7.41 (m, 1 Ar**H**), 7.64 (d, *J* = 9.0 Hz, 2 $\mathbf{H_2}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 106.7 ($\mathbf{C_1}$), 107.9 (d, *J* = 23.9 Hz, $\mathbf{C_{2'}}$ or $\mathbf{C_{4'}}$), 111.9 (d, *J* = 21.1 Hz, $\mathbf{C_{4'}}$ or $\mathbf{C_{2'}}$), 115.6 (d, *J* = 3.4 Hz, $\mathbf{C_{6'}}$), 118.5, 118.6 (**C**N, $\mathbf{C_3}$), 131.0 (d, *J* = 9.7 Hz, $\mathbf{C_{5'}}$), 134.2

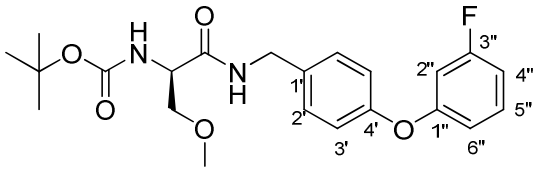
(**C2**), 156.2 (d, *J* = 10.3 Hz, **C1'**), 160.7 (**C4**), 163.6 (d, *J* = 247.1 Hz, **C3'**); HRMS (M+H$^+$)(ESI$^+$) not observed [M + H$^+$] (calcd for $C_{13}H_8FNOH^+$ 214.0668); Anal. Calcd. for $C_{13}H_8FNO$: C, 73.23; H, 3.78; F, 8.91; N, 6.57. Found: C, 73.18; H, 3.69; F, 8.68; N, 6.53.



Preparation of 4'-((3"-Fluoro)phenoxy)benzylamine (60). To a $LiAlH_4$ (3.21 g, 84.5 mmol) suspension in THF (300 mL) was added dropwise a THF (50 mL) solution of 4'-((3"-fluoro)phenoxy)benzonitrile (**57**) (6.00 g, 28.2 mmol) at 0 °C. The mixture was stirred at room temperature (16 h) and then H_2O (2.5 mL) was added dropwise at 0 °C followed by an aqueous NaOH solution (1.25 mL, 15% w/w) and then H_2O (2.5 mL). The mixture was stirred at room temperature (2 h) and the precipitate was filtered, and the pad was washed with CH_2Cl_2. The filtrate was concentrated in vacuo to give 4.00 g of a colorless oil (65%): R_f = 0.00 (hexanes/EtOAc 9/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55 (br s, N**H2**), 3.87 (s, C**H2**NH_2), 6.66–6.80 (br m, 3 Ar**H**), 7.01 (d, *J* = 7.5 Hz, 2 Ar**H**), 7.24–7.32 (m, 3 Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$) 45.8 (**C**H_2NH_2), 105.8 (d, *J* = 24.8 Hz, **C2'** or **C4'**), 109.7 (d, *J* = 20.9 Hz, **C4'** or **C2'**), 113.7 (d, *J* = 3.1 Hz, **C6'**), 119.7, 128.7 (2 Ar**C**), 130.4 (d, *J* = 10.0 Hz, **C5'**), 138.8 (**C2**), 155.0 (**C4**), 159.1 (d, *J* = 10.9 Hz, **C1'**), 163.5 (d, *J* = 244.2 Hz, **C3'**); HRMS (M-NH_2)$^+$ (ESI$^+$) 201.0698 [M - NH_2]$^+$ (calcd for $C_{13}H_{10}FO^+$ 201.0715).

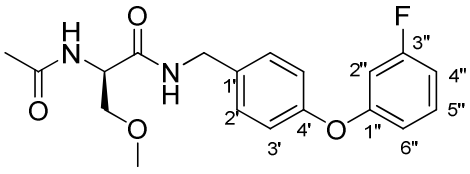


Preparation of (*R*)-*N*-4'-((3''-Fluoro)phenoxy)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-92). A THF solution (150 mL) of (*R*)-*t*-Boc-serine ((*R*)-**24**) (3.00 g, 14.6 mmol) was stirred and cooled at -78 °C under Ar and then 4-methylmorpholine (NMM) (1.9 mL, 17.6 mmol) was added dropwise. After 2 min of stirring at this temperature, isobutylchloroformate (IBCF) (2.3 mL, 17.6 mmol) was added dropwise leading to the precipitation of a white solid, and the reaction was allowed to proceed for additional 2 min, and then 4-((3'-fluoro)phenoxy)benzylamine (**60**) (3.50 g, 16.1 mmol) was added portionwise at -78 °C. The mixture was allowed to stir at room temperature (2 h), and the white solid filtered and the organic layer concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (0/10 to 7/3) as the eluant to obtain (*R*)-*N*-4'-((3"-fluoro)phenoxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-**92**) as a sticky white gum (3.55 g, 60%): R_f = 0.34 (hexanes/EtOAc 5/5); $[\alpha]^{25.9}_D$ +16.3° (*c* 1, $CHCl_3$); IR (nujol) 3322, 3265, 2917, 2858, 1659, 1600, 1525, 1458, 1375, 1270, 1119, 1011, 961, 849, 766, 670, 579, 510 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, (C**H**$_3$)$_3$), 3.33–3.44 (br m, O**H**), 3.64–3.73 (br m, C**H**H'), 4.06–4.22 (br m, CH**H'**, C**H**), 4.34–4.52 (br m, C**H**$_2$NH), 5.67 (d, *J* = 7.2 Hz, N**H**), 6.64–6.81 (m, 3 Ar**H**), 6.97 (d, *J* = 8.8 Hz, 2 Ar**H**), 7.11–7.19 (br m, N**H**), 7.21–7.29 (m, 3 Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2 ((**C**H$_3$)$_3$), 42.7 (N**C**H$_2$), 54.9 (OCH$_2$**C**H), 62.7 (O**C**H$_2$CH), 80.6 (**C**(CH$_3$)$_3$), 106.0 (d, *J* = 24.0 Hz, **C$_{2'}$** or **C$_{4'}$**), 109.9 (d, *J* = 20.9 Hz, **C$_{4'}$** or **C$_{2'}$**), 113.9 (d, *J* = 3.1 Hz, **C$_{6'}$**), 119.7, 129.1 (2 Ar**C**), 130.5 (d, *J* = 9.3 Hz, **C$_{5'}$**), 133.5 (Ar**C**), 155.6 (**C$_4$**), 156.3 (NH**C**(O)O), 158.7 (d, *J* = 10.1 Hz, **C$_{1'}$**), 163.5 (d, *J* = 245.4 Hz, **C$_{3'}$**), 171.4 (**C**(O)); HRMS (M+H$^+$)(ESI$^+$) 405.1826 [M + H$^+$] (calcd for $C_{21}H_{25}FN_2O_5H^+$ 405.1826); Anal. Calcd. for $C_{21}H_{25}FN_2O_5$•0.05H_2O: C, 62.22; H, 6.24; F, 4.69; N, 6.91. Found: C, 61.86; H, 6.53; F, 4.37; N, 6.88.



Preparation of (*R*)-*N*-4'-((3''-Fluoro)phenoxy)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-93). Ag_2O (8.86 g, 38.4

mmol) was added to a CH_3CN solution (150 mL) of (*R*)-*N*-4'-((3"-fluoro)phenoxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-**92**) (3.10 g, 7.7 mmol) and CH_3I (4.8 mL, 77.0 mmol) at room temperature under Ar. The reaction mixture was stirred at room temperature in the dark (3 d), filtered through Celite®, and the filtrate concentrated in vacuo to obtain a white solid. The solid was purified by flash column chromatography on silica gel with EtOAc/hexanes (5/95 to 50/50) as the eluant to obtain (*R*)-*N*-4'-((3"-fluoro)phenoxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-**93**) as a colorless oil (3.20 g, quant.): R_f = 0.42 (1/1 EtOAc/hexanes); IR (nujol) 3156, 2935, 1711, 1672, 1601, 1457, 1372, 1264, 1168, 1118, 960, 855, 774, 680, 507 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, $(C\mathbf{H_3})_3$), 3.37 (s, $OC\mathbf{H_3}$), 3.50 (dd, *J* = 6.4, 9.2 Hz, C**H**H'), 3.85 (dd, *J* = 4.0, 9.2 Hz, CH**H'**), 4.23–4.32 (br m, C**H**), 4.47 (br t, *J* = 4.4 Hz, $C\mathbf{H_2}NH$), 5.36–5.44 (br m, N**H**), 6.67 (dt, *J* = 2.4, 10.4 Hz, 1 Ar**H**), 6.74–6.71 (m, 2 Ar**H**, N**H**), 6.99 (d, *J* = 8.4 Hz, 2 $\mathbf{H_3}$), 7.22–7.29 (m, 3 Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2 ($(\mathbf{C}H_3)_3$), 42.8 ($N\mathbf{C}H_2$), 54.0 ($OCH_2\mathbf{C}H$), 59.1 ($O\mathbf{C}H_3$), 71.9 ($\mathbf{C}H_2O$), 80.3 ($\mathbf{C}(CH_3)_3$), 105.9 (d, *J* = 24.5 Hz, $\mathbf{C_{2'}}$ or $\mathbf{C_{4'}}$), 109.9 (d, *J* = 21.2 Hz, $\mathbf{C_{4'}}$ or $\mathbf{C_{2'}}$), 113.8 (d, *J* = 3.2 Hz, $\mathbf{C_{6'}}$), 119.7, 129.0 (2 Ar**C**), 130.5 (d, *J* = 9.7 Hz, $\mathbf{C_{5'}}$), 133.7 (Ar**C**), 155.6 (NH**C**(O)O), 158.8 (d, *J* = 10.9 Hz, $\mathbf{C_{1'}}$), 163.5 (d, *J* = 245.0 Hz, $\mathbf{C_{3'}}$), 170.3 (**C**(O)), the remaining aromatic peak was not detected and is believed to overlap with the observed signals; Anal. Calcd. for $C_{22}H_{27}FN_2O_5$: C, 63.14; H, 6.50; F, 4.54; N, 6.69. Found: C, 63.19; H, 6.63; F, 4.37; N, 6.63.

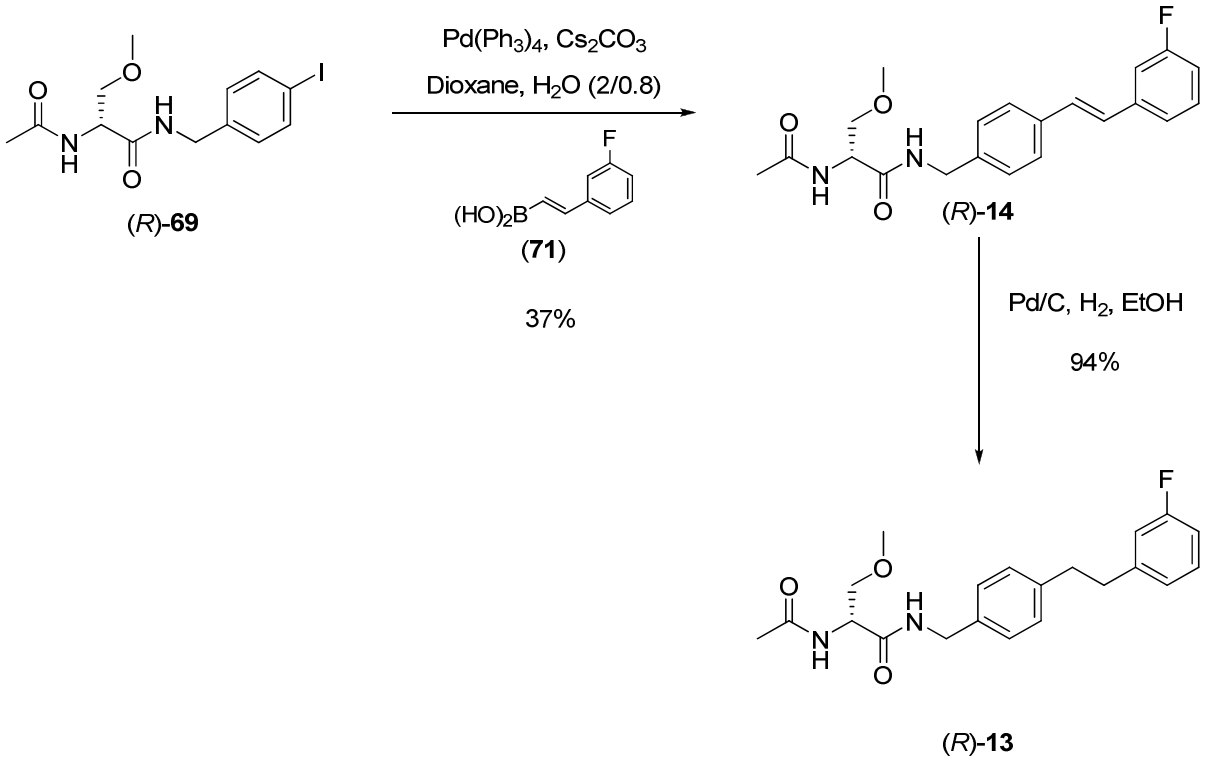


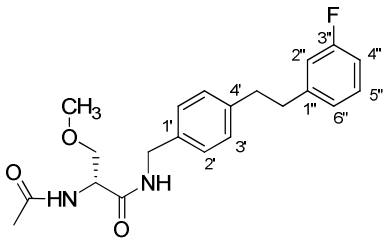
Preparation of (*R*)-*N*-4'-((3"-Fluoro)phenoxy)benzyl 2-*N*-Acetamido -3-methoxypropionamide ((*R*)-12). A saturated HCl solution in dioxane (1 mmol/2 mL, 16.7 mL) was added to an Et_2O (8 mL) solution of (*R*)-*N*-4'-((3"-fluoro)phenoxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-**93**) (3.50 g, 8.4 mmol) at 0 °C and the solution was stirred at room temperature (16 h). The reaction solution was concentrated in vacuo and dried (30 min).

The residue was dissolved in CH_2Cl_2 (40 mL) and Et_3N (3.52 mL, 25.1 mmol) and AcCl (0.91 mL, 12.5 mmol) were successively added at 0 °C. The mixture was stirred at room temperature (16 h), aqueous 10% citric acid (60 mL) was added, and then the organic layer was separated. The aqueous layer was washed with CH_2Cl_2 (2 x 30 mL). All of the organic layers were combined, washed with aqueous saturated $NaHCO_3$ (30 mL) and H_2O (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The solid was purified by flash column chromatography on silica gel with EtOAc as the eluant to obtain (*R*)-*N*-4'-((3"-fluoro)phenoxy)benzyl 2-*N*-acetamido-3-methoxypropionamide ((*R*)-**12**) as a white solid (1.30 g, 43%): R_f = 0.45 (EtOAc); mp 125–126 °C; $[\alpha]^{25.3}_D$ –14.8° (*c* 1, $CHCl_3$); IR (nujol) 3148, 2974, 2918, 1637, 1552, 1457, 1377, 1274, 1223, 1126, 963, 846, 764, 725, 606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.04 (s, C**H**$_3$C(O)), 3.39 (s, OC**H**$_3$), 3.45 (dd, *J* = 7.5, 9.3 Hz, C**H**H'), 3.81 (dd, *J* = 4.2, 9.3 Hz, C**H**H'), 4.45 (d, *J* = 6.0 Hz, C**H**$_2$NH), 4.53–4.59 (m, C**H**), 6.48 (br d, *J* = 6.0 Hz, N**H**C(O)CH_3), 6.68 (dt, *J* = 2.4, 10.2 Hz, 1 Ar**H**), 6.74–6.89 (m, 2 Ar**H**, N**H**), 6.99 (d, *J* = 9.0 Hz, 2 **H**$_3$), 7.21–7.34 (m, 3 Ar**H**), addition of excess (*R*)-(-)-mandelic acid to a $CDCl_3$ solution of (*R*)-**12** gave only one signal for the acetyl methyl protons; ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2 (**C**H_3C(O)), 42.9 (N**C**H_2), 52.4 (OCH_2**C**H), 59.1 (O**C**H_3), 71.6 (**C**H_2O), 106.0 (d, *J* = 24.4 Hz, **C**$_{2'}$ or **C**$_{4'}$), 109.9 (d, *J* = 21.3 Hz, **C**$_{4'}$ or **C**$_{2'}$), 113.9 (d, *J* = 2.5 Hz, **C**$_{6'}$), 119.6, 129.0 (2 Ar**C**), 130.5 (d, *J* = 9.6 Hz, **C**$_{5'}$), 133.6, 155.6 (2 Ar**C**), 158.7 (d, *J* = 10.9 Hz, **C**$_{1'}$), 163.5 (d, *J* = 245.7 Hz, **C**$_{3'}$), 170.0, 170.3 (2 **C**(O)); HRMS (M+H$^+$)(ESI$^+$) 361.1564 [M + H$^+$] (calcd for $C_{19}H_{21}FN_2O_4H^+$ 361.1563); Anal. Calcd. for $C_{19}H_{21}FN_2O_4$: C, 63.32; H, 5.87; F, 5.27; N, 7.77. Found: C, 63.35; H, 5.84; F, 5.06; N, 7.78.

9. Preparation of (*R*)-*N*-4'-((3''-Fluoro)phenethyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-13) and (2-*R,E*)-*N*-4'-((3''-Fluoro)styryl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-14).

Reaction Overview

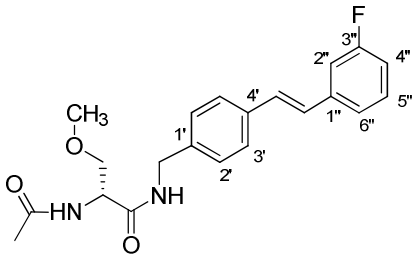




Preparation of (*R*)-*N*-4'-((3''-Fluoro)phenethyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-13)

Pd/C (18 mg) was added to an EtOH solution of (2-*R,E*)-*N*-4'-((3''-fluoro)styryl)benzyl 2-acetamido-3-methoxypropionamide ((*R*)-**14**) (180 mg, 0.49 mmol), and the mixture was stirred at room temperature under H_2 (1 atm) (36 h). The reaction mixture was filtered through a pad of Celite®, and the pad was washed successively with EtOH and CH_2Cl_2. The filtrate was concentrated under vacuum to obtain (*R*)-*N*-4'-((3''-fluoro)phenethyl)benzyl 2-acetamido-3-methoxypropionamide ((*R*)-**13**) (170 mg, 94%) as a white solid: R_f = 0.29 (EtOAc); mp 134-136 °C; $[\alpha]^{24.4}_D$ = -12.3° (*c* 0.48, $CHCl_3$); IR (nujol) 3140, 2943, 2870, 2729, 2670, 1631, 1542, 1457,

1374, 1305, 1136, 938, 842, 726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.03 (s, C**H**$_3$C(O)), 2.90 (s, 2 C**H**$_2$Ph), 3.38 (s, OC**H**$_3$), 3.43 (dd, *J* = 7.6, 9.2 Hz, C**H**H'), 3.81 (dd, *J* = 4.0, 9.2 Hz, CH**H'**), 4.40–4.47 (m, C**H**$_2$N), 4.50–4.55 (m, NC(**H**)CO), 6.41–6.47 (br m, CHN**H**), 6.68–6.75 (br m, CH_2N**H**), 6.84–6.94 (m, 3 Ar**H**), 7.11–7.25 (m, 5 Ar**H**), addition of excess (*R*)-(-)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-4'-((3''-fluoro)phenethyl)benzyl 2-acetamido-3-methoxypropionamide ((*R*)-**13**) gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2 (**C**H_3CO), 37.1 (**C**H_2Ar), 37.4 (d, *J* = 1.7 Hz, **C**H_2Ar), 43.3 (**C**H_2N), 52.4 (**C**HCH$_2$), 59.1 (O**C**H_3), 71.7 (**C**H_2OCH$_3$), 112.8 (d, *J* = 21.1 Hz, **C**$_{2'}$ or **C**$_{4'}$), 115.2 (d, *J* = 20.5 Hz, **C**$_{4'}$ or **C**$_{2'}$), 124.1 (d, *J* = 2.8 Hz, **C**$_{6'}$), 127.5, 128.7 (**C**$_2$, **C**$_3$), 129.7 (d, *J* = 8.0 Hz, **C**$_{1'}$), 135.6 (**C**$_1$), 140.5 (**C**$_4$), 144.1 (d, *J* = 6.8 Hz, **C**$_{5'}$), 162.8 (d, *J* = 243.6 Hz, **C**$_{3'}$), 169.9, 170.3 (2 **C**(O)); HRMS (M+H$^+$)(ESI$^+$) 373.1927 [M + H$^+$] (calcd for $C_{21}H_{25}FN_2O_3H^+$ 373.1927); Anal. Calcd. for $C_{21}H_{25}FN_2O_3$•0.32H_2O: C, 66.70; H, 6.83; N, 7.41. Found: C, 66.35; H, 6.59; N, 7.28.



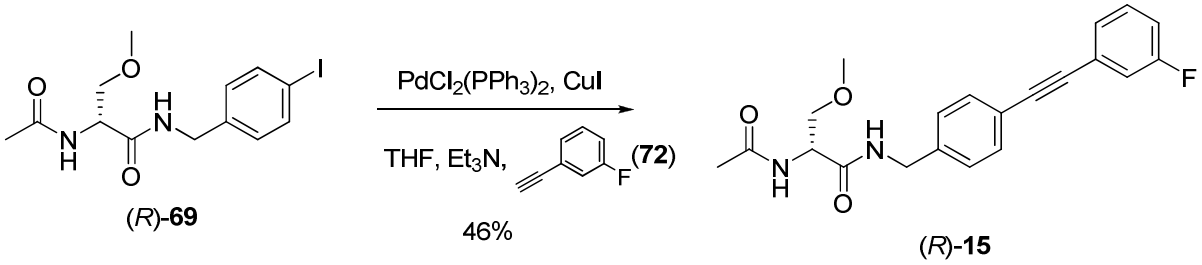
Preparation of (2-*R,E*)-*N*-4'-((3''-Fluoro)styryl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-14)

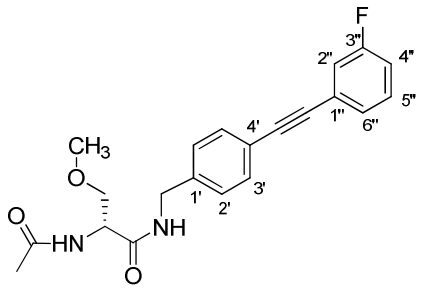
To a flame-dried Schlenck tube, under Ar, containing a dioxane (22.5 mL) solution of (*R*)-*N*-4'-(iodo)benzyl 2-acetamido-3-methoxypropionamide[4] ((*R*)-**69**) (1.50 g, 4.0 mmol), palladiumtetrakis(triphenylphosphine) (464 mg, 0.402) and *trans*-2-(3-fluorophenyl)vinylboronic acid (**71**) (800 mg, 4.82 mmol) was added an aqueous solution (9 mL) of Cs_2CO_3 (2.60 g, 8.0 mmol). The mixture was stirred at reflux (16 h). Then, MeOH and silica gel were added. The volatiles were concentrated in vacuo and the residue was purified by flash chromatography on silica gel with EtOAc/MeOH (10/0 to 9/1) as the eluant to obtain (2-*R,E*)-*N*-(4'-(3''-fluoro)styryl)benzyl 2-

acetamido-3-methoxypropionamide ((*R*)-**14**) (0.90 g, 60%) as a yellowish solid. To remove traces of palladium impurities, the solid was treated with 6.00 g of resin scavenger (SPM32, PhosPhonics) in CH_2Cl_2. The mixture was stirred at room temperature (2 h), and filtered, the filtrate evaporated under vacuum to obtain 560 mg (37%) of (*R,E*)-*N*-(4'-(3''-fluoro)styryl)benzyl 2-acetamido-3-methoxypropionamide ((*R*)-**14**) as a white solid: R_f = 0.53 (EtOAc); mp 206-208 °C; $[\alpha]^{27}_D$ = –20.6° (c 0.5, $CHCl_3$); IR (nujol mull) 3280, 3098, 2918, 2859, 1640, 1556, 1456, 1375, 1304, 1264, 1138, 1045, 963, 856, 780, 736, 605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (s, C**H**$_3$C(O)), 3.40 (s, OC**H**$_3$), 3.40-3.48 (m, C**H**H'O), 3.83 (d, *J* = 3.9, 8.7 Hz, CH**H'**O), 4.47–4.56 (m, C**H**$_2$N, NC(**H**)CO), 6.41–6.49 (br d, N**H**C(O)CH_3), 6.75–7.02 (br t, CH_2N**H**), 6.92–7.01 (m), 7.07 (d, *J* = 2.7 Hz), 7.18–7.35 (m), 7.47 (d, *J* = 8.4 Hz) (8 Ar**H**, 2 vinyl **H**), addition of excess (*R*)-(-)-mandelic acid to a $CDCl_3$ solution of (*R,E*)-*N*-4'-((3''-fluoro)styryl)benzyl 2-acetamido-3-methoxypropionamide ((*R*)-**14**) gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR (DMSO-d_6) δ 22.5 (**C**H_3CO), 41.7 (**C**H_2N), 52.6 (**C**HCH_2), 58.1 (O**C**H_3), 72.0 (**C**H_2OCH_3), 112.3 (d, *J* = 22.2 Hz, $\mathbf{C}_{2'}$ or $\mathbf{C}_{4'}$), 114.1 (d, *J* = 20.5 Hz, $\mathbf{C}_{4'}$ or $\mathbf{C}_{2'}$), 122.7–122.8 (br d, $\mathbf{C}_{6'}$), 126.4 (**C**$_2$ or **C**$_3$), 126.7 (C**H**=CH'), 127.3 (**C**$_3$ or **C**$_2$), 129.7 (CH=C**H'**), 130.5 (d, *J* = 8.5 Hz, $\mathbf{C}_{1'}$ or $\mathbf{C}_{5'}$), 135.1, 139.1(**C**$_1$, **C**$_4$), 139.7 (d, *J* = 8.6 Hz, $\mathbf{C}_{1'}$ or $\mathbf{C}_{5'}$), 162.5 (d, *J* = 241.3 Hz, $\mathbf{C}_{3'}$), 169.3, 169.7 (2 **C**(O)); LRMS (M+Na^+)(ESI^+) 393.1 [M + Na^+] (calcd for $C_{21}H_{23}FN_2O_3Na^+$ 393.1); Anal. Calcd. for $C_{21}H_{23}FN_2O_3$: C, 68.09; H, 6.26; F, 5.13; N, 7.56. Found: C, 67.81; H, 6.32; F, 4.88; N, 7.34.

10. Preparation of (*R*)-*N*-4'-(((3''-Fluoro)phenyl)ethynyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-15).

Reaction Overview





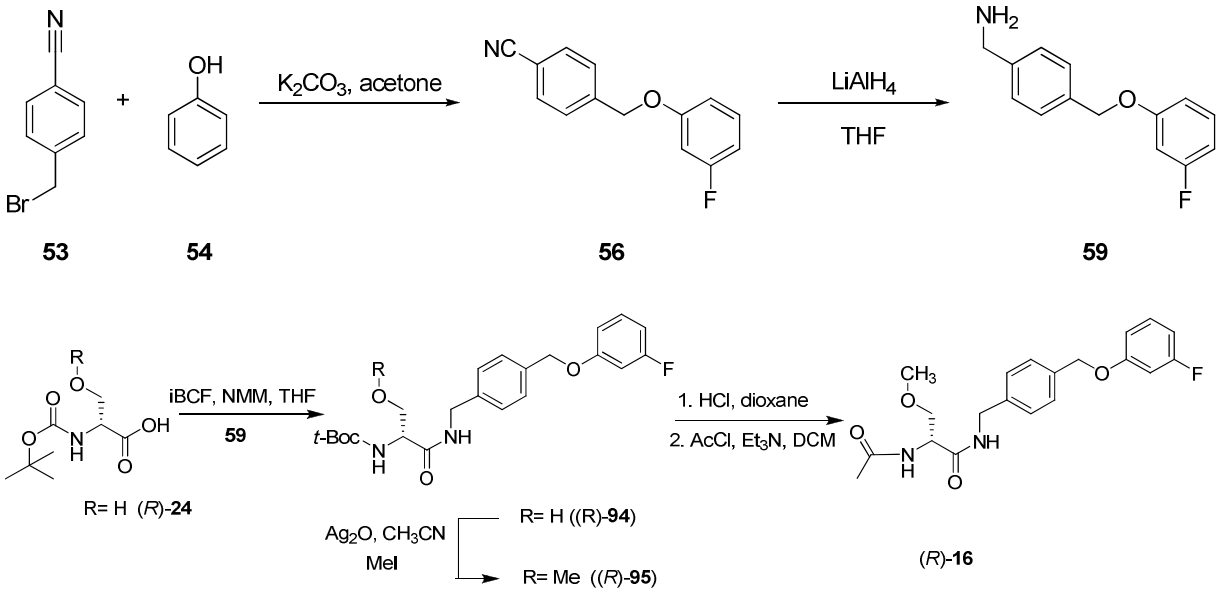
Preparation of (*R*)-*N*-4'-(((3''-Fluoro)phenyl)ethynyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-15)

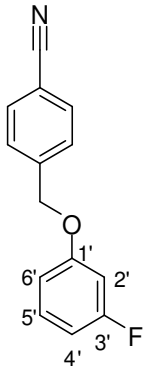
To an anhydrous THF (70 mL) solution of (*R*)-*N*-4'-(iodo)benzyl 2-acetamido-3-methoxypropionamide[4] ((*R*)-**69**) (2.60 g, 7.0 mmol) were sequentially added triethylamine (0.95 mL, 14.0 mmol), (3-fluoro)phenylacetylene (**72**) (1.20 ml, 10.37 mmol), dichlorobis(triphenylphosphine)palladium (II) (491 mg, 0.70 mmol), and CuI (200 mg, 0.1.05 mmol) under Ar. The mixture was stirred at room temperature (16 h), and then MeOH and silica gel were added. The volatiles were concentrated in vacuo and the residue was purified by flash chromatography on silica gel with EtOAc/MeOH (9/1) as the eluant to obtain (*R*)-*N*-4'-(((3''-fluoro)phenyl)ethynyl)benzyl 2-acetamido-3-methoxypropionamide ((*R*)-**15**) (2.40 g, 93%) as a yellowish solid. To remove traces of palladium impurities, the solid was treated with 21.00 g of resin scavenger (SPM32, PhosPhonics) in CH_2Cl_2. The mixture was stirred at room temperature (2 h), and filtered, the filtrate evaporated under vacuum. The solid was recrystallized with EtOAc to obtain 1.20 g (46%) of (*R*)-*N*-4'-(((3''-fluoro)phenyl)ethynyl)benzyl 2-acetamido-3-methoxypropionamide ((*R*)-**15**) as a white solid: R_f = 0.26 (EtOAc); mp 200-202 °C; $[\alpha]^{24}_D$ = –2.6° (c 0.5, $CHCl_3$); IR (nujol mull) 3285, 3097, 2934, 2862, 2356, 1638, 1566, 1457, 1375, 1307, 1264, 1203, 1135, 1104, 1045, 941, 863, 777, 737, 608, 524 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.88 (s, C**H$_3$**C(O)), 3.27 (s, OC**H$_3$**), 3.48–3.57 (m, C**H$_2$**O), 4.33 (d, J = 6.1 Hz, C**H$_2$**N), 4.45–4.53 (m, NC(**H**)CO), 7.25–7.32 (m, 3 Ar**H**), 7.38–7.53 (m, 5 Ar**H**), 8.13 (d, J = 6.3 Hz, N**H**C(O)CH_3), 8.56 (br t, J = 6.1 Hz, CH_2N**H**), addition of excess (*R*)-(-)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-4'-(((3''-fluoro)phenyl)ethynyl)benzyl 2-acetamido-3-methoxypropionamide ((*R*)-**15**) gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR (DMSO-d_6) δ 22.5 (**C**H_3CO), 41.7 (**C**H_2N), 52.6 (**C**HCH_2), 58.1

(O**C**H_3), 72.0 (**C**H_2OCH_3), 87.6 (**C**≡C), 90.2 (C≡**C**), 115.9 (d, *J* = 20.5 Hz, $\mathbf{C}_{2'}$ or $\mathbf{C}_{4'}$), 117.8 (d, *J* = 22.7 Hz, $\mathbf{C}_{4'}$ or $\mathbf{C}_{2'}$), 119.9 (**C**$_4$), 124.2 (d, *J* = 9.7 Hz, $\mathbf{C}_{1'}$ or $\mathbf{C}_{5'}$), 127.2 (**C**$_2$), 127.6 (d, *J* = 2.2 Hz, $\mathbf{C}_{6'}$), 130.8 (d, *J* = 8.6 Hz, $\mathbf{C}_{1'}$ or $\mathbf{C}_{5'}$), 131.3 (**C**$_3$), 140.6 (**C**$_1$), 161.8 (d, *J* = 243.1 Hz, $\mathbf{C}_{3'}$), 169.4, 169.8 (2 **C**(O)); HRMS (M+H^+)(ESI$^+$) 369.1614 [M + H^+] (calcd for $C_{21}H_{21}FN_2O_3H^+$ 369.1614); Anal. Calcd. for $C_{21}H_{21}FN_2O_3$: C, 68.46; H, 5.75; F, 5.16; N, 7.60. Found: C, 68.51; H, 5.92; F, 5.34; N, 7.56.

11. Preparation of (*R*)-*N*-4'-(((3''-Fluoro)phenoxy)methyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-16).

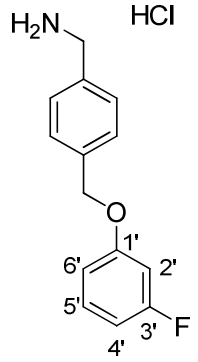
Reaction Overview





Preparation of 4-(((3'-Fluoro)phenoxy)methyl)benzonitrile (56)

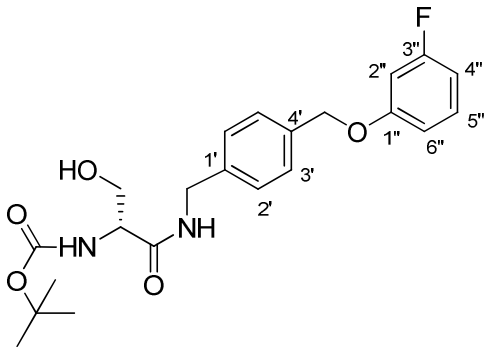
A mixture of 4-(bromomethyl)benzonitrile (**53**) (23.50 g, 120.0 mmol), K_2CO_3 (55.20 g, 400.0 mmol) and 3-fluorophenol (**54**) (11.21 g, 100.0 mmol) were heated at reflux in acetone (400 mL) (16 h). The volatiles were evaporated and the residue was diluted with CH_2Cl_2 (300 mL). The organic layer was washed with H_2O (300 mL), dried ($MgSO_4$) and concentrated in vacuo to give white needles (19.81 g, 87%): R_f = 0.40 (9/1 hexanes/ethyl acetate); mp 69-70 °C; ^{1}H NMR ($CDCl_3$) δ 5.02 (s, C**H$_2$**O), 6.56–6.67 (m, 3 Ar**H**), 7.16 (q, *J* = 7.7 Hz, 1 Ar**H**), 7.45 (d, *J* = 7.1 Hz, 2 Ar**H**), 7.59 (d, *J* = 8.1 Hz, 2 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 60.1 (**C**H$_2$O), 102.8 (d, *J* = 24.4 Hz, **C$_{2'}$** or **C$_{4'}$**), 108.3 (d, *J* = 21.1 Hz, **C$_{4'}$** or **C$_{2'}$**), 110.4 (d, *J* = 2.8 Hz, **C$_{6'}$**), 111.9 (Ar**C**), 118.6 (**C**N), 127.5 (Ar**C**), 130.4 (d, *J* = 9.7 Hz, **C$_{5'}$**), 132.4, 141.9 (2 Ar**C**), 159.4 (d, *J* = 10.8 Hz, **C$_{1'}$**), 163.6 (d, *J* = 244.2 Hz, **C$_{3'}$**); LRMS (M+Na$^+$) (ESI$^+$) 250.0 [M + Na$^+$] (calcd for $C_{14}H_{10}NONa^+$ 250.0).



Preparation of 4-(((3'-Fluoro)phenoxy)methyl)benzylamine Hydrochloride (59-HCl)

To a $LiAlH_4$ (5.02 g, 132.0 mmol) suspension in THF (400 mL) was added dropwise at 0 °C, a THF (30 mL) solution of 4-(((3'-fluoro)phenoxy)methyl)benzonitrile (**56**) (10.00 g, 44.0 mmol). The mixture was stirred at room temperature (16 h). Then, H_2O (4 mL) was added dropwise at 0 °C followed by an aqueous NaOH solution (2 mL, 15% w/w) and H_2O (4 mL). The mixture was stirred at room temperature (2 h), and the precipitate was filtered and the pad was washed with CH_2Cl_2. The filtrate was concentrated in vacuo. The residue was solubilized in Et_2O (50 mL) and then HCl in Et_2O (1 M) was added dropwise at 0 °C. The white precipitate was filtered to obtain 9.16 g (78%) of **59**-HCl as a white

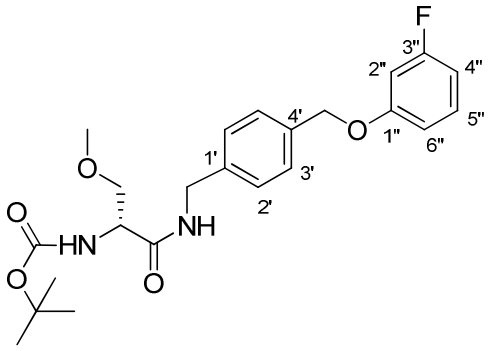
solid: R_f = 0.00 (hexanes/EtOAc 9/1); mp 240-245 °C; IR (nujol mull) 2896, 2726, 1595, 1458, 1376, 1275, 1135, 1029, 963, 828, 768 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.01 (s, C**H**$_2$NH$_2$), 5.14 (s,C**H**$_2$O), 6.74–6.91 (m, 2 Ar**H**), 7.20–7.39 (m, 2 Ar**H**), 7.48 (d, J = 7.9 Hz, 2 Ar**H**), 7.53 (d, J = 7.9 Hz, 2 Ar**H**), 8.38–8.64 (br s, N**H**$_3$Cl); ^{13}C NMR ($CDCl_3$) δ 41.7 (**C**H$_2$NH$_3$), 60.0 (**C**H$_2$O), 102.3 (d, J = 24.4 Hz, **C$_2$**' or **C$_4$**'), 107.3 (d, J = 21.0 Hz, **C$_4$**' or **C$_2$**'), 111.1 (d, J = 2.8 Hz, **C$_6$**'), 127.8, 129.1 (2 Ar**C**), 130.6 (d, J = 10.2 Hz, **C$_5$**'), 133.7, 136.7 (2 Ar**C**), 159.6 (d, J = 11.3 Hz, **C$_1$**'), 162.9 (d, J = 241.3 Hz, **C$_3$**'); HRMS (M+H$^+$)(ESI$^+$) 232.1138 [M + H$^+$] (calcd for $C_{14}H_{14}FNOH^+$ 232.1137).



Preparation of (*R*)-*N*-4'-(((3''-Fluoro)phenoxy)methyl)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-94)

Using the mixed anhydride coupling method, (*R*)-*t*-Boc-serine ((*R*)-**24** (5.00 g, 24.4 mmol), 4-methylmorpholine (NMM) (3.2 mL, 29.3 mmol), isobutylchloroformate (IBCF) (3.8 mL, 29.3 mmol), THF (300 mL) and 4-(((3'-fluoro)phenoxy)methyl)benzylamine **59** (6.20 g, 26.8 mmol) gave (*R*)-*N*-4'-(((3''-fluoro)phenoxy)methyl)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-**94**) as a white solid (5.20 g, 51%): R_f = 0.40 (EtOAc); mp 85-86 °C; $[\alpha]^{23.4}_D$ +27.9° (*c* 1, $CHCl_3$); IR (nujol mull) 3324, 2927, 1652, 1524, 1457, 1378, 1306, 1275, 1242, 1166, 1011, 835, 766, 674, 572 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, (C**H$_3$**)$_3$C), 3.42–3.58 (br m, C**H**H'), 3.61–3.72 (br m, CH**H'**), 4.02–4.11 (m, C**H**), 4.13–4.22 (br m, O**H**), 4.33–4.42 (br m, C**H$_2$**N), 5.00 (s, OC**H$_2$**), 5.63–5.74 (br m, N**H**), 6.34–6.75 (m, 3 Ar**H**), 7.09–7.26 (m, 4 Ar**H**), 7.35 (d, J = 7.5 Hz, Ar**H**); ^{13}C NMR ($CDCl_3$) δ 28.2 ((**C**H$_3$)$_3$C), 43.0 (N**C**H$_2$), 54.9 (OCH$_2$**C**H), 62.8 (O**C**H$_2$CH), 69.8 (O**C**H$_2$)80.6 ((CH$_3$)$_3$**C**), 102.6 (d, J = 24.5 Hz, **C$_4$**' or **C$_2$**'), 107.8 (d, J = 21.1 Hz, **C$_2$**' or

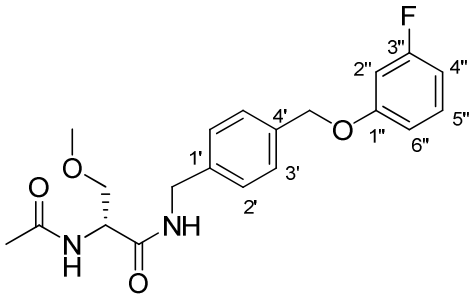
C$_{4'}$), 110.6 (d, *J* = 2.9 Hz, **C$_{6'}$**), 127.7, 127.8 (2 Ar**C**), 130.2 (d, *J* = 9.7 Hz, **C$_{5'}$**), 135.7, 137.7 (2 Ar**C**), 156.3 (O**C**(O)NH), 160.0 (d, *J* = 10.8 Hz, **C$_{1'}$**), 163.6 (d, *J* = 243.6 Hz, **C$_{3'}$**), 171.4 (**C**(O)); HRMS (M+H$^+$)(ESI$^+$) 419.1982 [M + H$^+$] (calcd for $C_{22}H_{27}FN_2O_5H^+$ 419.1982); Anal. Calcd. for $C_{22}H_{27}FN_2O_5$: C, 63.14; H, 6.50; F, 4.54; N, 6.69. Found: C, 62.90; H, 6.83; F, 4.18; N, 7.03.



Preparation of (*R*)-*N*-4'-(((3''-Fluoro)phenoxy)methyl)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-95)

Ag_2O (12.80 g, 55.0 mmol) was added to a CH_3CN solution (200 mL) of (*R*)-*N*-4'-(((3''-fluoro)phenoxy)methyl)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-**94**)(4.60 g, 11.0 mmol) and then CH_3I (6.85 mL, 110.0 mmol) was added at room temperature under Ar. The reaction mixture was stirred at room temperature (4 d), filtered, and the filtrate concentrated in vacuo. The residue was purified by column chromatography (SiO_2; 1/1 EtOAc/hexanes) to obtain 4.30 g (91%) of a white solid: R_f = 0.55 (1/1 EtOAc/hexanes); mp 77-79 °C; $[\alpha]^{26}_D$ -17.8° (*c* 1, $CHCl_3$); IR (nujol mull) 3101, 2927, 2860, 1689, 1648, 1529, 1458, 1375, 1323, 1266, 1165, 1087, 1048, 961, 825, 762, 674 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.43 (s, (C**H$_3$**)$_3$C), 3.36 (s, OC**H$_3$**), 3.50 (dd, *J* = 6.3, 9.3 Hz, C**H**H'OCH$_3$), 3.82–3.87 (m, CH**H'**OCH$_3$), 4.22–4.33 (br m, C**H**CHH'), 4.49 (d, *J* = 5.1 Hz, C**H$_2$**N), 5.02 (s, C**H$_2$**O), 5.39–5.46 (br m, N**H**), 6.66–6.76 (m, 3 Ar**H**, N**H**), 7.14–7.23 (m, 1 Ar**H**), 7.28 (d, *J* = 7.9 Hz, 2 Ar**H**), 7.37 (d, *J* = 7.9 Hz, 2 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 28.2 ((**C**H$_3$)$_3$C), 43.1 (N**C**H$_2$), 54.1 (OCH$_2$**C**H), 59.1 (O**C**H$_3$), 69.9 (O**C**H$_2$), 72.0 (O**C**H$_2$CH), 80.6 ((CH$_3$)$_3$**C**), 102.6 (d, *J* = 24.5 Hz, **C$_{4'}$** or **C$_{2'}$**), 107.8 (d, *J* = 21.0 Hz, **C$_{2'}$** or **C$_{4'}$**), 110.6 (d, *J* = 2.9 Hz, **C$_{6'}$**), 127.7, 127.8 (2 Ar**C**), 130.2 (d, *J* = 9.7 Hz, **C$_{5'}$**), 135.7, 138.0 (2 Ar**C**), 155.5 (O**C**(O)NH), 160.0 (d, *J* = 10.8 Hz, **C$_{1'}$**), 163.6 (d, *J* = 243.6 Hz, **C$_{3'}$**), 170.3 (**C**(O)); HRMS (M+H$^+$)(ESI$^+$) 433.2139 [M + H$^+$] (calcd for $C_{23}H_{29}FN_2O_5H^+$ 433.2138); Anal.

Calcd. For $C_{23}H_{29}FN_2O_5$: C, 63.87; H, 6.76; F, 4.39; N, 6.48. Found: C, 63.43; H, 6.76; F, 4.25; N, 6.57.



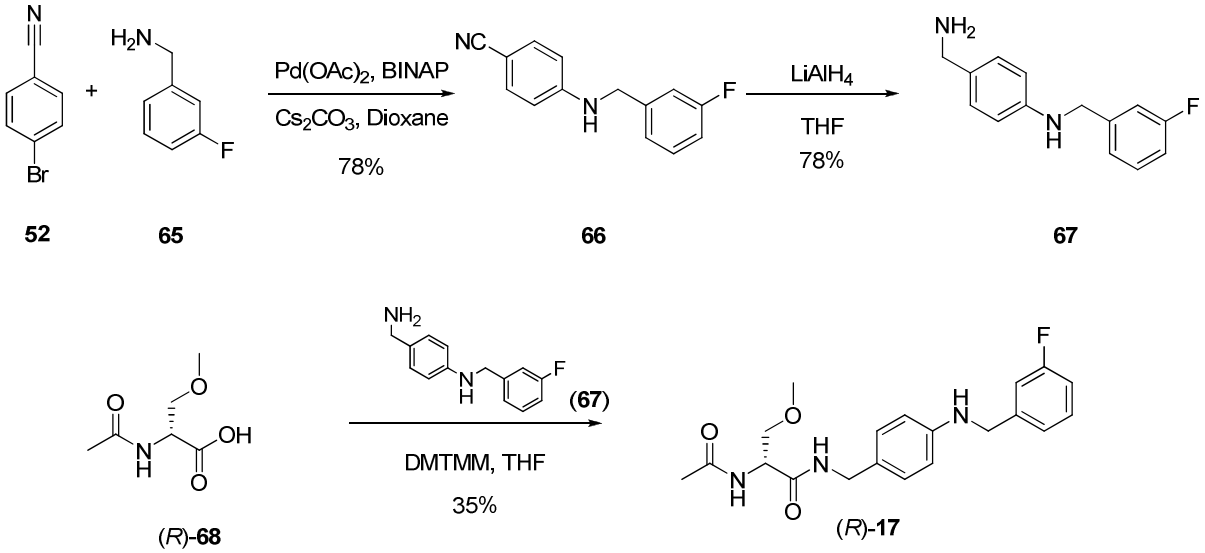
Preparation of (*R*)-*N*-4'-(((3'-Fluoro)phenoxy)methyl)benzyl 2-Acetamido- 3-methoxypropionamide ((*R*)-16)

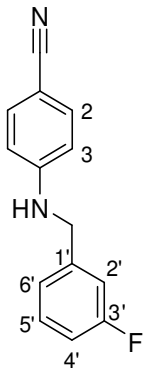
A saturated HCl solution in dioxane (1 mmol/2 mL, 10.2 mL) was added to (*R*)-*N*-4'-(((3''-fluoro)phenoxy)methyl)benzyl2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-**95**) (2.20 g, 5.1 mmol) at 0 °C and the solution was stirred at room temperature (2 h). The reaction solution was concentrated in vacuo and dried (30 min) to provide (*R*)-2-amino-*N*-4'-(((3'-fluoro)phenoxy)methyl)benzyl 3-methoxypropionamide hydrochloride as a white solid (1.80 g, quant.): mp 128–130 °C; $[\alpha]^{23.8}_D$ +17.6° (*c* 0.5, H_2O); IR (nujol mull) 3145, 2915, 1660, 1569, 1459, 1376, 1274, 1138, 1017, 961, 832, 777, 724, 683 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.30 (s, OC**H**$_3$), 3.72 (d, *J* = 5.1 Hz, C**H**$_2$), 3.99–4.11 (br m, C**H**), 4.35 (d, *J* = 3.6 Hz, NC**H**$_2$), 5.10 (s, OC**H**$_2$), 6.74–6.91 (m, 3 Ar**H**), 7.26–7.35 (m, 3 Ar**H**), 7.41 (d, *J* = 7.8 Hz, 2 Ar**H**), 8.28–8.41 (br s, N**H**$_3$), 9.11–9.19 (br t, N**H**C(O)); ^{13}C NMR (DMSO-d_6) δ 42.0 (N**C**H_2), 52.1 (OCH_2**C**H), 58.4 (O**C**H_3), 69.2 (**C**H_2O), 70.3 (O**C**H_2CH), 102.2 (d, *J* = 24.5 Hz, **C**$_{4'}$ or **C**$_{2'}$), 107.3 (d, *J* = 21.1 Hz, **C**$_{2'}$ or **C**$_{4'}$), 111.0–111.2 (br d, **C**$_{6'}$), 127.3, 127.8 (2 Ar**C**), 130.1 (d, *J* = 9.7 Hz, **C**$_{5'}$), 135.2, 138.3 (2 Ar**C**), 159.7 (d, *J* = 10.9 Hz, **C**$_{1'}$), 162.9 (d, *J* = 241.3 Hz, **C**$_{3'}$), 166.3 (**C**(O)); HRMS (M+H$^+$)(ESI$^+$) 333.1614 [M + H$^+$] (calcd for $C_{18}H_{21}FN_2O_3H^+$ 333.1614). Anal. Calcd. For $C_{18}H_{22}ClFN_2O_3$: C, 58.62; H, 6.01; Cl, 9.61; F, 5.15; N, 7.58. Found: C, 58.41; H, 6.19; Cl, 9.81; F, 4.93; N, 7.58.

Triethylamine (1.5 mL, 5.2 mmol) and acetyl chloride (380 μL, 10.7 mmol) were carefully added at 0 °C to a CH_2Cl_2 (20 mL) solution of (*R*)-*N*-4'-(((3''-fluoro)phenoxy)methyl)benzyl 2-amino-3-methoxypropionamide hydrochloride (1.30 g, 3.5 mmol) and the resulting solution was stirred at room temperature (2 h). An aqueous 10% citric acid solution (30 mL) was added and the organic layer was extracted with CH_2Cl_2 (3 x 30 mL). The organic layers were combined, washed with a saturated aqueous $NaHCO_3$ solution (40 mL), dried ($MgSO_4$), and concentrated in vacuo. The solid was recrystallized (EtOAc) to obtain 900 mg (68%) of the desired product as a white solid: R_f = 0.18 (EtOAc); mp 140-142 °C; $[\alpha]^{26.9}_D$ -21.0° (*c* 1, $CHCl_3$); IR (nujol mull) 3279, 2947, 2858, 1739, 1629, 1552, 1457, 1374, 1273, 1203, 1133, 1103, 1044, 960, 914, 829, 768, 724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (s, C**H$_3$**CO), 3.41 (s, OC**H$_3$**), 3.43 (dd, *J* = 7.5, 9.2 Hz, C**H**H'), 3.82 (dd, *J* = 3.9, 9.2 Hz, CH**H'**), 4.47–4.59 (m, C**H$_2$**N, C**H**), 5.03 (s, OC**H$_2$**), 6.38–6.43 (br d, N**H**C(O)CH_3), 6.64–6.78 (m, 3 Ar**H**, CH_2N**H**), 7.14–7.30 (m, 3 Ar**H**), 7.40 (d, *J* = 8.4 Hz, 2 Ar**H**), addition of excess (*R*)-(-)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-4'-(((3''-fluoro)phenoxy)methyl)benzyl 2-acetamido-3-methoxypropionamide ((*R*)-**16**) gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) 23.2 (C(O)**C**H_3), 43.2 (N**C**H_2), 52.4 (**C**HCH_2), 59.1 (O**C**H_3), 69.9 (Ar**C**H_2O), 71.7 (**C**H_2O), 102.6 (d, *J* = 25.1 Hz, **C$_{4'}$** or **C$_{2'}$**), 107.8 (d, *J* = 21.6 Hz, **C$_{2'}$** or **C$_{4'}$**), 110.5 (d, *J* = 2.9 Hz, **C$_{6'}$**), 127.7, 129.8 (2 Ar**C**), 130.2 (d, *J* = 9.7 Hz, **C$_{5'}$**), 135.7, 137.9 (2 Ar**C**), 160.0 (d, *J* = 10.8 Hz, **C$_{1'}$**), 163.6 (d, *J* = 244.2 Hz, **C$_{3'}$**), 170.0, 170.3 (2 **C**(O)); LRMS (M+Na^+)(ESI^+) 397.1 [M + Na^+] (calcd for $C_{20}H_{23}FN_2O_4H^+$ 397.1); Anal. Calcd. for $C_{20}H_{23}FN_2O_4$: C, 64.16; H, 6.19; F, 5.07; N, 7.48. Found: C, 63.86; H, 6.13; F, 4.88; N, 7.50.

12. Preparation of (*R*)-*N*-4'-((3''-Fluoro)benzylamino)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-17).

Reaction Overview

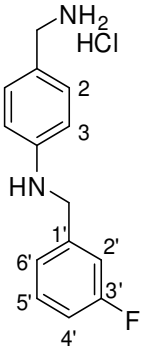




Preparation of 4-((3'-Fluoro)benzylamino)benzonitrile (66)

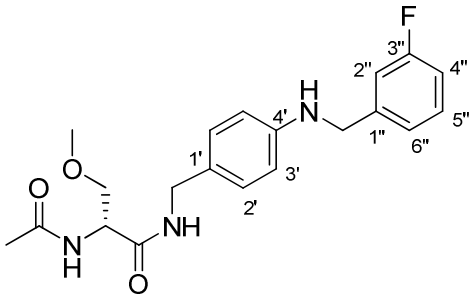
In a flame-dried Schlenk tube, $Pd(OAc)_2$ (304 mg, 1.3 mmol), Binap (1.69 g, 2.7 mmol), and 4-bromobenzonitrile (**52**) (5.00 g, 27.1 mmol) were added under Ar to a stirring solution of 3-fluorobenzylamine (**65**) (3.80 g, 30.4 mmol) and Cs_2CO_3 (13.20 g, 40.6 mmol) in dioxane (55 mL). The mixture was stirred at 80 °C (16 h) and then the volatiles were evaporated. CH_2Cl_2 (100 mL) and H_2O (100 mL) were added and the layers separated. The aqueous layer was washed with CH_2Cl_2 (2 x 100 mL). The organic layers were combined, dried and concentrated under vacuum. The crude residue was purified by column chromatography (SiO_2; EtOAc/hexanes 0/10 to 3/7) to obtain 4.90 g (78%) of a yellow solid: R_f = 0.36 (1/9 EtOAc/hexanes); mp 63-64 °C; IR (nujol mull) 2934, 2861, 2214, 1739, 1605, 1527, 1457, 1375, 1285, 1248, 1164, 915, 824, 784, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.39 (s, C**H**$_2$N), 4.59-4.74 (br m, N**H**),

6.57 (d, J = 8.8 Hz, 2 **H$_3$**), 6.94-7.05 (m, 2 Ar**H**), 7.11 (d, J = 7.5 Hz, **H$_{6'}$**), 7.28–7.36 (m, 1 Ar**H**), 7.42 (d, J = 8.8 Hz, 2 **H$_2$**); ^{13}C NMR ($CDCl_3$) δ 46.8 (d, J = 1.7 Hz, N**C**H$_2$), 99.9 (**C**N), 112.4 (Ar**C**), 113.9 (d, J = 22.2 Hz, **C$_{4'}$** or **C$_{2'}$**), 114.4 (d, J = 21.1 Hz, **C$_{2'}$** or **C$_{4'}$**), 120.3 (Ar**C**), 122.5 (d, J = 2.9 Hz, **C$_{6'}$**), 130.3 (d, J = 8.6 Hz, **C$_{5'}$**), 133.7 (Ar**C**), 140.6 (d, J = 6.8 Hz, **C$_{1'}$**), 150.9 (Ar**C**), 163.1 (d, J = 245.3 Hz, **C$_{3'}$**); HRMS (M+H$^+$) (ESI$^+$) 227.0985 [M + H$^+$] (calcd for $C_{14}H_{11}FN_2H^+$ 227.0984).



Preparation of 4-((3'-Fluoro)benzylamino)benzylamine Hydrochloride (67-HCl)

To a $LiAlH_4$ (1.01 g, 26.5 mmol) suspension in THF (75 mL) was added dropwise a THF (15 mL) solution of 4-((3'-fluoro)benzylamino)benzonitrile (**66**) (2.00 g, 8.8 mmol) at 0 °C. The mixture was stirred at room temperature (16 h) and then H_2O (815 μL) was added dropwise at 0 °C followed by an aqueous NaOH solution (407 μL, 15% w/w) and then H_2O (815 μL). The mixture was stirred at room temperature (2 h) and the precipitate was filtered and was washed with CH_2Cl_2. The filtrate was concentrated in vacuo, and then Et_2O (10 mL) followed by HCl (1 M) in Et_2O (13.3 mL, 13.3 mmol) were added to give 1.80 g of a yellow solid (78%): R_f = 0.00 (hexanes/EtOAc 9/1); mp 211 °C (decomp.) ^{1}H NMR (DMSO-d_6) δ 2.51 (br t, J = 1.8 Hz, N**H**), 3.79–3.90 (m, C**H$_2$**N), 4.39 (s, C**H$_2$**N), 6.87 (d, J = 7.8 Hz, 2 **H$_3$**), 7.03–7.12 (m, 1 Ar**H**), 7.24–7.41 (m, 5 Ar**H**), 8.21–8.32 (br s, N**H$_3$**); ^{13}C NMR (DMSO-d_6) δ 47.4, 47.8 (2 **C**H$_2$N), 113.9 (d, J = 20.5 Hz, **C$_{4'}$** or **C$_{2'}$**), 114.6 (d, J = 21.1 Hz, **C$_{2'}$** or **C$_{4'}$**), 115.3, 124.0 (2 Ar**C**), 124.4 (br m, **C$_{6'}$**), 130.0 (Ar**C**), 130.2 (d, J = 8.5 Hz, **C$_{5'}$**), 133.7 (Ar**C**), 140.7–140.8 (br m, **C$_{1'}$**), 144.8 (Ar**C**), 162.1 (d, J = 241.9 Hz, **C$_{3'}$**); HRMS (M+H$^+$)(ESI$^+$) 231.1298 [M + H$^+$] (calcd for $C_{14}H_{15}FN_2H^+$ 231.1297).



Preparation of (*R*)-*N*-4'-((3''-Fluoro)benzylamino)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-17)

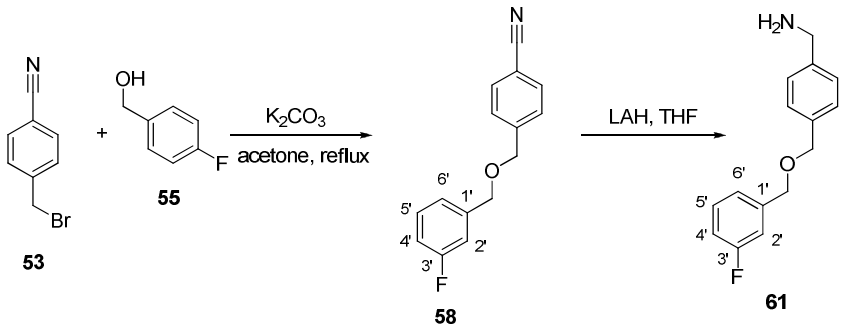
4-((3'-Fluoro)benzylamino)benzylamine hydrochloride (**67**) (293 mg, 1.1 mmol) was added to a THF (10 mL) solution of the (*R*)-2-acetamido-3-methoxypropanoic acid ((*R*)-**68**)[5] (161 mg, 1.0 mmol) and the mixture was stirred at room temperature (5 min) and then NMM (121 μL, 1.1 mmol) was added. The mixture was stirred at room temperature (5 min) and DMTMM[6] (332 mg, 1.2 mmol) was added, and the mixture was stirred at room temperature (16 h). The white precipitate was filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (5/5) to EtOAc/acetone (5/5) as the eluant to obtain (*R*)-*N*-4'-((3''-fluoro)benzylamino)benzyl 2-acetamido-3-methoxypropionamide ((*R*)-**17**) as a yellow solid (140 mg, 35%): R_f = 0.37 (EtOAc); mp 78-81 °C; $[\alpha]^{26.9}_D$ -15.0° (*c* 0.5, $CHCl_3$); IR (nujol mull) 3160, 2919, 2857, 1736, 1630, 1523, 1457, 1375, 1259, 1125, 784, 726 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.03 (s, C**H**$_3$CO), 3.36 (s, OC**H**$_3$), 3.40 (dd, *J* = 7.2, 9.0 Hz, C**H**H'), 3.82 (dd, *J* = 4.2, 9.0 Hz, CH**H'**), 4.12–4.19 (br m, CH_2N**H**), 4.31–4.37 (m, 2 C**H**$_2$N), 4.46–4.52 (m, C**H**), 6.38–6.45 (br m, N**H**C(O)CH_3), 6.57 (d, *J* = 9.0 Hz, 2 Ar**H**, N**H**), 6.91–6.89 (m, 1 Ar**H**), 7.05–7.15 (m, 4 Ar**H**), 7.27–7.34 (m, 1 Ar**H**), addition of excess (*R*)-(-)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-4'-((3''-fluoro)benzylamino)benzyl 2-acetamido-3-methoxypropionamide ((*R*)-**17**) gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) 23.2 (C(O)**C**H$_3$), 43.3 (N**C**H$_2$), 47.7 (d, *J* = 1.7 Hz, **C**H$_2$N(H)Ph), 52.4 (**C**HCH$_2$), 59.0 (O**C**H$_3$), 71.7 (**C**H$_2$O), 113.0 (**C$_3$**), 114.0 (d, *J* = 20.5 Hz, **C$_{2'}$** or **C$_{4'}$**), 114.1 (d, *J* = 21.7 Hz, **C$_{2'}$** or **C$_{4'}$**), 122.7 (d, *J* =

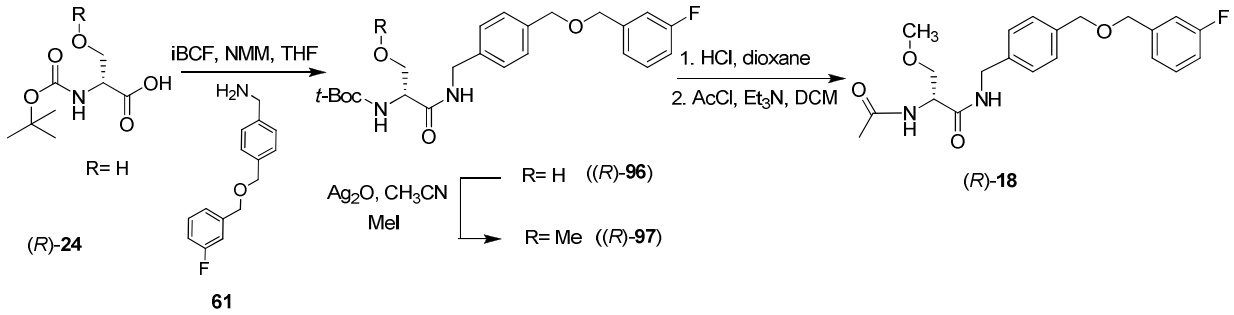
[5] Morieux, P.; Stables, J.P.; Kohn, H. *Bioorg. Med. Chem.* **2008**, *16*, 8968-8975.
[6] Kunishima, M.; Kawachi, C.; Monta, J.; Terao, K.; Iwasaki, F.; Tani, S. *Tetrahedron* **1999**, *55*, 13159-13170.

2.3 Hz, **C$_{6'}$**), 126.8 (**C$_1$**), 128.9 (**C$_2$**), 130.1 (d, *J* = 8.6 Hz, **C$_{5'}$**), 142.1 (d, *J* = 6.8 Hz, **C$_{1'}$**), 147.2 (**C$_4$**), 163.1 (d, *J* = 224.5 Hz, **C$_{3'}$**), 169.7, 170.2 (2 **C**(O)); HRMS (M+H$^+$)(ESI$^+$) 374.1880 [M + H$^+$] (calcd for $C_{20}H_{24}FN_3O_3H^+$ 374.1879).

13. Preparation of (*R*)-*N*-4'-(((3-Fluoro)benzyloxy)methyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-18).

Reaction Overview





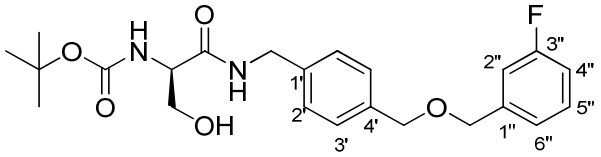
Preparation of 4-(((3'-Fluoro)benzyloxy)methyl)benzonitrile (58)

3-(Fluoro)benzylalcohol (**55**) (5.00 g, 39.6 mmol) in THF (50 mL) was added dropwise at 0 °C to a THF (100 mL) suspension of NaH (60%, 6.3 g, 158.4 mmol). The mixture was stirred at 0 °C (30 min). Then, a THF solution of 4-cyanobenzylbromide (**53**) (9.30 g, 47.6 mmol) was added dropwise at 0 °C and the mixture was stirred at room temperature (16 h). A saturated aqueous solution of NH_4Cl (40 mL) was added dropwise at 0 °C and the layers were separated. The aqueous layer was washed with CH_2Cl_2 (60 mL). The organics layers were combined,

dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (0/10 to 1/9) as the eluant to obtain 4-(((3'-fluoro)benzyloxy)methyl)benzonitrile (**58**) as a colorless oil (7.80 g, 81%): R_f = 0.65 (hexanes/EtOAc 8/2); IR (nujol) 2863, 2229, 1719, 1595, 1451, 1450, 1360, 1258, 1100, 1018, 945, 862, 790, 687, 554 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.59 (s, C**H**$_2$O), 4.61 (s, C**H**$_2$O), 6.97–7.14 (m, 3 Ar**H**), 7.26–7.37 (m, 1 Ar**H**), 7.47 (d, J = 7.5 Hz, 2 Ar**H**), 7.65 (d, J = 7.5 Hz, 2 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 71.2 (**C**H_2O), 71.9 (**C**H_2O), 113.4 (**C**CN), 114.4 (d, J = 21.6 Hz, **C$_{2'}$** or **C$_{4'}$**), 114.7 (d, J = 21.6 Hz, **C$_{4'}$** or **C$_{2'}$**), 118.8 (**C**N), 122.9 (d, J = 2.3 Hz, **C$_{6'}$**), 127.7 (Ar**C**), 130.0 (d, J = 9.2 Hz, **C$_{5'}$**), 132.2 (Ar**C**), 140.2 (d, J = 8.0 Hz, **C$_{1'}$**), 143.5 (Ar**C**), 162.9 (d, J = 244.8 Hz, **C$_{3'}$**); HRMS (M+Cs^+)(ESI^+) 373.9957 [M + Cs^+] (calcd for $C_{15}H_{12}FNOCs^+$ 373.9954); Anal. Calcd. for $C_{15}H_{12}FNO_2$: C, 74.67; H, 5.01; F, 7.87; N, 5.81. Found: C, 74.53; H, 4.93; F, 7.75; N, 5.81.

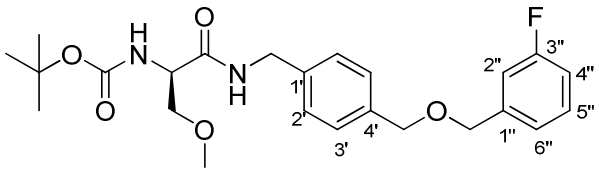
Preparation of 4-(((3'-Fluoro)benzyloxy)methyl)benzylamine (61)

To a $LiAlH_4$ (2.00 g, 53.4 mmol) suspension in THF (300 mL) was added dropwise a THF (20 mL) solution of 4-(((3'-fluoro)benzyloxy)methyl)benzonitrile (**58**) (4.30 g, 17.8 mmol) at 0 °C. The mixture was stirred at room temperature (16 h) and H_2O (1.6 mL) was added dropwise at 0 °C followed by an aqueous NaOH solution (0.8 mL, 15% w/w), and then H_2O (1.6 mL). The mixture was stirred at room temperature (2 h), and the precipitate filtered and washed with CH_2Cl_2. The filtrate was concentrated in vacuo and the solid triturated with Et_2O to obtain a white solid (1.60 g, 37%). The solid was used in the next step with no other purification: R_f = 0.00 (hexanes/EtOAc 8/2); mp > 138 °C (decomp.); IR (nujol) 3224, 3100, 3039, 2970, 2843, 1593, 1520, 1456, 1375, 1257, 1143, 1073, 940, 866, 733, 686, 549 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.87 (s, C**H**$_2$$NH_2$), 4.47–4.54 (m, 2 C**H**$_2$O), 7.08–7.45 (m, 8 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 43.1 (**C**H_2N), 70.4, 71.2 (2 **C**H_2O), 113.8 (d, J = 21.7 Hz, **C$_{2'}$** or **C$_{4'}$**), 114.1 (d, J = 20.5 Hz, **C$_{4'}$** or **C$_{2'}$**), 123.1 (d, J = 2.3 Hz, **C$_{6'}$**), 127.5 (Ar**C**), 128.1 (Ar**C**), 130.2 (d, J = 8.0 Hz, **C$_{5'}$**), 137.2, 137.3 (2 Ar**C**), 141.4 (d, J = 6.8 Hz, **C$_{1'}$**), 162.1 (d, J = 242.5 Hz, **C$_{3'}$**); HRMS (M+H^+)(ESI^+) 246.1294 [M + H^+] (calcd for $C_{15}H_{16}FNOH^+$ 246.1294).



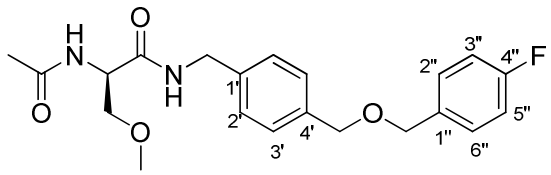
Preparation of (*R*)-*N*-4'-(((3''-Fluoro)benzyloxy)methyl)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-96)

A THF solution (100 mL) of (*R*)-*t*-Boc-serine ((*R*)-**24**) (2.35 g, 11.4 mmol) was stirred and cooled at -78 °C under Ar and then 4-methylmorpholine (NMM) (1.5 mL, 13.7 mmol) was added dropwise. After 2 min of stirring at this temperature, isobutylchloroformate (IBCF) (1.8 mL, 13.7 mmol) was added dropwise leading to the precipitation of a white solid, and the reaction was allowed to proceed for additional 2 min, and then 4-(((3'-fluoro)benzyloxy)methyl)benzylamine (**61**) (3.37 g, 13.7 mmol) was added portionwise at -78 °C. The mixture was allowed to stir at room temperature (2 h), and the white solid filtered and the organic layer concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (30/70 to 100/0) as the eluant to obtain (*R*)-*N*-4'-(((3''-fluoro)benzyloxy)methyl)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-**96**) as a white solid (3.30 g, 66%): R_f = 0.34 (hexanes/EtOAc 4/6); mp 79–81 °C; $[\alpha]^{25.2}_D$ +23.1° (*c* 1, $CHCl_3$); IR (nujol) 2954, 2856, 1651, 1527, 1457, 1374, 1307, 1256, 1166, 1075, 1010, 868, 726 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.39 (s, (C**H**$_3$)$_3$), 3.54–3.60 (br m, C**H**$_2$), 3.96–4.02 (m, C**H**), 4.25–4.36 (br m, C**H**$_2$N), 4.51 (s, C**H**$_2$O), 4.53 (s, C**H**$_2$O), 4.85 (t, *J* = 5.9 Hz, O**H**), 6.68 (br d, *J* = 8.1 Hz, N**H**), 7.08–7.30 (m, 7 Ar**H**), 7.36–7.44 (m, 1 Ar**H**), 8.33 (br t, *J* = 5.9 Hz, N**H**); ^{13}C NMR ($CDCl_3$) δ 28.2 ((**C**H$_3$)$_3$), 42.1 (N**C**H$_2$), 55.0 (OCH$_2$**C**H), 62.8 (O**C**H$_2$CH), 71.2 (d, *J* = 2.0 Hz, **C**H$_2$O), 71.9 (**C**H$_2$O), 80.6 (**C**(CH$_3$)$_3$), 114.3 (d, *J* = 21.3 Hz, **C$_{2'}$** or **C$_{4'}$**), 114.4 (d, *J* = 21.1 Hz, **C$_{4'}$** or **C$_{2'}$**), 123.0 (d, *J* = 2.9 Hz, **C$_{6'}$**), 127.6, 128.0 (2 Ar**C**), 129.9 (d, *J* = 8.0 Hz, **C$_{5'}$**), 137.2, 137.3 (2 Ar**C**), 140.8 (d, *J* = 7.1 Hz, **C$_{1'}$**), 156.3 (N(H)**C**(O)O), 161.4 (d, *J* = 244.2 Hz, **C$_{3'}$**), 171.3 (**C**(O)); HRMS (M+H$^+$)(ESI$^+$) Not observed [M + H$^+$] (calcd for $C_{23}H_{29}FN_2O_5H^+$ 433.2138); Anal. Calcd. for $C_{23}H_{29}FN_2O_5$: C, 63.87; H, 6.76; F, 4.39; N, 6.48. Found: C, 63.48; H, 6.79; F, 4.25; N, 6.48.



Preparation of (*R*)-*N*-4'-(((3''-Fluoro)benzyloxy)methyl)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-97)

Ag_2O (8.00 g, 34.7 mmol) was added to a CH_3CN solution (200 mL) of (*R*)-*N*-4'-(((3''-fluoro)benzyloxy)methyl)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-**96**) (3.00 g, 6.9 mmol) and CH_3I (4.30 mL, 69.4 mmol) at room temperature under Ar. The reaction mixture was stirred at room temperature (3 d), filtered, and the filtrate concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (6/4 to 10/0) as the eluant to obtain (*R*)-*N*-4'-(((3''-fluoro)benzyloxy)methyl)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-**97**) as a colorless oil (1.30 g, 42%): R_f = 0.35 (5/5 EtOAc/hexanes); $[\alpha]^{25.3}_D$ -17.7° (*c* 1, $CHCl_3$); IR (nujol) 2954, 2856, 1651, 1527, 1457, 1374, 1307, 1256, 1166, 1075, 1010, 868, 726 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (s, (C**H**$_3$)$_3$), 3.37 (s, OC**H**$_3$), 3.50 (dd, *J* = 6.0, 9.3 Hz, C**H**H'), 3.84 (dd, *J* = 3.8, 9.3 Hz, CH**H'**), 4.23–4.31 (br m, C**H**), 4.48 (br d, *J* = 4.5 Hz, C**H**$_2$N), 4.53 (s, OC**H**$_2$), 4.54 (s, OC**H**$_2$), 5.37–5.45 (br m, OC(O)N**H**), 6.73–6.81 (br t, CH_2N**H**), 6.98 (td, *J* = 6.3, 8.4 Hz, 1 Ar**H**), 7.06–7.14 (m, 2 Ar**H**), 7.24–7.34 (m, 5 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 28.2 ((**C**H$_3$)$_3$), 43.2 (N**C**H$_2$), 54.0 (OCH$_2$**C**H), 59.0 (O**C**H$_3$), 71.2 (d, *J* = 1.7 Hz, **C**H$_2$O), 71.9, 72.0 (2 **C**H$_2$O), 80.3 (**C**(CH$_3$)$_3$), 114.3 (d, *J* = 21.6 Hz, **C$_{2'}$** or **C$_{4'}$**), 114.4 (d, *J* = 21.1 Hz, **C$_{4'}$** or **C$_{2'}$**), 123.0 (d, *J* = 2.9 Hz, **C$_{6'}$**), 127.5, 128.1 (2 Ar**C**), 129.8 (d, *J* = 8.3 Hz, **C$_{5'}$**), 137.2, 137.5 (2 Ar**C**), 140.8 (d, *J* = 7.1 Hz, **C$_{1'}$**), 155.5 (N(H)**C**(O)O), 162.9 (d, *J* = 244.4 Hz, **C$_{3'}$**), 170.3 (**C**(O)); HRMS (M+H$^+$)(ESI$^+$) 447.2295 [M + H$^+$] (calcd for $C_{24}H_{31}FN_2O_5H^+$ 447.2295.

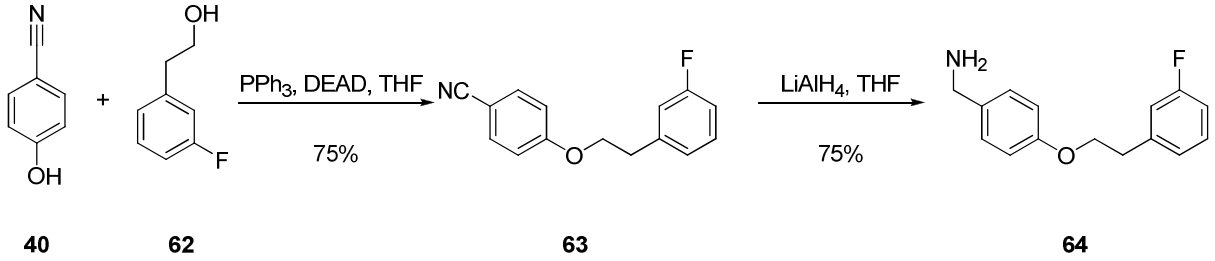


Preparation of (*R*)-*N*-4'-(((3''-Fluoro)benzyloxy)methyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-18)

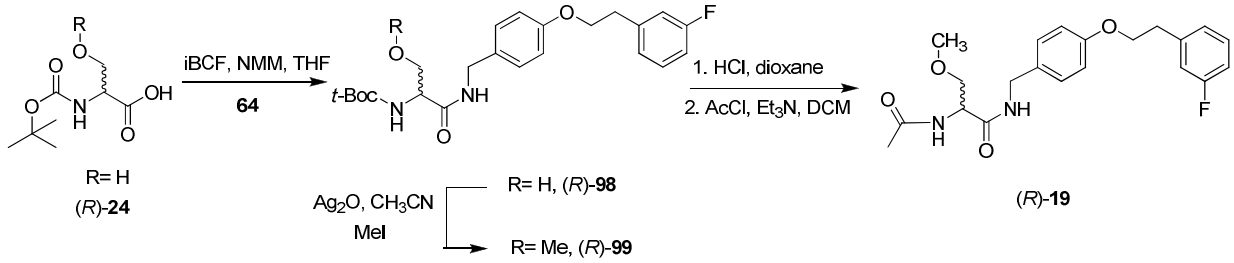
A saturated HCl solution in dioxane (1 mmol/2 mL, 1.2 mL) was added to (*R*)-*N*-4'-(((3''-fluoro)benzyloxy)methyl)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-**97**) (1.10 g, 5.8 mmol) at 0 °C and the solution was stirred at room temperature (16 h). The reaction solution was concentrated in vacuo and dried (30 min). The residue was dissolved in CH_2Cl_2 (20 mL) and Et_3N (1.40 mL, 9.8 mmol) and AcCl (356 μL, 4.9 mmol) were successively added at 0 °C. The mixture was stirred at room temperature (2 h), aqueous 10% citric acid (60 mL) was added, and then the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). All of the organic layers were combined, washed with aqueous saturated $NaHCO_3$ (30 mL) and H_2O (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The solid was recrystallized with EtOAc to obtain (*R*)-*N*-4'-(((3''-fluoro)benzyloxy)methyl)benzyl 2-acetamido-3-methoxypropionamide ((*R*)-**18**) (450 mg, 47%) as a white solid: R_f = 0.26 (EtOAc); mp 140–142 °C; $[\alpha]^{25.2}_D$ -21.0° (*c* 0.5, $CHCl_3$); IR (nujol) 3275, 3140, 2954, 2915, 2856, 1631, 1550, 1457, 1374, 1248, 1102, 1009, 917, 832, 779, 729, 612, 522 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (s, C**H**$_3$CO), 3.39 (s, OC**H**$_3$), 3.43 (dd, *J* = 7.8, 9.0 Hz, C**H**H'), 3.82 (dd, *J* = 3.9, 9.0 Hz, CH**H'**), 4.48 (d, *J* = 6.0 Hz, C**H**$_2$N), 4.48–4.56 (m, NC(**H**)CO), 4.54 (s, C**H**$_2$O), 4.55 (s, C**H**$_2$O), 6.42 (br d, *J* = 6.6 Hz, N**H**C(O)CH_3), 6.71–6.79 (br t, CH_2N**H**), 6.96–7.15 (m, 3 Ar**H**), 7.24–7.35 (m, 5 Ar**H**), addition of excess (*R*)-(-)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-4'-(((3''-fluoro)benzyloxy)methyl)benzyl 2-acetamido-3-methoxypropionamide ((*R*)-**18**) gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.2 (**C**H_3), 43.3 (N**C**H_2), 53.4 (OCH_2**C**H), 59.1 (O**C**H_3), 71.3, 71.6, 72.0 (3 **C**H_2O), 114.4 (d, *J* = 21.4 Hz, **C$_{2'}$** or **C$_{4'}$**), 114.5 (d, *J* = 21.1 Hz, **C$_{4'}$** or **C$_{2'}$**), 123.0 (d, *J* = 2.9 Hz, **C$_{6'}$**), 127.6, 128.1 (2 Ar**C**), 129.9 (d, *J* = 8.2 Hz, **C$_{5'}$**), 137.3, 137.4 (2 Ar**C**), 140.9 (d, *J* = 7.1 Hz, **C$_{1'}$**), 163.0 (d, *J* = 244.4 Hz, **C$_{3'}$**), 169.9, 170.3 (2 **C**(O)); HRMS (M+H$^+$)(ESI$^+$) 389.1877 [M + H$^+$] (calcd for $C_{21}H_{25}FN_2O_4H^+$ 389.1876); Anal. Calcd. for $C_{21}H_{25}FN_2O_4$: C, 64.93; H, 6.47; F, 4.89; N, 7.21. Found: C, 64.53; H, 6.47; F, 4.68; N, 7.37.

14. Preparation of (*R*)-*N*-4'-((3''-Fluoro)phenethoxy)benzyl 2-*N*-Acetamido-3-methoxypropionamide ((*R*)-19).

Reaction Overview

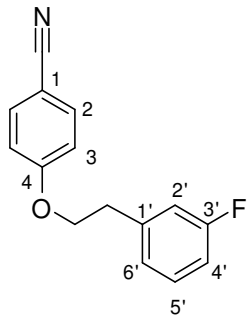


40 **62** **63** **64**



R= H
(*R*)-**24**

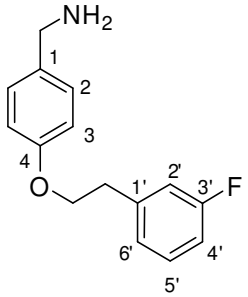
(*R*)-**19**



Preparation of 4-((3'-Fluoro)phenethoxy)benzonitrile (63).

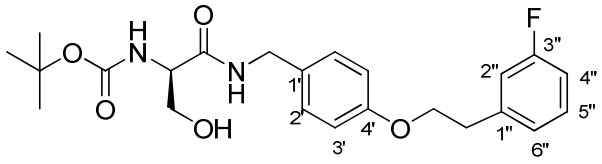
A THF (2 mL) solution of 3-(fluoro)phenethyl alcohol (**62**)(168 mg, 1.2 mmol) and DEAD (205 μL, 1.3 mmol) was very slowly added dropwise at 0 °C to a THF (4 mL) solution of triphenylphosphine (341 mg, 1.3 mmol) and 4-cyanophenol (**40**) (119 mg, 1.0 mmol). The mixture was stirred at 0 °C (30 min), and then at room temperature (16 h). A saturated aqueous solution of NH_4Cl (200 mL) was added dropwise at 0 °C. The volatiles were evaporated under vacuum and the residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (0/10 to 2/8) as the eluant to obtain 4-((3'-fluoro)phenethoxy)benzonitrile (**63**) as a white solid

(180 mg, 75%): R_f = 0.33 (EtOAc/hexanes 1/9); mp 79–81°C; IR (crystal) 3281, 2909, 2222, 1711, 1643, 1603, 1589, 1506, 1489, 1450, 1418, 1300, 1250, 1171, 1140, 1115, 1057, 1024, 941 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.11 (t, J = 7.0 Hz, C**H**$_2$), 4.22 (t, J = 7.0 Hz, OC**H**$_2$), 6.92–7.06 (m, 5 Ar**H**), 7.20–7.31 (m, 1 Ar**H**), 7.57 (d, J = 8.0 Hz, 2 **H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.2 (d, J = 1.6 Hz, **C**H$_2$), 68.5 (**C**H$_2$O), 104.1 (**C**$_1$), 113.6 (d, J = 21.0 Hz, **C**$_{2'}$ or **C**$_{4'}$), 115.2 (**C**$_3$), 115.9 (d, J = 20.9 Hz, **C**$_{4'}$ or **C**$_{2'}$), 119.1 (**C**N), 124.6 (d, J = 3.1 Hz, **C**$_{6'}$), 130.0 (d, J = 8.6 Hz, **C**$_{5'}$), 134.0 (**C**$_2$), 140.2 (d, J = 7.0 Hz, **C**$_{1'}$), 161.9 (**C**$_4$), 162.9 (d, J = 247.7 Hz, **C**$_{3'}$); HRMS (M+H$^+$)(ESI$^+$) not observed [M + H$^+$] (calcd for $C_{13}H_8FNOH^+$ 214.0668); Anal. Calcd. for $C_{15}H_{12}FNO$: C, 74.67; H, 5.01; F, 7.87; N, 5.81. Found: C, 74.46; H, 5.11; F, 7.89; N, 5.83.



Preparation of 4-((3'-Fluoro)phenethoxy)benzylamine (64). To a $LiAlH_4$ (3.80 g, 99.6 mmol) suspension in THF (350 mL) was added dropwise a THF (750 mL) solution of 4-((3'-fluoro)phenethoxy)benzonitrile (**63**) (8.00 g, 33.2 mmol) at 0 °C. The mixture was stirred at room temperature (16 h) and then H_2O (3.0 mL) was added dropwise at 0 °C followed by an aqueous NaOH solution (1. 5 mL, 15% w/w) and then H_2O (3.0 mL). The mixture was stirred at room temperature (2 h) and the precipitate was filtered and washed with CH_2Cl_2. The filtrate was concentrated in vacuo to give 5.50 g of a colorless oil (68%): R_f = 0.00 (hexanes/EtOAc 9/1); ^1H NMR (400 MHz, $CDCl_3$) δ 1.75 (br s, N**H**$_2$), 3.07 (t, J = 6.7 Hz, C**H**$_2$), 3.79 (s, C**H**$_2$NH$_2$), 4.16 (t, J = 6.7 Hz, OC**H**$_2$), 6.84–7.06 (m, 5 Ar**H**), 7.20–7.29 (m, 3 Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.5 (d, J = 1.6 Hz, **C**H$_2$), 45.8 (**C**H$_2$NH$_2$), 68.2 (**C**H$_2$O), 113.3 (d, J = 20.9 Hz, **C**$_{2'}$ or **C**$_{4'}$), 114.6 (**C**$_3$), 115.9 (d, J = 20.9 Hz, **C**$_{4'}$ or **C**$_{2'}$), 124.6 (d, J = 3.1 Hz, **C**$_{6'}$), 128.3 (**C**$_2$), 129.8 (d, J = 8.5 Hz, **C**$_{5'}$), 135.5 (**C**$_1$), 140.9 (d, J = 7.8 Hz, **C**$_{1'}$), 157.6 (**C**$_4$), 162.8 (d, J = 243.9 Hz, **C**$_{3'}$); HRMS (M+H$^+$)(ESI$^+$) 246.1294 [M + H$^+$]

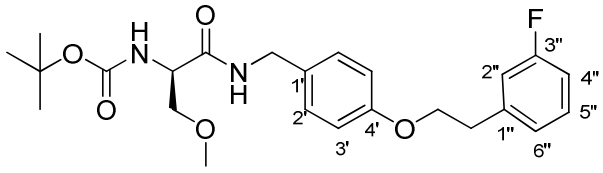
(calcd for $C_{15}H_{16}FNOH^+$ 246.1294); Anal. Calcd. for $C_{15}H_{16}FNO•0.15H_2O$: C, 72.65; H, 6.62; F, 7.66; N, 5.65. Found: C, 72.61; H, 6.58; F, 7.28; N, 5.46.



Preparation of (*R*)-*N*-4'-((3"-Fluoro)phenethoxy)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-98).

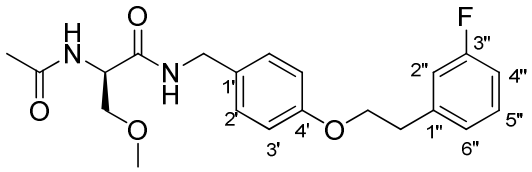
A THF solution (250 mL) of (*R*)-*t*-Boc-serine ((*R*)-**24**) (5.00 g, 21.6 mmol) was stirred and cooled at -78 °C under Ar and then 4-methylmorpholine (NMM) (2.9 mL, 26.0 mmol) was added dropwise. After 2 min of stirring at this temperature, isobutylchloroformate (IBCF) (3.4 mL, 26.0 mmol) was added dropwise leading to the precipitation of a white solid, and the reaction was allowed to proceed for additional 2 min, and then 4-((3'-fluoro)phenethoxy)benzylamine (**64**) (6.30 g, 26.0 mmol) was added portionwise at -78 °C. The mixture was allowed to stir at room temperature (2 h), and the white solid filtered and the organic layer concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (5/5 to 10/0) as the eluant to obtain (*R*)-*N*-4'-((3"-fluoro)phenethoxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-**98**) as colorless oil (3.00 g, 32%): R_f = 0.32 (hexanes/EtOAc 5/5); $[\alpha]^{26.3}_D$ +14.8° (*c* 1, $CHCl_3$); IR (nujol) 3329, 3281, 3252, 1691, 1657, 1643, 1549, 1524, 1388, 1366, 1300, 1277, 1238, 1171, 1140, 1113, 1034, 957, 781 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, $(CH_3)_3$), 3.07 (t, *J* = 6.6 Hz, CH_2), 3.34–3.49 (br m, OH), 3.61–3.72 (m, CHH'), 4.05–4.15 (m, OCH_2, CH, CHH'), 4.28–4.43 (m, $NHCH_2$), 5.65 (br d, *J* = 7.2 Hz, NH), 6.82 (d, *J* = 7.4 Hz, 2 ArH), 6.89–7.06 (m, NH, 3 ArH), 7.15 (d, *J* = 7.4 Hz, 2 ArH), 7.21–7.29 (m, 1 ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2 ($(CH_3)_3$), 35.4 (d, *J* = 1.6 Hz, CH_2), 42.9 (NCH_2), 54.9 (OCH_2CH), 62.8, 68.2 (2 CH_2O), 80.5 ($C(CH_3)_3$), 113.4 (d, *J* = 20.9 Hz, $C_{2'}$ or $C_{4'}$), 114.7 (C_3), 115.8 (d, *J* = 20.9 Hz, $C_{4'}$ or $C_{2'}$), 124.6 (d, *J* = 3.1 Hz, $C_{6'}$), 128.8 (C_2), 129.8 (d, *J* = 8.5 Hz, $C_{5'}$), 130.0 (C_1), 140.8 (d, *J* = 7.0 Hz, $C_{1'}$), 156.2 (OC(O)NH), 158.1 (C_4), 162.8 (d, *J* = 243.9 Hz, $C_{3'}$),

171.2 (**C**(O)); HRMS (M+Na$^+$)(ESI$^+$) 455.1958 [M + Na$^+$] (calcd for $C_{23}H_{29}FN_2O_5Na^+$ 455.1958).



Preparation of (*R*)-*N*-4'-((3''-Fluoro)phenethoxy)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-99).

Ag_2O (7.70 g, 33.5 mmol) was added to a CH_3CN solution (200 mL) of (*R*)-*N*-4'-((3"-fluoro)phenethoxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-**109**) (2.90 g, 6.7 mmol) and CH_3I (4.2 mL, 67.0 mmol) at room temperature under Ar. The reaction mixture was stirred at room temperature in the dark (3 d), filtered through Celite®, and the filtrate concentrated in vacuo to obtain a white solid. The solid was purified by flash column chromatography on silica gel with EtOAc/hexanes (3/7 to 6/4) as the eluant to obtain (*R*)-*N*-4'-((3"-fluoro)phenethoxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-**99**) as a white solid (2.40 g, 80%): R_f = 0.63 (1/1 EtOAc/hexanes); mp 64–67 °C; $[\alpha]^{25.7}_D$ -16.2° (*c* 0.5, $CHCl_3$); IR (crystal) 3314, 2928, 1686, 1647, 1414, 1452, 1391, 1317, 1240, 1167, 1138, 1084, 1038, 1020, 912 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, (C**H$_3$**)$_3$), 3.07 (t, *J* = 6.9 Hz, C**H$_2$**), 3.35 (s, OC**H$_3$**), 3.46–3.51 (m, C**H**H'), 3.81 (dd, *J* = 3.8, 9.0 Hz, CH**H'**), 4.15 (t, *J* = 6.9 Hz, OC**H$_2$**), 4.19–4.28 (br m, C**H**), 4.32–4.44 (br m, C**H$_2$**NH), 5.37–5.45 (br m, N**H**), 6.65–6.73 (br t, N**H**), 6.83 (d, *J* = 7.6 Hz, 2 Ar**H**), 6.87–7.05 (m, 3 Ar**H**), 7.17 (d, *J* = 7.6 Hz, 2 Ar**H**), 7.23–7.29 (m, 1 Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2 ((**C**H$_3$)$_3$), 35.4 (d, *J* = 1.5 Hz, **C**H$_2$), 42.9 (N**C**H$_2$), 54.0 (OCH$_2$**C**H), 59.0 (O**C**H$_3$), 68.2 (O**C**H$_2$), 72.1 (**C**H$_2$OCH$_3$), 80.3 (**C**(CH$_3$)$_3$), 113.3 (d, *J* = 20.9 Hz, **C$_{2'}$** or **C$_{4'}$**), 114.7 (**C$_3$**), 115.8 (d, *J* = 20.9 Hz, **C$_{4'}$** or **C$_{2'}$**), 124.6 (d, *J* = 3.1 Hz, **C$_{6'}$**), 128.8 (**C$_2$**), 129.8 (d, *J* = 8.5 Hz, **C$_{5'}$**), 130.3 (**C$_1$**), 140.8 (d, *J* = 6.9 Hz, **C$_{1'}$**), 155.5 (O**C**(O)NH), 158.0 (**C$_4$**), 162.8 (d, *J* = 244.7 Hz, **C$_{3'}$**), 170.2 (**C**(O)); HRMS (M+Na$^+$)(ESI$^+$) 469.2115 [M + Na$^+$] (calcd for $C_{24}H_{31}FN_2O_5Na^+$ 469.2114).



Preparation of (*R*)-*N*-4'-((3"-Fluoro)phenethoxy)benzyl 2-*N*-Acetamido-3-methoxypropionamide ((R)-19).

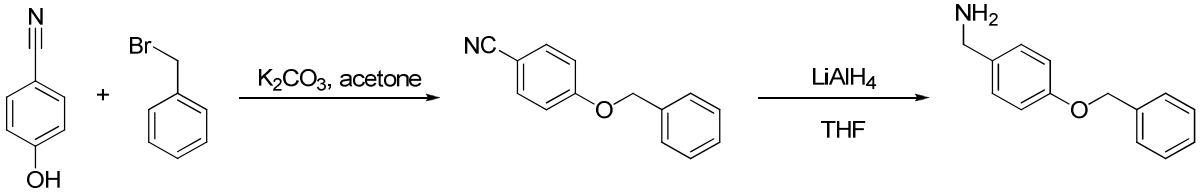
A saturated HCl solution in dioxane (1 mmol/2 mL, 10.0 mL) was added to an Et_2O (5 mL) solution of (*R*)-*N*-4'-((3"-fluoro)phenethoxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-**99**) (2.20 g, 5.0 mmol) at 0 °C and the solution was stirred at room temperature (16 h). The reaction solution was concentrated in vacuo and dried (30 min).

The residue was dissolved in CH_2Cl_2 (30 mL) and Et_3N (2.1 mL, 15.0 mmol) and AcCl (0.54 mL, 7.5 mmol) were successively added at 0 °C. The mixture was stirred at room temperature (16 h), aqueous 10% citric acid (60 mL) was added, and then the organic layer was separated. The aqueous layer was washed with CH_2Cl_2 (2 x 30 mL). All of the organic layers were combined, washed with aqueous saturated $NaHCO_3$ (30 mL) and H_2O (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The solid was recrystallized with EtOAc to obtain (*R*)-*N*-4'-((3"-fluoro)phenethoxy)benzyl 2-*N*-acetamido-3-methoxypropionamide ((*R*)-**19**) as a white solid (1.30 g, 66%): R_f = 0.28 (EtOAc); mp 147–148 °C; $[\alpha]^{25.2}_D$ –16.6° (*c* 0.5, $CHCl_3$); IR (crystal) 3323, 3240, 3001, 2938, 1738, 1634, 1553, 1541, 1514, 1456, 1368, 1304, 1231, 1217, 1207, 1175, 1134, 1109, 1097, 1034, 1007, 980, 864, 822 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.02 (s, C**H**$_3$C(O)), 3.08 (t, *J* = 7.1 Hz, C**H**$_2$), 3.36 (s, OC**H**$_3$), 3.39–3.44 (m, C**H**H'), 3.79 (dd, *J* = 4.8, 9.6 Hz, CH**H'**), 4.15 (t, *J* = 7.1 Hz, OC**H**$_2$), 4.33–4.44 (m, C**H**$_2$NH), 4.49–4.54 (m, C**H**), 6.44 (br d, *J* = 6.4 Hz, N**H**C(O)CH_3), 6.65–6.73 (br t, N**H**), 6.84 (d, *J* = 8.0 Hz, 2 Ar**H**), 6.90–7.06 (m, 3 Ar**H**), 7.16 (d, *J* = 8.0 Hz, 2 Ar**H**), 7.23–7.29 (m, 1 Ar**H**), addition of excess (*R*)-(-)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-4'-((3"-fluoro)phenethoxy)benzyl 2-*N*-acetamido-3-methoxypropionamide ((*R*)-**19**) gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2 (**C**H_3C(O)), 35.4 (d, *J* = 1.6 Hz, **C**H_2), 43.0 (N**C**H_2), 52.4 (OCH_2**C**H), 59.0 (O**C**H_3), 68.2 (O**C**H_2), 71.6 (**C**H_2O), 113.4 (d, *J* = 21.0 Hz, **C$_2$'** or **C$_4$'**), 114.7 (**C$_3$**), 115.8 (d, *J* = 20.9 Hz, **C$_4$'** or **C$_2$'**), 124.6 (d, *J* = 2.3 Hz, **C$_6$'**), 128.8 (**C$_2$**), 129.8 (d, *J* = 7.7 Hz, **C$_5$'**), 130.1 (**C$_1$**), 140.8 (d, *J* = 7.8 Hz, **C$_1$'**), 158.1 (**C$_4$**),

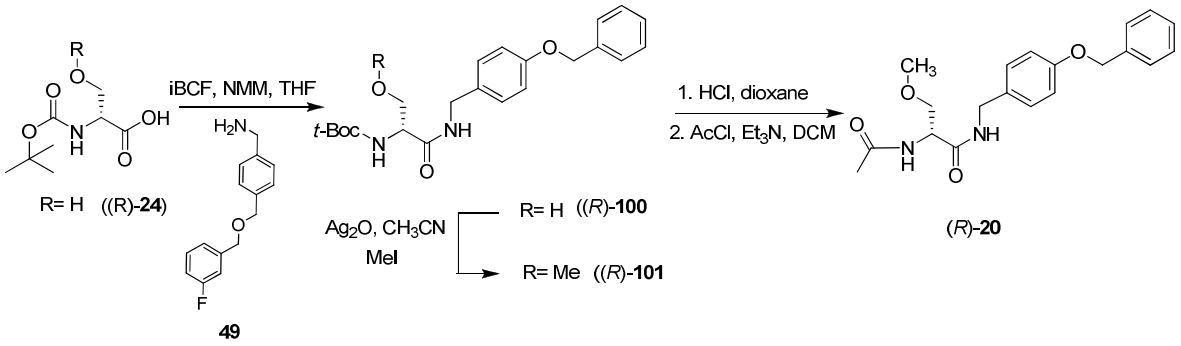
162.8 (d, J = 243.9 Hz, $\mathbf{C_{3'}}$), 169.8, 170.2 (2 **C**(O)); HRMS (M+Na^+)(ESI^+) 411.1696 [M + Na^+] (calcd for $C_{21}H_{25}FN_2O_4Na^+$ 411.1691); Anal. Calcd. for $C_{21}H_{25}FN_2O_4$: C, 64.93; H, 6.49; F, 4.89; N, 7.21. Found: C, 64.98; H, 6.57; F, 4.84; N, 7.10.

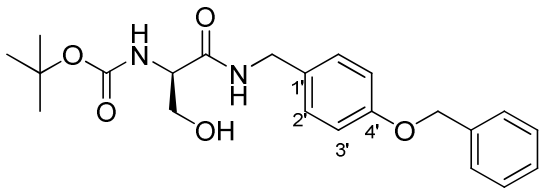
15. Preparation of (*R*)-*N*-4'-(Benzyloxy)benzyl 2-*N*-Acetamido-3-methoxypropionamide ((*R*)-20).

Reaction Overview



40 **41** **45** **49**

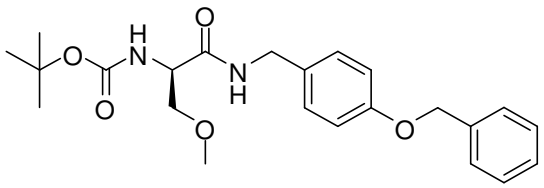




Preparation of (*R*)-*N*-4'-(Benzyloxy)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-100).

A THF solution (250 mL) of (*R*)-*t*-Boc-serine ((*R*)-**24**) (5.00 g, 21.6 mmol) was stirred and cooled at -78 °C under Ar and then 4-methylmorpholine (NMM) (2.9 mL, 26.0 mmol) was added dropwise. After 2 min of stirring at this temperature,

isobutylchloroformate (IBCF) (3.4 mL, 26.0 mmol) was added dropwise leading to the precipitation of a white solid, and the reaction was allowed to proceed for additional 2 min, and then 4-(benzyloxy)benzylamine (**49**)[7] (5.20 g, 26.0 mmol) was added portionwise at -78 °C. The mixture was allowed to stir at room temperature (2 h), and the white solid filtered and the organic layer concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (5/5 to 10/0) as the eluant to obtain (*R*)-*N*-4'-(benzyloxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-**100**) as a white solid (6.30 g, 73%): R_f = 0.31 (hexanes/EtOAc 5/5); mp 64–67 °C; $[\alpha]^{25.3}_D$ +18.0° (*c* 1, $CHCl_3$); IR (crystal) 3327, 2982, 2936, 2876, 1713, 1684, 1657, 1549, 1514, 1456, 1389, 1368, 1302, 1277, 1236, 1167, 1107, 1034, 1007 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, (C**H$_3$**)$_3$), 3.20–3.51 (br m, O**H**), 3.61–3.70 (br m, C**H**H'), 4.02–4.19 (br m, CH**H'**, C**H**), 4.26–4.46 (br m, C**H$_2$**NH), 5.04 (s, OC**H$_2$**), 5.59–5.68 (br m, N**H**), 6.91 (d, *J* = 8.4 Hz, 2 Ar**H**), 6.95–7.08 (br m, N**H**), 7.16 (d, *J* = 8.4 Hz, 2 Ar**H**), 6.30–7.43 (m, 5 Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2 ((**C**H_3)$_3$), 42.9 (N**C**H_2), 54.9 (OCH_2**C**H), 62.8 (O**C**H_2CH), 70.0 (O**C**H_2), 80.6 (**C**$(CH_3)_3$), 115.0, 127.4, 128.0, 128.6, 128.8, 130.1, 136.9 (7 Ar**H**), 156.2 (NH**C**(O)O), 158.2 (**C$_4$**), 171.2 (**C**(O)); HRMS (M+Na^+)(ESI^+) 423.1896 [M + Na^+] (calcd for $C_{22}H_{28}N_2O_5Na^+$ 423.1896); Anal. Calcd. for $C_{22}H_{28}N_2O_5$: C, 65.98; H, 7.05; N, 7.00. Found: C, 66.05; H, 7.15; N, 7.04.

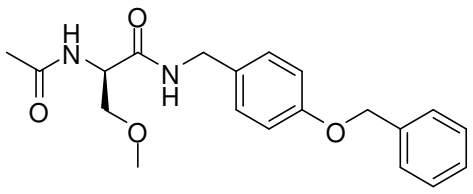


Preparation of (*R*)-*N*-4'-(Benzyloxy)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-101).

Ag_2O (14.40 g, 62.5 mmol) was added to a CH_3CN solution (350 mL) of (*R*)-*N*-4'-(benzyloxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-**100**) (5.00 g, 12.5 mmol) and CH_3I (7.8 mL, 125.0 mmol) at room temperature under

[7] Coburger, C.; Wollmann, J.; Baumert, C.; Krug, M.; Molnar, J.; Lage, H.; Hilgeroth, A. *J. Med. Chem.* **2008**, 51, 5871-5874

Ar. The reaction mixture was stirred at room temperature in the dark (3 d), filtered through Celite®, and the filtrate concentrated in vacuo to obtain a white solid. The solid was purified by flash column chromatography on silica gel with EtOAc/hexanes (5/5) as the eluant to obtain (*R*)-*N*-4'-(benzyloxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-**101**) as a white solid (5.10 g, quant.): R_f = 0.57 (1/1 EtOAc/hexanes); mp 103–104°C; $[\alpha]^{25.7}_D$ -38.0° (*c* 0.5, $CHCl_3$); IR (crystal) 3312, 2930, 1684, 1647, 1551, 1514, 1450, 1389, 1364, 1315, 1285, 1240, 1167, 1109, 1086, 1045, 1024 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, ($C\mathbf{H_3}$)$_3$), 3.36 (s, $OC\mathbf{H_3}$), 3.46–3.51 (br m, C**H**H'), 3.83 (dd, *J* = 3.2, 9.6 Hz, CH**H'**), 4.21–4.30 (br m, C**H**), 4.36–4.45 (br m, $C\mathbf{H_2}NH$), 5.06 (s, $OC\mathbf{H_2}$), 5.33–5.44 (br m, N**H**), 6.61–6.66 (br t, N**H**), 6.93 (d, *J* = 7.0 Hz, 2 Ar**H**), 7.18 (d, *J* = 7.0 Hz, 2 Ar**H**), 7.29–7.44 (m, 5 Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2 (($\mathbf{C}H_3$)$_3$), 43.0 ($N\mathbf{C}H_2$), 54.0 ($OCH_2\mathbf{C}H$), 59.0 ($O\mathbf{C}H_3$), 70.0, 72.0 (2 $O\mathbf{C}H_2$), 80.3 ($\mathbf{C}(CH_3)_3$), 115.0, 127.4, 127.9, 128.6, 128.8, 130.3, 136.9 (7 Ar**H**), 155.5 (NH**C**(O)O), 158.2 ($\mathbf{C_4}$), 170.1 (**C**(O)); HRMS (M+Na^+)(ESI^+) 437.2052 [M + Na^+] (calcd for $C_{23}H_{30}N_2O_5Na^+$ 437.2052); Anal. Calcd. for $C_{23}H_{30}N_2O_5$: C, 66.65; H, 7.30; N, 6.76. Found: C, 66.90; H, 7.25; N, 6.84.



Preparation of (*R*)-*N*-4'-(Benzyloxy)benzyl 2-*N*-Acetamido-3-methoxypropionamide ((*R*)-20).

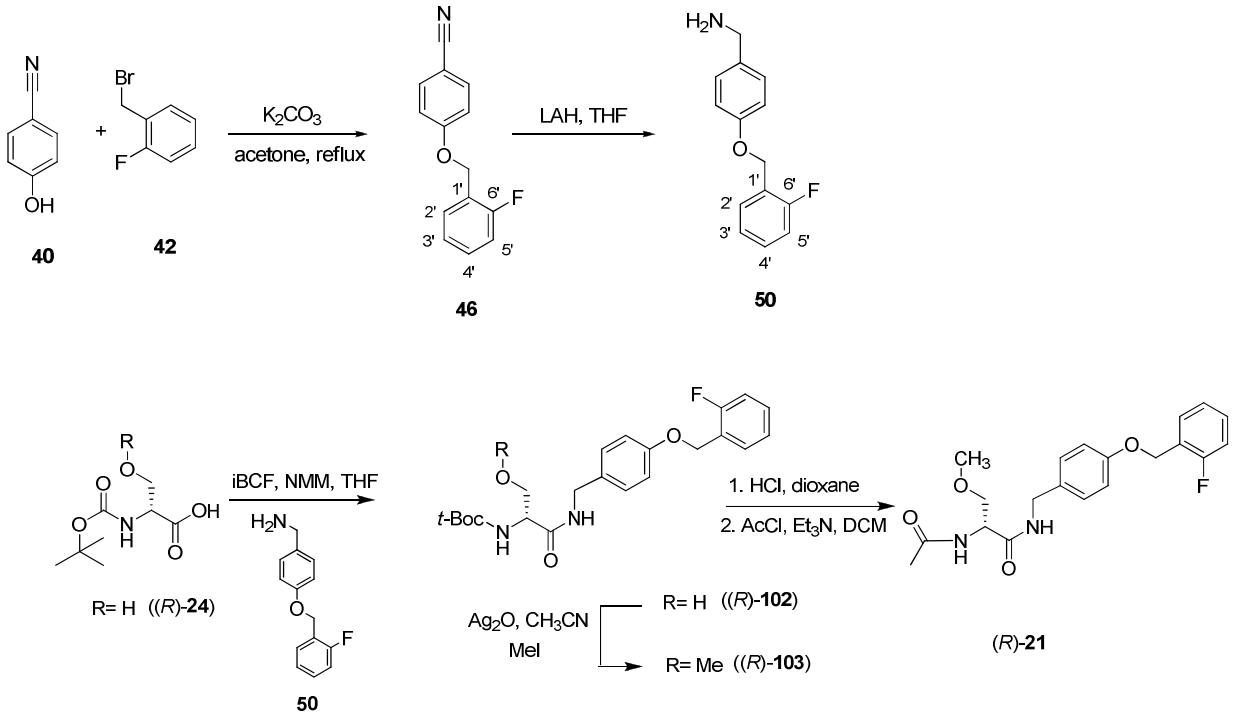
A saturated HCl solution in dioxane (1 mmol/2 mL, 24.1 mL) was added to an Et_2O (10 mL) solution of (*R*)-*N*-4'-(benzyloxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-**101**) (5.00 g, 12.1 mmol) at 0 °C and the solution was stirred at room temperature (16 h). The reaction solution was concentrated in vacuo and dried (30 min).

The residue was dissolved in CH_2Cl_2 (60 mL) and Et_3N (5.1 mL, 36.3 mmol) and AcCl (1.4 mL, 18.8 mmol) were successively added at 0 °C. The mixture was stirred at room temperature (16 h), aqueous 10% citric acid (60 mL) was added, and then the organic layer was separated. The aqueous layer was washed with CH_2Cl_2 (2

x 30 mL). All of the organic layers were combined, washed with aqueous saturated $NaHCO_3$ (30 mL) and H_2O (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The solid was recrystallized with EtOAc to obtain (*R*)-*N*-4'-(benzyloxy)benzyl 2-*N*-acetamido-3-methoxypropionamide ((*R*)-**20**) as a white solid (2.60 g, 60%): R_f = 0.28 (EtOAc); mp 149 °C; $[\alpha]^{25.1}_D$ –26.8° (*c* 0.5, $CHCl_3$); IR (crystal) 3283, 3028, 2940, 1738, 1719, 1636, 1551, 1514, 1454, 1433, 1368, 1304, 1229, 1217, 1177, 1140, 1099, 1036, 1026, 910, 810 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.02 (s, C**H$_3$**C(O)), 3.36 (s, C**H$_3$**), 3.39–3.44 (br m, C**H**H'), 4.02–3.79 (dd, *J* = 4.2, 9.4 Hz, CH**H'**), 4.36–4.44 (m, C**H$_2$**NH), 4.48–4.55 (m, C**H**), 5.05 (s, OC**H$_2$**), 6.42 (br d, *J* = 6.0 Hz, N**H**), 6.64–6.71 (br m, N**H**), 6.93 (d, *J* = 7.8 Hz, 2 Ar**H**), 7.18 (d, *J* = 7.8 Hz, 2 Ar**H**), 7.29–7.44 (m, 5 Ar**H**), addition of excess (*R*)-(-)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-4'-(benzyloxy)benzyl 2-*N*-acetamido-3-methoxypropionamide ((*R*)-**20**) gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2 (**C**H$_3$C(O)), 43.0 (N**C**H$_2$), 52.4 (OCH$_2$**C**H), 59.0 (O**C**H$_3$), 70.0, 71.6 (2 O**C**H$_2$), 115.0, 127.4, 128.0, 128.6, 128.8, 130.2, 136.8 (7 Ar**H**), 158.2 (**C$_4$**), 169.8, 170.2 (**C**(O)); HRMS (M+Na^+)(ESI^+) 379.1634 [M + Na^+] (calcd for $C_{20}H_{24}N_2O_4Na^+$ 379.1634); Anal. Calcd. for $C_{20}H_{24}N_2O_4$: C, 67.40; H, 6.79; N, 7.86. Found: C, 67.12; H, 6.68; N, 7.80.

16. Preparation of Preparation of (*R*)-*N*-4'-((2''-Fluoro)benzyloxy)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-21).

Reaction Overview

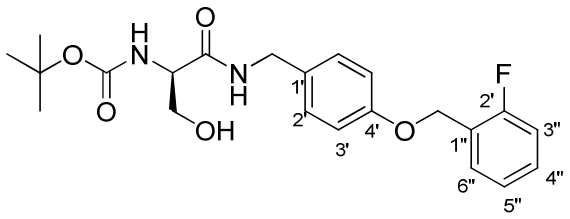


Preparation of 4-((2'-Fluoro)benzyloxy)benzonitrile (46).

A mixture of 4-cyanophenol (**40**) (11.91 g, 100.0 mmol), K_2CO_3 (55.20 g, 400.0 mmol), and 2-(fluoro)benzylbromide (**42**) (22.68 g, 120.0 mmol) were heated in acetone (400 mL) at reflux (5 h). The volatiles were evaporated and the residue was diluted in CH_2Cl_2 (300 mL), and then washed with H_2O (500 mL), dried ($MgSO_4$), and concentrated in vacuo. The solid was recrystallized with MeOH to give white needles (14.10 g, 62%): R_f = 0.90 (hexanes/EtOAc 9/1); mp 118-119 °C; IR (nujol) 3068, 2939, 2885, 2213, 1601, 1507, 1459, 1376, 1300, 1249, 1159, 994, 827, 720, 547, 509 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.18 (s, C**H**$_2$O), 7.01–7.21 (m, 4 Ar**H**), 7.32–7.39 (m, 1 Ar**H**), 7.47 (td, *J* = 1.5, 7.2 Hz, 1 Ar**H**), 7.60 (d, *J* = 9.0 Hz, 2 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 63.9 (d, *J* = 4.5 Hz, **C**H$_2$O), 104.5 (**C**CN), 115.4 (Ar**C**), 115.5 (d, *J* = 21.0 Hz, **C$_{3'}$**), 119.1 (**C**N), 122.9 (d, *J* = 14.2 Hz, **C$_{1'}$**), 124.4 (d, *J* = 3.7 Hz, **C$_{5'}$**), 129.7 (d, *J* = 3.7 Hz, **C$_{6'}$** or **C$_{4'}$**), 130.2 (d, *J* = 8.2 Hz, **C$_{4'}$** or **C$_{6'}$**), 134.0 (Ar**C**), 160.5 (d, *J* = 245.9 Hz, **C$_{2'}$**), 161.7 (Ar**C**); Anal. Calcd. for $C_{14}H_{10}FNO_2$: C, 74.00; H, 4.44; F, 8.36; N, 6.16. Found: C, 74.06; H, 4.28; F, 8.26; N, 6.16.

Preparation of 4-((2'-Fluoro)benzyloxy)benzylamine (50)

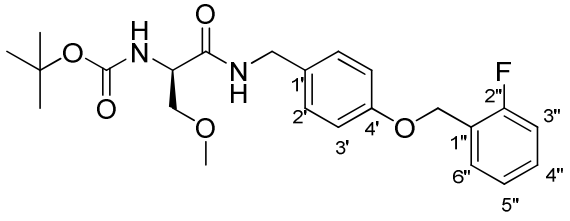
To a $LiAlH_4$ (6.50 g, 171.9 mmol) suspension in THF (500 mL) was added dropwise a THF (40 mL) solution of 4-((2'-fluoro)benzyloxy)benzonitrile (**46**) (13.00 g, 57.3 mmol) at 0 °C. The mixture was stirred at room temperature (16 h) and H_2O (5.4 mL) was added dropwise at 0 °C followed by an aqueous NaOH solution (2.7 mL, 15% w/w), and then H_2O (5.4 mL). The mixture was stirred at room temperature (2 h), and the precipitate filtered and washed with CH_2Cl_2. The filtrate was concentrated in vacuo to obtain a colorless oil (8.00 g, 64%): R_f = 0.00 (hexanes/EtOAc 9/1); IR (hydrochloride salt, nujol) 3081, 1608, 1519, 1457, 1380, 1300, 1240, 1181, 1051, 967, 836, 754, 558 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.63 (br s, N**H**$_2$), 3.80 (s, C**H**$_2$$NH_2$), 5.12 (s,C**H**$_2$O), 6.96 (d, J = 9.0 Hz, 2 Ar**H**), 7.05–7.34 (m, 5 Ar**H**), 7.50 (td, J = 1.5, 7.5 Hz, 1 Ar**H**); HRMS (M-NH_2^+)(ESI$^+$) 215.0878 [M – NH_2^+] (calcd for $C_{14}H_{12}FO^+$ 215.0872).



Preparation of (*R*)-*N*-4'-((2''-Fluoro)benzyloxy)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-102).

A THF solution (100 mL) of (*R*)-*t*-Boc-serine ((*R*)-**24**) (5.00 g, 24.4 mmol) was stirred and cooled at -78 °C under Ar and then 4-methylmorpholine (NMM) (3.2 mL, 29.3 mmol) was added dropwise. After 2 min of stirring at this temperature, isobutylchloroformate (IBCF) (3.8 mL, 29.3 mmol) was added dropwise leading to the precipitation of a white solid, and the reaction was allowed to proceed for additional 2 min, and then 4-((2'-fluoro)benzyloxy)benzylamine (**50**) (6.70 g, 29.3 mmol) was added portionwise at -78 °C. The mixture was allowed to stir at room temperature (2 h), and the white solid filtered and the organic layer concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (50/50 to 100/00) as the eluant to obtain (*R*)-*N*-4'-((2''-

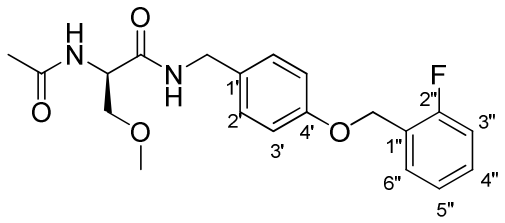
fluoro)benzyloxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-**102**) as a white solid (6.90 g, 68%): R_f = 0.51 (hexanes/EtOAc 4/6); mp 99-100 °C; $[\alpha]^{25.2}_D$ +14.2° (*c* 1, $CHCl_3$); IR (nujol) 3175, 2966, 1691, 1650, 1526, 1458, 1378, 1305, 1238, 1167, 1044, 1004, 828, 718, 664, 566 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, (C**H**$_3$)$_3$), 3.21–3.33 (br m, C**H**H'), 3.64–3.70 (br m, CH**H'**), 4.09–4.16 (br m, C**H**, O**H**), 4.29–4.43 (br m, C**H**$_2$N), 5.10 (s, C**H**$_2$O), 5.56–5.66 (br d, N**H**), 6.92 (d, *J* = 8.4 Hz, 2 Ar**H**), 6.96–7.04 (br m, N**H**), 7.05–7.19 (m, 4 Ar**H**), 7.28-7.34 (m, 1 Ar**H**), 7.48 (td, *J* = 1.2, 9.2 Hz, 1 Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3 ((**C**H$_3$)$_3$), 42.9 (N**C**H$_2$), 54.9 (OCH$_2$**C**H), 62.8 (O**C**H$_2$CH), 63.7 (d, *J* = 4.6 Hz, **C**H$_2$O), 80.6 (**C**(CH$_3$)$_3$), 115.0 (**C$_3$**), 115.4 (d, *J* = 21.2 Hz, **C$_{3'}$**), 124.1 (d, *J* = 14.2 Hz, **C$_{1'}$**), 124.3 (d, *J* = 3.2 Hz, **C$_{5'}$**), 128.9 (Ar**C**), 129.6 (d, *J* = 7.7 Hz, **C$_4$**, or **C$_{6'}$**), 129.7 (d, *J* = 11.5 Hz, **C$_6$**, or **C$_{4'}$**), 130.3 (Ar**C**), 156.3 (N**C**(O)O), 158.0 (**C$_4$**), 160.4 (d, *J* = 245.0 Hz, **C$_{2'}$**), 171.3 (**C**(O)); HRMS (M+H$^+$)(ESI$^+$) 419.1982 [M + H$^+$] (calcd for $C_{22}H_{27}FN_2O_5H^+$ 419.1982); Anal. Calcd. for $C_{22}H_{27}FN_2O_5$: C, 63.14; H, 6.50; F, 4.54; N, 6.69. Found: C, 63.09; H, 6.50; F, 4.36; N, 6.69.



Preparation of (*R*)-*N*-4'-((2''-Fluoro)benzyloxy)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-103).

Ag_2O (18.80 g, 81.2 mmol) was added to a CH_3CN solution (400 mL) of (*R*)-*N*-4'-((2''-fluoro)benzyloxy)benzyl 2-*N*-(*tert.*-butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-**102**) (6.80 g, 16.3 mmol) and CH_3I (10.12 mL, 162.5 mmol) at room temperature under Ar. The reaction mixture was stirred at room temperature (3 d), filtered, and the filtrate concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (3/7) as the eluant to obtain (*R*)-*N*-4'-((2'-fluoro)benzyloxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide as a white solid ((*R*)-**103**) (6.10 g, 87%): R_f = 0.56 (3/7 EtOAc/hexanes); mp 82-85 °C; $[\alpha]^{24.6}_D$ -16.7° (*c* 1, $CHCl_3$); IR (nujol) 3305, 2855, 1689, 1648, 1524, 1457, 1378, 1313, 1241, 1171, 1092, 1048,

916, 834, 757, 680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, (CH_3)$_3$), 3.28 (s, OC**H$_3$**), 3.41 (dd, *J* = 6.4, 8.8 Hz, C**H**H'), 3.73–3.77 (m, CH**H'**), 4.16–4.20 (br m, C**H**), 4.30–4.36 (br m, C**H$_2$**N), 5.05 (s, OC**H$_2$**), 5.30–5.34 (br m, OC(O)N**H**), 6.58–6.62 (br m, CH_2N**H**), 6.86 (d, *J* = 8.8 Hz, 2 Ar**H**), 7.01 (t, *J* = 8.8 Hz, 1 Ar**H**), 7.06–7.14 (m, 3 Ar**H**), 7.20–7.26 (m, 1 Ar**H**), 7.42 (t, *J* = 7.6 Hz, 1 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 28.3 (($\mathbf{C}H_3$)$_3$), 42.8 (N**C**H_2), 54.0 (OCH_2**C**H), 59.0 (OC**H$_3$**), 63.6 (d, *J* = 4.0 Hz, **C**H_2O), 72.0 (O**C**H_2CH), 80.2 (**C**(CH_3)$_3$), 114.9 (**C$_3$**), 115.2 (d, *J* = 21.1 Hz, **C$_{3'}$**), 124.1 (d, *J* = 14.1 Hz, **C$_{1'}$**), 124.2 (d, *J* = 3.4 Hz, **C$_{5'}$**), 128.8 (Ar**C**), 129.5–129.7 (br t, **C$_{4'}$**, **C$_{6'}$**), 130.6 (Ar**C**), 155.4 (N**C**(O)O), 157.8 (**C$_4$**), 160.3 (d, *J* = 245.9 Hz, **C$_{2'}$**), 170.1 (**C**(O)); HRMS (M+H^+)(ESI^+) 433.2139 [M + H^+] (calcd for $C_{23}H_{29}FN_2O_5H^+$ 433.2139); Anal. Calcd. for $C_{23}H_{29}FN_2O_5$: C, 63.87; H, 6.76; N, 6.48; F, 4.39. Found: C, 64.05; H, 6.76; N, 6.46; F, 4.21.



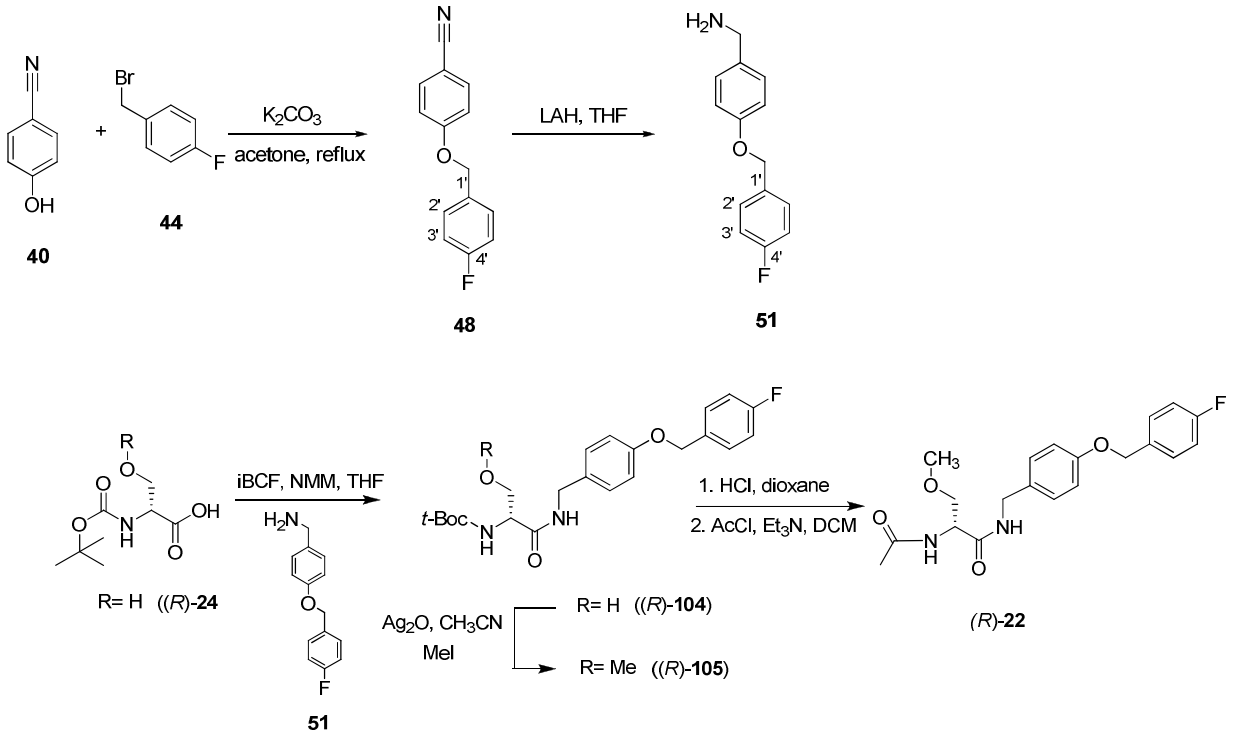
Preparation of (*R*)-*N*-4'-((2''-Fluoro)benzyloxy)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-21)

A saturated HCl solution in dioxane (1 mmol/2 mL, 11.57 mL) was added to (*R*)-*N*-4'-((2''-fluoro)benzyloxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-**103**) (2.50 g, 5.8 mmol) at 0 °C and the solution was stirred at room temperature (16 h). The reaction solution was concentrated in vacuo and dried (30 min): ^1H NMR (400 MHz, DMSO-d_6) δ 3.30 (s, OC**H$_3$**), 3.67 (d, *J* = 5.2 Hz, C**H$_2$**), 3.98–4.02 (br app t, C**H**), 4.28 (d, *J* = 5.6 Hz, C**H$_2$**N), 5.13 (s, OC**H$_2$**), 7.00 (d, *J* = 8.8 Hz, 2 Ar**H**), 7.19–7.27 (m, 4 Ar**H**), 7.39–7.45 (m, 1 Ar**H**), 7.54 (td, *J* = 1.6, 7.6 Hz, 1 Ar**H**), 8.18–8.24 (br s, N**H$_2$**), 8.56 (t , *J* = 5.8 Hz, N**H**); HRMS (M+H^+)(ESI^+) 333.1624 [M + H^+] (calcd for $C_{18}H_{21}FN_2O_3H^+$ 333.1614); Anal. Calcd. for $C_{18}H_{21}ClFN_2O_3$: C, 58.62; H, 6.01; Cl, 9.61; F, 5.15; N, 7.60. Found: C, 58.56; H, 5.98; Cl, 9.42; F, 5.06; N, 7.57.

The residue (1.70 g, 5.1 mmol) was dissolved in CH_2Cl_2 (20 mL) and Et_3N (2.10 mL, 15.3 mmol) and AcCl (550 μL, 7.6 mmol) were successively added at 0 °C. The mixture was stirred at room temperature (2 h), aqueous 10% citric acid (60 mL) was added and then the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). All of the organic layers were combined, washed with aqueous saturated $NaHCO_3$ (30 mL) and H_2O (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The solid was recrystallized with EtOAc to obtain (*R*)-*N*-4'-((2''-fluoro)benzyloxy)benzyl 2-acetamido-3-methoxypropionamide ((*R*)-**21**) (1.25 g, 65%) as a white solid: R_f = 0.28 (EtOAc); mp 173–174 °C; $[\alpha]^{24.6}_D$ -20.7° (*c* 1, $CHCl_3$); IR (nujol) 3276, 3230, 3167, 3094, 2750, 1635, 1550, 1457, 1375, 1298, 1236, 1147, 1236, 1147, 1113, 1011, 761, 724, 587 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.03 (s, C**H$_3$**CO), 3.37 (s, OC**H$_3$**), 3.42 (dd, *J* = 7.6, 9.0 Hz, C**H**H'), 3.79 (dd, *J* = 4.0, 9.0 Hz, CH**H'**), 4.34–4.44 (m, C**H$_2$**N), 4.49–4.54 (m, NC(**H**)CO), 5.12 (s, C**H$_2$**O), 6.43 (br d, *J* = 6.4 Hz, N**H**C(O)CH_3), 6.66-6.72 (br t, CH_2N**H**), 6.94 (d, *J* = 8.0 Hz, 2 Ar**H**), 7.06–7.21 (m, 4 Ar**H**), 7.28–7.34 (m, 1 Ar**H**), 7.49 (td, *J* = 1.6, 7.6 Hz, 1 Ar**H**), addition of excess (*R*)-(-)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-4'-((2''-fluoro)benzyloxy)benzyl 2-acetamido-3-methoxypropionamide ((*R*)-**21**) gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.2 (**C**H_3C(O)), 43.0 (N**C**H_2), 52.4 (OCH_2**C**H), 59.1 (O**C**H_3), 63.7 (d, *J* = 4.5 Hz, **C**H_2O), 71.6 (O**C**H_2CH), 115.0 (**C$_3$**), 115.3 (d, *J* = 21.2 Hz, **C$_{3'}$**), 114.8 (d, *J* = 14.1 Hz, **C$_{1'}$**), 124.2 (d, *J* = 3.3 Hz, **C$_{5'}$**), 128.8 (Ar**C**), 129.6 (d, *J* = 12.2 Hz, **C$_{4'}$** or **C$_{6'}$**), 129.7 (d, *J* = 8.4 Hz, **C$_{6'}$** or **C$_{4'}$**), 130.4 (Ar**C**), 158.0 (**C$_4$**), 160.4 (d, *J* = 245.7 Hz, **C$_{3'}$**), 169.8, 170.2 (2 **C**(O)); HRMS (M+H^+)(ESI$^+$) 375.1720 [M + H^+] (calcd for $C_{20}H_{23}FN_2O_4H^+$ 375.1720); Anal. Calcd. for $C_{20}H_{23}FN_2O_4$: C, 64.16; H, 6.19; F, 5.07; N, 7.48. Found: C, 63.95; H, 6.20; F, 5.14; N, 7.46.

17. Preparation of Preparation of (*R*)-*N*-4'-(4''-Fluoro)benzyloxy)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-22).

Reaction Overview

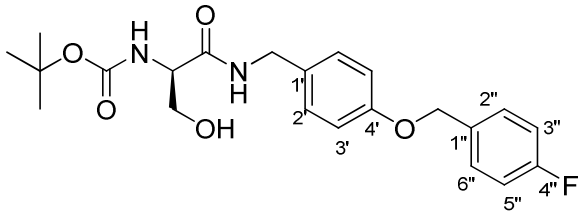


Preparation of 4-((4'-Fluoro)benzyloxy)benzonitrile (48).

A mixture of 4-cyanophenol (**40**) (11.91 g, 100.0 mmol), K_2CO_3 (55.20 g, 400.0 mmol), and 4-(fluoro)benzylbromide (**44**) (22.68 g, 120.0 mmol) were heated in acetone (400 mL) at reflux (5 h). The volatiles were evaporated and the residue was diluted in CH_2Cl_2 (300 mL), and then washed with H_2O (500 mL), dried ($MgSO_4$), and concentrated in vacuo. The solid was recrystallized with MeOH to give white needles (18.50 g, 81%): R_f = 0.89 (hexanes/EtOAc 9/1); mp 82-83 °C; ^{1}H NMR ($CDCl_3$) δ 5.07 (s, C**H**$_2$O), 7.01 (d, J = 9.0 Hz, 2 Ar**H**), 7.09 (t, J = 8.7 Hz, 2 Ar**H**), 7.37–7.42 (m, 2 Ar**H**), 7.59 (d, J = 9.0 Hz, 2 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 69.5 (**C**H$_2$O), 104.2 (**C**CN), 115.5 (Ar**C**), 115.6 (d, J = 22.5 Hz, **C$_{3'}$**), 119.0 (**C**N), 129.4 (d, J = 7.9 Hz, **C$_{2'}$**), 131.4 (**C$_{1'}$**), 133.9 (Ar**C**), 161.7 (Ar**C**), 162.6 (d, J = 245.6 Hz, **C$_{4'}$**); HRMS (M+H$^+$)(ESI$^+$) 228.0825 [M+H$^+$] (calcd for $C_{14}H_{10}FNOH^+$ 228.0824); Anal. Calcd. for $C_{14}H_{10}FNO_2$: C, 74.00; H, 4.44; F, 8.36; N, 6.16. Found: C, 74.06; H, 4.28; F, 8.26; N, 6.16.

Preparation of 4-((4'-Fluoro)benzyloxy)benzylamine (51).

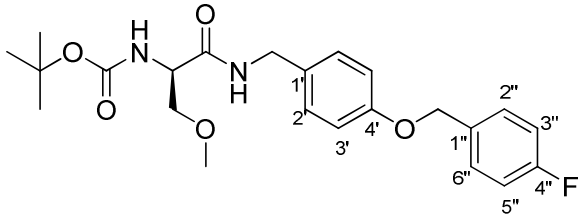
To a $LiAlH_4$ (6.50 g, 171.9 mmol) suspension in THF (500 mL) was added dropwise a THF (40 mL) solution of 4-((4'-fluoro)benzyloxy)benzonitrile (**48**) (13.00 g, 57.3 mmol) at 0 °C. The mixture was stirred at room temperature (16 h) and H_2O (5.4 mL) was added dropwise at 0 °C followed by an aqueous NaOH solution (2.7 mL, 15% w/w), and then H_2O (5.4 mL). The mixture was stirred at room temperature (2 h), and the precipitate filtered and washed with CH_2Cl_2. The filtrate was concentrated in vacuo to obtain a white solid (12.00 g, 92%): R_f = 0.00 (hexanes/EtOAc 9/1); ^{1}H NMR ($CDCl_3$) δ 1.43–1.79 (br s, N**H**$_2$), 3.81 (s, C**H**$_2$NH$_2$), 5.02 (s, C**H**$_2$O), 6.93 (d, *J* = 9.0 Hz, 2 Ar**H**), 7.07 (t, *J* = 8.2 Hz, 2 Ar**H**), 7.23 (d, *J* = 9.0 Hz, 2 Ar**H**), 7.38–7.43 (m, 2 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 45.7 (**C**H$_2$N), 69.2 (**C**H$_2$O), 114.7 (Ar**C**), 115.3 (d, *J* = 21.4 Hz, **C$_{3'}$**), 128.6 (Ar**C**), 129.1 (d, *J* = 8.2 Hz, **C$_{4'}$**), 132.6–132.7 (br d, **C$_{1'}$**), 135.8 (Ar**C**), 157.3 (Ar**C**), 162.3 (d, *J* = 244.7 Hz, **C$_{2'}$**).



Preparation of (*R*)-*N*-4'-((4'-Fluoro)benzyloxy)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-104).

A THF solution (100 mL) of (*R*)-*t*-Boc-serine ((*R*)-**24**) (5.00 g, 24.4 mmol) was stirred and cooled at -78 °C under Ar and then 4-methylmorpholine (NMM) (3.2 mL, 29.3 mmol) was added dropwise. After 2 min of stirring at this temperature, isobutylchloroformate (IBCF) (3.8 mL, 29.3 mmol) was added dropwise leading to the precipitation of a white solid, and the reaction was allowed to proceed for additional 2 min, and then 4-((4'-fluoro)benzyloxy)benzylamine (**51**) (6.70 g, 29.3 mmol) was added portionwise at -78 °C. The mixture was allowed to stir at room temperature (2 h), and the white solid filtered, and the organic layer concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (50/50 to 70/30) as the eluant to obtain (*R*)-*N*-4'-((4''-fluoro)benzyloxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-**104**) as a white solid (7.10 g, 69%): R_f = 0.33 (hexanes/EtOAc 4/6); mp 93-95 °C;

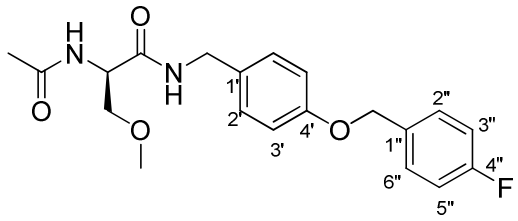
$[\alpha]^{25.6}_{D}$ +14.3° (*c* 1, $CHCl_3$); IR (nujol) 3160, 2942, 2838, 1685, 1637, 1513, 1454, 1373, 1304, 1237, 1164, 1012, 860, 818, 724, 600, 509 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, $(CH_3)_3$), 3.30–3.69 (br m, CHH', OH), 4.06 (d, *J* = 7.5 Hz, CHH'), 4.12–4.20 (br m, CH), 4.33–4.39 (br m, CH_2N), 4.98 (s, CH_2O), 5.61–5.69 (br t, NH), 6.88 (d, *J* = 6.2 Hz, 2 ArH), 7.03–7.09 (br m, 2 ArH, NH), 7.16 (d, *J* = 6.2 Hz, 2 ArH), 7.38 (t, *J* = 5.1 Hz, 2 ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3 ($(CH_3)_3$), 42.9 (NCH_2), 55.0 (OCH_2CH), 62.8 (OCH_2CH), 69.4 (CH_2O), 80.6 ($C(CH_3)_3$), 115.0 (C_3), 115.5 (d, *J* = 21.2 Hz, $C_{3'}$), 128.9 (ArC), 129.2 (d, *J* = 7.7 Hz, $C_{2'}$), 130.3 (ArC), 132.7 (d, *J* = 3.2 Hz, $C_{1'}$), 156.3 (NC(O)O), 158.0 (C_4), 162.5 (d, *J* = 245.0 Hz, $C_{4'}$), 171.3 (C(O)); HRMS (M+H^+)(ESI$^+$) 419.1982 [M + H^+] (calcd for $C_{22}H_{27}FN_2O_5H^+$ 419.1982); Anal. Calcd. for $C_{22}H_{27}FN_2O_5$: C, 63.14; H, 6.50; F, 4.54; N, 6.69. Found: C, 62.84; H, 6.49; F, 4.29; N, 6.67.



Preparation of (*R*)-*N*-4'-((4''-Fluoro)benzyloxy)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-105).

Ag_2O (18.80 g, 81.2 mmol) was added to a CH_3CN solution (400 mL) of (*R*)-*N*-4'-((4''-fluoro)benzyloxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-**104**) (6.80 g, 16.3 mmol) and CH_3I (10.12 mL, 162.5 mmol) at room temperature under Ar. The reaction mixture was stirred at room temperature (3 d), filtered, and the filtrate concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (3/7) as the eluant to obtain (*R*)-*N*-4'-((4''-fluoro)benzyloxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-**105**) as a white solid (6.00 g, 85%): R_f = 0.59 (3/7 EtOAc/hexanes); mp 84-87 °C; $[\alpha]^{25.3}_{D}$ -18.3° (*c* 1, $CHCl_3$); IR (nujol) 3305, 2880, 1649, 1527, 1458, 1375, 1319, 1241, 1166, 1094, 1050, 913, 864, 920, 677, 506 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, $(CH_3)_3$), 3.36 (s, OCH_3), 3.48 (dd, *J* = 5.6, 9.0 Hz, CHH'), 3.83 (dd, *J* = 4.0, 9.0 Hz, CHH'), 4.20–4.28 (br m, CH), 4.38–4.46 (br m, CH_2N), 5.01 (s, OCH_2), 5.33–5.42 (br m, OC(O)NH),

6.62–6.69 (br t, $CH_2N\mathbf{H}$), 6.90 (d, J = 8.4 Hz, 2 Ar**H**), 7.06 (t, J = 8.8 Hz, 2 Ar**H**), 7.19 (d, J = 8.4 Hz, 2 Ar**H**), 7.37-7.41 (m, 2 Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3 (($\mathbf{C}H_3)_3$), 42.9 ($N\mathbf{C}H_2$), 54.0 ($OCH_2\mathbf{C}H$), 59.1 ($O\mathbf{C}H_3$), 69.4 ($\mathbf{C}H_2O$), 72.1 ($O\mathbf{C}H_2CH$), 80.3 ($\mathbf{C}(CH_3)_3$), 115.0 (Ar**C**), 115.5 (d, J = 21.8 Hz, $\mathbf{C_{3'}}$), 128.9 (Ar**C**), 129.3 (d, J = 8.3 Hz, $\mathbf{C_{2'}}$), 130.6 (Ar**C**), 132.7 (d, J = 3.2 Hz, $\mathbf{C_{1'}}$), 155.5 ($N\mathbf{C}(O)O$), 158.0 ($\mathbf{C_4}$), 162.5 (d, J = 245.0 Hz, $\mathbf{C_{4'}}$), 170.2 (**C**(O)); HRMS ($M+H^+$)(ESI^+) 433.2139 [M + H^+] (calcd for $C_{23}H_{29}FN_2O_5H^+$ 433.2139); Anal. Calcd. for $C_{23}H_{29}FN_2O_5$: C, 63.87; H, 6.76; F, 4.39; N, 6.48. Found: C, 63.92; H, 6.86; F, 4.40; N, 6.53.



Preparation of (*R*)-*N*-4'-((4''-Fluoro)benzyloxy)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-22)

A saturated HCl solution in dioxane (1 mmol/2 mL, 11.57 mL) was added to (*R*)-*N*-4'-((4'-fluoro)benzyloxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-**105**) (2.50 g, 5.8 mmol) at 0 °C and the solution was stirred at room temperature (16 h). The reaction solution was concentrated in vacuo and dried (30 min): HRMS ($M+H^+$)(ESI^+) 333.1624 [M + H^+] (calcd for $C_{18}H_{21}FN_2O_3H^+$ 333.1614); Anal. Calcd. for $C_{18}H_{21}ClFN_2O_3 \bullet 0.25H_2O$: C, 57.91; H, 6.07; Cl, 9.50; F, 5.09; N, 7.50. Found: C, 57.59; H, 5.86; Cl, 9.47; F, 4.85; N, 7.50.

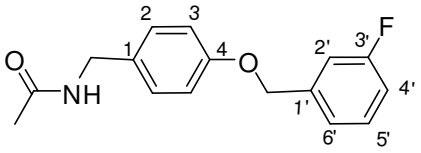
The residue (1.85 g, 5.6 mmol) was dissolved in CH_2Cl_2 (30 mL) and Et_3N (2.36 mL, 16.8 mmol) and AcCl (608 μL, 8.4 mmol) were successively added at 0 °C. The mixture was stirred at room temperature (2 h), aqueous 10% citric acid (60 mL) was added, and then the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). All of the organic layers were combined, washed with aqueous saturated $NaHCO_3$ (30 mL) and H_2O (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The solid was recrystallized with EtOAc to obtain (*R*)-*N*-4'-((4''-fluoro)benzyloxy)benzyl 2-acetamido-3-methoxypropionamide ((*R*)-**22**) (1.28 g, 61%) as a white solid: R_f = 0.22 (EtOAc); mp 166–167 °C; $[\alpha]^{25.2}_D$ -19.4° (*c* 1,

$CHCl_3$); IR (nujol) 3287, 3205, 3103, 2924, 2858, 1763, 1636, 1555, 1515, 1457, 1376, 1304, 1238, 1136, 1048, 827, 728, 608, 515 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.03 (s, C**H**$_3$CO), 3.37 (s, OC**H**$_3$), 3.42 (dd, J = 7.6, 9.4 Hz, C**H**H'), 3.79 (dd, J = 4.0, 9.4 Hz, CH**H'**), 4.40 (d, J = 5.2 Hz, C**H**$_2$N), 4.49–4.54 (m, NC(**H**)CO), 5.01 (s, C**H**$_2$O), 6.40 (br d, J = 5.6 Hz, N**H**C(O)CH_3), 6.62–6.69 (br t, CH_2N**H**), 6.92 (d, J = 8.8 Hz, 2 Ar**H**), 7.07 (t, J = 8.8 Hz, 2 Ar**H**), 7.18 (d, J = 8.0 Hz, 2 Ar**H**), 7.37–7.41 (m, 2 Ar**H**), addition of excess (*R*)-(-)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-4'-((4''-fluoro)benzyloxy)benzyl 2-acetamido-3-methoxypropionamide ((*R*)-**22**) gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1 (**C**H_3C(O)), 43.0 (N**C**H_2), 52.4 (OCH_2**C**H), 59.1 (O**C**H_3), 69.4 (**C**H_2O), 71.7 (O**C**H_2CH), 115.0 (**C**$_3$), 115.4 (d, J = 21.3 Hz, **C**$_{3'}$), 128.8 (Ar**C**), 129.3 (d, J = 7.7 Hz, **C**$_{2'}$), 130.4 (Ar**C**), 132.6 (d, J = 3.3 Hz, **C**$_{1'}$), 158.0 (**C**$_4$), 162.5 (d, J = 245.1 Hz, **C**$_{4'}$), 169.8, 170.3 (2 **C**(O)); HRMS (M+H^+)(ESI^+) 375.1720 [M + H^+] (calcd for $C_{20}H_{23}FN_2O_4H^+$ 375.1720); Anal. Calcd. for $C_{20}H_{23}FN_2O_4$: C, 64.16; H, 6.19; F, 5.07; N, 7.48. Found: C, 64.02; H, 6.16; F, 4.99; N, 7.45.

18. Preparation of *N*-4-((3'-Fluoro)benzyloxy)benzyl Acetamide (23)

Reaction Overview

32 **23**



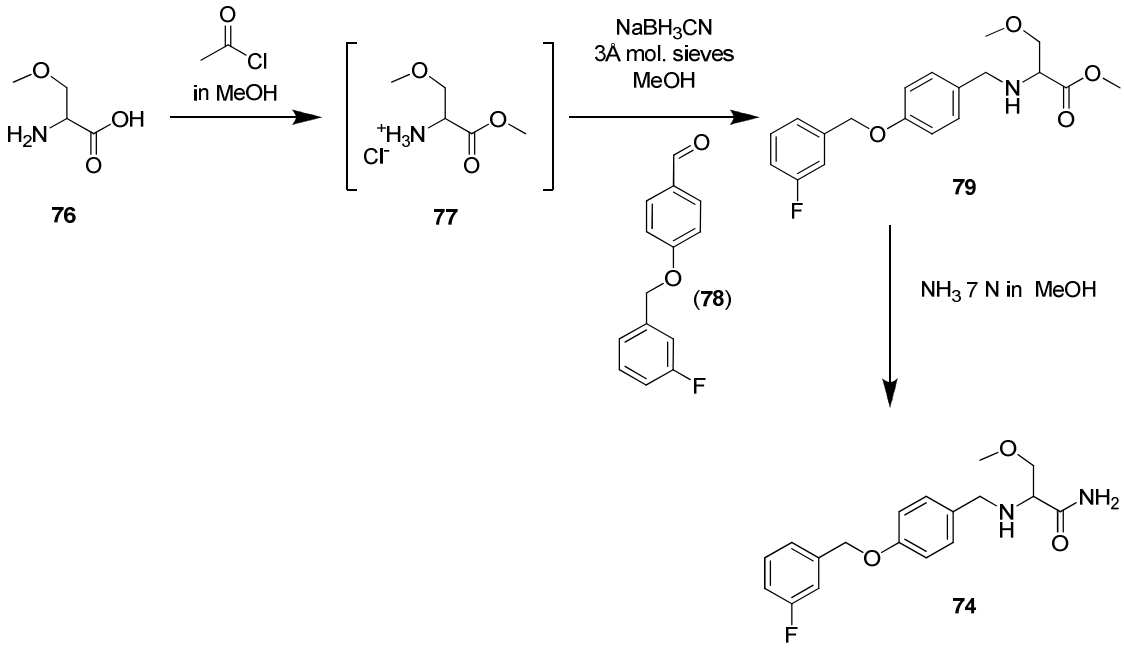
Preparation of *N*-4-((3'-Fluoro)benzyloxy)benzyl Acetamide (23)

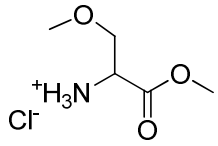
4-((3'-Fluoro)benzyloxy)benzylamine (**32**) (1.00 g, 4.3 mmol) was dissolved in CH_2Cl_2 (40 mL) and Et_3N (728 μL, 5.2 mmol) and AcCl (376 μL, 5.2 mmol) were

successively added at 0 °C. The mixture was stirred at room temperature (16 h), aqueous 10% citric acid (60 mL) was added and then the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). All of the organic layers were combined, washed with aqueous saturated $NaHCO_3$ (30 mL) and H_2O (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The solid was triturated with Et_2O to obtain *N*-4-((3'-fluoro)benzyloxy)benzyl) acetamide (**23**) (810 mg, 69%) as a white solid: R_f = 0.39 (EtOAc); mp 131–132 °C; IR (nujol) 3087, 2958, 2856, 1629, 1554, 1456, 1372, 1298, 1255, 1147, 1108, 1017, 932, 880, 781, 687, 630 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.84 (s, C**H**$_3$CO), 4.16 (d, J = 5.6 Hz, C**H**$_2$N), 5.11 (s, C**H**$_2$O), 6.95 (d, J = 8.8 Hz, 2 **C**$_3$), 7.11–7.18 (m, 3 Ar**H**), 7.24–7.29 (m, 2 Ar**H**), 7.40–7.45 (m, 1 Ar**H**), 8.21–8.24 (br t, N**H**); ^{13}C NMR ($CDCl_3$) δ 23.2 (**C**H_3C(O)), 43.2 (N**C**H_2), 69.2 (d, J = 1.7 Hz, **C**H_2O), 114.1 (d, J = 22.2 Hz, **C**$_{4'}$ or **C**$_{2'}$), 114.8 (d, J = 21.1 Hz, **C**$_{2'}$ or **C**$_{4'}$), 115.0 (**C**$_1$), 122.6 (d, J = 2.9 Hz, **C**$_{6'}$), 129.2 (**C**$_2$), 130.1 (d, J = 8.5 Hz, **C**$_{5'}$), 130.9 (**C**$_4$), 139.6 (d, J = 6.7 Hz, **C**$_{1'}$), 157.9 (**C**$_4$), 163.0 (d, J = 244.8 Hz, **C**$_{3'}$), 169.8 (**C**(O)); HRMS (M+Na^+)(ESI^+) 296.1063 [M + Na^+] (calcd for $C_{16}H_{16}FNO_2Na^+$ 296.1062); Anal. Calcd. for $C_{16}H_{16}FNO_2$: C, 70.31; H, 5.90; F, 6.95; N, 5.12. Found: C, 70.10; H, 5.84; F, 6.92; N, 5.17.

19. Preparation of Preparation of 2-(4'-((3''-Fluoro)benzyloxy)benzyl)amino-3-methoxypropionamide (74).

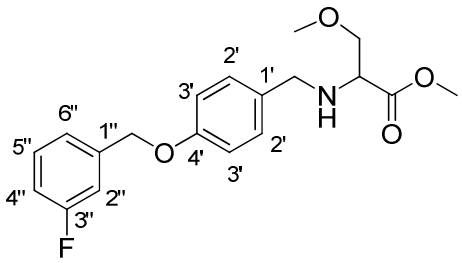
Reaction Overview





Preparation of Methyl 2-Amino-3-methoxypropionoate Hydrochloride (77).

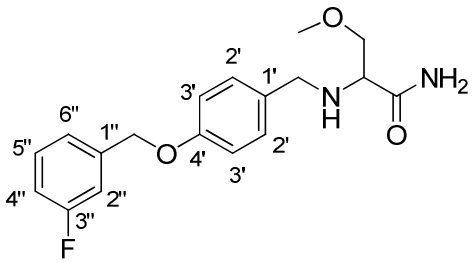
To precooled (0 ºC) MeOH (50 mL), acetyl chloride (4.5 mL, 63.0 mmol, 1.5 equiv) was added at 0 ºC. The resulting solution was stirred at room temperature (10 min). Then, DL-*O*-methylserine (**76**) (5.00 g, 42.0 mmol, 1 equiv) was added. The resulting solution was stirred at 50 ºC (16 h). The solution was then concentrated in vacuo to obtain methyl 2-amino-3-methoxypropionoate hydrochloride (**77**) as a pale yellow solid (7.30 g, qtive): R_f = 0.00 (EtOAc); mp 87–100 ºC; IR (nujol mull) 3228, 2921, 2851, 2726, 1945, 1743, 1592, 1519, 1457, 1375, 1323, 1239, 1098, 1009, 967, 905, 842, 787, 724, 637, 568, 473 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.29 (s, OC**H**$_3$), 3.75–3.83 (m, C(O)OC**H**$_3$, C**H**$_2$), 4.28–4.32 (br s, C**H**), 8.44–8.82 (br s, N**H**$_3^+$); ^{13}C NMR (DMSO-d_6) δ 51.7 (**C**H), 52.4 (O**C**H$_3$), 58.2 (O**C**H$_3$), 68.9 (**C**H$_2$), 167.6 (**C**(O)); M_r (+ESI) 134.08 $[M+H]^+$ (calcd for $C_5H_{11}NO_3H^+$ 134.08 $[M+H]^+$).



Preparation of Methyl 2-(4'-((3''-Fluoro)benzyloxy)benzyl)amino-3-methoxypropionoate (79).

To a suspension of methyl 2-amino-3-methoxypropionoate hydrochloride (**77**) (3.00 g, 17.69 mmol, 1.1 equiv) and powdered 3Å molecular sieves (4.0 g) in dry MeOH (100 mL) kept under Ar, $NaBH_3CN$ (810 mg, 1.07 mmol, 0.8 equiv) was added and the mixture was stirred at room temperature (15 min). Then, 4-(3-fluorobenzyloxy)benzaldehyde (**78**) (3.70 g, 16.08 mmol, 1 equiv) was added in a single portion (**CAUTION:** hydrogen cyanide is produced). The reaction mixture was stirred at room temperature (16 h). After filtration, the solvent was evaporated, CH_2Cl_2 (100 mL) was added, and the organic layer was successively washed with an aqueous saturated $NaHCO_3$ solution (2 x 50 mL), and brine (2 x 50 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash liquid chromatography on silica gel with EtOAc/hexanes (3/7 to 10/0) as the eluent to obtain methyl 2-(4'-((3''-fluoro)benzyloxy)benzyl)amino-3-methoxypropionoate (**79** as a yellow oil (2.45 g, 44%): R_f = 0.26 (EtOAc); IR (nujol mull) 3138, 3069, 3005, 2924, 2888, 2823, 2732, 1739, 1598, 1510, 1456, 1379, 1241, 1115, 1038, 970, 923, 785, 685, 632, 572, 518 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.32 (s, OC**H$_3$**), 3.46 (app t, J = 4.8 Hz, C**H**), 3.57 (dd, J = 4.8, 9.3 Hz, C**H**H'O), 3.63 (dd, J = 4.8, 9.3 Hz, CH**H'**O), 3.64 (½ AB_q, J = 13.0 Hz, C**H**H'N), 3.74 (s, C(O)OC**H$_3$**), 3.82 (½ AB_q, J = 13.0 Hz, CH**H'**N), 5.04 (s, C**H$_2$**Ar), 6.90 (d, J = 8.8 Hz, 2 **H$_{3'}$**), 6.99 (dt, J = 2.7, 8.5 Hz, 1 Ar**H**), 7.13–7.19 (m, 2 Ar**H**), 7.25 (d, J = 8.8 Hz, 2 **H$_{2'}$**), 7.30–7.35 (m, 1 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 51.4 (**C**H_2N), 51.9 (O**C**H_3), 59.2 (**C**H), 60.3 (O**C**H_3), 69.2 (d, J = 1.9 Hz, **C**H_2O), 73.6 (**C**H_2OCH_3), 114.1 (d, J = 21.8 Hz, **C$_{2''}$** or **C$_{4''}$**), 114.7 (d, J = 20.5 Hz, **C$_{4''}$** or **C$_{2''}$**), 114.7 (**C$_{3'}$**), 122.6 (d, J = 3.2 Hz, **C$_{6''}$**), 129.6 (**C$_{2'}$**), 130.1 (d, J = 7.7 Hz, **C$_{5''}$**), 132.3 (**C$_{1'}$**), 139.7 (d, J = 7.7 Hz, **C$_{1''}$**), 157.6 (**C$_{4'}$**), 163.0 (d, J = 244.4 Hz, **C$_{3''}$**), 173.6 (**C**(O)); M_r (+ESI) 348.19 $[M+H]^+$ (calcd for $C_{19}H_{22}FNO_4H^+$ 348.16 $[M+H]^+$). Anal.

Calcd for $C_{19}H_{22}FNO_4$: C, 65.69; H, 6.38; F, 5.47; N, 4.03. Found: C, 65.44; H, 6.32; F, 5.37; N, 4.01.

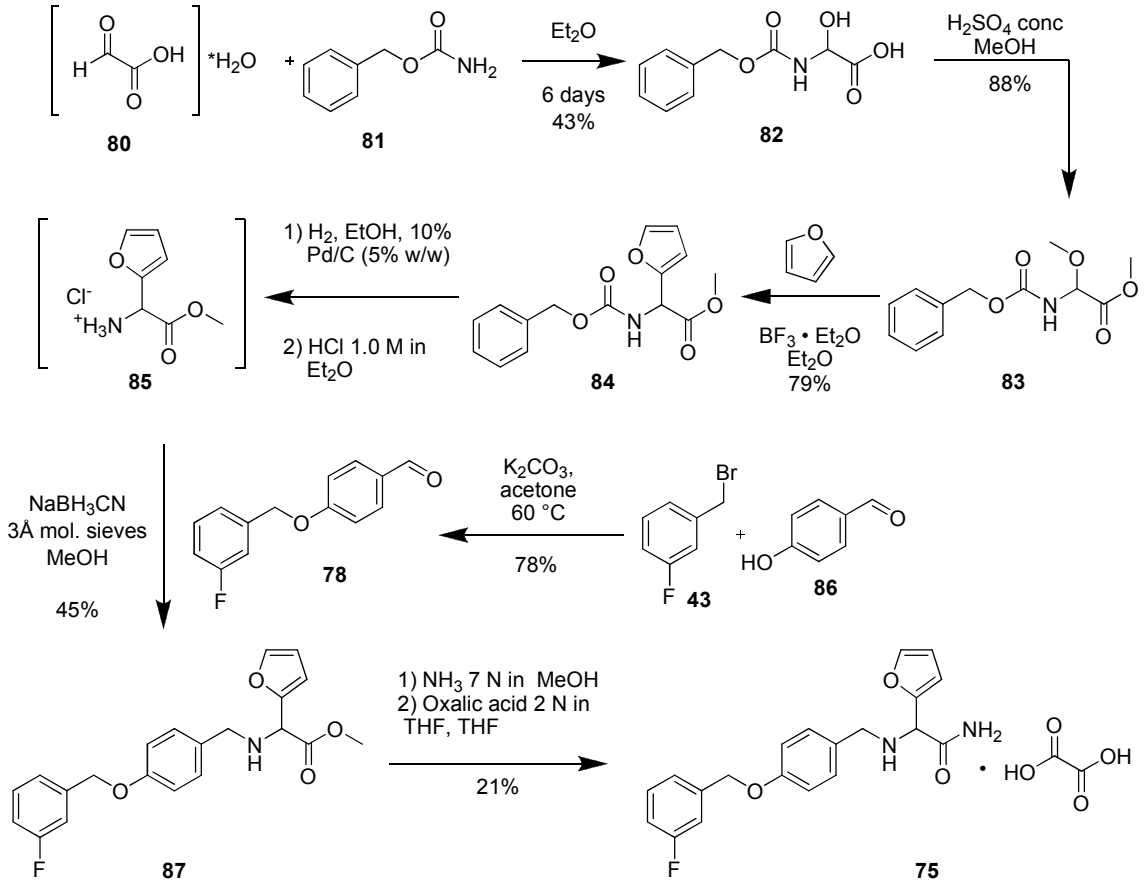


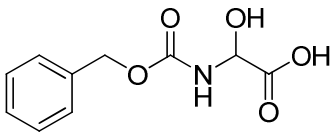
Preparation of 2-(4'-((3''-Fluoro)benzyloxy)benzyl)amino-3-methoxypropionamide (74).

A solution of methyl 2-(4'-((3''-fluoro)benzyloxy)benzyl)amino-3-methoxypropionoate (**79**) (1.5 g, 4.32 mmol) in NH_3 (7 N in MeOH, 150 mL) was stirred at room temperature in a sealed tube (7 d). The solution was concentrated in vacuo, and the residue was recrystallized with EtOAc to obtain 2-(4'-((3''-fluoro)benzyloxy)benzyl)amino-3-methoxypropionamide (**74**) as a white solid (350 mg, 24%): R_f = 0.25 (EtOAc); mp 84–85 ºC; IR (nujol mull) 3421, 3295, 3224, 3167, 3087, 2911, 2860, 2742, 1679, 1617, 1519, 1457, 1375, 1311, 1252, 1135, 1051, 953, 853, 790, 682, 647, 525, 454 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.31–3.36 (m, OC**H**$_3$, C**H**), 3.60 (d, J = 5.7 Hz, C**H**$_2$N), 3.71 (½ AB_q, J = 12.9 Hz, C**H**H'O), 3.78 (½ AB_q, J = 12.9 Hz, CH**H'**O), 5.06 (s, C**H**$_2$O), 5.40–5.44 (br s, N**H**), 7.10 (d, J = 9.0 Hz, 2 **H**$_{3'}$), 6.96–7.05 (br dt, 1 Ar**H**), 7.13–7.25 (m, 4 Ar**H**), 7.31–7.38 (m, 1 Ar**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.0 (**C**H$_2$N), 58.8 (**C**H), 61.5 (O**C**H$_3$), 69.2 (**C**H$_2$O), 72.2 (**C**H$_2$O), 114.2 (d, J = 22.2 Hz, **C**$_{2''}$ or **C**$_{4''}$), 114.8 (d, J = 18.2 Hz, **C**$_{4''}$ or **C**$_{2''}$), 114.9 (**C**$_{3'}$), 122.7 (d, J = 2.9 Hz, **C**$_{6''}$), 129.3 (**C**$_{2'}$), 130.1 (d, J = 8.0 Hz, **C**$_{5''}$), 132.1 (**C**$_{1'}$), 139.6 (d, J = 7.4 Hz, **C**$_{1''}$), 157.7 (**C**$_{4'}$), 163.0 (d, J = 244.9 Hz, **C**$_{3''}$), 174.8 (**C**(O)); M_r (+ESI) 355.16 $[M+Na]^+$ (calcd for $C_{18}H_{21}FN_2O_3Na^+$ $[M+355.14]^+$). Anal. Calcd for $C_{18}H_{21}FN_2O_3$: C, 65.05; H, 6.37; F, 5.72; N, 8.43. Found: C, 65.32; H, 6.32; F, 5.56; N, 8.42.

20. Preparation of 2-(4'-((3''-Fluoro)benzyloxy)benzyl)amino-2-(furan-2-yl)acetamide Oxalate (75).

Reaction Overview



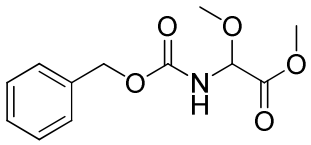


Preparation of 2-(Benzyloxycarbonyl)amino-2-hydroxyacetic Acid (82).[8]

Glyoxylic acid (**80**) (5.00 g, 54.3 mmol, 1.1 equiv) was dissolved in Et_2O (55mL) followed by addition of benzyl carbamate (**81**) (7.46 g, 49.4 mmol, 1 equiv). The solution was stirred at room temperature (6 d), filtered to obtain 2-(benzyloxycarbonyl)amino-2-hydroxyacetic acid (**82**) as a white solid (4.73 g, 43%):

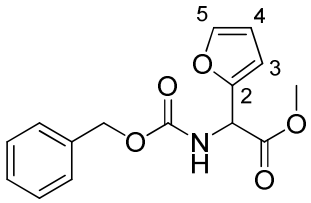
[8] Yoo, B.; Page, M. D. *Tetrahedron Lett.*, **2006**, *47*, 7327-7330.

R_f = 0.72 (EtOAc/MeOH, 9/1); mp 120-121 ºC; ^{1}H NMR (DMSO-d_6) δ 5.05 (s, C**H**$_2$), 5.22 (d, J = 9.0 Hz, C**H**NH), 7.31–7.37 (m, 5 Ar**H**), 8.15 (d, J = 9.0 Hz, CHN**H**).



Preparation of Methyl 2-(Benzyloxycarbonyl)amino-2-methoxyacetate (83).[9]

2-(Benzyloxycarbonyl)amino-2-hydroxyacetic acid (**82**) (4.73 g, 21.0 mmol, 1 equiv) was dissolved in MeOH (50 mL) and cooled at 0 ºC. Then, concentrated sulfuric acid was added (0.7 mL, 12.6 mmol, 0.6 equiv) and the reaction mixture was warmed to room temperature and stirred (4 d). The reaction was poured into a cold aqueous saturated $NaHCO_3$ solution (40 mL) and stirred (10 min). The aqueous layer was extracted with EtOAc (3 x 40 mL). The combined organic layers were dried, concentrated in vacuo to obtain methyl 2-(benzyloxycarbonyl)amino-2-methoxyacetate (**83**) as a beige solid (4.68 g, 88%): R_f = 0.90 (EtOAc); mp 74–75 ºC; ^{1}H NMR ($CDCl_3$) δ 3.47 (s, C(O)OC**H**$_3$), 3.81 (s, OC**H**$_3$), 5.16 (s, C**H**$_2$), 5.36 (d, J = 9.3 Hz, C**H**NH), 5.78–5.92 (br d, CHN**H**), 7.33–7.38 (m, 5 Ar**H**).

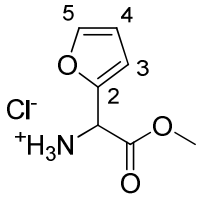


Preparation of Methyl 2-(Benzyloxycarbonyl)amino-2-(furan-2-yl)acetate (84).[10]

To an Et_2O solution (40 mL) of methyl 2-(benzyloxycarbonylamino)-2-methoxyacetate (**83**) (4.00 g, 15.8 mmol, 1 equiv), BF_3•Et_2O (3.2 mL, 25.3 mmol, 1.6 equiv) was added followed by the addition of furan (4.6 mL, 63.2 mmol, 4 equiv). The solution was stirred at room temperature (24 h). The solution was poured into a cold aqueous

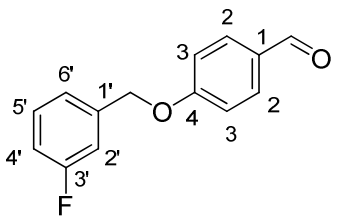
[9] Williams, R. M.; Aldous, D. J.; Aldous, S. C.; *J. Org. Chem.* **1990**, *55*, 4657-4663
[10] Ben-Ishai, D.; Sataty, I.; Bernstein, Z.; *Tetrahedron* **1976**, *32*,1571

saturated $NaHCO_3$ solution (60 mL), stirred (10 min), and then extracted with EtOAc (3 x 80 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by liquid chromatography on silica gel with EtOAc/MeOH (10/0 to 9/1) as the eluent to obtain methyl 2-(benzyloxycarbonyl)amino-2-(furan-2-yl)acetate (**84**) as a pale yellow solid (3.61 g, 79%): R_f = 0.82 (EtOAc); mp 74–76 ºC (lit[5] mp 78–79 ºC); ^{1}H NMR ($CDCl_3$) δ 3.77 (s, OC**H**$_3$), 5.12 (s, C**H**$_2$), 5.54 (d, J = 8.3 Hz, C**H**NH), 5.78 (d, J = 8.3 Hz, C**H**NH), 6.34–6.39 (m, **H**$_3$, **H**$_4$), 7.31–7.37 (m, 5 Ar**H**, **H**$_5$).



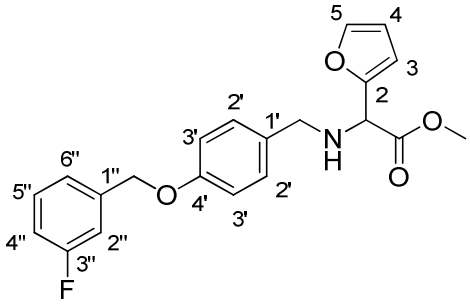
Preparation of Methyl 2-Amino-2-(furan-2-yl)acetate Hydrochloride (85).

An EtOH solution (70 mL) of methyl 2-(benzyloxycarbony)lamino-2-(furan-2-yl)acetate (**84**) (2.66 g, 9.20 mmol, 1 equiv) was treated with H_2 (1 atm) in presence of 10% Pd/C (133 mg) at room temperature (1 h). The mixture was carefully filtered through a bed of Celite® and the filtrate was evaporated in vacuo. The residue was dissolved in Et_2O (10 mL) and 1.0 M HCl in Et_2O (9.2 mL, 9.20 mmol, 1 equiv) was added dropwise. The solution was stirred at room temperature (10 min), and then filtered to give 1.15 g of a beige solid. The residue was used for the next step without further purification: R_f = 0.52 (EtOAc) (value for the free amine); ^{1}H NMR (DMSO-d_6) δ 3.76 (s, OC**H**$_3$), 5.53 (s, C**H**), 6.55 (dd, J = 1.8, 3.1 Hz, **H**$_4$), 6.70 (d, J = 3.1 Hz, **H**$_3$), 7.80 (d, J = 1.8 Hz, **H**$_5$), 8.85–9.15 (br s, N**H**$_3^+$).



Preparation of 4-((3'-Fluoro)benzyloxy)benzaldehyde (78).[11]

A mixture of 4-hydroxybenzaldehyde (**86**), 3-fluorobenzylbromide (**43**) and K_2CO_3 in acetone (25 mL) was stirred at reflux (60 ºC, 2 h). The mixture was concentrated in vacuo, and then H_2O (50 mL) and CH_2Cl_2 (50 mL) were added, and the mixture was extracted with CH_2Cl_2 (3 X 50 mL)). The combined organic layers were dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash liquid chromatography on silica gel with EtOAc/hexanes (1/9) as the eluent to obtain 4-((3'-fluoro)benzyloxy)benzaldehyde (**78**) as a yellow solid (14.55 g, 78%): R_f = 0.38 (EtOAc/hexanes, 1/9); mp 40–41 ºC (lit.[6] mp 43–45 ºC); ^{1}H NMR ($CDCl_3$) δ 5.15 (s, C**H**$_2$), 7.02–7.12 (m, 3 Ar**H**), 7.14–7.26 (m, 2 Ar**H**), 7.34–7.41 (m, 1 Ar**H**), 7.85 (d, J = 8.7 Hz, 2 **H**$_{2'}$), 9.90 (s, C**H**O); ^{13}C NMR ($CDCl_3$) δ 69.3 (d, J = 1.7 Hz, **C**H$_2$O), 114.2 (d, J = 22.2 Hz, **C**$_{2''}$ or **C**$_{4''}$), 115.1 (**C**$_{3'}$), 115.2 (d, J = 21.1 Hz, **C**$_{4''}$ or **C**$_{2''}$), 122.7 (d, J = 2.9 Hz, **C**$_{6''}$), 130.3 (**C**$_{2'}$), 130.3 (d, J = 8.0 Hz, **C**$_{5''}$), 132.0 (**C**$_{1'}$), 138.5 (d, J = 7.4 Hz, **C**$_{1''}$), 163.0 (d, J = 245.3 Hz, **C**$_{3''}$), 163.3 (**C**$_{4'}$), 190.7 (**C**HO).

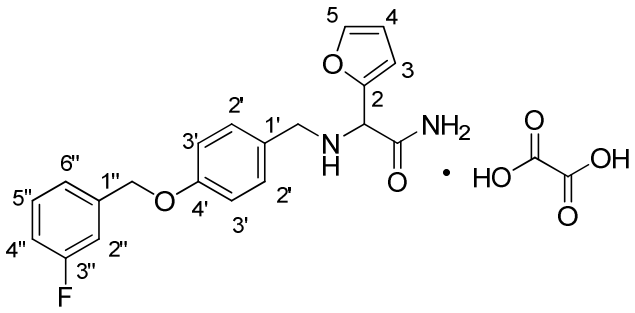


Preparation of Methyl 2-(4'-((3''-Fluoro)benzyloxy)benzyl)amino-2-(furan-2-yl)acetate (87).

To a suspension of methyl 2-amino-2-(furan-2-yl)acetate hydrochloride (**85**) (6.00 mmol, 1.1 equiv) and powdered 3Å molecular sieves (1.38 g) in dry MeOH (35 mL) kept under Ar, $NaBH_3CN$ (274 mg, 4.36 mmol, 0.8 equiv) was added and the mixture was stirred at room temperature (15 min). Then, 4-((3'-fluoro)benzyloxy)benzaldehyde (**78**) (1.26 g, 5.46 mmol, 1 equiv) was added in a

[11] Sundriyal, S.; Viswanad, B.; Bharathy, E.; Ramarao, P.; Chakraborti, A. K.; Bharatam, P. V. Bioorg. *Med. Chem. Lett*., **2008**, *18*, 3192-3195.

single portion (**CAUTION:** hydrogen cyanide is produced). The reaction mixture was stirred at room temperature (16 h). After filtration, the solvent was evaporated, CH_2Cl_2 (50 mL) was added and the organic layer was successively washed with an aqueous saturated $NaHCO_3$ solution (2 x 10 mL), and brine (2 x 10 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash liquid chromatography on silica gel with EtOAc/hexanes (0/10 to 2/8) as the eluent to obtain methyl 2-(4'-((3''-fluoro)benzyloxy)benzyl)amino-2-(furan-2-yl)acetate (**87**) as an orange oil (1.00 g, 45%): R_f = 0.96 (EtOAc); IR (nujol mull) 3136, 3071, 3009, 2924, 2854, 1743, 1599, 1509, 1453, 1378, 1301, 1238, 1171, 1014, 928, 825, 782, 747, 686, 601, 517 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.63–3.81 (m, C**H**$_2$N, OC**H**$_3$), 4.48 (s, C**H**), 5.05 (s, C**H**$_2$O), 6.30 (d, J = 3.1 Hz, **H**$_3$), 6.35 (dd, J = 1.8, 3.1 Hz, **H**$_4$), 6.91 (d, J = 8.4 Hz, 2 **H**$_{3'}$), 7.00 (dt, J = 2.6, 8.5 Hz, 1 Ar**H**), 7.14–7.26 (m, 4 Ar**H**), 7.31–7.35 (m, 1 Ar**H**), 7.39 (dd, J = 0.8, 1.8 Hz, **H**$_5$); ^{13}C NMR ($CDCl_3$) δ 50.5 (**C**H$_2$N), 52.5 (O**C**H$_3$), 58.1 (**C**H), 69.1 (d, J = 1.7 Hz, **C**H$_2$O), 108.2, 110.3 (**C**$_3$, **C**$_4$), 114.2 (d, J = 22.0 Hz, **C**$_{2''}$ or **C**$_{4''}$), 114.7 (d, J = 21.1 Hz, **C**$_{4''}$ or **C**$_{2''}$), 114.8 (**C**$_{3'}$), 122.6 (d, J = 2.9 Hz, **C**$_{6''}$), 129.6 (**C**$_{2'}$), 130.1 (d, J = 8.3 Hz, **C**$_{5''}$), 131.7 (**C**$_{1'}$), 139.7 (d, J = 7.1 Hz, **C**$_{1''}$), 142.6 (**C**$_5$), 150.7 (**C**$_2$), 157.7 (**C**$_{4'}$), 162.9 (d, J = 244.7, **C**$_{3''}$), 171.3 (**C**(O)); M_r (+ESI) 502.05 $[M+Cs]^+$ (calcd for $C_{21}H_{20}FNO_4Cs^+$ 502.04 $[M+Cs]^+$). Anal. Calcd for $C_{21}H_{20}FNO_4$: C, 68.28; H, 5.46; F, 5.14; N, 3.79. Found: C, 68.33; H, 5.33; F, 5.12; N, 3.87.



Preparation of 2-(4'-((3''-Fluoro)benzyloxy)benzyl)amino-2-(furan-2-yl)acetamide Oxalate (75).

A solution of 2-(4'-((3''-fluoro)benzyloxy)benzyl)amino-2-(furan-2-yl)acetate (**87**) (880 mg, 0.05 mmol) in NH_3 (7 N in MeOH, 88 mL) was stirred at 4 ºC (16 h). The solution was concentrated in vacuo, and the residue was dissolved in THF (2.3 mL) to obtain a 1 N solution. To this solution, oxalic acid (2 N in THF, 4.6 mL) was added. After

standing at room temperature (16 h) the precipitate was collected, dried, and recrystallized with *i*-PrOH. The white solid was recrystallized with absolute EtOH to obtain 2-(4'-((3''-fluoro)benzyloxy)benzyl)amino-2-(furan-2-yl)acetamide oxalate (**75**) as a white solid (520 mg, 51%): R_f = 0.15 (EtOAc); mp 194–195 ºC; IR (nujol mull) 2944, 2860, 2726, 2656, 2352, 1870, 1702, 1617, 1556, 1459, 1378, 1213, 1007, 935, 825, 793, 752, 709, 622, 515 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.75 (s, C**H**$_2$N), 4.54 (s, C**H**), 5.14 (s, C**H**$_2$O), 6.44–6.45 (m, **H**$_3$ or **H**$_4$), 6.48–6.50 (m, **H**$_4$ or **H**$_3$), 7.51 (d, J = 9.0 Hz, 2 **H**$_{3'}$), 7.03–7.19 (m, 1 Ar**H**), 7.26–7.31 (m, 3 Ar**H**), 7.41–7.51 (m, 2 Ar**H**), 7.71–7.73 (m, 1 Ar**H**, N**H**); ^{13}C NMR (DMSO-d_6) δ 48.6 (**C**H$_2$N), 56.1 (**C**H), 68.2 (**C**H$_2$O), 110.7 (d, J = 20.5 Hz, **C**$_{2''}$ or **C**$_{4''}$), 114.0, 114.2 (**C**$_3$, **C**$_4$), 114.5 (d, J = 21.7 Hz, **C**$_{4''}$ or **C**$_{2''}$), 114.7 (**C**$_{3'}$), 123.4 (d, J = 3.4 Hz, **C**$_{6''}$), 126.0 (**C**$_{1'}$), 130.4 (d, J = 8.0 Hz, **C**$_{5''}$), 131.0 (**C**$_{2'}$), 139.9 (d, J = 6.8 Hz, **C**$_{1''}$), 143.8 (**C**$_5$), 147.4 (**C**$_2$), 158.0 (**C**$_{4'}$), 162.1 (d, J = 241.4 Hz, **C**$_{3''}$), 162.7 (2 **C**(O)OH), 167.6 (**C**(O)); M_r (+ESI) 355.13 $[M+H]^+$ (calcd for $C_{22}H_{21}FN_2O_7H^+$ 355.15 $[M+H]^+$). Anal. Calcd for $C_{22}H_{21}FN_2O_7$: C, 59.46; H, 4.76; F, 4.27; N, 6.30. Found: C, 59.07; H, 4.75; F, 4.25; N, 6.33.

Table S1. Elemental Analysis of Newly Prepared Compounds.

No.	Formula	Calcd.					Found				
		C	H	N	F		C	H	N	F	
5	$C_{18}H_{19}FN_2O_3$•0.35 H_2O	64.21	5.90	8.32	5.64		63.83	5.56	8.22	5.49	
(*R*)-**6**	$C_{19}H_{21}FN_2O_3$	66.26	6.15	8.13	5.44		65.98	6.10	8.03	5.41	
(*S*)-**6**	$C_{19}H_{21}FN_2O_3$	66.26	6.15	8.13	5.44		65.98	6.11	8.05	5.44	
(*R*)-**7**	$C_{21}H_{25}FN_2O_3$	67.72	6.77	7.52	5.10		67.95	6.71	7.51	5.18	
(*R*)-**7**	$C_{22}H_{27}FN_2O_3$	68.37	7.04	7.25	4.92		68.31	7.20	7.25	5.08	
(*R,S*)-**9**	$C_{23}H_{22}FN_3O_3$	67.80	5.44	10.31	4.66		67.56	5.38	10.24	4.58	
(*R*)-**10**	$C_{20}H_{23}FN_2O_4$	64.16	6.19	7.48	5.07		64.14	6.15	7.37	5.05	
(*R*)-**11**	$C_{19}H_{21}FN_2O_3$	66.26	6.15	8.13	5.52		66.05	6.13	8.04	5.32	
(*R*)-**12**	$C_{19}H_{21}FN_2O_4$	66.32	5.87	7.77	5.27		63.35	5.84	7.78	5.06	
(*R*)-**13**	$C_{21}H_{25}FN_2O_3$•0.32H_2O	66.70	6.83	7.41			66.35	6.59	7.28		
(*R*)-**14**	$C_{21}H_{23}FN_2O_3$	68.09	6.26	7.56	5.13		67.81	6.32	7.34	4.88	
(*R*)-**15**	$C_{21}H_{21}FN_2O_3$	68.46	5.75	7.60	5.16		68.51	5.92	7.56	5.34	
(*R*)-**16**	$C_{20}H_{23}FN_2O_4$	64.16	6.19	7.48	5.07		63.86	6.13	7.50	4.88	
(*R*)-**18**	$C_{21}H_{25}FN_2O_4$	64.93	6.47	7.21	4.89		64.53	6.47	7.37	4.68	
(*R*)-**19**	$C_{21}H_{25}FN_2O_4$	64.93	6.49	7.21	4.89		64.98	6.57	7.10	4.84	
(*R*)-**20**	$C_{20}H_{24}N_2O_4$	67.40	6.79	7.86			67.12	6.68	7.80		
(*R*)-**21**	$C_{20}H_{23}FN_2O_4$	64.16	6.19	7.48	5.07		63.95	6.20	7.46	5.14	
(*R*)-**22**	$C_{20}H_{23}FN_2O_4$	64.16	6.19	7.48	5.07		64.02	6.16	7.45	4.99	
25	$C_{16}H_{16}FNO_2$	70.31	5.90	5.12	6.95		70.10	5.84	5.17	6.92	
(*R*)-**33**	$C_{24}H_{31}FN_2O_4$	66.96	7.26	6.51	4.41		67.23	7.22	6.28	4.47	
(*S*)-**34**	$C_{25}H_{33}FN_2O_4$	67.55	7.52	6.30			67.25	7.52	6.09		
37	$C_{21}H_{19}FN_2O_2$	71.98	5.47	5.42	8.00		72.12	5.36	5.29	7.98	
38	$C_{21}H_{18}FN_3O_3$	66.48	4.78	11.08	5.01		66.21	4.81	10.95	4.89	
46	$C_{14}H_{10}FNO_2$	74.00	4.44	6.16	8.36		74.06	4.28	6.16	8.26	
48	$C_{14}H_{10}FNO_2$	74.00	4.44	6.16	8.36		74.06	4.28	6.16	8.26	
57	$C_{13}H_8FNO$	73.23	3.78	6.57	8.91		73.18	3.39	6.53	8.68	
58	$C_{15}H_{12}FNO_2$	74.67	5.01	5.81	7.87		74.53	4.93	5.81	7.75	
63	$C_{15}H_{12}FNO$	74.67	5.01	5.81	7.87		74.46	5.11	5.83	7.89	
64	$C_{15}H_{16}FNO$•0.15H_2O	72.65	6.62	5.65	7.66		72.61	6.58	5.46	7.28	
74	$C_{18}H_{21}FN_2O_3$	65.05	6.37	8.43	5.72		65.32	6.32	8.42	5.56	
75	$C_{22}H_{21}FN_2O_7$	59.46	4.76	6.30	4.27		59.07	4.75	6.33	4.25	
79	$C_{19}H_{22}FNO_4$	65.69	6.38	4.03	5.47		65.44	6.32	4.01	5.37	
87	$C_{21}H_{20}FNO_4$	68.28	5.46	3.79	5.14		68.33	5.33	3.87	5.12	
(*R*)-**90**	$C_{22}H_{27}FN_2O_5$	63.14	6.50	6.69	4.54		63.12	6.55	6.65	4.38	
(*S*)-**90**	$C_{22}H_{27}FN_2O_5$	63.14	6.50	6.69	4.54		63.31	6.53	6.77	4.45	
(*R*)-**91**	$C_{23}H_{29}FN_2O_5$	63.87	6.76	6.48	4.39		63.57	6.75	6.39	4.13	
(*S*)-**91**	$C_{23}H_{29}FN_2O_5$	63.87	6.76	6.48	4.39		63.75	6.82	6.51	4.22	

(*R*)-**92**	$C_{21}H_{25}FN_2O_5 \cdot 0.05H_2O_5$	62.22	6.24	6.91	4.69		61.86	6.53	6.88	4.37	
(*R*)-**93**	$C_{22}H_{27}FN_2O_5$	63.14	6.50	6.69	4.54		63.19	6.63	6.63	4.37	
(*R*)-**94**	$C_{22}H_{27}FN_2O_5$	63.14	6.50	6.69	4.54		62.90	6.83	7.03	4.18	
(*R*)-**95**	$C_{23}H_{29}FN_2O_5$	63.87	6.76	6.48	4.39		63.43	6.76	6.57	4.25	
(*R*)-**96**	$C_{23}H_{29}FN_2O_5$	63.87	6.76	6.48	4.39		63.48	6.79	6.48	4.25	
(*R*)-**100**	$C_{22}H_{28}N_2O_5$	65.98	7.05	7.00			66.05	7.15	7.04		
(*R*)-**101**	$C_{23}H_{30}N_2O_5$	66.65	7.30	6.76			66.90	7.25	6.84		
(*R*)-**102**	$C_{22}H_{27}FN_2O_5$	63.14	6.50	6.69	4.54		63.09	6.50	6.69	4.36	
(*R*)-**103**	$C_{23}H_{29}FN_2O_5$	63.87	6.76	6.48	4.39		64.05	6.76	6.46	4.21	
(*R*)-**104**	$C_{22}H_{27}FN_2O_5$	63.14	6.50	6.69	4.54		62.84	6.49	6.67	4.29	
(*R*)-**105**	$C_{23}H_{29}FN_2O_5$	63.87	6.76	6.48	4.39		63.92	6.86	6.53	4.40	
23	$C_{16}H_{16}FNO_2$	70.31	5.90	5.12	6.95		70.10	5.84	5.17	6.92	

Table S2. Mass Spectra Data of Select Compounds.

No.	Formula	Calcd.	Found
(*R*)-**17**	$C_{20}H_{24}FN_3O_3H^+$	374.1879	374.1880
32	$C_{14}H_{10}NONa^+$ $C_{14}H_{12}O^+$	250.0641 215.087	250.0641 215.088
50	$C_{14}H_{12}FO^+$	215.0872	215.0878
56	$C_{14}H_{10}NONa^+$	250.0	250.0
59	$C_{14}H_{14}FNOH^+$	232.1137	232.1138
60	$C_{13}H_{10}FO^+$	201.0698	201.0715
61	$C_{15}H_{16}FNOH^+$	246.1294	246.1294
66	$C_{14}H_{11}FN_2H^+$	227.0984	227.0985
67	$C_{14}H_{15}FN_2H^+$	231.1297	231.1298
77	$C_5H_{11}NO_3H^+$	134.08	134.08
(*R*)-**97**	$C_{24}H_{31}FN_2O_5H^+$	447.2295	447.2295
(*R*)-**98**	$C_{23}H_{29}FN_2O_5Na^+$	455.1958	455.1958
(*R*)-**99**	$C_{24}H_{31}FN_2O_5Na^+$	469.2114	469.2115