Electronic Supplementary Material (ESI) for Chemical Communications

[^{18}F]Fluorination of Arylboronic Ester using [^{18}F]Selectfluor *bis*(triflate): Application to 6-[^{18}F]Fluoro-L-DOPA

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Supplementary Materials

Contents

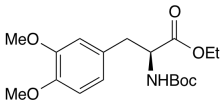
1. General Description

All chemicals were purchased from Sigma Aldrich, Apollo, Strem and Alfa Aesar and were used without further purification. The commercial 6-Fluoro-L-DOPA precursor (N-Formyl-3,4-di-tert-butoxycarbonyloxy-6-(trimethylstannyl)-L-phenylalanine ethyl ester) ***(S)*-1b** and the authentic 6-Fluoro-L-DOPA reference were obtained from ABX (ABX GmbH, Radeberg, Germany). 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(triflate) (F-TEDA-OTf) was prepared according to the literature.[1] All reactions involving air or moisture-sensitive reagents were carried out under an atmosphere of nitrogen or argon in flame-dried glassware. Thin layer chromatograms (TLC, silica gel 60 F254 plates) were run and visualised using UV light (254 nm) and/or potassium permanganate stain. Flash column chromatography was performed on Kieselgel 60 silica on a glass column or short path plastic cartridges (Isolute). Celite filtrations were performed using plastic cartridges. NMR spectra were recorded on Bruker DQX400, DPX200, DPX400, AVC500 and AVB500 spectrometers. The boron NMR spectra was processed by Dr Barbara Odell, University of Oxford. Chemical shifts (δ, ppm) were reported relative to $CDCl_3$, CD_2Cl_2, acetone-d_6 or DMSO-d_6. Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept =septet, m = multiplet, b = broad, app = apparent), coupling constant (*J*) in Hertz (Hz). Infrared (IR) spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as either a thin film ($CDCl_3$) or as solid as stated. Selected characteristic peaks are reported in cm^{-1}. Low-resolution mass spectra were recorded on a Waters LCT Premier XE spectrometer whereas high resolution mass spectra (HRMS, m/z) measurements were run on a Bruker MicroTOF using positive/negative electrospray ionisation. Elemental analyses were recorded by the elemental analysis service of Sheffield University.

2. Preparation of Precursors

*2.1 Synthesis of Boronic ester precursor **(S)-2***

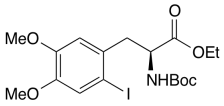
***N*-(*tert*-Butoxycarbonyl)-3,4-(dimethoxy)-L-phenylalanine ethyl ester (*(S)*-7a)**



N-(*tert*-Butoxycarbonyl)-3,4-(dimethoxy)-L-phenylalanine ethyl ester was prepared from L-DOPA by the formation of ethylester, Boc protection of the amine followed by methylation of the catechol functionality using the procedure described by Lemaire et al.[2] Thionyl chloride (3.1 mL, 42 mmol) was added to L-DOPA (4.90 g, 25 mmol) in dry ethanol (125 mL) at 0 °C under argon. The reaction mixture was refluxed for 20 hours, cooled and concentrated *in vacuo*. Toluene was added and the mixture concentrated *in vacuo* giving crude 3,4-dihydroxy-L-phenylalanine ethyl ester hydrochloride salt (6.50 g, > 99%). The ethyl ester (3.30 g, 12.6 mmol) was treated with triethylamine (1.8 mL, 1.31 g, 12.9 mmol) and di-*tert*-butyl dicarbonate (2.90 g, 13.3 mmol) in ethanol (55 mL) at room temperature. The reaction mixture was stirred for 2 hours and the solvent was evaporated *in vacuo*. The mixture was acidified with 1M HCl at 0 °C and extracted with EtOAc (3 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (15 – 50 % EtOAc/hexane) gave *N*-(*tert*-butoxycarbonyl)-3,4-(dihydroxy)-L-phenylalanine ethyl ester as a clear oil (3.67 g, 90%). Methyl iodide (1.4 mL, 22.5 mmol) was added to *N*-(*tert*-butoxycarbonyl)-3,4-(dihydroxy)-L-phenylalanine ethyl ester (1.63 g, 5 mmol) and potassium carbonate (6.22 g, 45 mmol) in DMF (11 mL). The reaction mixture was stirred for 24 hrs at room temperature under argon. The reaction mixture was filtered and diluted with water (20 mL). The pH was adjusted to 1-2 using 1M HCl

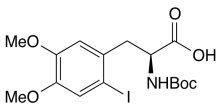
and extracted with diethyl ether (2 x 20 mL). The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (5% EtOAc/CH_2Cl_2) gave *N*-(*tert*-butoxycarbonyl)-3,4-(dimethoxy)-L-phenylalanine ethyl ester as a white solid (1.38 g, 78% from catechol). TLC (50 % EtOAc/hexane) R_f = 0.36. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.24 (t, *J* = 7.5 Hz, 3H), 1.42 (s, 9H), 3.03 (m, 2H), 3.86 (s, 6H), 4.17 (q, *J* = 7.0 Hz, 2H), 4.53 (b q, *J* = 7.5 Hz, 1H), 4.97 (bd, *J* = 8.0 Hz 1H), 6.65-6.68 (m, 2H), 6.78-6.80 (m, 1H). The ^{1}H NMR data ($CDCl_3$) corresponded with those reported in the literature.[3] ^{1}H NMR (400 MHz, acetone-d_6) δ = 1.24 (t, *J* = 7.0 Hz, 3H), 1.36 (s, 9H), 2.92 (dd, *J* = 8.0, 14.0 Hz, 1H), 3.05 (dd, *J* = 5.0 , 14.5 Hz, 1H), 3.77 (s, 3H), 3.79 (s, 3H), 4.10-4.16 (m, 2H), 4.32-4.38 (m, 1H), 6.05 (d, *J* = 8.0 Hz, 1H), 6.75-6.77 (m, 1H), 6.84-6.87 (m, 2H); ^{13}C NMR (100 MHz, acetone-d_6) δ = 14.6 (CH_3), 38.0 (3 x CH_3), 56.1 (CH_3), 56.2 (CH_3), 56.3 (CH_3), 61.5 (CH_2), 79.4 (tert. C), 112.9 (CH), 114.2 (CH), 122.3 (CH), 130.7 (tert. C), 149.4 (tert. C), 150.3 (tert. C), 156.2 (tert. C), 172.9 (tert. C); IR νmax ($CHCl_3$) 1229, 1367, 1739, 2970, 3555. HRMS found 376.1736 calc. 376.1736 $[C_{18}H_{27}NO_6 + Na]^+$.

N-(*tert*-Butoxycarbonyl)-3,4-(dimethoxy)-6-(iodo)-L-phenylalanine ethyl ester (*(S)*-11)



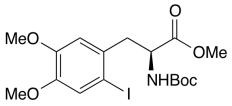
The method described by Fuchtner et al.[4] was used and modified by extending the reaction time. Bis(trifluoro-acetoxy)iodobenzene (0.77 g, 1.8 mmol) and iodine (0.38 g, 1.5 mmol) were added to *N*-(*tert*-butoxycarbonyl)-3,4-(dimethoxy)-L-phenylalanine ethyl ester (*S*)-**7a** (0.53 g, 1.5 mmol) in CH_2Cl_2 (25 mL) at 0 °C. The reaction mixture was stirred for 15 min at 0°C before being warmed up to room temperature and stirred for a further 3 hours followed by treatment with 1M sodium sulfite (aq, 15 mL). The organic phase was washed with water, brine and dried ($MgSO_4$). Flash column chromatography (10 – 20 % EtOAc/hexane) gave the product as a white solid (0.49 g, 68%). TLC (20 % EtOAc/hexane) R_f = 0.36. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.0 Hz, 3H), 1.38 (s, 9H), 3.04 (dd, *J* = 8.0, 14.5 Hz, 1H), 3.19 (dd, *J* = 6.5, 14.5 Hz, 1H), 3.84 (s, 6H), 4.19 (q, *J* = 7.0 Hz, 2H), 4.57 (b q, *J* = 8.0 Hz, 1H), 5.06 (b d, *J* = 8.0 Hz, 1H), 6.72 (s, 1H), 7.21 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 14.2 (CH_3), 28.4 (3 x CH_3), 42.9 (CH_2), 54.0 (CH), 56.0 (CH_3), 56.3 (CH_3), 61.7 (CH_2), 80.0 (tert. C), 89.1 (C-I), 112.9 (CH), 121.8 (CH), 131.9 (tert. C), 148.6 (tert. C), 149.4 (tert. C), 155.1 (tert. C), 172.1 (tert. C). IR νmax ($CHCl_3$) 1163, 1504, 1711, 2977, 3373. HRMS found 480.0878 calc. 480.0878 $[C_{18}H_{27}INO_6]^+$.

N-(*tert*-Butoxycarbonyl)-3,4-(dimethoxy)-6-(iodo)-L-phenylalanine (*(S)*-12)



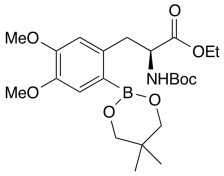
Lithium hydroxide (aq) (2.5 M, 0.8 mL, 2 mmol) was added to *N*-(*tert*-butoxycarbonyl)-3,4-(dimethoxy)-6-(iodo)-L-phenylalanine ethyl ester (*S*)-**11** (0.48 g, 1 mmol) in tetrahydrofuran (1.6 mL) and stirred for 2 hours at room temperature. The reaction mixture was cooled to 0 °C and acidified using 1M HCl (aq). The aqueous phase was extracted with EtOAc (3 x 5 mL), washed with brine and dried ($MgSO_4$). The crude product was isolated as a white solid (0.41 g, 91%). TLC (5 % MeOH/ 2 % AcOH/ CH_2Cl_2) R_f= 0.18. Crude ^{1}H NMR (200 MHz, DMSO-d_6) δ = 1.20 (s, 2H of 9H), 1.29 (s, 7H of 9H), 2.82 (dd, *J* = 10.0, 14.0 Hz, 1H), 3.06 (dd, *J* = 4.5, 14.0 Hz, 1H), 3.72 (s, 6H), 4.10-4.22 (m, 1H), 6.99 (s, 1H), 7.24 (s, 1H). IR νmax (neat) 1165, 1682, 1754, 3938, 3353. HRMS found 474.0387 calc. 474.0385 $[C_{16}H_{22}INO_6+Na]^+$.

N-(*tert*-Butoxycarbonyl)-3,4-(dimethoxy)-6-(iodo)-L-phenylalanine methyl ester (*(S)*-13)



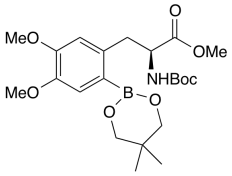
(Trimethylsilyl)diazomethane (2M, 1.9 mL, 3.80 mmol) was added slowly to *N*-(*tert*-butoxycarbonyl)-3,4-(dimethoxy)-6-(iodo)-L-phenylalanine *(S)*-**12** (0.34 g, 0.75 mmol) in dry methanol (1.5 mL) and dry CH_2Cl_2 (7.5 mL) at room temperature whereupon gas evolution was observed. After 10 min, the reaction mixture was concentrated *in vacuo*. Flash column chromatography (15 – 25 % EtOAc/hexane) gave the product as a white solid (0.35 g, > 99%). TLC (20 % EtOAc/hexane) R_f = 0.21. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H), 3.05 (dd, *J* = 8.0, 14.5 Hz, 1H), 3.22 (dd, *J* = 6.5, 14.0 Hz, 1H), 3.75 (s, 3H), 3.85 (s, 6H), 4.61 (q, *J* = 7.0 Hz, 1H), 5.05 (b d, *J* = 8.0 Hz, 1H), 6.71 (s, 1H), 7.22 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 28.4 (3xCH_3), 42.8 (CH_2), 52.6 (CH_3), 54.0 (CH), 56.3 (CH_3), 56.3 (CH_3), 61.7 (CH_2), 80.1 (tert. C), 89.0 (C-I), 112.9 (CH), 121.8 (CH), 131.8 (tert. C), 148.6 (tert. C), 149.4 (tert. C), 155.1 (tert. C), 172.5 (tert. C). IR νmax ($CHCl_3$) 1163, 1504, 1709, 2976, 3371. HRMS found 488.0542 calc. 488.0541 $[C_{17}H_{24}INO_6+Na]^+$.

N-(*tert*-Butoxycarbonyl)-3,4-dimethoxy-6-(1,3,2-dioxaborinane-5,5-dimethyl)-L-phenylalanine ethyl ester (*(S)*-2a)



Method modified from Skaff et al.[5] Bis(neopentyl glycolato)diboron (3.39 g, 15 mmol), Pd(dppf)Cl_2.CH_2Cl_2 (0.20 g, 0.25 mmol), potassium acetate (1.97 g, 20 mmol) were placed in a dry flask under N_2. DMSO (30 mL) was added and the mixture purged with nitrogen for at least 5 min. *N*-(*tert*-butoxycarbonyl)-3,4-(dimethoxy)-6-(iodo)-L-phenylalanine ethyl ester *(S)*-**11** (2.40 g, 5 mmol) was added and the mixture was heated to 80°C over 10 min and stirred at 80 °C for 17 hours. The reaction mixture was cooled to room temperature and a 50% saturated sodium chloride solution (aq) was added followed by extraction with EtOAc (3 x 15 mL). The combined extracts were washed with 50% saturated sodium chloride solution (aq) and dried ($MgSO_4$). Flash column chromatography (2 – 15 % EtOAc /CH_2Cl_2) gave two main fractions of which fraction one was a mixture of product and impurity (presumably diboron reagent) and fraction two contained product (855 mg, 37 %, >98% pure). TLC (15 % EtOAc/CH_2Cl_2) R_f = 0.22 *(The impurity can be visualised for a short period using potassium permanganate)*. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.05 (s, 2xCH_3, 6H), 1.25 (t, *J* = 7.5 Hz, CH_3, 3H), 1.30 and 1.35 (two b s, 9H), 3.19-3.21 (m, 2H), 3.80 (s, 4H), 3.89 (s, 6H), 4.18 (q, *J* = 7.5 Hz, 2H), 4.38 (m, 1H), 5.66 (b d, *J* = 8.0 Hz, 1H), 6.70 (s, 1H), 7.28 (s, 1H). ^{11}B NMR (160 MHz, $CDCl_3$) δ = 27.51. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 14.3 (CH_3), 22.0 (CH_3), 28.4 (3 x CH_3), 31.8 (tert. C), 37.1 (CH_2), 55.9 (CH_3), 56.3 (CH_3), 61.1 (CH_2), 72.4 (CH_2), 79.4 (tert. C), 113.2 (CH), 117.5 (CH), 136.7 (tert. C), 147.2 (tert. C), 150.8 (tert. C), 155.7 (tert. C), 173.2 (tert. C). IR νmax ($CHCl_3$) 1162, 1715, 2964, 3374. HRMS found 488.28 calc. 488.24 $[C_{23}H_{36}BNO_8 + Na]^+$. The ester was stable >12 months.

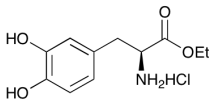
_N_-(_tert_-Butoxycarbonyl)-3,4-dimethoxy-6-(1,3,2-dioxaborinane-5,5-dimethyl)-L-phenylalanine methyl ester (_(S)_-2b)



In order to ease the purification, the amount of boron reagent was limited to fewer equivalents. *N*-(*tert*-butoxycarbonyl)-3,4-(dimethoxy)-6-(iodo)-L-phenylalanine methyl ester *(S)*-**13** (1.80 g, 3.9 mmol) was dissolved in DMSO (25 mL) and purged with N_2 for 10 min. Potassium acetate (1.20 g, 12.3 mmol), bis(neopentyl glycolato)diboron (1.01 g, 4.5 mmol) and Pd(dppf)Cl_2.CH_2Cl_2 (0.17 g, 0.2 mmol) were added and the mixture purged with nitrogen for 3 min. The mixture was heated to 80°C over 10 min and stirred at 80 °C for 17 hours. The reaction mixture was cooled to room temperature and a 50% saturated sodium chloride solution (aq, 20 mL) was added followed by extraction with EtOAc (2 x 40 mL). The combined extracts were washed with 50% saturated sodium chloride solution (aq, 3 x 40 mL) and dried ($MgSO_4$). Flash column chromatography (2 – 15 % EtOAc /CH_2Cl_2) gave two main fractions. Fraction one contained the product isolated as a white foam (600 mg, 33%, >99% pure) and fraction two was a mixture of the product and B_2R_2. TLC (5 % EtOAc /CH_2Cl_2) R_f = 0.29-0.47 (streaking) *(The impurity can be visualised for a short period using potassium permanganate).* ^{1}H NMR (200 MHz, $CDCl_3$) δ = 1.06 (s, 6H), 1.36 (s, 9H), 3.19-3.22 (bd, *J* = 7.5 Hz, 2H), 3.73 (s, 3H), 3.81 (s, 4H), 3.90 (s, 6H), 4.35-4.46 (m, 1H), 5.66 (bd, *J* = 8.0 Hz, 1H), 6.70 (s, 1H), 7.29 (s, 1H). ^{11}B NMR (160 MHz, $CDCl_3$) δ = 27.05. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 22.0 (CH_3), 28.4 (3 x CH_3), 31.8 (tert. C), 37.0 (CH_2), 52.2 (CH_3), 55.9 (CH_3), 56.0 (CH_3), 56.3 (CH), 72.5 (CH_2), 79.5 (tert. C), 113.2 (CH), 117.5 (CH), 136.6 (tert. C), 147.2 (tert. C), 150.8 (tert. C), 155.7 (tert. C), 173.7 (tert. C). Anal. found: C, 58.04; H, 7.80; N, 2.99. Calc. for $C_{22}H_{34}BNO_8$: C, 58.55; H, 7.59; N, 3.10%. IR νmax ($CHCl_3$) 1161, 1718, 1742, 2970, 3375. HRMS found 474.2281 calc. 474.2270 $[C_{22}H_{34}BNO_8+Na]^+$. The ester was stable > 6 months.

2.2 Synthesis of arylstannane precursor ***(S)*-1a** *– used in the 'cold' fluorination optimisation studies*

3,4-dihydroxy-L-phenylalanine ethyl ester (hydrochloride salt) (*(S)*-14)

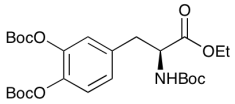


The 3,4-dihydroxy-L-phenylalanine ethyl ester (hydrochloride salt) *(S)*-**14** was synthesised according to the literature.[6] $SOCl_2$ (18 mL, 253.6 mmol) was carefully added dropwise to a solution of 3,4-dihydroxy-L-phenylalanine (10.0 g, 50.7 mmol) in EtOH (60 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h and at room temperature for 12 hours. Concentration of the reaction mixture *in vacuo* gave the desired product as a dense yellow oil in quantitative yield (13.3 g, >99 %), which was used without further purification. The data were consistent with those reported in the literature.[6]

^{1}H NMR (D_2O, 400 MHz), δ = 1.10 (t, *J* = 13.2 Hz, 3H), 3.07 – 2.95 (ABX system, bm, 2H), 3.64 (t, *J* = 6.5 Hz, 1H), 4.14 (q, *J* = 6.9 Hz, 2H), 6.56 (d, *J* = 8.0 Hz, 1H), 6.63 (s, 1H), 6.75 (d, *J* = 9.00 Hz, 1H); ^{13}C NMR (D_2O, 101 MHz) δ = 14.1 (*C*H_3), 39.3 (*C*H_2), 55.0 (*C*H), 61.4 (*C*H_2), 115.9 (Ar*C*H), 116.8 (Ar*C*H), 120.8 (Ar-

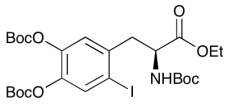
*C*H), 127.9 (tert. C), 144.2 (tert. C), 145.1 (tert. C), 174.2 (tert. C); LRMS(ESI)$^+$ m/z: for [$C_{11}H_{15}NO_4$+H^+] found 227.13 calc. 227.11.

N-(*tert*-Butoxycarbonyl)-3,4-di(tert-butoxycarbonyloxy)-L-phenylalanine ethyl ester (*(S)*-4a)



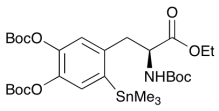
N-(*tert*-Butoxycarbonyl)-3,4-di(tert-butoxycarbonyloxy)-L-phenylalanine ethyl ester *(S)*-**4a** was synthesised according to the literature.[6] Triethylamine (23.4 mL, 167.6 mmol) was added to a solution of 3,4-dihydroxy-L-phenylalanine ethyl ester (hydrochloride salt) *(S)*-**14** (13.3 g, 50.8 mmol) in DMF (33 mL), cooled to 0 ^oC,. To this solution, di-*tert*-butyl dicarbonate (47.9 mL) in DMF (33 mL) were added dropwise and the mixture was stirred first at 0 ^oC for 2 hours and then for 48 hours at room temperature. After dilution with EtOAc (100 mL), the solution was washed with water (50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude compound was purified by flash column chromatography (5 % EtOAc/CH_2Cl_2) to give the desired product as a dense yellow oil (22.92 g, 86 %). The data were consistent with those reported in the literature. [6]
^{1}H NMR (CD_2Cl_2, 400 MHz), δ = 1.29 (t, *J* = 7.3 Hz, 3H), 1.47 (s, 9H), 1.58 (s, 18H), 3.23 – 3.07 (ABX system, bm, 2H), 4.21 (q, *J* = 6.9 Hz, 2H), 4.57 (bm, 1H), 5.15 (bd, *J* = 8.1 Hz, 1H), 7.06 (d, *J* = 8.6 Hz, 1H), 7.10 (s, 1H), 7.25 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (CD_2Cl_2, 101 MHz) δ = 15.3 (*C*H_3), 28.5 (*C*H_3), 28.7 (*C*H_3), 29.5 (*C*H_3), 38.8 (*C*H_2), 55.8 (*C*H), 62.8 (*C*H_2), 81.0 (NHC(O)O*C*$(CH_3)_3$), 85.0 (tert. C), 124.2 (Ar*C*H), 125.3 (Ar*C*H), 128.6 (Ar*C*H), 136.6 (tert. C), 142.9 (tert. C), 143.8 (tert. C), 152.0 (2 x tert. C), 156.3 (tert. C), 172.8 (tert. C); LRMS(ESI)$^+$ m/z: for [$C_{26}H_{39}NO_{10}$+Na^+] found 548.20 calc. 548.26.

N-(*tert*-Butoxycarbonyl)-3,4-di(tert-butoxycarbonyloxy)-6-iodo-L-phenylalanine ethyl ester (*(S)*-15).



N-(*tert*-Butoxycarbonyl)-3,4-di(tert-butoxycarbonyloxy)-6-iodo-L-phenylalanine ethyl ester *(S)*-**15** was synthesised according to the literature.[4] Bis-(trifluoroacetoxy)iodobenzene (0.84 g, 1.96 mmol) and iodine (0.41 g, 1.63 mmol) were added to a stirred solution of *N*-(*tert*-Butoxycarbonyl)-3,4-di(*tert*-butoxycarbonyloxy)-L-phenylalanine ethyl ester *(S)*-**4a** (0.86 g, 1.63 mmol) in dry CH_2Cl_2 at 0 ^oC and the resulting solution was stirred at this temperature for 15 minutes. The mixture was allowed to warm up to room temperature and stirred for a further 90 minutes. After dilution with CH_2Cl_2 (10 mL), the mixture was washed with 1M $Na_2S_2O_3$ (15 mL x 2), water, brine and dried ($MgSO_4$). The organic phase was filtered and concentrated *in vacuo*. Purification by flash column chromatography (10 % EtOAc/hexane) yielded the desired product as a yellow oil (0.72 g, 79%). The data were consistent with those reported in the literature.[4]
^{1}H NMR (CD_2Cl_2, 400 MHz), δ = 1.27 (t, *J* = 7.3 Hz, 3H), 1.42 (s, 9H), 1.57 (s, 18H), 3.30 – 3.08 (ABX system, dd and bm, 2H), 4.20 (q, *J* = 6.9 Hz, 2H), 4.58 (bm, 1H), 5.13 (bd, *J* = 8.1 Hz, 1H), 7. 15 (s, 1H), 7.75 (s, 1H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ = 15.3 (*C*H_3), 28.5 (*C*H_3), 28.7 (*C*H_3), 29.5 (*C*H_3), 43.8 (*C*H_2), 55.8 (*C*H), 62.8 (*C*H_2), 81.0 (85.0 (tert. C), 85.0 (2 x tert. C), 96.5 (Ar*C*H), 125.2 (Ar*C*H), 134.6 (Ar*C*H), 139.6 (tert. C), 142.9 (tert. C), 143.0 (tert. C), 151.6 (2 x tert. C), 156.3 (tert. C), 172.8 (tert. C); LRMS(ESI)$^+$ m/z: for [$C_{26}H_{38}INO_{10}$+Na^+] found 651.18 calc. 651.15.

_N_-(_tert_-Butoxycarbonyl)-3,4-di(tert-butoxycarbonyloxy)-6-trimethylstannyl-L-phenylalanine ethyl ester (_(S)_-1a).



_N_-(_tert_-Butoxycarbonyl)-3,4-di(tert-butoxycarbonyloxy)-6-trimethylstannyl-L-phenylalanine ethyl ester _(S)_-**16** was synthesised acoording to the literature.[6] A solution of _N_-(_tert_-Butoxycarbonyl)-3,4-di(tert-butoxycarbonyloxy)-6-iodo-L-phenylalanine ethyl ester _(S)_-**15** (2.00 g, 3.1 mmol) in dioxane (40 mL) was placed in a pressure tube and degassed with argon for 10 minutes. Hexamethylditin (1.34 mL, 4.0 mmol) and tetrakis(triphenylphosphino)palladium(0) (0.20 g, 0.21 mmol) were added under an inert atmosphere and the tube was sealed under vacuum. The reaction mixture was heated to 105 ^{o}C and stirred for 6 hours, before being allowed to cool to room temperature. The reaction mixture was filtered and diluted with EtOAc (70 mL), washed with water and brine and dried ($MgSO_4$). The organic phase was filtered and concentrated _in vacuo_. Purification by flash column chromatography (10 % EtOAc/Hexane) afforded the desired product as a clear oil (1.63 g, 65% yield). The data were consisted with those reported in the literature. [6]

^{1}H NMR (CD_2Cl_2, 400 MHz), δ = 0.40 (s, with tin satellites J^2_{Sn-H} = 54.0 Hz, 9H), 1.25 (t, J = 7.3 Hz, 3H), 1.41 (s, 9H), 1.55 (s, 18H), 3.17 – 2.99 (ABX system, dd and bm, 2H), 4.20 (q, J = 6.9 Hz), 4.48 (bm, 1H), 5.01 (bd, J = 8.1 Hz, 1H), 7.09 (s, with tin satellites J^4_{Sn-H} = 15.8 Hz, 1H), 7.30 (s, with tin satellites J^3_{Sn-H} = 46.2 Hz, 1H); ^{13}C NMR (CD_2Cl_2, 101 MHz) δ = -7.81 (s, CH$_3$, with tin satellites J^1_{Sn-C} = 339 Hz), 15.3 (CH$_3$), 28.5 (CH$_3$), 28.7 (CH$_3$), 29.5 (CH$_3$), 41.8 (CH$_2$), 55.8 (CH), 62.8 (CH$_2$), 81.0 (tert. C), 85.0 (2 x tert. C), 124.5 (s, with tin satellites J^3_{Sn-H} = 41.0 Hz, ArCH), 131.2 (s, with tin satellites J^2_{Sn-H} = 43.0 Hz, ArCH), 142.1 (ArC-CH$_2$), 141.2 (tert. C), 142.9 (tert. C), 143.0 (tert. C), 151.6 (2 x tert. C), 156.3 (tert. C), 172.3 (tert. C); LRMS(ESI)$^+$ m/z: for [$C_{29}H_{47}NO_{10}Sn+Na^+$] found 711.41 calc. 711.43.

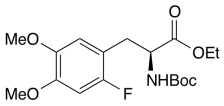
3. 'Cold' fluorination optimisation studies

3.1 Boronated precursor **_(S)_-2a**

Boronated precursor **_(S)_-2a** (0.125 mmol, 1 equiv.) was added to sodium hydroxide (1.2 equiv.) in dry methanol (5 mL/mmol boronic ester) in a round-bottomed flask (10 mL) and stirred under nitrogen for 3 hours. The reaction mixture was cooled to 0 °C and silver triflate (3 eq) was added. The reaction mixture was stirred at 0 °C under nitrogen for 30 min followed by evaporation of methanol _in vacuo_ while keeping the flask at 0 °C. The solvent was further co-evaporated with acetone (2 x 5 mL) at 0 °C under the same conditions and then dried under vacuum for a minimum of 20 min at 0 °C. The mixture was subsequently suspended in acetone (5 mL/mL R-BR') followed by addition of Selectfluor (1.05 eq) and powdered mol. sieves (0-500 mg/mmol). The reaction mixture was left stirring for 30 min at room temperature, concentrated _in vacuo,_ suspended in CH_2Cl_2 and filtered through a celite plug. The ratio of (_S_)-**6a** : (_S_)-**7a** was calculated from the crude reaction mixture using ^{1}H NMR. The mixture of (_S_)-**6a** and (_S_)-**7a** was isolated after flash column chromatography (10 – 20% EtOAc/hexane).

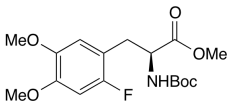
Fluorinated Products

N-(*tert*-Butoxycarbonyl)-3,4-di(tert-butoxycarbonyloxy)-6-fluoro-L-phenylalanine ethyl ester ((*S*)-6a)



^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.25 (t, *J* = 7.2 Hz, 3H), 1.41 (s, 9H), 3.03-3.08 (m, 2H), 3.83 (s, 3H), 3.84 (s, 3H), 4.15-4.20 (m, 2H), 4.53 (bq, *J* = 6.0 Hz, 1H), 5.06 (b d, *J* = 8.1 Hz 1H), 6.59-6.62 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2 (CH_3), 28.5 (CH_3), 31.6 (CH_2), 53.9 (CH), 56.2 (CH_3), 56.5 (CH_3), 61.6 (CH_2), 80.0 (tert. C), 100.1 (d, *J* = 28.4 Hz, CH), 113.6 (d, *J* = 17.1 Hz, tert. C), 113.6 (d, *J* = 6.0 Hz, CH), 145.2 (tert. C), 148.9 (tert. C), 155.2 (tert. C), 155.6 (d, *J* = 238 Hz, tert. C), 172.0 (tert. C). ^{19}F NMR (377 MHz, decoupled, $CDCl_3$) δ = -124.7; IR νmax ($CHCl_3$) 1167, 1517, 1713, 2977, 3369. MS found 394.16 calc. 394.16 [$C_{18}H_{26}FNO_6$ + Na]$^+$. HRMS found 394.1628 calc. 394.1636 [$C_{18}H_{26}FNO_6$ + Na]$^+$.

N-(*tert*-Butoxycarbonyl)-3,4-di(tert-butoxycarbonyloxy)-6-fluoro-L-phenylalanine methyl ester ((*S*)-6b).

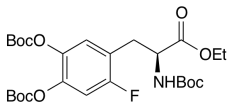


^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.41 (s, 9H), 2.99-3.13 (m, 2H), 3.73 (s, 3H), 3.83 (s, 3H), 3.84 (s, 3H), 4.53 (b q, *J* = 6.0 Hz, 1H), 5.05 (b d, *J* = 8.2 Hz 1H), 6.58-6.62 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.5 (CH_3), 31.6 (CH_2), 52.5 (CH_3), 53.9 (CH), 56.2 (CH_3), 56.5 (CH_3), 80.1 (tert. C), 100.1 (d, *J* = 28.0 Hz, CH), 113.6 (d, *J* = 18.0 Hz, tert. C), 113.7 (d, *J* = 6.4 Hz, CH), 145.2 (tert. C), 149.0 (tert. C), 154.6 (tert. C), 155.2 (tert. C), 155.2 (tert. C), 155.6 (d, *J* = 237 Hz, tert. C), 156.5 (tert. C), 172.4; ^{19}F NMR (377 MHz, decoupled, $CDCl_3$) δ = -125.0; IR νmax ($CHCl_3$) 1167, 1517, 1715, 2978, 3362. MS found 380.14 calc. 380.15 [$C_{17}H_{24}FNO_6$ + Na]$^+$. MS found 380.1467 calc. 380.1480 [$C_{17}H_{24}FNO_6$ + Na]$^+$.

3.2 Arylstannane precursor **((*S*)-1a)**

Silver triflate (2.0 equiv.) and Selectfluor (1.2 equiv.) were added to a solution of *N*-(*tert*-butoxycarbonyl)-3,4-di(tert-butoxycarbonyloxy)-6-trimethylstannyl-*L*-phenylalanine ethyl ester (*(S)*-**1a** (1 equiv.) in acetone (28 mL/mmol) at room temperature (whereupon the reaction mixture changed colour from clear to grey). The reaction mixture was stirred at room temperature for 30 min before being concentrated *in vacuo*. The ratio of (*S*)-**3a** : (*S*)-**4a** was calculated from the crude reaction mixture using ^{1}H NMR. The mixture of (*S*)-**3a** and (*S*)-**4a** was isolated after flash column chromatography (10 – 20% EtOAc/hexane).

N-(tert-Butoxycarbonyl)-3,4-di(tert-butoxycarbonyloxy)-6-fluoro-L-phenylalanine ethyl ester ((*S*)-3a).



^{1}H NMR (CD_2Cl_2, 400 MHz), δ = 1.29 (t, *J* = 7.3, 3H), 1.47 (s, 9H), 1.58 (s, 18H), 3.23 – 3.09 (ABX system, bm, 2H), 4.17 (q, *J* = 7.3 Hz, 2H), 4.57 (bm, 1H), 5.91 (bd, *J* = 8.1 Hz, 1H), 7.06 (d, $J^3_{F\text{-}H}$ = 9.9 Hz, 1H), 7.09 (d, $J^4_{F\text{-}H}$ = 6.9 Hz, 1H); ^{13}C NMR (CD_2Cl_2, 101 MHz) δ = 14.9 (CH_3), 27.5 (CH_3), 28.7 (2 x CH_3), 34.8 (CH_2),

52.8 (*C*H), 62.8 (*C*H_2), 81.0 (tert. C), 85.0 (2 x tert. C), 111.2 (Ar*C*H, d, J_{F-C} =30 Hz), 125.3 (Ar*C*H, d, J_{F-C} =15 Hz), 136.6 (tert. C), 142.9 (tert. C), 143.8 (tert. C), 152.0 (2 x tert. C), 152.3 (tert. C), 156.8 (Ar*C*-F, d, J_{F-C} =247 Hz), 172.8 (tert. C); ^{19}F NMR (CD_2Cl_2, 400MHz) δ = -121.6 (Ar-*F*); LRMS(ESI)$^+$ m/z: for [$C_{29}H_{47}NO_{10}Sn$+Na^+] found 711.41 calc. 711.43. The data were consisted with those reported in the literature.[6]

4. Radiochemical [^{18}F]fluorination protocols

4.1 Synthesis of [^{18}F]F_2 and [^{18}F]Selectfluor bis(triflate)

Synthesis of high specific activity [^{18}F]F_2

[^{18}F]F^- was obtained in the nuclear reaction ^{18}O(p,n)^{18}F by irradiating oxygen-18 enriched water (2.2 mL) for either 15 (Precursor **(*(S)*-2b)** studies) or 30 minutes (Precursor **(*(S)*-1b)** studies) with a 17 MeV proton beam of 35 μA produced with a CC-18/9 cyclotron (Efremov Institute of Electrophysical Apparatuses, St Petersburg, Russia). At the end of bombardment, the [^{18}F]F^- was solubilised in a carbonate/acetonitrile aqueous solution and transferred into the reaction vessel in the hot cell, followed by the standard azeotropic drying procedure using Kryptofix$_{222}$ and acetonitrile. [^{18}F]F_2 gas was prepared following the post-target synthesis described by Bergman and Solin.[7]

Synthesis of high specific activity [^{18}F]Selectfluor bis(triflate), [^{18}F]9

The [^{18}F]F_2 gas was bubbled into a vial containing a mixture of 1-chloromethyl-4-aza-1-azoniabicyclo[2.2.2]octane triflate **8** (2 μmol (0.003 M) or 7.5 μmol (0.01 M)) and lithium triflate (1 equivalent) in acetone-d_6 (0.75 mL) at -10 °C for ~ 30 seconds. [^{18}F]Selectfluor *bis*(triflate) [^{18}F]**9** formed instantaneously.[1a] The activity of the crude stock solution in acetone-d_6 ranged from 5 to 10 GBq, depending on the cyclotron irradiation time. Aliquots (0.2 mL) of this crude stock solution were used directly in labeling reactions.

4.2 Boronated precursor **(*(S)*-2b)**

This compound required activation prior to labeling. This was achieved by reacting 4.5 mg (10 μmol) of (*S*)-**2b** with sodium hydroxide (1.2 equivalents) in methanol (50 μL) for 3 hours at room temperature. Subsequent treatment of the crude reaction mixture with silver triflate (3 equivalents) at 0 °C for 30 minutes led to the transmetalated aryl silver complex **(*(S)*-5b)**. After removal of the solvent and co-evaporation with acetone (3 x 200 μL) at 0 °C. [^{18}F]**9** in acetone-d_6 (0.003 M, 0.2 mL) was added and the reaction mixture was stirred for 20 minutes at room temperature. Subsequently, acetone-d_6 was evaporated at room temperature under a stream of helium. Hydrolysis was carried out with 57% HI (0.3 mL) at 130 °C for 15 minutes.

4.3 Arylstannane precursor **(*(S)*-1b)**

[^{18}F]**9** in acetone-d_6 (2 μmol (0.003 M) or 7.5 μmol (0.01 M), 0.2 mL) was added to a reaction vial containing either precursor **(*(S)*-1b)** (10 μmol) and silver triflate (20 μmol) The solution was stirred at room temperature for 20 minutes. Subsequently, acetone-d_6 was evaporated at room temperature under a stream of nitrogen. Hydrolysis of [^{18}F](S)-**10** was carried out with 48% HBr (0.3 mL) at 130 °C for 5 minutes.

*Analysis of [^{18}F](S)-**10***

For both precursors a sample from the reaction mixture was taken after the fluorination. Samples were analysed by HPLC (System A and B). The fraction corresponding to the protected intermediates [^{18}F]*(S)*-**3b** or [^{18}F]-**6b**, was collected. The same procedure was repeated after hydrolysis, when the fraction corresponding to [^{18}F]*(S)*-**10** was collected and analysed for the calculation of the specific activity (System C).

Statistics

Statistical analyses were performed using the program Graph Prism, version 5.01 (GraphPad Software, San Diego, CA, USA). Comparison of radiochemical yields were tested using unpaired t-test with Welch's correction. Results are expressed as means ± SD for the indicated number of observations. Means were considered significantly different when $p<0.05$.

5. CALCULATION OF RCY (%) AND SA (GBq/µmol)

The radiochemical yields (RCY) of the [^{18}F]labelled protected intermediates [^{18}F]*(S)*-**3b** and [^{18}F](*S*)-**6b** were calculated by injecting an aliquot of the reaction mixture of known radioactivity into the HPLC (System A). The fraction corresponding to [^{18}F]*(S)*-**3b** or [^{18}F] (*S*)-**6b** was collected and its activity was measured. The RCY was calculated as the percentage of the collected fraction activity over the total activity of the aliquot.

The same procedure as above was carried out to calculate the RCY of [^{18}F]*(S)*-**10**. This result was then multiplied with the available activity (activity of reaction mixture per total activity of reaction mixture and reaction vial) to afford the corrected RCY (%) of [^{18}F]*(S)*-**10**.

Determination of SA was carried out in HPLC system C. The fraction corresponding to [^{18}F]*(S)*-**10** was collected and its activity was measured The mass of 6-fluoro-L-DOPA in the collected fraction was calculated by comparing HPLC retention times and peak intensities to a reference compound of known concentration. The SA of the product was decay-corrected to EOS of [^{18}F]**9**.

Entry	SF prec. **8** (µmol)/ LiOTf (µmol)[A]	Available activity (%)	RCY (%)[D] of [^{18}F](S)-**3b**	RCY (%)[E] of [^{18}F]*(S)*-**10**	SA (GBq/µmol)
1	2.0/2.0	27	14	15	3.23
2	2.0/2.0	31	14	17	3.40
3	2.0/2.0	49	13	13	3.38
4	2.0/2.0	56	25	10	3.45
5	2.0/2.0	60	22	7	3.46
6[B]	2.0/2.0	39	20	10	3.47
7 Mean	-	43.7	17.7	12.1	3.40
8 Std. Dev.	-	13.5	5.1	3.7	0.1
9	7.5/7.5	19	9	4	3.36
10[C]	7.5/7.5	25	11	7	3.34
11[B]	7.5/7.5	35	17	9	3.31
12[C]	7.5/7.5	34	16	6	2.94
13[B]	7.5/7.5	38	9	9	2.85
14	7.5/7.5	35	6	6	2.75
Mean	-	31.0	11.4	6.8	3.09
Std. Dev.	-	7.3	4.1	1.8	0.30

[A] [^{18}F]**9** concentration: Entries 1-6 = 0.003 M, Entries 9-14 = 0.01 M. [B] $NaHCO_3$ (1 equiv.) added. [C] $NaHCO_3$ (1 equiv.), MeOH (10 µL) added. [D] Proportion collected (%) of the radioactivity detected following analytical HPLC of protected 6-[^{18}F]fluoro-L-DOPA intermediate (decay-corrected). [E] Proportion collected (%) of the radioactivity detected following semi-preparative HPLC of 6-[^{18}F]fluoro-L-DOPA multiplied by the available activity (decay-corrected).

Table 1. Summary of results, Available activity, RCY (%), SA (GBq/µmol) for precursor [^{18}F]*(S)*-**1b** *(at modulated [^{18}F]***9** *stock concentrations.*

Entry	[^{18}F]SF conc. (M) /LiOTf (µmol)[A]	Available activity (%)	RCY (%)[B] of [^{18}F] *(S)*-**6b**	RCY (%)[C] of [^{18}F] *(S)*-**10**	SA (GBq/µmol)
1	2.0/2.0	37	7	9	2.73
2	2.0/2.0	53	17	16	2.85
3	2.0/2.0	35	17	12	2.80
4	2.0/2.0	75	27	40	2.16
5	2.0/2.0	58	9	18	2.25
6 Mean	-	51.6	15.3	19.0	2.56
7 Std. Dev.	-	16.4	7.9	12.2	0.33

[A] [^{18}F]**9** concentration: Entries 1-5 = 0.003 M. [B] Proportion collected (%) of the radioactivity detected following analytical HPLC of protected 6-[^{18}F]fluoro-L-DOPA intermediate (decay-corrected).

[C] Proportion collected (%) of the radioactivity detected following semi-preparative HPLC of 6-[^{18}F]fluoro-L-DOPA multiplied by the available activity (decay-corrected).

Table 2. Summary of Results: Available activity, RCY (%), SA (GBq/µmol) for precursor [^{18}F]*(S)*-**2b**.

6. HPLC Systems

6.1 General HPLC system for 'cold' fluorination optimisation studies

High performance liquid chromatography (HPLC) was performed on a Dionex UltiMate 3000 with a UliMate 3000 detector and a UltiMate 3000 Variable Wavelength Detector (λ=280 nm). Studies were performed using a reverse phase analytical column (Waters Nova-Pak C-18 Column, 150mm x 3.9mm). Elution was performed us a gradient of acetonitrile:water (5:95 to 95:5% over 15 min) with a flow rate of 1 mL/min.)

6.2 HPLC systems for [^{18}F]radiolabelling studies

High performance liquid chromatography (HPLC) was performed on a Spectra SYSTEM P2000 with a Spectra SYSTEM UV2000 detector and a Bioscan flow-count radioactivity detector in series, or a VWR-Hitachi L-2130 HPLC pump (VWR Hitachi, VWR International GmbH, Darmstadt, Germany) combined with a VWR-Hitachi L-2400 UV-absorption detector (λ=280 nm) and a 2 x 2 inch NaI-crystal for radioactivity detection.

SYSTEM A and B

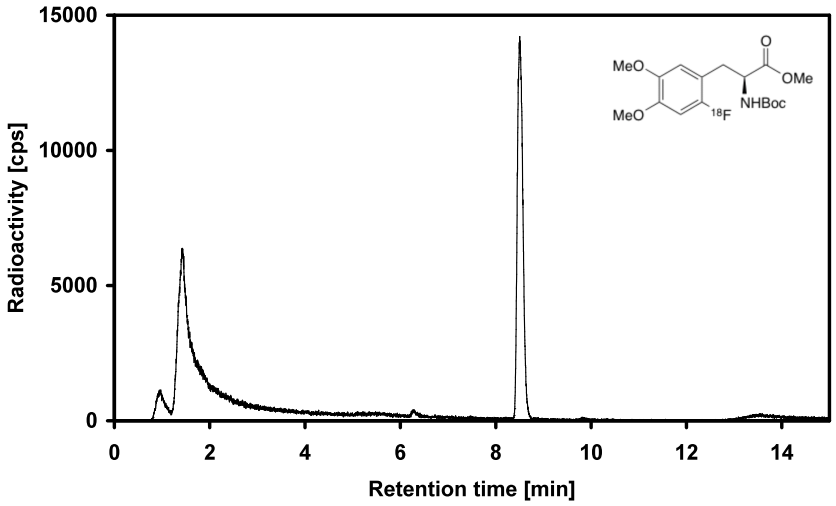
Semi-preparative (A) and analytical (B) HPLC studies of protected 6-[^{18}F]fluoro-L-dopa ([^{18}F]*(S)*-**3b** and [^{18}F]*(S)*-**6b** were performed using a reverse phase analytical column (Waters Nova-Pak C-18 Column, 150mm x 3.9mm). Elution was performed at a gradient of acetonitrile:water (5:95 to 80:20 % over 10 min) with a flow rate of 1 mL/min.

SYSTEM C

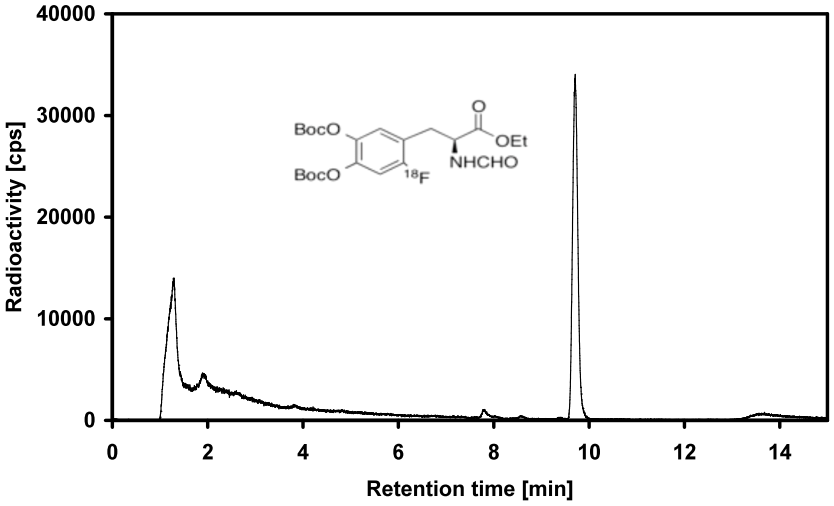
Specific radioactivity measurements of 6-[^{18}F]fluoro-L-dopa [^{18}F]*(S)*-**10** were performed using a reverse phase analytical column (Waters Atlantis dC18 Column 5µm, 150mm x 3,9mm). Elution was performed with 70mM KH_2PO_4, with a flow rate of 1 mL/min.

7. HPLC Chromatograms

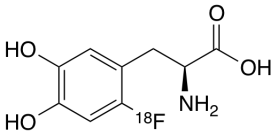
[^{18}F](*S*)-6b



[^{18}F](*S*)-3b



6-[^{18}F]fluoro-L-DOPA – ([^{18}F](*S*)-10)



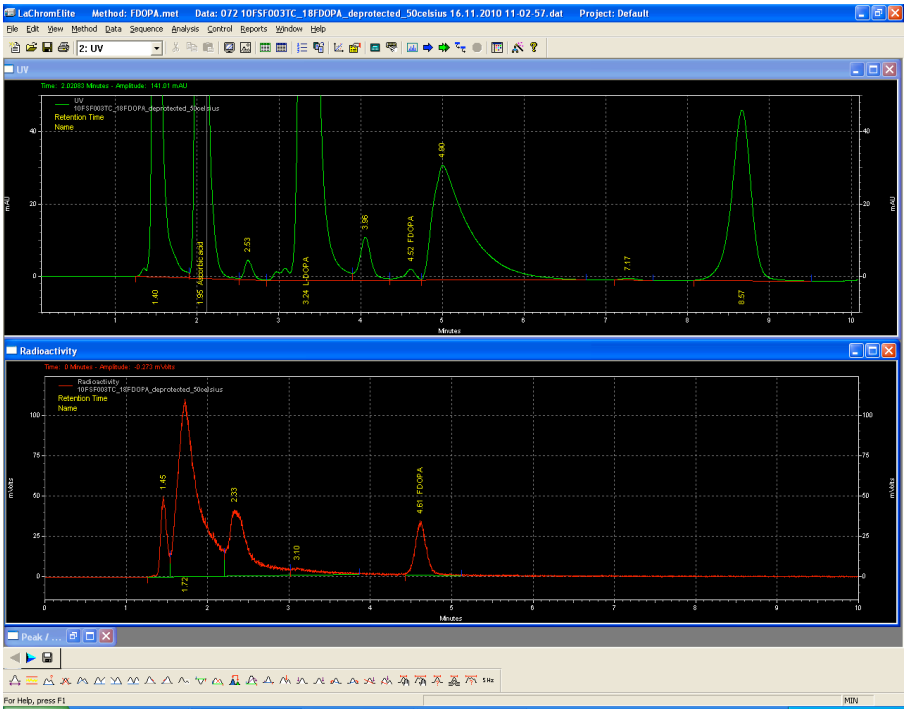


Figure A. Crude reaction mixture of 6-[^{18}F]Fluoro-L-DOPA analysed by HPLC using System C. **Green**: UV absorption at 280 nm. Product retention time: 4.52 min. **Red**: Radioactivity. Product retention time: 4.61 min.

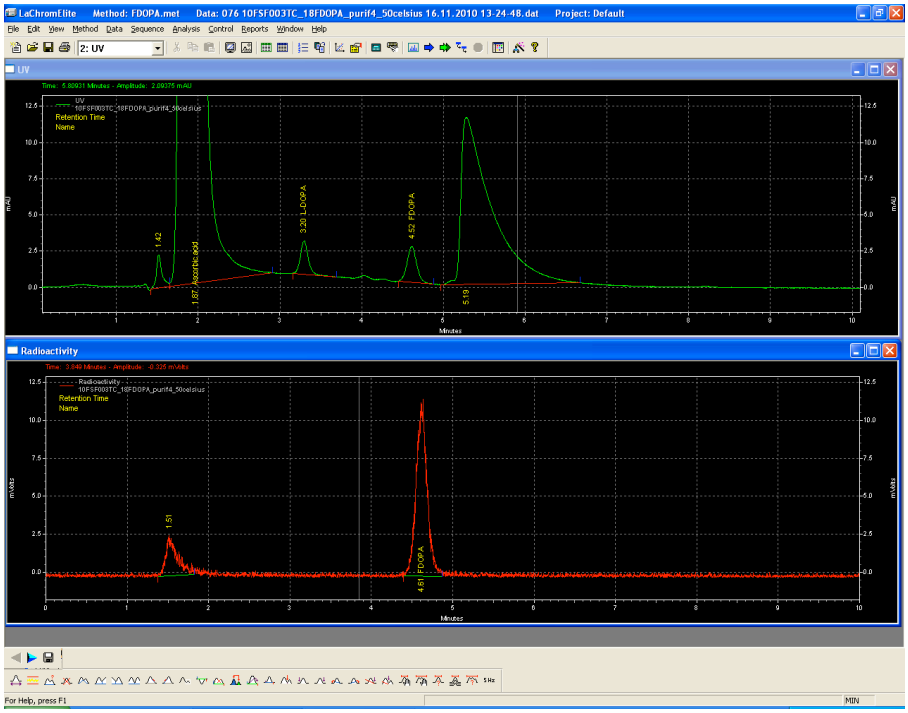


Figure B. After preparative HPLC separation of 6-[^{18}F]-Fluoro-L-DOPA using System C. **Green**: UV absorption at 280 nm. Product retention time: 4.52 min. **Red**: Radioactivity. Product retention time: 4.61 min.

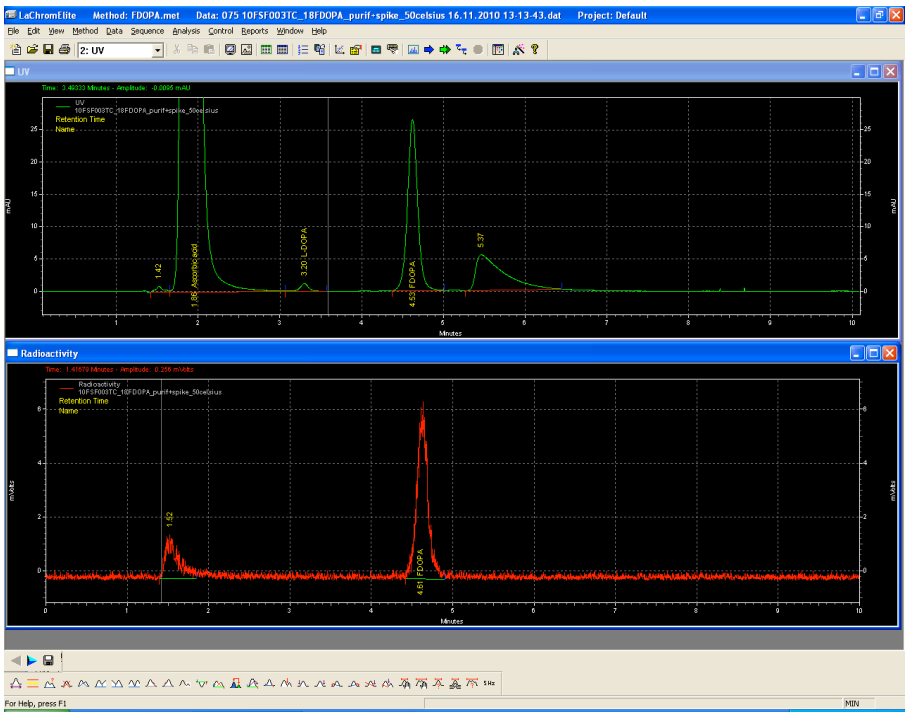
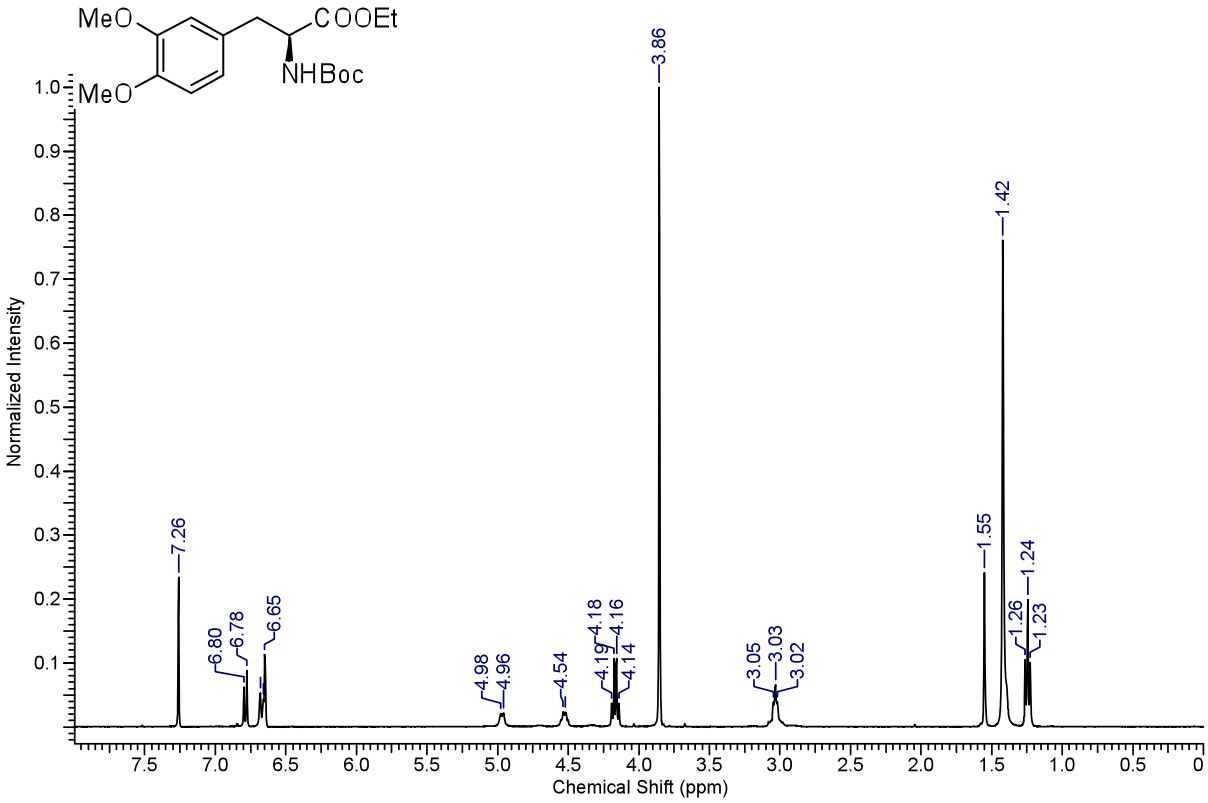


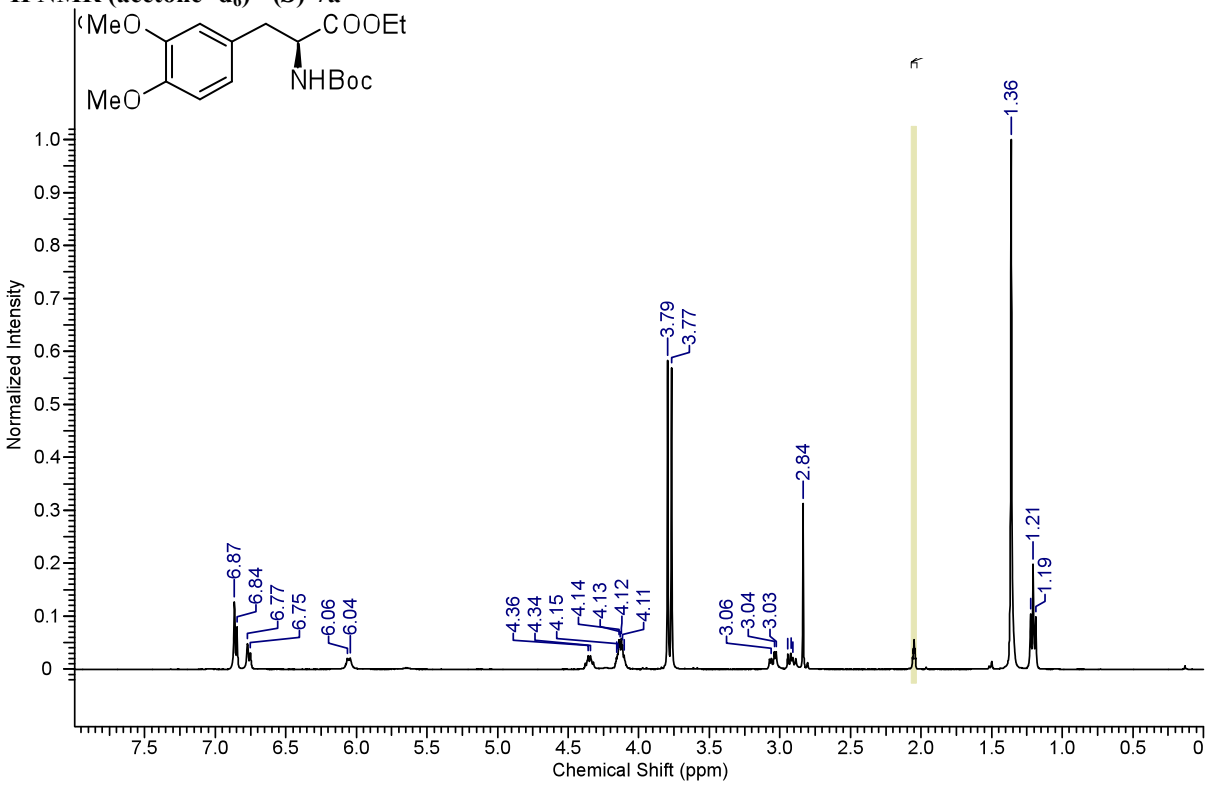
Figure C. 6-[^{18}F]-Fluoro-L-DOPA after preparative HPLC separation co-injected with authentic 6-Fluoro-L-DOPA using System C. **Green**: UV absorption at 280 nm. Product retention time: 4.52 min. **Red**: Radioactivity. Product retention time: 4.61 min.

8. NMR spectra of novel compounds

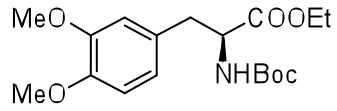
^{1}H NMR ($CDCl_3$) – (*S*)-7a

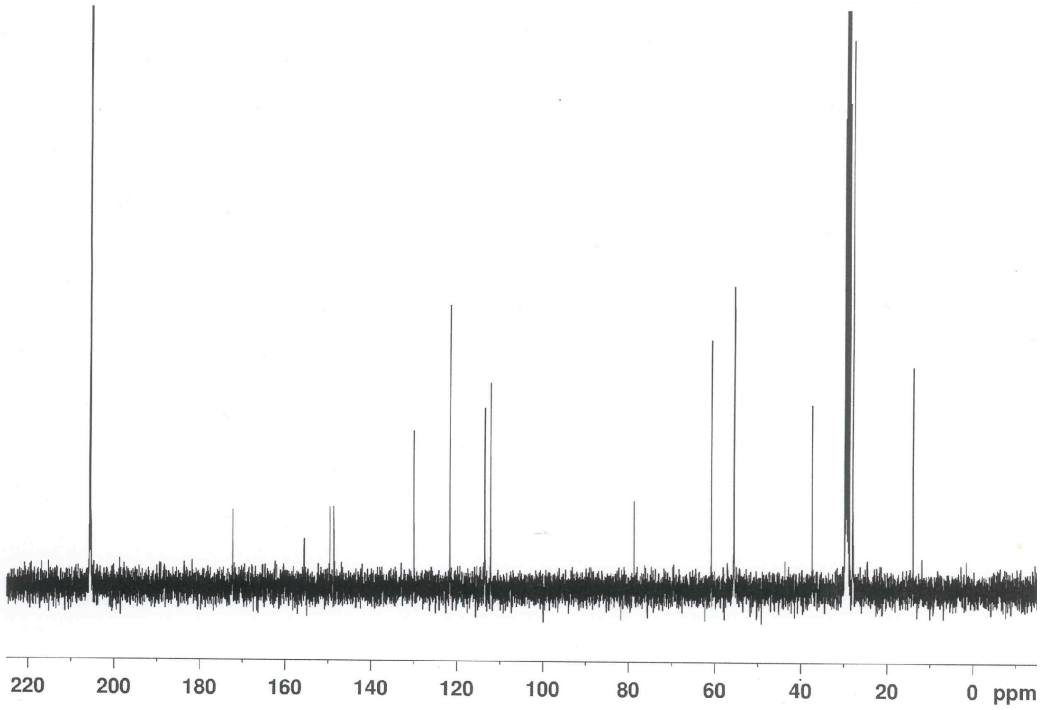


^{1}H NMR (acetone- d_6) - (*S*)-7a

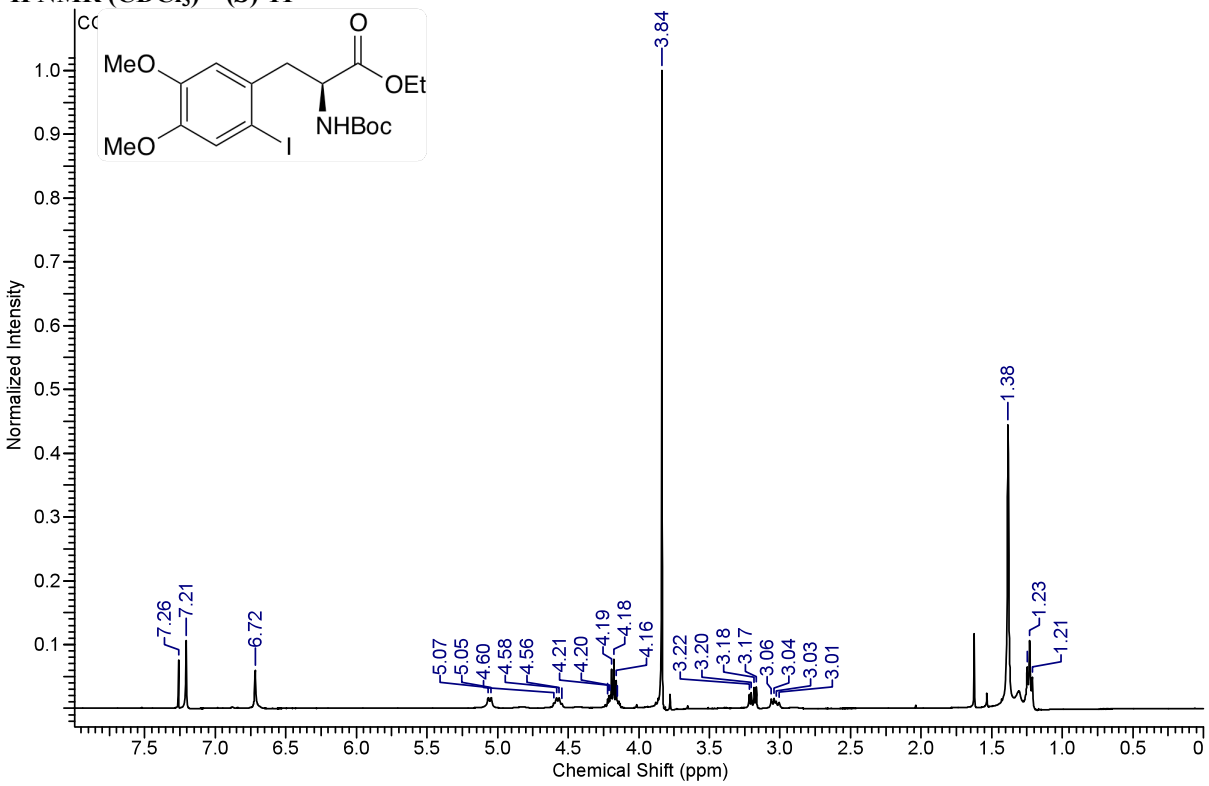


^{13}C NMR (acetone- d_6) - (*S*)-7a

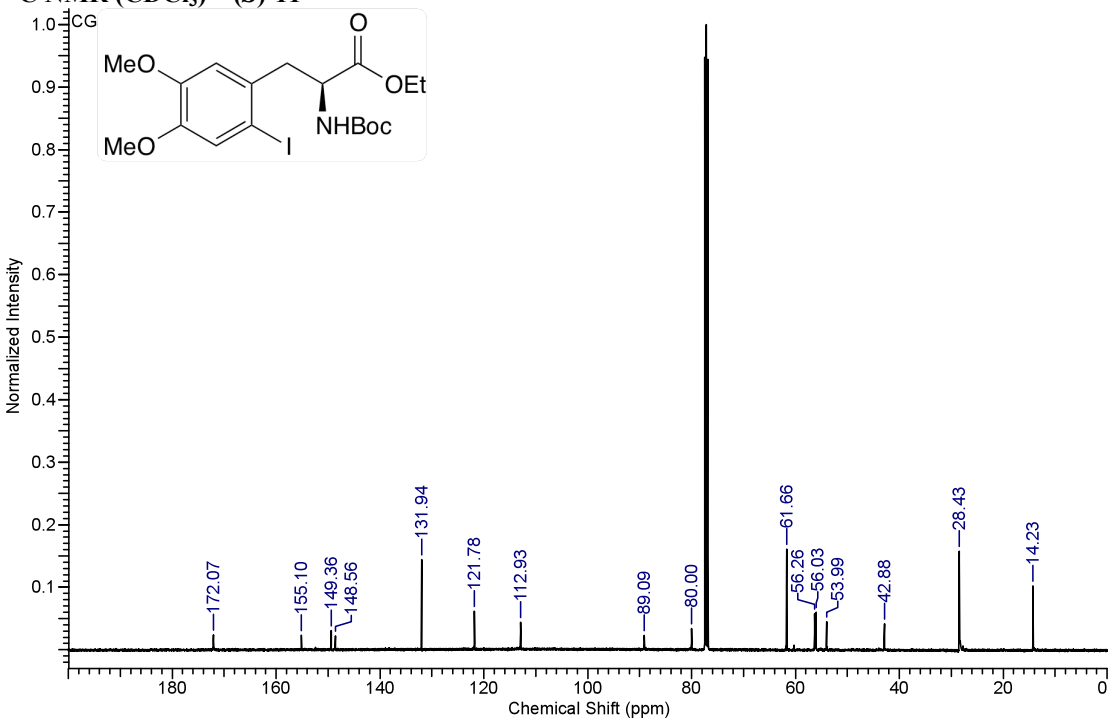




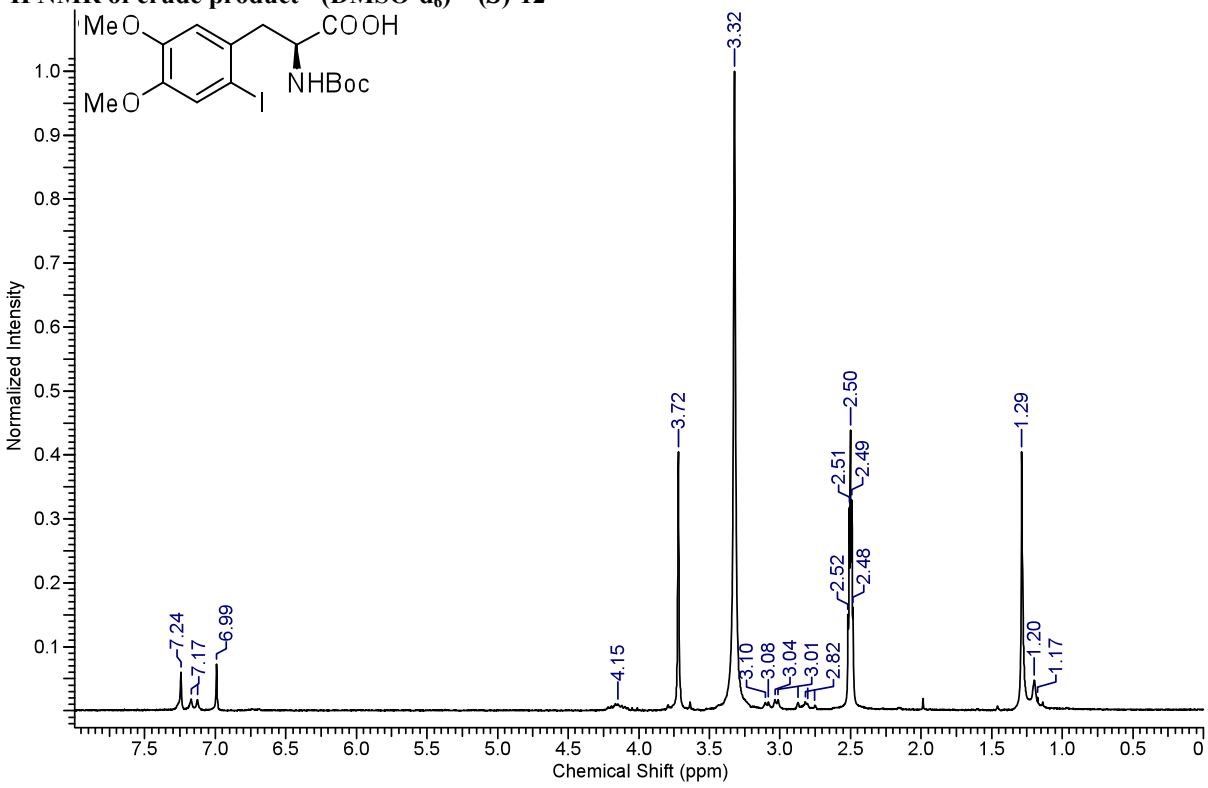
^{1}H NMR ($CDCl_3$) – (*S*)-11



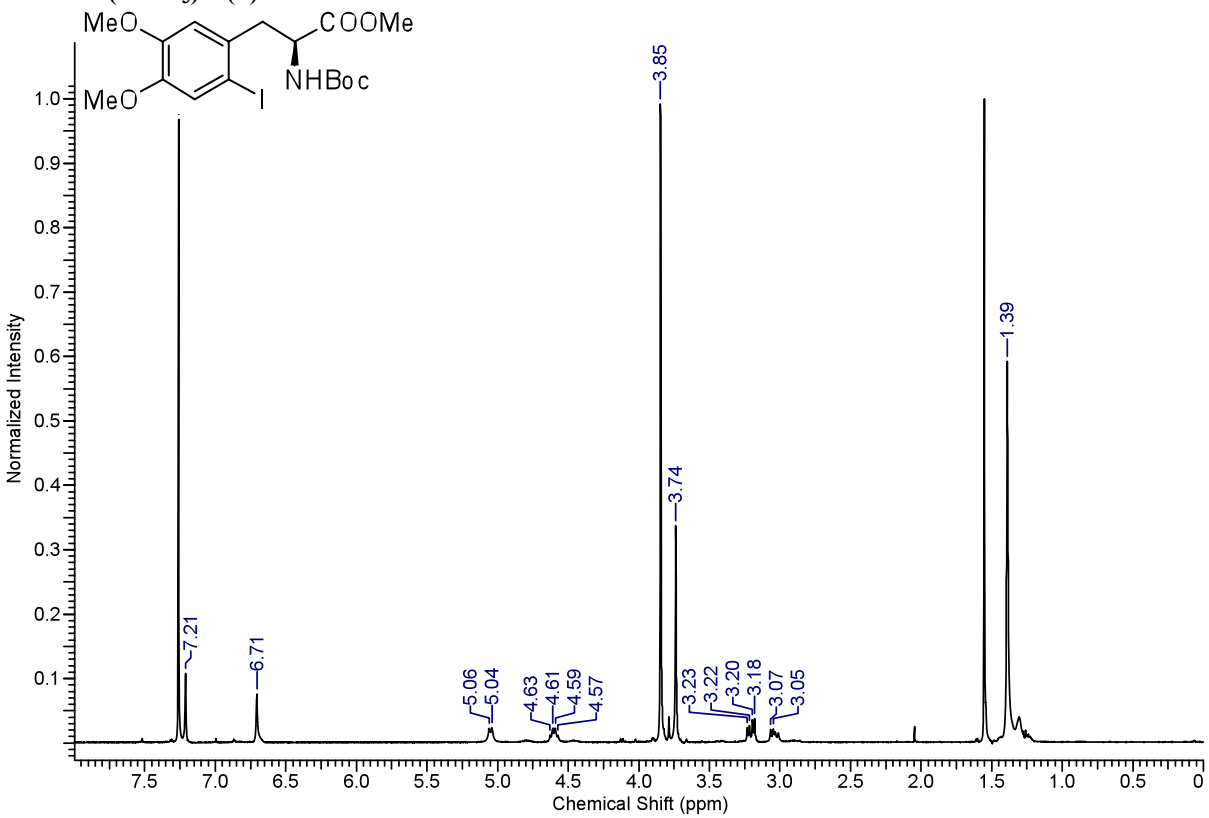
^{13}C NMR ($CDCl_3$) – (*S*)-11



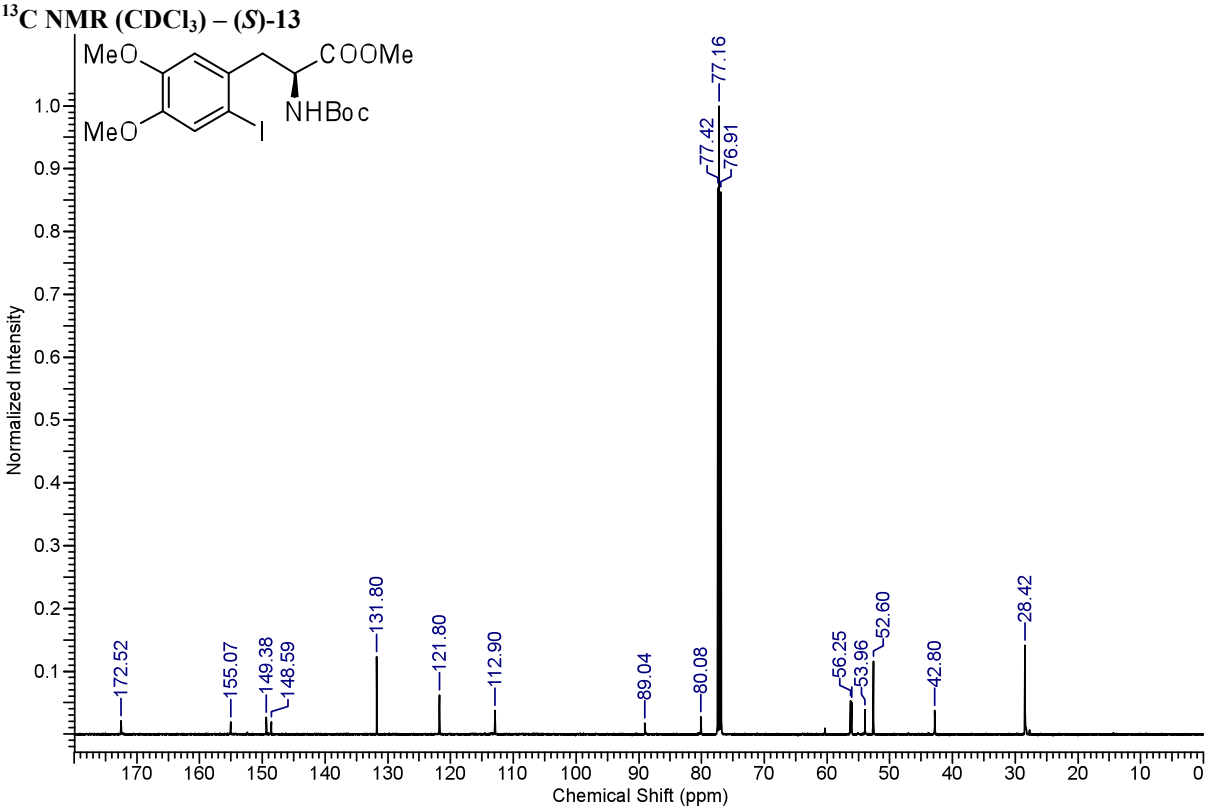
^{1}H NMR of crude product - ($DMSO\text{-}d_6$) – (*S*)-12



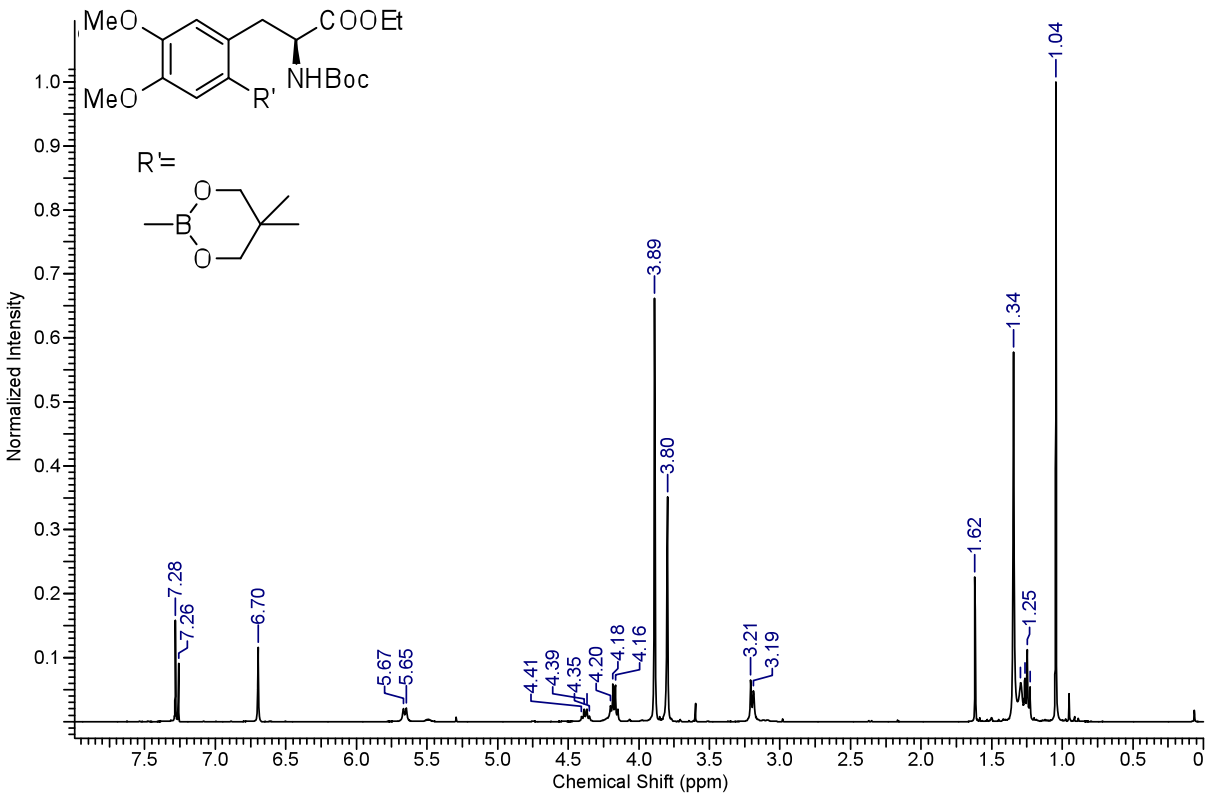
^{1}H NMR ($CDCl_3$) – (*S*)-13



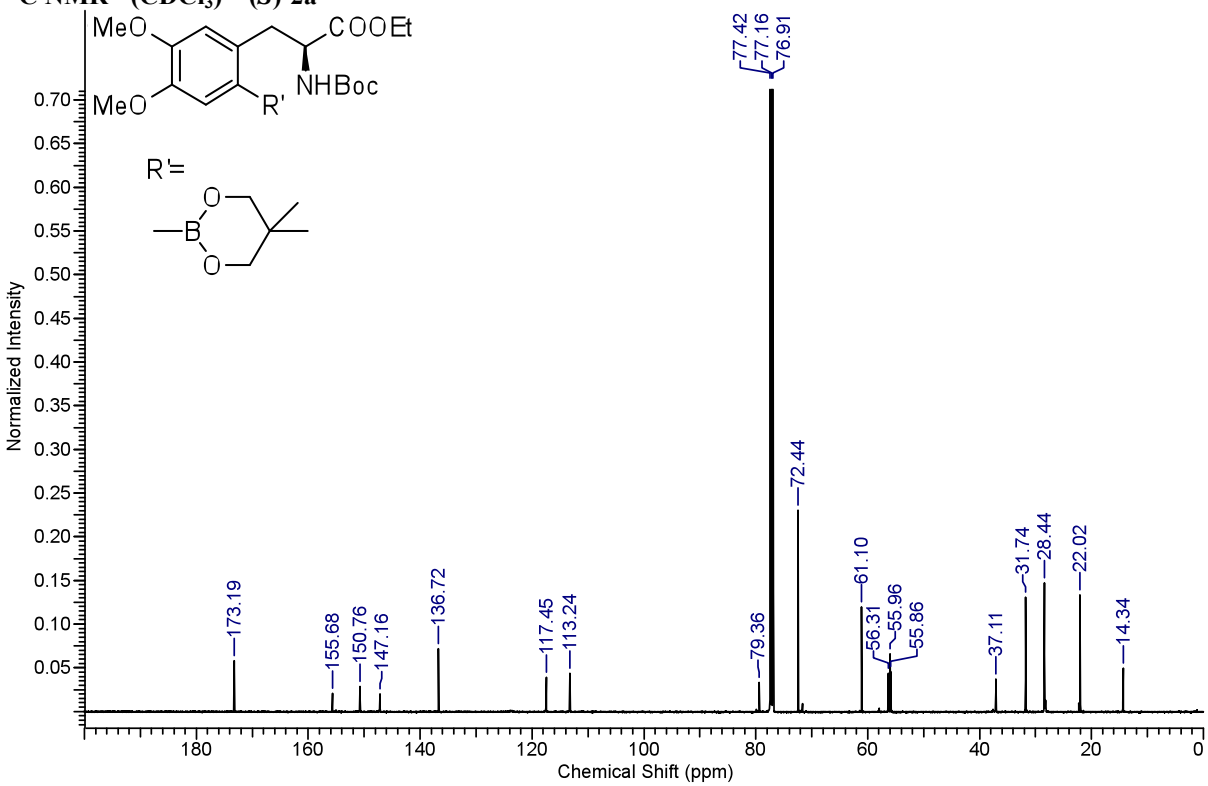
^{13}C NMR ($CDCl_3$) – (*S*)-13



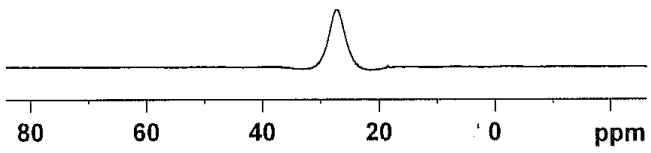
^{1}H NMR - ($CDCl_3$) – (*S*)-2a



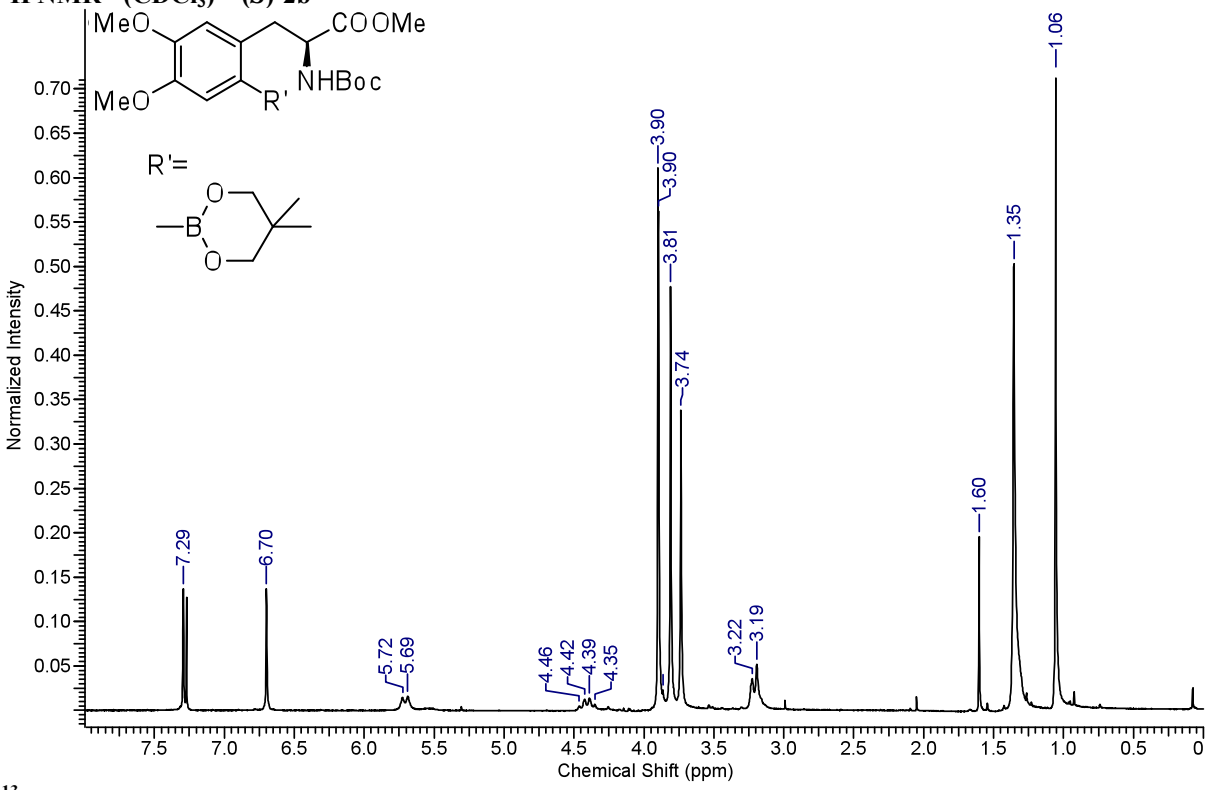
^{13}C NMR - ($CDCl_3$) – (*S*)-2a



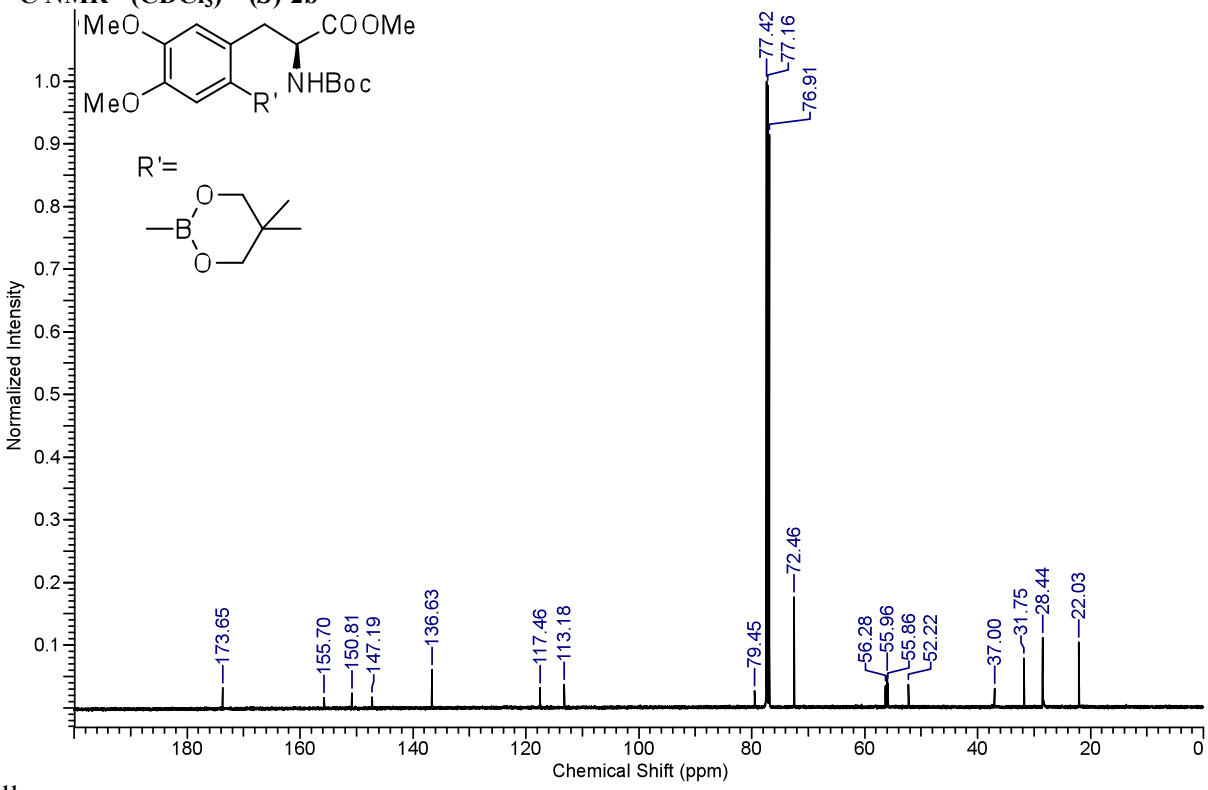
^{11}B NMR - ($CDCl_3$) – (*S*)-2a



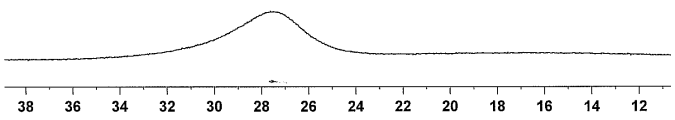
^{1}H NMR - ($CDCl_3$) – (*S*)-2b



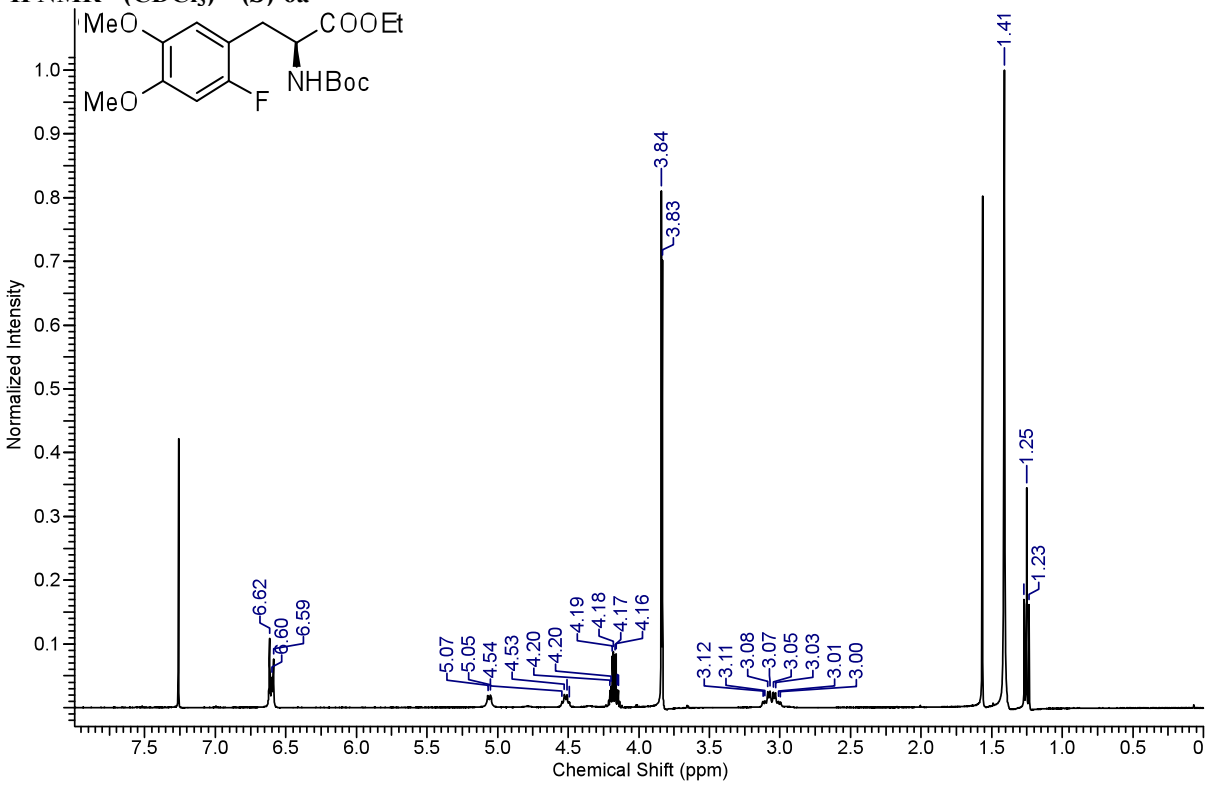
^{13}C NMR - ($CDCl_3$) – (*S*)-2b



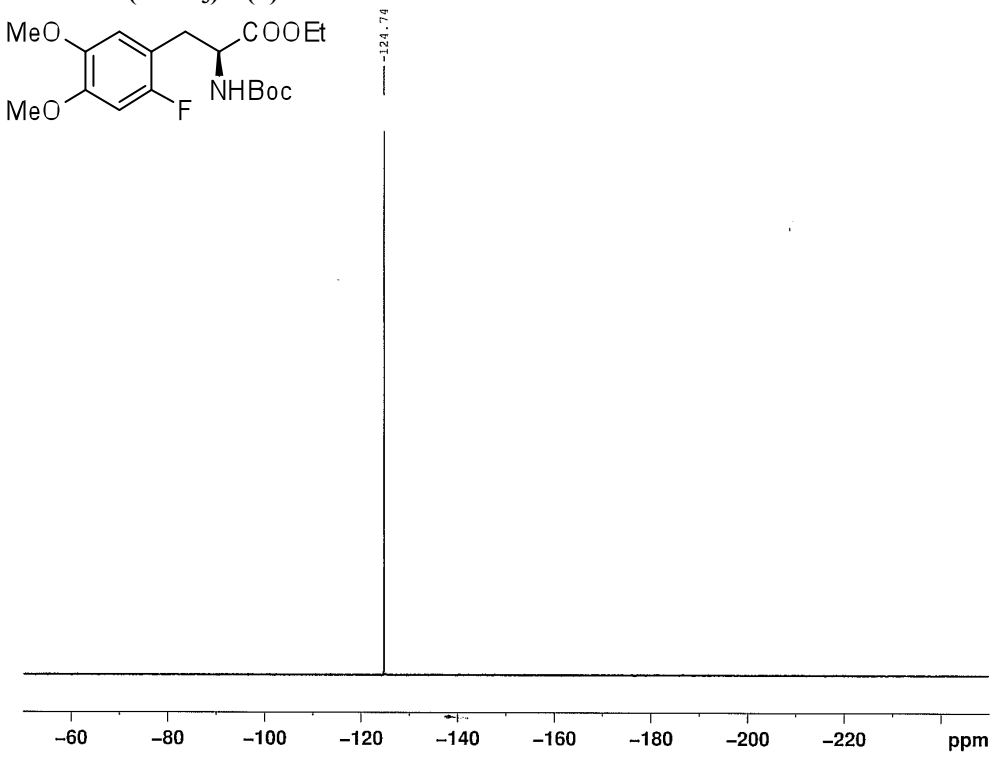
^{11}B NMR - ($CDCl_3$) – (*S*)-2b



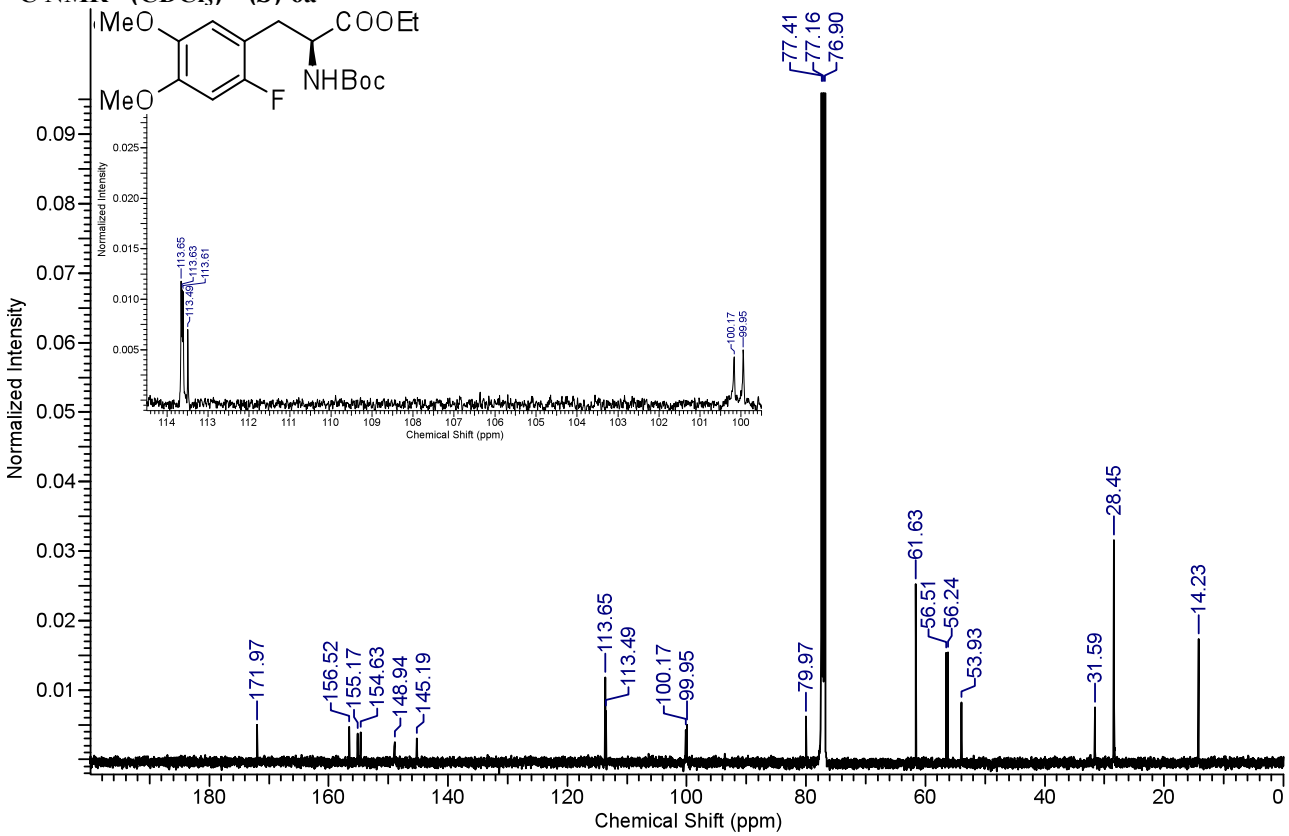
^{1}H NMR - ($CDCl_3$) – (*S*)-6a



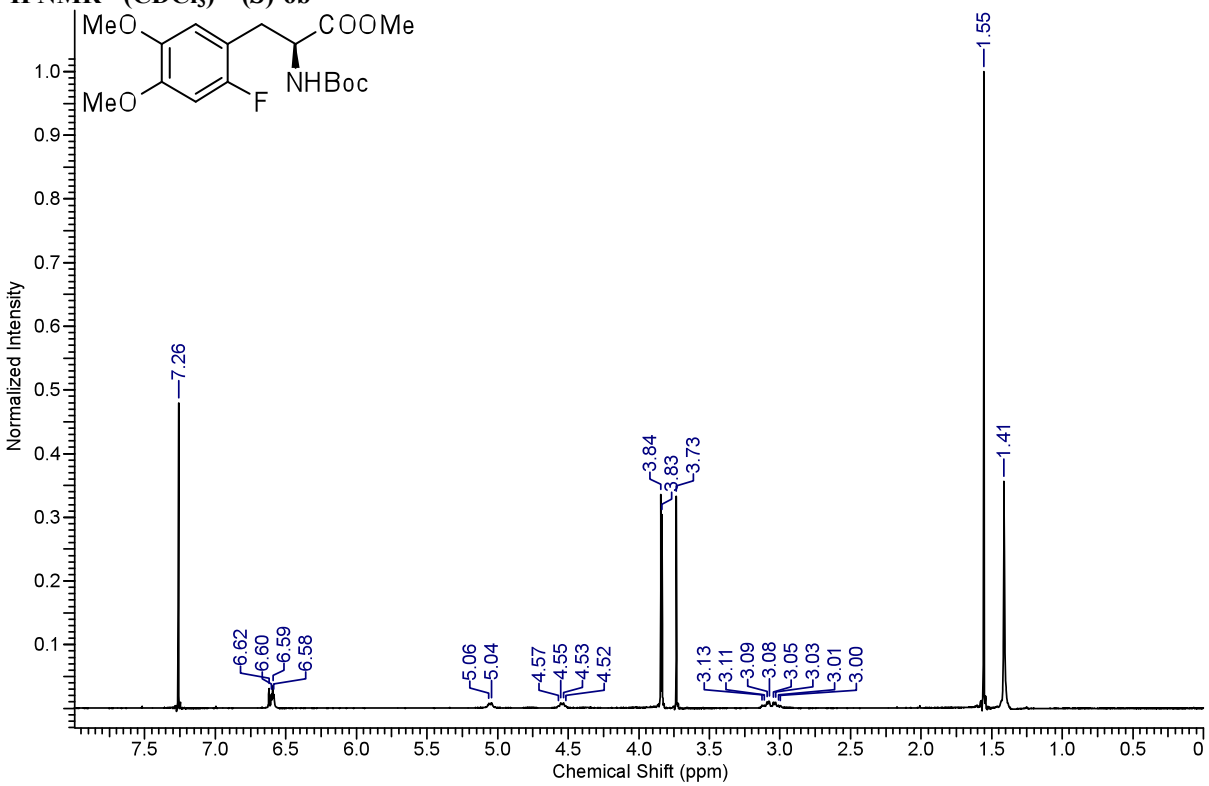
^{19}F NMR - ($CDCl_3$) – (*S*)-6a



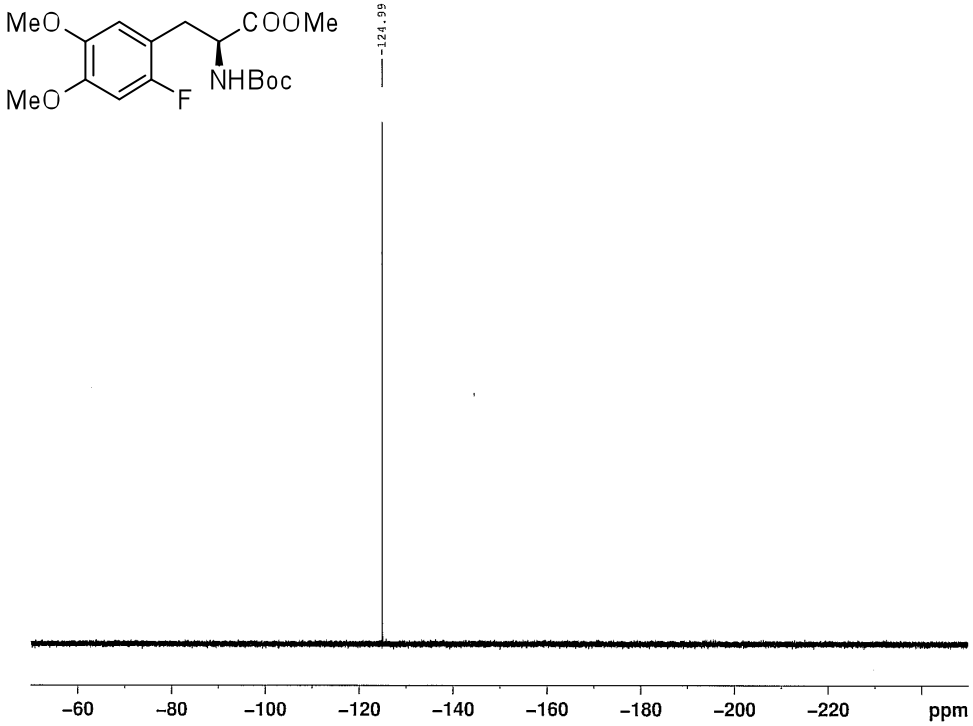
^{13}C NMR - ($CDCl_3$) – (*S*)-6a



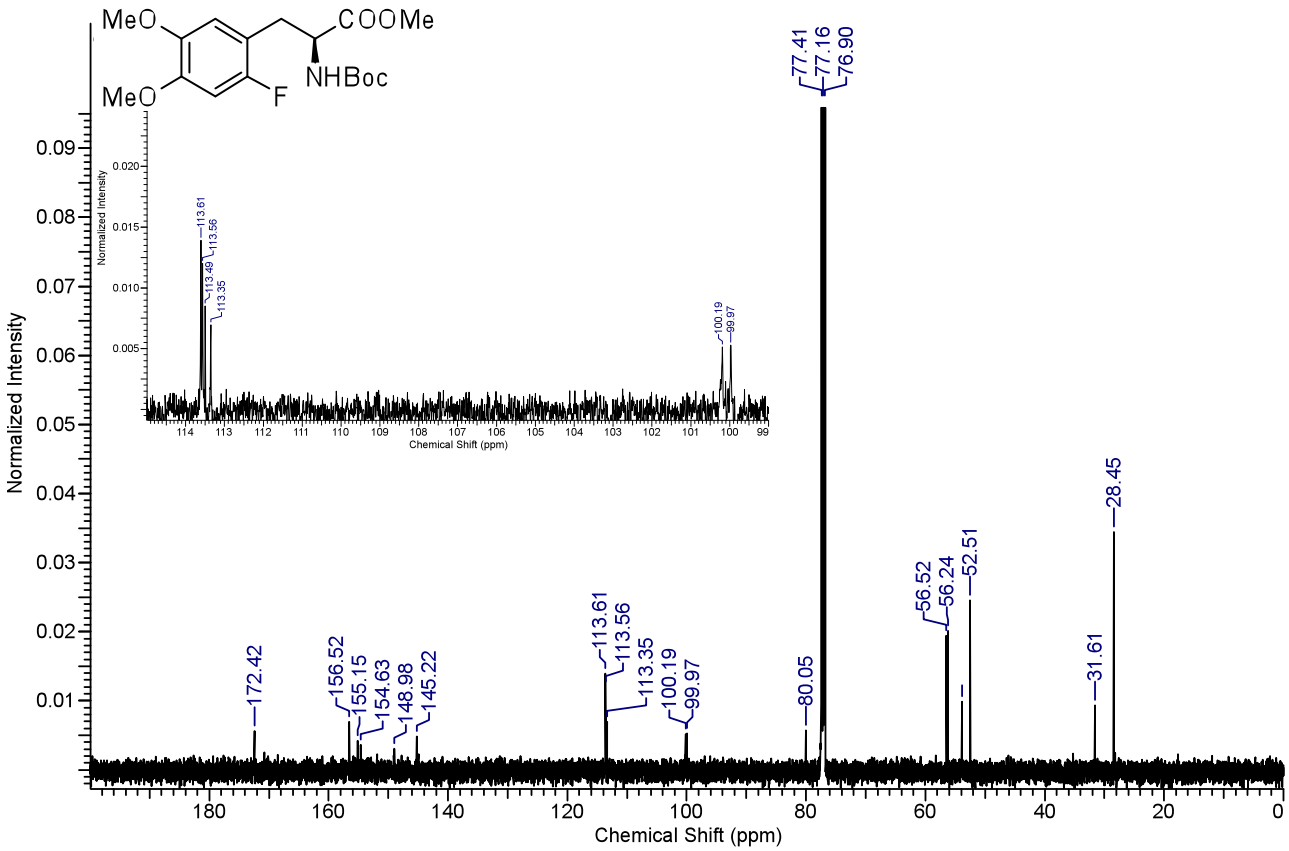
^{1}H NMR - ($CDCl_3$) – (*S*)-6b



^{19}F NMR - ($CDCl_3$) – (*S*)-6b



^{13}C NMR - ($CDCl_3$) – (*S*)-6b



9. References

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