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TETRAHEDRON: *ASYMMETRY*

Convenient syntheses of 2-, 5- and 6-fluoro- and 2,6-difluoro-L-DOPA

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Abstract—Alkylation under phase transfer conditions of the chiral glycine synthon **2** (prepared from the commercially available Oppolzer chiral sultam) with fluorinated analogues of 3,4-dimethoxybenzyl chloride proceeded with high diastereoselectivity. Hydrolysis of the Schiff base, removal of the chiral auxiliary and HBr demethylation produced 2-, 5-, 6-fluoro- and 2,6-difluoro-L-DOPA in e.e. of >99%. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

[^{18}F]-Radiolabeled 2-(2-Fluoro-4,5-dihydroxyphenyl)-L-alanine (6-[^{18}F]fluoro-L-DOPA), an in vivo precursor of 6-[^{18}F]fluorodopamine, is used extensively as a PET-scanning agent to quantify regional dopamine activity in the central nervous system.[1]

Other ring-fluorinated analogues of DOPA have also been investigated as potential PET-scanning agents, but have not proven as useful because of problematic pharmacodynamics.[2] Although there is ample evidence for the facile enzymatic conversion of 6-fluoro-L-DOPA to 6-fluorodopamine,[3] there appears to have been no detailed comparative kinetic study of the isomeric fluoro-DOPAs toward aromatic amino acid decarboxylase (AADC).[4] Furthermore, recent reports have provided details of possible alternative reaction paths available to L-DOPA that relate to the decarboxylase mechanism or that may contribute to L-DOPA-induced side effects. These include a Pictet–Spengler reaction with pyridoxal phosphate,[5] the AADC cofactor, and Maillard reaction between L-DOPA and D-glucose.[6] Such reactions that involve alkylation of the electron-rich aromatic ring could be influenced significantly by the altered electronic properties caused by fluorine substitution.

The above considerations prompted us to undertake a detailed examination of the effects of fluorine substitution on the enzymatic decarboxylation of L-DOPA. Parameters to be examined are the effects of fluorination on K_m, V_{max}, and the propensity to participate in a competing Pictet–Spengler reaction. The kinetic analyses and examination of any competing condensation and decarboxylation reactions require working with the pure L-isomers, since the unnatural D-enantiomers could take part in the former but not the latter process. As part of this effort, we describe in this paper the stereoselective syntheses of 2-, 5-, 6-, and 2,6-difluoro-L-DOPA **1a**–**d** using an efficient diastereoselective alkylation of a chiral glycine synthon.

As a reflection of the extensive biological applications of fluoro-DOPAs, many syntheses of these compounds have been reported. In 1957 Kaiser and Burger reported the synthesis of 2-fluoro-D,L-DOPA using an acetamidomalonic ester synthesis.[7] To study the behavior of fluoro-DOPAs as substrates for catechol *O*-methyl transferase, we synthesized 2-, 5-, and 6-fluoro-D,L-DOPA using a similar strategy.[8] Both normal and radiofluorinated enantioselective syntheses of 6-fluoro-L-DOPA, by side-chain elaboration of fluorinated precursors, have been reported.[9] Several procedures have been developed for direct electrophilic fluorination of L-DOPA and derivatives to prepare [^{18}F]fluoro-L-DOPAs.[10] Radiofluorodestannylation has also provided a regioselective route to 6-[^{18}F]fluoro-L-DOPA.[11]

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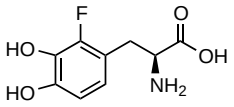
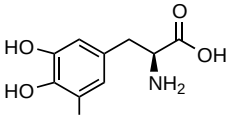
We report herein a new, convenient, and highly efficient procedure for the preparative-scale syntheses of 2-, 5- and 6-fluoro-L-DOPA, and 2,6-difluoro-L-DOPA analogs **1a-d**. We provide complete characterization of these compounds, including, to our knowledge for the first time, specific rotation values for these compounds.



1a



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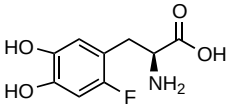
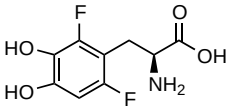


1c



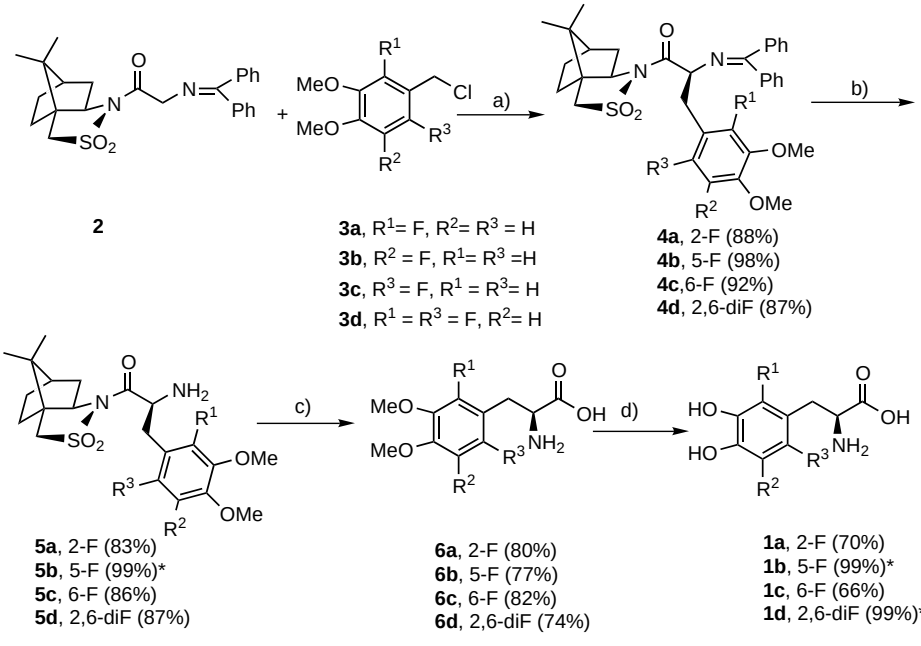
1d

2. Results and discussion

There are now many procedures available for the syntheses of enantiomers of α-amino acids, including both enantioselective and diastereoselective strategies.[12] We chose a diastereoslective procedure based on the readily available fluorinated benzyl chlorides **3a–d** and the convenience of preparation of chiral glycine synthon **2** (Scheme 1). This is prepared from the commercially available Oppolzer chiral sultam. The ability of the chiral amide **2**, first reported by Chassaing's group,[13a] to direct highly diastereoselective alkylations has been demonstrated in several studies.[13]

A number of the starting fluorinated dimethoxybenzylchlorides have been prepared previously. 4-(Chloromethyl)-5-fluoroveratrole **3c** is readily obtained by one-step chloromethylation of commercial 4-fluoroveratrole,[14] 4-(chloromethyl)-3-fluoroveratrole **3a** is readily obtained by one-step chloromethylation of 3-fluoroveratrole, the methylation product of commercial 2-fluoro-6-methoxyphenol,[15] whereas **3b** and **3d** are prepared from the corresponding benzaldehydes by reduction to the alcohol and treatment with hydrochloric acid. The synthon **2** was synthesized according to the literature.[12]

The preparation of 6-fluoro-L-DOPA **1c** illustrates the procedure. Using solid–liquid PTC reaction condition[13d] (3 eq. K_2CO_3, 0.1 eq. n-Bu_4NBr and CH_3CN at 50°C), chiral amide **2** readily reacted with 4-(chloromethyl)-5-fluoroveratrole **3c**[14] to furnish alkylation product **4c** in 92% yield. ^1H NMR analysis indicated **4c** was formed with >97% diastereoisomeric excess (d.e.). This was purified by one recrystalllization (CH_2Cl_2/Hexane) to give **3c** with d.e. ~100%. The absolute configuration of the newly formed carbon center was assumed as *S*-configuration based on literature precedence. Compound **4c** was hydrolyzed with 1 M HCl at room temperature to remove the benzophenone group to give an 86% yield of amine **5c**. Removal of the chiral auxiliary was readily accomplished by treatment with 2.5 M LiOH/THF at 0°C to give amino acid **6c** (82%), isolated by precipitation from the neutralized reaction mixture. Heating **6c** (145°C) in 48% HBr effected hydrolysis of the methyl ethers. After evaporation of water and acid the residue was redissolved in water. Neutralization to pH 4–5 by $NaHCO_3$ and cooling to 0°C caused precipitation of the free amino acid. The suspension was filtered to give a 66% yield of 6-fluoro-L-DOPA **1c** (overall yield: 43%).



Scheme 1. *Reagents and conditions*: (a) 3.0 eq. K_2CO_3, cat. Bu_4NBr, CH_3CN, 50°C; (b) 1 M HCl, CH_2Cl_2, rt; (c) 2.5 M LiOH, H_2O/THF, 0°C; (d) 48% HBr, 145°C, 1 h. *Yields without further purification.

Although the literature gave no indication that racemization occurs when this hydrolysis procedure is used, we were concerned about the use of strong acid and high temperature (145°C). Nonetheless, we determined by chiral HPLC that the e.e. value of 6-fluoro-L-DOPA was >99% (see Section 4).

Essentially the same results were obtained when the sequence was initiated with **3a**, **3b**, and **3d.** The corresponding amino acids, 2-, 5-fluoro and 2,6-difluoro-L-DOPA **1a, 1b, 1d**, were obtained in similar overall yield using the same sequence (Scheme 1). Following removal of the chiral auxiliary of **5a**, the free amino acid **6a** was not precipitated by simple neutralization, so an ion exchange column was used (see Section 4).

3. Conclusion

In conclusion, the synthetic pathway described in this paper is an excellent practical method for the synthesis of the 2-, 5-, 6-fluoro- and 2,6-difluoro-L-DOPAs. The amino acids are obtained in high overall yield (43% for **1c** and similar yields for other three fluorinated **1a,b,d**) and with excellent enantiomeric purity (>99%). These analogues are now being investigated as substrates for aromatic amino acid decarboxylase.

4. Experimental section

4.1. General

Melting points are uncorrected. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded at 300.1, 75.5 and 282.2 MHz. Chemical shifts (δ) of protons and carbons are relative to TMS (0 ppm), and the fluorine shifts are relative to trifluoroacetic acid (0 ppm), all in ppm. Coupling constants are presented in Hz. The solvent is $CDCl_3$ unless otherwise noted. Low resolution MS (LRMS) was performed with chemical ionization under ammonia gas. High resolution MS (HRMS) was done with FAB ionization under xenon gas. Silica gel Merck 60 (0.040–0.063 mm) was used for column chromatography, Uniplate™ GF (Analteck) was used for preparative TLC. HPLC was performed on a chiral phase column Crownpak® CR (Diacel Ltd., 250×4 mm, equipped with a precolumn 80×4 mm, aq. $HClO_4$ pH = 1.6, flow rate 1.0 mL/min). All reagents and dry solvents were purchased from Aldrich if not otherwise indicated and used without further purification or drying.

4.1.1. 1-Fluoro-2,3-dimethoxy-5-chloromethylbenzene, 3b. A solution of 5-fluoroveratraldehyde[16] (1.64 g, 8.91 mmol) in THF (15 mL) was added dropwise to a suspension of $NaBH_4$ (0.674 g, 17.8 mmol) in THF (30 mL) and the mixture was stirred for 1 h at 40°C. Excess $NaBH_4$ was decomposed by the addition of water and a few crystals of NaH_2PO_4. THF and water were removed by rotary evaporation, and the residue was extracted three times with ether. The ether layer was dried over $CaCl_2$ and evaporated yielding the crude alcohol of sufficient purity for the next step. Without further purification, the alcohol was treated with concentrated HCl (11.8 mL) at 110°C for 30 min. After standard extractive work-up, the residue was purified with flash column chromatography (eluent: hexane:ethyl acetate = 6:1) to give compound **3c** as a clear oil (1.22 g, 78%, two steps). ^{1}H NMR: 6.77 (1H, dd, 2.1, 10.8), 6.73 (1H, br. s), 4.51 (2H, s), 3.93 (3H, s), 3.90 (3H, s). HRMS calcd. For $C_9H_{10}ClFO_2$: 204.0353. Found: 204.0355.

4.1.2. 2-Chloromethyl-1,3-difluoro-4,5-dimethoxy-benzene, 3d. Using the procedure described for the preparation of **3c**, 2,6-difluoroveratraldehyde[17] (800 mg, 3.97 mmol) gave **3d** (617 mg, 70%). ^{1}H NMR: 6.50 (1H, dd, 2.1, 11.1), 4.63 (1H, s), 3.89 (3H, s), 3.87 (3H, s). HRMS calcd. For $C_9H_9F_2ClO_2$: 202.0259. Found: 202.0252.

4.1.3. (2*R*)-*N*-[(2*S*)-2-((Diphenylmethylidene)amino)-2-(2′-fluoro-4′,5′-dimethoxybenzyl)-ethan-1-oyl]bornane-10,2-sultam, 4c. To a stirred mixture of potassium carbonate (1.65 g, 12.0 mmol) and tetrabutylammonium bromide (132 mg, 0.4 mmol) in anhydrous acetonitrile (50 mL) was added synthon **2** (1.75 g, 4.0 mmol) and 4-(chloromethyl)-5-fluoroveratrole **3c** (1.64 g, 8.0 mmol). The resulting mixture was stirred for 10 h at 50°C (TLC monitoring), then filtered, and the filtrate evaporated under vacuum. The residue was chromatographed on silica gel under pressure, eluting with hexane:ethyl acetate mixtures of increasing polarity, from 9:1 to 2:1. The product **4c** was further purified by recrystallization from dichloromethane and hexane (2.22 g, 92%). Mp 196.5–198.5°C $[\alpha]_D^{20} = -106.5$ (*c* 0.68, $CHCl_3$). ^{1}H NMR: 7.65 (2H, d, 7.2), 7.26–7.45 (6H, m), 6.94–6.96 (2H, m), 6.44–6.50 (2H, m), 5.08 (1H, t, 7.2), 3.90 (1H, dd, 4.8, 7.5), 3.78 (3H, s), 3.62 (3H, s), 3.34 (2H, s), 3.23 (1H, dd, 6.6, 12.9), 3.06 (1H, dd, 7.8, 12.9), 2.05 (1H, dd, 7.8, 13.2), 1.77–1.92 (4H, m), 1.29–1.41 (2H, m), 0.88 (3H, s), 0.78 (3H, s). ^{13}C NMR: 171.9, 170.9, 155.4 (d, 240.6, C-F), 148.5 (d, 9.8), 144.9, 139.8, 135.8 (d, 13.6), 135.8, 130.4, 129.1, 128.6, 128.4, 128.2, 128.0, 114.1 (d, 9.6), 113.5 (d, 5.4), 99.7 (d, 28.1), 66.4, 65.2, 56.2, 56.0, 53.3, 48.5, 47.8, 44.7, 38.4, 33.9, 32.9, 26.6, 20.4, 20.0. ^{19}F NMR: −48.81 (t, 11.0). HRMS calcd. For $C_{34}H_{38}FN_2O_5S$: 605.2485 (M+1). Found: 605.2498.

4.1.4. (2*R*)-*N*-[(2*S*)-2-((Diphenylmethylidene)amino)-2-(2′-fluoro-3′,4′-dimethoxybenzyl)-ethan-1-oyl]bornane-10,2-sultam (4a). Prepared as for **4c**, the product **4a** was obtained in 88% yield as a single diastereoisomer. Mp 185–187°C $[\alpha]_D^{20} = -107.3$ (*c* 0.24, $CHCl_3$). ^{1}H NMR: 7.65 (2H, d, 6.6), 7.26–7.50 (6H, m), 6.96–7.10 (2H, m), 6.70 (1H, t, 8.4), 6.49 (1H, d, 9.0), 5.06 (1H, t, 7.2), 3.89 (1H, dd, 4.5, 7.2), 3.78 (3H, s), 3.77 (3H, s), 3.31 (2H, s), 3.27 (1H, dd, 7.2, 13.2), 3.02 (1H, dd, 6.6, 13.2), 2.04 (1H, dd, 7.5, 13.5), 1.75–1.84 (4H, m), 1.26–1.39 (2H, m), 0.87 (3H, s), 0.72 (3H, s). ^{13}C NMR: 171.9, 171.0, 155.1 (d, 248.1, C-F), 152.7 (d, 4.6), 139.8, 137.1 (d, 13.7), 135.8, 130.4, 129.1, 128.7, 128.3, 128.2, 128.0, 125.3 (d, 5.7), 117.4 (d, 15.1), 107.1 (d, 2.9), 66.0, 65.2, 61.5 (d, 4.0), 56.4, 53.2, 48.4, 47.7,

44.7, 38.4, 34.3, 33.0, 26.6, 20.6, 20.0. ^{19}F NMR: –49.05 (t, 11.0). HRMS calcd. For $C_{34}H_{38}FN_2O_5S$: 605.2485 (M+1). Found: 605.2493.

4.1.5. (2*R*)-*N*-[(2*S*)-2-((Diphenylmethylidene)amino)-2-(5′-fluoro-3′,4′-dimethoxybenzyl)-ethan-1-oyl]bornane-10,2-sultam (4b). Prepared as for **4c**, the product **4b** was obtained in 98% yield as a single diastereoisomer. Mp 217°C dec. $[\alpha]_D^{20}=-121.5$ (*c* 0.59, $CHCl_3$). ^{1}H NMR: 7.64–7.68 (2H, m), 7.27–7.41 (6H, m), 6.85–6.88 (2H, m), 6.43 (1H, dd, 2.1, 11.1), 6.30 (1H, t, 1.8), 4.99 (1H, dd, 6.0, 7.8), 3.92 (1H, dd, 4.8, 7.8), 3.86 (3H, d, 1.2), 3.62 (3H, s), 3.36 (2H, s), 3.29 (1H, dd, 5.4, 12.6), 2.30 (1H, dd, 8.1, 12.6), 2.07 (1H, dd, 7.8, 14.1), 1.79–1.93 (4H, m), 1.31–1.43 (2H, m), 0.91 (3H, s), 0.87 (3H, s). ^{13}C NMR: 171.3, 170.7, 155.2 (d, 241.6, C–F), 152.8 (d, 5.7), 139.1, 135.4, 132.3 (d, 9.1), 130.1, 128.6, 128.2, 127.8 (d, 5.7), 127.7, 110.0, 109.7, 108.9, 66.9, 64.9, 61.2 (d, 3.5), 55.6, 52.9, 48.1, 47.4, 44.3, 40.8, 38.0, 32.5, 26.1, 20.1, 19.5. ^{19}F NMR: -56.07 (d, 10.7). HRMS calcd. For $C_{34}H_{38}FN_2O_5S$: 605.2485 (M+1). Found: 605.2508.

4.1.6. (2*R*)-*N*-[(2*S*)-2-((Diphenylmethylidene)amino)-2-(2′,6′-difluoro-3′,4′-dimethoxybenzyl)-ethan-1-oyl]-bornane-10,2-sultam (4d). Prepared as for 4a, the product 4d was obtained in 87% yield as a single diastereoisomer. Mp 187–189 °C $[\alpha]_D^{20}=-90.6$ (c 0.40, $CHCl_3$). ^{1}H NMR: 7.61–7.66 (2H, m), 7.24–7.45 (6H, m), 7.12–7.15 (2H, m), 6.33 (1H, dd, 1.8, 10.8), 5.12 (1H, t, 7.2), 3.90 (1H, dd, 4.8, 7.8), 3.78 (3H, s), 3.74 (3H, s), 3.32 (2H, s), 3.36 (1H, dd, 7.8, 13.2), 2.92 (1H, dd, 6.6, 13.2), 2.06 (1H, dd, 7.8, 13.5), 1.76–1.94 (4H, m), 1.28–1.40 (2H, m), 0.88 (3H, s), 0.78 (3H, s). ^{13}C NMR: 171.7, 171.0, 157.0 (d, 242.5, C-F), 155.2 (d, 245.9, C-F), 152.7 (dd, 6.8, 11.9), 139.7, 135.6, 134.0 (dd, 5.2, 14.3), 130.3, 129.0, 128.7, 128.3, 128.2,127.9, 105.0 (t, 19.9), 95.6 (d, 25.1), 65.3, 64.2, 61.6, 56.3, 53.2, 48.3, 47.7, 44.7, 38.2, 32.9, 28.0, 26.5, 20.4, 19.9. ^{19}F NMR: –41.65 (d, 12.4), –54.14. HRMS calcd. For $C_{34}H_{37}F_2N_2O_5S$: 623.2391(M+1). Found: 623.2405.

4.1.7. (2*R*)-*N*-[(2*S*)-2-Amino-2-(2′-fluoro-4′,5′-dimethoxybenzyl)-ethan-1-oyl]bornane-10,2-sultam, 5c. A vigorously stirred mixture of **4c** (604 mg, 1.0 mmol) in 10 mL of dichloromethane and 10 mL of 1 M hydrochloric acid was left at room temperature for 5 h (TLC monitoring). After adding 50 mL of hexane, the two phases were separated, the aqueous layer was washed with 30 mL of diethyl ether, then was basified with sodium bicarbonate and extracted with ethyl acetate. The combined organic solvent was dried with magnesium sulfate and evaporated to dryness. After flash column chromatography (eluent: hexane:ethyl acetate = 1:2), 509 mg of product **5c** was obtained (86% of yield) as a colorless solid. Mp 65–67°C $[\alpha]_D^{20}=-15.3$ (*c* 0.27, $CHCl_3$). ^{1}H NMR: 6.76 (1H, d, 7.2), 6.58 (1H, d, 10.8), 4.32 (1H, t, 7.2), 3.79–3.87 (7H, m), 3.43 (2H, d, 3.6), 2.95 (2H, d, 7.2), 1.79–2.03 (5H, m), 1.29–1.41 (2H, m), 0.92 (3H, s), 0.82 (3H, s). ^{13}C NMR: 175.6, 155.5 (d, 239.5, C-F), 148.8 (d, 9.7), 145.2, 114.3 (d, 17.2), 113.5 (d, 5.7), 100.0 (d, 28.7), 65.2, 56.4, 56.2, 55.4, 53.2, 48.7, 47.8, 44.9, 38.3, 34.5, 33.0, 26.6, 20.5, 20.0. ^{19}F NMR: –48.93 (t, 11.0). HRMS calcd. For $C_{21}H_{30}FN_2O_5S$: 441.1859 (M+1). Found: 441.1847.

4.1.8. (2*R*)-*N*-[(2*S*)-2-Amino-2-(2′-fluoro-3′,4′-dimethoxybenzyl)-ethan-1-oyl]bornane-10,2-sultam, 5a. Prepared as described for the preparation of **5c**, the product **5a** was obtained in 83% yield as a colorless solid. Mp 152–153°C $[\alpha]_D^{20}=-10.6$ (*c* 0.5, $CHCl_3$). ^{1}H NMR: 6.87 (1H, t, 9.1), 6.59 (1H, d, 9.4), 4.32 (1H, t, 7.2), 3.78–3.90 (7H, m,) 3.42 (2H, d, 3.9), 2.96 (2H, d, 6.0), 1.79–2.05 (5H, m), 1.29–1.42 (2H, m), 0.92 (3H, s), 0.81 (3H, s). ^{13}C NMR: 175.7, 155.2 (d, 246.4, C-F), 152.8, 137.3 (d, 14.3), 124.9 (d, 5.7), 117.5 (d, 15.1), 107.3 (d, 3.4), 65.2, 61.7, 56.4, 55.1, 53.2, 48.7, 47.8, 44.9, 38.3, 34.8, 33.1, 26.6, 20.7, 20.0. ^{19}F NMR: –57.85 (d, 5.4). HRMS calcd. For $C_{21}H_{30}FN_2O_5S$: 441.1859 (M+1). Found: 441.1868.

4.1.9. (2*R*)-*N*-[(2*S*)-2-Amino-2-(5′-fluoro-3′,4′-dimethoxybenzyl)-ethan-1-oyl]bornane-10,2-sultam, 5b. Using the same procedure described for **5b**, the product **5c** was obtained in 99% yield as a colorless solid. Mp 138–140°C $[\alpha]_D^{20}=+4.9$ (*c* 0.44, $CHCl_3$). ^{1}H NMR: 6.64 (1H, t, 1.8), 6.59 (1H, dd, 1.5, 11.1), 4.31 (1H, t, 7.5), 3.83–3.89 (7H, m) 3.44 (2H, d, 4.2), 2.97 (1H, dd, 7.8, 13.2), 2.78 (1H, dd, 7.2, 13.2), 2.00 (1H, dd, 7.5, 13.2), 1.69–1.92 (4H, m), 1.28–1.42 (2H, m), 0.92 (3H, s), 0.83 (3H, s). ^{13}C NMR: 175.2, 155.7 (d, 245.2, C-F), 153.5 (d, 5.7), 135.8 (d, 13.8), 132.7 (d, 8.6), 110.1 (d, 20.6), 109.0 (d, 2.3), 65.1, 61.5 (d, 3.4), 56.2, 56.0, 53.1, 48.6, 47.7, 44.7, 41.7, 38.2, 32.9, 26.5, 20.4, 19.8. ^{19}F NMR: -55.70 (d, 11.0). HRMS calcd. For $C_{21}H_{30}FN_2O_5S$: 441.1859 (M+1). Found: 441.1863.

4.1.10. (2*R*)-*N*-[(2*S*)-2-Amino-2-(2,6′-difluoro-3′,4′-dimethoxybenzyl)-ethan-1-oyl]bornane-10,2-sultam, 5d. Using the procedure describe for the preparation of **5c**, 800 mg of alkylation product **4d** gave 512 mg of **5d** (87%) as a colorless solid. Mp 114–115°C $[\alpha]_D^{20}=-22.5$ (*c* 0.25, $CHCl_3$). ^{1}H NMR: 6.43 (1H, dd, 2.1, 10.8), 4.35 (1H, t, 6.9), 3.78–3.90 (7H, m,) 3.43 (2H, d, 3.6), 3.10 (1H, dd, 7.8, 13.5), 2.90 (1H, dd, 6.6, 13.5), 2.05 (1H, dd, 7.8, 13.8), 1.80–1.96 (4H, m), 1.26–1.42 (2H, m), 0.93 (3H, s), 0.89 (3H, s). ^{13}C NMR: 175.6, 157.1 (d, 241.3, C-F), 155.3 (d, 244.7, C-F), 152.8 (dd, 6.8, 12.5), 133.9 (d, 14.8), 105.3 (t, 19.4), 95.9 (dd, 3.4, 28.4), 65.3, 61.8, 56.5, 54.1, 53.2, 48.7, 47.8, 44.9, 38.3, 33.1, 28.6, 26.6, 20.7, 20.1. ^{19}F NMR: -42.74 (d, 9.0), –55.22. HRMS calcd. For $C_{21}H_{29}F_2N_2O_5S$: 459.1765 (M+1). Found: 459.1776.

4.1.11. 6-Fluoro-L-3,4-dimethoxyphenylalanine, 6c. Aqueous lithium hydroxide solution (2.5 M, 0.6 mL, 1.5 mmol) was added at 0°C to a magnetically stirred solution of **5c** (220 mg, 0.5 mmol) in THF (1 mL). The resulting mixture was stirred at this temperature for an additional 1 h. THF was evaporated, the aqueous solution was acidified with 1 M hydrochloric acid until pH = 2 and the mixture was extracted with ethyl acetate (3×5 mL). The aqueous phase was neutralized with 1 M sodium bicarbonate solution until pH = 5–6. At this point, precipitation of a colorless solid occurred. The

precipitate was filtered and dried under vacuum to afford product **6c** (100 mg, 82%). Mp 210–212°C dec. $[\alpha]_D^{20} = -15.6$ (*c* 0.55, 1 M HCl) ^{1}H NMR (D_2O, DCl): 6.86 (1H, d, 3.0), 6.83 (1H, d, 7.5), 4.28 (1H, t, 6.3), 3.77 (3H, s), 3.76 (3H, s), 3.28 (1H, dd, 5.6, 14.7), 3.15 (1H, dd, 7.5, 14.7). ^{13}C NMR (D_2O, DCl): 173.8, 156.2 (d, 234.9, C-F), 147.1 (d, 11.5), 143.1, 118.1, 113.5 (d, 17.1), 104.2 (d, 27.0), 57.1, 56.1, 54.3, 31.3. ^{19}F NMR (D_2O, DCl): −48.76 (d, 11.0). HRMS calcd. For $C_{11}H_{15}FNO_4$: 244.0985 (M+1). Found: 244.0986.

4.1.12. 2-Fluoro-L-3,4-dimethoxyphenylalanine, 6a. Aqueous lithium hydroxide solution (2.5 M, 1.5 mL, 3.88 mmol) was added at 0°C to a stirred solution of **5a** (400 mg, 0.91 mmol) in THF (2 mL). The resulting mixture was stirred at this temperature for an additional 2 h. The THF solvent was evaporated, and the aqueous solution was acidified with 1 M hydrochloric acid until pH = 2. The solution was extracted with ethyl acetate (3×5 mL). The aqueous phase was neutralized with 1 M sodium bicarbonate solution until pH = 5–6, then evaporated to dryness. This residue was purified using a Dowex (50w×8-200) ion-exchange resin column to give **6a** as a colorless solid (177 mg, 80%). Mp 170–172°C dec. $[\alpha]_D^{20} = -16.3$ (c 0.77 1 M HCl) ^{1}H NMR (D_2O, DCl): 6.91 (1H, t, 8.4), 6.75 (1H, d, 8.7), 4.19 (t, 6.6), 3.73 (6H, s), 3.21 (1H, dd, 6.3, 15.0), 3.08 (1H, dd, 6.9, 15.0). ^{13}C NMR (D_2O, DCl): 171.3, 154.7 (d, 243.1, C-F), 153.3, 136.3 (d, 13.7), 126.3, 114.6 (d, 13.7), 108.9, 62.0, 56.5, 53.3, 29.4. ^{19}F NMR (D_2O, DCl): -59.35 (d, 8.2). HRMS calcd. For $C_{11}H_{15}FNO_4$: 244.0985 (M+1). Found: 244.0987.

4.1.13. 5-Fluoro-L-3,4-dimethoxyphenylalanine, 6b. Treatment of compound **5b** (433 mg) as for preparation of **6c** gave **6b** as a colorless solid (177 mg, 74%). Mp 175°C dec. $[\alpha]_D^{20} = +2.5$ (*c* 0.32, 1 M HCl) ^{1}H NMR (D_2O, DCl): 6.75–6.85 (2H, m) 4.00 (1H, dd, 5.7, 8.1), 3.92 (3H, s), 3.25 (1H, dd, 5.4, 14.7), 3.11 (1H, dd, 7.8, 14.7). ^{13}C NMR (D_2O, DCl): 174.9, 155.9 (d, 244.2, C-F), 153.4 (d, 5.7), 135.5 (d, 13.4), 132.4 (d, 9.4), 110.3 (d, 20.1), 109.7 (d, 2.6), 62.0 (d, 3.4), 56.6, 56.3, 37.0. ^{19}F NMR (D_2O, DCl): −55.76 (d, 9.0). HRMS calcd. For $C_{11}H_{15}FNO_4$: 244.0985 (M+1). Found: 244.0978.

4.1.14. 2,6-Difluoro-L-3,4-dimethoxyphenylalanine, 6d. Treatment of compound **5d** (400 mg) as for preparation of **6c**, gave **6d** as a colorless solid (168 mg, 74%). Mp 242–244°C $[\alpha]_D^{20} = +16.9$ (*c* 0.40, 1 M HCl) ^{1}H NMR (D_2O, DCl): 6.75 (1H, dd, 2.4, 12.0), 4.23 (t, 6.9), 3.81 (3H, s), 3.79 (3H, s), 3.17–3.32 (2H, m). ^{13}C NMR (D_2O, DCl): 171.3, 157.5 (dd, 10.6, 241.9, C–F), 154.8 (dd, 11.5, 244.5, C-F), 153.5 (dd, 7.2, 13.1), 133.1 (dd, 4.6, 14.6), 102.7 (dd, 19.2, 21.6), 97.0 (dd, 2.6, 28.1), 62.1 (d, 2.6), 56.7, 52.7, 23.4. ^{19}F NMR (D_2O, DCl): −43.18 (d, 12.1), −57.42. HRMS calcd. For $C_{11}H_{14}F_2NO_4$: 262.0891 (M+1). Found: 262.0898.

4.1.15. 6-Fluoro-L-3,4-dihydroxyphenylalanine, 1c. Under nitrogen, compound **6c** (87 mg, 0.34 mmol) was suspended in 48% aqueous HBr (2 mL). This reaction mixture was stirred at 145°C for 1 h, then evaporated under vacuum to dryness. The dry mixture was neutralized with 1 M aqueous sodium bicarbonate solution until pH = 4–5. The neutralized solution was placed in a refrigerator and the off-white solid that precipitated was filtered and washed with cold water and acetone. This solid was dried under vacuum to afford off-white solid **1c** (51 mg, 66%). Chiral HPLC analysis of this sample showed that the product e.e. was >99.5%, retention times of racemate:[8] 7.02 min (*S*), 4.96 min (*R*). Mp 234–238°C dec. $[\alpha]_D^{20} = -5.5$ (c 0.50, 1 M HCl). ^{1}H NMR (CD_3OD): 6.70 (1H, d, 7.5), 6.54 (1H, d, 10.8), 3.71 (1H, dd, 4.5, 9.0), 3.23 (1H, dd, 3.9, 14.7), 2.86 (1H, dd, 9.0, 14.7). ^{13}C NMR (CD_3OD): 173.8, 156.2 (d, 234.9, C-F), 147.1 (d, 11.5), 143.1, 118.1, 113.5 (d, 17.1), 104.2 (d, 27.0), 57.1, 31.3. ^{19}F NMR (CD_3OD): −52.76 (t, 8.2). HRMS calcd. For $C_9H_{11}FNO_4$: 216.0672 (M+1). Found: 216.0670.

4.1.16. 2-Fluoro-L-3,4-dihydroxyphenylalanine, 1a. Prepared as for **1c**, the product **1a** was obtained in 70% yield as an off-white solid. Chiral HPLC analysis of this sample showed that the product e.e. was >99.5%, retention times of racemate:[8] 5.74 min (*S*), 4.20 min (*R*). Mp 259–262 °C dec. $[\alpha]_D^{20} = -4.6$ (*c* 0.48, 1 M HCl). ^{1}H NMR (D_2O, DCl): 6.50–6.60 (2H, m), 4.14 (1H, t, 6.6), 3.16 (1H, dd, 6.0, 15.0), 3.00 (1H, dd, 7.5, 15.0). ^{13}C NMR (D_2O, DCl): 171.4, 151.4 (d, 238.3, C-F), 146.2 (d, 4.8), 132.7 (d, 15.4), 121.8, 113.3 (d, 14.1), 112.0, 53.5, 29.4. ^{19}F NMR (D_2O, DCl): −63.89 (d, 5.6). HRMS calcd. For $C_9H_{11}FNO_4$: 216.0672 (M+1). Found: 216.0678.

4.1.17. 5-Fluoro-L-3,4-dihydroxyphenylalanine·HBr, 1b. Under nitrogen, compound **6b** (115 mg, 0.47 mmol) was suspended in 48% aqueous HBr (2 mL). This reaction mixture was stirred for 1.5 h at 145°C, then evaporated under vacuum to dryness. The resulting residue **1c** was obtained in >99% yield. (NMR indicated >97% purity without further purification). $[\alpha]_D^{20} = -5.4$ (*c* 0.93, 1 M HCl). Chiral HPLC analysis of this sample showed that the product e.e. was >99.4%, retention times of racemate:[8] 8.68 min (*S*), 5.98 min (*R*). ^{1}H NMR (D_2O, DCl): 6.83–6.87 (2H, m), 4.54 (1H, dd, 6.0,7.8), 3.39 (1H, dd, 6.0, 15.0), 3.26 (1H, dd, 7.8, 14.7). ^{13}C NMR (D_2O, DCl): 171.6, 152.6 (d, 238.4, C-F), 146.6 (d, 5.6), 132.0 (d, 15.8), 126.1 (d, 8.8), 113.2, 109.4 (d, 19.5), 54.4, 32.2. ^{19}F NMR (D_2O, DCl): -59.72 (d, 12.4). HRMS calcd. For $C_9H_{11}FNO_4$: 216.0672 (M+1). Found: 216.0672.

4.1.18. 2,6-Difluoro-L-3,4-dihydroxyphenylalanine·HBr, 1d. Using the same procedure, **6d** (80 mg, 0.31 mmol) gave **1d** in >99% yield (>97% pure by NMR). Chiral HPLC analysis of this sample on a CROWNPAK CR-(+) column eluted with aqueous $HClO_4$ (pH 1.6) at a flow rate of 0.5 mL/min showed that it is >99.9% e.e., retention times of racemate:[18] 11.28 min (*S*), 8.44 min (*R*). Mp 145–147°C ^{1}H NMR (D_2O, DCl): 6.52 (1H, d, 10.8), 4.23 (1H, t, 6.9), 3.26 (1H, dd, 6.0, 15.0), 3.16 (1H, dd, 7.5, 15.0). ^{13}C NMR (D_2O, DCl): 171.5, 154.6 (dd, 9.7, 235.7, C-F), 151.0 (dd, 11.4, 236.8), 146.5 (dd, 8.0, 14.3), 129.2 (d, 15.4), 101.5 (dd, 18.8, 21.7), 99.5 (d, 26.2), 53.0, 23.4. ^{19}F NMR (D_2O, DCl): −50.25 (t, 6.2), −62.01. HRMS calcd. For $C_9H_{10}F_2NO_4$: 234.0578 (M+

1). Found: 234.0579. HRMS calcd. for $C_9H_{11}FNO_4$: 216.0672 (M+1). Found: 216.0672.

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