

Total Synthesis of Martinelllic Acid, a Naturally Occurring Bradykinin Receptor Antagonist

Dawei Ma*, Chengfeng Xia, Jiqing Jiang and Jianhua Zhang

*State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute
of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032,
China*

Supporting information

Experimental

(S)-Ethyl 3-amino-6-hydroxyhexanoate 6. To a solution of (S)-ethyl 3-[*N*-benzyl-*N*-[(*S*)-1-phenylethyl]amino]-6-benzyloxyhexanoate **5** (100 g, 0.22 mol) in 600 mL of ethanol was added concentrated HCl (22 mL, 0.26 mol), 30 mL of H₂O and 5 g of 10% Pd/C. After the reaction mixture was stirred under hydrogen (50 atm) at 50 °C for 6 h, Pd/C was filtered off and filtrate was neutralized by adding aqueous saturated NaHCO₃ to pH = 8. Another 5 g of 10% Pd/C was added and the resultant suspension was hydrogenated under above condition for 8 h. After Pd/C was filtrated the solvent was evaporated under reduced pressure to give 38 g (98%) of **6**. ¹H NMR (300 MHz, CDCl₃) δ 6.65 (m, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.71-3.59 (m, 3H), 2.95 (dd, *J* = 17.1, 6.8 Hz, 1H), 2.76 (dd, *J* = 17.1, 5.9 Hz, 1H), 1.96 (m, 1H), 1.83 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 3H); MS *m/z* 176 (M⁺ + H⁺). HRMS found *m/z* 175.1230 (M⁺); C₈H₁₇NO₃ requires 175.1211.

(S)-Methyl 6-hydroxy-3-(4-iodo-phenylamino)-hexanoate 7. To a solution of the amino ester **6** (8.0 g, 45.7 mmol) in 100 mL of DMF were added 1,4-diiodobenze (18.0 g, 54.8 mmol), potassium carbonate (19.0 g, 137 mmol), cuprous iodine (0.87 g, 4.6 mmol) and 0.5 mL of water. After the mixture was heated at 100 °C under N₂ for 2 days, the solvent was removed under reduced pressure and then 100 mL of chloroform was added. The resultant solution was acidified to pH = 5 by adding 1 N HCl. The organic layer was separated and aqueous was extracted with chloroform for three times. The combined

organic layers were washed with brine and dried over anhydrous Na₂SO₄ and concentrated to dryness to give crude *N*-aryl β-amino acid.

To a solution of the above crude amino acid in 200 mL of methanol was added thionyl chloride (4.8 mL, 55 mmol) in a dropwise manner at 0 °C. The mixture was stirred overnight at room temperature before the methanol was evaporated. After 50 mL of aqueous saturated NaHCO₃ was added to neutralize the residue, the mixture was extracted with ethyl acetate for three times. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography eluting with 1/1 ethyl acetate/petroleum ether to afford 8.8 g (53% for two steps) of **7**. $[\alpha]_D^{20}$ -20.4 (*c* 1.0, CHCl₃); IR (KBr) 3388, 2947, 1727, 1590, 1500, 1437, 1294, 1183, 1061, 813 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.40 (d, *J* = 7.0 Hz, 2H), 6.41 (d, *J* = 7.0 Hz, 2H), 3.72 (m, 1H), 3.64 (s, 3H), 2.50 (m, 2H), 1.75-1.59 (m, 4H); EIMS *m/z* 363 (M⁺), 304, 290, 237, 178, 104; HRMS found *m/z* 363.0323 (M⁺); C₁₃H₁₈INO₃ requires 363.0331.

(*S*)-2-(3-Acetoxypropyl)-1-acetyl-6-iodo-4-oxo-1,2,3,4-tetrahydroquinoline

8. A solution of **7** (15.5 g, 42.7 mmol) in 200 mL of acetic anhydride was heated to 100 °C for 2 h. The solvent was evaporated under reduced pressure and the residue was dissolved in 200 mL of MeOH. To this solution were added 100 mL of H₂O and NaOH (6.4 g, 160 mmol). The reaction mixture was stirred for 20 h before concentrated HCl was added to quench the reaction. The MeOH was removed under reduced pressure and the aqueous was extracted with 100 mL of CHCl₃ for three times. The organic layers were dried over anhydrous Na₂SO₄ and concentrated to give crude alcohol, which was dissolved in 150 mL of Ac₂O. After the resultant solution was stirred for 2 h at 80 °C, the solvent was removed

in vacuo. The residue was dissolved in 100 mL of 1,4-dioxane and 50 mL of H₂O before it was stirred at 50 °C for 0.5 h. Chloroform extract work up followed by removal of solvent afforded the crude acid.

To a magnetic stirred suspension of above acid (10.0 g, 23 mmol) and 0.05 mL DMF in 100 mL dry CH₂Cl₂ was added oxalyl chloride (3 mL, 34.6 mmol) over 10 min at 0 °C. The mixture was aged another 10 min at 0 °C and then 1 h at room temperature before the solvent was evaporated to dryness. After the residue was dissolved in another 100 mL of dry CH₂Cl₂, AlCl₃ (9.8 g, 73.6 mmol) was added in four portions at 0 °C. The reaction mixture was stirred for 12 h at room temperature, then cautiously poured into a rapidly stirred mixture of 200 g of ice and 100 mL of CHCl₃. The organic layer was separated and the aqueous layer was extracted with CHCl₃. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated. The residue was purified by flash chromatography to give 5.9 g (52% overall yield) of **8**. $[\alpha]_D^{20} +203.0$ (c 1.1, CHCl₃); IR (KBr) 3448, 2952, 1736, 1664, 1586, 1473, 1390, 1245, 1051, 832 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.31 (d, *J* = 1.9 Hz, 1H), 7.86 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.10 (m, 1H), 5.18 (m, 1H), 3.97 (t, *J* = 5.5 Hz, 2H), 3.01 (dd, *J* = 18.1, 5.8 Hz, 1H), 2.65 (d, *J* = 18.0 Hz, 1H), 2.33 (s, 3H), 1.96 (s, 3H), 1.76-1.54 (m, 4H); EIMS *m/z* 415 (M⁺), 373, 272; HRMS found *m/z* 415.0298 (M⁺); C₁₆H₁₈INO₄ requires 415.0281.

(S)-2-(3-*tert*-Butyldimethylsilyloxypropyl)-4-oxo-1,2,3,4-tetrahydroquino-line-6-carboxylic acid methyl ester 4. To a solution of **8** (5.0 g, 12.1 mmol) in 50 mL of DMF and 2 mL of MeOH were added Et₃N (3.3 mL, 24.1 mmol), dppp (247 mg, 0.6 mmol) and Pd(OAc)₂ (135 mg, 0.6 mmol) under nitrogen. The resulting suspension was purged

with CO and stirred at 80 °C in a CO atmosphere (balloon pressure) for 12 h. The cooled solution was evaporated in vacuo and then the residue was diluted with 100 mL CHCl₃. The solution was washed with water, dried over Na₂SO₄ and concentrated. The residue was chromatographed (silica gel, ½ ethyl acetate/petroleum ether as eluent) to afford 3.86 g (93%) of carbonylation product.

The above ester (3.86 g, 11.1 mmol) was dissolved in 30 mL of saturated HCl/MeOH and 3 mL of H₂O. The reaction mixture was stirred overnight at room temperature. After the solvent was removed under reduced pressure, and the residue was neutralized with aqueous saturated NaHCO₃. The mixture was extracted with chloroform for three times. The combined organic layers were dried over anhydrous Na₂SO₄, and concentrated. The residue was dissolved in 30 mL of chloroform and then Et₃N (1.9 mL, 13.8 mmol), catalytic amount of DMAP, and a solution of *tert*-butyldimethylsilyl chloride (1.64 g, 10.9 mmol) in 2 mL of CH₂Cl₂ were added respectively. The reaction mixture was stirred at room temperature for 6 h before it was quenched with 30 mL of H₂O. The aqueous phase was extracted with CH₂Cl₂ twice. The combined extracts were washed with brine and dried over Na₂SO₄. After removal of solvent, the residue was purified by flash chromatography on silica gel gave 3.6 g (79% from **8**) of **4** as a straw yellow solid. $[\alpha]_D^{20}$ -120.5 (*c* 1.0, CHCl₃); IR (KBr) 3344, 2954, 2930, 2858, 1713, 1666, 1626, 1286, 1249, 1103 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.50 (d, *J* = 2.1 Hz, 1H), 7.93 (dd, *J* = 8.7, 2.1 Hz, 1H), 6.64 (d, *J* = 8.7 Hz, 1H), 5.19 (m, 1H), 3.87 (s, 3H), 3.69 (t, *J* = 5.3 Hz, 2H), 2.73 (dd, *J* = 16.1, 4.1 Hz, 1H), 2.53 (dd, *J* = 16.1, 11.6 Hz, 1H), 1.26-1.75 (m, 4H), 0.92 (s, 9H), 0.08 (s, 6H); EIMS *m/z* 377 (M⁺), 346, 320, 246, 228, 204; HRMS found *m/z*

377.2049 (M⁺); C₂₀H₃₁NO₄Si requires 377.2021.

(2*S*,4*S*)-4-(3-*tert*-Butyldimethylsilyloxypropyl)-3,3a,4,5-tetrahydro-2H-pyrrolo[3, 2-*c*]quinoline-8-carboxylic acid, methyl ester 9. To a solution of **4** (1.0 g, 2.7 mmol) in 2.5 mL of anhydrous THF was slowly added a solution of lithium hexamethyldisilazide (1.0 M, 5.6 mL, 5.6 mmol) in THF at -78 °C. After the reaction mixture was allowed to warm to -40 °C in 30 min, BrCH₂CH₂OTf (1.6 g, 5.8 mmol) was added at the same temperature. The mixture was stirred for 1 h at -40 °C before it was partitioned between EtOAc and saturated NH₄Cl. The aqueous layer was separated and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo. The residue was allowed to pass a short column of silica gel eluting with ½ ethyl acetate/petroleum ether to afford crude alkylation product. This product was directly dissolved in 10 mL of DMF. To this solution was added sodium azide (345 mg, 5.3 mmol). This slurry was stirred for 10 h at room temperature under nitrogen atmosphere. After the solvent was evaporated in vacuo, the residue was partitioned between water and ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over Na₂SO₄, and concentrated in vacuo to provide the crude azide, which was dissolved in 10 mL of THF. To this solution were added PPh₃ (0.94 g, 3.6 mmol) and H₂O (0.2 mL). The resultant solution was stirred at ambient temperature for 14 h before it was concentrated under reduced pressure. The residue was purified by column chromatography to produce 512 mg (48% yield from **4**) of **9**. [α]_D²⁰ -68.9 (c 0.50, CHCl₃); IR (KBr) 3231, 2953, 2920, 2857, 1702, 1620, 1276, 1104, 772 cm⁻¹; ¹H NMR (300 MHz,

CDCl₃) δ 8.56 (d, J = 1.8 Hz, 1H), 7.86 (dd, J = 8.7, 2.0 Hz, 1H), 6.60 (d, J = 8.4 Hz, 1H), 4.90 (m, 1H), 4.19 (m, 1H), 3.93 (s, 3H), 3.82 (m, 1H), 3.76 (m, 2H), 3.20 (m, 1H), 2.81 (m, 1H), 2.27 (m, 1H), 1.82 (m, 1H), 1.74-1.62 (m, 4H); EIMS m/z 402 (M^+), 345, 269, 242, 229; HRMS found m/z 402.2311 (M^+); C₂₂H₃₄N₂O₃Si requires 402.2330.

(1*S*,2*S*,4*S*)-4-(3-*tert*-Butyldimethylsilyloxypropyl)-1,5-bistrifluoroacetyl-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[3,2-*c*]quinoline-8-carboxylic acid, methyl ester **10.** To a solution of **9** (232 mg, 0.58 mmol) in 5 mL of MeOH at -40 °C was added NaBH₄ (87 mg, 2.3 mmol). After it was stirred at the same temperature for 30 min, the reaction mixture was allowed to warm to room temperature in 1 h. The solvent was removed under reduced pressure and the residue was partitioned between water and chloroform. The organic layer was separated and the aqueous layer was extracted with chloroform. The combined organic layers were dried over Na₂SO₄, and concentrated to dryness to give crude reduction product, which was dissolved in 5 mL of dry methylene chloride. To this solution were added Et₃N (0.28 mL, 2.03 mmol), DMAP (10 mg, 0.08 mmol) and a solution of (CF₃CO)₂O (0.25 mL, 1.74 mmol) in 1 mL of CH₂Cl₂. After the reaction mixture was stirred for 2 h at room temperature, it was partitioned between 10 mL of methylene chloride and 10 mL of water. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic extracts were dried over anhydrous Na₂SO₄, and concentrated to dryness. The residue was purified by flash chromatography eluting with 1/8 ethyl acetate/petroleum ether to give 245 mg (71%) of **10** as a colorless oil and 89 mg (25%) of its 4-epimer. **10**: $[\alpha]_D^{20}$ +19.5 (c 0.74, CHCl₃); IR (KBr) 2964, 2859, 1726, 1692, 1440, 1282, 1206, 1147, 837, 773 cm⁻¹; ¹H NMR (300

MHz, CDCl₃) δ 8.46 (d, J = 1.4 Hz, 1H), 8.05 (dd, J = 8.3, 1.5 Hz, 1H), 7.43 (m, 1H), 5.39 (m, 1H), 4.72 (m, 1H), 3.95 (s, 3H), 3.53 (m, 2H), 2.74 (m, 1H), 2.33 (m, 1H), 2.13 (m, 1H), 1.64-1.41 (m, 6H), 0.83 (s, 9H), 0.02 (s, 6H); ¹⁹F NMR (60 MHz, CDCl₃): δ -4.7, -4.0; MS m/z 581 (M⁺ - Me), 518, 450, 423, 395; HRMS found m/z 581.1918 (M⁺ -Me); C₂₅H₃₁F₆N₂O₅Si requires 581.1907. The data for 4-epimer of **10**: $[\alpha]_D^{20}$ +310.3 (c 0.59, CHCl₃); IR (KBr) 2957, 2860, 1698, 1618, 1489, 1446, 1263, 1208, 1153, 1107, 837, 776 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.02 (dd, J = 8.3, 1.9 Hz, 1H), 7.62 (s, 1H), 7.35 (d, J = 8.1 Hz), 4.58 (m, 1H), 4.37 (d, J = 11.8 Hz, 1H), 4.24 (t, J = 9.2 Hz, 1H), 3.93 (s, 3H), 3.77 (m, 1H), 3.61 (m, 2H), 2.25(m, 1H), 1.97 (m, 1H), 1.80-1.71 (m, 3H), 1.56-1.48 (m, 2H), 0.86 (s, 9H), 0.02 (s, 6H); ¹⁹F NMR (60 MHz, CDCl₃) δ -9.7, -4.0; MS m/z 581 (M⁺-Me), 518, 450, 423, 395; HRMS found m/z 596.2150 (M⁺); C₂₆H₃₄F₆N₂O₅Si requires 581.1907.

(1S,2S,4S)-1-Trifluoroacetyl-2,3,3a,3b,4,5,6,11b-octahydro-1H-dipyrrolo[1,2-a; 3',2'-c]quinoline-10-carboxylic acid, methyl ester 11. To a solution of **10** (14 mg, 0.023 mmol) in 1 mL of THF were added TBAF (12 mg, 0.046 mmol) and HOAc (2 μ L). The reaction solution was stirred for 2 h at room temperature before it was partitioned between 5 mL of CH₂Cl₂ and 5 mL of H₂O. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic extracts were dried over anhydrous Na₂SO₄, and concentrated to dryness. The residue was dissolved in 1 mL of methylene chloride and then Et₃N (7 μ L, 0.05 mmol) and MsCl (3 μ L, 0.039 mmol) was added via syringe. After the reaction mixture was stirred for 1 h at room temperature, it was partitioned between water and methylene chloride. The organic layer was dried over

Na₂SO₄, and concentrated. The residue was purified by flash chromatography to produce 7 mg (83%) of **11**. [α]_D²⁰ -29.4 (*c* 0.94, CHCl₃); IR (KBr) 2947, 1705, 1685, 1604, 1519, 1434, 1264, 1253, 1193, 1162, 1133, 767 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.55 (s, 1H), 7.86 (d, *J* = 8.6 Hz, 1H), 6.49 (d, *J* = 8.6 Hz, 1H), 5.06 (d, *J* = 5.5 Hz, 1H), 3.89 (m, 1H), 3.84 (s, 3H), 3.64 (m, 1H), 3.45 (m, 2H), 3.01 (m, 1H), 2.29 (m, 1H), 2.21-2.10 (m, 2H), 1.97 (m, 2H), 1.63 (m, 2H); MS *m/z* 368 (M⁺), 339, 308, 271, 228.

(1S,2S,4S)-4-(3-Azidopropyl)-1,5-bistrifluoroacetyl-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[3,2-c]quinoline-8-carboxylic acid, methyl ester 12. To a solution of **10** (241 mg, 0.40 mmol) in 5 mL of THF was added 1 mL of trifluoroacetic acid and the mixture was stirred at room temperature for 16 h. The solvent was evaporated under reduced pressure to dryness and the residue was dissolved in 5 mL of methylene chloride. To this stirring solution were added Et₃N (78 μ L, 0.56 mmol) and MsCl (36 μ L, 0.46 mmol) by syringe. The reaction mixture was stirred for 1 h at room temperature before the reaction was quenched by adding water. Methylene chloride extract work up followed by removal of solvent provided the crude mesylate, which was dissolved in 5 mL of DMF. To this solution was added sodium azide (60 mg, 0.90 mmol). The resultant solution was stirred for 10 h under nitrogen atmosphere before it was partitioned between ethyl acetate and water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄, and concentrated to dryness. The residue was purified by flash chromatography to give 134 mg (71% overall yield) of **12**. [α]_D²⁰ +41.0 (*c* 0.95, CHCl₃); IR (KBr) 2956, 2101, 1725, 1693, 1614, 1440, 1282, 1204, 1145, 768 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.45 (d, *J* =

1.6 Hz, 1H), 8.06 (dd, $J = 8.4, 1.7$ Hz, 1H), 7.33 (m, 1H), 5.34 (m, 1H), 4.73 (m, 1H), 3.91 (s, 3H), 3.56 (m, 1H), 3.24 (t, $J = 5.9$ Hz, 2H), 2.68 (m, 1H), 2.33 (m, 1H), 2.13 (m, 1H), 1.69-1.47 (m, 5H); ^{19}F NMR (60 MHz, CDCl_3) δ -11.0, -5.1; MS m/z 507 (M^+), 476, 382, 365; HRMS found m/z 507.1342 (M^+); $\text{C}_{20}\text{H}_{19}\text{F}_6\text{N}_5\text{O}_4$ requires 507.1341.

(1*S*,2*S*,4*S*)-4-(3-Aminopropyl)-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[3,2-*c*]quinoline-8-carboxylic acid, methyl ester, hydrochloride salt **3.** A solution of **12** (134 mg, 0.26 mmol), PPh_3 (208 mg, 0.79 mmol) and H_2O (0.1 mL) in 2 mL of THF was stirred at ambient temperature for 14 h. The reaction mixture was concentrated to dryness under reduced pressure. The residue was dissolved in 5 mL of saturated methanolic hydrochloride and 1 mL of water before it was stirred overnight. The reaction mixture was concentrated to dryness under reduced pressure. The residue was partitioned between ethyl acetate and water. The aqueous layer was separated, washed with ethyl acetate twice, and concentrated to produce 76 mg (81%) of **3** as a hydrochloride salt. $[\alpha]_{\text{D}}^{20} -49.9$ (c 1.25, CH_3OH); IR (KBr) 3420, 2940, 1618, 1509, 1298, 1252 cm^{-1} ; ^1H NMR (300 MHz, CD_3OD) δ 8.03 (d, $J = 1.5$ Hz, 1H), 7.76 (dd, $J = 8.6, 1.3$ Hz, 1H), 6.88 (d, $J = 8.7$ Hz, 1H), 4.69 (d, $J = 3.8$ Hz, 1H), 3.84 (s, 3H), 3.41 (m, 2H), 3.13 (m, 1H), 3.04 (m, 2H), 2.45 (m, 2H), 2.18 (m, 1H), 1.92-1.74 (m, 4H); MS m/z 289 (M^+), 259 ($\text{M}^+ - \text{CH}_2\text{NH}_2$), 245, 228, 214; HRMS found m/z 259.1437 ($\text{M}^+ - \text{CH}_2\text{NH}_2$); $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_2$ requires 259.1447.

14a,21a-Bis(*tert*-butoxycarbonyl)-martinellic acid, methyl ester **14.** To a solution of **3** (62 mg, 0.16 mmol), **13** (200 mg, 0.78 mmol), and Et_3N (0.26 mL, 1.87 mmol) in 2 mL of MeCN and 1 mL of MeOH was added a solution of AgNO_3 (185 mg, 1.09 mmol) in 0.5 mL of MeCN over 30 min. After the reaction mixture was stirred overnight in dark,

the precipitate was filtered off and the filtrate was concentrated to dryness. The residue was partitioned between water and chloroform. The organic layer was separated and the aqueous layer was extracted with chloroform. The combined organic layers were dried over anhydrous Na₂SO₄, and concentrated to dryness. The residue was purified by flash chromatography eluting with 30:1 chloroform/methanol to give 68 mg (65%) of **14**. $[\alpha]_D^{20}$ -94.2 (*c* 0.28, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.99 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 6.62 (m, 1H), 5.71 (m, 1H), 5.29 (m, 1H), 5.20 (m, 1H), 3.81 (s, 3H), 3.75 (m, 1H), 3.40-3.32 (m, 6H), 3.12 (m, 1H), 2.34-2.27 (m, 3H), 2.06 (m, 2H), 1.73 (s, 3H), 1.72 (s, 3H), 1.67 (s, 3H), 1.66 (s, 3H), 1.59-1.45 (m, 4H), 1.52 (s, 9H), 1.49 (s, 9H); ¹³C NMR (150.9 MHz, CDCl₃) δ 167.4, 163.8, 160.1, 159.8, 146.5, 142.2, 137.1, 131.7, 130.0, 120.3, 119.6, 118.2, 113.8, 112.8, 78.1, 53.4, 51.4, 50.6, 46.7, 46.4, 42.7, 42.5, 42.0, 40.1, 39.5, 39.4, 38.0, 37.0, 29.6, 28.5, 28.4, 28.0, 27.9, 25.6, 22.1, 17.9, 14.0, 13.2; ESIMS *m/z* 733 (*M* + Na⁺), 711 (*M* + H⁺), 610 (*M*⁺-Boc); HRMS found *m/z* 710.4600 (*M* + H⁺); C₃₈H₅₉N₇O₆ requires 710.4605.

Martinellie acid 1. To a solution of **14** (21 mg, 0.03 mmol) in 3 mL of MeOH was added 1 mL of 0.15 N aqueous NaOH. The reaction mixture was refluxed for 10 h and then neutralized with 0.1 N HCl cautiously. MeOH was removed under reduced pressure and the residue was extracted with CHCl₃ for three times. The combined organic layers were dried over Na₂SO₄, and concentrated. The residue was purified by flash chromatography eluting with 5/1 chloroform/methanol to give 19 mg of acid. This acid was dissolved in 2 mL of anhydrous CH₂Cl₂ before 0.05 mL of anisole and 0.1 mL of anhydrous trifluoroacetic acid were added. The mixture was stirred at room temperature

for 14 h. After the solvent was evaporated in vacuo, the residue was purified by reversed phase chromatography (C₁₈) to give 15 mg (65%) of **1** as a trifluoroacetic salt. $[\alpha]_{\text{D}}^{20}$ –122.7 (*c* 0.31, MeOH); ¹H NMR (400 MHz, CDCl₃) δ 7.65 (s, 1H), 7.55 (d, *J* = 8.5 Hz, 1H), 6.59 (d, *J* = 8.5 Hz, 1H), 5.34 (t, *J* = 6.6 Hz, 1H), 5.31 (d, *J* = 6.5 Hz, 1H), 5.18 (t, *J* = 6.8 Hz, 1H), 3.97 (dd, *J* = 15.3, 6.5 Hz, 1H), 3.87 (dd, *J* = 15.3, 6.3 Hz, 1H), 3.74 (d, *J* = 6.6 Hz, 2H), 3.39 (m, 2H), 3.28 (m, 1H), 3.14 (m, 2H), 2.45 (m, 1H), 2.08 (m, 1H), 1.74 (s, 3H), 1.70 (s, 3H), 1.69 (s, 3H), 1.64 (s, 3H), 1.69-1.63 (m, 2H), 1.56-1.45 (m, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 167.2, 155.5, 154.3, 146.4, 136.1, 135.7, 130.5, 130.1, 119.6, 119.2, 117.1, 115.8, 113.3, 53.1, 49.1, 45.7, 40.7, 39.7, 39.2, 38.8, 33.4, 26.3, 25.5, 25.4, 25.2, 18.0, 17.9; ESIMS *m/z* 724 (M + H⁺ + 2CF₃COOH), 610 (M + H⁺ + CF₃COOH), 496 (M + H⁺), 428;