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Enantiospecific Synthesis of Genetically Encodable Fluorescent Unnatural Amino Acid L-3-(6-Acetylnaphthalen-2-ylamino)-2-aminopropanoic Acid

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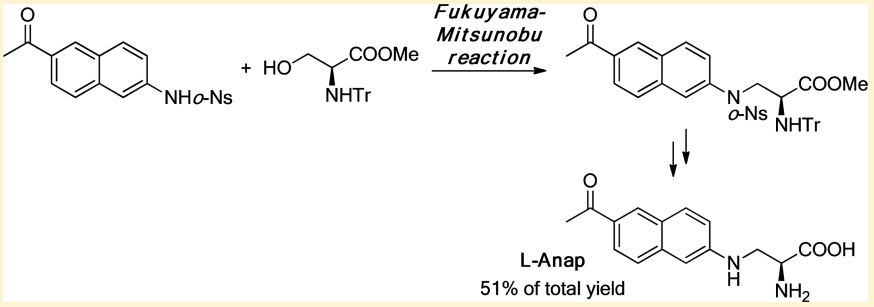
Supporting Information

ABSTRACT:



Fluorescent unnatural amino acids (UAAs), when genetically incorporated into proteins, can provide unique advantages for imaging biological processes in vivo. Synthesis of optically pure L-enantiomer of fluorescent UAAs is crucial for their effective application in live cells. An efficient six-step synthesis of L-3-(6-acetylnaphthalen-2-ylamino)-2-aminopropanoic acid (L-Anap), a genetically encodable and polarity-sensitive fluorescent UAA, has been developed. The synthesis takes advantage of a high-yield and enantiospecific Fukuyama−Mitsunobu reaction as the key transformation.

The past decade has witnessed the dramatic progress on site-specific incorporation of unnatural amino acids (UAAs) into proteins in live cells through the expansion of the genetic code.[1−4] Using engineered tRNA-synthetase pairs orthogonal to endogenous counterparts in the host cell, more than 70 UAAs have been incorporated into proteins in *Escherichia coli*, yeast, or mammalian cells, which enable new opportunities to study biological problems with expanding nonproteinogenic chemistries. Fluorescent UAAs (Figure 1), including L-dansylalanine (**1**),[5−7] L-(7-hydroxycoumrin-4-yl)ethylglycine (**2**),[8] and L-Anap (**3**),[9] are of particular interest for molecular and cellular biology, which may complement and enchance the widely used fluorescent proteins (FPs).[10] These fluorescent UAAs can be incorporated at virtually any site of a protein, whereas the fusion of FPs is often limited to the N- or C-terminus or certain loop regions. In addition, fluorescent UAAs are much smaller than FPs, which helps to mitigate undesired perturbations to the structure and function of the target protein. Moreover, when developing fluorescent reporters, sensitivity to different environment cues such as pH and polarity can be chemically designed and integrated[11] into the fluorescent UAAs, a flexibility not readily available for FPs.

Despite the potential advantages, effective application of fluorescent UAAs in live cells faces multiple challenges. Efficient synthesis of optically pure UAAs is a foremost demand.

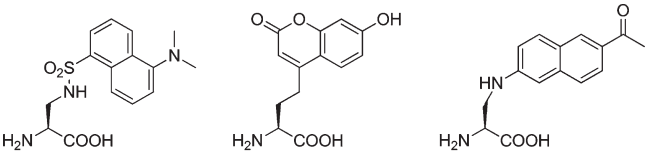


Figure 1. Genetically encoded fluorescent UAAs.

When racemic UAAs are fed to cells, the D-enantiomer competes for cellular uptake yet cannot be incorporated into proteins by the ribosome.[2] This reduces the net intracellular concentration of the bioactive L-enantiomer, leading to lower incorporation efficiency. For fluorescent UAAs in particular, the intracellular D-enantiomer further increases background fluorescence, which is a critical issue for cell imaging with UAAs. Synthetic routes to enantiomerically pure **1** and **2** have been developed,[5,12] but only a racemic synthesis is available for UAA **3**.[9] Anap is sensitive to polarity with changes in intensity and emission wavelength.[9] UAA **3**, when selectively incorporated into proteins, has the potential to

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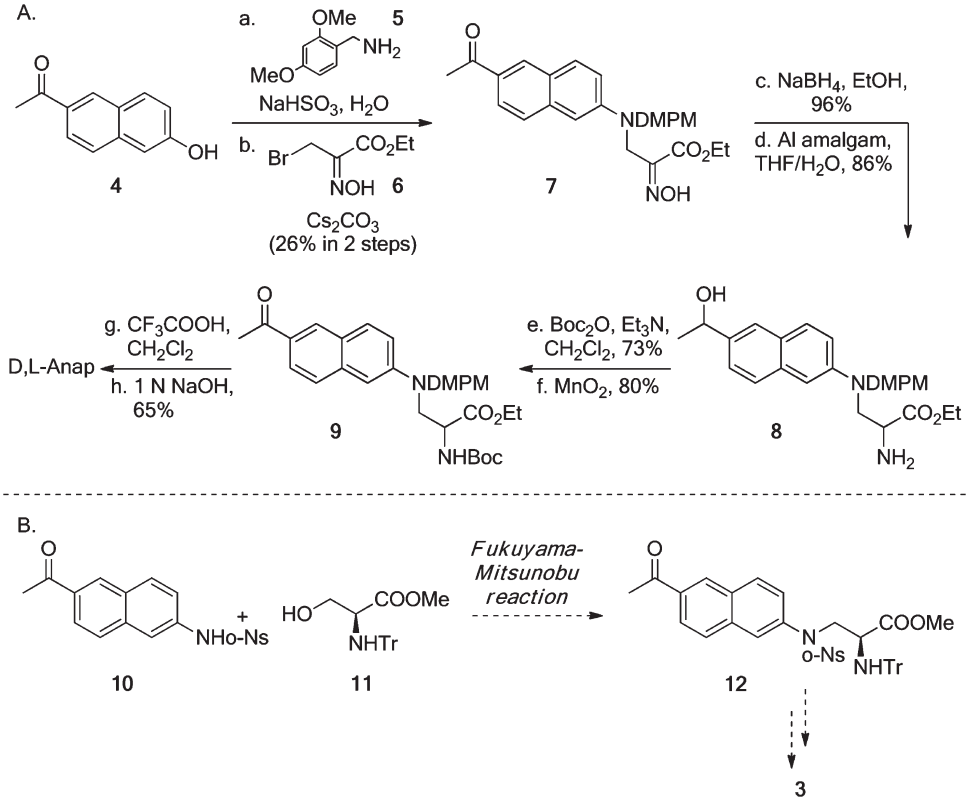
Scheme 1. Synthetic Approach for D,L-Anap (A) and Synthetic Strategy for L-Anap (B)



fluorescently report protein conformational changes, interactions, modifications, and activities in live cells. Herein, we report a concise and efficient synthetic approach of L-Anap, which offers significant improvements over the current synthesis.

L-Anap has been incorporated into proteins in *Saccharomyces cerevisiae* by Schultz and co-workers.[9] They developed a synthetic approach of racemic Anap, which gives 8.1% of total yield over eight steps (Scheme 1A). The synthesis was based on the nucleophilic substitution of ethyl bromopyruvate oxime (**6**) developed by Gilchrist and co-workers.[13,14] Presumably due to the low nucleophilicity of the Burcherer reaction product of **4** and **5**, compound **7** was synthesized in only 26% yield over two steps from compound **4**.[15] Another drawback of this synthesis resides in the nonstereoselective reduction of **7**, which leads to the final racemic product.

To synthesize sufficient amounts of L-Anap, we decided to develop an efficient and enantiospecific synthetic pathway toward L-Anap (Scheme 1B). Our synthetic strategy involves Fukuyama–Mitsunobu reaction[16−18] as the key step, which couples compound **10** with *N*-trityl-L-serine methyl ester **11**[19] to give intermediate **12**. This approach has two features: First, both the nucleophile and the electrophile are channeled to facilitate the intermolecular coupling by tuning the electronic effect of the protecting groups. *o*-Nitrobenzenesulfonyl group makes **10** a good nucleophile under Mitsunobu condition and can be removed easily under mild conditions. Trityl group of compound **11** can conduct the reactive intermediate through the intermolecular coupling and circumvent β-elimination as the side reaction. Second, the Mitsunobu reactions of **11** with different nucleophiles have been proved to be free of racemization;[19] therefore, intermediate **12** is expected to be synthesized enantiospecifically.

We commenced with the synthesis of 6-acyl-2-naphthylamine (**13**) via two pathways (Scheme 2). In approach A, the selective Heck reaction[20−22] and Cu(I)-catalyzed C−N[23,24] bond formation were employed to introduce the acetyl and amino groups. 6-Bromo-2-naphthol (**14**) was transformed to triflate **15**, which was coupled with butyl vinyl ether through Cabri's procedure,[20−22] followed by treatment with acid, to give intermediate **16**. Under Buchwald's condition,[25] compound **16** underwent the C−N bond formation to give intermediate **17** in 75% yield. After deprotection, compound **13** was obtained in 54% yield over four steps. Although this approach provided gram-scale synthesis of **13** with satisfactory yield, approach B, which took three steps less than A, was explored in parallel. Approach B features the direct conversion of the hydroxyl group of compound **4** to an amino group. Although this transformation via Burcherer reaction[26] has been reported by Cho and his co-workers,[27] the procedure involves stirring the reaction mixture at 140 °C for 96 h in a steel-bomb reactor, which is not viable in many biology laboratories. Inspired by recent advances in one-pot alkylation−Smiles rearrangement−hydrolysis[28] sequence, we applied Mizuno and Yamano's procedure to the transformation of **4** to **13**. Monitoring the reaction with TLC showed the complete conversion of the alkylation and Smiles rearrangement steps. However, the in situ hydrolysis of **19** under basic conditions was incomplete and the final product **13** was difficult to separate from intermediate **19**. Therefore, the crude product of **19** was separated and hydrolyzed under acidic condition, which provided compound **13** in 73% yield.

With compound **13** in hand, we set out to explore the Fukuyama–Mitsunobu reaction (Scheme 3). Compound **13** was treated with *o*-nitrobenzenesulfonyl chloride and pyridine to give compound **10**. In the presence of diisopropyl

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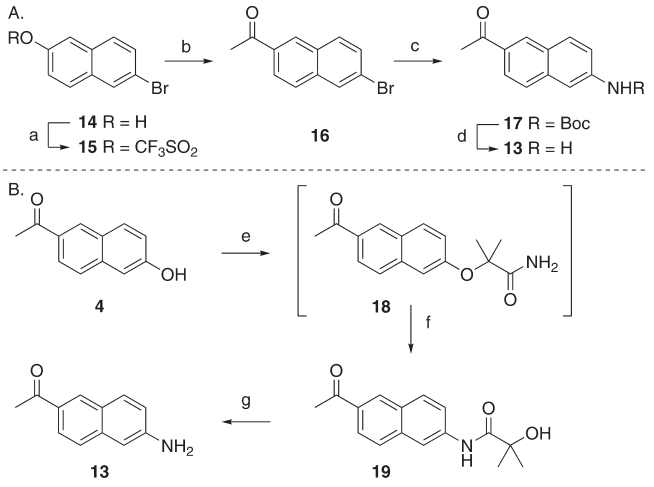
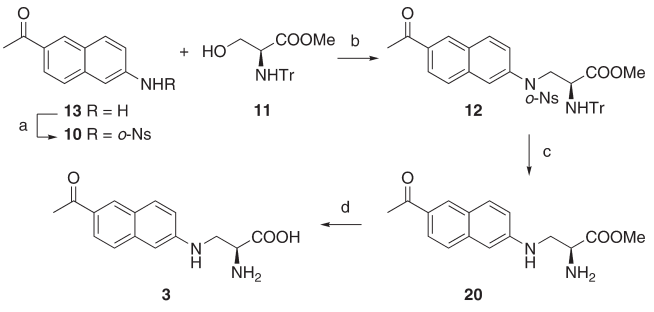
Scheme 2. Synthesis of Compound 13



Reagents and conditions: (a) $PhNTf_2$, DIPEA, CH_2Cl_2, rt, 12 h; (b) butyl vinyl ether, $Pd(OAc)_2$, dppp, Et_3N, DMF, 80 °C, 2 h; then 1 M HCl, 72% over 2 steps; (c) *t*-butyl carbamate, CuI, *N,N′*-dimethylethylenediamine, K_2CO_3, toluene, 110 °C, 75%; (d) CF_3COOH, CH_2Cl_2, 99%; (e) NaOH, 2-bromo-^{2}-methylpropanamide, DMA, (f) NaOH, 50 °C; (g) HCl, reflux, 73%

Scheme 3. Synthesis of L-Anap



Reagents and conditions: (a) *o*-NsCl, pyridine, CH_2Cl_2; (b) DIAD, PPh_3, toluene, 88% over 2 steps; (c) i. CF_3COOH, CH_2Cl_2, ii. PhSH, K_2CO_3, DMF, 80%; (d) 2 M HCl, 60 °C, 8 h, 99%

azodicarboxylate and triphenylphosphine, compounds **10** and **11** were coupled to give intermediate **12** in 88% yield over two steps. Sequential deprotection of trityl group and *o*-nitrobenzensulfonyl group furnished L-Anap methyl ester (**20**). Deprotection of **20** under acidic condition[29,30] furnished L-Anap as its hydrochloride salt. The enantiomeric purity of **3** was examined with the Mosher method,[31] and the dr value was above 40:1, which indicated that less than 3% racemization had occurred during deprotection (see Supporting Information).

In conclusion, we developed an efficient synthetic route to enantiomerically pure L-Anap, which gives 51% of total yield. Compared to the previous method, our synthetic approach not only afforded a bioactive L-enantiomer but also enabled a 12-fold increase in yield with fewer steps. All the reactions of our approach proceeded under mild conditions as well as in gram-scale. The general approach demonstrated here can also be applied to the synthesis of other 3-*N*-aryl-2,3-diaminopropanoic acids, which serve as important building blocks for medicinal small molecules.[32−34] The application of L-Anap to image protein modifications and activities in mammalian cells is in process and will be reported in due course.

EXPERIMENTAL SECTION

1-(6-Bromonaphthalen-2-yl)ethanone 16. To a solution of 6-bromo-2-naphthol **14** (2.231 g, 10 mmol) in CH_2Cl_2 (50 mL) were added DIPEA (1.92 mL, 11 mmol) and $PhNTf_2$ (3.930 g, 11 mmol) at room temperature. The reaction mixture was stirred under nitrogen for 12 h and concentrated under vacuum. The residue was filtered through a short silica gel column and eluted with EtOAc/hexanes (1/19). The solution was concentrated under vacuum to give the crude product of **15** as a yellow oil. **15** was dissolved in DMF (20 mL). Et_3N (2.79 mL, 20 mmol), butyl vinyl ether (6.47 mL, 50 mmol), dppp (113.4 mg, 0.275 mmol), and $Pd(OAc)_2$ (56.1 mg, 0.25 mmol) were added to the solution sequentially. The mixture was stirred under nitrogen at 80 °C for 2 h and then cooled to 0 °C. A 2 M HCl solution (20 mL) was added to the reaction mixture slowly, and the mixture was stirred for 0.5 h. Water (120 mL) and EtOAc (50 mL) were added to the mixture. The two phases were separated, and the aqueous phase was washed twice with EtOAc (50 mL). The organic phases were combined and washed with brine (30 mL), dried over anhydrous Na_2SO_4, concentrated, and purified with flash chromatography (EtOAc/hexanes = 1/7) to give compound **16** (1.798 g, 72%) as white solid. R_f = 0.23 (EtOAc/hexances = 1/6). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.41 (s, 1 H), 8.05 (d, J = 1.5 Hz, 1H), 8.04 (s, 1H), 7.82 (d, J = 9.0 Hz, 1H), 7.79 (d, J = 8.5 Hz, 1H), 7.62 (dd, J = 9.0, 2.0 Hz, 1H), 2.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.8, 136.6, 134.9, 131.2, 131.1, 130.4, 130.1, 127.6, 125.2, 123.0, 26.8. HRMS (EI): calcd for $C_{12}H_9BrO$: 247.9831, found 247.9832.

***tert*-Butyl 6-Acetylnaphthalen-2-ylcarbamate 17.** To the mixture of compound **16** (1.993 g, 8 mmol), *tert*-butyl carbamate (1.125 g, 9.6 mmol), CuI (76.2 mg, 0.40 mmol), and K_2CO_3 (2.211 g, 16 mmol) was added *N,N′*-dimethylethylenediamine (86.1 μL, 0.80 mmol) and toluene (16 mL). The mixture was stirred under nitrogen at 110 °C for 24 h. After being cooled to room temperature, the reaction mixture was filtered and washed with EtOAc (20 mL). The filtrate was concentrated and purified by flash chromatography (EtOAc/hexanes = 1/3) to give compound **17** (1.719 g, 75%) as white solid. R_f = 0.29 (EtOAc/hexanes = 3/7). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.37 (s, 1H), 8.07 (s, 1H), 7.99 (dd, J = 9.0, 1.5 Hz, 1H), 7.86 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.42 (dd, J = 8.5, 2.0 Hz, 1H), 6.85 (s, 1H), 2.70 (s, 3H), 1.56 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.1, 152.7, 138.5, 136.7, 133.3, 130.7, 130.0, 128.9, 127.9, 124.8, 119.9, 114.0, 81.2, 28.5, 26.7. HRMS (ESI-FT): $[M + H]^+$ calcd for $C_{17}H_{20}NO_3$, 286.1438; found 286.1441.

6-Acyl-2-naphthylamine 13. To a solution of compound **17** (1.427 g, 5 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added TFA (5 mL) dropwise. The reaction mixture was stirred at room temperature for 3 h and concentrated under vacuum. The residue was dissolved in dichloromethane (100 mL) and washed with saturated Na_2CO_3 aqueous solution and brine. The organic phase was dried over Na_2SO_4 and concentrated to give compound **13** (0.919 g, 99%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.31 (d, J = 1.5 Hz, 1H), 7.92 (dd, J = 8.5, 1.5 Hz, 1H), 7.75 (d, J = 8.5 Hz, 1H), 7.58 (d, J = 8.5 Hz, 1H), 6.97 (dd, J = 8.5, 2.5 Hz, 1H), 6.95 (d, J = 2.0 Hz, 1H), 4.08 (br s, 2 H), 2.66 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.0, 146.9, 137.8, 131.5, 131.3, 130.6, 126.6, 126.1, 124.8, 118.9, 108.0, 26.6.

6-Acyl-2-naphthylamine 13. To a solution of compound **4** (558.6 mg, 3 mmol) in DMA (6 mL) was added NaOH (360 mg, 9 mmol). The resulting mixture was stirred at room temperature for 1 h. 2-Bromo-2-methylpropanamide (1.494 g, 9 mmol) was added to the mixture. After the mixture was stirred at room temperature overnight, TLC showed complete conversion of compound **4**. NaOH (1.080 g, 27 mmol) was added, and the resulting mixture was stirred at 50 °C for 5 h. Water (60 mL) was added to the mixture and was extracted with CH_2Cl_2 (25 mL) for three times. The combined organic phase was concentrated and redissolved in ethanol (15 mL) and 6 M HCl solution (15 mL). The mixture was refluxed until TLC showed complete conversion of

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compound **19**. After the mixture was cooled to room temperature, most of EtOH was removed under reduced pressure. The residue was diluted with EtOAc and water. The aqueous solution was neutralized with 1 M NaOH solution. The mixture was extracted with EtOAc for three times. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated, and purified by flash chromatography (EtOAc/hexanes = 1/1) to give **13** (406.8 mg, 73%) as a yellow solid.

(*S*)-Methyl 3-(*N*-(6-Acetylnaphthalen-2-yl)-2-nitrophenylsulfonamido)-2-(tritylamino)propanoate 12. To a solution of **13** (555.7 mg, 3 mmol) in CH_2Cl_2 (30 mL) were added pyridine (0.27 mL, 3.3 mmol) and *o*-NsCl (698.1 mg, 3.15 mmol) sequentially at 0 °C. The reaction was stirred at room temperature overnight. The reaction mixture was washed with 1 M HCl solution (20 mL), water, and brine and dried over Na_2SO_4. The solution was concentrated, and the resulting red solid was dissolved in toluene (30 mL) and stirred at 0 °C. To this mixture were added **11** (2.169 g, 6 mmol) and PPh_3 (1.574 g, 6 mmol). DIAD (1.18 mL, 6 mmol) was added dropwise to the solution. The reaction mixture was stirred overnight at room temperature. The solution was concentrated and purified by flash chromatography (EtOAc/hexanes = 2/3) to give compound **12** (1.892 g, 88%) as a red solid. R_f = 0.28 (EtOAc/hexanes = 1/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.43 (s, 1H), 8.06 (dd, J = 8.5, 1.5 Hz, 1H), 7.89 (d, J = 9.0 Hz, 1H), 7.88 (s, 1H), 7.60 (dd, J = 8.0, 1.5 Hz, 1H), 7.56 (dt, J = 8.0, 1.0 Hz, 1H), 7.45 (dd, J = 8.5, 2.0 Hz, 1H), 7.42 (dd, J = 8.0, 1.0 Hz, 1H), 7.33−7.29 (m, 1H), 7.28−7.26 (m, 6H), 7.11−7.05 (m, 9H), 4.36 (dd, J = 15.0, 4.5 Hz, 1H), 4.29 (dd, J = 14.5, 7.0 Hz, 1H), 3.53 (br s, 1H), 3.16 (s, 3 H), 2.72 (s, 3H), 2.66 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.8, 173.0, 145.5, 138.6, 135.7, 135.4, 133.9, 132.3, 131.8, 131.7, 131.2, 131.0, 129.7, 128.8, 128.69, 128.66, 128.0, 127.9, 127.0, 126.5, 125.0, 124., 71.4, 56.7, 56.6, 52.0, 26.9. HRMS (ESI-FT): $[M + Na]^+$ calcd for $C_{41}H_{35}N_3O_7SNa$, 736.2089; found 736.2086. $[\alpha]^{23}_D$ +69.6 (c 1.00, $CHCl_3$).

(*S*)-Methyl 3-(6-Acetylnaphthalen-2-ylamino)-2-aminopropanoate 20. To a solution of **12** (1.428 g, 2 mmol) in CH_2Cl_2 (16 mL) were added TFA (2.0 mL) and water (2.0 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 h and concentrated under vacuum. The residue was dissolved in DMF (10 mL). Thiophenol (440.4 mg, 4.0 mmol) and K_2CO_3 (2.76 g, 20 mmol) were added to the solution sequentially. The reaction mixture was stirred at room temperature for 2 h. Water (80 mL) was added to the mixture, and the solution was extracted with EtOAc (40 mL) three times. The combined organic phase was washed with brine (40 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated and purified by flash chromatography (EtOAc/hexanes = 1/1, then MeOH/MeOH = 1/20) to give compound **20** (459.6 mg, 80%) as a yellow solid. R_f = 0.15 (MeOH/CH_2Cl_2 = 1/20). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.29 (s, 1 H), 7.92 (dd, J = 9.0, 2.0 Hz, 1H), 7.72 (d, J = 9.0 Hz, 1H), 7.61 (d, J = 8.5 Hz, 1H), 6.95 (dd, J = 8.5, 2.0 Hz, 1H), 6.84 (d, J = 2.0 Hz, 1H), 4.75 (br s, 1H), 3.82 (br s, 1H), 3.78 (s, 3H), 3.65−3.63 (m, 1H), 3.35 (dd, J = 12.0, 7.5 Hz, 1H), 2.66 (s, 3H), 1.70 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.9, 147.9, 138.0, 131.2, 131.0, 130.4, 126.3, 126.2, 124.9, 118.9, 104.4, 53.6, 52.5, 46.9, 26.5. HRMS (ESI-FT): $[M + H]^+$ calcd for $C_{16}H_{19}N_2O_3$, 287.1390; found 287.1395. $[\alpha]^{24}_D$ +74.0 (c 1.00, $CHCl_3$).

L-Anap 3. A solution of compound **16** (286.3 mg, 1 mmol) in 2 M HCl solution (10 mL) was stirred at 60 °C for 8 h. The reaction mixture was lyophilized to give a yellow solid. After being washed with diethyl ether, the solid was dried under vacuum to give L-Anap (306.8 mg, 99%) as a yellow solid. ^{1}H NMR (500 MHz, D_2O): δ = 7.82 (s, 1H), 7.45 (dd, J = 8.5, 2.0 Hz, 1H), 7.39 (d, J = 8.5 Hz, 1H), 7.32 (d, J = 8.5 Hz, 1H), 6.87 (dd, J = 8.5, 2.0 Hz, 1H), 6.71 (s, 1H), 3.53−3.51 (m, 1H), 3.47 (dd, J = 13.0, 4.5 Hz, 1H), 3.23 (dd, J = 13.0, 7.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 197.1, 169.5, 148.0, 137.6, 130.5, 130.4, 130.2, 125.7, 125.5, 124.1, 119.0, 102.9, 51.5, 42.9, 26.4. HRMS (ESI-FT): $[M + H]^+$ calcd for $C_{15}H_{17}N_2O_3$, 273.1234; found 273.1239. $[\alpha]^{25}_D$ +74.2 (c 1.07, DMSO).

■ ASSOCIATED CONTENT

Supporting Information. General experimental information and spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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