Synthesis of 2-Fluoro- and 6-Fluoro-(2*S*,3*R*)-(3,4-dihydroxyphenyl)serine as Potential in Vivo Precursors of Fluorinated Norepinephrines

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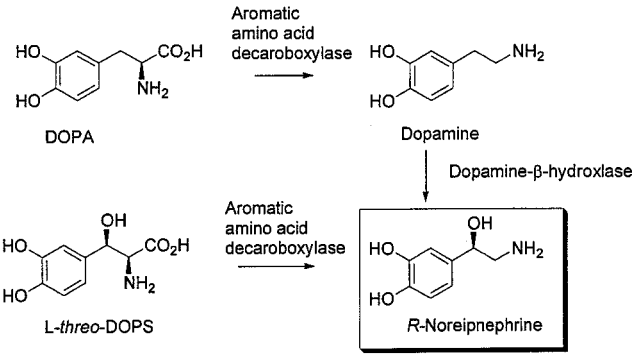
The title compounds were prepared by the aldol condensation of 3,4-dibenzyloxy-2-fluorobenzaldehyde and 4,5-dibenzyloxy-2-fluorobenzaldehyde with the oxazolidinone **2**, a chiral glycine equivalent. Removal of the chiral auxiliary and blocking groups produced the target amino acids 2-fluoro- and 6-fluoro-(2*S*,3*R*)-(3,4-dihydroxyphenyl)serine (**1b** and **1c)** in >98% ee.

Introduction

The final step in the biosynthesis of norepinephrine, an important neurotransmitter of the sympathetic and central nervous systems, is enzymatic side-chain hydroxylation of dopamine (Scheme 1). Recently, much attention has focused on (2*S*,3*R*)-(3,4-dihydroxyphenyl)-serine (L-*threo*-DOPS) (**1a**) as a possible alternative biological precursor of norepinephrine that would be independent of dopamine biosynthesis, since enzymatic decarboxylation would produce norepinephrine directly (Scheme 1). In addition to potential activity in the periphery,[1] there is substantial evidence that administered L-*threo*-DOPS crosses the blood−brain barrier and is subsequently decarboxylated to produce norepinephrine in the central nervous system.[1,2] In fact, several clinical trials suggest that L-*threo*-DOPS may be beneficial in treating disorders of both the central and sympathetic nervous systems. For example, orthostatic hypotension, characterized by adrenergic deficiency, has received particular attention,[3] and certain symptoms of Parkinson's disease can be alleviated by treatment with L-*threo*-DOPS.[4]

For several years, we have been investigating fluorinated analogues of biogenic amines, including norepinephrine. In this research, we discovered that ring fluorination affects the interaction of norepinephrine with adrenergic receptors and that this effect depends on the site of the fluorine substituent. Thus, fluorine in the 2-position renders the analogue selective for β-adrenergic receptors, whereas fluorine in the 6-position produces an analogue that is selective for α-adrenergic receptors. These selectivities of fluorinated norepinephrine and other adrenergic agonists have made such compounds very useful pharmacological tools.[5] It follows from the biological interest and therapeutic potential of L-*threo*-DOPS that ring-fluorinated analogues of this amino acid, as precursors of the corresponding fluorinated norepinephrines, could be useful tools to study mechanistic aspects of the biological activities of L-*threo*-DOPS. In particular, such studies could give evidence as to whether α-adrenergic or β-adrenergic receptors are involved. It is possible that more selective medicinal agents could also result.

Scheme 1



We have previously reported the synthesis of racemic dihydroxyphenylserines fluorinated in the 2- or 6-position.[6] In this paper, we describe the stereoselective synthesis of fluorinated analogues (**1b**,**c**) of L-*threo*-DOPS.

Results and Discussion

The key structural feature of L-*threo*-DOPS is the *S*-configuration of the α-amino group and the *R*-configuration of the benzylic alcohol, corresponding to the stereochemistry of the natural amino acid and the active enantiomer of norepinephrine formed upon enzymatic decarboxylation. There are a variety of synthetic methods that have been used successfully to prepare such *syn*-1,2-amino alcohol subunits. The application of several of these methods to the synthesis of ring-fluorinated L-*threo*-

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Table 1. Aldol Optimization

base (equiv)	**1** (equiv)	Lewis acid (equiv)	*T* (°C)	dr (**4c**/others)[a]	yield of **4c** (%)
N-ethylpiperidine (1.5)	1.3	$Sn(OTf)_2$ (1.1)	−78		
N-ethylpiperidine (1.5)	1.2	$Sn(OTf)_2$ (1.2)	−78 to −50 to 0		
LHMDS (1.4)	1.4		−78	4:1	52
LHMDS (1.0)	1.0	$Sn(OTf)_2$ (1.0)	−78		34
LHMDS (1.3)	1.3	$Sn(OTf)_2$ (1.3)	−78	10:1	50
LHMDS (2.0)	2.0	$Sn(OTf)_2$ (2.0)	−78	20:1[b]	81

[a] Determined by ^{1}H NMR analysis of crude reaction mixtures. [b] Estimated ratio, no other isomers detected.

DOPS was unsuccessful but provided significant insight.[7] For example, the addition of nucleophiles to aldehydes **3b** and **3c**[8] was made difficult by low reactivity of the carbonyl groups. The ready racemization of the benzylic position of key intermediates under acidic conditions ruled out approaches requiring strong acid, and unprotected catechol rings are easily oxidized under basic conditions. In part because of these problems, most of our early approaches to the title compounds provided intermediates exhibiting low diastereo- and enantiomeric ratios. Clearly, we needed a method that would enable us to overcome these difficulties.

Evans and co-workers have developed the isothiocyanate **2** as a chiral glycine equivalent and have used this for the synthesis of β-hydroxy-α-amino acids.[9] Outstanding selectivities and yields have been documented using this approach, and we anticipated achieving similar results. Oxazolidinone **2** was expected to drive the reaction to completion by providing an internal trap in the isothiocyanate. Furthermore, the synthesis could be adjusted to allow for protecting groups that could be removed without affecting the catechol or the integrity of the benzylic stereocenter.

We began our endeavor by studying the aldol condensation between oxazolidinone **2** and aldehyde **3c**. Generation of the tin enolate of oxazolidinone **2** in the presence of tin(II) triflate with *N*-ethylpiperidine followed by the addition of aldehyde **3c** provided a trace amount of the product carbamate **4c** (Table 1). Adjustment of all variables for this standard protocol failed to provide meaningful quantities of the aldol product. The use of 1.4 equiv of a lithium enolate, generated with lithium hexamethyldisilazane (LHMDS), resulted in the partial consumption of the starting aldehyde. A separable pair of diastereomeric thiocarbamates **4c** were obtained in a 4:1 ratio (^{1}H NMR), the major isomer being isolated in 52% yield. Deprotonation of the acyloxazolidinone **2** with LHMDS (1.3 equiv) in the presence of $Sn(OTf)_2$ (1.3 equiv) followed by the addition of the aldehyde **3c** provided a 10:1 ratio of diastereomers. The major diastereomer was identical to the major diastereomer formed using the lithium enolate and was isolated in 50% yield. The use of stoichiometric quantities of substrate and enolate resulted in diminished yield (34%). Our final optimization entailed the use of 2 equiv of the tin/lithium enolate at −78 °C for 1.5 h, a procedure that routinely provided a 20:1 ratio of diastereomeric thiocarbamates **4c**. The isomers were readily separable by chromatography, and the major diastereomer was obtained in 81% yield. A slight erosion of selectivity and yield (8.5:1 dr, 72% yield) was observed for the 2-fluoro isomer **4b** using the same protocol (Scheme 2).

The use of the isothiocyanate derived oxazolidinone **2** enabled us to overcome the diminished reactivity of aldehyde **3** and provided the aldol products in good yield. The amino alcohols were obtained in their protected form, as thiocarbamates. However, the extreme conditions required to remove the thiocarbamate are incompatible with our substrate. The Evans strategy circumvents this difficulty by transforming the thiocarbamate to an oxocarbamate. To prepare for this transformation, the chiral auxiliary was removed with methoxymagnesium bromide to provide methyl esters **5b** (88%) and **5c** (93%). The thiocarbamate nitrogen was protected as a *tert*-butyl carbamate (**6b**,**c**) in good yield.

We began with the sulfur to oxygen protocol described[9] for related systems. Thus, thiocarbamate **6c** was allowed to react with a mixture of formic acid and hydrogen peroxide to provide cyclic carbamate **7c**. The yield of the reaction was highly variable, ranging between 10% and 63%, and the relative product distribution changed frequently. ^{1}H NMR studies revealed that neither hydrogen peroxide nor formic acid alone was the source of difficulty. Substitution of trifluoroacetic acid or acetic acid in the reaction met with limited success. Only a trace of product was observed using *m*-CPBA[10] to effect the conversion.

We also examined a variety of exotic reagent combinations in an effort to overcome the difficulties. The use of yeast in a pH 7 buffer[11] and the use of manganese oxide[12] both failed to provide any conversion to the product. Nitrosonium tetrafluoroborate[13] and the combination of iodine and potassium *tert*-butoxide[14] resulted in the destruction of the molecule. We were delighted to discover that using merury(II) acetate[15] in dichloromethane resulted in the smooth conversion of thiocarbamate **6c** to the oxygen analogue **7c**. The product was routinely obtained in 85−90% yield, independent of the scale of

(7) For a review of the methods examined in the context of DOPS and fluorinated norepinephrine analogues, see: Kirk, K. L.; Herbert, B.; Lu, S.-F.; Jayachandran, Padgett, W. L.; Olufunke, O.; Daly, J. W.; Haufe, G.; Laue, K. W. In *Asymmetric Synthesis of Fluoro-Organic Compounds;* Ramachandran, P. V., Ed.; ACS Symposium Series 746; American Chemical Society: Washington, DC, 2000; pp 194−209.

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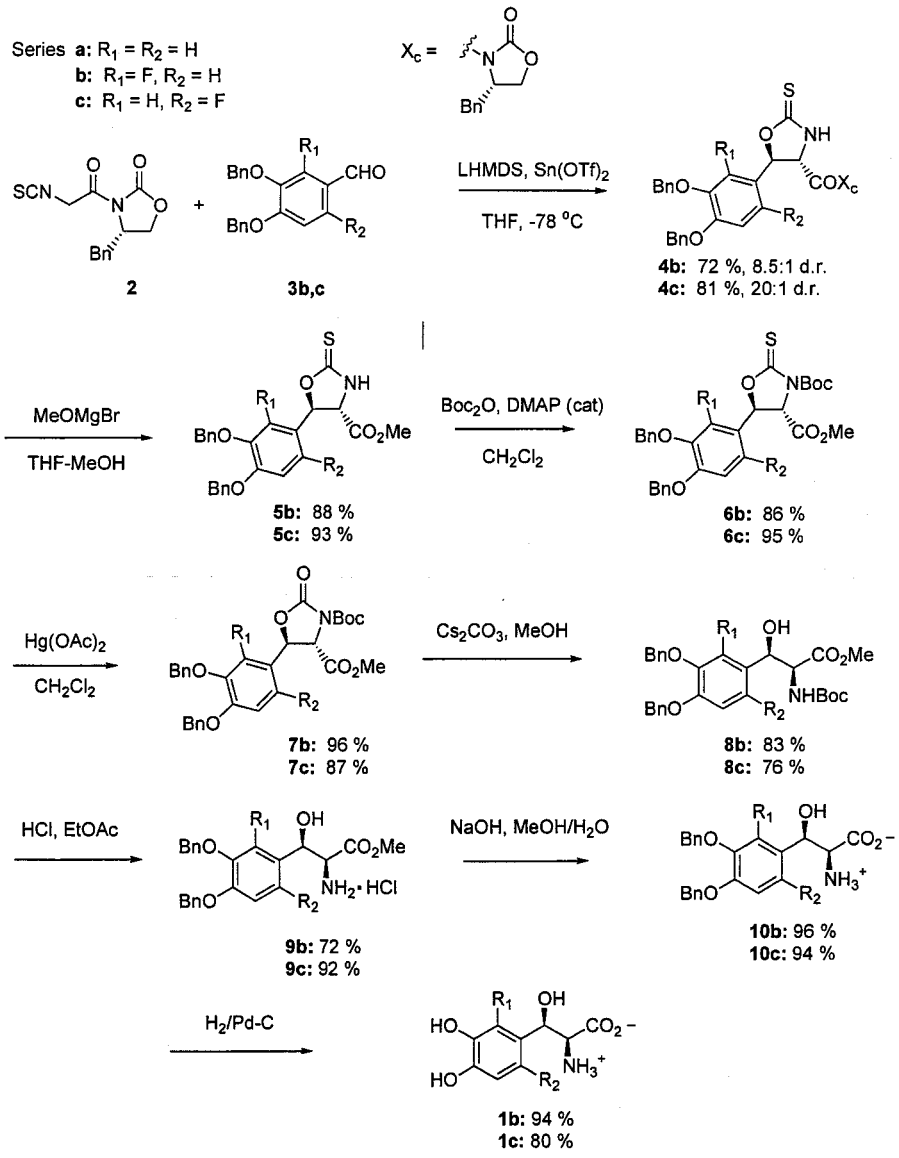
Scheme 2



the reaction. The 2-fluoro analogue **6b** was similarly converted to the corresponding carbamate **7b** in 96% yield.

The remaining tasks to complete the synthesis of the fluorinated L-*threo*-DOPS entailed the removal of the protecting groups. The cyclic carbamates **7b** and **7c** were cleaved (Cs_2CO_3 in MeOH), and the Boc group was cleaved with gaseous HCl in ethyl acetate[16] to furnish the amino acid methyl ester **9b**,**c** in good yields. Chiral HPLC analysis of amino alcohols **9b** and **9c** revealed that each compound was essentially a single enantiomer (≥98% ee). The methyl esters were readily saponified to provide (2*S*,3*R*)-3-(3,4-dibenzyloxy-2-fluorophenyl)serine (**10b**) and (2*S*,3*R*)-3-(4,5-dibenzyloxy-2-fluorophenyl)-serine (**10c**).

The low solubility of the saponified zwitterionic amino acids **10b**,**c** presented difficulties in the final step. For example, hydrogenolysis of **10c** with 10% Pd−C was performed using 60 mg of substrate partially dissolved in 24 mL of methanol. This procedure cleanly produced (2*S*,3*R*)-3-(4,5-dihydroxy-2-fluorophenyl)serine (L-*threo*-6FDOPS, **1c**).[17] Although **1c** is only slightly soluble in methanol and is insoluble in water, it readily dissolved in 1 N HCl. However, ^{1}H NMR analysis revealed that **1c** undergoes epimerization at the benzylic position under these acidic conditions to give the erythro diastereomer as a contaminant. For this reason, direct comparison of the sign of the optical rotations of L-*threo*-DOPS (**1a**)[18] and L-*threo*-6FDOPS (**1c**) in 1 N HCl could not be made.

In contrast to the above results, (2*S*,3*R*)-3-(3,4-dihydroxy-2-fluorophenyl)serine (L-*threo*-2FDOPS, **1b**), prepared from **10b** under the conditions we used to prepare pure **1c**, consistently was contaminated with unknown byproducts. Furthermore, repeated attempts to purify **1b** by recrystallization, using many solvent systems, met with failure. Fortunately, we discovered that the use of methanol and 3 N HCl (4/1) as hydrogenation solvent suppressed the side reaction, and we obtained relatively clean **1b**. Unlike the behavior of **1c**, there was no

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(17) ^{1}H NMR analysis showed no evidence of diastereomer formation during the final manipulations, confirming that no loss of stereochemical integrity had occurred.

(18) L-*threo*-DOPS: $[\alpha]^{20}_D = -42.6$ ($c = 1$, 1 M HCl). Tanaka, C.; Fujiwara, H.; Nakamura, M.; Ohmura, I. *J. Pharm. Pharmacol.* **1981**, *33*, 772−777.

epimerization of the benzylic position, as determined by ^{1}H NMR. After removal of Pd−C (Celite filtration), the product was further purified using a Dowex ion-exchange column to give pure L-*threo*-2FDOPS (**1b**).

Conclusion

We have developed routes to fluorinated analogues of L-*threo*-DOPS. We expect these compounds to prove useful for examination of the mechanisms of actions of the parent compound. However, for this to be true, **1b**,**c** must (1) cross the blood−brain barrier and (2) be decarboxylated to give the corresponding fluorinated norepinephrines. Accordingly, experiments are underway to determine the efficiency of blood−brain barrier transport as well as the behavior of **1b**,**c** as substrates for aromatic amino acid decarboxylase.

Experimental Section

General Methods. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, with $CDCl_3$, CD_3OD, and DMSO-d_6 as solvents. Elemental analyses were performed at Atlantic Microlab, Inc. HPLC was performed on a chiral-phase column Chiralpak AD (Diacel Ltd., 250 × 4 mm, equipped with a precolumn 80 × 4 mm, *n*-hexane/EtOH = 1:1 + 0.2% diethylamine, flow rate 1 mL/min). THF and ether were distilled from sodium benzophenone ketyl under nitrogen prior to use. Methylene chloride was distilled from CaH_2, and ethyl acetate was distilled from P_2O_5. All reactions were performed under a dry N_2 atmosphere. Analytical TLC was performed on Kisegel 60 GF_{254} (Merck), and flash column chromatography was performed with silica gel 60 (230−400 mesh, Merck).

(4*S*)-4-Benzyl-3-[(4*S*,5*R*)-1-[5-[3,4-bis(benzyloxy)-2-fluorophenyl]-2-thioxooxazolidin-4-yl]methanoyl]oxazolidin-2-one (4b). Freshly generated lithium hexamethyldisilazane was prepared by addition of 1.0 mL of a 2.5 M (2.5 mmol) solution of *n*-butyllithium to a cooled (0 °C) solution of 1,1,1,3,3,3-hexamethyldisilazane (0.54 mL, 2.56 mmol) in dry THF (2 mL). After the mixture was stirred for 30 min at 0 °C, the reagent was transferred to a cooled (−78 °C) solution of oxazolidinone **2** (704 mg, 2.55 mmol) and stannous triflate (1.06 g, 2.54 mmol) in dry THF (5.2 mL). After the mixture was stirred for 30 min at −78 °C, the aldehyde **3b** (434 mg, 1.29 mmol) was added in one portion. The reaction mixture was stirred for 1.5 h at −78 °C and then was quenched with 10 mL of a 1:1 mixture of pH 7 phosphate buffer and saturated aqueous NH_4Cl. The mixture was poured into CH_2Cl_2, and the organic layer was washed with 1 M $NaHSO_4$ and brine. The organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated. The solid residue was purified by flash column chromatography (2:1 hexane/ethyl acetate) to give 566 mg (72%) of compound **4b**: colorless solid; mp 89−90 °C (from EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.56 (br s, 1H), 7.45−7.31 (m, 14H), 7.20 (d, J = 6.9 Hz, 1H), 7.09 (t, J = 8.4 Hz, 1H), 6.80 (dd, J = 8.7, 1.8 Hz, 1H), 6.67 (d, J = 4.5 Hz, 1H), 5.15 (s, 2H), 5.10 (s, 2H), 4.95 (d, J = 4.5 Hz, 1H), 4.82−4.75 (m, 1H), 4.44−4.34 (m, 2H), 3.23 (dd, J = 13.5, 3.3 Hz, 1H), 3.00 (dd, J = 13.5, 8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 188.0, 165.3, 154.1 (d, J = 4.9 Hz), 153.65 (d, J = 245.9 Hz), 153.6, 136.7, 136.44 (d, J = 11.4 Hz), 136.0, 134.0, 129.3 (2C), 129.0 (2C), 128.5 (2C), 128.3 (2C), 128.2 (2C), 128.13, 128.12, 127.6, 127.3 (2C), 121.5 (d, J = 4.6 Hz), 117.6 (d, J = 11.9 Hz), 109.4 (d, J = 2.9 Hz), 78.9 (d, J = 2.9 Hz), 75.7 (d, J = 2.3 Hz), 71.0, 67.5, 64.0, 55.1, 37.3; MS (FAB$^+$) m/z (M + H$^+$) calcd 613.1808, obsd 613.1818; $[\alpha]^{23}_D$ +121.7 (*c* 2.30, $CHCl_3$). Anal. Calcd for $C_{34}H_{29}FN_2O_6S$: C, 66.65; H, 4.77; N, 4.57. Found: C, 66.48; H, 4.77; N, 4.56.

(4*S*)-4-Benzyl-3-[(4*S*,5*R*)-1-[5-[4,5-bis(benzyloxy)-2-fluorophenyl]-2-thioxooxazolidin-4-yl]methanoyl]oxazolidin-2-one (4c). Using the same procedure, from 3.49 g (12.6 mmol) of **2** and 2.12 g (6.3 mmol) of **3c** there was obtained 3.12 g (81%) of **4c**: white solid; mp 92−93 °C (from EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.61 (br s, 1H), 7.47−7.29 (m, 13H), 7.18 (dd, J = 6.6, 1.5 Hz, 2H), 6.98 (d, J = 7.2 Hz, 1H), 6.68 (d, J = 12.0 Hz, 1H), 6.60 (d, J = 4.8 Hz, 1H), 5.14 (d, J = 11.0 Hz, 2 H), 5.10 (d, J = 11.0 Hz, 2H), 4.96 (dd, J = 4.2, 1.2 Hz, 1H), 4.74 (ddd, J = 12.0, 7.5, 3.6 Hz, 1H), 4.35 (dd, J = 14.0, 9.3 Hz, 1H), 4.33 (dd, J = 11.0, 1.5 Hz, 1H), 3.25 (dd, J = 14.0, 3.3 Hz, 1H), 2.96 (dd, J = 14.0, 8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 188.0, 165.4, 154.2 (d, J = 241.3 Hz), 153.7, 150.9 (d, J = 10.2 Hz), 145.4 (d, J = 2.9 Hz), 136.5, 136.0, 133.9, 129.4 (2C), 129.2 (2C), 128.6 (2C), 128.5 (2C), 128.12, 128.06, 127.8, 127.7 (2C), 127.2 (2C), 115.2 (d, J = 14.3 Hz), 113.6 (d, J = 4.6 Hz), 102.9 (d, J = 25.6 Hz), 78.7 (d, J = 2.3 Hz), 72.2, 71.2, 67.6, 64.2 (d, J = 1.7 Hz), 55.1, 37.4; MS m/z (M$^+$) calcd 612.1726, obsd 612.1730; $[\alpha]^{23}_D$ +148 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{34}H_{29}FN_2O_6S$: C, 66.65; H, 4.77; N, 4.57. Found: C, 66.44; H, 4.77; N, 4.63.

(4*S*,5*R*)-5-[3,4-Bis(benzyloxy)-2-fluorophenyl]-2-thioxooxazolidine-4-carboxylic Acid Methyl Ester (5b). To a cooled (0 °C) solution of 3 M methylmagnesium bromide (0.68 mL, 2.04 mmol) in anhydrous THF (6.5 mL) was added dropwise 13 mL of anhydrous MeOH, and the mixture was stirred for 5 min. To this was added compound **4b** (834 mg, 1.36 mmol) in anhydrous THF (6.5 mL). After the resulting solution was stirred for 20 min at 0 °C, the reaction was quenched with 1 M $NaHSO_4$. The mixture was concentrated under vacuum to remove methanol and THF, and the aqueous solution was diluted with water and extracted three times with CH_2Cl_2. The combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography (2:1 hexane/ethyl acetate) to give 562 mg (88%) of compound **5b**: colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.43−7.31 (m, 11H), 7.04 (t, J = 8.4 Hz, 1H), 6.79 (dd, J = 8.9, 1.8 Hz, 1H), 6.09 (d, J = 6.0 Hz, 1H), 5.15 (s, 2H), 5.12 (s, 2H), 4.50 (d, J = 5.7 Hz, 1 H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 188.5, 168.3, 154.3 (d, J = 4.8 Hz), 154.1 (d, J = 247.7 Hz), 136.6, 136.5 (d, J = 12.8 Hz), 135.9, 128.5 (2C), 128.3 (2C), 128.2 (2C), 128.11, 128.07, 127.3 (2C), 121.9 (d, J = 4.3 Hz), 117.0 (d, J = 11.6 Hz), 109.3 (d, J = 2.9 Hz), 80.9 (d, J = 2.6 Hz), 75.6 (d, J = 2.3 Hz), 71.0, 63.2, 53.3; MS (FAB$^+$) m/z (M + H$^+$) calcd 468.1281, obsd 468.1281; $[\alpha]^{23}_D$ +42.6 (c 2.41, $CHCl_3$). Anal. Calcd for $C_{25}H_{22}FNO_5S$: C, 64.23; H, 4.74; N, 3.00. Found: C, 64.25; H, 4.88; N, 2.99.

(4*S*,5*R*)-5-[4,5-Bis(benzyloxy)-2-fluorophenyl]-2-thioxooxazolidine-4-carboxylic Acid Methyl Ester (5c). A similar procedure was used as described for **5b**. To a cooled (0 °C) solution of 1 M methylmagnesium bromide (2.7 mL, 2.7 mmol) in anhydrous THF (5 mL) was added anhydrous MeOH (23 mL) dropwise. After 5 min, compound **4c** (1.41 g, 2.3 mmol) in anhydrous THF (6 mL) was added, and the solution was stirred for 35 min at the same temperature. The reaction mixture was quenched with pH 7 phosphate buffer (10 mL), and CH_2Cl_2 was added. Isolation and purification as with **5b** gave 1.0 g (93%) of compound **5c**: colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.45−7.33 (m, 11H), 6.92 (d, J = 6.9 Hz, 1H), 6.71 (d, J = 11.7 Hz, 1H), 6.05 (d, J = 5.7 Hz, 1H), 5.15 (s, 2H), 5.14 (d, J = 12.0 Hz, 1 H), 5.09 (d, J = 12.0 Hz, 1H), 4.45 (d, J = 5.7 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 188.7, 168.3, 154.7 (d, J = 242.5 Hz), 151.2 (d, J = 9.7 Hz), 145.2 (d, J = 2.3 Hz), 136.5, 135.9, 128.6 (2C), 128.5 (2C), 128.1, 128.0, 127.7 (2C), 127.1 (2C), 114.5 (d, J = 13.7 Hz), 113.9 (d, J = 4.5 Hz), 102.9 (d, J = 26.2 Hz), 80.7 (d, J = 2.3 Hz), 72.2, 71.1, 63.4 (d, J = 1.1 Hz), 53.4; MS m/z (M$^+$) calcd 467.1203, obsd 467.1215; $[\alpha]^{23}_D$ +51.0 (c 1.1, $CHCl_3$). Anal. Calcd for $C_{25}H_{22}FNO_5S$: C, 64.23; H, 4.74; N, 3.00. Found: C, 64.47; H, 4.85; N, 2.95.

(4*S*,5*R*)-5-[3,4-Bis(benzyloxy)-2-fluorophenyl]-2-thioxooxazolidine-3,4-dicarboxylic Acid 3-*tert*-Butyl Ester 4-Methyl Ester (6b). To a solution of compound **5b** (271 mg, 0.58 mmol) in anhydrous CH_2Cl_2 (5 mL) were added di-*tert*-butyl dicarbonate (253 mg, 1.16 mmol) and DMAP (7 mg, 0.06 mmol). The reaction mixture was stirred for 40 min at room temperature, cooled to 0 °C, quenched with 1 M $NaHSO_4$, and extracted three times with CH_2Cl_2. The combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography (3:1

hexane/ethyl acetate) to give 283 mg (86%) of compound **6b**: white solid; mp 107−108 °C; ^{1}H NMR ($CDCl_3$) δ 7.42−7.32 (m, 10H), 7.00 (t, J = 8.4 Hz, 1H), 6.78 (dd, J = 8.7, 1.2 Hz, 1H), 5.68 (d, J = 4.8 Hz, 1H), 5.15 (s, 2H), 5.13 (s, 2H), 4.83 (d, J = 4.8 Hz, 1 H), 3.87 (s, 3H), 1.53 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 182.3, 168.2, 154.5 (d, J = 4.6 Hz), 153.9 (d, J = 246.4 Hz), 148.4, 136.6, 136.5 (d, J = 12.5 Hz), 135.9, 128.5 (2C), 128.3 (2C), 128.2 (2C), 128.18, 128.15, 127.3 (2C), 121.4 (d, J = 4.5 Hz), 116.7 (d, J = 11.9 Hz), 109.3 (d, J = 3.5 Hz), 85.6, 77.1, 75.6 (d, J = 2.3 Hz), 71.0, 66.1 (d, J = 1.1 Hz), 53.2, 27.7 (3C); MS (FAB$^+$) m/z (M + H$^+$) calcd 568.1805, obsd 568.1802; $[\alpha]^{23}_D$ +7.8 (*c* 1.88, $CHCl_3$). Anal. Calcd for $C_{30}H_{30}FNO_7S$: C, 63.48; H, 5.33; N, 2.47. Found: C, 63.50; H, 5.34; N, 2.49.

(4*S*,5*R*)-5-[4,5-bis(benzyloxy)-2-fluorophenyl]-2-thioxooxazolidine-3,4-dicarboxylic Acid 3-*tert*-Butyl Ester 4-Methyl Ester (6c). A similar procedure as described for **6b** was used. Compound **5c** (3.12 g, 6.67 mmol) in anhydrous CH_2Cl_2 (33 mL) was stirred with di-*tert*-butyl dicarbonate (1.7 mL, 7.4 mmol) and DMAP (10 mg, 0.08 mmol) for 1 h at room temperature. The reaction mixture was poured onto water and separated, and the CH_2Cl_2 solution was washed with saturated brine. Isolation and purification as for **6b** gave 3.61 g (95%) of compound **6c**: colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.43−7.29 (m, 10H), 6.88 (d, J = 7.2 Hz, 1H), 6.72 (d, J = 11.0 Hz, 1H), 5.66 (d, J = 5.1 Hz, 1H), 5.14 (s, 2H), 5.13 (d, J = 12.0 Hz, 1 H), 5.08 (d, J = 12.0 Hz, 1 H), 4.79 (d, J = 5.1 Hz, 1H), 3.84 (s, 3H), 1.52 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 182.3, 168.2, 154.5 (d, J = 241.9 Hz), 151.2 (d, J = 9.7 Hz), 148.4, 145.3 (d, J = 2.9 Hz), 136.4, 135.9, 128.7 (2C), 128.5 (2C), 128.2, 128.1, 127.7 (2C), 127.1 (2C), 114.4 (d, J = 13.7 Hz), 113.4 (d, J = 4.5 Hz), 102.9 (d, J = 25.6 Hz), 85.7, 76.7 (d, J = 2.9 Hz), 72.2, 71.2, 66.3 (d, J = 1.1 Hz), 53.3, 27.7 (3C); MS m/z (M$^+$) calcd 567.1727, obsd 567.1719; $[\alpha]^{23}_D$ +23.6 (*c* 0.98, $CHCl_3$). Anal. Calcd for $C_{30}H_{30}FNO_7S$: C, 63.48; H, 5.33; N, 2.47. Found: C, 63.85; H, 5.42; N, 2.44.

(4*S*,5*R*)-5-[3,4-bis(benzyloxy)-2-fluorophenyl]-2-oxooxazolidine-3,4-dicarboxylic Acid 3-*tert*-Butyl Ester 4-Methyl Ester (7b). Solid $Hg(OAc)_2$ (302 mg, 0.95 mmol) was added in one portion to a cooled (0 °C) solution of compound **6b** (358 mg, 0.63 mmol) in CH_2Cl_2 (13 mL). The mixture was stirred for 1 h at 0 °C, was allowed to come to room temperature, and was stirred for an additional 2.5 h. The resulting white suspension was recooled to 0 °C, quenched with 10 mL of 1 M K_2CO_3, and extracted three times with CH_2Cl_2. The combined organic layer was washed with brine, dried with anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography (5:2 hexane/ethyl acetate) to give 334 mg (96%) of compound **7b**: colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.41−7.31 (m, 10H), 7.00 (t, J = 8.3 Hz, 1H), 6.78 (dd, J = 8.9, 1.5 Hz, 1H), 5.46 (d, J = 4.2 Hz, 1H), 5.14 (s, 2H), 5.12 (s, 2H), 4.61 (d, J = 4.5 Hz, 1 H), 3.86 (s, 3H), 1.51 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 168.8, 154.3 (d, J = 4.9 Hz), 153.9 (d, J = 246.8 Hz), 150.5, 148.3, 136.59, 136.57 (d, J = 12.8 Hz), 135.9, 128.6 (2C), 128.3 (2C), 128.24 (2C), 128.19, 128.15, 127.3 (2C), 121.0 (d, J = 4.5 Hz), 117.4 (d, J = 11.6 Hz), 109.2 (d, J = 2.9 Hz), 84.8, 75.7 (d, J = 2.3 Hz), 71.9 (d, J = 3.2 Hz), 71.0, 62.7, 53.1, 27.7 (3C); MS (FAB$^+$) m/z (M + H$^+$) calcd 551.2034, obsd 551.2040; $[\alpha]^{23}_D$ +54.4 (*c* 2.15, $CHCl_3$). Anal. Calcd for $C_{30}H_{30}FNO_8$: C, 65.33; H, 5.48; N, 2.54. Found: C, 65.44; H, 5.54; N, 2.59.

(4*S*,5*R*)-5-[4,5-Bis(benzyloxy)-2-fluorophenyl]-2-oxooxazolidine-3,4-dicarboxylic Acid 3-*tert*-Butyl Ester 4-Methyl Ester (7c). Compound **6c** (601 mg, 1.06 mmol) in CH_2Cl_2 (10 mL) was treated as above with 405 mg (1.27 mmol) of $Hg(OAc)_2$ for 1 h, then at room temperature for 4 h. Isolation and purification by column chromatography (5:2 hexane/ethyl acetate) gave 509 mg (87%) of compound **7c**: colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.43−7.30 (m, 10H), 6.90 (d, J = 7.2 Hz, 1H), 6.73 (d, J = 11.4 Hz, 1H), 5.45 (d, J = 4.8 Hz, 1H), 5.14 (s, 2H), 5.10 (s, 2H), 4.58 (d, J = 4.5 Hz, 1H), 3.84 (s, 3H), 1.51 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 168.8, 154.5 (d, J = 241.4 Hz), 151.1 (d, J = 10.3 Hz), 150.6, 148.3, 145.3 (d, J = 2.3 Hz), 136.5, 136.0, 128.7 (2C), 128.5 (2C), 128.2, 128.1, 127.6 (2C), 127.2 (2C), 115.0 (d, J = 13.7 Hz), 113.2 (d, J = 4.6 Hz), 103.0 (d, J = 25.7 Hz), 84.9, 72.3, 71.5 (d, J = 2.9 Hz), 71.2, 63.0, 53.2, 27.8 (3C); MS m/z (M$^+$) calcd 551.1955, obsd 551.1963; $[\alpha]^{23}_D$ +69.3 (*c* 1.2, $CHCl_3$). Anal. Calcd for $C_{30}H_{30}FNO_8$: C, 65.33; H, 5.48; N, 2.54. Found: C, 65.52; H, 5.55; N, 2.53.

(2*S*,3*R*)-3-[3,4-bis(benzyloxy)-2-fluorophenyl]-2-*tert*-butoxycarbonylamino-3-hydroxypropionic Acid Methyl Ester (8b). Solid Cs_2CO_3 (25 mg, 0.08 mmol) was added to a solution of compound **7b** (208 mg, 0.38 mmol) in anhydrous MeOH (9.5 mL), and the mixture was stirred for 3.5 h at room temperature. The reaction mixture was then cooled to 0 °C, quenched with 1 M HCl (2 mL), and concentrated in vacuo to remove MeOH. The mixture was extracted three times with CH_2Cl_2, dried with anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography (2:1 hexane/ethyl acetate) to give 165 mg (83%) of compound **8b**: colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.45−7.30 (m, 10H), 7.07 (t, J = 8.1 Hz, 1H), 6.73 (dd, J = 8.4 Hz, 1H), 5.44 (t, J = 3.8 Hz), 5.25 (d, J = 8.7 Hz, 1H), 5.10 (s, 2H), 5.09 (s, 2H), 4.58 (d, J = 7.2 Hz, 1 H), 3.78 (s, 3H), 2.92 (brs, 1H), 1.33 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 171.0, 155.7, 153.5 (d, J = 244.1 Hz), 152.7 (d, J = 4.6 Hz), 137.1, 136.5, 136.0 (d, J = 13.1 Hz), 128.5 (2C), 128.4 (2C), 128.2 (2C), 128.03, 127.96, 127.3 (2C), 121.3 (d, J = 5.2 Hz), 121.0 (d, J = 11.9 Hz), 109.1 (d, J = 2.9 Hz), 80.0, 75.7 (d, J = 2.3 Hz), 71.1, 68.2, 58.2, 52.5, 28.1 (3C); MS (FAB$^+$) m/z (M + H$^+$) calcd 526.2241, obsd 526.2228; $[\alpha]^{23}_D$ −20.2 (*c* 1.52, $CHCl_3$). Anal. Calcd for $C_{29}H_{32}FNO_7$: C, 66.27; H, 6.14; N, 2.67. Found: C, 66.30; H, 6.24; N, 2.65.

(2*S*,3*R*)-3-[4,5-Bis(benzyloxy)-2-fluorophenyl]-2-*tert*-butoxycarbonylamino-3-hydroxypropionic Acid Methyl Ester (8c). Using a similar procedure (quenching with 1 M $NaHSO_4$), compound **7c** (2.66 g, 4.82 mmol) in anhydrous MeOH (60 mL) and Cs_2CO_3 (318 mg, 0.98 mmol) gave 1.92 g (76%) of **8c**: colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.45−7.28 (m, 10H), 7.08 (d, J = 7.2 Hz, 1H), 6.66 (d, J = 11.4 Hz, 1H), 5.43 (t, J = 3.6 Hz, 1H), 5.30 (d, J = 8.4 Hz, 1H), 5.12−5.04 (m, 4H), 4.57 (d, J = 7.5 Hz, 1H), 3.75 (s, 3H), 2.86 (d, J = 15.6 Hz, 1H), 1.34 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 171.0, 155.7, 154.1 (d, J = 245.9 Hz), 149.5 (d, J = 10.3 Hz), 145.1, 137.1, 136.5, 128.55 (2C), 128.46 (2C), 128.0, 127.9, 127.5 (2C), 127.2 (2C), 118.6 (d, J = 14.9 Hz), 114.2 (d, J = 5.2 Hz), 102.6 (d, J = 26.8 Hz), 80.2, 72.3, 71.3, 68.1, 58.2, 52.6, 28.1 (3C); MS m/z (M$^+$) calcd 525.2163, obsd 525.2154; $[\alpha]^{23}_D$ −3.27 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{29}H_{32}FNO_7$: C, 66.27; H, 6.14; N, 2.67. Found: C, 66.35; H, 6.20; N, 2.66.

(2*S*,3*R*)-2-Amino-3-[3,4-bis(benzyloxy)-2-fluorophenyl]-3-hydroxypropionic Acid Methyl Ester (9b). To a solution of compound **8b** (200 mg, 0.38 mmol) in 8.0 mL of ethyl acetate was added 4.0 mL of ethyl acetate that had been saturated with HCl gas. The solution was stirred for 5 h at room temperature. The resulting white heterogeneous reaction mixture was then cooled to 0 °C, filtered, and washed with hexane. The white solid was purified by recrystallization from methanol, ethyl acetate, and ether to give 127 mg (72%) of compound **9b**: white solid; mp 152−153 °C; ^{1}H NMR (CD_3OD) δ 7.48−7.24 (m, 11H), 7.00 (d, J = 9.0 Hz, 1H), 5.38 (d, J = 4.8 Hz, 1H), 5.18 (s, 2H), 5.08 (s, 2H), 4.16 (d, J = 4.8 Hz, 1 H), 3.80 (s, 3H); ^{13}C NMR (CD_3OD) δ 169.0, 155.1 (d, J = 243.0 Hz), 155.0 (d, J = 4.6 Hz), 138.6, 137.5, 137.4 (d, J = 13.7 Hz), 129.74 (2C), 129.69 (2C), 129.45 (2C), 129.38, 129.32, 129.0 (2C), 123.2 (d, J = 5.2 Hz), 121.1 (d, J = 11.9 Hz), 111.0 (d, J = 2.9 Hz), 76.9 (d, J = 2.3 Hz), 72.3, 66.7 (d, J = 2.3 Hz), 59.3, 53.9; MS (FAB$^+$) m/z (M + H$^+$) calcd 426.1717, obsd 426.1722; $[\alpha]^{23}_D$ +3.18 (*c* 1.56, MeOH). Anal. Calcd for $C_{24}H_{25}ClFNO_5$: C, 62.41; H, 5.46; N, 3.03. Found: C, 62.43; H, 5.55; N, 3.03. HPLC: ee ≥99% (Chiralpak AD; 1:1 *n*-hexane/EtOH + 0.2% diethylamine; flow rate 1 mL/min; retention time (2*S*,3*R*)-enantiomer = 16.22 min, (2*R*,3*S*)-enantiomer = 10.02 min).

(2*S*,3*R*)-2-Amino-3-[4,5-bis(benzyloxy)-2-fluorophenyl]-3-hydroxypropionic Acid Methyl Ester (9c). In the same manner, compound **8c** (620 mg, 1.18 mmol) in 4.0 mL ethyl acetate was treated with 2.0 mL of ethyl acetate saturated with HCl gas. Workup as before and purification by recrystallization from methanol, ethyl acetate, and ether gave 502

mg (92%) of **9c** as a white solid: mp 147−148 °C; ^{1}H NMR (CD_3OD) δ 7.47−7.44 (m, 4H), 7.38−7.30 (m, 6H), 7.28 (d, J = 7.5 Hz, 1H), 6.91 (d, J = 12.0 Hz, 1H), 5.39 (d, J = 4.8 Hz, 1H), 5.15 (s, 2H), 5.12 (s, 2H), 4.15 (d, J = 4.8 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (CD_3OD) δ 169.0, 155.7 (d, J = 237.9 Hz), 151.8 (d, J = 10.3 Hz), 147.0 (d, J = 2.9 Hz), 138.7, 138.2, 129.7 (2C), 129.6 (2C), 129.3, 129.2, 129.0 (2C), 128.8 (2C), 118.9 (d, J = 14.9 Hz), 115.6 (d, J = 5.1 Hz), 104.0 (d, J = 27.3 Hz), 73.4, 72.4, 66.4, 59.4, 53.9; MS m/z (M^+) calcd 425.1639, obsd 425.1641; $[\alpha]^{23}_D$ +0.62 (c 1.0, MeOH). Anal. Calcd for $C_{24}H_{25}ClFNO_5$: C, 62.41; H, 5.46; N, 3.03. Found: C, 62.28; H, 5.46; N, 3.03. HPLC: ee ≥98% (Chiralpak AD; 1:1 *n*-hexane/EtOH + 0.2% diethylamine; flow rate 1 mL/min; retention time (2*S*,3*R*)-enantiomer = 14.68 min, (2*R*,3*S*)-enantiomer = 11.22 min).

(2*S*,3*R*)-2-Amino-3-[3,4-bis(benzyloxy)-2-fluorophenyl]-3-hydroxypropionic Acid (10b). To a solution of compound **9b** (40 mg, 0.87 mmol) in MeOH (2.5 mL) immersed in a room-temperature water bath was added dropwise 2 N NaOH (2.5 mL). The heterogeneous milky reaction mixture was stirred for 1 d at room temperature and then concentrated in vacuo to remove MeOH. The aqueous solution was then cooled to 0 °C and neutralized to pH 6−7 by slow addition of concentrated HCl followed by final adjustment with 1 N HCl. The resulting white precipitate was filtered and washed with cold water and ether to give 34.4 mg (96%) of compound **10b**: white solid; mp 170−172 °C; ^{1}H NMR (DMSO-d_6) δ 7.48−7.32 (m, 10H), 7.17 (d, J = 8.4 Hz, 1H), 6.98 (d, J = 8.7 Hz, 1H), 5.28 (d, J = 3.3 Hz, 1H), 5.18 (d, J = 12.6 Hz, 1H), 5.14 (d, J = 12.6 Hz, 1H), 5.02 (s, 2H), 3.31 (d, J = 3.6 Hz, 1 H); ^{13}C NMR (DMSO-d_6) δ 167.9, 153.0 (d, J = 242.5 Hz), 151.8 (d, J = 4.6 Hz), 137.2, 136.8, 135.3 (d, J = 13.7 Hz), 128.5 (2C), 128.2 (2C), 128.1 (2C), 128.04, 127.98, 127.7 (2C), 122.7 (d, J = 12.5 Hz), 122.1, 109.1, 75.0, 70.3, 64.9, 58.3; MS (FAB$^-$) m/z (M^+-H) calcd 410.1404, obsd 410.1390; $[\alpha]^{23}_D$ −6.2 (c 0.52, DMSO).

(2*S*,3*R*)-2-Amino-3-[4,5-bis(benzyloxy)-2-fluorophenyl]-3-hydroxypropionic Acid (10c). Saponification of **9c** (40 mg, 0.87 mmol) in MeOH (2 mL) by the same procedure gave 34 mg (94%) of **10c**: white solid; mp 147−148 °C; ^{1}H NMR (CD_3OD) δ 7.47−7.30 (m, 11H), 6.88 (d, J = 11.7 Hz, 1H), 5.51 (d, J = 3.0 Hz, 1H), 5.13 (br s, 4H), 3.74 (d, J = 3.6 Hz, 1H); ^{13}C NMR (CD_3OD) δ 172.0, 155.7 (d, J = 237.9 Hz), 151.2 (d, J = 10.2 Hz), 146.8 (d, J = 2.9 Hz), 138.9, 138.4, 129.7 (2C), 129.6 (2C), 129.2, 129.1, 129.0 (2C), 128.8 (2C), 121.0 (d, J = 15.3 Hz), 115.8 (d, J = 5.6 Hz), 104.2 (d, J = 26.7 Hz), 73.4, 72.4, 66.7, 61.0; MS (FAB$^-$) m/z (M^+ − H) calcd 410.1404, obsd 410.1402; $[\alpha]^{23}_D$ −15.3 (c 0.15, MeOH).

(2*S*,3*R*)-3-(3,4-Dihydroxyphenyl-2-fluorophenyl)-serine (2-F-L-*threo*-DOPS) (1b). Compound **10b** (50 mg, 0.12 mmol) was dissolved in a 4:1 mixture of MeOH and 3 N HCl (20 mL), and 50 mg of 10% Pd/C was added. The heterogeneous solution was put under hydrogen balloon and stirred for 2 h at room temperature. The mixture was filtered through a pad of Celite to remove catalyst and then concentrated in vacuo. The residue was purified using a Dowex 50-8x column to give 30.5 mg (94%) of the desired **1b**: gray solid, mp >250 °C; ^{1}H NMR (CD_3OD) δ 6.90 (t, J = 8.4 Hz, 1H), 6.67 (d, J = 8.7 Hz, 1H), 5.46 (d, J = 3.9 Hz, 1H), 4.09 (d, J = 3.9 Hz, 1H); ^{13}C NMR (CD_3OD) δ 169.9, 150.7 (d, J = 236.8 Hz), 149.1 (d, J = 4.0 Hz), 134.8 (d, J = 16.0 Hz), 119.2 (d, J = 11.9 Hz), 117.9 (d, J = 4.6 Hz), 112.1 (d, J = 2.3 Hz), 66.8 (d, J = 2.3 Hz), 59.3; MS (FAB$^+$) m/z (M^+ + H) calcd 232.0621, obsd 232.0620; $[\alpha]^{23}_D$ −13.1 (c 1.0, 1 M HCl), −15.1 (c 0.65, MeOH).

(2*S*,3*R*)-3-(4,5-Dihydroxyphenyl-2-fluorophenyl)-serine (6-F-L-*threo*-DOPS) (1c). To a solution of compound **10c** (60 mg, 0.146 mmol) in MeOH (24 mL) was added 120 mg of 10% Pd/C. The flask was connected to a hydrogen-filled balloon and stirred for 2 h at room temperature. After removal of catalyst by filtration and concentration, the resulting solid was purified by recrystallization from MeOH and ether to give 27 mg (80%) of the desired **1c**: dark brown solid; mp >250 °C; ^{1}H NMR (CD_3OD) δ 7.00 (d, J = 7.5 Hz, 1H), 6.54 (d, J = 11.4 Hz, 1H), 5.45 (d, J = 3.3 Hz, 1H), 3.71 (d, J = 3.6 Hz, 1H); ^{13}C NMR (CD_3OD) δ 172.3, 154.5 (d, J = 234.5 Hz), 147.2 (d, J = 11.4 Hz), 143.0 (d, J = 2.3 Hz), 119.3 (d, J = 14.8 Hz), 114.9 (d, J = 5.1 Hz), 104.1 (d, J = 26.2 Hz), 66.9, 61.1; MS (FAB$^+$) m/z (M^+ + H) calcd 232.0621, obsd 232.0618; $[\alpha]^{23}_D$ −22.6 (c 0.073, MeOH).

Supporting Information Available: The IR spectra of compounds **1b**,**c**−**10b**,**c** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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