

An improved synthesis of (*S*)-1-[[4-(dimethylamino)-3-methylphenyl]methyl]-5-(diphenylacetyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylic acid ditrifluoroacetate dihydrate (PD123319)

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Abstract

The following report describes several improvements to the earlier synthesis of the non-peptide Angiotensin II antagonist (*S*)-1-[[4-(dimethylamino)-3-methylphenyl]-methyl]-5-(diphenylacetyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylic acid ditrifluoroacetate dihydrate (**1**) (PD123319).

Keywords: Angiotensin II, Blankley's protocol

Introduction

The peptide hormone Angiotensin II (Ang II) is responsible for a variety of physiological functions.^{1,2} Progress in the study of Ang II receptor subtypes and their functional diversity has been facilitated by the discovery of a class of non-peptide antagonists. One of these compounds PD123319 (**1**) has been used to demonstrate the existence of non-vascular Ang II binding sites in a narrow range of tissue types³ and has been examined as a potential antihypertensive agent.

To augment evaluation studies, we required gram quantities of **1**. A survey of the literature yielded only one report describing the synthesis.⁴ In our hands, however, the procedures described therein were problematic and not amenable to scale-up. The present report details a modified synthesis protocol capable of delivering gram quantities of **1**, and provides a more comprehensive spectroscopic examination of the intermediates and final product than was previously available.

Results and Discussion

The procedure employed for the synthesis of **1** is presented in Scheme 1. The preparation of the di-*t*-butoxycarbonyloxy derivative **3** of L-histidine methyl ester dihydrochloride was carried out according to the method reported by Hodges.⁵ With the careful exclusion of moisture this procedure yielded **3** in 82% yield. In order to alkylate the unsubstituted imidazole nitrogen atom, following Blankley's details, the triflate (**4**) of 3-methyl-4-nitrobenzyl alcohol was prepared *in situ* and reacted with **3** at $-70\text{ }^{\circ}\text{C}$ to afford the coupled product **5** in a 61% yield after a buffered quench.

Ester hydrolysis and deprotection of the amino functionality in **5** was achieved using 6N hydrochloric acid thereby furnishing the amino acid bis-hydrochloride salt (**6**) as an amorphous foam in 80% yield. This was in contrast to the quantitative yield of a gum-like material reported by Blankley *et al.*⁴ Conversion of **6** to the imidazopyridine **7** was not possible using the procedure of Blankley *et al.*⁴ despite numerous attempts. Accordingly, an alternative procedure based on the same publication of Blankley⁴ was employed without incident. In this alternative method the annulation was carried out in 12 N hydrochloric acid and subsequently **7** was available in 71% yield.

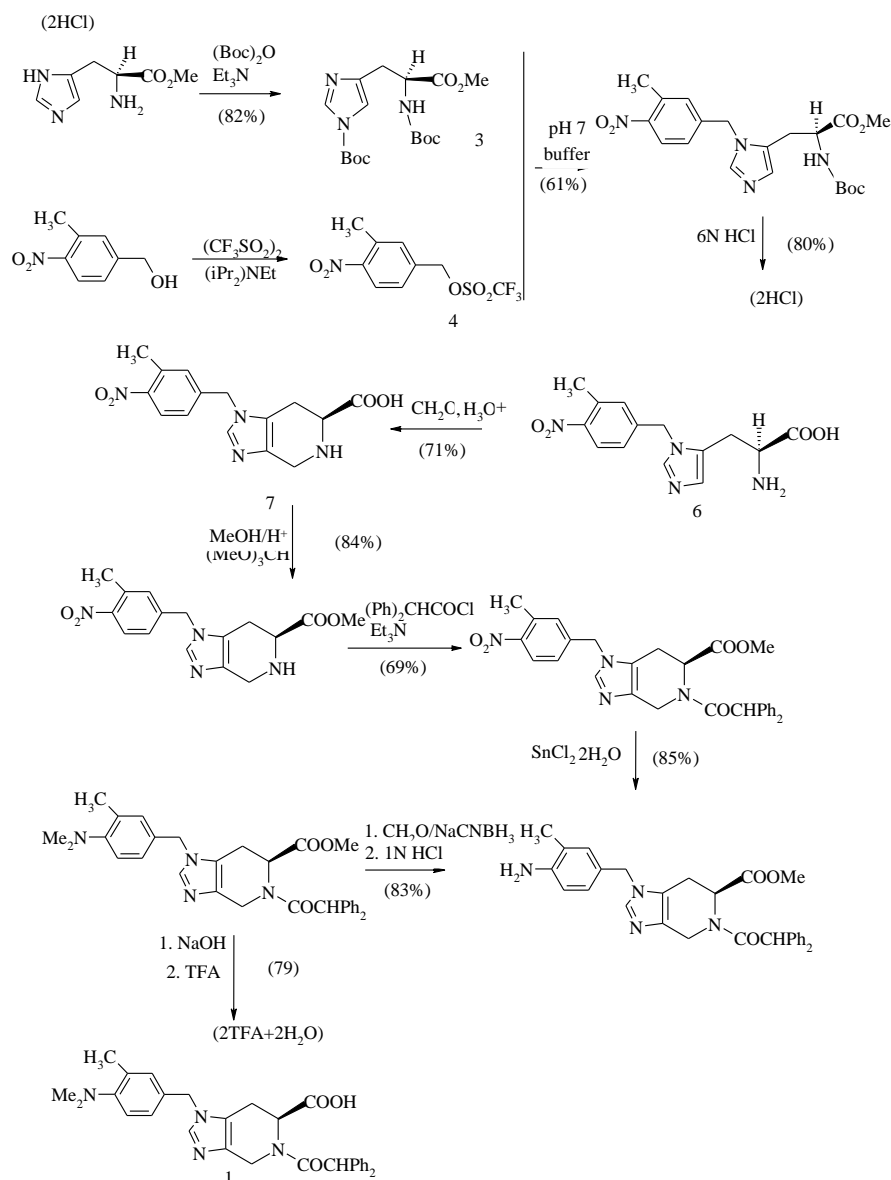
The published procedure⁴ for the conversion of **7** to the corresponding methyl ester (**8**) by treatment with trimethyl orthoformate in the presence of acid was used without modification and provided the desired product in 85% yield. In our hands, however, the *N*-acylation of **8** through treatment with dicyclo-hexylcarbodiimide (DCC) / 1-hydroxybenzotriazole (BtOH) in the presence of diphenylacetic acid proved capricious. Alternatively, we found that reaction of **8** with diphenylacetyl chloride and triethylamine resulted in a rapid conversion to the acetamide (**9**) in good yield.

Blankley's protocol for the synthesis of **9** – **10** suggested that the reduction of the aromatic nitro group of **9** could be effected by either stannous chloride or Raney nickel. Our experience however, was that the use of Raney nickel consistently led to products contaminated with starting material and an uncharacterised polymeric by-product. On the other hand the stannous chloride mediated procedure routinely provided the aniline (**10**) in 85% yield.

The final two transformations (reductive methylation and saponification) were reportedly⁴ carried out without isolation of the intermediate *N,N*-dimethyl ester, and the final product was purified by reverse phase chromatography. In our hands this one pot method proved unsatisfactory for gram scale batches. We examined a stepwise approach and investigated a number of reagents for reductive methylation, including sulfuric acid mediated sodium borohydride / formaldehyde,⁷ sodium cyanoborohydride formaldehyde in glacial acetic acid,⁸ and direct treatment with dimethyl sulfate.⁹ From this we determined that the combination of sodium cyanoborohydride / formaldehyde in methanol and 1 N hydrochloric acid was the most satisfactory method. Using this modification the dimethylaniline (**11**) could be purified by flash column chromatography in gram quantities. The hydrolysis of the methyl ester and subsequent salt formation with trifluoroacetic acid was accomplished without isolation of the free

dimethylamino carboxylic acid. This procedure provided material which required only a rapid pass through a plug of reverse phase silica to obtain **1** in 79% yield. The overall yield of **1** by this current procedure is 9%.

In conclusion, the authors of this present report have developed an improved method for the gram scale preparation of PD123319 (**1**). This method circumvents the limitations associated with of the preparation of **1** as outlined by Blankley.⁴



Scheme 1. Synthesis of PD123319.

Experimental Section

***N*-1-Bis[*t*-butoxycarbonyl]-*L*-histidine methyl ester (3).** Triethylamine (82.8 mL, 0.594 mol) was slowly added over a 15 min period to a mixture of *L*-histidine methyl ester dihydrochloride (72.0 g, 0.297 mol) in methanol (660 mL) and the resulting solution was stirred at room temperature for 30 min. A mixture of di-*t*-butyl dicarbonate (130 g, 0.596 mol) in methanol (330 mL) was then added dropwise over 30 min and stirring was continued for 48 h at room temperature. The solvent was then evaporated to dryness under vacuum and the residue partitioned between water (0.5 L) and CH₂Cl₂ (1 L). The organic fraction was washed with 10% citric acid (2 x 500 mL), dried (MgSO₄) and solvent removed under vacuum yielding a light yellow oil which was dissolved in petroleum ether (200 mL). Evaporation of the solvent and redissolution with petroleum ether (200 mL) followed by agitation with a glass rod liberated a white crystalline precipitate. Upon cooling overnight and filtration, the title compound **3** was isolated as a fine white solid (90.4 g, 82% yield): mp 86–88 °C (lit.⁵ 85–88 °C); ¹H NMR (CDCl₃): δ 7.99 (d, *J* = 1.1 Hz, 1H), 7.16 (s, 1H), 5.79 (d, *J* = 8.5 Hz, 1H), 4.61–4.54 (m, 1H), 3.73 (s, 3H), 3.05 (d, *J* = 5.0 Hz, 2H), 1.61 (s, 9H), 1.44 (s, 9H); ¹³C NMR (CDCl₃): δ 172.1, 155.3, 146.7, 138.4, 136.7, 114.4, 85.4, 79.5, 53.0, 52.1, 30.0, 28.1, 27.7.

***N*-(*t*-Butoxycarbonyl)-3-[(3-methyl-4-nitrophenyl)methyl]-*L*-histidine methyl ester (5).** A solution of 3-methyl-4-nitrobenzyl alcohol (23.7g, 0.142 mol), diisopropyl-ethylamine (24.8 mL, 0.142 mol) and CH₂Cl₂ (200 mL) was added dropwise, over a 10 min period to a mixture of triflic anhydride (40.0 g, 23.9 mL, 0.142 mol) in CH₂Cl₂ (200 mL) at –78 °C. After 30 min at that temperature a solution of **3** in CH₂Cl₂ (200 mL) was added at such a rate that the reaction temperature did not exceed –70 °C. The reaction was allowed to warm up to room temperature slowly overnight and was then poured into a 0.25 M potassium phosphate buffer (pH 7, 1.2 L). This mixture was stirred for an additional 3 h at room temperature followed by the addition of an aliquot of CH₂Cl₂ (1 L). The organic layer was separated, washed with more of the buffer (0.5 L), dried (MgSO₄) and solvent removed under vacuum yielding a light yellow foam. Purification by flash chromatography with silica gel, eluting with CHCl₃/MeOH (99:1) gave **5** as a white foam (36.0 g, 61% yield). ¹H NMR (CDCl₃): δ 7.83 (d, *J* = 8.5 Hz, 1H), 7.42 (s, 1H), 6.95 (m, 2H), 6.78 (s, 1H), 5.48 (d, *J* = 7.4 Hz, 1H), 5.11 (d, *J* = 3.2 Hz, 2H), 4.40–4.28 (m, 1H), 3.62 (s, 3H), 2.95–2.73 (m, 2H), 2.46 (s, 3H), 1.32 (s, 9H); ¹³C NMR (CDCl₃): δ 171.3, 154.9, 148.3, 141.5, 138.0, 134.3, 130.5, 128.7, 126.3, 125.2, 124.7, 79.9, 52.9, 52.3, 47.3, 28.0, 26.7, 20.2.

3-[(3-Methyl-4-nitrophenyl)methyl]-*L*-histidine dihydrochloride (6). 6 M HCl (750 mL) was added to a solution of **5** (34.0 g, 0.813 mol) in MeOH (50 mL) and heated under reflux for 90 min. After cooling to room temperature the volatile components were removed under vacuum and the residue dissolved in water (500 mL). The solution was treated with activated charcoal, filtered through celite, the celite was washed with water (2 x 100 mL) and the combined aqueous extracts evaporated yielding **6** as a white foam (24.5 g, 80% yield); ¹H NMR (D₂O): δ 8.90 (s, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.58 (s, 1H), 7.32 (s, 1H), 7.28 (d, *J* = 10.4 Hz, 1H), 5.57 (s, 2H), 4.11 (t, *J* = 7.1 Hz, 1H), 3.31 (t, *J* = 6.3 Hz, 2H), 2.50 (s, 3H); ¹³C NMR (D₂O): δ 174.3, 153.2,

142.9, 140.9, 139.6, 136.3, 132.7, 130.5, 130.1, 124.3, 55.4, 54.1, 28.5, 23.9.

(S)-4,5,6,7-Tetrahydro-1-[(3-methyl-4-nitrophenyl)methyl]-1H-imidazo[4,5-c]pyridine-6-carboxylic acid dihydrochloride (7). A solution of **6** (26.7 g, 70.8 mmol) in water (155 mL) was treated with 36% aqueous CH₂O (17.6 mL, 229 mmol) and allowed to stir at room temperature for 30 min and then at reflux for 2 h. The cooled solution was treated with concentrated HCl (2.8 mL) and evaporated to dryness under vacuum yielding a thick yellow oil. The crude material was heated to 80 °C and ethanol added until a precipitate formed. The cooled (0 °C) mixture was filtered and the resultant solid dried under high vacuum affording **7** as a white foam (19.6 g, 71% yield): m.p 260–261 °C, (lit.⁴ 260–263 °C); [α]²⁵D+59.8° (c 0.99, H₂O); ¹H NMR (D₂O): δ 8.99 (s, 1H), 8.02 (d, *J* = 8.2 Hz, 2H), 7.33 (s, 1H), 7.30 (d, *J* = 8.6 Hz, 1H), 5.55 (d, *J* = 4.0 Hz, 2H), 4.58 (q, *J* = 17.9 Hz, 2H), 4.49–4.39 (m, 1H), 3.38 (dd, *J* = 16.9, 5.4 Hz, 1H), 2.93 (dd, *J* = 17.2, 9.7 Hz, 1H), 2.52 (s, 3H); ¹³C NMR (D₂O): δ 173.7, 152.9, 142.6, 141.0, 139.5, 136.2, 130.5, 130.0, 129.9, 126.1, 58.2, 54.2, 42.7, 25.1, 23.9; MS (ES+) *m/z* 317; (ES-) *m/z* 315.

(S)-4,5,6,7-Tetrahydro-1-[(3-methyl-4-nitrophenyl)methyl]-1H-imidazo[4,5-c]pyridine-6-carboxylic acid methyl ester (8). A solution of **7** (9.5 g, 24.4 mmol), trimethyl orthoformate (24.1 mL, 220 mmol) in dry methanol (350 mL) was treated with a stream of anhydrous HCl. The solution was heated at reflux for 24 h, allowed to cool to room temperature, reduced to dryness under vacuum and dissolved/suspended in dichloromethane (150 mL). The mixture was quenched with cold 10% Na₂CO₃ (150 mL) and the layers separated. The aqueous phase was extracted with more dichloromethane (3 x 150 mL) and the organic extracts combined, dried (MgSO₄) and reduced to dryness to afford a yellow oil. This oil was triturated with Et₂O (100 mL) and the resultant precipitate collected by filtration affording **8** as a pale brown solid (6.8 g, 84% yield): mp 117–120 °C (lit. 100–104 °C); [α]²⁵D-31.1° (c 0.99, DMF); ¹H NMR (CDCl₃): δ 7.93 (d, *J* = 8.8 Hz, 1H), 7.48 (s, 1H), 7.03–6.97 (m, 2H), 5.08 (s, 2H), 4.03–3.83 (m, 2H), 3.79–3.71 (m, 4H), 2.98 (bs, 1H), 2.80–2.58 (m, 2H), 2.56 (s, 3H); ¹³C NMR (CDCl₃): δ 172.3, 148.3, 141.3, 136.1, 136.0, 134.2, 130.4, 125.1, 124.6, 122.6, 55.1, 52.0, 47.2, 43.0, 24.2, 20.2; MS: (APCI+) *m/z* 331; (APCI-) *m/z* 329.

(S)-5-(Diphenylacetyl)-4,5,6,7-tetrahydro-1-[(3-methyl-4-nitrophenyl)methyl]-1H-imidazo[4,5-c]pyridine-6-carboxylic acid methyl ester (9). A solution of diphenylacetyl chloride (2.10 g, 9.11 mmol) in acetonitrile (20 mL) was added dropwise to a mixture of **8** (3.00 g, 9.08 mmol), triethylamine (1.95 mL, 14.0 mmol) and acetonitrile (20 mL) at 0 °C. The resultant mixture was then stirred at room temperature for 30 min. The solution was vacuum filtered to remove the so-formed Et₃N. HCl and the collected filtrate reduced to dryness at reduced pressure. Dichloromethane (50 mL) was added and the organic solution washed with 10% NaHCO₃ (3 x 50 mL), dried (MgSO₄), filtered and again reduced to dryness *in vacuo*. The desired product was isolated by column chromatography using silica gel (CH₂Cl₂/MeOH (99:1)) to afford a gum upon evaporation. The gum was dissolved in MeOH, the solution reduced in volume until a slurry formed and then Et₂O added to effect crystallisation affording **9** as a pale brown solid (3.29 g, 69% yield): [α]²⁵D+13.6° (c 1.08, CHCl₃); ¹H NMR (CDCl₃): δ 7.95 (d, *J* =

8.8 Hz, 2H), 7.66 (s, 1H), 7.33–7.13 (m, 10H), 7.05 (bs, 2H), 6.04 (d, $J = 4.8$ Hz, 1H), 5.35 (s, 1H), 5.16 (s, 2H), 4.73 (d, $J = 15.2$ Hz, 1H), 4.30 (d, $J = 15.4$ Hz, 1H), 3.60 (s, 3H), 3.15 (d, $J = 15.7$ Hz, 1H), 2.69 (dd, $J = 6.4, 15.5$ Hz, 1H), 2.59 (s, 3H); ^{13}C NMR (CDCl_3): δ 172.5, 170.3, 148.5, 140.9, 138.7, 138.1, 137.3, 134.4, 132.7, 130.6, 128.9, 128.9, 128.6, 128.3, 128.2, 128.1, 126.9, 126.9, 125.2, 124.8, 122.5, 55.4, 52.3, 50.5, 47.5, 43.4, 21.9, 20.3; MS: (APCI+) m/z 525; (APCI-) m/z 523. (Note: Resonances due to both *E* and *Z* amide conformers rotamers are present in *ca.* a 7:1 ratio in CDCl_3 , however only the major series of peaks are included).

(S)-1-[(4-Amino-3-methylphenyl)-methyl]-5-(diphenylacetyl)-4,5,6,7-tetrahydro-1H-imidazo[4,5-*c*]pyridine-6-carboxylic acid methyl ester (10). A suspension of **9** (13.1 g, 25.0 mmol) and $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (33.7 g, 149 mmol) in EtOAc (350 mL) was heated at reflux for 2 h. The solution was left to cool and treated with saturated aqueous NaHCO_3 (1 L) with vigorous stirring to break up the lumps formed. The mixture was filtered and the solid washed with EtOAc (100 mL). The aqueous phase was separated from the organic layer and then extracted with more EtOAc (3 x 400 mL). The organic extracts were combined, dried (MgSO_4), filtered and reduced to dryness. The residue was purified by column chromatography (silica gel, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (98:2)) to afford **10** as a colourless solid (10.5 g, 85% yield). $[\alpha]_D^{25} + 34.2^\circ$ (c 1.2, CHCl_3); ^1H NMR (CDCl_3): δ 7.41 (s, 1H), 7.38–7.07 (m, 10H), 6.81 (s, 1H), 6.79 (d, $J = 9.4$ Hz, 1H), 6.62 (d, $J = 8.8$ Hz, 1H), 6.00 (d, $J = 6.2$ Hz, 1H), 5.36 (s, 1H), 4.87 (d, $J = 6.4$ Hz, 1H), 4.77 (d, $J = 15.2$ Hz, 1H), 4.28 (d, $J = 16.8$ Hz, 1H), 3.64 (bs, 2H), 3.53 (s, 3H), 3.22 (d, $J = 15.7$ Hz, 1H), 2.70 (dd, $J = 15.8, 6.0$ Hz, 1H), 2.08 (s, 3H); ^{13}C NMR (CDCl_3): δ 172.7, 170.6, 144.7, 138.9, 138.2, 136.8, 131.9, 129.5, 129.0, 128.9, 128.7, 128.6, 128.4, 128.3, 127.0, 126.1, 124.6, 122.5, 114.8, 55.4, 52.3, 50.6, 48.6, 43.5, 22.3, 17.2; MS: (APCI+) m/z 495. (Note: Resonances due to both *E* and *Z* amide rotamers are present in *ca.* a 7:1 ratio in CDCl_3 , however only the major series of peaks is included).

(S)-1-[[4-(Dimethylamino)-3-methylphenyl]-methyl]-5-(diphenylacetyl)-4,5,6,7-tetrahydro-1H-imidazo[4,5-*c*]pyridine-6-carboxylic acid methyl ester (11). 1 N HCl (61 mL, 61 mmol) was added at room temperature over a period of 1 h to a mixture of the amine **10** (10.0 g, 20.2 mmol), MeOH (400 mL), 37% CH_2O soln. (8.0 mL, 10.1 mmol) and NaCNBH_3 (3.8 g, 60.6 mmol). After stirring for a further 2 h an aliquot of CH_2Cl_2 (1 L) was added and washed sequentially with sat. Na_2CO_3 (2 x 400 mL), sat. NaCl (2 x 400 mL), dried (MgSO_4), filtered and solvent removed under vacuum. Purification of the residue via flash chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, (98:2)) yielded **11** as a fine white solid (8.8 g, 83% yield). ^1H NMR (CDCl_3): δ 7.40 (s, 1H), 7.32–7.11 (m, 10 H), 6.96–6.77 (m, 3H), 6.01 (d, $J = 4.6$ Hz, 1H), 5.37 (s, 1H), 4.91 (d, $J = 4.4$ Hz, 2H), 4.76 (d, $J = 14.8$ Hz, 1H), 4.28 (d, $J = 14.7$ Hz, 1H), 3.58 (s, 3H), 3.21 (d, $J = 14.6$ Hz, 1H), 2.73–2.56 (m, 7H), 2.23 (s, 3H); ^{13}C NMR (CDCl_3): δ 172.8, 170.7, 152.8, 139.0, 138.3, 137.1, 132.6, 132.2, 130.0, 129.1, 129.1, 128.8, 128.8, 128.5, 128.4, 127.1, 125.3, 122.6, 118.6, 55.6, 52.5, 50.7, 48.5, 44.0, 43.7, 22.4, 18.5. (Note: Resonances due to both *E* and *Z* amide rotamers are present in *ca.* a 7:1 ratio in CDCl_3 , however only the major series of peaks is included).

(S)-1-[[4-(Dimethylamino)-3-methylphenyl]-methyl]-5-(diphenylacetyl)-4,5,6,7-tetrahydro-

1*H*-imidazo[4,5-*c*]pyridine-6-carboxylic acid ditrifluoroacetate dihydrate (1). Sodium hydroxide (0.35 g, 8.8 mmol) was added to a mixture of the amine **10** (4.62 g, 8.8 mmol) in THF (50 mL) and methanol (5 mL) and stirred overnight. The resultant mixture was cooled in an ice bath and 1M HCl added dropwise to adjust the *pH* to ~ 6. The resulting mixture was extracted with ethyl acetate (4 x 50 mL). The combined organic extracts were dried (MgSO₄), filtered and reduced under vacuum to yield a viscous colourless oil. Aqueous trifluoroacetic acid was added until a *pH* of 1 was reached. Removal of the water and excess trifluoroacetic acid under high vacuum yielded a white solid which was purified by reverse phase flash chromatography (CH₃CN: 1% aqueous TFA, (25:75)). The fractions containing the title compound were combined and reduced under vacuum, freeze dried and the product isolated as a fluffy white solid (8.65 g, 79% yield): mp 104–106 °C; [α]²⁵D+5.9° (c 0.98, MeOH); ¹H NMR (CDCl₃): δ 8.76 and 8.62 (s, 1H), 7.73 and 7.66 (d, *J* = 8.5 Hz, 1H), 7.37–7.09 (m, 12H), 5.62 (d, *J* = 14.3 Hz, 1H), 5.56 (dd, *J* = 6.2, 2.7 Hz, 0.55H), 5.35 (d, *J* = 18.4 Hz, 0.45H), 5.26 (dd, *J* = 17, 1.3 Hz, 0.45H), 5.14 (d, *J* = 5.0 Hz, 0.45H), 4.85 (d, *J* = 16.5 Hz, 0.55H), 4.45 (d, *J* = 16.6 Hz, 0.55H), 4.30 (d, *J* = 16.9 Hz, 0.45H), 3.25 (s, 6H), 3.10 (d, *J* = 17.0 Hz, 0.55H), 2.88 (d, *J* = 16.4 Hz, 0.45H), 2.75 (dd, *J* = 16.6, 6.2 Hz, 0.55H), 2.46 (d, *J* = 25.9 Hz, 3H), 2.01 (dd, *J* = 16.9, 6.6 Hz, 0.45H). Anal. Calcd. for C₃₅H₃₈N₄O₉F₆: C, 54.41; H, 4.96; N, 7.25. Found: C, 54.72; H, 4.81; N, 7.58. (Note: Resonances due to both *E* and *Z* amide rotamers are present in *ca.* a 3:2 ratio in D₂O, all peaks are included).

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