Regioselective Asymmetric Aminohydroxylation Approach to a β-Hydroxyphenylalanine Derivative for the Synthesis of Ustiloxin D

Haengsoon Park, Bin Cao, and Madeleine M. Joullié*

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323

mjoullie@sas.upenn.edu

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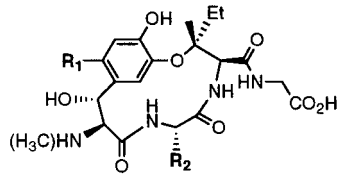
β-Hydroxy-α-amino acids are often found as key motifs in biologically active natural products. For example, β-hydroxytyrosine and β-hydroxyphenylalanine residues are structural subunits of many important macrocyclic peptide antibiotics such as vancomycin,[1] bouvardin,[2] orienticins,[3] and phomopsins.[4] These amino acids are also useful building blocks for the synthesis of β-lactams.[5] As part of our synthetic studies toward ustiloxin D[6a] (**1d**, Figure 1), an efficient method was sought for the asymmetric synthesis of a β-hydroxyphenylalanine derivative (**2**, Scheme 1) as a key intermediate. Ustiloxins,[6] whose structures are closely related to those of phomopsins, were isolated from the water extracts of false smut balls caused on the panicles of the rice plant by a fungus, *Ustilaginoidea virens*. They are potent inhibitors of microtubule assembly and anticancer drug leads.[6d,f]

A literature survey revealed that several strategies have been devised for the asymmetric syntheses of β-hydroxy-α-amino acids: the alkylation of chiral enolates from oxazolidinones, bis-lactims, oxazolines, oxazolidines, and imidazolidinones; the cycloaddition of chiral azomethine ylids; enzymatic transformations; and syntheses via catalytic asymmetric epoxidation, dihydroxylation, aminohydroxylation, and aldol reactions.[7] Since most of these synthetic routes involve a multistep



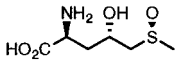
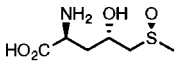
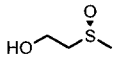
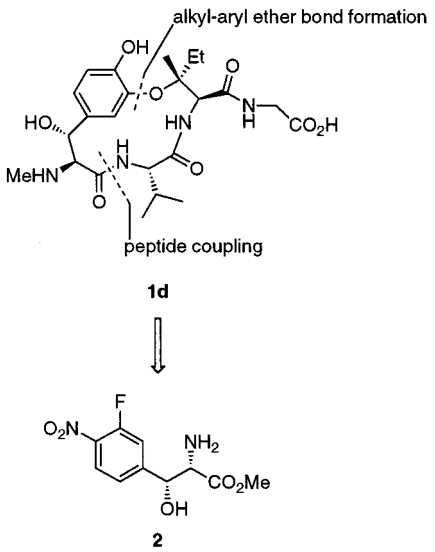
Coumpound Name	R_1	R_2
Ustiloxin A (**1a**)		$CH(CH_3)_2$
Ustiloxin B (**1b**)		CH_3
Ustiloxin C (**1c**)		CH_3
Ustiloxin D (**1d**)	H	$CH(CH_3)_2$
Ustiloxin F (**1e**)	H	CH_3

Figure 1. Structures of ustiloxins.

Scheme 1



preparation of each corresponding chiral auxiliary, intermediate, or a chiral catalyst system, rapid and efficient methods for the synthesis of these important building blocks are still desired. For the synthesis of β-hydroxyphenylalanine derivative **2**, we investigated the Sharpless asymmetric aminohydroxylation[8] (AA) which could install the requisite stereochemistry of the vicinal amino alcohol function of **2** in a single step. Sharpless and co-workers recently discovered that the use of the AQN ligand

* To whom correspondence should be addressed. E-mail: mjoullie@sas.upenn.edu.

(1) (a) Williams, D. H. *Acc. Chem. Res.* **1984**, *17*, 364 and references therein. (b) Kopecka, H.; Harris, T. M. *J. Am. Chem. Soc.* **1983**, *105*, 6915 and references therein.

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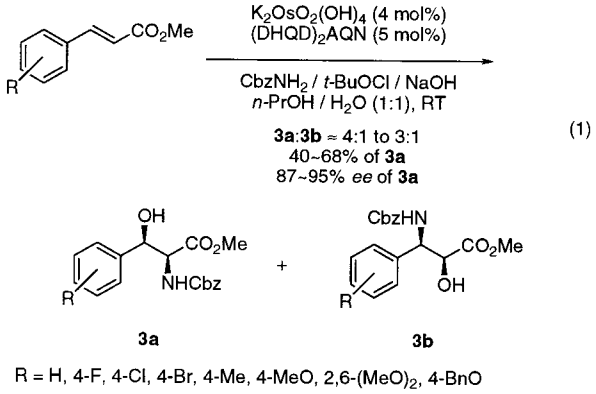
system in the osmium-catalyzed AA reaction of cinnamates reversed the regiochemical outcomes of the previously known PHAL ligand system, affording the N-protected β-hydroxy-α-amino regioisomer as the major product (eq 1).[7j] Yet, the regioselectivities were moderate, ranging from 4:1 to 3:1, and did not reach to the levels which can be produced for the corresponding α-hydroxy-β-amino regioisomers by the PHAL ligand. Electron-deficient cinnamates were also found to be problematic substrates with the AQN ligand; the AA of *m*-nitrocinnamate afforded a 1:1 mixture of two regioisomers (enantioselectivities not reported) and a substantial quantity of the diol byproduct. Panek and co-workers, using the same ligand, found that *p*-aryl esters substituted with strong electron-withdrawing groups (e.g., *p*-NO_2) precluded the aminohydroxylation process.[9] On the other hand, in the AA of cinnamates, the PHAL ligand system appeared less affected by the electronic properties of the substrates. This ligand preferentially delivered the nitrogen to the β position with good regioselectivity and enantioselectivity to afford nitro-substituted α-hydroxy-β-amino derivatives.[8b,10,11]



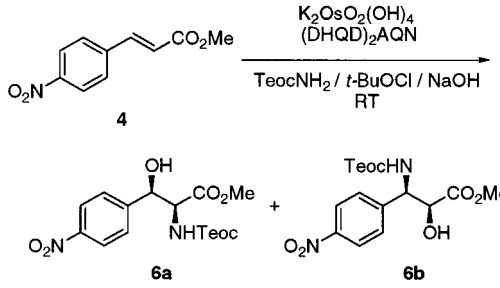
(1)

R = H, 4-F, 4-Cl, 4-Br, 4-Me, 4-MeO, 2,6-$(MeO)_2$, 4-BnO

In general, the selectivities of asymmetric catalytic reactions are highly substrate dependent. Herein, we wish to extend the scope of the Sharpless AA reaction to electron-deficient olefinic substrates using the AQN ligand for the synthesis of β-hydroxy-α-amino acid derivatives. This method may prove useful for the asymmetric syntheses of nitro- and/or fluoro-substituted aromatic amino acid building blocks[12,13] as well as other amino acids[14] employed in organic synthesis.

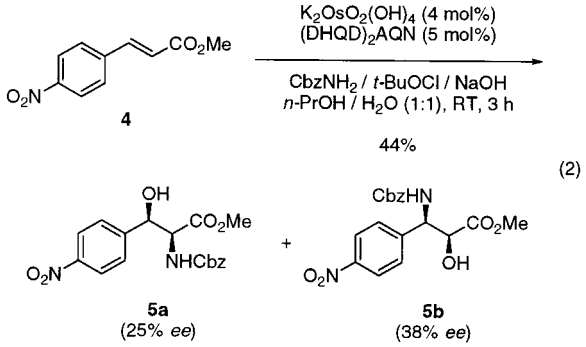
Initial tests for the AA reactions were carried out with *p*-nitrocinnamate **4** under standard carbamate conditions[7j] using benzyl carbamate and the $(DHQD)_2AQN$ ligand (eq 2). The reaction provided a mixture of two regioisomers (**5a** and **5b**, ca. 1:1) in 44% combined yield and significant amounts of the diol byproduct (~8%). The enantioselectivity obtained for the desired product **5a** was only 25%. To improve this result, other nitrogen sources were screened. The reported 2-trimethylsilylethyl carbamate ($TeocNH_2$)[10] seemed to be the reagent of choice for this substrate.

Table 1. AA Reactions Using $TeocNH_2$



entry	cat/lig[a] (mol %)	solvent 50% aq	selectivity[b] **6a**:**6b**	% yield[c] **6a**, **6b**	% ee[d] **6a**, **6b**
1	4/5	*n*−PrOH	7:3	45, 21	57, 68
2	8/9	*n*−PrOH	7:3	37, 17	67, 75
3	4/5	CH_3CN	1:1	26, 27	71, 92

[a] Catalyst = $K_2OsO_2(OH)_4$, Ligand = $(DHQD)_2AQN$. [b] Ratio of **6a** to **6b** determined by ^1H NMR (500 MHz) integration prior to separation. [c] Isolated yield of **6a** and **6b** after separation by column chromatography. [d] Enantiomeric excesses of **6a** and **6b** determined by HPLC analysis using a Chiralpak AD column with *n*-hexane/*i*-PrOH as the eluent.



(2)

The regioselectivities and enantioselectivities of the aminohydroxylation reactions using $TeocNH_2$ varied with reaction conditions (Table 1). The AA reaction with 4 mol % of the catalyst proceeded with a shorter reaction time of 1.5 h and a regioselectivity of 7:3 for **6a** and **6b**, affording a 45% isolated yield of the desired isomer **6a** in 57% ee (entry 1 of Table 1). Doubling the amount of the osmium catalyst and the AQN ligand slightly enhanced the enantioselectivities of **6a** and **6b** to 67 and 75%, respectively (entry 2 of Table 1). On the other hand, using CH_3CN/H_2O (1:1) as the solvent also led to a slight improvement in the enantioselectivity but diminished the regioselectivity to 1:1 (entry 3 of Table 1). Cinnamate **4** was unreactive to the aminohydroxylation at 0 °C. In all three cases, the formation of a small amount of dihydroxylated byproduct (<5%) was observed.

Encouraged by the results from the Teoc carbamate-based aminohydroxylation, we decided to prepare the desired β-hydroxyphenylalanine derivative **2** (Scheme 2). Although previously reported as a side product,[12e] cin-

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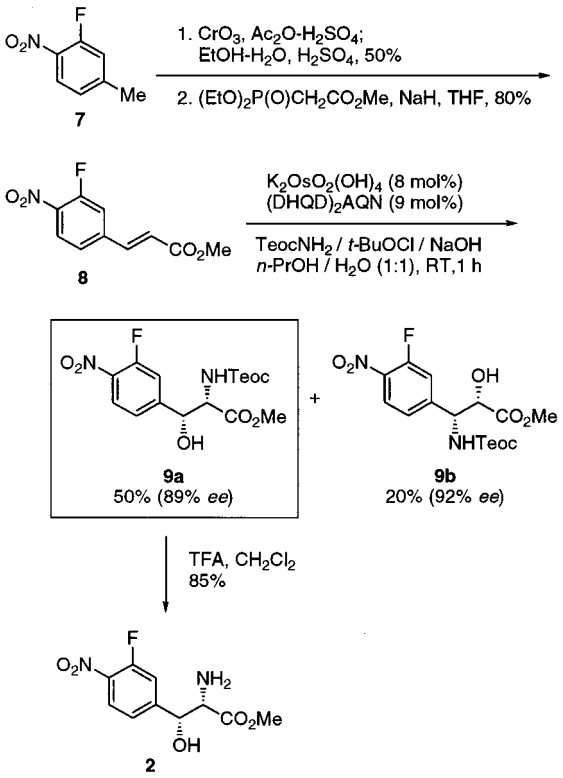
Scheme 2



namate **8** was prepared from commercially available 3-fluoro-4-nitrotoluene by chromium trioxide oxidation followed by acidic hydrolysis[15] and Horner−Emmons olefination. The following aminohydroxylation of cinnamate **8**, similar to the previous case, afforded two regioisomers **9a** and **9b** with a regioselectivity of 7:3 (50% of **9a**, 20% of **9b**). However, the enantioselectivity observed for **9a** (89% ee)was higher than that for **6a** (67% ee). The preparation of the desired amino alcohol **2** was achieved by removal of the Teoc protective group from **9a** with TFA in 85% yield.

In conclusion, the use of 2-trimethylsilylethyl carbamate as the nitrogen source in the Os(VIII)/$(DHQD)_2AQN$-catalyzed AA provided an efficient route to fluoro-, nitro-substituted β-hydroxyphenylalanine derivatives, which are useful building blocks[12] in synthetic and medicinal chemistry. Therefore, we have expanded the scope of the AA to electron-deficient aromatic substrates. Nitro-substituted phenyl β-hydroxyamino acid derivatives will allow the incorporation not only of the hydroxyl group but also of other nitrogen functional groups into natural products.[1] The method will be generally applicable for the asymmetric synthesis of other substituted aromatic amino acids[13,14] required for diverse purposes. Further studies toward the total synthesis of ustiloxin D based on these results will be reported in due course.

Experimental Section

General. Reactions requiring air-sensitive manipulations were conducted under nitrogen. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification. Methylene chloride was distilled from calcium hydride. The literature procedure was used to prepare 2-trimethylsilylethyl carbamate.[10] Analytical TLC was performed on 0.25 mm E. Merck silica gel 60 F_{254} plates. Merck silica gel (60, particle size 0.040−0.063 mm) was used for flash column chromatography. All ^{1}H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively. High-resolution mass spectra (HRMS) were recorded on a Micromass AutoSpec spectrometer using methane chemical ionization (CI) or electron impact (EI). Optical rotations were recorded on a Perkin-Elmer model 341 polarimeter at the sodium D line. Enantiomeric excesses were determined by HPLC using a Chiralpak AD column (conditions: 15% *i*-PrOH/hexane, 1 mL min^{-1}, 254 nm).

General Procedure for the Osmium-Catalyzed AA Reactions. Sodium hydroxide (60 mg, 1.5 mmol) was dissolved in water (4 mL), and 0.5 mL of this NaOH solution was transferred to a small vial containing $K_2OsO_2(OH)_4$ (0.020 mmol for 4 mol % and 0.040 mmol for 8 mol %) for later use. To the remainder of the NaOH solution were added the carbamate (1.55 mmol) and *n*-PrOH (2 mL). The mixture was stirred for 2−3 min and placed in a water bath before *tert*-butylhypochlorite[16] (175 μL, 1.52 mmol) was slowly added with vigorous stirring. Then, the resulting solution was sequentially treated with a solution of $(DHQD)_2AQN$ (0.025 mmol for 5 mol % and 0.045 mmol for 9 mol %) in *n*-PrOH (1 mL), the cinnamate (0.50 mmol), the previously prepared solution of $K_2OsO_2(OH)_4$, and *n*-PrOH (1 mL). The reaction mixture was monitored by TLC to establish completion, quenched by the addition of saturated aqueous sodium sulfite (4 mL) while being cooled in an ice−water bath, and stirred for an additional 30 min. The separated aqueous phase was extracted with EtOAc (3 × 5 mL), and the combined organic extracts were washed with water (3 mL) followed by brine (5 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography (EtOAc/hexanes) on a silica gel column.

Methyl (2*S*,3*R*)-2-[*N*-[(Benzyloxy)carbonyl]amino]-3-hydroxy-3-(4-nitrophenyl)propionate (5a) and Methyl (2*S*,3*R*)-3-[*N*-[(Benzyloxy)carbonyl]amino]-2-hydroxy-3-(4-nitrophenyl)propionate (5b). The reaction mixture (ca. **5a**:**5b** = 1:1) was chromatographed using 3:7 EtOAc/hexanes to yield 160 mg (44% combined yield) of the mixture of **5a** and **5b**. **5a**: ee = 25% [30.4 min (2*S*, 3*R*), 37.1 min (2*R*, 3*S*)]; R_f = 0.52 (1:1 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.17 (d, J = 8.2 Hz, 2H), 7.55 (d, J = 8.5 Hz, 2H), 7.40−7.25 (m, 5H), 5.55 (d, J = 8.1 Hz, 1H), 5.45 (s, 1H), 5.04 (d, J_{AB} = 12.2 Hz, 1H), 4.96 (d, J_{AB} = 12.2 Hz, 1H), 4.71 (d, J = 8.3 Hz, 1H), 3.88 (s, 3H), 2.86 (br s, 1H);^{13}C NMR ($CDCl_3$) δ 170.5, 156.1, 147.7, 146.6, 135.9, 128.5, 128.4, 128.1, 126.9, 123.6, 72.9, 67.3, 59.4, 53.0; HRMS (CI) calcd for $C_{18}H_{19}N_2O_7$ (M + H$^+$) 375.1192, found 375.1208. **5b**: ee = 38% [50.3 min (2*S*, 3*R*), 28.0 min (2*R*, 3*S*)]; R_f = 0.58 (1:1 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.23 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.2 Hz, 2H), 7.40−7.36 (m, 5H), 5.79 (d, J = 9.3 Hz, 1H), 5.39 (d, J = 8.9 Hz, 1H), 5.14−5.08 (m, 2H), 4.51 (br s, 1H), 3.86 (s, 3H), 3.30 (d, J = 3.4 Hz, 1H);^{13}C NMR ($CDCl_3$) δ 172.5, 155.6, 147.6, 146.2, 135.9, 128.5, 128.3, 128.1, 127.8, 123.8, 72.8, 67.3, 56.0, 53.4; HRMS (CI) calcd for $C_{18}H_{19}N_2O_7$ (M + H$^+$) 375.1192, found 375.1196.

Methyl (2*S*,3*R*)-3-Hydroxy-3-(4-nitrophenyl)-2-[*N*-[(trimethylsilylethoxy)carbonyl]amino]propionate (6a) and Methyl (2*S*,3*R*)-2-Hydroxy-3-(4-nitrophenyl)-3-[*N*-[(trimethylsilylethoxy)carbonyl]amino]propionate (6b) (Entry 1, Table 1). The reaction mixture (ca. **6a**:**6b** = 7:3) was chromatographed using EtOAc/hexanes (2:8 → 4:6, gradient elution) to yield 86 mg (45% yield) of **6a** and 41 mg (21% yield) of **6b**. **6a** (major isomer): $[\alpha]^{20}_D$ = −14.0 (*c* 0.56, $CHCl_3$); ee = 57% [14.4 min (2*S*, 3*R*), 21.4 min (2*R*, 3*S*)]; R_f = 0.52 (1:1 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.24 (d, J = 8.7 Hz, 2H), 7.60 (d, J = 8.6 Hz, 2H), 5.44 (s, 1H), 5.39 (br d, J = 8.0 Hz, 1H), 4.68 (br d, J = 7.3 Hz, 1H), 4.07 (br m, 2H), 3.84 (s, 3H), 2.98 (s, 1H), 0.91 (br m, 2H), 0.02 (s, 9H);^{13}C NMR ($CDCl_3$) δ 170.6, 156.5, 147.7, 146.8, 126.9, 123.6, 73.0, 64.0, 59.4, 52.9, 17.6, −1.6; HRMS (CI) calcd for $C_{16}H_{25}N_2O_7Si$ (M + H$^+$) 385.1430, found 385.1455. **6b** (minor isomer): $[\alpha]^{20}_D$ = −17.3 (*c* 0.55, $CHCl_3$); ee = 68% [20.8 min (2*S*, 3*R*), 12.8 min (2*R*, 3*S*)]; R_f = 0.60 (1:1 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.25 (d, J = 8.5 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 5.60 (d, J = 9.1 Hz, 1H), 5.37 (d, J =

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8.6 Hz, 1H), 4.51 (s, 1H), 4.17 (t, J = 8.5 Hz, 2H), 3.91 (s, 3H), 3.26 (br s, 1H), 1.00 (br t, J = 8.1 Hz, 2H), 0.05 (s, 9H);^{13}C NMR ($CDCl_3$) δ 172.6, 155.8, 147.6, 146.5, 127.9, 123.8, 72.9, 63.9, 55.9, 53.5, 17.6, −1.5; HRMS (CI) calcd for $C_{16}H_{25}N_2O_7Si$ (M + H^+) 385.1430, found 385.1433.

Methyl (2*S*,3*R*)-3-[(3-Fluoro-4-nitro)phenyl]-3-hydroxy-2-[*N*-[(trimethylsilylethoxy)carbonyl]amino]propionate (9a) and Methyl (2*S*,3*R*)-3-[(3-Fluoro-4-nitro)phenyl]-2-hydroxy-3-[*N*-[(trimethylsilylethoxy)carbonyl]amino]propionate (9b). The reaction mixture (ca. **9a**:**9b** = 7:3) was chromatographed using EtOAc/hexanes (2:8 → 3:7, gradient elution) to yield 100 mg (50% yield) of **9a** and 39 mg (20% yield) of **9b**. **9a** (major isomer): $[\alpha]^{20}_D$ = −25.6 (*c* 0.44, $CHCl_3$); ee = 89% [11.0 min (2*S*, 3*R*), 16.3 min (2*R*, 3*S*)]; R_f = 0.36 (4:6 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.09 (t, J = 8.0 Hz, 1H), 7.43−7.32 (m, 2H), 5.42 (s, 1H), 5.36 (br d, J = 8.8 Hz, 1H), 4.67 (br d, J = 7.8 Hz, 1H), 4.10 (t, J = 8.3 Hz, 2H), 3.85 (s, 3H), 3.00 (s, 1H), 0.93 (br m, 2H), 0.03 (s, 9H);^{13}C NMR ($CDCl_3$) δ 170.4, 155.9, 155.5 (d, J = 265.5 Hz), 148.9 (d, J = 7.8 Hz), 136.6, 126.1, 121.9 (d, J = 3.7 Hz), 116.2 (d, J = 21.9 Hz), 72.3, 64.1, 59.2, 53.0, 17.6, −1.6; HRMS (EI) calcd for $C_{16}H_{23}N_2O_7FNaSi$ (M + Na^+) 425.1155, found 425.1184. **9b** (minor isomer): $[\alpha]^{20}_D$ = −21.4 (*c* 0.56, $CHCl_3$); ee = 92% [13.8 min (2*S*, 3*R*), 9.5 min (2*R*, 3*S*)]; R_f = 0.48 (4:6 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.06 (t, J = 8.0 Hz, 2H), 7.37−7.33 (m, 2H), 5.56 (d, J = 9.2 Hz, 1H), 5.29 (br d, J = 8.7 Hz, 1H), 4.47 (s, 1H), 4.15 (t, J = 8.5 Hz, 2H), 3.88 (s, 3H), 3.25 (d, J = 3.1 Hz, 1H), 0.99−0.95 (m, 2H), 0.02 (s, 9H);^{13}C NMR ($CDCl_3$) δ 172.4, 155.8, 155.6 (d, J = 265.7 Hz), 148.4, 136.6, 126.3, 123.0, 117.1 (d, J = 21.6 Hz), 72.6, 64.0, 55.6, 53.5, 17.6, −1.5; HRMS (EI) calcd for $C_{16}H_{23}N_2O_7FNaSi$ (M + Na^+) 425.1155, found 425.1175.

Methyl (2*S*,3*R*)-2-Amino-3-hydroxy-3-[(3-fluoro-4-nitro)-phenyl]propionate (2). A solution of **9a** (20 mg, 0.050 mmol) in CH_2Cl_2 (80 μL) was treated with trifluoroacetic acid (80 μL, 1.0 mmol) at 0 °C under nitrogen. The reaction mixture was stirred for 1 h, diluted with EtOAc (10 mL), and neutralized with saturated aqueous $NaHCO_3$. The separated aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with water followed by brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed using 1:10 MeOH/$CHCl_3$ to yield 11 mg (85% yield) of amino alcohol **2** as a white solid. **2**: ^{1}H NMR ($CDCl_3$) δ 8.06 (t, J = 8.0 Hz, 1H), 7.38−7.27 (m, 2H), 4.95 (d, J = 4.5 Hz, 1H), 3.75 (s, 3H), 3.62 (d, J = 4.5 Hz, 1H), 1.65 (br s, 3H);^{13}C NMR (DMSO-d_6) δ 173.7, 154.3 (d, J = 260.8 Hz), 153.1 (d, J = 7.9 Hz), 135.3, 125.5, 122.9 (d, J = 3.1 Hz), 116.1 (d, J = 21.3 Hz), 72.6, 60.0, 51.7; HRMS (EI) calcd for $C_{10}H_{11}N_2O_5FNa$ (M + Na^+) 281.0549, found 281.0544.

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