Total Synthesis of (-)-Strychnine

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General. All manipulations were performed under an argon atmosphere unless otherwise mentioned. Solvents were distilled under an argon atmosphere from sodium-benzophenone (THF, Et₂O and toluene), CaH₂ (CH₂Cl₂, C₃H₇CN, DMF and DMSO), or sodium (EtOH). All other solvents, and reagents, were purified when necessary using standard procedures.

¹H and ¹³C NMR were recorded on a JEOL EX 270, a JEOL AL 400 or Bruker ARX 500 spectrometer. IR spectra were recorded on a Perkin-Elmer 1605 FT-IR instrument. Specific rotations were recorded on a JASCO P-1030 polarimeter. Analytical HPLC was performed on a JASCO liquid chromatograph. Column chromatography was performed on silica gel 60 (Merck, 70-230 or 230-400 mesh) using the indicated solvent.

Preparation of 2-(silyloxymethyl)-2-cyclohexenyl diethylphosphate (1c). To a solution of 2-tert-butyldimethylsilyloxymethyl-2-cyclohexenol ref. (250 mg, 1.0 mmol), pyridine (0.17 mL, 2.0 mmol) and DMAP (187 mg, 1.5 mmol) in CH₂Cl₂ (5 mL) was added diethyl chlorophosphate (0.22 mL, 1.5 mmol). The resulting mixture was stirred at room temperature for 3 h. Then AcOEt was added, and the organic layer was washed with brine, dried over Na₂SO₄, and concentrated. Elution with
hexane/AcOEt (2:1) gave 342.6 mg (905 µmol, 88%) of 1c as a colorless oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.03 (s, 6 H), 0.88 (s, 9 H), 1.30 (t, $J$ = 7.2 Hz, 6 H), 1.55-1.62 (m, 1 H), 1.66-1.79 (m, 2 H), 1.92-2.13 (m, 3 H), 4.08 (q, $J$ = 7.2 Hz, 4 H), 4.14 (dd, $J$ = 4.0, 2.4 Hz, 2 H), 4.80 (dd, $J$ = 4.0, 2.8 Hz, 1 H), 5.93 (br s, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ -5.3, 16.2, 17.6, 18.4, 24.8, 26.0, 30.0, 63.5, 63.8, 71.8, 127.2, 135.3; IR (neat) 2930, 2857, 1264, 1037, 988, 753 cm$^{-1}$; LR MS $m/z$ 321 (M$^+$-tBu), 224 (M$^+$-(EtO)$_2$P(O)OH), 167; HR MS calcd for C$_{13}$H$_{26}$O$_5$SiP 321.1287 (M$^+$-tBu), found 321.1287.

(4aS,9aS)-4a-Cyanomethyl-9-(4-methylbenzenesulfonyl)-2,4a,9,9a-tetrahydro-1H-carbazole (4a). A solution of 9 (1.00 g, 2.25 mmol), Pd(OAc)$_2$ (10.1 mg, 45.0 µmol), Me$_2$PPh (13.0 µL, 91.3 µmol), and Ag$_2$CO$_3$ (620 mg, 2.25 mmol) in DMSO (4.5 mL) was heated at 90 °C for 17 h. After cooling to room temperature, the solution was filtered through the pad of Celite. Then AcOEt was added and the organic layer was washed with brine, dried over Na$_2$SO$_4$, and concentrated. The residue was purified by column chromatography on silica gel. Elution with hexane/CH$_2$Cl$_2$ (1:1) gave 714.2 mg (1.96 mmol, 87%) of 4a as a white solid. A single recrystallization of 4a (964 mg, 84% ee) from EtOH afforded the nearly enantiomerically pure 4a (702 mg, 99% ee, 73% recovery). The ee of 4a was determined using DAICEL CHIRALPAK AD (hexane/$^1$PrOH=95:5); $^1$H NMR (270 MHz, CDCl$_3$) $\delta$ 1.36 (d, $J$ = 16.8 Hz, 1 H), 1.68-1.78 (m, 1 H), 1.82 (d, $J$ = 16.8 Hz, 1 H), 2.08-2.19 (m, 2 H), 2.24-2.34 (m, 1 H), 2.39 (s, 3 H), 4.16 (dd, $J$ = 11.2, 5.2 Hz, 1 H), 5.83 (br d, $J$ = 9.2 Hz, 1 H), 6.09 (ddd, $J$ = 9.2, 5.3, 3.6 Hz, 1 H), 7.07 (t, $J$ = 7.9 Hz, 1 H), 7.09 (d, $J$ = 7.9 Hz, 1 H), 7.28 (d, $J$ = 7.9 Hz, 2 H), 7.30 (t, $J$ = 7.9 Hz, 1 H), 7.70-7.74 (m, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 22.1, 22.5, 28.3, 31.1, 46.8, 66.6, 116.6, 116.9, 123.5, 124.9, 125.3, 126.9, 129.5, 130.1, 131.6, 135.3, 135.5, 138.9, 139.3; IR (nujol) 2244 cm$^{-1}$; LR MS $m/z$ 364 (M$^+$), 324 (M$^+$-CH$_2$CN), 209 (M$^+$-Ts), 155, 91; HR MS calcd for C$_{21}$H$_{20}$N$_2$O$_2$S 364.1245, found 364.1227; $[\alpha]^{22}_D = -35.5$ (c
(3aS,6aS,11aR)-7-(3-Bromoacryloyl)-1,2,3a,4,6a,7-hexahydropyrrolo[2,3-d]carbazole-3-carboxylic acid tert-butyl ester (14). To a solution of 12 (32.2 mg, 69.0 µmol) in THF (0.5 mL) was added 3.5 mL (700 µmol) of 0.2 M sodium naphthalenide in THF, which was prepared from naphthalene (128.2 mg, 1.0 mmol), sodium (23.1 mg, 1.0 mmol) in THF (5 mL), at −78 °C. After stirring at −78 °C for 15 min, the solution was allowed to stand at 0 °C. Water was added and the organic layer was washed with brine, and dried over Na₂SO₄. After removal of the solvent, the residue was purified by short column chromatography on silica gel. Elution with hexane/AcOEt (2:1) gave 19.2 mg (61.4 µmol, 89%) of (3aS,6aS,11aR)-1,2,3a,4,6a,7-hexahydropyrrolo[2,3-d]carbazole-3-carboxylic acid tert-butyl ester as a colorless oil, which was dissolved in THF (2 mL). To the solution were added K₂CO₃ (42.4 mg, 307 µmol) and then a THF solution (2 mL) of (Z)-3-Bromoacryloyl chloride (15.6 mg, 92.1 µmol) at 0 °C. After stirring at 0 °C for 30 min, Et₂O was added and the organic layer was washed with brine, dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on silica gel. Elution with hexane/AcOEt (4:1) gave 18.0 mg (40.5 µmol, 66%) of 14 as a yellow oil; ¹H NMR (400 MHz, CD₃OD) δ 1.45 (s, 9 H), 1.95-2.15 (m, 2 H), 2.20-2.26 (m, 1 H), 2.28-2.40 (m, 0.4 H), 2.45-2.53 (m, 0.6 H), 3.50 (ddd, J = 12.9, 5.0, 2.9 Hz, 1 H), 3.57 (br dd, J = 12.9, 5.0, 2.9 Hz, 1 H), 3.67-3.79 (m, 1 H), 4.17 (s, 1 H), 5.81 (br s, 0.6 H), 5.87 (br s, 1 H), 6.01 (br s, 0.4 H), 6.91 (d, J = 8.2 Hz, 1 H), 7.07 (d, J = 8.0 Hz, 1 H), 7.11 (t, J = 8.0 Hz, 1 H), 7.21 (d, J = 8.2 Hz, 1 H), 7.24-7.26 (m, 1 H), 8.12 (d, J = 8.0 Hz, 1 H); ¹³C NMR (100 MHz, CD₃OD) δ 28.1, 28.8, 38.8, 46.0, 61.0, 65.9, 81.5, 116.3, 118.9, 123.6, 124.4, 126.9, 129.1, 129.8, 130.2, 138.7, 141.6, 156.4, 165.1; IR (neat) 2974, 1690, 1652, 1593, 1480, 1390 cm⁻¹; LR MS m/z 444 (M⁺), 388 (M⁺-²Bu), 344 (M⁺-Boc), 265, 168; HR MS calcd for C₂₂H₂₅N₂O₃Br 444.1048, found 444.1041; [α]₂²_D = +122.8 (c 1.42, CHCl₃) (99% ee).
(3aR, 11bS, 13aS)-9-Oxo-1,2,3,11a,11b,13a-hexahydro-9H-pyrido[1,2,3-lm]pyrrolo[2,3-d]carbazole-1-carboxylic acid tert-butyl ester (15). A DMSO solution (1 mL) of 14 (15.0 mg, 33.7 µmol) was added to a solution of Pd(OAc)$_2$ (0.76 mg, 3.38 µmol), PPh$_3$ (1.76 mg, 6.71 µmol) and iPr$_2$NEt (18 µL, 10.3 µmol) in DMSO (1 mL), and then the solution was heated at 80 °C for 1.5 h. After cooling to the room temperature, Et$_2$O was added and the organic layer was washed with brine, dried over Na$_2$SO$_4$, and concentrated. The residue was purified by column chromatography on silica gel. Elution with hexane/AcOEt (3:1) gave 5.6 mg (15.4 µmol, 46%) of 15 as a yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) δ 1.43 (s, 9 H), 2.15-2.27 (m, 2 H), 3.40 (br s, 2 H), 3.61 (br t, $J = 9.2$ Hz, 1 H), 3.70-3.87 (m, 1 H), 4.07 (br s, 1 H), 4.55 (s, 1 H), 5.82 (d, $J = 9.7$ Hz, 1 H), 5.91-5.98 (m, 2 H), 6.31 (br d, $J = 9.7$ Hz, 1 H), 7.07 (t, $J = 8.2$ Hz, 1 H), 7.13 (d, $J = 8.2$ Hz, 1 H), 7.29 (t, $J = 8.2$ Hz, 1 H), 8.18 (t, $J = 8.2$ Hz, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 28.5, 36.8, 39.0, 43.8, 51.5, 61.1, 67.3, 80.2, 115.3, 121.3, 122.8, 123.5, 124.7, 128.7, 130.3, 132.1, 136.8, 140.3, 154.2, 166.6; IR (neat) 3044, 2976, 1692, 1659, 1596 cm$^{-1}$; LR MS m/z 364 (M$^+$), 308 (M$^+$-tBu), 264 (M$^+$-Boc); HR MS calcd for C$_{22}$H$_{24}$N$_2$O$_3$ 364.1787, found 364.1786; [α]$_{22}^D$ = +99.6 (c 0.49, CHCl$_3$) (99% ee).

(3aR, 11bS, 13aS)-1-[(Z)-4-(tert-Butyldimethylsilyloxy)-2-iodo-2-butenyl]-1,2,3,11a,11b,13a-hexahydro-9H-pyrido[1,2,3-lm]pyrrolo[2,3-d]carbazol-9-one (17). To a solution of 15 (8.4 mg, 23.0 µmol) in iPrOH (2.0 mL) was added 0.1 mL of NaO$i$Pr solution (prepared from 14 mg of Na in 3 mL of iPrOH). The solution was stirred at room temperature for 1 h. Then CH$_2$Cl$_2$ was added, and the organic layer was washed with water, dried over Na$_2$SO$_4$, and concentrated. The residue was purified by column chromatography on silica gel. Elution with hexane/AcOEt (2:1) gave 6.8 mg (18.7 µmol, 81%) of (3aR, 11bS, 13aS)-9-Oxo-1,2,3,11b,13,13a-hexahydro-9H-pyrido[1,2,3-lm]pyrrolo[2,3-d]carbazole-1-carboxylic acid tert-butyl
ester as a yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) δ 1.42 (s, 9 H), 2.10-2.23 (m, 2 H), 2.25-2.40 (m, 1 H), 2.76-2.84 (m, 0.7 H), 2.95-3.02 (m, 0.3 H), 3.50-3.60 (m, 1 H), 3.65-3.70 (m, 1 H), 3.71-3.78 (dd, $J = 5.0$, 2.5 Hz, 1 H), 4.65 (m, 1 H), 6.00 (d, $J = 9.4$ Hz, 1 H), 6.01-6.05 (m, 1 H), 6.88 (br d, $J = 9.4$ Hz, 1 H), 7.05 (t, $J = 8.0$ Hz, 1 H), 7.08 (d, $J = 8.0$ Hz, 1 H), 7.26 (d, $J = 8.0$ Hz, 1 H), 8.16 ($J = 8.0$ Hz, 1 H), $^{13}$C NMR (100 MHz, CDCl$_3$) δ 28.5, 29.4, 36.0, 42.5, 51.2, 57.3, 62.3, 79.9, 115.3, 122.9, 124.3, 124.9, 127.5, 128.7, 130.6, 136.9, 137.8, 140.6, 154.4, 161.4; IR (neat) 3006, 2970, 1694, 1651, 1596, 1574 cm$^{-1}$; LR MS $m/z$ 364 (M$^+$), 308 (M$^+$-tBu), 264 (M$^+$-Boc); HR MS calcd for C$_{22}$H$_{24}$N$_2$O$_3$ 364.1787, found 364.1786; $[\alpha]_{D}^{22} = -119.0$ ($c$ 0.49, CHCl$_3$) (99% ee). To a solution of this compound (6.8 mg, 18.7 µmol) in CH$_2$Cl$_2$ (0.5 mL) was added CF$_3$CO$_2$H (0.5 mL) at 0 °C and the solution was stirred for 30 min. The solvent was removed to give an oily product (8.0 mg), which was dissolved in DMF (1 mL). To this solution was added slowly Li$_2$CO$_3$ (8.3 mg, 112.3 µmol), and then DMF solution (0.9 mL) of (Z)-1-Bromo-4-(tert-butyldimethylsilyloxy)-2-iodo-2-butene (14.6 mg, 37.3 µmol). After stirring at 40 °C for 14 h, Et$_2$O was added and the organic layer was washed with brine, dried over Na$_2$SO$_4$, and concentrated. The residue was purified by column chromatography on silica gel. Elution with hexane/AcOEt (3:1) gave 7.1 mg (12.4 µmol, 66%) of 17 as a yellow solid; $^1$H NMR (400 MHz, CDCl$_3$) δ 2.09 (ddd, $J = 13.4$, 10.0, 6.0 Hz, 1 H), 2.15-2.18 (m, 1 H), 2.23-2.30 (m, 1 H), 2.37-2.45 (m, 1 H), 2.64 (dt, $J = 11.2$, 4.1 Hz, 1 H), 2.87 (dd, $J = 10.0$, 5.2 Hz, 1 H), 3.28 (dt, $J = 9.2$, 6.6 Hz, 1 H), 3.44 (d, $J = 13.5$ Hz, 1 H), 3.61 (d, $J = 13.5$ Hz, 1 H), 4.24 (d, $J = 5.0$ Hz, 2 H), 4.59 (s, 1 H), 5.97 (d, $J = 9.9$ Hz, 1 H), 6.00-6.05 (m, 1 H), 6.10 (t, $J = 5.0$ Hz, 1 H), 6.87 (d, $J = 9.9$ Hz, 1 H), 7.05 (t, $J = 7.7$ Hz, 1 H), 7.22 (t, $J = 7.7$ Hz, 1 H), 7.83 (d, $J = 7.7$ Hz, 1 H), 8.11 (d, $J = 7.7$ Hz, 1 H), $^{13}$C NMR (100 MHz, CDCl$_3$) δ -5.0, 18.3, 23.4, 25.8, 37.2, 47.1, 51.7, 60.4, 62.5, 63.0, 67.9, 104.8, 114.6, 123.9, 124.9, 126.0, 128.0, 128.1, 131.0, 136.8, 138.1, 138.7, 140.4, 161.5; IR (neat) 2953, 1650, 1479, 1419, 1110, 837 cm$^{-1}$; LR MS $m/z$ 574 (M$^+$), 517 (M$^+$-tBu), 446 (M$^+$-HI), 263; HR MS calcd for
C_{27}H_{35}N_2O_2Si 574.1495, found 574.1504; \([\alpha]^{22}_D = -208.9\ (c 0.51, \text{CHCl}_3)\ (99\%\ ee)\).

\((-)-(21E)-8,11,12,13\text{-Tetradehydro-24-}({\text{ tert-butyl}})\text{-dimethylsilyl})-12,24\text{-secostrychnidin-10-one(18)}\). A solution of 17 (8.8 mg, 15.3 µmol), Pd(OAc)_2 (0.69 mg, 3.07 µmol), PPh_3 (1.6 mg, 6.10 µmol), K_2CO_3 (10.6 mg, 76.7 µmol) and Bu_4NCl (6.4 mg, 23.0 µmol) in DMF (2 mL) was heated at 70 °C for 0.5 h. After cooling to room temperature, Et_2O was added and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel. Elution with CH_2Cl_2/MeOH (30:1) gave 3.3 mg (7.39 µmol, 48%) of 18 as a yellow oil; ^1H NMR (400 MHz, CDCl_3), δ 0.05 (s, 6 H), 0.88 (s, 9 H), 1.25(d, J = 14.0 Hz, 1 H), 1.92 (dd, J = 12.1, 4.6 Hz, 1 H), 2.32 (td, J = 12.5, 6.6 Hz, 1 H), 2.57-2.64 (m, 1 H), 3.04 (d, J = 15.6 Hz, 1 H), 3.13 (d, J = 12.1, 6.3 Hz, 1 H), 3.34-3.39 (td, J = 12.5, 5.1 Hz, 1 H), 3.63 (s, 1 H), 4.07-4.18 (m, 2 H), 4.30-4.33 (m, 1 H), 5.54 (br s, 1 H), 6.46 (d, J = 9.2 Hz, 1 H), 7.22-7.27 (m, 2 H), 7.37 (t, J = 8.0 Hz, 1 H), 7.40 (d, J = 8.0 Hz, 1 H), 8.55 (d, J = 8.0 Hz, 1 H); ^13C NMR (100 MHz, CDCl_3) δ -5.1, 18.4, 26.0, 31.1, 34.5, 46.1, 55.5, 56.2, 56.6, 59.7, 61.2, 117.5, 117.9, 119.3, 120.9, 126.3, 128.4, 129.0, 136.4, 138.6, 139.3, 140.5, 153.0, 161.4; IR (neat) 2953, 2850, 1672, 1622, 1585, 1459 cm\(^{-1}\); LR MS m/z 446 (M\(^+\)), 389 (M\(^+\)-tBu), 314 (M\(^+\)-TBSOH), 301; HR MS calcd for C_{27}H_{34}N_2O_2Si 446.2369, found 446.2383; \([\alpha]^{22}_D = -255.5\ (c 0.81, \text{CHCl}_3)\ (99\%\ ee)\).

\((+)-\text{Isostrychnine}\). To a solution of LiAlH_4 (41.6 mg, 93.0 µmol) in Et_2O (2.5 mL) was added a solution of 18 (50 mg, 1.32 mmol) in Et_2O (1.5 mL) and THF (1.5 mL) at 0 °C for 25 min. After 1.5 h total, MeOH (1.5 mL) was added slowly, and then water (3.0 mL) was added. Then CH_2Cl_2 was added, and the organic layer was washed with water, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel. Elution with CH_2Cl_2/MeOH (30:1) gave 19.6 mg (43.7 µmol, 47%) of \((-)-(21E)-12,13\text{-Didehydro-24-}({\text{ tert-butyl}})\text{-dimethylsilyl})-
12,24-secostrychnidin-10-one as a yellow oil. $^1$H NMR (400 MHz, CDCl$_3$), $\delta$ 0.08 (s, 6 H), 0.88 (s, 9 H), 1.44 (d, $J = 13.8$ Hz, 1 H), 2.10-2.17 (m, 1 H), 2.20-2.31 (m, 1 H), 2.91-2.95 (m, 2 H), 3.00 (d, $J = 17.4$ Hz, 1 H), 3.10-3.23 (m, 2 H), 3.50 (br s, 1 H), 3.59 (s, 1 H), 3.72 (s, 1 H), 4.21-4.25 (m, 1 H), 4.30 (d, $J = 5.5$ Hz, 2 H), 5.50 (t, $J = 5.5$ Hz, 1 H), 5.79-5.81 (m, 1 H), 7.08 (t, $J = 8.0$ Hz, 1 H), 7.16-7.24 (m, 2 H), 8.15 (d, $J = 8.0$ Hz, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ -5.0, 18.4, 24.3, 25.9, 34.3, 36.7, 44.3, 52.2, 52.5, 52.7, 59.1, 62.4, 65.5, 114.8, 121.3, 122.7, 124.4, 129.0, 129.2; 134.4, 136.6, 141.3, 141.9, 167.9; IR (neat) 2927, 2855, 1674, 1597, 1483 cm$^{-1}$; LR MS m/z 448 (M+), 391 (M+-tBu), 316 (M+-TBSOH), 303; HR MS calcd for C$_{27}$H$_{36}$N$_{2}$O$_{2}$Si 448.2527, found 448.2540; [$\alpha$]$^\text{22}_D$ = -31.5 (c 0.67, CHCl$_3$) (99% ee).

An aqueous solution of HCl (1 N, 1 mL) was added to a solution of the silyl ether (19.6 mg, 43.7 µmol) in THF (0.5 mL), and the whole solution was stirred at room temperature for 3 h. Then CH$_2$Cl$_2$ was added, and the organic layer was washed with water, dried over Na$_2$SO$_4$, and concentrated. The residue was purified by column chromatography on silica gel. Elution with CH$_2$Cl$_2$/MeOH (7:1) gave 14.1 mg (42.2 µmol, 96%) of isostrychnine as a white solid. $^1$H NMR (400 MHz, CDCl$_3$), $\delta$ 1.43 (d, $J = 14.1$ Hz, 1H), 1.95 (br s, 1 H), 2.07-2.26 (m, 3 H), 2.80-2.94 (m, 3 H), 3.05 (dd, $J = 17.4$, 6.4 Hz, 1 H), 3.21-3.24 (m, 1 H), 3.59 (m, 2 H), 3.66 (s, 1 H), 4.22 (d, $J = 4.0$ Hz, 2 H), 4.25 (m, 1 H), 5.59 (t, $J = 4.0$ Hz, 1 H), 5.84-5.87 (m, 1 H), 7.09 (t, $J = 8.0$ Hz, 1 H), 7.21-7.24 (m, 2 H), 8.13 (d, $J = 8.0$ Hz, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 14.2, 25.3, 34.5, 36.9, 45.6, 52.3, 52.6, 53.6, 58.3, 63.1, 66.7, 114.6, 120.8, 122.5, 124.3, 128.2, 128.5, 133.6, 137.1, 141.3, 141.7, 168.2; IR (neat) 3344, 2927, 1668, 1596, 1483, 1460, 1397, 1286, 908 cm$^{-1}$; LR MS m/z 334 (M+), 316 (M+-H$_2$O), 303; HR MS calcd for C$_{21}$H$_{22}$N$_{2}$O$_{2}$ 334.1681, found 334.1684; [$\alpha$]$^\text{22}_D$ = +23.7 (c 0.31, EtOH) (99% ee).

(-)-Strychnine. A solution of (+)-isostrychnine (19.6 mg, 58.6 µmol) in 2 mL of 1.5 % KOH/EtOH was heated at 85°C for 6 h. Then the solvent was removed and the
residue was dissolved in CH$_2$Cl$_2$. The organic layer was washed with water, dried over Na$_2$SO$_4$, and concentrated. The residue was purified by column chromatography on silica gel. Elution with CH$_2$Cl$_2$/MeOH/Et$_3$N (90:10:1) gave 3.0 mg (9.0 µmol, 16%) of (-)-strychnine, whose data agreed with those of (-)-strychnine reported in the literature.$^4$ \[^1\]H NMR (400 MHz, CDCl$_3$), $\delta$ 1.27 (m, 1H), 1.49 (d, $J = 12.8$ Hz, 1 H), 1.90-1.99 (m, 2 H), 2.36 (dt, 14.4, 4.4 Hz, 1 H), 2.65 (dd, $J = 18.0$, 3.7 Hz, 1 H), 2.78 (br d, $J = 18.0$ Hz, 1 H), 2.90 (dd, $J = 16.4$, 8.8 Hz, 1 H), 3.10-3.18 (m, 2 H), 3.24 (br s, 1 H), 3.75 (d, $J = 14.7$ Hz, 1 H), 3.86 (d, $J = 10.4$ Hz, 1 H), 4.00-4.07 (m, 2 H), 4.15 (dd, $J = 14.1$, 6.6 Hz, 1 H), 4.25-4.30 (m, 1 H), 5.93-5.99 (m, 1 H), 7.09 (t, $J = 8.0$ Hz, 1 H), 7.17 (d, $J = 8.0$ Hz, 1 H), 7.25 (m, 1 H), 8.09 (d, $J = 8.0$ Hz, 1 H).