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

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Supporting information

Experimental

(*S*)-Ethyl 3-amino-6-hydroxylhexanoate 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 H_2O and 5 g of 10% Pd/C. After the reaction mixture was stirred under hydrogen (50 atm) at 50 ^oC for 6 h, Pd/C was filtered off and filtrate was neutralized by adding aqueous saturated $NaHCO_3$ 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, $CDCl_3$) δ 6.65 (m, 2H), 4.15 (q, *J* = 7.1Hz, 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^+); $C_8H_{17}NO_3$ 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 ^oC under N_2 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 Na_2SO_4 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 $NaHCO_3$ 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 Na_2SO_4 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, $CHCl_3$); IR (KBr) 3388, 2947, 1727, 1590, 1500, 1437, 1294, 1183, 1061, 813 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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^+); $C_{13}H_{18}INO_3$ 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 H_2O 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 $CHCl_3$ for three times. The organic layers were dried over anhydrous Na_2SO_4 and concentrated to give crude alcohol, which was dissolved in 150 mL of Ac_2O. 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 H_2O before it was stirred at 50 ^oC 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 CH_2Cl_2 was added oxalyl chloride (3 mL, 34.6 mmol) over 10 min at 0 ^oC. The mixture was aged another 10 min at 0 ^oC 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 CH_2Cl_2, $AlCl_3$ (9.8 g, 73.6 mmol) was added in four portions at 0 ^oC. 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 $CHCl_3$. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over Na_2SO_4, 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, $CHCl_3$); IR (KBr) 3448, 2952, 1736, 1664, 1586, 1473, 1390, 1245, 1051, 832 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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^+); $C_{16}H_{18}INO_4$ 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 Et_3N (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 $CHCl_3$. The solution was washed with water, dried over Na_2SO_4 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 H_2O. 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 $NaHCO_3$. The mixture was extracted with chloroform for three times. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated. The residue was dissolved in 30 mL of chloroform and then Et_3N (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 CH_2Cl_2 were added respectively. The reaction mixture was stirred at room temperature for 6 h before it was quenched with 30 mL of H_2O. The aqueous phase was extracted with CH_2Cl_2 twice. The combined extracts were washed with brine and dried over Na_2SO_4. 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, $CHCl_3$); IR (KBr) 3344, 2954, 2930, 2858, 1713, 1666, 1626, 1286, 1249, 1103 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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^+); $C_{20}H_{31}NO_4Si$ 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, $BrCH_2CH_2OTf$ (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 NH_4Cl. The aqueous layer was separated and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, 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 Na_2SO_4, and concentrated in vacuo to provide the crude azide, which was dissolved in 10 mL of THF. To this solution were added PPh_3 (0.94 g, 3.6 mmol) and H_2O (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**. $[\alpha]_D^{20}$ –68.9 (*c* 0.50, $CHCl_3$); IR (KBr) 3231, 2953, 2920, 2857, 1702, 1620, 1276, 1104, 772 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$) 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^+); $C_{22}H_{34}N_2O_3Si$ 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 $NaBH_4$ (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 Na_2SO_4, and concentrated to dryness to give crude reduction product, which was dissolved in 5 mL of dry methylene chloride. To this solution were added Et_3N (0.28 mL, 2.03 mmol), DMAP (10 mg, 0.08 mmol) and a solution of $(CF_3CO)_2O$ (0.25 mL, 1.74 mmol) in 1 mL of CH_2Cl_2. 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 CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, 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, $CHCl_3$); IR (KBr) 2964, 2859, 1726, 1692, 1440, 1282, 1206, 1147, 837, 773 cm^{-1}; ^1H NMR (300

MHz, $CDCl_3$) 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); ^{19}F NMR (60 MHz, $CDCl_3$): δ -4.7, -4.0; MS *m/z* 581 (M^+ - Me), 518, 450, 423, 395; HRMS found *m/z* 581.1918 (M^+ -Me); $C_{25}H_{31}F_6N_2O_5Si$ requires 581.1907. The data for 4-epimer of **10**: $[\alpha]_D^{20}$ +310.3 (*c* 0.59, $CHCl_3$); IR (KBr) 2957, 2860, 1698, 1618, 1489, 1446, 1263, 1208, 1153, 1107, 837, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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); ^{19}F NMR (60 MHz, $CDCl_3$) δ -9.7, -4.0; MS *m/z* 581 (M^+-Me), 518, 450, 423, 395; HRMS found *m/z* 596.2150 (M^+); $C_{26}H_{34}F_6N_2O_5Si$ requires 581.1907.

(1*S*,2*S*,4*S*)–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 μL). The reaction solution was stirred for 2 h at room temperature before it was partitioned between 5 mL of CH_2Cl_2 and 5 mL of H_2O. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, and concentrated to dryness. The residue was dissolved in 1 mL of methylene chloride and then Et_3N (7 μL, 0.05 mmol) and MsCl (3 μL, 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

Na_2SO_4, and concentrated. The residue was purified by flash chromatography to produce 7 mg (83%) of **11**. $[\alpha]_D^{20}$ –29.4 (*c* 0.94, $CHCl_3$); IR (KBr) 2947, 1705, 1685, 1604, 1519, 1434, 1264, 1253, 1193, 1162, 1133, 767 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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.

(1*S*,2*S*,4*S*)–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 Et_3N (78 μL, 0.56 mmol) and MsCl (36 μL, 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 Na_2SO_4, and concentrated to dryness. The residue was purified by flash chromatography to give 134 mg (71% overall yield) of **12**. $[\alpha]_D^{20}$ +41.0 (*c* 0.95, $CHCl_3$); IR (KBr) 2956, 2101, 1725, 1693, 1614, 1440, 1282, 1204, 1145, 768 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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^+); $C_{20}H_{19}F_6N_5O_4$ 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. $[\alpha]_D^{20}$ –49.9 (*c* 1.25, CH_3OH); IR (KBr) 3420, 2940, 1618, 1509, 1298, 1252 cm^{-1}; ^{1}H 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 (M^+-CH_2NH_2), 245, 228, 214; HRMS found *m/z* 259.1437 (M^+-CH_2NH_2); $C_{15}H_{19}N_2O_2$ 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 Na_2SO_4, 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, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (150.9 MHz, $CDCl_3$) 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 ($M + H^+$); $C_{38}H_{59}N_7O_6$ requires 710.4605.

Martinellic 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 $CHCl_3$ for three times. The combined organic layers were dried over Na_2SO_4, 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 CH_2Cl_2 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 (C_{18}) to give 15 mg (65%) of **1** as a trifluoroacetic salt. $[\alpha]_D^{20}$ –122.7 (*c* 0.31, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (400 MHz, $CDCl_3$) 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 ($M + H^+ + 2CF_3COOH$), 610 ($M + H^+ + CF_3COOH$), 496 ($M + H^+$), 428;